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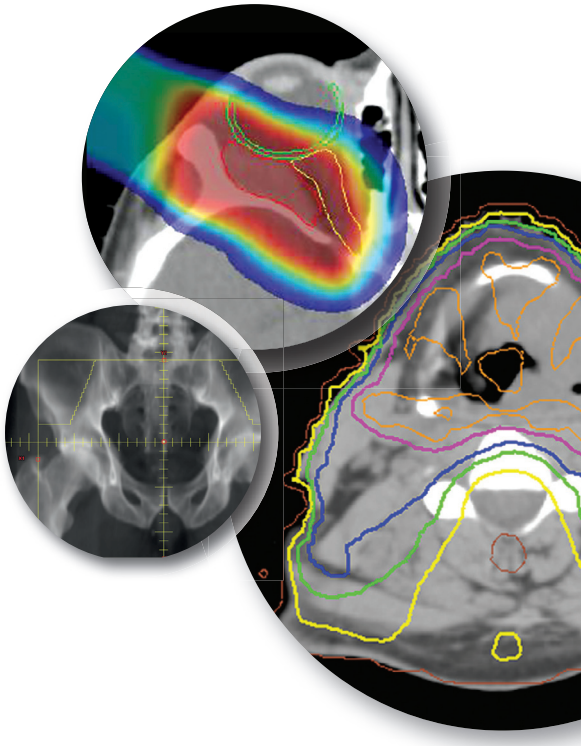
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To Katheryn, my wife of 50 years in December 2014, to our children and their spouses (Chad and Chrissy, Whitney and Jeff, Stacie and Nick, Ryan and Danna, Scott and Cindy) and to our grandchildren (Olivia and Adam; Rebecca, Andrew, Katie, and Matthew; Sam, Anna, Michael, and Ellie; Grant, Ian, and Amelia; Landon, Parker, Rhys, and Brooke) for their love and support.

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Leonard L. Gunderson

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PREFACE

The radiation oncology community has received the three previous editions of *Clinical Radiation Oncology* very well, and it has become the standard radiation oncology textbook for many physicians. For the fourth edition of *Clinical Radiation Oncology*, the intent is to maintain the many excellent features of the previous editions while adding some new features, new chapters and chapter authors, and one new Associate Editor. The most exciting new feature is that the chapters in the online version of the fourth edition of *Clinical Radiation Oncology* (www.expertconsult.com) will be periodically updated.

The fourth edition again has separate sections on Scientific Foundations of Radiation Oncology, Techniques and Modalities, and Disease Sites. Within the section on Scientific Foundations of Radiation Oncology, a new chapter has been added, "Radiation Physics: Stereotactic." In the section on Techniques and Modalities, the chapter on stereotactic irradiation has been divided into separate chapters, "Stereotactic Irradiation: CNS Tumors" and "Stereotactic Body Irradiation: Extracranial Tumors," in view of the expanded interest in and outcomes data for stereotactic body irradiation.

The associate editors for Disease Sites chapters were an important component of the success of the three previous editions and have been maintained. One new associate editor has been selected for the fourth edition—Dr. Andrea Ng for Lymphoma and Hematologic Malignancies. Associate editors are involved in the selection of chapter authors and in editing the chapters for scientific content and accuracy. For most Disease Sites, the associate editors also wrote an Overview that allowed them to discuss issues common to various Disease Sites within the section and to give their unique perspective on important issues.

Features that are retained within Disease Sites chapters include an opening page format summarizing the most important issues, a full-color format throughout each chapter, liberal use of tables and figures, and a closing section with a discussion of controversies and problems and a treatment algorithm that reflects the treatment approach of the authors. Chapters have been edited not only for scientific accuracy, but also for organization, format, and adequacy of outcome data (disease control, survival, and treatment tolerance).

We are again indebted to the many national and international experts who contributed to the fourth edition of *Clinical Radiation Oncology* as associate editors, senior authors, or coauthors. Their outstanding efforts combined with ours will hopefully allow this new edition to be a valuable contribution and resource in the coming years.

Leonard L. Gunderson
Joel E. Tepper

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We wish to thank our wives, Katheryn and Laurie, and Dr. Tepper's secretary, Betty Bush, for their patience and assistance during the many months we were involved in the preparation of the fourth edition of *Clinical Radiation Oncology*.

We also thank the associate editors and the many chapter senior authors and co-authors for their time, efforts, and outstanding contributions to this edition.

We acknowledge the editors and production staff at Elsevier, especially Kate Dimock, Deidre Simpson, and Rachel McMullen, who have done an outstanding job in collating and producing the fourth edition of *Clinical Radiation Oncology*.

VIDEO CONTENTS

Video 1: Intraoperative Irradiation

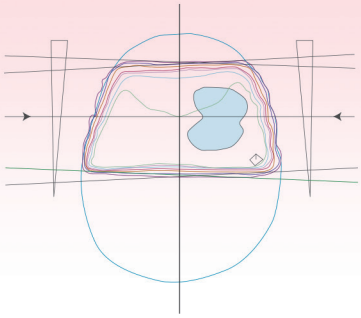
Video 2: Prostate Brachytherapy

Video 3: Ocular Melanoma

Video 4: Penile Brachytherapy

CHAPTER 1

The Biological Basis of Radiation Oncology



Elaine M. Zeman

WHAT IS RADIATION BIOLOGY?

In the most general sense, *radiation biology is the study of the effects of electromagnetic radiation on biological systems*. Three aspects of this definition deserve special mention. First, effects may include everything from DNA damage to genetic mutations, chromosome aberrations, cell killing, disturbances in cell cycle transit and cell proliferation, neoplastic transformation, early and late effects in normal tissues, teratogenesis, cataractogenesis, and carcinogenesis, to name but a few. Electromagnetic radiation refers to any type of radiant energy in motion with wave or particulate characteristics that has the capacity to impart some or all of its energy to the medium through which it passes. The amount of energy deposited can vary over some 25 orders of magnitude, depending on the type of electromagnetic radiation. For example, 1 kHz radio waves have energies in the range of 10^{-11} eV to 10^{-12} eV, whereas x- or γ-rays may have energies upwards of 10 MeV or more. The more energetic forms of electromagnetic radiation, the ionizing radiations, deposit energy as they traverse the medium by setting secondary particles in motion that can go on to produce further ionizations. Finally, biological systems may be, for example, simple cell-free extracts of biomolecules, or increasingly complex, from prokaryotes to single-celled eukaryotes, to mammalian cells in culture, to tissues and tumors in laboratory animals or humans, to entire ecosystems.

Radiotherapy-oriented radiobiology focuses on that portion of the electromagnetic spectrum energetic enough to cause ionization of atoms. This ultimately results in the breaking of chemical bonds that can lead to damaging important biomolecules. The most significant effect of ionizing radiation in this context is cell killing, which directly or indirectly is at the root of nearly *all* of the normal tissue and tumor responses noted in patients.

Cytotoxicity is not the only significant biological effect caused by radiation exposure, although it will be the main focus of this chapter. Other important radiation effects, carcinogenesis, for example, will also be discussed, although the reader should be aware that radiation carcinogenesis is a large discipline in and of itself, involving investigators from fields as diverse as biochemistry, toxicology, epidemiology, environmental sciences, molecular biology, tumor biology, health and medical physics, as well as radiobiology. Most radiation protection standards are based on minimizing the risks associated with mutagenic and carcinogenic events. Radiologic health professionals therefore are de facto educators of and advocates for the general public when it comes to ionizing radiation and need to be fully conversant in the potential risks and benefits of medical procedures involving radiation.

Finally, the majority of this chapter will be devoted to so-called classical radiobiology, that is, studies that largely predate the revolution in molecular biology and biotechnology during the 1980s and 1990s. Although the reader might be tempted to view this body of knowledge as rather primitive by today's standards, relying too heavily on phenomenology, empiricism, and descriptive models and theories, the real challenge is to integrate the new biology into the already existing framework of classical radiobiology; this will be discussed in detail in Chapter 2.

RADIOTHERAPY-ORIENTED RADIOBIOLOGY: A CONCEPTUAL FRAMEWORK

Before examining any one aspect of radiobiology in depth, it is important to introduce several general concepts to put the information in its proper perspective.

The Therapeutic Ratio

The most fundamental of these concepts is what is termed the *therapeutic ratio*, which is in essence a risk-versus-benefit approach to planning a radiotherapy treatment regimen. Many of the radiobiological phenomena to be discussed in this chapter are thought to play important roles in optimizing, or at least fine-tuning the therapeutic ratio. In theory, it should be possible to eradicate any malignant tumor simply by delivering a sufficiently high dose of radiation. Of course in practice, the biological consequences for normal tissues that are necessarily irradiated along with the tumor limit the total dose that can be safely administered. As such, a balance must be struck between what is deemed an acceptable probability of a radiation-induced complication in a normal tissue and the probability of tumor control. Ideally, one would hope to achieve the maximum likelihood of tumor control that does not produce unacceptable normal tissue damage.

The concept of therapeutic ratio is best illustrated graphically by comparing dose-response curves for both tumor control and normal tissue complication rates plotted as a function of dose. Examples of this approach are shown in Figure 1-1, for cases in which the therapeutic ratio is either "unfavorable," "favorable," or "optimal," bearing in mind that these are theoretical curves. Actual dose-response curves derived from experimental or clinical data are much more variable, particularly for tumors, which tend to show much shallower dose responses.[1] This serves to underscore how difficult it can be in practice to assign a single numerical value to the therapeutic ratio in any given situation.

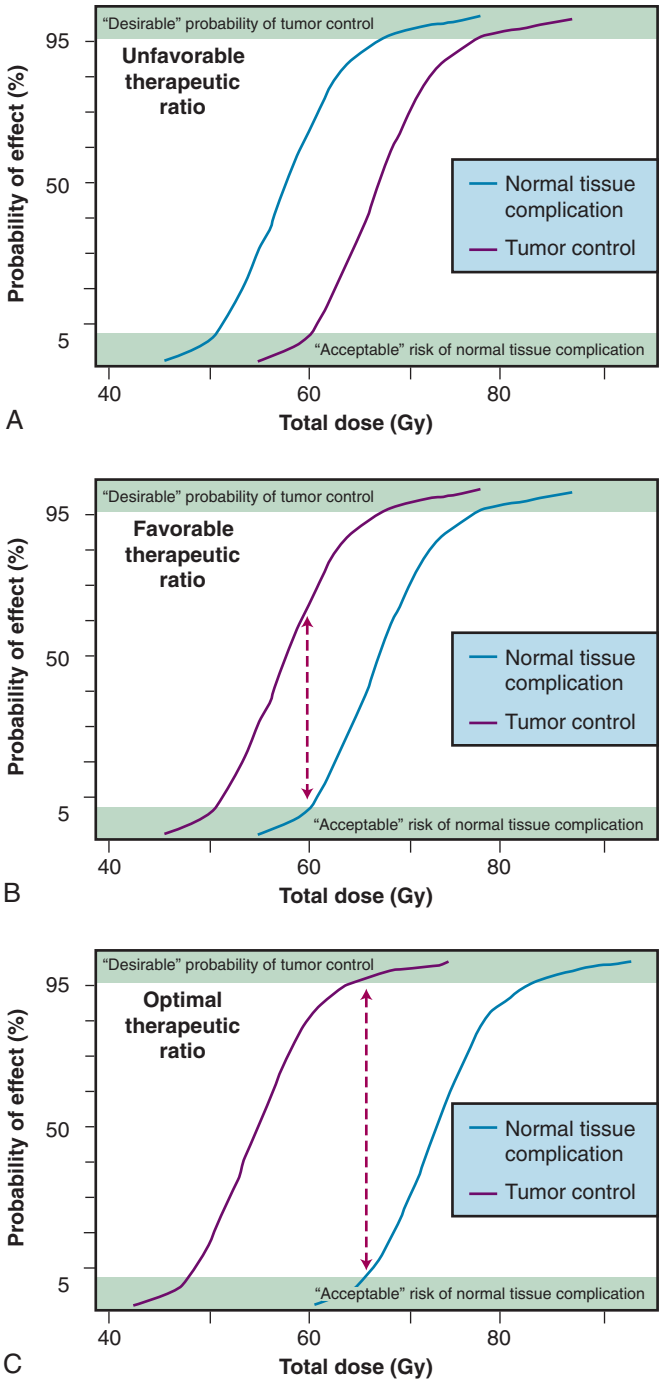


Figure 1-1 Illustrating the concept of therapeutic ratio under conditions in which the relationship between the normal tissue tolerance and tumor control dose-response curves is unfavorable *(upper panel)*, favorable *(middle panel)*, and optimal *(lower panel)*.

Many of the radiobiological properties of cells and tissues can have a favorable or adverse effect on the therapeutic ratio. Therefore, in planning a course of radiation therapy, the goal should be to optimize the therapeutic ratio as much as possible; in other words, using our graphical approach, increase the separation between the tumor control and normal tissue complication curves. This can be accomplished either by shifting the tumor control curve to the left with respect to the dose axis (toward lower doses, that is, radiosensitization), the normal tissue complication curve to the right (toward higher doses, that is, radioprotection), or perhaps, some combination of both. The key however is to shift these curves *differentially*, which is not necessarily an easy task given that there are not that many exploitable differences in the radiobiology of cells derived from tumors and those derived from normal tissues.

The Radiation Biology "Continuum"

There is a surprising continuity between the physical events that occur in the first few femtoseconds after ionizing radiation interacts with the atoms of a biomolecule and the ultimate consequences of that interaction on tissues. The consequences themselves may not become apparent until days, weeks, months, or even years after the radiation exposure. Some of the important steps in this radiobiology continuum are listed in Table 1-1. The orderly progression from one stage of the continuum to the next—from physical to physico-chemical to biochemical to biological—is particularly noteworthy not only because of the vastly different time scales over which the critical events occur, but also because of the increasing biological complexity associated with each of the endpoints or outcomes. Each stage of the continuum also offers a unique radiobiological window of opportunity: the potential to intervene in the process and thereby modify all the events and outcomes that follow.

Levels of Complexity in Radiobiological Systems

Another important consideration in all radiobiological studies is the nature of the experimental system used to study a particular phenomenon, the assay(s) used, and the endpoint(s) assessed. For example, one investigator may be interested in studying DNA damage caused by ionizing radiation, and in particular, the frequency of DNA double-stranded breaks (DSBs) produced per-unit dose. As an experimental system, he or she might choose DNA extracted from mammalian cells. Then, using a DNA elution assay, the rate at which the irradiated DNA passes through a semipermeable membrane is measured as an endpoint and compared with the rate of elution of DNA extracted from cells that had not been previously irradiated. DNA containing more DSBs elutes faster than DNA containing fewer breaks, allowing a calibration curve to be generated that relates the dose received to the elution rate. A second investigator, on the other hand, may be interested in improving the control rate of head and neck cancers with radiation therapy by employing a nonstandard fractionation schedule. In this case, the type of experiment would be a clinical trial. The experimental system would be a cohort of patients, some of whom are randomized to receive nonstandard fractionation, and the rest, standard fractionation. The endpoints assessed could be one or more of the following: loco-regional control, long-term survival, disease-free survival, normal tissue complication frequency, and so on and evaluated at specific times after completion of the radiation therapy.

In considering both the strengths and weaknesses of these two investigators' studies, any number of pertinent questions may be asked. Which is the more complex or heterogeneous system? Which is the more easily manipulated and controlled system? Which is more relevant for the day-to-day practice of radiation therapy? What kinds of results are gleaned from each, and can these results be obtained in a timely manner? In this example, it is clear that human patients with spontaneously arising tumors represent a far more heterogeneous and complex experimental system than an extract of mammalian DNA. On the other hand, the DNA system is much more easily manipulated, possible confounding factors can be more easily

TABLE 1-1 Stages in the Radiobiology Continuum

Time Scale of Events (Stage)	Initial Event	Final Event	Response Modifiers/ Possible Interventions
10^{-16} to 10^{-12} second (Physical)	Ionization of atoms	Free radicals formed in biomolecules	Type of ionizing radiation; shielding
10^{-12} to 10^{-2} second (Physico-chemical)	Free radicals formed in biomolecules	DNA damage	Presence or absence of free radical scavengers, molecular oxygen, or oxygen-mimetic radiosensitizers
1.0 second to several hours (Biochemical)	DNA damage	Unrepaired or mis-rejoined DNA damage	Presence or absence of functioning DNA damage recognition and repair systems; repair-inhibiting drugs; altering the time required to complete repair processes
Hours to years (Biological)	Unrepaired or mis-rejoined DNA damage	Clonogenic cell death; apoptosis; mutagenesis; transformation; carcinogenesis; early and late effects normal tissues; whole-body radiation syndromes; tumor control, etc.	Cell-cell interactions; biological response modifiers; adaptive mechanisms; structural and functional organization of tissues; cell kinetics; etc.

controlled, and the measurement of the desired endpoint (elution rate) plus the data analysis can be completed within a day or two. Obviously, this is not the case with the human studies, in which numerous confounding factors can and do influence results, manipulation of the system can be difficult if not impossible, and the experimental results typically take years to obtain.

The issue of relevance is an even thornier one. Arguably, both studies are relevant to the practice of radiation therapy insofar as the killing of cells is at the root of normal tissue and tumor toxicity caused by radiation, and that cell killing usually is, either directly or indirectly, a consequence of irreparable damage to DNA. As such, any laboratory findings that contribute to the knowledge base of radiation-induced DNA damage are relevant. Clearly however, clinical trials with human patients not only are a more familiar experimental system to radiation oncologists, but also efficacy in cancer patients is, ultimately, what leads to new standards of care in clinical practice, and becomes the gold standard against which all newer therapeutic strategies are judged.

All things considered then, there is a time and place both for relatively simple systems and more complex ones. The relatively simple, homogeneous, and easily manipulated systems are best suited for the study of the mechanisms of radiation action, such as measuring DNA or chromosomal damage, changes in gene expression, perturbations of the cell cycle, or the survival of irradiated cells maintained in culture. The more complicated and heterogeneous systems, with their unique endpoints, are more clinically relevant, such as assays of tumor control or normal tissue complication rates. Both types of assay systems have inherent strengths and weaknesses, yet both are critically important if we hope to improve the practice of radiation therapy based on sound biological principles.

Tissue Heterogeneity

Why is radiation therapy successful at controlling one patient's tumor but not another's, even when the two tumors seem identical? Why are we generally more successful at controlling certain types of cancers than others? The short answer to such questions is that, although the tumors may appear identical macroscopically, their component cells may be quite different phenotypically or genotypically. Also there may be important differences between the two patients' normal tissues.

Normal tissues, being composed of more than one type of cell, are somewhat heterogeneous, and tumors, owing both to the genetic instability of individual tumor cells and to microenvironmental differences, are heterogeneous. Different subpopulations of cells have been isolated from many types of human and experimental cancers, and these may differ in antigenicity, metastatic potential, and sensitivity to radiation and chemotherapy (for reviews, see Heppner et al[2], Suit et al[3]). This heterogeneity is manifest both within a particular patient, and to a much greater extent, between patients with otherwise similar tumors. Both intrinsic and extrinsic factors contribute to this heterogeneity. Intrinsic factors may include the following: inherent radiosensitivity, gene expression, biochemical repair processes, modes of cell death (e.g., mitotic catastrophe versus apoptosis), genomic instability, cell cycle kinetics, and how the tissue is structurally and functionally arranged. Extrinsic factors, on the other hand, tend to be related to physiological differences between tissues, such as the degree of vascularity, availability of oxygen and nutrients, pH, energy charge, and the proximity of, and degree of contact between, normal host tissue and the tumor.

What are the practical implications of normal tissue and tumor heterogeneity? First, if one assumes that normal tissues are the more uniform and predictable in behavior of the two, then tumor heterogeneity is responsible, either directly or indirectly, for most radiotherapy failures. If so, this suggests that a valid clinical strategy might be to identify the radioresistant subpopulation(s) of tumor cells, and then, tailor therapy specifically to cope with them. This approach is much easier said than done. Some clinical studies—both prospective and retrospective—now include one or more determinations of, for example, extent of tumor hypoxia,[4,5] or potential doubling time of tumor clonogens.[6] And although such measurements are not done routinely (because of their labor and intensiveness and longer turn-around times for results), the hope is that someday subsets of patients bearing tumors with different biological characteristics will be able to be assigned prospectively to different treatment groups.

Another consequence of tissue heterogeneity is that any radiobiological endpoint measured in an intact tissue is necessarily related to the radiosensitivities of all the subsets of cells, plus all the other intrinsic and extrinsic factors contributing to the overall response of the tissue. And because data on normal tissue tolerances and tumor control probabilities are also averaged across large numbers of patients, heterogeneity is even more pronounced.

Powers of Ten

Tumor control is achieved only when all clonogenic cells are killed or otherwise rendered unable to sustain tumor growth

indefinitely. To estimate the likelihood of cure, it is necessary to know, or at least have an appreciation for, approximately how many clonogenic cells the tumor contains, how radiosensitive these cells are (i.e., some measure of killing efficiency per unit radiation dose), and what the relationship is between the number of clonogenic cells remaining after treatment and the probability of recurrence. The latter is perhaps the easiest to ascertain, given our knowledge of both the random and discrete nature of radiation damage and the general shape of dose-response curves for mammalian cells and tissues. For a given number of surviving cells per tumor, the probability of local control can be derived from Poisson statistics using the equation $P = e^{-n}$, where P is the tumor control probability and n is the average number of surviving clonogenic tumor cells. For example, when, for a large number of tumors, an average of one clonogenic cell per tumor, remains at the end of radiation therapy, the tumor control rate will be about 37%, meaning that about 6 out of 10 tumors of the same size and relative radiosensitivity will recur. Should the treatment reduce clonogenic cell numbers to an average of 0.1 per tumor, the tumor control probability would increase to 90%, 0.05 per tumor, 95%, and 0.01 per tumor, 99%, respectively.

The tumor control probability for a given fraction of surviving cells is not particularly helpful if the total number of cells at risk is unknown, however, and this is where an understanding of logarithmic relationships and exponential cell killing is useful. Based on the resolution of existing tools and technology for cancer detection, let us assume that a 1-cm^3 (1-g) tumor mass can be identified reliably. A tumor of this size has been estimated to contain approximately 10^9 cells,[7] admittedly a theoretical value that assumes all cells are perfectly "packed" and uniformly sized and that the tumor contains no stroma. A further assumption, that all such cells are clonogenic (which is rarely, if ever, the case), suggests that at least 9 logs of cell killing would be necessary before any appreciable tumor control (about 37%) would be achieved, and 10 logs of cell killing would be required for a high degree of tumor control (i.e., 90%).

After the first log or two of cell killing however, some tumors respond by shrinking, which is a partial response. After two to three logs of cell killing, the tumor may shrink to a size below the current limits of clinical detection, that is, a complete response. Although partial and complete responses are valid clinical endpoints, a complete response does not necessarily mean tumor cure. At least six more logs of cell killing would still be required before any significant probability of cure would be expected. This explains why radiation therapy is not halted if the tumor disappears during the course of treatment; this concept is illustrated graphically in Figure 1-2.

Finally, it should be noted that although the goal of curative radiation therapy is to reduce tumor cell survival by at least nine logs, even for the smallest tumor likely to be encountered, it is much less clear how many logs of cell killing a particular normal tissue can tolerate before it loses its structural or functional integrity. This would depend on how the tissue is organized structurally, functionally, and proliferatively; which constituent cells are the most and least radiosensitive; and which cells are the most important to the integrity of the tissue. It is unlikely however that many normal tissues could tolerate a depletion of two logs (99%) of their cells, let alone nine or more logs.

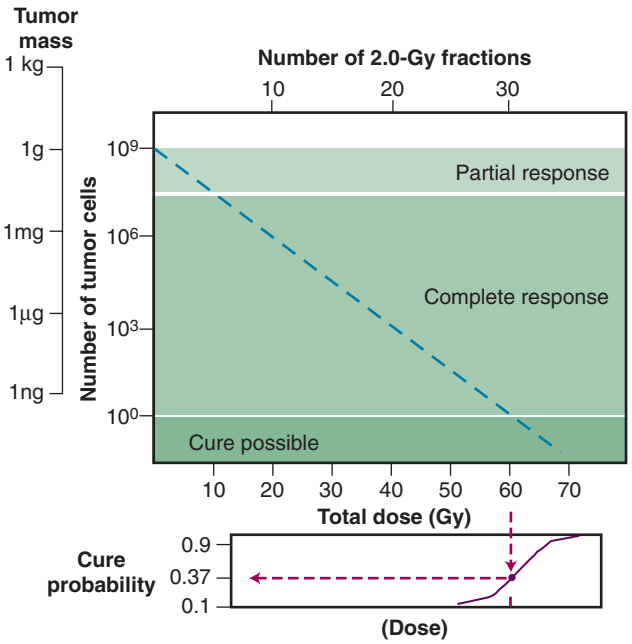


Figure 1-2 The relationship between radiation dose and tumor cell survival during fractionated radiotherapy of a hypothetical, 1-g tumor containing 10^9 clonogenic cells. Although a modest decrease in cell surviving fraction can cause the tumor to shrink (partial response) or disappear below the limits of clinical detection (complete response), few if any cures would be expected until at least 9 logs of clonogenic cells have been killed. In this example, a total dose of at least 60 Gy delivered daily, 2 Gy fractions would be required to produce a tumor control probability of 0.37, assuming each dose reduced the surviving fraction to 0.5.
Adapted from Steel G, Adams G, Peckham M, editors: The biological basis of radiotherapy, New York, 1983, Elsevier.

RADIATION BIOLOGY AND THERAPY: THE FIRST 50 YEARS

In less than four years after the discovery of x-rays by Roentgen,[8] radioactivity by Becquerel,[9] and radium by the Curies,[10] the new modality of cancer treatment known as radiation therapy claimed its first apparent cure of skin cancer.[11] Today, nearly 120 years later, radiotherapy is most commonly given as a series of small daily dose fractions of approximately 1.8 to 2.0 Gy each, 5 days per week, over a period of 5 to 7 weeks to total doses of 50 to 70 Gy. Although it is true that the historical development of this conventional radiotherapy schedule was empirically based, there were a number of early radiobiological experiments that suggested this approach.

In the earliest days of radiotherapy, both x-rays and radium were used for cancer treatment. Because of the greater availability and convenience of using x-ray tubes and the higher intensities of radiation output achievable, it was fairly easy to deliver large single doses in short overall treatment times. Thus, from about 1900 to the 1920s, this "massive-dose technique"[12] was a common way of administering radiation therapy. Unfortunately, normal tissue complications were often quite severe, and to make matters worse, the rate of local tumor recurrence was still unacceptably high.

Radium therapy was used more extensively in France. Because of the low activities available, radium applications necessarily involved longer overall treatment times to reach comparable total doses. Although extended treatments were less convenient, clinical results were often superior. Perceiving that the change in overall time was the critical factor, physicians began to experiment with the use of multiple, smaller x-ray doses delivered over extended periods. By that time, there was already a radiobiological precedent for expecting improvement in tumor control when radiation treatments were protracted.

As early as 1906, Bergonié and Tribondeau observed histologically that the immature, dividing cells of the rat testis showed evidence of damage at lower radiation doses than the mature, nondividing cells of the stroma.[13] Based on these observations, they put forth some basic laws, stating that x-rays were more effective on cells that were actively dividing, likely to continue to divide indefinitely, and poorly differentiated.[13] Because tumors were already known to contain cells that not only were less differentiated, but also exhibited greater mitotic activity, they reasoned that several radiation exposures might preferentially kill these tumor cells, but not their slowly proliferating, differentiated counterparts in the surrounding normal tissues.

The end of common usage of the single-dose technique in favor of fractionated treatment came during the 1920s as a consequence of the pioneering experiments of Claude Regaud et al.[14] Using the testes of the rabbit as a model tumor system (because the rapid and unlimited proliferation of spermatogenic cells simulated to some extent the pattern of cell proliferation in malignant tumors), Regaud showed that only through the use of multiple, smaller radiation doses could animals be completely sterilized without producing severe injury to the scrotum.[15] Regaud suggested that the superior results afforded the multifraction irradiation scheme were related to alternating periods of relative radioresistance and sensitivity in the rapidly proliferating germ cells.[16] These principles were soon tested in the clinic by Henri Coutard, who first used fractionated radiotherapy for the treatment of head and neck cancers, with, comparatively speaking, spectacularly improved results.[17,18] Largely as a result of these and related experiments, fractionated treatment subsequently became the standard form of radiation therapy.

Time-dose equivalents for skin erythema published by Reisner,[19] Quimby and MacComb,[20] and others[21,22] formed the basis for the calculation of equivalents for other tissue and tumor responses. By plotting the total doses required for each of these "equivalents" for a given level of effect in a particular tissue (as a function of a treatment parameter such as overall treatment time, number of fractions, dose per fraction, etc.) an isoeffect curve could be derived. All time-dose combinations that fell along such a curve would, theoretically, produce tissue responses of equal magnitude. Isoeffect curves, relating the total dose to the overall treatment time, which were derived in later years from some of these data,[23] are shown in Figure 1-3.

The first published isoeffect curves were produced by Strandqvist in 1944[24] and are also shown in Figure 1-3. When transformed on log-log coordinates, isoeffect curves for a variety of skin reactions and the cure of skin cancer were drawn as parallel lines, with common slopes of 0.33. These results implied that there would be no therapeutic advantage to using prolonged treatment times (i.e., multiple small fractions versus one, or a few, large doses) for the preferential eradication of tumors while simultaneously sparing normal tissues.[25] It was somewhat ironic that the Strandqvist curves were so popular in the years that followed because it was already known that the therapeutic ratio *did* increase (at least to a point) with prolonged, as opposed to very short, overall treatment times. However, the overarching advantage was that these isoeffect curves were quite reliable at predicting skin reactions, which were the dose-limiting factors at that time.

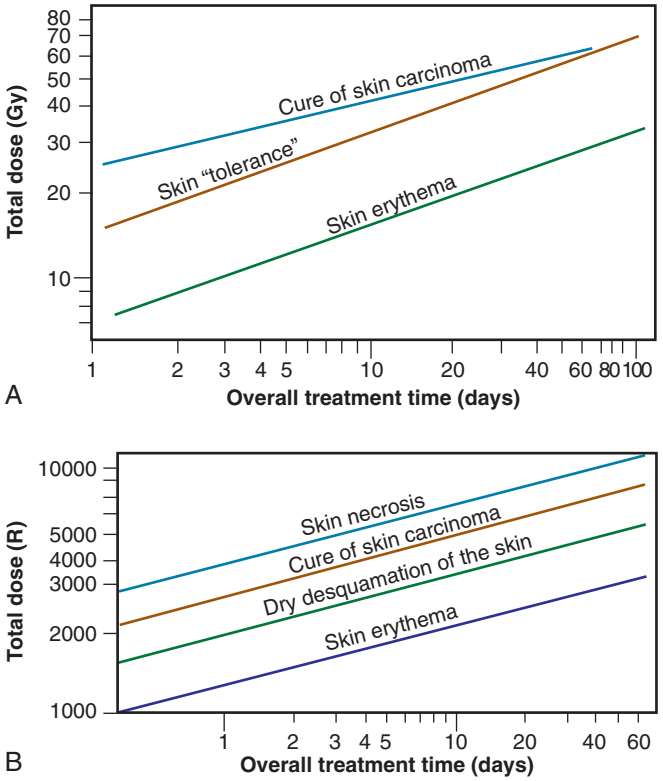


Figure 1-3 Isoeffect curves relating the log of the total dose to the log of the overall treatment time for various levels of skin reaction, and the cure of skin cancer. **A,** Isoeffect curves constructed by Cohen, based on a survey of previously published data on radiotherapy equivalents.[19-22,189] See text for details. The slope of the curves for skin complications was 0.33, and that for tumor control, 0.22. **B,** Strandqvist's[24] isoeffect curves, first published in 1944. All lines were drawn parallel, and had a common slope of 0.33.
A, *Adapted from Cohen L: Radiation response and recovery: Radiobiological principles and their relation to clinical practice. In Schwartz E, editor: The biological basis of radiation therapy, Philadelphia, 1966, JB Lippincott, p 208;* ***B,*** *adapted from Strandqvist M: Studien uber die kumulative Wirkung der Roentgenstrahlen bei Fraktionierung. Acta Radiol Suppl 55:1, 1944.*

THE GOLDEN AGE OF RADIATION BIOLOGY AND THERAPY: THE SECOND 50 YEARS

Perhaps the defining event that ushered in the golden age of radiation biology was the publication of the first survival curve for mammalian cells exposed to graded doses of ionizing radiation.[26] This first report of a quantitative measure of intrinsic radiosensitivity of a human cell line (HeLa, derived from a cervical carcinoma[27]), was published by Puck and Marcus in 1956.[26] To put this seminal work in the proper perspective, however, it is first necessary to review the physicochemical basis for why ionizing radiation is toxic to biological materials.

The Interaction of Ionizing Radiation with Biological Materials

As mentioned in the introductory section of this chapter, ionizing radiation deposits energy as it traverses the absorbing medium through which it passes. The most important feature of the interaction of ionizing radiation with biological materials is the random and discrete nature of the energy deposition. Energy is deposited in increasingly energetic packets referred to as "spurs" (100 eV or less deposited), "blobs"(100 to 500 eV), or "short tracks" (500 to 5000 eV), each of which can leave from approximately three to several dozen ionized atoms in its wake. This is illustrated in Figure 1-4, along with a segment of (interphase) chromatin shown to scale. The

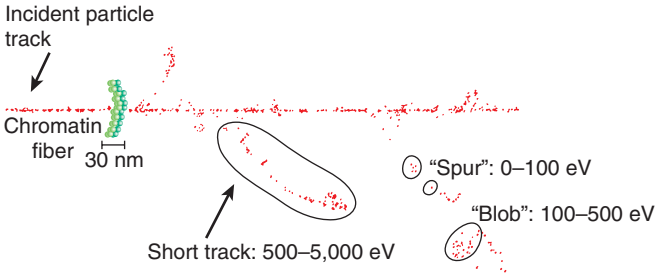


Figure 1-4 Hypothetical α-particle track through an absorbing medium, illustrating the random and discrete energy deposition events along the track. Each event can be classified according to the amount of energy deposited locally, which in turn determines how many ionized atoms will be produced. A segment of chromatin is also shown, approximately to scale.
Adapted from Goodhead DT: Physics of radiation action: microscopic features that determine biological consequences. In Hagen U, Harder D, Jung H, et al, editors: Radiation research 1895-1995, Proceedings of the 10th International Congress of Radiation Research. Volume 2: Congress Lectures, Wurzburg, 1995, Universitatsdruckerei H. Sturtz AG, pp 43-48.

frequency distribution and density of the different types of energy deposition events along the track of the incident photon or particle are measures of the radiation's linear energy transfer or LET (see also the "Relative Biological Effectiveness" section later in this chapter). Because these energy deposition events are discrete, it follows that although the average energy deposited in a macroscopic volume of biological material is rather modest, the distribution of this energy on a microscopic scale may be quite large. This explains why ionizing radiation is so efficient at producing biological damage; the total amount of energy deposited in a 70-kg human that will result in a 50% probability of death is only about 70 calories, which is about as much energy as is absorbed by drinking one sip of hot coffee.[28] The key difference is that the energy contained in the sip of coffee is uniformly distributed, not random and discrete.

Those biomolecules receiving a direct hit from a spur or blob receive, relatively speaking, a huge radiation dose, that is, a large energy deposition in a small volume. For photons and charged particles, this energy deposition results in the ejection of orbital electrons from atoms, causing the target molecule to be converted first into an ion pair and then into a free radical. Further, the ejected electrons—themselves energetic charged particles—can go on to produce additional ionizations. For uncharged particles such as neutrons, the interaction is between the incident particles and the nuclei of the atoms in the absorbing medium, causing the ejection of recoil protons (charged) and lower energy neutrons. The cycle of ionization, free radical production, and release of secondary charged particles continues until all the energy of the incident photon or particle is expended. These interactions are complete within a picosecond after the initial energy transfer. After that time, the chemical reactions of the resulting free radicals predominate the radiation response (see below).

Any and all cellular molecules are potential targets for the localized energy deposition events that occur in spurs, blobs, or short tracks. Whether the ionization of a particular biomolecule results in a measurable biological effect depends on a number of factors including how probable a target the molecule represents from the point of view of the ionizing particle, how important the molecule is to the continued health of the cell, how many copies of the molecule are normally present in the cell and to what extent the cell can react to the loss of working copies, how important the cell is to the structure or function of its corresponding tissue or organ, and so on. DNA for example is obviously an important cellular macromolecule and one that is present only as a single, double-stranded copy. On the other hand, other molecules in the cell may be less crucial to survival, yet are much more abundant than DNA, and therefore have a much higher probability of being hit and ionized. By far, the most abundant molecule in the cell is water, comprising some 70% to 80% of the cell on a per-weight basis. The highly reactive free radicals formed by the radiolysis of water are capable of augmenting the DNA damage resulting from direct energy absorption by migrating to the DNA and damaging it indirectly. This mechanism is referred to as indirect radiation action to distinguish it from the aforementioned direct radiation action.[29] The direct and indirect action pathways for ionizing radiation are illustrated next.

Direct Effect

$$\mathrm{DNA} \underset{\text{(irradiate)}}{\rightarrow} [\mathrm{DNA}^{+} + \mathrm{e}^{-}] \underset{\text{(ion pair)}}{\rightarrow} \underset{\text{(DNA free radical)}}{\mathrm{DNA}^{\bullet}}$$

Indirect Effect

$$\mathrm{H_2O} \underset{\text{(irradiate)}}{\rightarrow} [\mathrm{H_2O}^{+} + \mathrm{e}^{-}] \underset{\text{(ion pair)}}{\rightarrow} \underset{\substack{\text{(other radical reactions)}}}{\bullet\mathrm{OH} + \mathrm{DNA} \rightarrow \underset{\text{(DNA free radical and water)}}{\mathrm{DNA}^{\bullet} + \mathrm{H_2O}}}$$

The most highly reactive and damaging species produced by the radiolysis of water is the hydroxyl radical (•OH), although other free radical species are also produced in varying yields.[30,31] Cell killing by indirect action constitutes some 70% of the total damage produced in DNA for low LET radiation.

How do the free radicals produced by the direct and indirect action of ionizing radiation go on to cause the myriad lesions that have been identified in irradiated DNA? Because they contain unpaired electrons, free radicals are highly reactive chemically and will undergo multiple reactions in an attempt to either acquire new electrons, or rid themselves of remaining unpaired ones. These reactions are considered quite slow compared to the time scale of the initial ionization events but are still fast relative to normal enzymatic processes in a typical mammalian cell. For all intents and purposes, free radical reactions are complete in milliseconds after irradiation. The •OH radical is capable of both abstraction of hydrogen atoms from other molecules and addition across carbon-carbon or other double bonds. More complex macromolecules that have been converted to free radicals can undergo a series of transmutations in an attempt to rid themselves of unpaired electrons, many of which result in the breakage of nearby chemical bonds. In the case of DNA, these broken bonds may result in the loss of a base or an entire nucleotide, or a frank scission of the sugar phosphate backbone, involving either one or both DNA strands. In some cases, chemical bonds are broken initially but then are rearranged, exchanged, or rejoined in inappropriate ways. Bases in DNA may be modified by the addition of one or more hydroxyl groups (e.g., the base thymine converted to thymine glycol), pyrimidines may become dimerized, or the DNA may become cross-linked to itself or to associated protein components. And again, because the initial energy deposition events are discrete, the free radicals produced also are clustered, and therefore, undergo their multiple chemical reactions and produce multiple damages in a highly localized area. This has been termed the "multiply-damaged site"[32] or "cluster"[33] hypothesis. Examples of the types of damage found in irradiated DNA are shown in Figure 1-5.

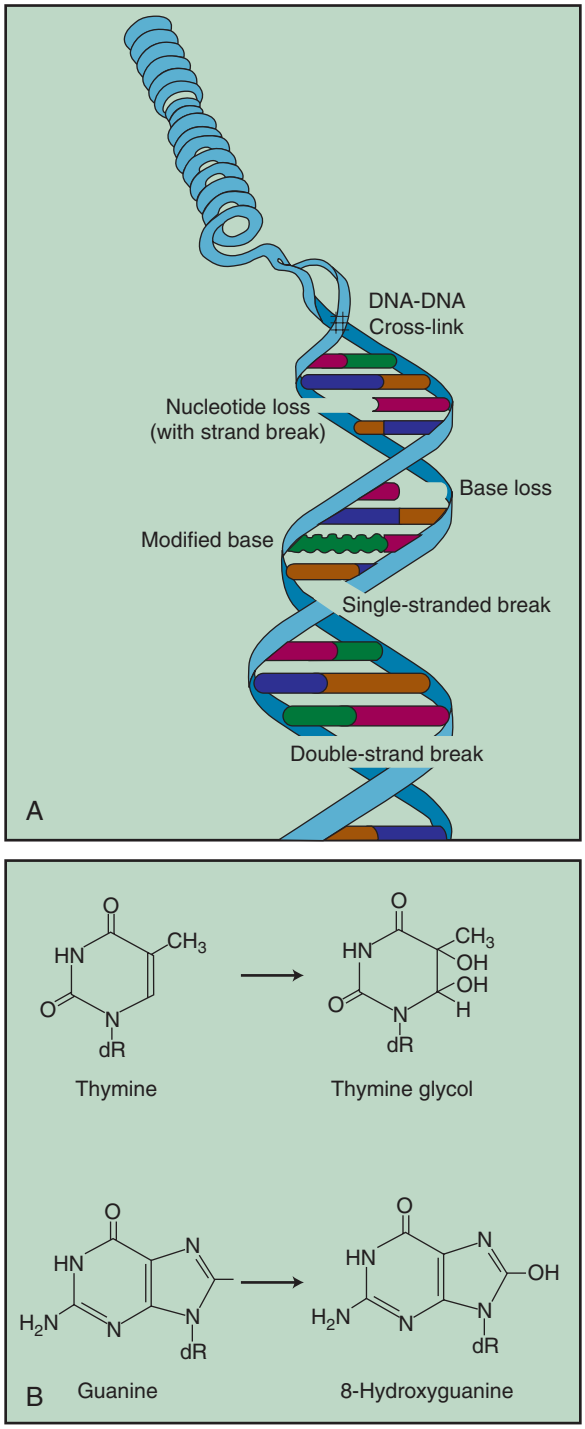


Figure 1-5 Types of DNA damage produced by ionizing radiation. **A,** Segment of irradiated DNA containing single- and double-stranded breaks, cross-links, and base damage. **B,** Two types of modified bases observed in irradiated DNA include thymine glycol, which results from the addition of two hydroxyl (OH) groups across the carbon-carbon double bond of thymine, and 8-hydroxyguanine, produced by •OH radical addition to guanine.

Biochemical Repair of DNA Damage

DNA is unique insofar as it is the only cellular macromolecule with its own repair system. Until as recently as 30 years ago, little was known about DNA repair processes in mammalian cells, particularly because of the complexities involved and the relative lack of spontaneously occurring mutants defective in genes involved with DNA repair. As a result, most studies of DNA repair were carried out either in bacteria or yeasts and usually employed ultraviolet (UV) radiation as the tool for producing DNA damage. Although these were rather simple and relatively clean systems in which to study DNA repair, their relevance to mammalian repair systems, and to the broader spectrum of DNA damage produced by ionizing radiation, ultimately limited their usefulness.

The study of DNA repair in mammalian cells received a significant boost during the late 1960s with publications by Cleaver[34,35] that identified the molecular defect responsible for the human disease xeroderma pigmentosum (XP). Patients with XP are exquisitely sensitive to sunlight and highly prone to (skin) cancer. Cleaver showed that cells derived from such patients were likewise sensitive to UV radiation and defective in the nucleotide excision repair pathway (see discussion in this chapter). These cells were not especially sensitive to ionizing radiation however. Several years later, Taylor et al[36] reported that cells derived from patients with a second cancer-prone disorder, ataxia telangiectasia (AT), were extremely sensitive to ionizing radiation and radiation-mimetic drugs, however not UV radiation. In the years that followed, cell cultures derived from patients with these two conditions were used to help elucidate the complicated processes of DNA repair in mammalian cells. Today, dozens of other clinical syndromes associated with either radiosensitivity, cancer proneness, or both have been identified.[37,38]

Today, many rodent and human genes involved in DNA repair have been cloned and extensively characterized.[39] Some 30 to 40 proteins participate in excision repair of base damage and about half that many are involved in the repair of strand breaks.[37] Many of these proteins function as component parts of larger repair complexes; some of these parts are interchangeable and participate in other DNA repair and replication pathways as well. It is also noteworthy that some are not involved with the repair process per se, but rather link DNA repair to other cellular functions, including transcription, cell cycle arrest, chromatin remodeling, and apoptosis.[40] This attests to the fact that the maintenance of genomic integrity results from a complex interplay between not only the repair proteins themselves, but also with others that serve as damage sensors, signaling mediators and transducers, and effectors. Collectively, this complex network of proteins that sense, initiate, and coordinate DNA damage signaling and repair with other cellular activities is termed the *DNA damage response* (DDR).[37,41] For example, the defect responsible for the disease AT is not in a gene that codes for a repair protein, but rather in a gene that acts as a damage sensor and also participates in the related pathway that normally prevents cells from entering S phase and beginning DNA synthesis while residual DNA damage is present. This is the *G_1 cell cycle checkpoint response*.[42] Because of this genetic defect, AT cells do not experience the normal G_1 arrest after irradiation, and they enter S phase with residual DNA damage. This accounts both for the exquisite radiosensitivity of AT cells and the resulting genomic instability that can lead to carcinogenesis.

The molecular and biochemical intricacies of DNA repair in mammalian cells are described in detail in Chapter 2, however a brief overview is also presented here.

Base Excision Repair

The repair of base damage is initiated by DNA repair enzymes, *glycosylases*, which recognize specific types of damaged bases and excise them without otherwise disturbing the DNA strand.[43] The action of the glycosylase results in the formation of another type of damage observed in irradiated DNA—an apurinic or apyrimidinic (AP) site. The AP site is then

recognized by another repair enzyme, an endonuclease that nicks the DNA adjacent to the lesion, in effect creating a DNA single-stranded break. This break then becomes the substrate for an exonuclease, which removes the abasic site along with a few additional bases. The small gap that results is patched by DNA polymerase using the opposite, and hopefully undamaged, DNA strand as a template. Finally, DNA ligase seals the patch in place.

Nucleotide Excision Repair

The DNA glycosylases that begin the process of base excision repair do not recognize all known forms of base damage however, particularly bulky or complex lesions.[43] In such cases, another group of enzymes, *structure-specific endonucleases*, initiate the excision repair process. These repair proteins do not recognize the specific lesion, but they are thought instead to recognize more generalized structural distortions in DNA, which necessarily accompany a complex base lesion. The structure-specific endonucleases incise the affected DNA strand on both sides of the lesion, releasing an oligonucleotide fragment made up of the damage site and several bases on either side of it. After this step, the remainder of the nucleotide excision repair process is similar to that of base excision repair; the gap is then filled by DNA polymerase and sealed by DNA ligase.

For both types of excision repair, active genes in the process of transcription are repaired preferentially and more quickly. This has been termed *transcription-coupled repair*.[44]

Single-Stranded Break Repair

Single-stranded breaks in the DNA backbone are common lesions, produced in the tens of thousands per day as part of normal cellular metabolism,[45] as well as any additional breaks introduced by radiation exposure. These are repaired using the machinery of excision repair, that is, gap filling (if any) by DNA polymerase and sealing by DNA ligase.

Double-Stranded Break Repair

Despite the fact that unrepaired or mis-rejoined DSBs often have the most catastrophic consequences for the cell in terms of loss of reproductive integrity,[46] how mammalian cells repair these lesions has been more difficult to elucidate than how they repair base damage. Much of what was originally discovered about these repair processes is derived from studies of rodent cells that were sensitive to x-rays and that were later discovered to harbor specific defects in strand break repair.[47] Since then, dozens of other rodent and human cells characterized by DDR defects have been identified and are also used to help probe these fundamental processes.

With respect to the repair of DSBs, the situation is more complicated in that the damage on each strand of DNA may be different, and therefore, no intact template would be available to guide the repair process. Under these circumstances, cells must rely on an error-prone process that rejoins the break(s) regardless of the loss of intervening base pairs for which there is no template (nonhomologous end joining [NHEJ]) or else depend on genetic recombination in which a template for presumably error-free repair is obtained from recently replicated DNA of a sister chromatid (homologous recombination [HR])[48] to cope with the damage. NHEJ occurs throughout the cell cycle but predominates in cells that have not yet replicated their DNA in anticipation of a subsequent cell division, that is, cells in the G_1 or G_0 phases of the cell cycle. NHEJ involves a heterodimeric enzyme complex consisting of the proteins Ku-70 and Ku-80, the catalytic subunit of DNA protein kinase ($DNA\text{-}PK_{CS}$), and DNA ligase IV. Cells that have already replicated most or all of their DNA—in the late S or G_2 phases of the cell cycle—depend on HR to repair DSBs. HR involves the assembly of a nucleoprotein filament that contains, among others, the proteins Rad51 and Rad52. This filament then invades the homologous DNA sequence of a sister chromatid, which becomes the template for repair. The BRCA2 protein is also implicated in HR as it interacts with the Rad51 protein.[38] Defects in either the *BRCA1* (which helps determine which DSB repair pathway will be used in a particular situation) or *BRCA2* genes are associated with hereditary breast and ovarian cancer.[49]

Mismatch Repair

The primary role of mismatch repair (MMR) is to eliminate from newly synthesized DNA errors such as base/base mismatches and insertion/deletion loops caused by DNA polymerase.[50] Descriptively, this process consists of three steps: mismatch recognition and assembly of the repair complex, degradation of the error-containing strand, and repair synthesis. In humans, MMR involves at least five proteins, including hMSH2, hMSH3, hMSH6, hMLH1, and hPMS2, as well as other members of the DNA repair and replication machinery.

Radiation-induced DNA lesions are not targets for MMR per se; however, one manifestation of a defect in MMR is germane to any study of oncogenesis: genomic instability,[51] which renders affected cells hypermutable. This mutator phenotype is associated with several cancer predisposition syndromes, in particular, hereditary nonpolyposis colon cancer ([HNPCC], sometimes called Lynch syndrome).[52,53] Genomic instability is considered one of the main enablers of nonmalignant cells to accumulate cancer-causing mutations and also drives tumor progression to more aggressive and potentially treatment-resistant phenotypes.

The DDR as a Clinical Target

Historically, attempts to inhibit the repair of radiation-induced DNA damage were of interest to researchers probing these fundamental processes; however, clinical translation was typically lacking, mostly out of concern that normal tissues would also be affected in an adverse way. More recently however, it has become clear that the cells of many tumors harbor one or more defects in the DDR, as a consequence of genomic instability, that are not present in normal cells and that this difference might be exploitable clinically.

One approach along these lines currently in clinical trials is the use of inhibitors of the protein poly(ADP-ribose) polymerase (PARP).[54,55] As of 2012, nearly a dozen trials, most in Phase I or II, were under way using PARP inhibitors.[37,55] PARP is an enzyme involved in the repair of DNA damage by base excision repair and SSB repair; its inhibition leads to the persistence of existing SSBs as well as the creation of new ones. If left unrejoined, these breaks can cause the collapse of replication forks in DNA that then impede both DNA replication and HR repair,[55] leading to radiosensitization and ultimately, cell death.[56]

In normal cells, little or no toxicity caused by PARP inhibition would be expected because all DDR pathways are intact and salvage repair pathways to bypass PARP inhibition are active. In tumor cells harboring defects in HR however, salvage pathways are typically dysregulated or absent, suggesting that PARP inhibition would be preferentially toxic to such repair-defective cells. One clinical example is the targeting of breast cancers harboring cellular defects in the BRCA1 and BRCA2 proteins—which either orchestrate or are directly involved in HR—for PARP inhibition. This overall approach of using the combined lethal effect of two genetic defects (one inherent HR defect, plus an additional synthetic one induced by PARP inhibition) that are otherwise nonlethal singly is termed *synthetic lethality*.[54-56] Approaches using synthetic lethality

targeting DDR proteins (including those other than PARP) likely will play increasingly important roles in the future.

Cytogenetic Effects of Ionizing Radiation

When cells divide following radiation exposure, chromosomes frequently contain visible structural aberrations, most of which are lethal to the cell. In some cases, these aberrations physically interfere with the processes of mitosis and cytokinesis and result in prompt cell death. In other cases, cell division can occur, but the loss or uneven distribution of genetic material between the cell's progeny is ultimately lethal as well, although the affected cells may linger for several days before they die (some may even be able to go through a few more cell divisions in the interim). It is clear that these aberrations are the result of any unrepaired or mis-rejoined DNA damage that persists from the time of irradiation until the time of the next cell division.

Most chromosome aberrations result from an interaction between two damage sites, and therefore, can be grouped into three different types of "exchange" categories. A fourth category is reserved for those chromosome aberrations that are thought to result from a single damage site.[57] These categories are described here, and representative types of aberrations from each category are also shown in Figure 1-6:

1. *Intraarm Exchanges*: an interaction between lesions on the same arm of a single chromosome (e.g., interstitial deletion).
2. *Interarm Exchanges*: an interaction between lesions on opposite arms of the same chromosome (e.g., centric ring).
3. *Interchanges*: an interaction between lesions on different chromosomes, either homologous or nonhomologous (e.g., dicentric).
4. *"Single-Hit" Breaks*: the complete severance of part of one arm of a single chromosome not obviously associated with any more than a single lesion (e.g., terminal deletion).

These four categories can be further subdivided according to whether the initial radiation damage occurred before or after the DNA is replicated during S phase of the cell cycle (a chromosome- vs. chromatid-type aberration, respectively), and, for the three exchange categories, whether the lesion interaction was symmetrical or asymmetrical. Asymmetrical exchanges always lead to the formation of acentric fragments, which are usually lost in subsequent cell divisions and therefore are nearly always fatal to the cell. These fragments may be retained transiently in the cell's progeny as extranuclear chromatin bodies, micronuclei. Symmetrical exchanges are more insidious in that they do not lead to the formation of acentric fragments and the accompanying loss of genetic material at the next cell division, they are sometimes difficult to detect cytologically, and they are not invariably lethal to the cell. As such, they will be transmitted to all the progeny of the original cell. Some types of symmetrical exchanges (e.g., a reciprocal translocation) have been implicated in radiation carcinogenesis, insofar as they have the net effect of either bringing new combinations of genes together or separating preexisting groups of genes.[28] Depending on where in the genome the translocation takes place, genes normally on could be turned off or vice versa, possibly with adverse consequences.

Quantitation of the types and frequencies of chromosome aberrations in irradiated cells can be used to probe dose-response relationships for ionizing radiation, and to a first approximation, they also can serve as a radiation dosimeter. For example, the dose-response curve for the induction of exchange-type aberrations after exposure to low LET radiation

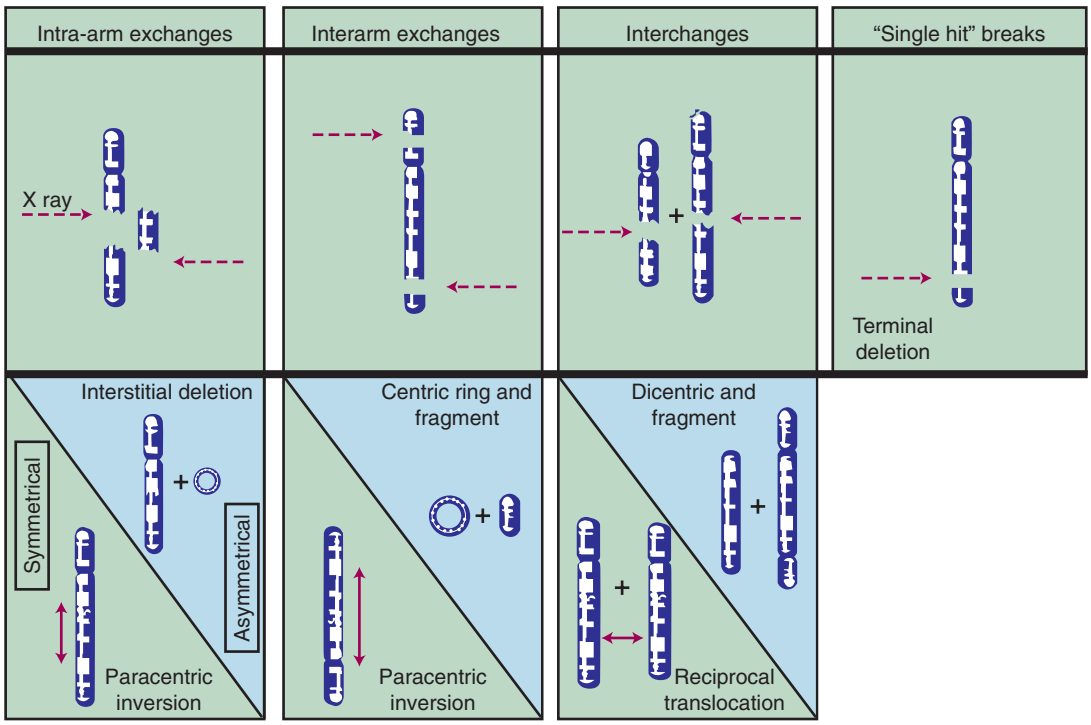


Figure 1-6 Types of radiation-induced chromosome aberrations that are the result of unrepaired or mis-rejoined DNA damage. Aberrations are classified according to whether they involve a single or multiple chromosomes, whether the damage is thought to be caused by the passage of a single charged particle track (one-hit aberration), or by the interaction of damages produced by two different tracks (two-hit aberration), and whether the irradiation occurred before or after the chromosomes had replicated (chromosome- vs. chromatid-type aberrations, respectively; only chromosome-type aberrations are shown). The aberrations can be further subdivided according to whether broken pieces of the chromosome rearrange themselves symmetrically (with no net loss of genetic material) or asymmetrically (acentric fragments produced).

tends to be linear-quadratic in shape, whereas that for single hit aberrations tends to be linear. In mathematical terms, the incidence, *I*, of a particular aberration as a function of radiation dose, *D*, can be expressed as:

$$I = \alpha D + \beta D^2 + c \quad \text{for exchange-type aberrations}$$
$$I = \alpha D + c \quad \text{for single hit aberrations}$$

where α and β are proportionality constants related to the yields of the particular type of aberration, and *c* is the spontaneous frequency of that aberration in unirradiated cells. For fractionated doses or continuous low dose rates of low LET radiation, the yield of exchange type aberrations decreases relative to that for acute doses, and the dose-response curve tends to become more linear. For high LET radiations, dose-response curves for aberration induction become steeper (higher aberration yields) and more linear compared to those for low LET radiations.

Cell Survival Curves and Survival Curve Theory

What Is Cell Death?

The traditional definition of death as a permanent, irreversible cessation of vital functions is not the same as what constitutes death to the radiation biologist or oncologist. For proliferating cells, including those maintained in vitro, the stem cells of normal tissues and tumor clonogens, cell death in the radiobiological sense refers to a loss of reproductive integrity, that is, an inability to sustain proliferation indefinitely. This type of reproductive or clonogenic death does not preclude the possibility that a cell may remain physically intact, metabolically active, and continue its tissue-specific functions for some time after irradiation. In fact, some reproductively dead cells can even complete a few additional mitoses before death in the more traditional sense.[58]

Compared to nearly 60 years ago, when the term *clonogenic death* was first coined and used as an endpoint in assays of cellular radiosensitivity,[26,59] it is now clearly an operationally defined term that encompasses several distinct mechanisms by which cells die, all of which result in a cell losing its ability to divide indefinitely. These modes of cell death include mitotic catastrophe, apoptosis, autophagy, necrosis, senescence, and strictly speaking, differentiation as well because differentiated cells lose their ability to divide.[60,61]

Mitotic catastrophe is the major cause of radiation-induced death for most mammalian cells, and occurs secondary to chromosome aberrations or spindle defects that interfere with the cell-division process.[62,63] Accordingly, this type of cell death occurs during or soon after an attempted cell division after irradiation (although not necessarily at the first division attempt) and leaves in its wake large, flattened, and multinucleated cells that are typically aneuploid. Apoptosis, or programmed cell death, is a type of nonmitotic or interphase death commonly associated with embryonic development and normal tissue remodeling and homeostasis.[64] However, certain normal tissue and tumor cells also undergo apoptosis following irradiation, including normal cells of hematopoeitic or lymphoid origin, crypt cells of the small intestine, salivary gland cells, plus some experimental tumor cell lines of gynecological and hematological origin.[65] Cells undergoing apoptosis exhibit a number of characteristic morphological (nuclear condensation and fragmentation, membrane blebbing, etc.) and biochemical (DNA degradation) changes that culminate in the fragmentation and lysis of the cell, often within 12 hours of irradiation and before the first postirradiation mitosis. Ultimately, the remains of apoptotic cells are phagocytized by neighboring cells, and therefore do not cause the type of inflammatory response, tissue destruction, and disorganization characteristic of necrosis. Apoptosis is an active and carefully regulated pathway that involves several genes and gene products and an appropriate stimulus that activates the pathway. The molecular biology of apoptosis, the apoptosis-resistant phenotype noted for many types of tumor cells, and the role that radiation may play in the process are discussed in detail in Chapter 2. Senescence refers to a type of genetically controlled cellular growth arrest that, although not eliminating damaged cells, does halt permanently their continued movement through the cell cycle, even in the presence of growth factors.[66] Radiation can also induce senescence, presumably as a result of the permanent triggering of cell cycle checkpoints; however it might better be termed *radiation-induced permanent growth arrest*, to distinguish it from the normal process of cell-age–related senescence.[67] The roles played by autophagy and necrosis, which are two additional modes of cell death that usually occur in response to diverse types of cellular stress, remain unclear with respect to radiation-induced cell death. Autophagy is defined as the controlled lysosomal degradation of cytoplasmic organelles or other cytoplasmic components[68,69] in response to cellular stressors, including nutrient deprivation, hypoxia, DNA damage, or an excess of reactive oxygen species. Likewise, necrosis—characterized by cell swelling followed by membrane rupture and the release of cellular contents into the extracellular space—can occur as a somewhat passive response to nutrient deprivation, but it also can follow a molecular program initiated by immune cells or various toxins.[70,71]

Most assays of radiosensitivity of cells and tissues, including those described in this chapter, use reproductive integrity, either directly or indirectly, as an endpoint. Although such assays have served the radiation oncology community well in terms of elucidating dose-response relationships for normal tissues and tumors, it is now clear that reproductive death is not necessarily the whole story. What remains unclear is whether and to what extent other modes of cell death, particularly apoptosis, contribute to our traditional measures of radiosensitivity based on clonogenic survival, and whether, for example, pretreatment assessment of apoptotic propensity in tumors or dose-limiting normal tissues is of prognostic significance. The interrelationships between these different pathways of cell death can be quite complex. Meyn[65] has suggested that a tumor with a high spontaneous apoptotic index may be inherently more radiosensitive because cell death might be triggered by lower doses than are usually required to cause reproductive death. Also, tumors that readily undergo apoptosis may have higher rates of cell loss, the net effect of which would be to partially offset cell production, thereby reducing the number of tumor clonogens. On the other hand,, recent studies suggest that the caspases that orchestrate the removal of radiation-damaged cells via apoptosis also may stimulate tumor cell repopulation during and after radiotherapy,[72] which is a decidedly undesirable outcome.

Cell Survival and Dose-Response Curve Models

Survival curve theory originated in a consideration of the physics of energy deposition in matter by ionizing radiation. Early experiments with macromolecules and prokaryotes established that dose-response relationships could be explained, in principle, by the random and discrete nature of energy absorption, if it was assumed that the response resulted from critical "targets" receiving random "hits."[73] With an increasing number of shouldered survival and dose response curves being described for cells irradiated both in vitro and in vivo, various equations were developed to fit these data. Target theory pioneers studied a number of different endpoints in the context of target theory, including enzyme

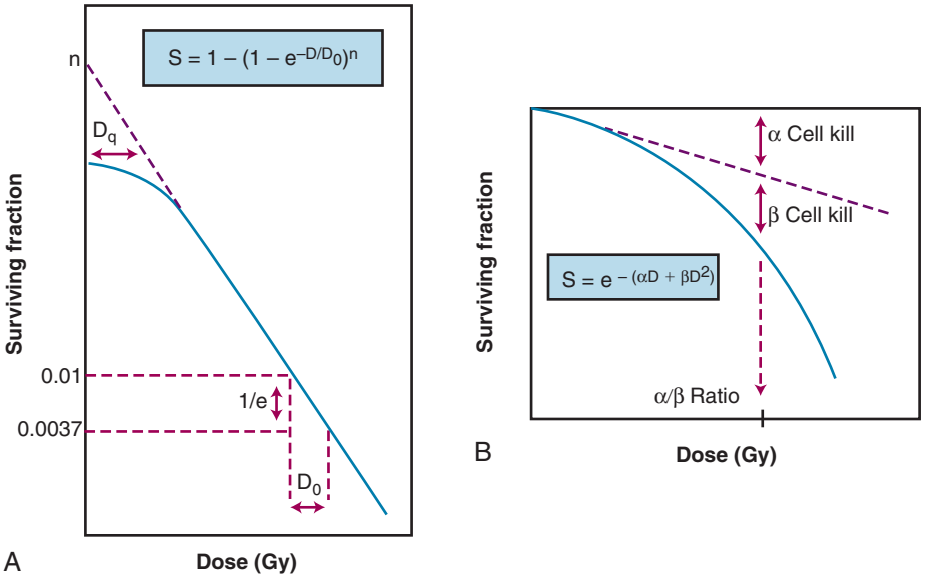


Figure 1-7 A comparison of two mathematical models commonly used to fit cell survival curve data. Left panel: The single-hit, multitarget model and its associated parameters, D_0, n, and D_q. Although this model has since been invalidated, values for its parameters are still used for comparative purposes. Right panel: The linear-quadratic model and its associated parameters, α and β. This model forms the basis for current isoeffect formulae used in radiation therapy treatment planning.

inactivation in cell-free systems,[29] cellular lethality, chromosomal damage, and radiation-induced cell cycle perturbations in microorganisms.[29,74] Survival curves, in which the log of the survival of a certain biological activity was plotted as a function of the radiation dose, were found to be either exponential or sigmoid in shape with the latter usually noted for the survival of more complex organisms.[29]

Exponential survival curves were thought to result from the single-hit, "all-or-nothing," inactivation of a single target, resulting in the loss of activity. A mathematical expression used to fit this type of dose-response relationship was $S = e^{-D/D_0}$. In this equation, S is the fraction of cells that survive a given dose; D and D_0 are the dose increment that reduces the cell survival to 37% (1/e) of some initial value on the exponential portion of the curve (i.e., a measure of the reciprocal of the slope). The sigmoid curves, characterized by a shoulder at low doses, were consistent with target theory if one assumed that either multiple targets or multiple hits in a single target (or a combination of both) were necessary for radiation inactivation. A mathematical expression based on target theory that provided a fairly good fit to survival data was $S = 1 - (1 - e^{-D/D_0})^n$, with n being the back extrapolation of the exponential portion of the survival curve to zero dose. Implicit in this multitarget model was that damage had to accumulate before the overall effect was registered.

It soon became apparent that some features of this model were inadequate.[75] The most obvious problem was that the single-hit, multitarget equation predicted that survival curves should have initial slopes of zero, that is, that for vanishingly small doses (e.g., repeated, small doses per fraction or continuous low-dose rate exposure), the probability of cell killing would approach zero. This was *not* what was observed in practice for either mammalian cell survival curves or as inferred from clinical studies in which highly fractionated or low-dose rate treatment schedules were compared to more conventional fractionation. There was no fractionation schedule that produced essentially no cell killing, that is, all other radiobiological factors being equal.

A somewhat different interpretation of cell survival was proposed by Kellerer and Rossi[76] in the late 1960s and early 1970s. The linear-quadratic or alpha-beta equation, $S = e^{-(\alpha D + \beta D^2)}$, was shown to fit many survival data quite well, particularly in the low-dose region of the curve, and also provided for the negative initial slope investigators had described.[75] In this expression, S is again the fractional cell survival following a dose D, α is the rate of cell kill by a single-hit process, and β is the rate of cell kill by a two-hit mechanism. The theoretical derivation of the linear-quadratic equation is based on two different sets of observations. Based on microdosimetric considerations, Kellerer and Rossi[76] proposed that a radiation-induced lethal lesion resulted from the interaction of two sublesions. According to this interpretation, the αD term is the probability of these two sublesions being produced by a single event (the "intratrack" component), whereas βD^2 is the probability of the two sublesions being produced by two separate events (the "intertrack" component). Chadwick and Leenhouts[77] derived the same equation based on a different set of assumptions, namely that a DSB in DNA was a lethal lesion and that such a lesion could be produced by either a single energy deposition involving both strands of DNA or by two separate events, each involving a single strand.

A comparison of the features and parameters of the target theory and linear-quadratic survival-curve expressions is shown in Figure 1-7.

Clonogenic Assays In Vitro

As mentioned previously, it was not until the mid-1950s that mammalian cell culture techniques were sufficiently refined to allow quantitation of the radiation responses of single cells.[59,78] Puck and Marcus'[26] acute-dose, x-ray survival curve for the human tumor cell line HeLa, is shown in Figure 1-8. Following graded x-ray doses, the reproductive integrity of single HeLa cells was measured by their ability to form macroscopic colonies of at least 50 cells (corresponding to approximately 6 successful postirradiation cell divisions) on petri dishes. A number of features of this survival curve were of particular interest. First, qualitatively at least, the curve was similar in shape to those previously determined for many microorganisms and was characterized by a shoulder at low doses and a

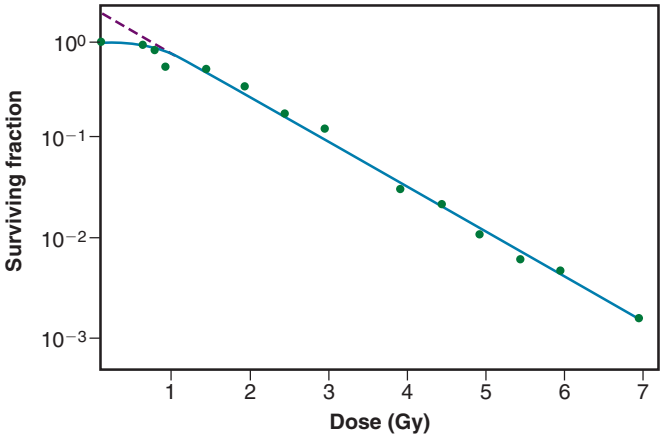


Figure 1-8 Clonogenic survival of HeLa cells in vitro as a function of x-ray dose. Like many mammalian cells of tumorigenic and nontumorigenic origin, the HeLa cell survival curve is characterized by a modest initial shoulder region (n = 2.0) followed by an approximately exponential final slope ($D_0 \approx 1.0$ Gy).
Adapted from Puck TT, Marcus PI: Action of x rays on mammalian cells. J Exp Med 103:653, 1956; copyright permission of The Rockefeller University Press.

roughly exponential region at high doses. Of note, however, was the finding that the D_0 for HeLa cells was only 96 R, which was some 10- to 100-fold less than D_0 determined for microorganisms, and 1,000- to 10,000-fold less than D_0 for the inactivation of isolated macromolecules.[58] Thus, cellular reproductive integrity was found to be a much more radiosensitive endpoint for HeLa cells than for prokaryotes or primitive eukaryotes. The value of the extrapolation number, n, was approximately 2.0, indicating that the survival curve did have a small shoulder, but again, much smaller than typically observed for microorganisms. Puck and Marcus suggested that the n value was a reflection of the number of critical targets in the cell, each requiring a single hit before the cell would be killed, and they further postulated that the targets were, in fact, the chromosomes themselves.[26] However, the potential pitfalls of deducing mechanisms of radiation action from parameters of a descriptive survival curve model were soon realized.[79,80]

Survival curves for other types of mammalian cells, regardless of whether they were derived from humans or laboratory animals or from tumors or normal tissues, have been shown to be qualitatively similar to the original HeLa cell survival curve.

Clonogenic Assays In Vivo

To bridge the gap between the radiation responses of cells grown in culture and in an animal, Hewitt and Wilson developed an ingenious method to assay single cell survival in vivo.[81] Lymphocytic leukemia cells obtained from the livers of donor CBA mice were harvested, diluted, and inoculated into disease-free recipient mice. By injecting different numbers of donor cells, a standard curve was constructed that allowed a determination of the average number of injected cells necessary to cause leukemia in 50% of the recipient mice. It was determined that the endpoint of this titration, the "50% take dose" or TD_{50}, corresponded to an innoculum of a mere two leukemia cells. Using this value as a reference, Hewitt and Wilson then injected leukemia cells harvested from γ-irradiated donor mice into recipients and again determined the TD_{50} following different radiation exposures. In this way, the surviving fraction after a given radiation dose could be calculated from the ratio of the TD_{50} for unirradiated cells to that for the irradiated cells. Using this technique, a complete survival curve was constructed that had a D_0 of 162 R, and an n value close to 2.0, which were values quite similar to those generated for cell lines irradiated in vitro. For the most part, in vivo survival curves for a variety of cell types were also similar to corresponding in vitro curves.

A similar trend was apparent when in vivo survival curves for nontumorigenic cells were first produced. The first experiments by Till and McCulloch,[82,83] using normal bone marrow stem cells, were inspired by the knowledge that failure of the hematopoietic system was a major cause of death following total body irradiation and that lethally irradiated animals could be "rescued" by a bone marrow transplant. The transplanted, viable bone marrow cells were observed to form discrete nodules or colonies in the otherwise sterilized spleens of irradiated animals. Subsequently, these authors transplanted known quantities of irradiated donor bone marrow into lethally irradiated recipient mice, were able to count the resulting splenic nodules, and then calculate the surviving fraction of the injected cells in much the same way as was done for in vitro experiments. The D_0 for mouse bone marrow was 0.95 Gy.[83] Other in vivo assay systems based on the counting of colonies or nodules included the skin epithelium assay of Withers,[84] the intestinal crypt assays of Withers and Elkind,[85,86] and the lung colony assay of Hill and Bush.[87] During the late 1960s and early 1970s, it also became possible to do excision assays, in which tumors irradiated in vivo were removed, enzymatically dissociated, and single cells plated for clonogenic survival in vitro, thereby allowing more quantitative measurement of survival and avoiding some of the pitfalls of in vivo assays (e.g., Rockwell et al[88]).

Nonclonogenic Assays In Vivo

Unfortunately some normal tissues and tumors are not amenable to clonogenic assays. Thus, new assays were needed that had clinical relevance, yet did not rely on reproductive integrity as an endpoint. Use of such assays required one leap of faith however, namely that the endpoints assessed would have to be a consequence of the killing of clonogenic cells, although not necessarily in a direct, one-to-one manner. Because nonclonogenic assays do not directly measure cell survival as an endpoint, data derived from them and plotted as a function of radiation dose are properly called dose-response curves rather than cell survival curves, although such data are often analyzed and interpreted similarly.

Historically, among the first nonclonogenic assays was the mean lethal dose or LD_{50} assay, in which the (whole body) radiation dose to produce lethality in approximately 50% of the test subjects is determined, usually at a fixed time after irradiation, such as 30 ($LD_{50/30}$) or 60 days ($LD_{50/60}$). Clearly, the LD_{50} assay is not specific in that the cause of death can result from damage to a number of different tissues.

Another widely used nonclonogenic method to assess normal tissue radioresponse is the skin reaction assay, which was originally developed by Fowler et al.[89] Pigs were often used because their skin is similar to that of humans in several key respects. An ordinate scoring system was used to compare and contrast different radiation schedules and was derived from the average severity of the skin reaction noted during a certain time period (specific to the species and whether the endpoint occurs early or late) following irradiation. For example, for early skin reactions, a skin score of "1" might correspond to mild erythema, whereas a score of "4" might correspond to confluent moist desquamation over more than half of the irradiated area.

Finally, two common nonclonogenic assays for tumor response are the growth delay/regrowth delay assay[90] and the tumor control dose assay.[91] Both assays are simple and direct,

are applicable to most solid tumors, and are clinically relevant. The growth delay assay involves the periodic measurement of a tumor's dimensions as a function of time after irradiation and a calculation of the tumor's approximate volume. For tumors that regress rapidly during and after radiotherapy, the endpoint scored is typically the time in days it takes for the tumor to regrow to its original volume at the start of irradiation. For tumors that regress more slowly, a more appropriate endpoint might be the time it takes for the tumor to grow or regrow to a specified size, such as three times its original volume. Dose-response curves are generated by plotting the amount of growth delay as a function of radiation dose.

The tumor control assay is a logical extension of the growth delay assay. The endpoint of this assay is the total radiation dose required to achieve a specified probability of local tumor control—usually 50% (TCD_{50})—in a specified period of time after irradiation. The TCD_{50} value is obtained from a plot of the percentage of tumors locally controlled as a function of total dose. The slope of the resulting dose-response curve may be used for comparative purposes as a measure of the tumor's inherent "radiosensitivity" or its degree of heterogeneity. More heterogeneous tumors tend to have shallower dose-response curves than more homogeneous ones, as do spontaneous tumors relative to experimental ones maintained in inbred strains of mice.

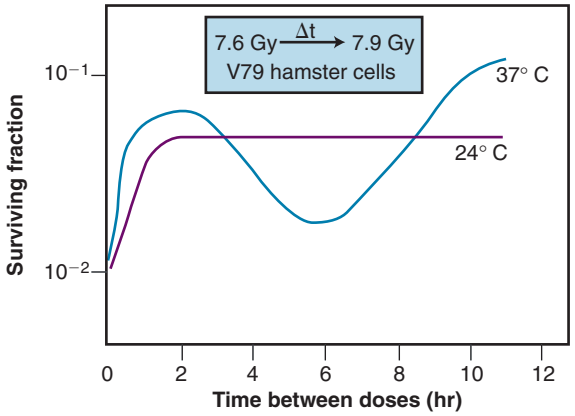


Figure 1-9 Split-dose or sublethal damage recovery demonstrated in cultured V79 hamster cells that received a first x-ray dose at time = 0, followed by a second dose after a variable radiation-free interval. Cells were maintained at room temperature (24° C) or at 37° C during the split time.
Adapted from Elkind M, Sutton-Gilbert H, Moses W, et al: Radiation response of mammalian cells grown in culture. V. Temperature dependence of the repair of x-ray damage in surviving cells (aerobic and hypoxic). Radiat Res 25:359, 1965.

Cellular Repair: Sublethal and Potentially Lethal Damage Recovery

Taking the cue from target theory that the shoulder region of the radiation survival curve indicated that hits had to accumulate before cell killing, Elkind and Sutton[92,93] sought to better characterize the nature of the damage caused by these hits and how the cell processed this damage. Even in the absence of any detailed information about DNA damage and repair at that time, a few things seemed obvious. First, those hits or damages that were registered as part of the accumulation process, yet did not in and of themselves produce cell killing, were, by definition, sublethal. Second, sublethal damage (SLD) only became lethal when it interacted with additional SLD, that is, when the total amount of damage had accumulated to a sufficient level to cause cell lethality. But what would be the result of deliberately interfering with the damage accumulation process, by, for example, delivering part of the intended radiation dose, inserting a radiation-free interval, and then delivering the remainder of the dose? The results of such split-dose experiments turned out to be crucial to the understanding of why and how fractionated radiation therapy works as it does. The discovery and characterization of SLD, as low tech and operational the concept may be by today's standards, still stands as arguably the single-most important contribution radiation biology has made to the practice of radiation oncology.

By varying the time interval between two doses of approximately 5.0 Gy and plotting the log of the surviving fraction of cells after both doses (i.e., 10 Gy total dose) as a function of the time between the doses, the resulting split-dose recovery curve was observed to rise to a maximum after about 2 hours and then level off. In other words, the overall surviving fraction of cells following 10 Gy was higher if the dose was split into two fractions with a time interval in between than delivered as a single dose. Elkind interpreted these results as indicating that the cells that survived the initial dose fraction had "repaired" some of the damage during the radiation-free interval, and as such, this damage was no longer available to interact with the damage inflicted by the second dose. At the time, Elkind referred to this phenomenon as *sublethal damage repair* (SLDR); however, in retrospect, it is perhaps preferable to call it *sublethal damage recovery*, because biochemical DNA repair processes were not actually measured, only changes in cell survival were.

Of additional interest was the observation that the shape of the split-dose recovery curve varied with the temperature during the radiation-free interval (Figure 1-9). When the cells were maintained at room temperature between the split doses, the SLDR curve rose to a maximum after about 2 hours and then leveled off. When the cells were returned to an incubator at 37°C for the radiation-free interval, a different pattern emerged. Initially, the split-dose recovery curve rose to a maximum after 2 hours, but then, the curve exhibited a series of oscillations, dropping to a second minimum for a split of about 4 to 5 hours and then rising again to a higher maximum for split dose intervals of 10 hours or more. The interpretation of this pattern of SLDR was that other radiobiological phenomena operated simultaneously with cellular recovery. In this case, the fine structure of the split-dose recovery curve was not caused by an oscillating repair process, but rather, by a superimposed cell cycle effect: the so-called radiation age response through the cell cycle. This is discussed in detail in the "Ionizing Radiation and the Cell Cycle" section (see also Figure 1-14).

Since Elkind and Sutton's original work, SLDR kinetics have been described for many different types of mammalian cells in culture[58] and for most normal and tumor tissues in vivo (e.g., Belli et al,[94] Emery et al[95]). Pertinent findings include:

1. The amount of SLD capable of being repaired for a given cell type varies both with the radiation quality (less for radiations of increasing LET) and the oxygenation status of the cells (recovery reduced or absent at extremely low-oxygen tensions).[28]
2. The half-time for SLDR in mammalian cells in culture is, on average, about 1 hour, although there is evidence that it may be somewhat longer for late responding normal tissues in vivo.[28]
3. The survival increase between split doses is a manifestation of the "regeneration" of the shoulder of the radiation survival curve. After an initial radiation dose and an adequate time interval for SLDR, the response of surviving cells to graded additional doses is nearly identical to that obtained

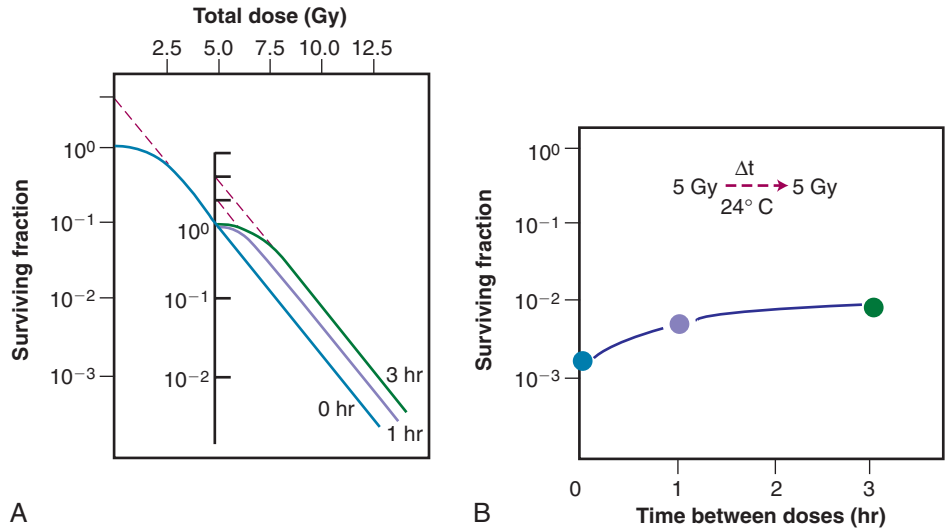


Figure 1-10 Sublethal damage recovery manifests as a return of the shoulder on the radiation survival curve when a total dose is delivered as two fractions separated by a time interval **(A)**. If the interfraction interval is shorter than the time it takes for this recovery to occur, the shoulder will only be partially regenerated (compare the shoulder regions of the survival curves for intervals of 1 vs. 3 hours). Regeneration of the shoulder **(B)** accounts for the observed survival increase in the corresponding split-dose assay (see Figure 1-9).

from cells without previous radiation exposure. Thus, the width of the shoulder of the survival curve came to be associated with the capacity of the cells for recovery from sublethal damage. This concept is illustrated in Figure 1-10.

4. Cells are able to undergo repeated cycles of damage and recovery without an apparent change in recovery capacity. As such, one would predict an equal effect per-dose fraction during the course of fractionated radiotherapy. In a more practical sense, this means that a multifraction survival curve can be generated using the formula $SF_n = (SF_1)^n$, where SF_1 is the surviving fraction of cells after a single-dose fraction (determined from a single-dose survival curve), and SF_n is the surviving fraction of cells after n dose fractions. Accordingly, multifraction survival curves are shoulderless and exponential (Figure 1-11).
5. Sublethal damage recovery is largely responsible for the dose rate effect for low LET radiation, which will be discussed in detail later in this chapter. As the dose per fraction (intermittent radiation) or dose rate (continuous irradiation) is decreased and the overall treatment time increased, the biological effectiveness of a given total dose is reduced. (Note that SLDR also occurs during continuous irradiation, that is, that a radiation-free interval is not required per se.)

A second type of cellular recovery following irradiation is termed po*tentially lethal damage repair or recovery* (PLDR) and was first described for mammalian cells by Phillips and Tolmach[96] in 1966. PLD is, by definition, a spectrum of radiation damage that may or may not result in cell lethality depending on the cells' postirradiation conditions. Conditions that favor PLDR include maintenance of cells in overcrowded conditions (plateau phase or contact-inhibited[97,98]) and incubation following irradiation at either reduced temperature,[99] in the presence of certain metabolic inhibitors,[96] or in balanced salt solutions rather than complete culture medium.[99] What these treatment conditions have in common is that they are suboptimal for continued growth of cells. Presumably, resting cells (regardless of why they are resting) have more opportunity to repair DNA damage before cell division than cells that continue traversing the cell cycle immediately after irradiation. Phillips and Tolmach[96] were the first to propose this repair-fixation or competition model to explain PLDR.

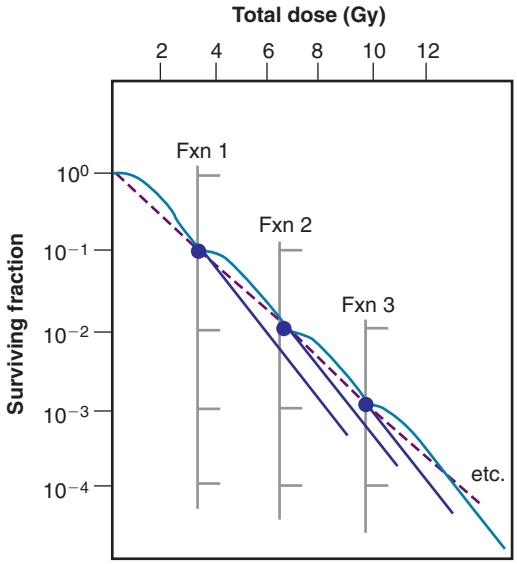


Figure 1-11 Hypothetical multifraction survival curve *(dashed line)* for repeated 3.0-Gy fractions under conditions in which sufficient time between fractions is allowed for full sublethal damage recovery and cell cycle and proliferative effects are negligible. The multifraction survival curve is shallower than its corresponding single-dose curve *(solid lines)* and has no shoulder (i.e., the surviving fraction is an exponential function of total dose).

Although admittedly, some of these postirradiation conditions are not likely to be encountered in vivo, slow growth of cells in general, with or without a large fraction of resting cells, is a common characteristic of many tissues. As might be expected, tumors (and subsequently, select normal tissues amenable to clonogenic assay) were shown to repair PLD.[98] Experiments using rodent tumors were modeled after comparable studies using plateau phase cells in culture, that is, a "delayed plating" assay was used. For such an experiment, irradiated cell cultures or animal tumors are left in a confluent state (either in the overcrowded cell culture or in the intact

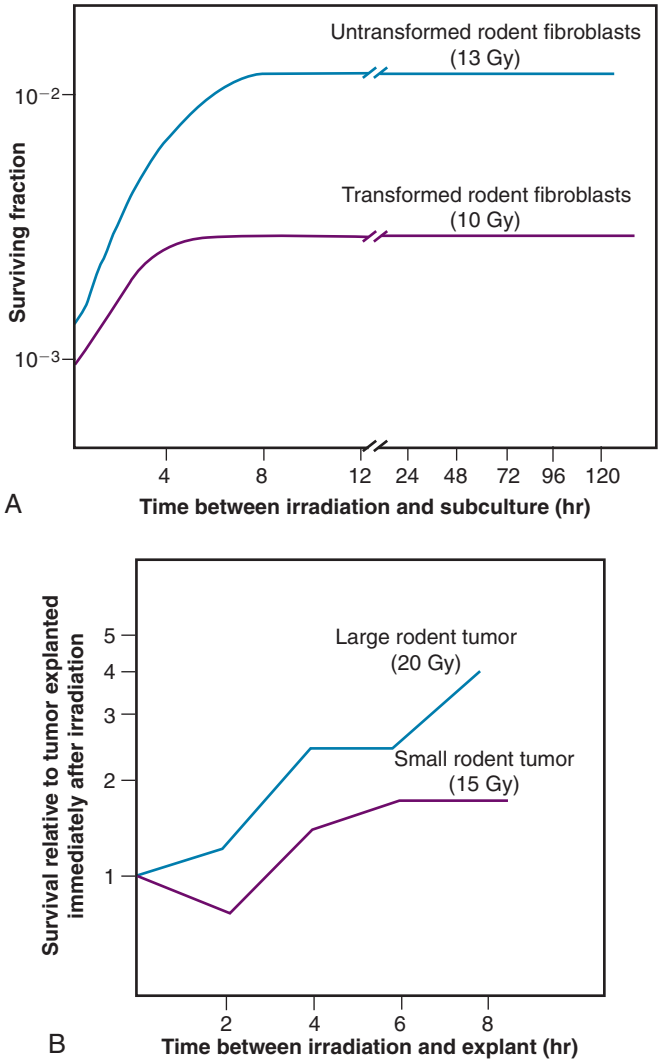


Figure 1-12 Potentially lethal damage recovery can be demonstrated using a delayed-plating assay in which a variable delay time is inserted between exposure to a large, single dose of radiation and the harvesting of the cells for a clonogenic assay. If cells are maintained in overcrowded or nutrient-deprived conditions during the delay period, the surviving fraction increases relative to that obtained when there is no delay. **A,** Potentially lethal damage recovery occurs in vitro in a nontumorigenic rodent fibroblast cell line and its transformed, tumorigenic counterpart. **B,** Potentially lethal damage recovery occurs in vivo in small and large mouse fibrosarcomas.
***A,** Adapted from Zeman E, Bedford J: Dose-rate effects in mammalian cells. V. Dose fractionation effects in noncycling C3H 10T1/2 cells. Int J Radiat Oncol Biol Phys 10:2089, 1984; **B,** adapted from Little J, Hahn G, Frindel E, et al: Repair of potentially lethal radiation damage in vitro and in vivo. Radiology 106:689, 1973.*

tumor in the animal) for varying lengths of time before removing them, dissociating them into single-cell suspensions and plating the cells for clonogenic survival at a low density. The longer the delay between irradiation and the clonogenic assay, the higher the resulting surviving fraction of individual cells, even though the radiation dose is the same. In general, survival rises to a maximum within 4-6 hours and levels off thereafter (Figure 1-12).

The kinetics and extent of recovery from both SLD and PLD are correlated with the molecular repair of DNA and the rejoining of chromosome breaks.[100,101] For the purposes of radiation therapy, however, the most important consideration is that both processes have the potential to increase the surviving fraction of cells between subsequent dose fractions. Such a survival increase could be manifest clinically as either increased normal tissue tolerance or decreased tumor control. It is also important to appreciate that small differences in recovery capacity between normal and tumor cells after a single-dose fraction are magnified into large differences after 30 or more dose fractions.

Repair in Tissues

When considering repair phenomenon in intact tissues, it is important to remember that both the magnitude of the repair (related both to the shape of the shoulder region of the corresponding dose-response curve and the dose delivered) and the rate of the repair can influence how the tissue behaves during a course of radiation therapy. For example, a particular tissue—normal or tumor—may be quite capable of repairing most damage produced by each dose fraction, but if the interfraction interval is so short as to not allow all the damage to be repaired before the next dose, the tolerance of that tissue will be less than otherwise anticipated. Second, although the sparing effect of dose fractionation for both normal and tumor tissues can be explained largely by SLD recovery between fractions, at sufficiently small doses per fraction, the degree of sparing will reach a maximum below which no further sparing occurs, that is, all other radiobiological factors being equal. This is a reflection of the fact that some radiation damage is necessarily lethal and not modifiable by either further fractionation or changing postirradiation conditions.

Ionizing Radiation and the Cell Cycle

Another basic feature of the cellular response to ionizing radiation is perturbation of the cell cycle. Such effects can modify the radioresponsiveness of tissues either directly or indirectly, depending on the fraction of cycling cells present in the tissue, their proliferation rates, and the kinetic organization of the tissue or tumor as a whole.

Advances in techniques for the study of cell cycle kinetics during the 1950s and 1960s paved the way for the generation of survival curves as a function of cell age. Using a technique known as autoradiography, Howard and Pelc[102] were able to identify the S, or DNA synthesis, phase of the cell cycle. When combined with the other cytologically obvious cell cycle marker, mitosis, they were able to discern the four phases of the cell cycle for actively growing cells: G1, S, G2, and M.

Methodology

Several techniques were subsequently developed for the collection of synchronized cells in vitro. One of the most widely used was the mitotic harvest or shake-off technique first described by Terasima and Tolmach.[103,104] By agitating cultures, mitotic cells, which tend to round up and become loosely attached to the culture vessel's surface, can be dislodged, collected along with the overlying growth medium, and inoculated into new culture flasks. By incubating these flasks at 37° C, cells begin to proceed synchronously into G1 phase (and semisynchronously thereafter). Thus, by knowing the length of the various phase durations for the cell type being studied and then delivering a radiation dose at a time of interest after the initial synchronization, the survival response of cells in different phases of the cell cycle can be determined.

A second synchronization method involved the use of DNA synthesis inhibitors such as fluorodeoxyuridine,[105] and later, hydroxyurea,[106] to selectively kill S phase cells, yet allow cells in other phases to continue cell cycle progression until they become blocked at the border of G1 and S phase. By incubating

cells in the presence of these inhibitors for times sufficient to collect nearly all cells at the block point, large numbers of cells can be synchronized. In addition, the inhibitor technique has two other advantages, namely that some degree of synchronization is possible in vivo[107] as well as in vitro, and that by inducing synchrony at the end of G1 phase, a higher degree of synchrony can be maintained for longer periods than if synchronization had been at the beginning of G1. On the other hand, the mitotic selection method does not rely on the use of drugs that themselves could perturb the normal cell cycle kinetics of the population.

Developments in the early 1970s, however, provided what is now considered among the most valuable tools for the study of cytokinetic effects: the flow cytometer and its offshoot, the fluorescence-activated cell sorter.[108] These have largely replaced the aforementioned longer and more labor-intensive cell cycle synchronization methods. Using this powerful technique, single cells are stained with a fluorescent probe that binds stoichiometrically to a specific cellular component, for example, DNA in the case of cell cycle distribution analysis. The stained cells are then introduced into a pressurized flow cell and forced to flow single file and at a high rate of speed through a focused laser beam that excites the fluorescent dye. The resulting light emission from each cell is collected by photomultiplier tubes, recorded, and output as a frequency histogram of cell number as a function of relative fluorescence, with the amount of fluorescence directly proportional to DNA content. Accordingly, cells with a "1X" DNA content would correspond to cells in G1 phase, cells with a "2X" DNA content in G2 or M phase, and cells with DNA contents between "1X" and "2X" in the S phase of the cell cycle. By performing a mathematical fit to the DNA histogram, the proportion of cells in each phase of the cell cycle can be determined, the phase durations can be derived, and differences in DNA ploidy can be identified. DNA flow cytometry is quite powerful in that not only can a static measure of cell cycle distribution be obtained for a cell population of interest, but also, dynamic studies of, for example, transit through the various cell cycle phases or treatment-induced kinetic perturbations, can be monitored over time (Figure 1-13). A flow cytometer can be outfitted to include a cell sorting feature; in this case, cells analyzed for a property of interest can be collected in separate "bins" after they pass through the laser beam, and if possible, used for other experiments.

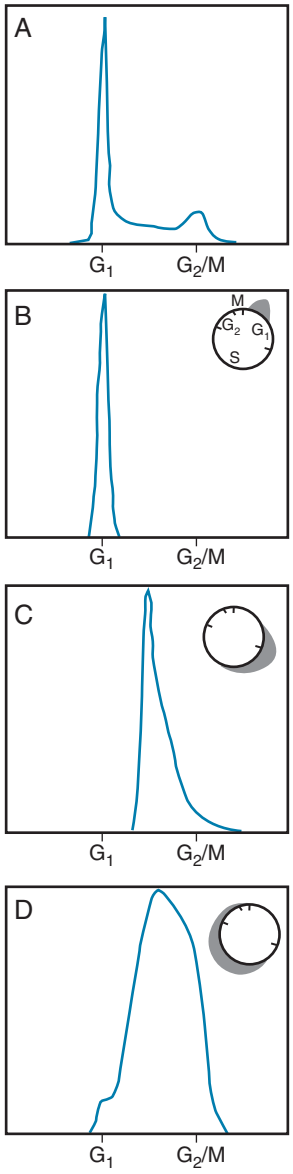


Figure 1-13 The analytic technique of flow cytometry has revolutionized the study of cell cycle kinetics by allowing rapid determination of DNA content in cells stained with a fluorescent dye that binds stoichiometrically to cellular DNA. **A,** Frequency distribution for a population of exponentially growing cells. The large and small peaks correspond to cells with G_1 (1×) and G_2/M (2×) phase DNA content, respectively; the cells in S phase have an intermediate DNA content. *B* to *D*, DNA histograms for a cell population synchronized initially in mitosis and then allowed to progress into G_1 **(B)**, S, and G_2/M (**C** and **D**).

Age Response Through the Cell Cycle

Results of an age response experiment of Terasima and Tolmach,[104] using synchronized HeLa cells, are shown in the lower panel of Figure 1-14. Following a single dose of 5 Gy of x-rays, cells were found to be most radioresistant in late S phase. Cells in G1 were resistant at the beginning of the phase but became sensitive toward the end of the phase, and G2 cells were increasingly sensitive as they moved toward the most sensitive M phase. In subsequent experiments by Sinclair,[109,110] age response curves for synchronized Chinese hamster V79 cells showed that the peak in resistance observed in G1 HeLa cells was largely absent for V79 cells. This is also illustrated in Figure 1-14 *(upper panel)*. Otherwise, the shapes of the age response curves for the two cell lines were similar. The overall length of the G1 phase determines whether the resistant peak in early G1 will be present; in general, this peak of relative radioresistance is only observed for cells with long G1 phases. For cells with short G1 phases, the entire phase is often of intermediate radiosensitivity. An analysis of the complete survival curves for synchronized cells[110,111] confirms that the most sensitive cells are those in M and late G2 phase, in which survival curves are steep and largely shoulderless, and the most resistant cells are those in late S phase. The resistance of these cells is conferred by the presence of a broad survival curve shoulder, rather than by a significant change in survival curve slope (Figure 1-15). When high LET radiations are used, the age response variation through the cell cycle is significantly reduced or eliminated because survival curve shoulders are either decreased or removed altogether by such exposures (see also "Relative Biological Effectiveness"). Similar age response patterns have been identified for cells synchronized in vivo.[107]

The existence of a cell cycle age response for ionizing radiation provided an explanation for the unusual pattern of SLDR observed for cells maintained at 37°C during the recovery interval (see Figure 1-9). In Elkind and Sutton's experiments,

exponentially growing cells were used, that is, cells that were asynchronously distributed across the different phases of the cell cycle. The cells that survived irradiation tended to be those most radioresistant. Thus, the remaining population became enriched with the more resistant cells. For low LET radiation, those cells that were most resistant were in S phase at the time of the first radiation dose. However, at 37°C, cells continued to progress through the cell cycle, so those surviving cells in S phase at the time of the first dose may have moved into G2 phase by the time the second dose was delivered. Thus, the observed survival nadir in the SLDR curve was not the result of a loss or reversal of repair, but rather, because the population of cells was now enriched in G2 phase cells, which are inherently more radiosensitive. For even longer radiation-free intervals, it is possible that the cells surviving the first dose would transit from G2 to M, and back into G1 phase, dividing and doubling their numbers. In this case, the SLDR curve again shows a surviving fraction increase because the number of cells has increased. None of these cell cycle-related phenomena occur when the cells are maintained at room temperature during the radiation-free interval because continued movement through the cell cycle is inhibited under such conditions; in that case, all that is noted is the initial survival increase resulting from SLDR.

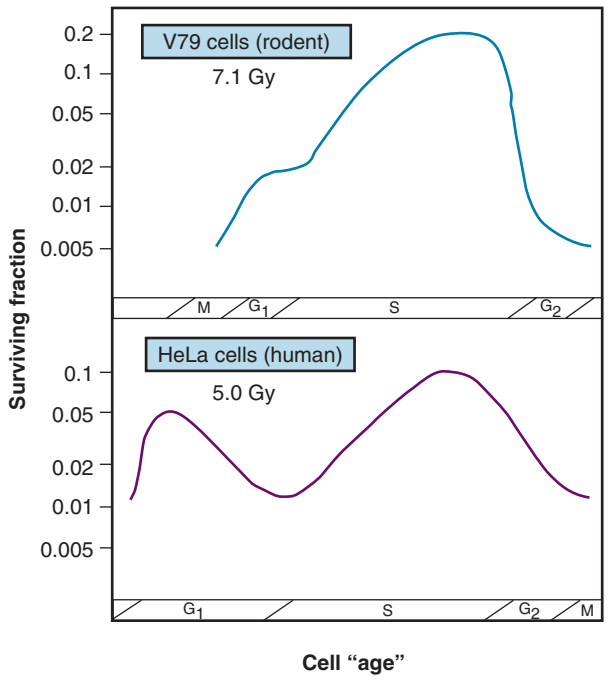


Figure 1-14 Cell cycle age response for sensitivity to radiation-induced cell killing in a representative rodent cell line (V79, *upper panel*) having a short G_1 phase duration and in a representative human cell line (HeLa, *lower panel*) having a long G_1 phase duration. Both cell lines exhibit a peak of radioresistance in late S phase and maximum radiosensitivity in late G_2/M phase. A second trough of radiosensitivity can be discerned near the G_1/S border for cells with long G_1-phase durations. *Adapted from Sinclair W: Dependence of radiosensitivity upon cell age. In Proceedings of the carmel conference on time and dose relationships in radiation biology as applied to radiotherapy. BNL Report 50203, Upton, NY, 1969, Brookhaven National Laboratory.*

Radiation-Induced Cell Cycle Blocks and Delays

Radiation is also capable of disrupting the normal proliferation kinetics of cell populations. This was recognized by Canti and Spear[112] in 1927 and studied in conjunction with radiation's ability to induce cellular lethality. With the advent of mammalian cell culture and synchronization techniques and time-lapse cinemicrography, it became possible for investigators to study mitotic and division delay phenomena in greater detail.

Mitotic delay, defined as a delay in the entry of cells into mitosis, is a consequence of upstream blocks or delays in the movement of cells from one cell cycle phase to the next. Division delay, which is a delay in the time of appearance of new cells at the completion of mitosis, is caused by the combined effects of mitotic delay, and any further lengthening of the mitosis process itself. Division delay increases with dose and is, on average, about 1 to 2 hours per Gray[104] depending on the cell line.

The cell cycle blocks and delays primarily responsible for mitotic and division delay are, respectively, a block in the G2-to-M phase transition and a block in the G1-to-S phase transition. The duration of the G2 delay, like the overall division delay, varies with cell type, but for a given cell type is dependent on both dose and cell cycle age. In general, the length of the G2 delay increases linearly with dose. For a given dose, the G2 delay is longest for cells irradiated in S or early G2 phase and shortest for cells irradiated in G1 phase.[113] Another factor contributing to mitotic and division delay is a block in the flow of cells from G1 into S phase. For x-ray doses of at least 6 Gy, there is a 50% decrease in the rate of tritiated thymidine uptake (indicative of entry into S phase) in

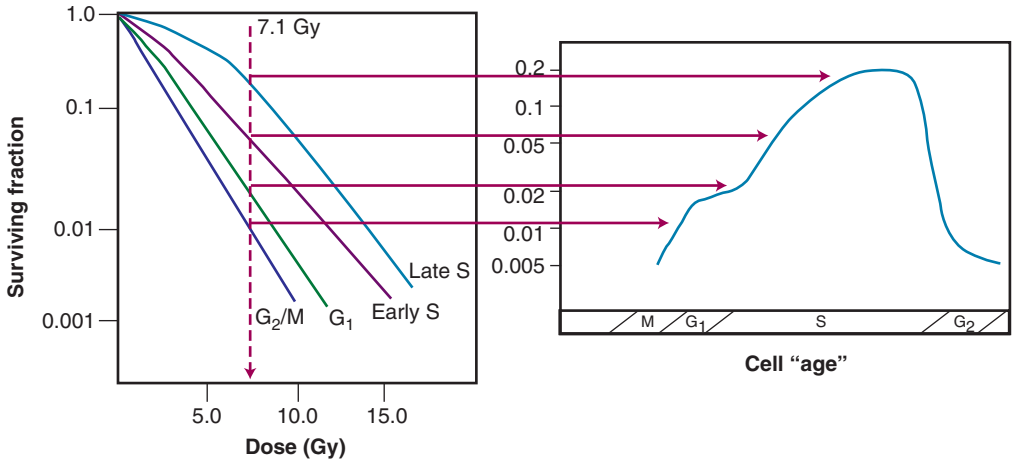


Figure 1-15 Cell survival curves for irradiated populations of Chinese hamster cells synchronized in different phases of the cell cycle *(left panel)*, illustrating how these radiosensitivity differences translate into the age-response patterns shown in the *right panel* (see Figure 1-14).

exponentially growing cultures of mouse L cells. Little[114] reached a similar conclusion from G1 delay studies using human liver LICH cells maintained as confluent cultures.

A possible role for DNA damage and its repair in the etiology of division delay was bolstered by the finding that certain cells types that either did not exhibit the normal cell cycle delays associated with radiation exposure (such as AT cells[42]), or conversely, were treated with chemicals (such as caffeine) that ameliorated the radiation-induced delays,[115] tended to contain higher amounts of residual DNA damage, and to show increased radiosensitivity.

It is now known that the radiation-induced perturbations in cell cycle transit are under the control of cell cycle checkpoint genes, whose products normally govern the orderly (and unidirectional) flow of cells from one phase to the next. The checkpoint genes are responsive to feedback from the cell as to its general condition and readiness to transit to the next cell cycle phase. DNA integrity is one of the criteria used by these genes to help make the decision whether to continue traversing the cell cycle, or to pause, either temporarily, or in some cases, permanently. Cell cycle checkpoint genes are discussed in Chapter 2.

Redistribution in Tissues

Because of the age response through the cell cycle, an initially asynchronous population of cells surviving a dose of radiation becomes enriched with S phase cells. As a result of variations in the rate of further cell cycle progression, however, this partial synchrony decays rapidly. Such cells are said to have redistributed[116] with the net effect of sensitizing the population as a whole to a subsequent dose fraction (relative to what would have been expected had the cells remained in their resistant phases). A second type of redistribution, in which cells accumulate in G2 phase (in the absence of cell division) during the course of multifraction or continuous irradiation because of a buildup of radiation-induced cell cycle blocks and delays, also has a net sensitizing effect. This has been observed during continuous irradiation by several investigators,[117] and in some of these cases, a net *increase* in radiosensitivity is seen at certain dose rates. This so-called inverse dose rate effect, in which certain dose rates are more effective at cell killing than other, higher dose rates, was extensively studied by Bedford et al (for a review, see Bedford et al[118]). The magnitude of the sensitizing effect of redistribution varies with cell type depending on what dose rate is required to stop cell division. For dose rates below the critical range that causes redistribution, some cells can escape the G2 block and proceed on to cell division.

Densely Ionizing Radiation

Linear Energy Transfer (LET)

The total amount of energy deposited in biological materials by ionizing radiation (usually expressed in units of keV, ergs or joules per g or kg) is in and of itself insufficient to describe the net biological consequences of those energy deposition events. For example, 1 Gy of x-rays, although physically equivalent in terms of total energy imparted per unit mass to 1 Gy of neutrons or α-particles, does not produce equivalent biological effects. It is the microdosimetric pattern of that energy deposition, that is, the spacing or density of the ionization events, that determines biological effectiveness. This quantity—the average energy deposited locally per unit length of the ionizing particle's track—is termed its LET.

LET is a function both of the charge and mass of the ionizing particle. Photons set in motion fast electrons that have a net negative charge but a negligible mass. Neutrons on the other hand give rise to recoil protons or α-particles, that possess one or two positive charges, respectively, and are orders of magnitude more massive than electrons. Neutrons therefore have a higher LET than photons and are said to be densely ionizing, whereas the x- or γ-rays are considered sparsely ionizing. The LET concept is illustrated in Figure 1-16 for both densely and sparsely ionizing radiations. For a given ionizing particle, the rate of energy deposition in the absorbing medium increases as the particle slows down. Therefore, a beam of radiation can only be described as having an average value for LET.

Representative LET values for types of radiations that have been used for radiation therapy include 0.2 keV/μm for ^{60}Co γ-rays; 2.0 keV/μm for 250 kVp x-rays; approximately 0.5 to 5.0 keV/μm for protons of different energies; approximately 50 to 150 keV/μm for neutrons of varying energy; 100 to 150 keV/μm for α-particles and anywhere from 100 to 2500 keV/μm for "heavy ions."

Relative Biological Effectiveness (RBE)

Insofar as the "quality" (LET) of the type of radiation influences its biological effectiveness, two questions immediately come to mind. First, why do seemingly subtle differences in microdosimetric energy deposition patterns lead to vastly different biological consequences? Second, how is this differing biological effectiveness manifest in terms of the commonly used assays and model systems of classical radiobiology, and how can this difference be expressed in a quantitative way?

Because high LET radiations are more densely ionizing than their low LET counterparts, it follows that energy deposition in a particular "micro" target volume will be greater, and therefore, more severe damage to biomolecules would be expected. In this case, the fraction of cell killing attributable to irreparable and unmodifiable DNA damage increases in relation to that caused by the accumulation of sublethal damage. Because of this, a number of radiobiological phenomena commonly associated with low LET radiation are decreased or eliminated when high LET radiation is used. For example, there is little, if any, sublethal[58] or potentially lethal damage recovery.[113] This is manifest as a reduction or loss of the shoulder of the acute-dose survival curve, little or no sparing effect of dose fractionation or dose rate, and a corresponding

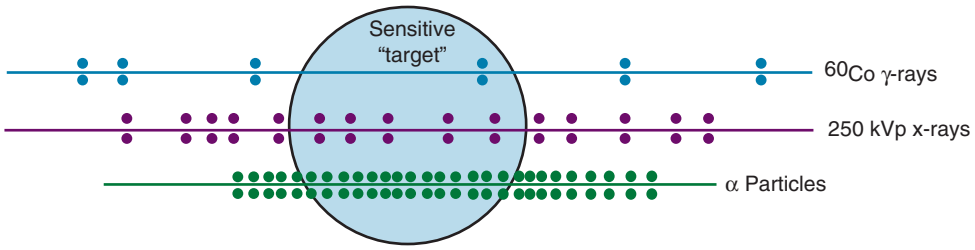


Figure 1-16 Variation in the density of ionizing events along an incident particle's track for radiations of different values of linear energy transfer (LET). The more closely the ionizing events are spaced, the more energy will be deposited in the target volume, and to a point, the more biologically effective per unit dose the type of radiation will be.

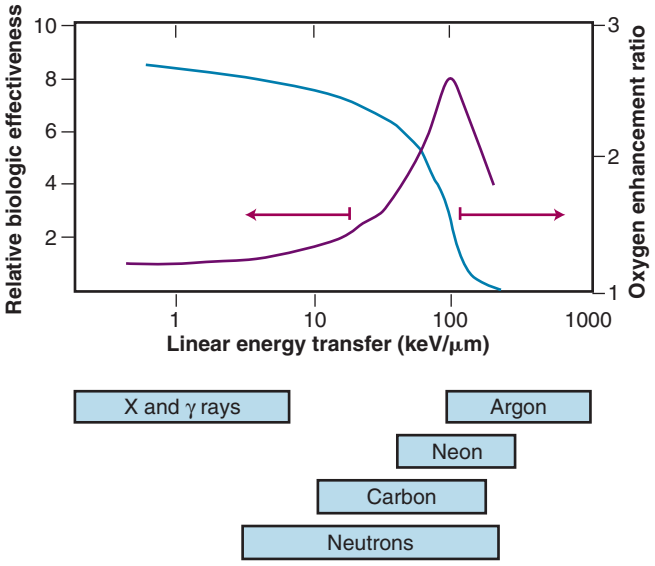


Figure 1-17 Relative biological effectiveness (RBE) is demonstrated on the left *y*-axis as a function of linear energy transfer (LET) for a number of biological endpoints, including production of chromosomal aberrations, cell kill, and tissue reactions. The RBE rises to a maximum corresponding to an LET of approximately 100 KeV/μm and then decreases as the LET continues to rise. Shown below the *x*-axis are the ranges of LET for photons plus several different types of particulate radiations that have been used clinically. Dependence of the oxygen enhancement ratio (OER) on LET is shown on the *y*-axis.

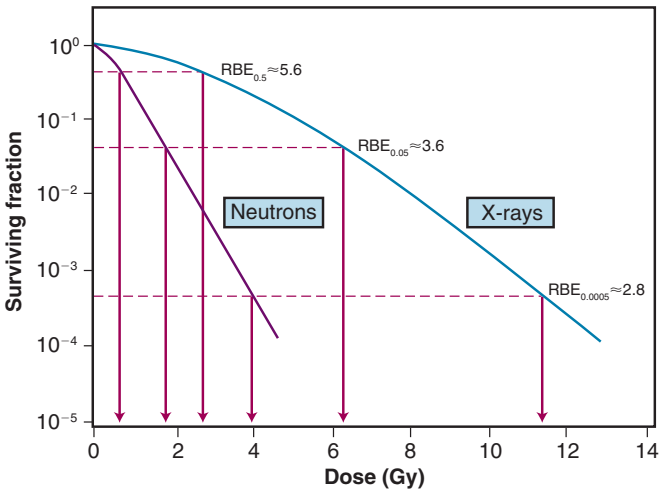


Figure 1-18 Theoretical cell survival curves for x-rays and neutrons, illustrating the increase in relative biological effectiveness (RBE) with decreasing dose. This occurs because higher linear energy transfer (LET) radiations preferentially decrease or eliminate the shoulder on cell survival curves.
Adapted from Nias A: Clinical radiobiology, ed 2, New York, 1988, Churchill Livingstone.

reduction in the tolerance doses for normal tissue complications, particularly for late-responding tissues.[119] Variations in the age response through the cell cycle also are reduced or eliminated for high LET radiation,[107] and the oxygen enhancement ratio (OER), which is a measure of the differential radiosensitivity of poorly- versus well-oxygenated cells (see discussion in this chapter), decreases with increasing LET.[120] The dependence of OER on LET is illustrated in Figure 1-17; at an LET of approximately 100 keV/μm, the relative radioresistance of hypoxic cells is eliminated.

In light of these differences between high and low LET radiations, the term *relative biological effectiveness* (RBE) has been coined to compare and contrast two radiation beams of different LET. RBE is defined as the ratio of doses of a known type of low LET radiation (historically, 250 kVp x-rays were the standard, but ^{60}Co γ-rays also can be used) to that of a higher LET radiation, to yield the same biological endpoint. RBE does not increase indefinitely with increasing LET however, but it reaches a maximum at approximately 100 keV/μm, and then decreases again, yielding an approximately bell-shaped curve.

One interpretation as to why the RBE reaches a maximum at an LET of approximately 100 keV/μm is that at this ionization density, the average separation between ionizing events corresponds roughly to the diameter of the DNA double helix (approximately 2 nm). As such, radiations of this LET have the highest probability of producing DSBs in DNA, the putative lethal lesion, by the passage of a single charged particle. Lower LET radiations have a smaller likelihood of producing such "two-hit" lesions from a single particle track, and therefore are less biologically effective. Radiation beams of higher LET than the optimum are also less biologically effective because some of the energy is wasted because more ionization events than minimally necessary to kill a cell are deposited in the same local area. This phenomenon has been termed the *overkill effect*.

Factors That Influence RBE

RBE is highly variable and depends on several parameters including the type of radiation, total dose, dose rate, dose fractionation pattern, and the biological effect being assayed. Therefore, when quoting an RBE value the exact experimental conditions used to measure it must be stated. Because increasing LET differentially reduces the shoulder region of the radiation survival curve compared to its exponential or near-exponential high-dose region, the single-dose RBE increases with decreasing dose (Figure 1-18). Second, the RBE determined by comparing two isoeffective acute doses is less than the RBE calculated from two isoeffective (total) doses given either as multiple fractions or at a low dose rate. This occurs because the sparing effect of fractionation magnifies differences in the initial slope or shoulder region of cell survival or tissue dose-response curves (Figure 1-19).

The Oxygen Effect

Perhaps the best known chemical modifier of radiation action is molecular oxygen. As early as 1909, Schwarz recognized that applying pressure to skin and thereby decreasing blood flow (and oxygen supply) caused a reduction in radiation-induced skin reactions.[121] For many decades thereafter, radiation oncologists and biologists continued to suspect that the presence or absence of oxygen was capable of modifying radiosensitivity. In 1955, however, Thomlinson and Gray[122] brought this idea to the forefront of radiation biology and therapy by proposing that tumors contain a fraction of still-clonogenic, hypoxic cells that, if persistent throughout treatment, would adversely affect clinical outcome. Although commonly considered a negative prognostic indicator for radiation therapy, hypoxia nevertheless has one particularly attractive feature: built-in specificity for tumors, to the extent that most normal tissues contain few, if any, hypoxic cells.

By studying histological sections of a human bronchial carcinoma, Thomlinson and Gray[122] noted that necrosis was always seen in the centers of cylindrical tumor cords having a radius in excess of approximately 200 μm. Further, regardless of how large the central necrotic region was, the sheath of

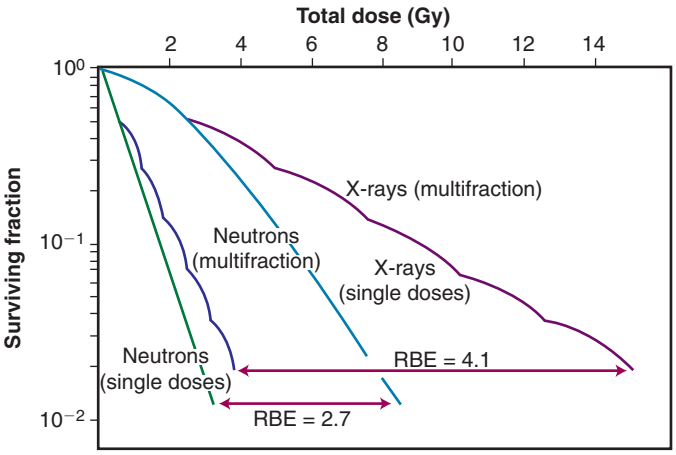


Figure 1-19 Increase in the relative biological effectiveness (RBE) of neutrons relative to x-rays when comparing single radiation doses with fractionated treatment. For a given level of cell kill (or other approximately isoeffective endpoint), the more highly fractionated the treatment, the higher the RBE.

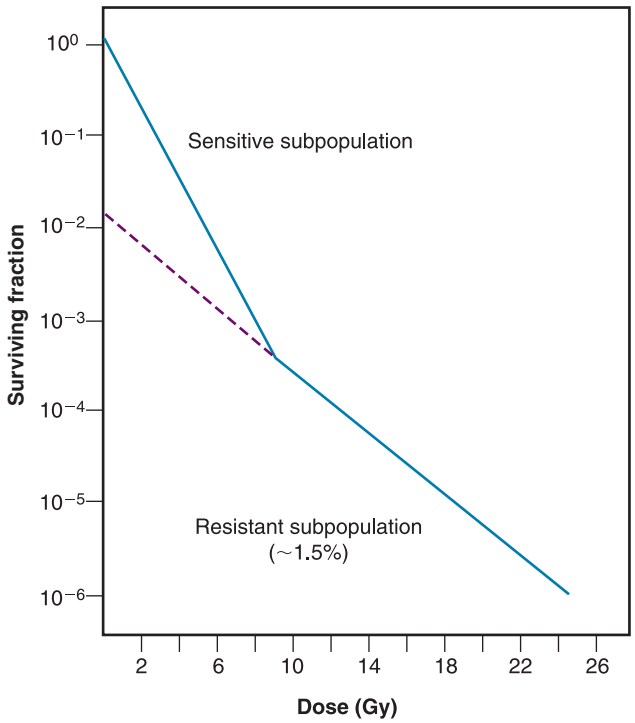


Figure 1-20 Cell survival curve for a murine lymphosarcoma growing subcutaneously and irradiated in vivo. The biphasic curve suggests the presence of a small but relatively radioresistant subpopulation of cells, determined in accompanying experiments to represent the tumor's clonogenic hypoxic fraction.
Adapted from Powers WE, Tolmach LJ: A multicomponent x-ray survival curve for mouse lymphosarcoma cells irradiated. Nature 197:710, 1963.

apparently viable cells around the periphery of this central region never had a radius greater than about 180 µm. The authors went on to calculate the expected maximum diffusion distance of oxygen from blood vessels and found that the value of 150 to 200 µm agreed quite well with the radius of the sheath of viable tumor cells observed histologically. With the advent of more sophisticated and quantitative methods for measuring oxygen utilization in tissues, the average diffusion distance of oxygen has since been revised downward to approximately 70 µm.[28] Thus, the inference was that the oxygenation status of tumor cells varied from fully oxic to completely anoxic depending on where the cells were located in relation to the nearest blood vessels. Accordingly, tumor cells at intermediate distances from the blood supply would be hypoxic and radioresistant, yet remain clonogenic.

The first unambiguous demonstration that a solid rodent tumor did contain clonogenic, radioresistant hypoxic cells was by Powers and Tolmach[123] in 1963. These authors used the dilution assay to generate an in vivo survival curve for mouse lymphosarcoma cells. The survival curve for this solid tumor was biphasic, having an initial D_0 of about 1.1 Gy, and a final D_0 of 2.6 Gy (Figure 1-20). Because the survival curve for lymphoid cells is shoulderless, it was simple to back-extrapolate the shallower component of the curve to the surviving fraction axis and determine that the resistant fraction of cells constituted about 1.5% of the total population. This was considered compelling evidence (yet did not unambiguously prove) that this subpopulation of cells was both hypoxic and clonogenic.

The question then became how to prove that this small fraction of tumor cells was radioresistant because of hypoxia, as opposed to being radioresistant for other reasons. An elegant if somewhat macabre method was developed to address this dilemma, called the *paired survival curve technique*.[123,124] In this assay, laboratory animals bearing tumors were divided into three treatment groups, one group irradiated while breathing air, a second group irradiated while breathing 100% oxygen, and a third group killed first by cervical dislocation and then promptly irradiated. Within each group, animals received graded radiation doses so that complete survival curves were generated for each treatment condition. When completed, the paired survival curve method yielded three different tumor cell survival curves: a fully oxic curve (most radiosensitive), a fully hypoxic curve (most radioresistant), and the survival curve for air-breathing animals, which, if the tumor contained viable hypoxic cells, was biphasic and positioned between the other two curves. It was then possible to mathematically strip the fully aerobic and hypoxic curves from the curve for air-breathing animals and determine the radiobiologically hypoxic fraction.

Across a variety of rodent tumors evaluated to date using the paired survival curve method, the percentage of hypoxic cells was found to vary between 0% and 50%, with an average of about 15%.[124]

Mechanistic Aspects of the Oxygen Effect

A more rigorous analysis of the nature of the oxygen effect is possible with cells or bacteria grown in vitro. Historically, oxygen had been termed a dose-modifying agent, that is, that the ratio of doses to achieve a given survival level under hypoxic and aerobic conditions was constant, regardless of the survival level chosen. This dose ratio to produce the same biological endpoint is termed the *OER* and is used for comparative purposes (Figure 1-21). The OER typically has a value of between 2.5 and 3.0 for large single doses of x- or γ-rays, 1.5 to 2.0 for radiations of intermediate LET, and 1.0 (i.e., no oxygen effect) for high LET radiations.

Increasingly, there is evidence that oxygen is not strictly dose modifying. Several studies have shown that the OER for sparsely ionizing radiation is lower at lower doses than at higher doses. Lower OERs for doses per fraction in the range commonly used in radiotherapy have been inferred indirectly from clinical and experimental tumor data and more directly in experiments with cells in culture.[125,126] It has been suggested that the lower OERs result from an age response for the oxygen

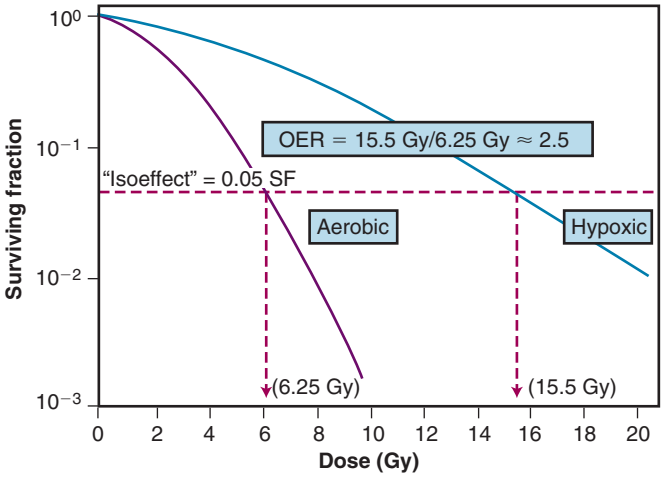


Figure 1-21 Representative survival curves for cells irradiated with x-rays in the presence (aerobic) or virtual absence (hypoxic) of oxygen. The oxygen enhancement ratio (OER) is defined as the ratio of doses under hypoxic-to-aerobic conditions to yield the same biological effect, which in this case is a cell surviving fraction (SF) of 0.05.

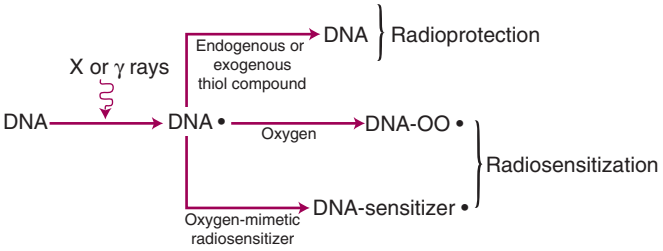


Figure 1-22 Schematic representation of the proposed mechanism of action for the oxygen effect. The radical competition model holds that oxygen acts as a radiosensitizer by forming peroxides in DNA already damaged by radiation, thereby fixing the damage. In the absence of oxygen, DNA can be restored to its preirradiated state by hydrogen donation from endogenous reducing species in the cell, such as the free radical scavenger glutathione. An oxygen-mimetic, hypoxic cell radiosensitizer may be used to substitute for oxygen in these fast, free radical reactions, or an exogenously supplied thiol compound may be used to act as a radioprotector.

effect, not unlike the age responses for inherent radiosensitivity and cell cycle delay.[28] Assuming cells in G1 phase of the cell cycle have a lower OER than those in S phase, and because G1 cells are also more radiosensitive, they would tend to dominate the low dose region of the cell survival curve.

Although the exact mechanism(s) of the oxygen effect are obviously complex, a fairly simplistic model can be used to illustrate our current understanding of this phenomenon (Figure 1-22). The radical competition model holds that oxygen acts as a radiosensitizer by forming peroxides in important biomolecules (including but not necessarily limited to, DNA) already damaged by radiation exposure, thereby "fixing" the radiation damage. In the absence of oxygen, DNA can be restored to its preirradiated condition by hydrogen donation from endogenous reducing species in the cell, such as the free radical scavenger glutathione, a thiol compound. In essence, this can be considered a type of fast chemical restitution or repair. These two processes, fixation and restitution, are considered to be in a dynamic equilibrium, such that changes in the relative amounts of either the radiosensitizer, oxygen, or the radioprotector, glutathione, tip the scales in favor of either fixation (more damage, more cell killing, greater

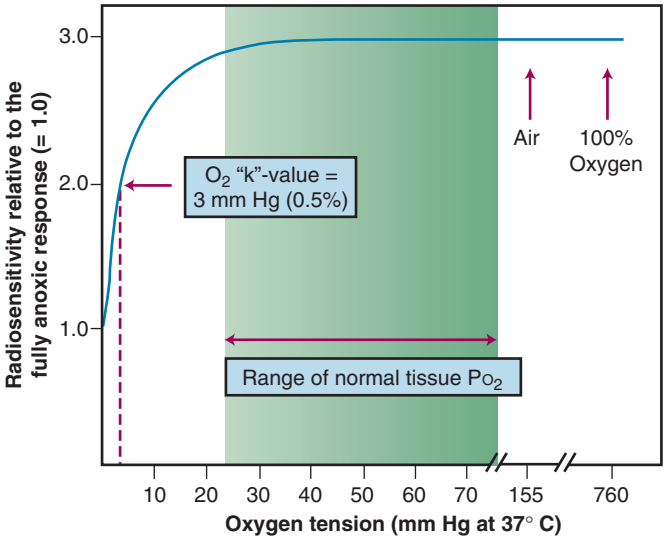


Figure 1-23 An oxygen *k-curve* illustrates the dependence of radiosensitivity on oxygen concentration. If a fully anoxic cell culture is assigned a relative radiosensitivity of 1.0, introducing even 0.5% (3 mm Hg) oxygen into the system increases the radiosensitivity of cells to 2.0. By the time the oxygen concentration reaches about 2%, cells respond as if they are fully aerated (i.e., radiosensitivity ≈ 3.0). The *green-shaded area* represents the approximate range of oxygen concentrations encountered in human normal tissues.

radiosensitivity) or restitution (less damage, less cell killing, greater radioresistance).

Consistent with this free radical-based interpretation of the oxygen effect is the finding that, for all intents and purposes, oxygen need only be present *during* the irradiation (or no more than a few milliseconds after irradiation) to produce an aerobic radioresponse.[127,128] The concentration of oxygen necessary to achieve maximum sensitization is quite small, evidence for the high efficiency of oxygen as a radiosensitizer. A sensitivity midway between a fully hypoxic and fully aerobic radioresponse is achieved at an oxygen tension of about 3 mm of mercury, corresponding to about 0.5% oxygen, which is much lower than partial pressures of oxygen usually encountered in normal tissues. This value of 0.5% has been termed *oxygen's k-value* and is obtained from an oxygen k-curve of relative radiosensitivity plotted as a function of oxygen tension[129] (Figure 1-23).

Reoxygenation in Tumors

After the convincing demonstration of hypoxic cells in a mouse tumor,[123] it was assumed that human tumors contained a viable hypoxic fraction as well. However, if human tumors contained even a tiny fraction of clonogenic hypoxic cells, simple calculations suggested that tumor control would be nearly impossible with radiation therapy.[130] Because therapeutic successes obviously do occur, some form of reoxygenation must take place during the course of multifraction irradiation. This was not an unreasonable idea because the demand for oxygen by sterilized cells would gradually decrease as they were removed from the tumor, and a decrease in tumor size, a restructuring of tumor vasculature, or intermittent changes in blood flow could make oxygen available to these previously hypoxic cells.

The reoxygenation process was extensively studied by van Putten and Kallman,[131] who serially determined the fraction of hypoxic cells in a mouse sarcoma during the course of a clinically relevant multifraction irradiation protocol. The fact that the hypoxic fraction was about the same at the end of

treatment as at the beginning of treatment was strong evidence for a reoxygenation process, because otherwise, the hypoxic fraction would be expected to increase over time as a result of repeated enrichment with resistant cells after each dose fraction. Reoxygenation of hypoxic, clonogenic tumor cells during an extended multifraction treatment would increase the therapeutic ratio, assuming that normal tissues remained well oxygenated. This is thought to be another major factor in the sparing of normal tissues relative to tumors during fractionated radiation therapy.

What physiological characteristics would lead to tumor reoxygenation during a course of radiotherapy, and at what rate would this be expected to occur? One possible cause of tumor hypoxia, and by extension, a possible mechanism for reoxygenation, was suggested by Thomlinson and Gray's pioneering work.[122] The type of hypoxia that they described is what is now called *chronic*, or *diffusion-limited hypoxia*. This results from the tendency of tumors both to outgrow their blood supply and have high oxygen consumption rates. It follows therefore that natural gradients of oxygen tension should develop as a function of distance from blood vessels. Cells situated beyond the diffusion distance of oxygen would be expected to be dead or dying of anoxia, yet in regions of chronically low-oxygen tension, clonogenic and radioresistant hypoxic cells could persist. Should the tumor shrink as a result of radiation therapy, or if the cells killed by radiation cause a decreased demand for oxygen, it is likely that this would allow some of the chronically hypoxic cells to reoxygenate. However, such a reoxygenation process could be quite slow—on the order of days or more—depending on how quickly tumors regress during treatment. The patterns of reoxygenation in some experimental rodent tumors are consistent with this mechanism of reoxygenation, but others are not.

Other rodent tumors reoxygenate quickly, on a time scale of minutes to hours.[132] This occurs in the absence of any measurable tumor shrinkage or change in oxygen utilization by tumor cells. In such cases, the model of chronic, diffusion-limited hypoxia and slow reoxygenation does not fit the experimental data. During the late 1970s, Brown[133] proposed that a second type of hypoxia may exist in tumors, an acute, *perfusion-limited hypoxia*. Based on the growing understanding of the vascular physiology of tumors, it was clear that tumor vasculature was often abnormal in both structure and function secondary to abnormal angiogenesis. If tumor vessels were to close transiently from temporary blockage, vascular spasm or high interstitial fluid pressure in the surrounding tissue, the tumor cells in the vicinity of those vessels would become acutely hypoxic almost immediately. Then, assuming blood flow resumed in minutes to hours, these cells would reoxygenate. However, this type of hypoxia can also occur in the absence of frank closure or blockage of tumor vessels (which is now considered a less common cause of acute hypoxia), from, for example, vascular shunting, longitudinal oxygen gradients, decreased red cell flux or overall blood flow rate, abnormal vascular geometry, and so on.[134] Because of this, perfusion-*limited* hypoxia is perhaps misleading; a better moniker might be *fluctuant* or *intermittent* hypoxia. Although intermittent hypoxia would explain the rapid reoxygenation observed for some tumors, it does not preclude the simultaneous existence of chronic, diffusion-limited hypoxia.

Intermittent hypoxia has since been demonstrated unambiguously for rodent tumors by Chaplin et al.[135] and human tumors by Lin et al.[134,136] It is still not clear how many human tumors contain regions of hypoxia (although many do—see discussion in this chapter), what type(s) of hypoxia is present, whether this varies with tumor type or site, and whether and how rapidly reoxygenation occurs. However, the knowledge that tumor hypoxia is a diverse and dynamic process opens up a number of possibilities for the development of novel interventions designed to cope with, or even exploit, hypoxia.

Measurement of Hypoxia in Human Tumors

Despite prodigious effort directed at understanding tumor hypoxia and developing strategies to combat the problem, it was not until the late 1980s that these issues could be addressed for human tumors because there was no way to measure hypoxia directly. Before that time, the only way to infer that a human tumor contained treatment-limiting hypoxic cells was by using indirect, nonquantitative methods. Some indirect evidence supporting the notion that human tumors contained clonogenic, radioresistant, hypoxic cells includes the following:

1. An association between anemia and poor local control rates, which, in some cases, could be mitigated by preir-radiation blood transfusions.[137]
2. Success of some clinical trials in which hyperbaric oxygen breathing was used to better oxygenate tumors.[138,139]
3. Success of a few clinical trials of oxygen-mimetic hypoxic cell sensitizers combined with radiation therapy.[140,141]

In 1988, one of the first studies showing a strong association between directly measured oxygenation status in tumors and clinical outcome was published by Gatenby.[142] An oxygen-sensing electrode was inserted into the patient's tumor, and multiple readings were taken at different depths along the probe's track. The electrode was also repositioned in different regions of the tumor to assess intertrack variability in oxygen tension. Both the arithmetic mean pO2 value for a particular tumor, as well as the tumor volume-weighted pO2 value, directly correlated with local control rate. A high tumor oxygen tension was associated with a high complete response rate, and vice versa. In a similar, prospective study, Höckel et al[4,143] concluded that pretreatment tumor oxygenation was a strong predictor of outcome among patients with intermediate and advanced stage cervical carcinoma (Figure 1-24).

Unfortunately, the use of oxygen electrodes has its limitations. One weakness is that relative to the size of individual tumor cells, the electrode is large, averaging an outer diameter of 300 µm, a tip recess of 120 µm, and a sampling volume of about 12 µm in diameter.[144] Thus, not only is the oxygen tension measurement regional, but the insertions and removals of the probe also no doubt perturb the oxygenation status. Another problem is that there is no way to determine whether

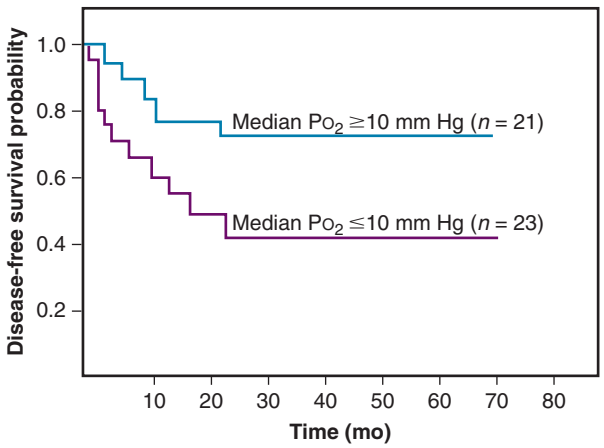


Figure 1-24 The disease-free survival probability of a small cohort of patients with cervical cancer stratified according to pretreatment tumor oxygenation measured using an oxygen electrode.
Adapted from Höckel M, Knoop C, Schlenger K, et al: Intratumoral Po_2 predicts survival in advanced cancer of the uterine cervix. Radiother Oncol 26:45, 1993.

the tumor cells are clonogenic or not. If such cells were hypoxic yet not clonogenic, they would not be expected to impact on radiotherapy outcome.

A second direct technique for measuring oxygenation status takes advantage of a serendipitous finding concerning how hypoxic cell radiosensitizers are metabolized. Certain classes of radiosensitizers, including the nitroimidazoles, undergo a bioreductive metabolism in the absence of oxygen that leads to their becoming covalently bound to cellular macromolecules.[145,146] Assuming that the bioreductively bound drug could be quantified by radioactive labeling,[147] or tagged with an isotope amenable to detection using positron emission tomography[148] or magnetic resonance spectroscopy,[149] a direct measure of hypoxic fraction can be obtained. Another approach to detecting those cells containing bound drug was developed by Raleigh et al.[150,151] This immunohistochemical method involved the development of antibodies specific for the already-metabolized, bound nitroimidazoles. After injecting the parent drug, allowing time for the reductive metabolism to occur, taking biopsies of the tumor and preparing histopathology slides, the specific antibody is then applied to the slides and regions containing the bound drug are visualized directly. This immunostaining method has the distinct advantages that hypoxia can be studied at the level of individual tumor cells,[152] spatial relationships between regions of hypoxia and other tumor physiological parameters can be assessed,[153] and the drug does not perturb the tumor microenvironment. However, the method remains an invasive procedure, is labor intensive, does not address the issue of the clonogenicity of stained cells (although such cells do have to be metabolically active), and requires that multiple samples be taken because of tumor heterogeneity.

One hypoxia marker based on the immunohistological method is commercially available and called HypoxyProbe-1; it detects reductively bound pimonidazole and has been used in experimental and clinical studies around the world (e.g., Bussink et al,[154] Nordsmark et al[155]). Applying HypoxyProbe-1 to human tumor specimens yields a range of hypoxic fractions similar to that noted for experimental rodent tumors and a mean value of approximately 15%.[151,156] This marker can also be used to probe disease states other than cancer that may have the induction of tissue hypoxia as part of their etiology, such as cirrhosis of the liver[157,158] and ischemia-reperfusion injury in the kidney.[159]

There is also considerable interest in *endogenous* markers of tissue hypoxia[160,161] that could reduce to some extent the procedural steps involved in, and the invasive aspects of, detecting hypoxia using exogenous agents. Among the endogenous cellular proteins being investigated in this regard are the hypoxia-inducible factor 1-alpha (HIF-1α, that acts as a transcription factor for hypoxia-regulated genes[162]), the enzyme carbonic anhydrase IX (CA-9 or CAIX, involved in respiration and maintenance of the proper acid-base balance in tissues[163,164]), glucose transporter-1 (GLUT-1, which facilitates glucose transport into cells[165-167]), lysyl oxidase (LOX, which oxidizes lysine residues in extracellular matrix proteins that can enhance the processes of tumor invasion and metastasis[168,169]) and osteopontin (OPN, a glycoprotein recently identified as a promoter of tumor angiogenesis, invasion, and metastasis[170-172]).

Clearly, although aberrant expression of some individual hypoxia markers has been associated with poor clinical outcome, no one marker is likely to be sufficiently robust or reproducible to either be diagnostic for the presence of a malignancy (or at least, the presence of hypoxia in an already-diagnosed tumor) or be prognostic of treatment outcome. Thus, there has been increasing interest in the study of patterns of hypoxia-associated gene or protein expression for multiple markers simultaneously (e.g., Le,[5] Erpolate et al,[172] Toustrup et al[173]).

Radiosensitizers, Radioprotectors, and Bioreductive Drugs

The perceived threat that tumor hypoxia posed spawned much research into ways of overcoming the hypoxia problem. One of the earliest proposed solutions was the use of high LET radiations,[174] which were less dependent on oxygen for their biological effectiveness. Other agents enlisted to deal with the hypoxia problem included hyperbaric oxygen breathing,[138] artificial blood substitutes with increased oxygen carrying capacity,[175] oxygen-mimetic hypoxic cell radiosensitizers such as misonidazole or etanidazole,[140] hyperthermia,[176] normal tissue radioprotectors such as amifostine,[177] vasoactive agents thought to modify tumor blood flow such as nicotinamide,[178] agents that modify the oxygen-hemoglobin dissociation curve such as pentoxifylline,[179] and bioreductive drugs designed to be selectively toxic to hypoxic cells such as tirapazamine.[180,181]

Radiosensitizers

Radiosensitizers are loosely defined as chemical or pharmacological agents that increase the cytotoxicity of ionizing radiation. True radiosensitizers meet the stricter criterion of being relatively nontoxic in and of themselves, acting only as potentiators of radiation toxicity. Apparent radiosensitizers still produce the net effect of making the tumor more radioresponsive, yet the mechanism is not necessarily synergistic, nor is the agent necessarily nontoxic when given alone. Ideally, a radiosensitizer is only as good as it is selective for tumors. Agents that show little or no differential effect between tumors and normal tissues do not improve the therapeutic ratio, and therefore may not be of much clinical utility. Table 1-2 summarizes some of the classes of radiosensitizers (and radioprotectors, see discussion) that have been used in the clinic.

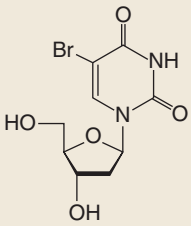
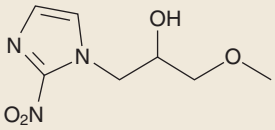
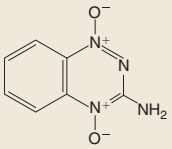
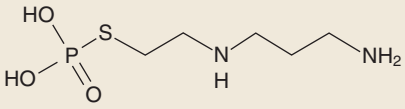
Hypoxic Cell Radiosensitizers

The increased radiosensitivity of cells in the presence of oxygen is believed to be as a result of oxygen's affinity for the electrons produced by the ionization of biomolecules. Molecules other than oxygen also have this chemical property known as electron affinity,[182] including some agents that are not otherwise consumed by the cell. Assuming such an electron-affinic compound is not used by the cell, it should diffuse further from capillaries and reach hypoxic regions of a tumor, and acting in an oxygen-mimetic fashion, sensitize hypoxic cells to radiation.

One class of compounds that represented a realistic tradeoff between sensitizer efficiency and diffusion effectiveness was the nitroimidazoles, which include such drugs as metronidazole, misonidazole, etanidazole, pimonidazole, and nimorazole. The nitroimidazoles consist of a nitroaromatic imidazole ring, a hydrocarbon side chain that determines the drug's lipophilicity, and a nitro group that determines the drug's electron affinity. Misonidazole was extensively characterized in cellular and animal model systems, culminating in its use in clinical trials. Clinical experiences with misonidazole and some of its successor compounds are discussed in Chapter 7.

The relative efficacy of a particular hypoxic cell radiosensitizer is most often described in terms of its sensitizer enhancement ratio (SER), which is a parameter similar in concept to the OER. Whereas the OER is the ratio of doses to produce the same biological endpoint under hypoxic versus aerobic conditions, the SER is the dose ratio for an isoeffect under hypoxic conditions alone versus under hypoxic conditions in the presence of the hypoxic cell sensitizer. Accordingly, if a dose of a sensitizer produces an SER of 2.5 to 3.0 for large single doses

TABLE 1-2 Selected Chemical Modifiers of Radiation Therapy

Chemical Structure	Name (Type of Compound)	Mechanism of Action	Clinic Status
	5-Bromodeoxyuridine (Halogenated Pyrimidine)	Radiosensitizer of rapidly proliferating cells through incorporation into DNA during S phase. Uptake results in decrease or removal of the shoulder of the radiation survival curve.	No clear evidence of clinical efficacy has been established to date. The drug continues to be used in a research setting.
	Misonidazole (2-Nitroimidazole)	Radiosensitizer of hypoxic cells. Principal mechanism of action is mimicry of oxygen's ability to "fix" free radical damage caused by exposure to radiation and some toxic chemicals.	Clinical trial results were disappointing overall, except in selected sites, most notably, head and neck cancer. The drug's failure largely has been ascribed to a dose-limiting toxicity, peripheral neuropathy.
	Tirapazamine (Organic Nitroxide)	Bioreductive drug selectively toxic to hypoxic cells. The drug is reduced to a toxic intermediate capable of producing DNA strand breaks only in the relative absence of oxygen.	Phase II and II clinical trials to date have been disappointing overall, except in select subsets of patients with head and neck or lung cancer. Some trials are still ongoing for the drug combined with radiotherapy and cis-platinum.
	Amifostine (Thiol Free Radical Scavenger)	Radioprotector capable of restituting free radical damage caused by exposure to radiation and some toxic chemicals.	FDA-approved indications for amifostine include protection against the nephro- and ototoxicity of platinum drugs, and to reduce the incidence and severity of xerostomia in patients receiving radiotherapy for head and neck cancer.

of low LET radiation, it can be considered, to a first approximation, as effective as oxygen. This statement can be misleading however, in that the dose of the sensitizer required to produce the SER of 3.0 would be higher than the comparable dose of oxygen and high enough in some cases to preclude its use clinically. Finally, because the primary mechanism of action of the nitroimidazoles is substitution for oxygen in radiation-induced free radical reactions, these drugs need only be present in hypoxic regions of the tumor at the time of irradiation.

Unfortunately, the nitroimidazoles also have characteristics that decrease their clinical usefulness. The hydrocarbon side chain of the molecule determines its lipophilicity, and this chemical property affects the drug's pharmacokinetics, which is a primary determinant of drug-induced side effects.[183] The dose-limiting toxicity of the fairly lipophilic agent misonidazole is peripheral neuropathy, an unanticipated and serious side effect.[140,184] Etanidazole was specifically designed to be less lipophilic[185] in the hopes of decreasing the neurological toxicity. Although this goal was accomplished as a proof of concept, clinical results with etanidazole were otherwise disappointing[186] (see also Chapter 7).

Finally, in considering the prodigious amount of research and clinical effort that has gone into the investigation of hypoxic cell radiosensitizers over the past 50 years, it is difficult not to be discouraged by the predominantly negative results of the clinical trials. However, these negative results have prompted a rethinking of the hypoxia problem and novel approaches to dealing with it, as well as consideration of other factors that may have contributed to the lack of success of the nitroimidazole radiosensitizers.[184] Among the more obvious questions raised include:

1. Did the patients entered on the various clinical trials actually have tumors that contained clonogenic hypoxic cells? At the time of most of these studies, hypoxia markers were not yet available, so it was not possible to triage patients into subgroups in advance of treatment.
2. Do hypoxic cells really matter to the outcome of radiotherapy? If reoxygenation is fairly rapid and complete during radiotherapy, the presence of hypoxic cells before the start of treatment may be of little consequence.
3. Given that the OER is lower for small than for large doses, it follows that the SER would be reduced as well. If so, a benefit in a subgroup of patients might not be readily observed, at least not at a level of statistical significance.

Bioreductive Drugs

In the wake of the failure of most hypoxic cell radiosensitizers to live up to their clinical potential, a new approach to

combating hypoxia emerged: the use of bioreductive drugs that are selectively toxic to hypoxic cells. Although these agents kill rather than sensitize hypoxic cells, the net effect of combining them with radiation therapy is an apparent sensitization of the tumor, resulting from the elimination of an otherwise radioresistant subpopulation. Such drugs have been shown to outperform the nitroimidazole radiosensitizers in experimental studies with clinically relevant fractionated radiotherapy.[187] To the extent that hypoxic cells are also resistant to chemotherapy because of tumor microenvironmental differences in drug delivery, pH or the cell's proliferative status, complementary tumor cell killing might be anticipated for combinations of bioreductive agents and anticancer drugs as well.[188]

Most hypoxia-specific cytotoxic drugs fall into three categories: the nitroheterocyclics, the quinone antibiotics, and the organic nitroxides.[189] All require bioreductive activation by nitroreductase enzymes, such as cytochrome P450, DT-diaphorase, and nitric oxide synthase, to reduce the parent compound to its cytotoxic intermediate, which is typically an oxidizing free radical capable of damaging DNA and other cellular macromolecules. The active species is either not formed or else immediately back-oxidized to the parent compound in the presence of oxygen, which accounts for its preferential toxicity under hypoxic conditions. Examples of nitroheterocyclic drugs with bioreductive activity include misonidazole and etanidazole[190,191] and dual function agents such as RSU 1069.[192] The latter drug is *dual function* because its bioreduction also activates a bifunctional alkylating moiety capable of introducing cross-links into DNA. Mitomycin C and several of its analogs (including porfiromycin and EO9) are quinones with bioreductive activity that have been tested in randomized clinical trials in head and neck tumors (e.g., Haffty et al[193]).

The lead compound for the third class of bioreductive drugs, the organic nitroxides, is tirapazamine (SR 4233, see Table 1-2).[180,181,187] The dose-limiting toxicity for single doses of tirapazamine is a reversible hearing loss; other effects observed include nausea and vomiting and muscle cramps.[194]

Tirapazamine is particularly attractive because it both retains its hypoxia-selective toxicity over a broader range of (low) oxygen concentrations than the quinones and nitroheterocyclic compounds,[195] and its hypoxic cytotoxicity ratio, which is the ratio of drug doses under hypoxic versus aerobic conditions to yield the same amount of cell killing, averages an order of magnitude higher than for the other classes of bioreductive drugs.[188] Laboratory and clinical data also support a tumor sensitizing role for tirapazamine in combination with the chemotherapy agent cisplatinum.[194]

To date, randomized Phase II and III clinical trials with tirapazamine combined with radiotherapy and/or chemotherapy (particularly, cisplatinum) have yielded mixed results[194,196,197]; however, it has improved outcomes for some standard treatments. Although it is disappointing that tirapazamine hasn't made a more significant impact on clinical practice, the search for more effective agents from the same or similar chemical class continues.

Proliferating Cell Radiosensitizers

Another source of apparent radioresistance is the presence of rapidly proliferating cells. Such cells may not be inherently radioresistant, but rather, have the effect of making the tumor seem refractory to treatment because the production of new cells outpaces the cytotoxic action of the therapy.

Analogs of the DNA precursor thymidine, such as bromodeoxyuridine (BrdUdR) or iododeoxyuridine (IdUdR), can be incorporated into the DNA of actively proliferating cells in place of thymidine because of close structural similarities between the compounds. Cells containing DNA substituted with these halogenated pyrimidines are more radiosensitive than normal cells, with the amount of sensitization directly proportional to the fraction of thymidine replaced.[198] In general, the radiosensitization takes the form of a decrease in or elimination of the shoulder region of the radiation survival curve. To be maximally effective, the drug must be present for at least several rounds of DNA replication before irradiation. Although the mechanism by which BrdUdR and IdUdR exert their radiosensitizing effect remains somewhat unclear, it is likely that both the formation of more complex radiation-induced lesions in the vicinity of the halogenated pyrimidine molecules and interference with DNA damage sensing or repair are involved.[199]

The clinical use of halogenated pyrimidines began in the late 1960s, with a major clinical trial in head and neck cancer.[200] In retrospect, the choice of head and neck tumors for this study was far from ideal because the oral mucosa is also a rapidly proliferating tissue and was similarly radiosensitized, causing severe mucositis and a poor therapeutic ratio overall. In later years, tumors selected for therapy with halogenated pyrimidines were chosen in the hopes of better exploiting the differential radiosensitization between tumors and normal tissues.[201] Aggressively growing tumors surrounded by slowly proliferating or nonproliferating normal tissues, such as high-grade brain tumors or some sarcomas, have been targeted for example.[202,203] Later strategies for further improving radiosensitization by BrdUdR and IdUdR involved changing the schedule of drug delivery: giving the drug as a long, continuous infusion both before and during radiotherapy[204] and administering the drug as a series of short, repeated exposures.[205] Overall however, the use of halogenated pyrimidines in the clinic has remained experimental and has not become mainstream.

Chemotherapy Drugs as Radiosensitizers

Several chemotherapy agents have long been known to increase the effectiveness of radiotherapy, despite not being true radiosensitizers like the nitroimidazoles. This has driven the clinical practice of treating many more patients today than in the past with chemotherapy and radiation therapy given concurrently. Two drugs in particular used for chemoradiotherapy are 5-fluorouracil (5-FU, effective against GI malignancies[206]) and cisplatinum (effective against head and neck[207] and cervical cancers[208]).

Based on these clinical successes in combining radiation with concurrent chemotherapy and with ever-increasing numbers of molecularly targeted drugs and biologics available today, it is naturally of interest whether any of these novel compounds could also act as radiosensitizers. Two classes of such drugs already have entered the clinical mainstream as sensitizers: the anti-epidermal growth factor receptor (EGFR) inhibitors and the anti-vascular endothelial growth factor (VEGF) inhibitors. Cetuximab is a monoclonal antibody raised against the EGFR that has been shown to improve outcomes in advanced head and neck cancers when combined with radiation therapy,[209] and bevacizumab, a humanized monoclonal antibody raised against VEGF, prolongs overall and progression-free survival in patients with advanced colorectal cancer when combined with standard chemotherapy.[210] It is hoped that these and other targeted agents will play greater roles in cancer therapy in the future.

Normal Tissue Radioprotectors

Amifostine (WR 2721, see Table 1-2) is a phosphorothioate compound developed by the U.S. Army for use as a radiation protector. Modeled after naturally occurring radioprotective sulfhydryl compounds such as cysteine, cysteamine, and glutathione,[211] amifostine's mechanism of action involves the scavenging of free radicals produced by ionizing radiation, which are radicals that otherwise could react with oxygen and "fix" the chemical damage. Amifostine can also detoxify other

reactive species through the formation of thioether conjugates, and in part because of this, the drug can also be used as a chemoprotective agent.[212] Amifostine is a pro-drug that is dephosphorylated by plasma membrane alkaline phosphatase to the free thiol WR 1065, the active metabolite. As is the case with the hypoxic cell radiosensitizers, amifostine need only be present at the time of irradiation to exert its radioprotective effect.

In theory, if normal tissues could be made to tolerate higher total doses of radiation through the use of radioprotectors, then the relative radioresistance of hypoxic tumor cells would be less likely to limit radiation therapy. However, encouraging preclinical studies demonstrating radioprotection of a variety of cells and tissues notwithstanding,[213,214] radioprotectors like amifostine would *not* be expected to increase the therapeutic ratio unless they could be introduced selectively into normal tissues but not tumors. The pioneering studies of Yuhas et al[177,215,216] addressed this issue by showing that the drug's active metabolite reached a higher concentration in most normal tissues than in tumors and that this mirrored the extent of radio- or chemoprotection. The selective protection of normal tissues results from slower tumor uptake of the drug, and tumor cells being both less able to convert amifostine to WR 1065 (resulting from lower concentrations of the required phosphatases) and to transport this active metabolite throughout the cell.

Dose reduction factors (DRFs, the ratio of radiation doses to produce an isoeffect in the presence versus the absence of the radioprotector) in the range of 1.5 to 3.5 are achieved for normal tissues, whereas the corresponding DRFs for tumors seldom exceed 1.2. Those normal tissues exhibiting the highest DRFs include bone marrow, gastrointestinal tract, liver, testes, and salivary glands.[177] Brain and spinal cord are not protected by amifostine, and oral mucosa is only marginally protected.[177] Comparable protection factors are obtained for some chemotherapy agents, including cyclophosphamide and cisplatin.[217,218] The dose-limiting toxicities associated with the use of amifostine include hypotension, emesis, and generalized weakness or fatigue.[219]

Amifostine is currently indicated for the reduction of renal toxicity associated with repeated cycles of cisplatin chemotherapy in patients with advanced ovarian and non–small cell lung cancer. It is also approved for use in patients receiving radiotherapy for head and neck cancer, in the hopes of reducing xerostomia secondary to exposure of the parotid glands.

Finally, just as there are apparent radiosensitizers, there are also apparent radioprotectors that have the net effect of allowing normal tissues to better tolerate higher doses of radiation and chemotherapy but through mechanisms of action not directly related to the scavenging of free radicals. Various biological response modifiers, including cytokines, prostaglandins (such as misoprostol[220,221]), anticoagulants (such as pentoxifylline[222,223]), and protease inhibitors are apparent radioprotectors because they can interfere with the chain of events that normally follows the killing of cells in tissues by, for example, stimulating compensatory repopulation or preventing the development of fibrosis. Finally, there is also growing interest in the use of biologics that inhibit apoptosis as normal tissue radioprotectors.[224,225] Such agents should have little or no effect on tumor cells, most of which are already resistant to apoptosis.

CLINICAL RADIOBIOLOGY

Growth Kinetics of Normal Tissues and Tumors

In the simplest sense, normal tissues are normal because the net production of new cells, if it occurs at all, exactly balances the loss of old cells from the tissue. In tumors, the production of new cells exceeds cell loss, even if only by a small amount. Although the underlying radiobiology of cells in vitro applies equally to the radiobiology of tissues, the imposition by growth kinetics of this higher level of organizational behavior makes the latter far more complex systems.

Descriptive Classification Systems

Two qualitative classification systems based loosely on the proliferation kinetics of normal tissues are in use. Borrowing heavily from the pioneering work of Bergonié and Tribondeau,[13] Rubin and Casarett's[226] classification system for tissue radiosensitivity consists of four main categories:

Type I or vegetative intermitotic (VM) cells are considered the most radiosensitive and consist of regularly dividing, undifferentiated stem cells, such as are found in the bone marrow, intestinal crypts, and the basal layer of the epidermis of the skin.

Type II or differentiating intermitotic (DIM) cells are somewhat less radiosensitive and consist of transitional cells that are in the process of developing differentiated characteristics, yet are still capable of a limited number of cell divisions. Myelocytes of the bone marrow and spermatocytes of the testis are examples of Type II cells.

Type III or reverting postmitotic (RPM) cells are relatively radioresistant and consist of those few types of cells that are fully differentiated and do not divide regularly, yet under certain conditions can revert to a stem cell-like state and divide as needed. Examples of Type III cells include hepatocytes and lymphocytes, although the latter are unique in that they are a notable exception to the Rubin and Casarett classification system—an RPM cell type that is exquisitely radiosensitive.

Type IV or fixed postmitotic (FPM) cells are the most radioresistant and consist of the terminally differentiated, irreversibly postmitotic cells characteristic of most normal tissue parenchyma, such as neurons and muscle cells. Should such cells be killed by radiation, they typically cannot be replaced.

A second, simpler classification system, based on anatomical and histological considerations, has been proposed by Michalowski.[227] Using this system, tissues are categorized on the basis of whether the tissue stem cells, if any, and the functional cells are compartmentalized (so-called Type H or hierarchical tissues, such as skin, gut epithelium, testis, etc.), or intermixed (Type F or flexible tissues, such as lung, liver, kidney, and spinal cord).

Growth Kinetic Parameters and Methodologies

To predict the response of an intact tissue to radiation therapy in a more quantitative way, a number of kinetic parameters have been described that provide a better picture of the proliferative organization of tumors and normal tissues (Table 1-3).

Growth Fraction

Among the first kinetic characteristics described was the growth fraction (GF). The presence of a fraction of slowly or noncycling cells in experimental animal tumors was first noted by Mendelsohn et al[228,229] and subsequently, in human tumors by others. Although normal tissues don not grow and therefore do not have a growth fraction per se, many are composed of noncycling cells that have differentiated to carry out tissue-specific functions. Some normal tissues do contain a small fraction of actively proliferating stem cells, and others contain apparently dormant or resting cells that are temporarily out of the traditional four-phase cell cycle but are capable of renewed proliferation in response to appropriate stimuli.

TABLE 1-3 Estimated Cell Cycle Kinetic Parameters for Human Tumors

Parameter	Definition	How Measured	Representative Values for Human Solid Tumors	Notes
T_c	(Average) cell cycle time	Percent labeled mitosis technique; flow cytometry	0.5-6.5 days (median ≈ 2.5 days)	T_c in vivo usually longer than for comparable cells cultured in vitro
GF	Growth fraction	Estimated from continuous labeling technique	0.05-0.90 (median ≈ 0.40?)	Difficult to measure directly; not much data available
T_{pot}	Potential doubling time	Flow cytometry (relative movement method: $T_{pot} = \lambda T_s/LI$)	2-19 days (median ≈ 5 days)	$T_{pot} \approx T_c$ as GF approaches 1.0
ϕ	Cell loss factor	$1 - T_{pot}/T_d$	0.30-0.95 (median ≈ 0.90?)	Thought to be the major cause of long T_d for human tumors; particularly high in carcinomas
T_d	Volume doubling time	Direct measurement of tumor dimensions over time	5-650 days (median ≈ 90 days)	Increases with increasing tumor size, often because of increases in Tc and f, and a decrease in GF
T_{eff}/T_p	Effective clonogen doubling time	Estimated from clinical data on the loss of local control with increasing overall treatment time	4-8 days	T_p approaches T_{pot} toward the end of a course of fractionated radiotherapy

Data from Steel GG: Growth kinetics of tumours, Oxford, 1977, Clarendon Press; and Joiner M, van der Kogel A, editors: Basic clinical radiobiology, ed 4. London, 2009, Hodder Arnold.

Lajtha gave these resting but recruitable cells of normal tissues the designation G_0.[230] Although a tumor counterpart of the G_0 cell may or may not exist, the majority of slowly or noncycling tumor cells are thought to be in such a state because of nutrient deprivation, not because of a normal cell cycle regulatory mechanism. Thus, Dethlefsen[231] has suggested that the term *Q cell* be reserved for quiescent cells in tumors to distinguish them from the G_0 cell of normal tissues.

Measurement of a tumor's growth fraction is problematic,[232,233] but an estimate can be obtained with a technique known as continuous thymidine labeling. Using this method, the tumor receives a continuous infusion of radio-labeled thymidine for a period of time long enough for all proliferating cells to have gone through at least one round of DNA synthesis and incorporated the radioactive label. Then, a biopsy of the tumor is obtained and tissue sections prepared for autoradiography. Once the slides are processed and scored, the continuous labeling index, which is that fraction of the total population of tumor cells containing tritiated thymidine, is calculated. This value is a rough estimate of the tumor's growth fraction.

Cell Cycle and Volume Doubling Times

The percent labeled mitosis (PLM) technique of Quastler and Sherman[234] was a key development in the study of the cell cycle in vivo because it provided a unique window into the behavior of that small fraction of cells within a tissue that was actively proliferating. By focusing on cells in mitosis, the assay allowed both the overall cell cycle time (T_c) and the durations of the individual cell cycle phases to be determined without the uncertainties introduced by the presence of noncycling cells in the population. Today, flow cytometric methods have largely replaced the arduous and time-consuming PLM assay.

Briefly, the PLM technique involves tracking a cohort of proliferating cells over time that initially was in S phase (and exposed briefly to tritiated thymidine) and then proceeded through subsequent mitotic divisions. Serial biopsy samples from the tissue of interest are obtained at regular intervals following labeling, and the fraction of cells both in mitosis (identified cytologically) *and* carrying the radioactive label is determined. A first peak of labeled mitoses is observed within 24 hours after labeling, and as cells pass through their second division, a second wave of labeled mitoses is noted. The average T_c for the population of proliferating cells corresponds to the peak-to-peak interval of the resulting PLM curve, a plot of the fraction of labeled mitoses as a function of time following the radioactive pulse. With sufficiently robust data, the durations of the individual cell cycle phases can be obtained as well. The PLM technique is illustrated schematically in Figure 1-25.

Historically, the interpretation of PLM curves was sometimes hampered by technical artifacts and by the fact that proliferating cell populations have distributed cell cycle times.[232,233,235] Despite these limitations, it is clear that most cells in vivo proliferate more slowly than their in vitro counterparts. Although the variation in intermitotic times is quite large, a median value for T_c of 2-3 days is a reasonable estimate.[232]

Although the cycle times of proliferating cells in vivo are long by cell culture standards, they are quite short when compared to the corresponding population or volume doubling times (T_d) for human tumors. Although highly variable from tumor type to tumor type and somewhat difficult to measure, the T_d for human solid tumors averages about 3-4 months.[232] In many cases, sample calculations further suggest that the discrepancy between T_c for proliferating tumor cells and T_d for the tumor as a whole cannot be accounted for solely by the tumor having a low growth fraction.

Cell Loss Factor

Cell kineticists initially adhered to the notion that the continued growth of tumors over time reflected abnormalities in cell production. Pathologists and tumor biologists meanwhile had ample evidence that tumors routinely lost large numbers of cells, which was the result of cell death, maturation, or emigration.[232,236,237] It is now clear that the overall rate of tumor growth, as reflected by its T_d, is governed by the competing processes of cell production and cell loss. In fact, the cell loss factor, ϕ, which is the rate of cell loss expressed as a fraction of the cell production rate, is surprisingly high for both experimental and human tumors, as high as 0.9 or more for carcinomas, and lower, on average, for sarcomas.[232] Cell loss is usually

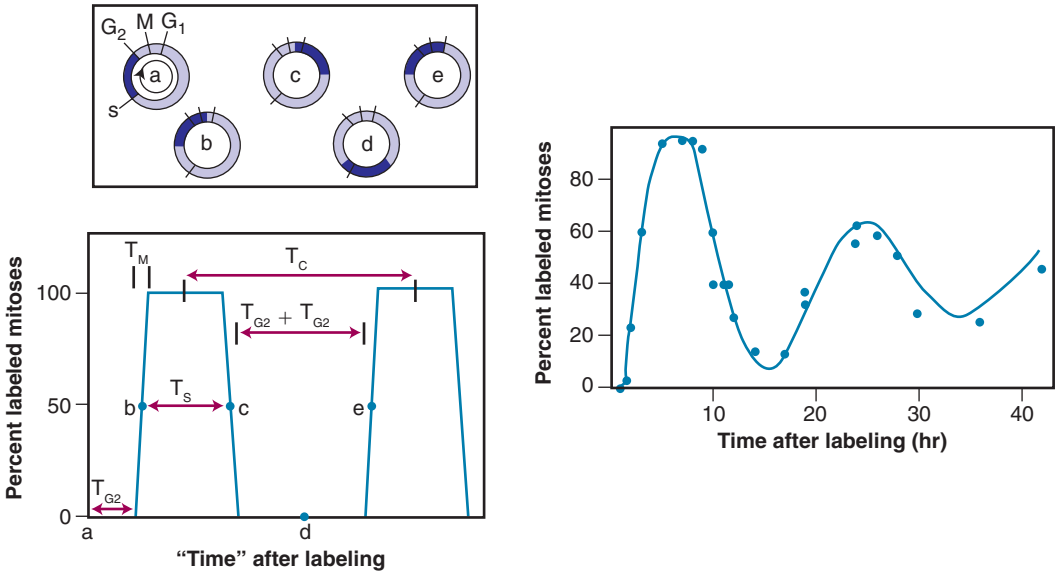


Figure 1-25 The technique of percent labeled mitoses (PLM) for an idealized cell population with identical cell cycle times *(left panels)* and for a representative normal tissue or tumor with a dispersion in cell cycle times *(right panel)*. *Upper left panel*, After a brief exposure to tritiated thymidine or equivalent at time a, the labeled cohort of S-phase cells continues *(dark shading)* around the cell cycle and is sampled at times b, c, d, and e. *Lower left panel*, For each sample, the percentage of cells both in mitosis and containing the thymidine label is determined, and it is plotted as a function of time. From such a graph, individual cell cycle phase durations can be derived. *Right panel*, In this more practical example, a mathematical fit to the PLM data would be needed to calculate the (average) cell cycle phase durations.

the most important factor governing the overall volume doubling time of solid tumors.

The clinical implications of tumors having high rates of cell loss are obvious. First, any attempts at making long-term predictions of treatment outcome based on short-term regression rates of tumors during treatment are misleading. Second, although regression rate may not correlate well with eventual outcome, it may be a reasonable indicator of when best to schedule subsequent therapy, on the assumption that a smaller tumor will be more radio- and chemo-sensitive, as well as easier to remove surgically.

Potential Doubling Time and Effective Doubling Time

With the recognition that cell loss plays a major role in the overall growth rate of tumors and that it can mask a high cell production rate, a better measure of the potential repopulation rate of normal tissues and tumors was needed.[238] One indicator of regenerative capacity is the potential doubling time, or T_{pot}.[232,239] By definition, T_{pot} is an estimate of the time that would be required to double the number of clonogenic cells in a tumor in the absence of cell loss. It follows therefore that T_d will usually be much longer than T_{pot} because of cell loss, and T_c will usually be shorter than T_{pot} because of the presence of non-proliferating cells.[235]

T_{pot} can be estimated from a comparison of the S phase pulse labeling index (LI) and the duration of S phase (T_S) by using the following equation,

$$T_{pot} = \lambda\, T_S / LI$$

where λ is a correction factor related to the nonuniform distribution of cell ages in a growing population (usually, $\lambda \approx 0.8$). T_S and LI can determined by the relative movement method.[239,240] This technique involves an injection of a thymidine analog, usually BrdUrd, which is promptly incorporated into newly synthesized DNA and whose presence can be detected using flow cytometry. The labeled cohort of cells is then allowed to continue movement through the cell cycle, and a biopsy of the tumor is taken several hours later, at which point the majority of the cells containing BrdUrd have progressed into G_2 phase or beyond. A value for LI is determined from the fraction of the total cell population that contains BrdUrd, and T_S is calculated from the rate of movement of the labeled cohort during the interim between injection of the tracer and biopsy.

Values for T_{pot} for human tumors have been measured, and although quite variable, typically range between 2 and 20 days.[232,238,241] These findings lend support to the important idea that slowly growing tumors can contain subpopulations of rapidly proliferating cells. To the extent that these cells retain unlimited reproductive potential, they may be considered the tumor's stem cells (in a generic sense at least) capable of causing recurrences after treatment. These cells represent a serious threat to local control of the tumor by conventional therapies, especially protracted treatments (that provide them additional time to proliferate).

The use of a cell kinetic parameter such as T_{pot} as either a predictor of a tumor's response to therapy or as a means of identifying subsets of patients particularly at risk for recurrence has been attempted, with some positive, but mostly negative, results.[6,139,242] Lest these negative findings suggest that proliferation in tumors is *un*important, bear in mind that it is unlikely that a pretreatment estimate of T_{pot}—or any other single cell kinetic parameter (e.g., LI) for that matter—would be relevant once treatment commences and the growth kinetics of the tumor are perturbed.

One approach to dealing with this problem is to measure proliferative activity *during* treatment. Although not without other limitations, the use of an effective clonogen doubling time (T_{eff} or T_p) has been advocated.[243-245] Estimates of T_p can be obtained from two types of experiments. In an experimental setting, T_p can be inferred from the additional dose necessary to keep a certain level of tissue reaction constant as the overall treatment time is increased. (When expressed in terms of dose rather than time, the proper term would be D_{eff}, although the underlying concept is the same.) For example,

acute skin reactions usually both develop and begin to resolve during the course of radiation therapy, suggesting that the production of new cells in response to injury gradually surpasses the killing of existing cells by each subsequent dose fraction. By intensifying treatment once this repopulation begins, it should be theoretically possible to reach a steady state wherein the tissue reaction remains constant. In a clinical setting, T_p can be estimated from a comparison of tumor control rates for treatment schedules in which the dose per fraction and total dose used were held approximately constant, but the overall treatment time varied. In some cases, the rate of loss of local control with increasing overall treatment time provides an estimate not only of T_p but also of the delay time before the repopulation begins, sometimes referred to as T_k, which is the repopulation kickoff time.[246-248]

Repopulation in Tumors and Normal Tissues

As discussed previously, both normal tissues and tumors are capable of increasing their cell production rate in response to depopulation caused by radiation exposure, a process known as regeneration or repopulation. The time of onset of the regenerative response varies with the turnover rate of the tissue or tumor because cell death (and depopulation) following irradiation is usually linked to cell division. Generally, tissues that naturally turn over fairly rapidly repopulate earlier and more vigorously than tissues that turn over slowly. However, it has been shown that the repopulation patterns of normal tissues and tumors following the start of irradiation tend to be characterized by a delay (of at least several weeks in many cases; see T_k discussion) before the rapid proliferative response.[246-248] Once this proliferative response begins, however, it can be quite vigorous. Although this is clearly desirable for early-responding normal tissues attempting to recover from radiation injury, rapid proliferation in tumors is certainly counterproductive.[249] For example, clinical studies of local control of head and neck tumors indicate that an average of about 0.6 Gy per day is lost to repopulation.[243] Unfortunately, attempts to counteract this accelerated proliferation by dose intensification during the latter part of a treatment course can be problematic because late-responding normal tissues do not benefit from accelerated repopulation during treatment and risk incurring complications.

Increased cell production in response to injury is thought to occur by one or more of three basic mechanisms: a decrease in the cell loss rate, a shortening of the cell cycle time, or an increase in the growth fraction.[57,232] Normal tissues are capable of using at least the latter two strategies to accelerate repopulation. It is still not clear how, when, and to what extent tumors accelerate their proliferation in response to cell killing. Laboratory and clinical findings suggest that a decrease in cell loss may be a major mechanism, possibly as a consequence of resistance to apoptosis, which is a hallmark of most types of cancer.[244,250,251] This is a provocative finding in that it suggests that there may be a fundamental—and potentially exploitable—difference in the way normal and tumor tissues respond to ionizing radiation.

Early and Late Effects in Normal Tissues

Early versus Late

Normal tissue complications observed following radiation therapy are the result, either directly or indirectly, of the killing of critical target cells within the tissue that are crucial to the tissue's continued functional or structural integrity. The loss of these target cells can occur either as a direct consequence of the cytotoxic action of the radiation or indirectly as a result of the radiation injury or killing of other cells. In some cases, the tissue's response to the depletion of its component cells can exacerbate the injury, for example, when a hyperproliferation of fibroblasts and the resulting collagen deposition replace a tissue's parenchymal cells, resulting in fibrosis.

It is important to realize that a particular tissue or organ may contain more than one type of target cell, each with its own radiosensitivity. One tissue may manifest more than one complication following radiation therapy, with the severity of each determined by the radiosensitivity of the particular target cell and the time-dose fractionation schedule employed. It follows from this that the severity of one complication does not necessarily predict for the severity of another complication, even within the same tissue (although consequential late effects secondary to severe early reactions are possible in some cases[252]). For example, dry or moist desquamation of the skin results from the depletion of the basal cells of the epidermis, fibrosis results from damage to dermal fibroblasts, and telangiectasia results from damage to small blood vessels in the dermis. For many tissues however, the target cell(s) whose death is (are) responsible for a particular normal tissue injury remain unclear.

Although the radiosensitivity of the putative target cells determines the severity of an early or late effect in a normal tissue, the earliness or lateness of the clinical manifestation of that injury is related to the tissue's proliferative organization (discussed previously). The distinction between the radiosensitivity of a tissue's cells and the radioresponsiveness of the tissue as a whole can be a source of confusion. Bergonié and Tribondeau's laws,[13] for example, confused the concepts of radiosensitivity and radioresponsiveness to some extent, referring to tissues that responded to damage early as radiosensitive, when this was not necessarily the case.

Whole-Body Radiation Syndromes

Many human beings have been exposed to total body irradiation, including the survivors of Hiroshima and Nagasaki, Polynesian Islanders and military personnel present during aboveground nuclear tests during the 1950s, and victims of accidental exposures in the workplace (including Chernobyl, and possibly, Fukushima). Of the latter, about 100 fatalities resulting from radiation accidents have been documented since the mid-1940s.[253-255]

The whole-body radiation syndromes are considered early effects of radiation exposure because, for sufficiently high doses, death occurs within weeks after irradiation. The clinical syndromes described herein only occur when most or all of the body is irradiated. Also, although total body irradiation (TBI) is a prerequisite for the manifestation of these syndromes, neither the dose received nor its biological consequences are necessarily uniform. The radiosensitivities of the respective target cells determine the effective threshold dose below which the syndrome does not occur, whereas the onset time of individual symptoms is governed more by the proliferative organization of the tissue.

The mean lethal dose or LD_{50} is defined as the (whole body) dose that results in mortality for 50% of an irradiated population. The LD_{50} value is often expressed in terms of the time scale over which the deaths occur, such as at either 30 or 60 days after irradiation. For humans, the single-dose $LD_{50/60}$ for x- or γ-rays is approximately 3.5 Gy in the absence of medical intervention and about twice that with careful medical management.[28,255] The LD_{50} increases with decreasing dose rate of low LET radiation and decreases for radiations of higher LET.

The Prodromal Syndrome

The prodromal syndrome consists of one or more transient, neuromuscular and gastrointestinal symptoms that begin soon after irradiation and persist for up to several hours. The symptoms, which can include anorexia, nausea, vomiting,

diarrhea, fatigue, disorientation, and hypotension, and their severity and duration, increase with increasing dose. Because in most radiation accident situations the dose victims received is unknown initially, careful attention to the prodromal syndrome can be used as a crude dosimeter.

The Cerebrovascular Syndrome

The cerebrovascular syndrome occurs for total body doses in excess of 50 Gy. The onset of signs and symptoms is almost immediate following exposure, consisting of severe gastrointestinal and neuromuscular disturbances including nausea and vomiting, disorientation, ataxia, and convulsions.[28,255] The cerebrovascular syndrome is invariably fatal, and survival time is seldom longer than about 48 hours. Only a few instances of accidental exposure to such high doses have occurred, two of which (a nuclear criticality accident at Los Alamos National Laboratory in 1958, and a ^{235}U reprocessing plant accident in Rhode Island in 1964) have been extensively documented in the medical literature.[256,257]

The immediate cause of death for the cerebrovascular syndrome is likely vascular damage leading to progressive brain edema, hemorrhage, or cardiovascular shock.[255] Following such high doses delivered acutely, even cells traditionally considered radioresistant, such as neurons and the parenchymal cells of other tissues and organs, will be killed, as well as the more radiosensitive vascular endothelial cells and the various glial cells of the central nervous system.

The Gastrointestinal Syndrome

For doses upward of about 8 Gy, the gastrointestinal syndrome predominates, characterized by lethargy, vomiting and diarrhea, dehydration, electrolyte imbalance, malabsorption, weight loss, and ultimately, sepsis. These symptoms begin to appear within a few days of irradiation and are progressive in nature, culminating in death after 5 to 10 days. The target cells for the gastrointestinal syndrome are principally the crypt stem cells of the gut epithelium. As mature cells of the villi are lost over a several-day period, no new cells are available to replace them, so the villi begin to shorten and eventually become completely denuded. This greatly increases the risk of bleeding and sepsis, both of which are aggravated by declining blood counts.

Before the Chernobyl accident, in which approximately a dozen firefighters received total doses sufficient to succumb to the gastrointestinal syndrome, there was only one other documented case of a human dying of gastrointestinal injury.[28,255] To date, no human has survived a documented whole-body dose of 10 Gy of low LET radiation.

The Hematopoietic Syndrome

Acute doses of approximately 2.5 Gy or more are sufficient to instigate the hematopoietic syndrome, which is a consequence of the killing of bone marrow stem cells and lymphocytes. This syndrome is characterized by a precipitous (within a day or two) reduction in the peripheral blood lymphocyte count, followed by a more gradual reduction (over a period of 2 to 3 weeks) in the numbers of circulating leukocytes, platelets, and erythrocytes. The granulocytopenia and thrombocytopenia reach a maximum within 30 days after exposure, and death, if it is to occur, is usually a result of infection or hemorrhage.[28,255] Theoretically, the use of antibiotics, blood transfusions, and bone marrow transplantation can save the lives of individuals who receive doses at or near the LD_{50}. In practice however, the exact dose is seldom known and should it be high enough to reach the threshold for the gastrointestinal syndrome, such heroic measures would be in vain. Unfortunately, this was the case for all but 2 of the 13 Chernobyl accident victims who received bone marrow transplants.[28] Of the two survivors, only one can rightfully be claimed as having had his life saved by the transplant; the other survivor showed autologous bone marrow repopulation.

Teratogenesis

One of the most anxiety-provoking risks of irradiation in the eyes of the general public is prenatal exposure of the developing embryo or fetus.[254,255] In part, such concern is warranted because teratogenic effects are quite sensitive to induction by ionizing radiation, with readily measurable neurological abnormalities noted in individuals exposed prenatally to doses as low as approximately 0.06 Gy.[28] The radiation-induced excess relative risk of teratogenesis during the most sensitive phase of gestation is approximately 40% per Gy.[28] (By comparison, the spontaneous incidence of a congenital abnormality occurring during an otherwise normal pregnancy is about 5% to 10%.[255])

Information on the teratogenic effects of radiation in humans come from two major sources, the Japanese atomic bomb survivors and patients who received diagnostic or therapeutic irradiation either before the establishment of modern radiation protection standards or in clinical emergency situations. Although a range of abnormalities have been identified in individuals irradiated in utero (including anecdotal reports of miscarriages and stillbirths, cataracts and other ocular defects, gross malformations, sterility, etc.), the most commonly reported are microcephaly, mental retardation, other, more subtle neurological defects, and growth retardation.[28,254,255] Each of these teratogenic effects has a temporal relationship to the stage of gestation at the time of irradiation, as well as a radiation dose and dose rate dependency. Lethality is the most common consequence of irradiation during the preimplantation stage (within 10 days of conception), growth retardation has been noted for irradiation during the implantation stage (10 to 14 days after conception), and during the organogenesis period (about 15 to 50 days after conception), the embryo is sensitive to both lethal, teratogenic, and growth retarding effects.[255] Radiation-induced gross abnormalities of the major organ systems do not occur during the fetal period (more than 50 days after conception), although generalized growth retardation and some neurological defects have been noted for radiation doses in excess of 1 Gy.

Radiation-Induced Cataracts

Late effects resulting from irradiation of the eye were noted within a few years of the discovery of x-rays,[226,255] with cataracts being the most frequent pathological finding. From a clinical perspective, the induction of a cataract following radiotherapy is a normal tissue complication that can be corrected surgically, and as such, is not considered quite as dire as other late effects. In addition, some radiation-induced lens opacities are subtle and do not interfere with vision. From a radiobiologic perspective, however, cataracts are unique among the somatic effects of radiation in several respects. First, although the lens of the eye is a self-renewing tissue complete with a stem cell compartment of epithelial cells that divide and gradually differentiate into mature lens fibers, there appears to be no clear mechanism of cell loss.[28] As such, the primitive cells damaged by radiation (which manifest themselves as abnormal, opaque lens fibers) persist, eventually leading to a cataract. Second, radiation-induced cataracts are among the few lesions that *can* be distinguished pathologically from their spontaneously occurring counterparts; radiation-induced cataracts first appear in the posterior pole of the lens, whereas spontaneous cataracts usually begin in the anterior pole.[258] Third, radiogenic cataracts exhibit a variable latency period (anywhere from about one year to several decades) that decreases with increasing radiation dose. Finally,

cataract formation is a nonstochastic (deterministic) process; that is, there is a threshold dose below which no cataracts occur, but above the threshold, the severity of the cataract increases with increasing dose.[258] For low LET radiation, the single-dose threshold for cataractogenesis in humans is approximately 2 Gy, and this increases to about 4 Gy for fractionated exposures. Neutrons are also known to be quite effective at inducing cataracts, with RBEs of about 5 to 10 commonly observed in laboratory rodents.[255]

Radiation Carcinogenesis

Unrepaired or mis-rejoined DNA damage caused by radiation exposure is usually lethal to the cell, although this is not invariably the case, particularly when the genetic material is simply rearranged rather than deleted. Whether such changes have further implications for the cell bearing them depends on the location of the damage in the genome, the nature and extent of the mutational event, whether working copies of proteins can still be produced from the gene or genes involved, what function these proteins normally have, and the type of cell. There is compelling evidence that some of these radiation-induced genetic rearrangements—particularly ones that activate oncogenes or inactivate tumor suppressor genes—either alone or in combination with other such changes, predispose a cell to neoplastic transformation, a necessary early step in the process of tumor induction.[254,259]

Laboratory Studies

Although ionizing radiation is one of the most studied and best understood carcinogens, it is not a particularly potent one. This fact hampers studies of radiation carcinogenesis in humans because the investigator must identify a modest radiogenic increment of excess risk with a long latency period against a high background spontaneous cancer rate and multiple confounding factors. Nevertheless, from a public health perspective, carcinogenesis is the most important somatic effect of radiation for doses of 1.5 Gy or less.[28]

The use of cell cultures and laboratory rodents to study carcinogenesis avoid some of the pitfalls of human epidemiological studies but have their own inherent limitations. Cell culture systems employ neoplastic transformation as the endpoint, which is a prerequisite for, but by no means equal to, carcinogenesis in vivo. Neoplastic transformation is defined as the acquisition of one or more phenotypic traits in nontumorigenic cells that are usually associated with malignancy, such as immortalization, reduced contact inhibition of growth, increased anchorage-independent growth, reduced need for exogenously supplied nutrients and growth factors, various morphological and biochemical changes, and in nearly all cases, the ability to form tumors in histocompatible animals.[235] Such systems can be used to study relatively early events in the carcinogenesis process, have much greater sensitivity and statistical resolution than in vivo assays, and can be used to measure dose-response relationships. Laboratory animal studies however are considered more relevant in that tumor formation is the endpoint, latency periods are shorter, statistical variability is reduced, and the carcinogen exposure conditions can be carefully controlled.

Pertinent results from laboratory studies of radiation carcinogenesis include:

1. Carcinogenesis is a stochastic effect, that is, a probabilistic function of the dose received, with no evidence of a dose threshold. Increasing the radiation dose increases the probability of the effect but not its severity.[254,259]
2. The neoplastic transformation frequency increases with dose, at least over the low-dose range (about 1.5 Gy or less).
3. There is a dose rate effect for transformation and carcinogenesis (for low LET radiations); protracted exposures carry a reduced risk relative to acute exposures.
4. The processes of neoplastic transformation and carcinogenesis are necessarily in competition with the cell killing effects of ionizing radiation.[28] As such, dose-response curves for tumor formation in vivo tend to be bell-shaped as a function of dose (e.g., Upton[260]). In vitro, where cytotoxicity can be assessed separately from transformation and appropriate corrections made, dose-response curves tend to be linear.

Epidemiological Studies in Humans

In humans, most of the information useful for risk estimation is derived from epidemiological studies, with the dose almost always exceeding 0.1 Gy, and often, exceeding 1.0 Gy. However, most of the controversy concerns doses less than 0.1 Gy, delivered over protracted, rather than acute, time periods. Therefore, to infer low-dose effects from high-dose data, epidemiologists make extrapolations and assumptions about dose-response relationships that may or may not be valid in all cases.

Many sources of error can also plague epidemiological data, including selection bias, small sample size, heterogeneous population characteristics, and dose uncertainties.[255] The human populations that have been, and continue to be, evaluated for radiation-induced excess cancers are Japanese atomic bomb survivors, persons exposed to fallout from nuclear tests or accidents, radiation workers receiving occupational exposure, populations living in areas characterized by above-average natural background radiation, or in proximity to artificial sources of radiation, and patients exposed to repeated diagnostic or therapeutic radiation. Pertinent findings from these studies include:

1. Within the limits of statistical resolution, the shape of the dose response curve is *not inconsistent* with a linear, no threshold model.[254,259]
2. Different tissues have different sensitivities to radiation-induced carcinogenesis, with bone marrow (leukemias other than chronic lymphocytic), breast (female), salivary glands, and thyroid the most susceptible, followed by colon, stomach, lung, ovary, and skin.[255]
3. The latency period between irradiation and the clinical presentation of a solid tumor averages 20 years or more and about half that for hematological malignancies. However, the latency period varies with the age of the individual, generally increasing with decreasing age at exposure.
4. Two risk-projection models have been used to predict the risk of radiation carcinogenesis in the human population: the absolute risk model and the relative risk model. Using the absolute risk model, excess risk in an irradiated population begins after the latency period has passed and is *added* to the age-adjusted spontaneous cancer risk. After a period of time, the cancer risk returns to spontaneous levels. The relative risk model predicts that the excess cancer risk is a *multiple* of the spontaneous incidence. It remains debatable which model is the most appropriate for estimating the excess cancer risk.[255] At present, the epidemiological data tend to support the relative risk model for most solid tumors and the absolute risk model for leukemia.
5. The current recommendations of the International Commission on Radiological Protection (ICRP) state that the nominal probability of radiation-induced cancer death is approximately 4% per Sievert (Sv) for working adults and about 5% per Sv for the whole population, under conditions of chronic, low-dose exposure.[261] These risk estimates double for acute, high-dose exposures. The Sv is a unit of dose equivalent used for radiation protection purposes and

is equal to the radiation dose (in Gy) multiplied by a quality factor specific for the type of radiation (with the quality factor roughly equivalent to the radiation's RBE).

Carcinogenic Risk from Prenatal Irradiation

The risk of carcinogenesis as a result of prenatal radiation exposure is made even more controversial by conflicting results of epidemiological studies. One major study cohort consisted of several thousand children (plus a demographically similar population of unirradiated children) who received prenatal exposure from diagnostic procedures during the 1950s and 1960s. The Oxford Survey of Childhood Cancer[262] reported nearly twice the incidence of leukemia in children who had received prenatal irradiation. Although other epidemiological studies lend credence to the Oxford Survey's findings,[254,259] it is still unclear whether factors other than the x-ray exposure may have caused, or at least contributed to, the excess cancer risk. Other studies, particularly from the Japanese A-bomb survivors who were pregnant at the time of the bombing, did not support the Oxford Survey's findings of increased risk of childhood malignancy but did support an increased risk of malignancy later in life.[28]

On the assumption that it is preferable to overestimate risk than underestimate it, it is prudent to assume that the carcinogenic risk of radiation exposure to the embryo or fetus is about twice that for postnatal exposure.

Carcinogenic Risk from Medical Imaging Procedures

Recent data gleaned from the Japanese A-bomb survivors indicate a small but statistically significant excess cancer risk even for doses as low as 35 to 150 mSv.[263,264] That this is in the range of doses delivered during a CT scan—in particular, a pediatric CT scan[265,266]—has made the headlines and both sparked controversy[267] as well as increased awareness[268] of radiation's risks. Estimates are that an abdominal helical CT scan of a pediatric patient results in a risk of a fatal cancer later in life of approximately one in a thousand.[264]

A small risk of radiation carcinogenesis from a CT scan may seem trivial, especially to the radiation oncologist who typically delivers more than ten times that dose to a patient each day (albeit not to the whole body). Nevertheless, the finding of a radiation-induced excess cancer risk associated with a medical imaging procedure whose use has skyrocketed over the past 35 years,[264] certainly has the makings of a public health issue. Currently, more than 70 million CT scans are performed annually in the United States.[264] That disproportionately, this increase in CT scanning has been in a pediatric population both inherently more sensitive to ionizing radiation *and* with the longest life span in which to express those radiation-induced malignancies, is all that much more concerning.

Because of this, radiation oncologists, as de facto experts on the health and medical effects of ionizing radiation, should be willing to serve as educators of the public as to both the benefits and risks associated with the common procedures they employ.

Early and Late Effects Following Radiotherapy

It is not the intent of this section to provide either an exhaustive review of the various histopathological changes observed in the irradiated normal tissues of radiation therapy patients, but the reader is referred to several textbooks and pertinent review articles on the subject (e.g., Rubin et al,[226] Mettler et al,[255] Fajardo[269]). This section will focus instead on recent developments that promise to increase our understanding of the etiology of normal tissue injury, and hopefully, provide clues as to how to decrease or even prevent their occurrence.

Molecular Cascades and Cytokines

As mentioned previously, the early and late effects that occur in irradiated normal tissues result directly or indirectly from the killing of critical target cells. Although this statement is true in a general sense, it is clearly an oversimplification of what is now known to be a highly complex and dynamic process of cellular signaling, radiation-induced gene expression, multiple modes of cell death, and compensatory proliferative responses. Cytokines and growth factors, inducible proteins released by irradiated tissues that stimulate other cells to produce a biological response, participate in some of these processes. Although produced locally within the irradiated volume and intended to influence the behavior of cells in the same tissue, some cytokines also enter the circulation and can stimulate cells distant from the irradiated site.

For example, the radiation-inducible cytokines interleukin-1 (IL-1) and tumor necrosis factor (TNF), released by leukocytes and tumor cells, alter the growth of hematopoietic progenitor cells, stimulate the growth of vascular endothelial cells, and induce collagen deposition.[270,271] These same molecules are involved in the acute inflammatory response often noted in irradiated tissues, and along with ICAM-1, an intracellular adhesion molecule, in the changes in vascular permeability that lead to edema. Lung irradiation results in the expression of TNF, several interleukins, transforming growth factor-β (TGF-β) and basic fibroblast growth factor (bFGF), all of which are involved in acute radiation pneumonitis or late fibrosis.[272,273] Finally, TNF, bFGF, and platelet-derived growth factor (PDGF) are associated with aberrant growth of cells within blood vessels. These proteins are induced in the vascular endothelium to stimulate cell proliferation and minimize radiation-induced apoptosis.[274]

Functional Subunits and Volume Effects

Radiation oncologists traditionally reduce the total dose when the irradiation field involves a large volume of normal tissue. Although this practice evolved empirically, the biological basis for decreasing normal tissue tolerance with increasing irradiation volume remains unclear. Withers[238,275] proposed a descriptive model for the pathogenesis of radiation injury in normal tissues based on the structural and functional organization of the tissue at risk for a complication. Conceptually, tissues are considered to be organized into functional subunits (FSUs), which can be inactivated by radiation exposure secondary to the killing of their constituent target cell(s). These FSUs may be anatomically defined, such as the nephron of the kidney or the lobule of the liver, or anatomically undefined (skin, nervous system).[28] The main difference between the two is that surviving target cells from surrounding FSUs have the potential to migrate and help repopulate anatomically undefined FSUs, but not anatomically defined ones, presumably because of the lack of any structural demarcation. This could have the net effect of making anatomically undefined FSUs able to tolerate higher radiation doses.

Whether the inactivation of one or more FSUs impacts the overall tissue function (in the form of a radiation-induced complication) depends on how many of the tissue's FSUs are in the irradiation field and their spatial arrangement. The spinal cord responds to changing irradiation volume as if its corresponding FSUs are arranged in series. There is a steep reduction in the tolerance dose for white matter necrosis of the rat spinal cord with increasing treatment volume for small radiation fields (up to about 2 cm exposed cord length), but little or no volume dependence for larger treatment fields, presumably because inactivation of one FSU inactivates the entire cord.[139] The lung on the other hand, seems to have a large functional reserve, and it is only when much larger

volumes are irradiated, and correspondingly large numbers of FSUs inactivated, that a functional deficit develops. This is more in keeping with a tissue whose functional subunits operate relatively independently and are arranged in parallel. Some other organs are believed to behave as if they have both serial and parallel components.

One immediate clinical implication for tissues with parallel versus serially arranged FSUs is that a small dosimetric hotspot would be relatively innocuous for a parallel tissue but potentially catastrophic for a serial tissue.

Reirradiation Tolerance

A common problem that radiation oncologists face is whether or not to risk reirradiation of a previously treated site. If a decision is made to retreat, even in the most ideal case in which the previous treatment course is well-documented and the treatment fields still identifiable, the clinician is nevertheless left with the uncertainty of what time, dose, and fractionation pattern to use.

Radiobiological research in this area has been slow in coming (given the nature of studies involving late effects), but some progress has been made and some of the factors thought to be important in normal tissue tolerance to retreatment have been identified. These include whether the initial treatment course was to "full tolerance" or not, the likelihood that residual damage from the first treatment course has persisted, the amount of time that has elapsed between the first course and the second, the target volume to be reirradiated compared to the original target volume, and the structural and function makeup of the tissue at risk.

A few general concepts are beginning to emerge from studies with laboratory rodents (for reviews, see Joiner et al,[139] Travis et al,[276] Thames et al[277]):

1. For rapidly proliferating tissues such as skin, bone marrow, or testis, recovery following the first course of treatment is rapid, such that the tissue can be reirradiated to near the full tolerance dose within about 2-3 months.
2. Some slowly proliferating tissues such as spinal cord and lung are capable of more limited long-term recovery after the first course of treatment and can be retreated to a partial (50% to 75%) tolerance dose, with the dose generally increasing the longer the time between the two treatments (3 to 6 months minimum).
3. Other slowly dividing tissues like bladder seem to show permanent, residual injury from the first treatment, such that the total dose for a second course must be reduced by at least half, regardless of how much time has elapsed between treatments. In addition, there is evidence that complications arising from retreatment tend to occur much earlier (relative to the second treatment) than they would have from a single treatment.
4. One apparent exception to this type of classification system is the kidney, for which retreatment tolerance decreases with time between the first and second treatment courses.

A model that is consistent with these observations suggests that target cells that survive the initial treatment course have three possible fates. Some may regenerate their numbers over time, making the tissue as a whole better able to tolerate a second treatment, with the rate of regeneration determining how much time should elapse between the two treatments and what total dose can be delivered safely during the second course. Other target cells may maintain a steady state number of survivors after the first treatment, and therefore, the tissue would appear to harbor residual damage and never be able to tolerate a full second course of radiation therapy. Finally, some target cells may undergo continued depletion after the first treatment, such that tolerance to a second treatment course will actually decrease the longer the time between treatments. This may be related to a progressive expression of otherwise subclinical residual damage from the initial treatment.

Radiation-Induced Second Malignancies

With increasing numbers of long-term cancer survivors, the risk of second malignancies arising as a consequence of prior treatment becomes significant. Leukemia is thought to account for about 20% of second malignancies, with the remainder presenting as solid tumors in and around the previously irradiated site.[278,279] Certain subpopulations of patients previously treated are at an even higher risk than the majority and deserve special attention, including children and young adults, those with a known genetic predisposition to cancer, immunocompromised individuals, and those with known exposure to other carcinogens (such as chemotherapy). For example, large epidemiological studies have assessed the breast and lung cancer risk in Hodgkin's lymphoma survivors,[280,281] leukemia and sarcomas in cervical cancer survivors,[282] and sarcomas in long-term survivors of childhood retinoblastoma.[283]

A final concern with respect to radiation-induced second malignancies is the growing use of highly conformal, intensity-modulated radiation therapy, designed specifically to deliver lower doses to normal tissues immediately surrounding the tumor but at the expense of leaked or scattered dose to larger volumes of the body.[284] Such conditions—large volumes and low doses—tend to be those most associated with radiation carcinogenesis.

Dose Rate and Dose Fractionation Effects

Although the sparing effects of fractionated, external beam radiotherapy and brachytherapy are assumed to be a result of the repair of SLD, other factors may be involved as well, most notably, repopulation. In the isoeffect relationship derived by Strandqvist,[24] however, the time factor included both the effects of dose fractionation (presumably, the result of SLDR) and overall treatment time (presumably, repopulation). It was not until 1963 that Fowler et al[89,130,285] attempted to separate the contributions of these two factors by performing fractionation experiments with pig skin. In their experiments, five equal fractions were given in overall treatment times of either 4 or 28 days, and three different-sized doses per fraction were used to make sure that at least one of them would result in a measurable level of early skin reaction. In changing from an overall time of 4 days to 28 days, only an additional 6 Gy was required to reach the same level of skin response. This was thought to reflect the contribution of overall time (i.e., repopulation) to the isoeffect total dose because the size and number of fractions was kept constant. In a parallel series of experiments in which the overall time was kept constant (28 days), but the number of fractions was increased from 5 to 21, it was found that an additional 13 Gy was required to reach the skin isoeffect level. This increase was almost as great as the 16 Gy additional dose required when changing from a single-dose treatment to a treatment protocol of five fractions in 4 days, implying that the change in fraction number was more important than the change in the overall treatment time.

During the 1960s and 1970s, dose rate effects were studied extensively. The clinical community was also becoming more attuned to the biological underpinnings of radiation therapy, especially the "Four R's of Radiotherapy": repair, reoxygenation, redistribution, and repopulation.[286] These are considered key radiobiological phenomena that influence the outcome of multifraction radiotherapy.

Bedford and Hall[287,288] generated in vitro survival curves for HeLa cells irradiated at various dose rates between about 0.1 Gy per hour and 7.3 Gy per minute. The killing effectiveness per unit dose decreased as the dose rate was reduced,

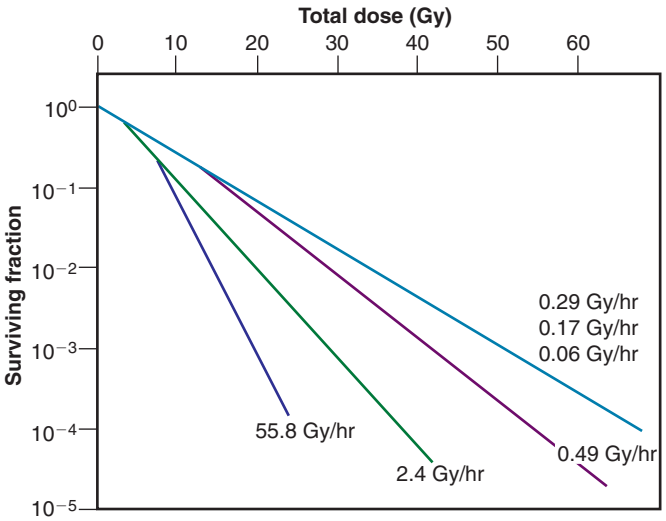


Figure 1-26 The dose rate effect for nonproliferating C3H 10T1/2 mouse cells maintained in vitro. As the dose rate decreases from about 56 to 0.3 Gy/hr, survival curves become progressively shallower, reflecting the repair of radiation damage during the continuous irradiation interval. For dose rates less than about 0.3 Gy/hr, no further sparing effect of dose protraction is observed, suggesting that there is an effective limit to the repair-dependent dose rate effect. This is considered compelling evidence that cell survival curves have nonzero initial slopes.
Adapted from Wells R, Bedford J: Dose-rate effects in mammalian cells. IV. Repairable and nonrepairable damage in non-cycling C3H 10T1/2 cells. Radiat Res 94:105, 1983.

TABLE 1-4 Recovered Dose as a Function of Dose per Fraction for Skin Reactions in Human Radiotherapy Patients

Single Dose (D_s)	Split Dose (2 D_i)*	Recovered Dose ($D_r = 2D_i - D_s$)
15 Gy	2 × 8.5 Gy	2 Gy
13 Gy	2 × 7.5 Gy	2 Gy
8 Gy	2 × 5.5 Gy	3 Gy
6 Gy	2 × 4 Gy	2 Gy
3.5 Gy	2 × 2 Gy	≤0.5 Gy

Data from Dutreix J, Wambersie A, Bounik C: Cellular recovery in human skin reactions: application to dose fraction number overall time relationship in radiotherapy. Eur J Cancer 9:159-167, 1973.
**Interfraction interval (i) was 6 hours.*

however, a limit to this dose rate or dose fractionation effect was reached under conditions in which cell cycle and proliferative effects were eliminated by the use of lower temperatures[289] or by growing cells to plateau phase before irradiation[290-292] (Figure 1-26).

Similar conclusions about the nature of dose rate and dose fractionation effects were reached from clinical studies. Dutreix et al[293] studied dose fractionation effects in human skin under conditions where cell cycle and proliferative effects were minimized (i.e., short interfraction intervals and overall treatment times). Their data indicated that the incremental dose recovered as a result of SLDR when a single dose was replaced by two equal fractions became small when the size of the dose per fraction dropped below approximately 2 Gy (Table 1-4). This finding is consistent with the hypothesis that survival curves have negative (rather than zero) initial slopes, and therefore, that a limit to the repair-dependent dose fractionation effect should be reached for smaller and smaller-sized dose fractions or dose rates. Accordingly, these authors cautioned that isoeffect equations in common clinical use at the time (the NSD model—see discussion in this chapter) would be inaccurate for predicting tolerances when doses per fraction were quite small. Further, small differences in the initial slopes of survival curves for different cell types could be magnified into large differences in the limiting slopes for continuous or multifraction survival curves.

Time-Dose-Fractionation Relationships

The NSD Model

Based on Strandqvist's isoeffect curves,[24] Fowler and Stern's pig skin experiments,[89,285] and other laboratory and clinical findings,[23] Ellis[294,295] formulated the NSD concept in 1969. The NSD equation, $D = (NSD)\ N^{0.24}\ T^{0.11}$, where D is the total dose delivered, N the number of fractions used, T the overall treatment time, and NSD the nominal standard dose (a proportionality constant thought to be related to the tolerance of the tissue being irradiated), became widely used for the design of biologically equivalent treatment schedules, particularly when its more mathematically convenient derivatives, such as the TDF[296] or CRE[297] equations became available.

The introduction of the NSD equation theoretically allowed radiotherapy treatment practices worldwide to be compared and contrasted with respect to putative biological equivalence. It also permitted the calculation of dose equivalents for split-course treatments and brachytherapy and provided a means of revising treatment prescriptions in the event of unforeseen treatment interruptions. Because the NSD formula was based on observations of early-onset radiation effects, it was quite useful as a predictor of some tissue tolerances, as long as it was not used for treatments involving extremes of fraction number or overall time.

On the other hand, the NSD formula was ill-equipped to deal with some clinical problems, particularly the prediction of late effects in normal tissues (especially at nonstandard doses per fraction), and the patterns of repopulation in normal tissues and tumors.[241] The use of a fixed exponent for the overall time component, T, gave the false impression that extra dose to counteract proliferation would be needed from the outset of treatment, rather than after a delay of several weeks, which is what is observed in practice (e.g., Joiner et al,[139] Denekamp[298]).

In light of the growing frustration with the NSD model, and research at the time focusing on the shape of the shoulder region of cell survival curves and the nature of dose rate and dose fractionation effects, new, radiobiologically based approaches to isoeffect modeling were developed during the late 1970s and early 1980s.

The Linear-Quadratic Isoeffect Model

In ambitious multifraction experiments using laboratory rodents in which a broad range of fraction sizes and interfraction intervals was used, Douglas and Fowler[299] developed a novel method of data analysis in which they interpreted their resulting isoeffect curves in terms of the shape of the underlying dose-response curves for the putative target cells. Because overall treatment times were kept quite short, proliferative effects were assumed to be negligible, so repair was thought to be the only factor involved. The shapes of the underlying dose-response curves were deduced by plotting $1/D$, where D was the total dose delivered ($D = n \times d$), as a function of d, the dose per fraction. This was termed a reciprocal dose plot and is used to obtain values for the ratio α/β, parameters of the linear-quadratic survival curve formula,[76,77] which, as

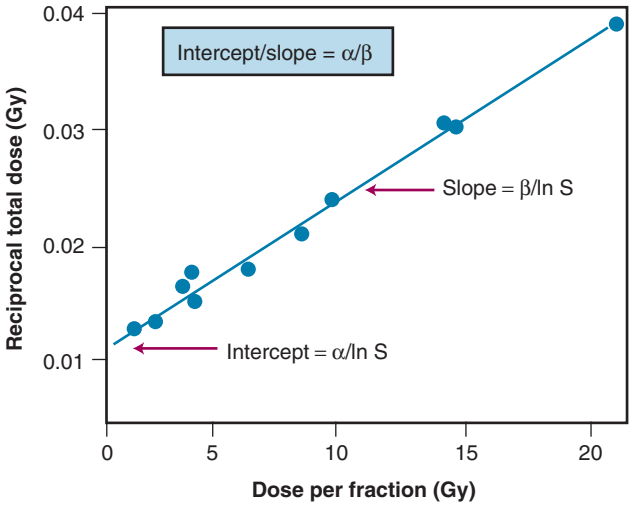


Figure 1-27 The reciprocal dose or Fe plot technique of Douglas and Fowler is used to determine a normal tissue or tumor's α/β ratio. Using this method, the reciprocal of the total dose necessary to reach a given isoeffect is plotted as a function of the dose per fraction. Assuming that the killing of target cells responsible for the tissue effect can be modeled using the linear-quadratic cell survival expression, $S = e^{-(\alpha D - \beta D^2)}$, the α/β ratio can be obtained from the ratio of the isoeffect curve's intercept to slope.
Adapted from Douglas B, Fowler J: The effect of multiple small doses of x rays on skin reactions in the mouse and a basic interpretation. Radiat Res 66:401, 1976.

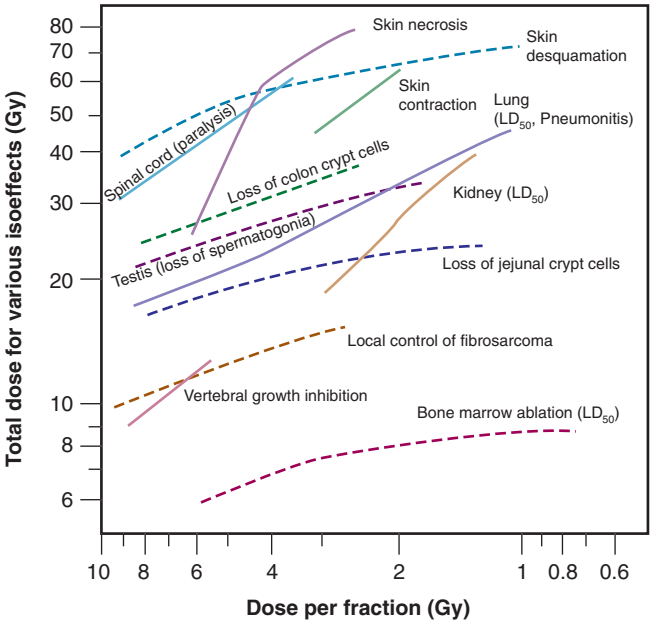


Figure 1-28 Isoeffect curves in which the total dose necessary to produce a certain normal tissue or tumor endpoint (indicated on the graph) is plotted as a function of the dose per fraction under conditions in which cell proliferation is negligible. Isoeffect curves for late-responding normal tissues *(solid lines)* tend to be steeper than those for early-responding normal tissues and tumors *(dashed lines)*. This suggests that for the same total dose, late reactions may be spared by decreasing the size of the dose per fraction used. It also follows that by using smaller dose fractions, a somewhat higher total dose could be given for the same probability of a late reaction but with the hope of higher tumor control probability.
Adapted from Withers H, Thames H, Peters L, et al: Normal tissue radioresistance in clinical radiotherapy. In Withers H, Thames H, Peters L, editors: Biological basis and clinical implications of tumor radioresistance, New York, 1983, Masson, p 139.

discussed previously, provided good fits to experimental survival data, at least over the first two decades of cell killing. A representative reciprocal dose plot is shown in Figure 1-27. However, it should be noted that the curves obtained using this technique are not true cell survival curves, but rather, effective dose-response curves derived from isoeffect data for different time, dose, and fractionation combinations.

This new approach to isoeffect analysis, in which attention was focused on repair parameters and dose-response curve shapes, emphasized that the critical parameter in radiotherapy is the size of the dose per fraction, more so than the overall treatment time. During the course of experimental and clinical fractionation studies, it became clear that there was a systematic difference between early- and late-responding tissues and tumors in their responses to different fractionation patterns. In other words, the capacity for repair of radiation damage was somehow related to the proliferative state of the tissues being irradiated (Figure 1-28).[300,301] Isoeffect curves for the slowly or nonproliferating normal tissues, such as kidney and spinal cord for example, are steeper in general than those for more rapidly proliferating, early-responding tissues, such as skin and gut epithelium, and significantly, most tumors.[300,301] A steep isoeffect curve implies that late effects tissues are more sensitive to changes in the size of the dose per fraction, experiencing greater sparing with decreasing fraction size than their early effects counterparts (Figure 1-29). This difference is also reflected in the α/β ratios derived for these tissues, which are usually low for late-responding tissues (on the order of 1 to 6 Gy, with an average of about 3 Gy), and high for early-responding tissues and tumors (usually 7 to 20 Gy, with an average of about 10 Gy) (Tables 1-5 and 1-6).

Clinical Applications of the Linear Quadratic Isoeffect Model

The most important assumptions of the linear-quadratic model are[300,301]: an isoeffect in a tissue is a reflection of the isosurvival of appropriate target cells; turnover kinetics of target cells determine the time of expression of radiation injury; radiation damage is either repairable or irreparable, with the repairable damage accounting for the sparing effect of dose fractionation; sufficient time is allowed between dose fractions for the repairable damage to be completely repaired; repopulation during the course of treatment is negligible; and the damage caused by each successive dose fraction is the same as that produced by the prior dose fraction, that is, there is an equal effect per fraction.

Within this conceptual framework then, the shapes of tissue and tumor isoeffect curves and their calculated α/β ratios have a number of clinical applications. One possible application is to design radiotherapy treatments for which the α/β ratios for the dose-limiting tissues are known reasonably well.[246] It is also possible using α/β ratios to equate treatment schedules employing different-sized doses per fraction to match the probability of causing a tissue injury, assuming the overall treatment times are similar in both schedules or the tissue at risk of a complication is relatively insensitive to treatment duration.[246] The equation, $D_2/D_1 = (\alpha/\beta + d_1) / (\alpha/\beta + d_2)$ can be used for this purpose, where D_1 and d_1 are, respectively, the total dose and dose per fraction (in Gy) of one radiotherapy treatment plan, D_2 and d_2 are the total dose and dose per fraction for an alternate treatment plan designed to be biologically equivalent for a particular tissue effect, and with the fractionation sensitivity of that tissue defined by its unique α/β ratio. Of course, avoiding a normal tissue complication is not the

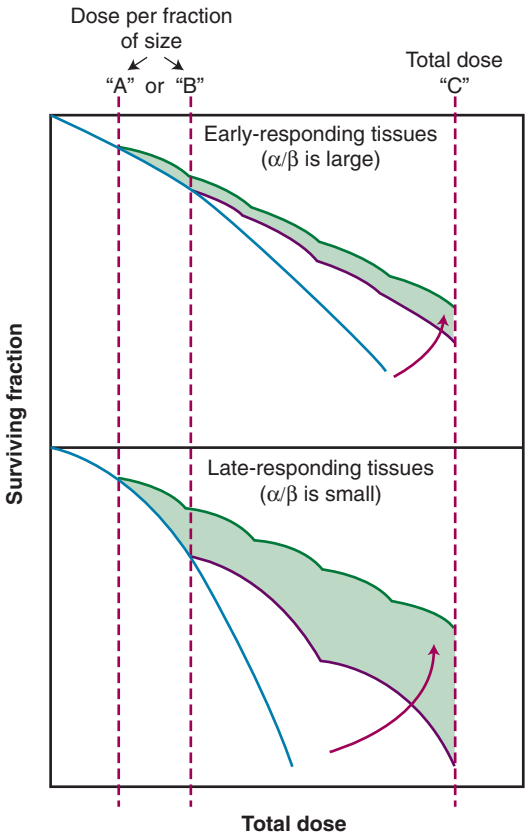


Figure 1-29 Hypothetical survival curves for target cells whose deaths are responsible for an acute *(upper panel)* or late *(lower panel)* effect in an irradiated normal tissue, depending on whether the total dose C is delivered using dose fractions of size A or B. Because of the difference in the initial slopes of the corresponding single-dose survival curves for these cell types, reducing the fraction size from B to A preferentially spares late-responding normal tissues *(green-shaded areas). Adapted from Withers H, Thames H, Peters L: Differences in the fractionation response of acutely responding and late-responding tissues. In Karcher K, Kogelnik H, Reinartz G, editors: Progress in radio-oncology II, New York, 1982, Raven Press, p 287.*

TABLE 1-5 Representative α/β Ratios for Human Normal Tissues and Tumors

Tissue Type (and Endpoint)	α/β Ratio (± 95% Confidence Interval)
Early-Responding Normal Tissues	
Skin: erythema	10.6 (1.8; 22.8) Gy
Desquamation	11.2 (8.5; 17.6) Gy
Lung: pneumonitis ≤90 days after radiotherapy	>8.8 Gy
Oral mucosa: mucositis	8-15 Gy
Late-Responding Normal Tissues	
Skin: telangiectasia	~2.7 (–0.1; 8.1) Gy
Fibrosis	1.7 (0.6; 3.0) Gy
Breast: cosmesis	3.4 (2.3; 4.5) Gy
Fibrosis	3.1 (1.8; 4.4) Gy
Lung: pneumonitis >90 days after radiotherapy	4.0 (2.2; 5.8) Gy
Fibrosis	3.1 (–0.2; 8.5) Gy
Bowel: perforation/stricture	3.9 (2.5; 5.3) Gy
Various other	4.3 (2.2; 9.6) Gy
Spinal cord: myelopathy	<3.3 Gy
Muscle, vasculature, or cartilage: impaired movement	3.5 (0.7; 6.2) Gy
Nerve: brachial plexopathy	2.0-3.5 Gy
Optic neuropathy	1.6 (–7; 10) Gy
Head and neck: various	3.5-4 Gy
Tumors	
Head and neck: nasopharynx	16 (–11; 43) Gy
Vocal cord	~13 Gy
Buccal mucoas	~6.6 (2.9; ∞) Gy
Tonsil	7.2 (3.6; ∞) Gy
Larynx	14.5 (4.9; 24) Gy
Lung: squamous cell carcinoma	~50-90 Gy
Cervix: squamous cell carcinoma	>13.9 Gy
Skin: squamous cell carcinoma	8.5 (4.5; 11.3) Gy
Melanoma	0.6 (–1.1; 2.5) Gy
Prostate	1.1 (–3.3; 5.6) Gy
Breast (early stage invasive ductal, lobular, and mixed)	4.6 (1.1; 8.1) Gy
Esophagus	4.9 (1.5; 17) Gy
Liposarcoma	0.4 (–1.4 ; 5.4) Gy

Data from Joiner M, van der Kogel A, editors: Basic clinical radiobiology, ed 4, London, 2009, Hodder Arnold.

sole criterion used in treatment planning; in considering a particular time, dose and fraction size combination, the responses of the tumor, and *all* incidentally irradiated normal tissues should be taken into account simultaneously.

An important implication of the steeper isoeffect curves for late-responding tissues compared to those for tumors is that it might be possible to increase the therapeutic ratio by using larger numbers of smaller fractions to a somewhat higher total dose than traditionally used.[246,247,302] Although such treatments might be expected to exacerbate acute effects in normal tissues and the tumor, late effects would be spared preferentially. The use of multiple fractions per day of smaller than conventional size (less than about 1.8 Gy) but to a somewhat higher total dose, with little or no change in overall treatment time, has been termed *hyperfractionation*. With particularly aggressive tumors that proliferate rapidly, it has been suggested that multiple treatments per day might also be useful to decrease the overall treatment time, thereby allowing less time for repopulation of clonogenic tumor cells.[303,304] Treatment with multiple daily fractions of approximately standard size and number (and to about the same total dose), but in shorter overall times, has been called *accelerated fractionation*. In practice, however, a combination of accelerated and hyperfractionated treatment is often used.[277] Finally, *hypofractionation*, the use of one or a few large dose fractions delivered over short periods of time (e.g., stereotactic radiosurgery or radiotherapy, intraoperative radiation therapy, or, to some extent, high dose rate brachytherapy) is also an option. Indications for such would include cases where the frank ablation of small tumors is the goal, or in the relatively unusual circumstance in which the tumor is suspected of having a low, rather than high, α/β ratio. Prostate cancer appears to be a tumor type that meets this criteria, although this remains a controversial and sometimes contentious subject, as does the use of hypofractionation in general.[305-307] Whatever the case, extra care must be taken to exclude late-responding normal tissues from the treatment field when hypofractionation is considered because the use of high doses per fraction for tissues with low α/β ratios is associated with higher complication frequencies.

TABLE 1-6 Summary of the Linear-Quadratic Isoeffect Model Parameters and Concepts

Tissue Type	α/β Ratio*	Dose-Response Curve Shape†	Isoeffect Curve Shape‡
Early-responding normal tissues and most tumors	High (6-30 Gy)	Steep initial slope (α is large)	Shallow
Late-responding normal tissues	Low (1-6 Gy)	Shallow initial slope (α is small)	Steep

**Determined from the reciprocal dose plot technique of Douglas BG, Fowler JF: The effect of multiple small doses of x-rays on skin reactions in the mouse and a basic interpretation, Radiat Res 66:401-426, 1976.*

†Based on the assumption that differences in the calculated α/β ratio are usually caused by differences in α rather than β.

‡Using the Thames and colleagues isoeffect curve plot. Thames HD, Withers HR, Peters LJ, et al: Changes in early and late radiation responses with altered dose fractionation: implications for dose-survival relationships, Int J Radiat Oncol Biol Phys 8:219-226, 1982. (See also Figure 1-28.)

The decision to opt for one of these fractionation protocols would depend not only on the α/β ratios for the tissues being irradiated but also on their relative repair rates and proliferative responses before, during, and after exposure. At present, although data related to the former parameters continue to accumulate and become more reliable, data on proliferation characteristics, especially for tumors, are still lacking.[241,303]

With nonstandard fractionation now the standard, radiation oncologists find themselves confronted with the same problem faced by their counterparts in the 1930s, that is, how to compare and contrast different treatment schedules for presumptive isoeffectiveness? The biologically effective dose (BED) method,[248] another derivative of the linear-quadratic model, attempts to address this issue. Although this method is a bit confusing to use in practice, conceptually, the ideas are fairly straightforward. Knowing that cell survival and dose-response curves have negative initial slopes, and that, for a sufficiently low dose per fraction or dose rate, a limit to the repair-dependent dose fractionation effect occurs that "traces" this initial slope, the question may be asked, "In the limit, for an infinite number of infinitely small dose fractions, what total radiation dose will correspond to normal tissue tolerance, tumor control, or any other endpoint of interest?" Clearly, this theoretical dose will be quite large for a tissue characterized by a dose-response or survival curve with a shallow initial slope (like many late-responding normal tissues) and appreciably smaller for a tissue characterized by a dose-response curve with a steep initial slope (like most tumors and early-responding normal tissues). *It is also important to bear in mind that BEDs are not real doses, but rather extrapolates based on the limiting slope of the multifraction dose response curves for the tissues at risk, which in turn depend on the α/β ratio.* For this reason, the units used to describe these extrapolated doses are, for example, Gy_3 and Gy_{10}, rather than Gy, where the subscripts 3 and 10 refer to the assumed α/β ratio of the tissue at risk. A second caveat is that, although two different radiotherapy treatment schedules can be compared qualitatively on the basis of their respective Gy_3 *or* Gy_{10} doses, Gy_3 *and* Gy_{10} cannot be intercompared.

A mathematical rearrangement of the linear-quadratic survival expression $S = e^{-(\alpha D + \beta D2)}$, yields:

$$\text{B.E.D.} = E/\alpha = nd\,(1 + d/\alpha/\beta)$$

where *E* is the (iso)effect being measured (*E* is divided by α to obtain the BED value in units of dose), *n* is the number of fractions, *d* is the dose per fraction, and the α/β ratio is specific for the tissue at risk. The factor "(1 + d/α/β)" has been called the *relative effectiveness term* because, in essence, it is a correction factor for the fact that treatment is not really given as an infinite number of infinitely small dose fractions but rather as a finite number of fractions of a finite size.

Perhaps the best way to illustrate the use of the BED equation is by example. Suppose that a radiation oncologist is developing a clinical protocol in head and neck cancer comparing standard fractionation (30 fractions of 2 Gy to a total dose of 60 Gy in an overall treatment time of about 6 weeks) to a schedule of 50 fractions of 1.4 Gy to a total dose of 70 Gy in approximately the same overall treatment time. The tissues of most concern for radiation injury are the tumor, the oral mucosa, and the spinal cord, that is, two early- and one late-responding tissues. Finally, assume an α/β ratio of 10 Gy is appropriate for the tumor and oral mucosa, and an α/β ratio of 3 Gy is appropriate for the spinal cord. *For calculation purposes, an α/β ratio of 10 Gy can be used for most early-responding normal tissues and tumors, and 3 Gy for most late-responding normal tissues, unless more robust, better-vetted values are available.* For example, an α/β ratio of 4 Gy may be more appropriate for breast cancer; 20 Gy for non–small cell lung cancer; approximately 2 Gy for central nervous system, kidney and prostate cancer; and approximately 0.6 Gy for melanoma.[245]

For the standard fractionation schedule therefore:

For tumor and mucosa:

$$E/\alpha = 60\text{ Gy}\,(1 + 2\text{ Gy}/10\text{ Gy}) = 72\text{ Gy}_{10}$$

For the spinal cord:

$$E/\alpha = 60\text{ Gy}\,(1 + 2\text{ Gy}/3\text{ Gy}) = 100\text{ Gy}_3$$

And, for the more highly fractionated schedule (rounded off to the nearest whole number):

For tumor and mucosa:

$$E/\alpha = 70\text{ Gy}\,(1 + 1.4\text{ Gy}/10\text{ Gy}) = 80\text{ Gy}_{10}$$

For the spinal cord:

$$E/\alpha = 70\text{ Gy}\,(1 + 1.4\text{ Gy}/3\text{ Gy}) = 103\text{ Gy}_3$$

Although little quantitative information can be gleaned from this exercise, a few qualitative statements can be made. First, a comparison of the Gy_{10} values for the two treatment schedules suggests that the more highly fractionated schedule should result in somewhat better tumor control, albeit at the expense of more vigorous mucosal reactions (i.e., 72 Gy_{10} compared to 80 Gy_{10}, an 11% increase in "biodose"). However, the comparison of the Gy_3 values for the two schedules suggests that the spinal cord tolerance would be essentially unchanged (i.e., 100 Gy_3 compared to 103 Gy_3, a 3% increase).

Even with the BED concept being only semiquantitative at best, its use for treatment planning purposes over the past two decades has provided a wealth of clinical data that has allowed a better definition of what is or is not tolerable for a particular normal tissue, in terms of Gy_3 or Gy_{10}. Using head and neck cancer as an example, Fowler et al[245,308,309] have suggested that the tolerance dose for acute mucosal reactions is in the range

TABLE 1-7 Current Status of Existing and Proposed Parameters of the Linear-Quadratic Isoeffect Model for Human Normal Tissues and Tumors

Parameter	Property Governed	Availability of Data with Respect to:		
		Early Effects	Late Effects	Tumors
α/β Ratio	Fractionation sensitivity	Can assume 10 Gy for most	Can assume 3 Gy for most	Can assume 10 Gy for most
$T_{1/2}$ (Repair half-time)	Repair kinetics	Poor/fair	Poor	None/poor
Tp (Effective clonogen doubling time) or T_k (Kickoff time—time proliferation begins relative to the start of treatment)	Dose lost to accelerated proliferation during radiotherapy	Fair	Poor; N/A	Poor/fair
Volume effect	Variation in tissue tolerance with increasing target volume	Poor	Poor	None/poor
γ (Normalized dose response gradient)	Steepness of dose-response curve for effect; can be used to estimate the normal tissue complication probability	Fair	Fair	Fair

Modified from Bentzen SM: Estimation of radiobiologic parameters from clinical data. In Hagen U, Jung H, Streffer C, editors: Radiation research 1895-1995: volume 2, congress lectures. Wurzburg, 1995, Universitatsdruckerei H. Sturtz AG, pp 833-838, with permission.

of 59 to 63 Gy_{10}, and for late reactions, in the range of 110 to 117 Gy_3.

Finally, another way of using the BED equation would be to design schedules to match an acceptable probability of a complication, radiation myelitis for example, and then calculate the expected benefit (or lack thereof) with respect to tumor control.

It would be remiss to conclude any discussion of the linear-quadratic isoeffect model, or any biologically based model with potential clinical application, without a few words of warning. First, this model, although certainly more robust than the NSD model and much better grounded in biological principles, is still a theoretical model. Some limitations of the basic model are obvious: an overly simplistic assumption that an isoeffect in a tissue directly corresponds to an isosurvival of a particular cell type; no provision for the influence of cell cycle, proliferative or microenvironmental effects in the overall dose-response relationship; no way to account for differences in repair rates between different tissues; no consideration of volume effects; uncertainty surrounding the model's applicability for extremes of fractionation; and a limited understanding of how to apply the model in patients receiving multimodality therapy.

Various add-ons to the linear-quadratic model have been proposed,[310-312] especially with respect to compensating for tumor cell repopulation and differing repair rates between different tissues. However, the lack of robust values at present for the parameters introduced in such calculations (e.g., potential doubling times, half-times for repair, repopulation kick-off times, etc.), ultimately limit their usefulness beyond rough approximations or proofs-of-concept. The current status of some of the existing and proposed parameters of the linear-quadratic model for human tumors and normal tissues is summarized in Table 1-7.

RADIATION BIOLOGY IN THE 21ST CENTURY

Since the mid-1980s, most graduate students pursuing careers in oncology necessarily trained as molecular, cellular, or tumor biologists, and not as radiation biologists per se, although a few may have worked with ionizing radiation as a tool for probing fundamental cellular processes or as part of translational research designed to develop new cancer therapies. Even fewer have ever taken a formal course in radiation biology, let alone in its more clinical aspects. This shift in focus and training is part of the natural evolution of the oncologic sciences over the years and surely not an unexpected or unwarranted one. However, the fact remains that the field of radiation biology as a distinct entity, with its rich, 120-year history that has contributed in major ways to fields as diverse as carcinogenesis, epidemiology, toxicology, DNA damage and repair, genetics and cytogenetics, cell cycle biology, and radiation oncology to name but a few, is threatened with extinction.

This too could be viewed as a necessary price of scientific progress, were it not for the fact that there remains a need for all radiologic science professionals (from radiologic technologists and radiation therapists, medical physicists and dosimetrists, to radiologists and radiation oncologists) to be at least reasonably well-versed in the basic principles of radiation biology. Physicians in particular need to be familiar both with the classical and modern aspects of the field, in keeping with the close relationship between the histories of ionizing radiation itself, radiation biology, and the medical specialties of radiology and radiation oncology. And unfortunately, since the events of September 11, 2001, a new mandate has emerged: the need to provide expertise in the basics of radiation biology and radiation protection to emergency responders, civic leaders, and the general public in the event of a radiological or nuclear terrorist attack.

Nevertheless, 21st-century radiation biology continues to flourish and remains cutting edge in many respects. Fundamental studies of genomic instability,[313,314] epigenetics,[315,316] and cell signaling as it applies to radiation response[317,318] continue to be active areas of research. Our growing understanding of the complex roles played by cytokines in the etiology of normal tissue complications following radiation exposure[319,320] promises to someday deliver novel, molecularly based radioprotectors that may benefit radiation accident victims, first responders during radiation emergencies, and astronauts on deep-space missions. Radiation cytogeneticists study the role telomeres and telomerase play in cellular aging

and neoplastic transformation.[321] Radiation scientists have also been important contributors to the fields of genomics and proteomics, functional and molecular imaging and molecularly targeted cancer therapy, and to the search for tumor-specific biomarkers that can aid in cancer diagnosis, staging, and the monitoring of treatment progress.

As long as the molecular underpinnings of some of these fundamental processes remain poorly understood, and a more comprehensive picture of the full range of radiation-induced gene expression and signaling remains elusive, there will always be a role for radiation biology research.

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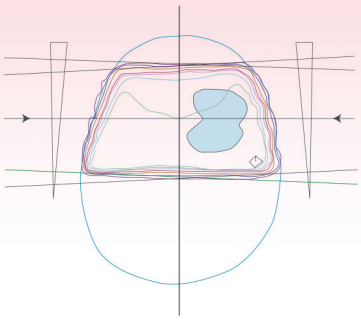
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CHAPTER

2 Molecular and Cellular Biology



Mary Ann Stevenson and Stuart K. Calderwood

The past two decades have seen revolutions in two areas of cell and molecular biology that are closely related to radiation therapy. The pathways involved in response to genomic stress, including mechanisms for sensing DNA damage and responding by cell cycle changes and DNA repair, have been elucidated by studies of model organisms, particularly the yeast *Saccharomyces cerevisiae*.[1,2] In the second major area, understanding pathways of programmed cell death (PCD), which may play a major role in treatment response, studies of *Caenorhabditis elegans* were the most informative in demonstrating the significance of individual death genes.[3] The challenge is to combine these two areas of knowledge and provide a rational understanding of how tumor cells can be made to enter the death pathways and how the processing of DNA damage could be minimized. Considerable technological improvements also have enabled significant progress in the translation of experimental advances, including rational, *in silico* drug design and high-throughput screening of chemical libraries, which could permit the application of advances in molecular biological knowledge to the development of drugs for use in combination with radiation therapy.

ESSENTIAL STEPS IN TUMOR PROGRESSION

Much evidence suggests that tumors are formed by a stepwise progression of cells from a minimally altered state, where they are able to grow and form nodules or polyps (e.g., solid tumors) to a state of maximal transformation, characterized by multiply deviated cells that are capable of unlimited growth, manipulation of their local environment, invasion of surrounding tissues, and escape into the circulation to establish new colonies of secondary tumors, or metastases.[4] Tumor progression involves an array of molecular and morphologic changes. In their landmark review, Hanahan and Weinberg suggested organizing these traits into six essential alterations in cell physiology: self-sufficiency in growth signals, insensitivity to growth inhibition, evasion of PCD, limitless replicative potential, sustained angiogenesis, and tissue invasion and metastasis.[5] Although the initial steps are believed to occur earlier in tumor progression, the exact order of occurrence varies among different malignancies, and some phenotypic transformations appear to require more than one molecular change.[6,7] The occurrence in tumor cells of this series of radical, primarily genetic alterations in physiology is in part the result of an evolving instability of the tumor genome resulting from a breakdown in the DNA repair pathways that accompanies tumor progression.

In addition to progressing and acquiring enhanced malignant capabilities, most human tumors undergo further selections through exposure to various forms of cytotoxic therapy such as irradiation and chemotherapy, leading to the development of resistant phenotypes in the surviving cells.[8] However a new paradigm is emerging that may challenge our views of tumorigenesis. This is the concept that only a small proportion of the tumor cell population can give rise to tumor initiation and these cells have many of the properties of stem cells.[9] According to this theory, tumors contain a small population of cancer stem cells that renew by dividing slowly and that also give rise to more "differentiated" progeny forming the bulk of tumors. Tumor eradication would thus involve killing this small, slowly dividing, and often treatment-resistant population. Studies in this area could revolutionize the cell and molecular underpinnings of radiation biology.

All cancer treatments are aimed at reversing the hallmarks of neoplastic transformation and tipping the balance toward tumor cell death in both the bulk population and the stem cell fraction. Ionizing radiation kills cells almost exclusively through the generation of DNA double-stranded breaks (DSBs).[10] The evolving modification of the cellular phenotype during tumorigenesis leads to the development of resistance to therapy. Our major task is to explore the links among DSB response pathways, engagement of cell death mechanisms, and the outcome of radiation therapy.

RADIATION THERAPY AND RADIATION BIOLOGY

Ionizing radiation has long been known to be a potent modality in cancer therapy, killing cells and leading to tumor regression.[11] Killing by ionizing radiation involves the oxygen-dependent generation of free radicals and subsequent damage to multiple molecular structures within the cell.[10] The generation of DSBs is the dominant mechanism of direct lethality. Indeed, it has been estimated that the existence of even one unrepaired DSB can lead to cell death.[12] Within whole organisms, direct and indirect forms of lethality occur. Radiation can cause the death of hematopoietic stem cells in the bone marrow and stem cells in crypts of the small intestine, which leads to secondary damage caused by immunosuppression and infection, as the gastrointestinal lining is eroded.[13,14] The challenge facing radiation therapy is to enhance cell killing within tumors while avoiding dose-related complications in organs containing rapidly renewing stem cell populations.

Early studies using the clonogenic cell survival assay established the notion of optimizing radiobiological parameters such as dose, fractionation, and cell cycle inhibition as a means of inhibiting reproductive cell death in critical normal tissues.[15] The clonogenic cell survival assay is a useful measure of cell inactivation because the effects of ionizing radiation seen in vitro often mirror the responses of tumors in vivo.[10] However, a weakness in the informative power of the method is that it does not allow for discrimination or elucidation of the various mechanisms leading to cell death. That kind of detailed information is essential for the successful combination of radiation therapy with other modalities, which may result in sensitization, protection, or both. Irradiation activates a number of pathways that mediate reproductive death, including various forms of PCD (e.g., apoptosis, autophagy), replicative senescence, and necrosis, the default pathway that often dominates when other types of cell death are inhibited.[16,17] The susceptibility to each of these forms of cell death changes over the course of tumor progression, and the tumor cell response to ionizing radiation is likely to reflect the aggregate of genetic changes that accompany tumor progression. The task of

radiation biology is to examine mechanisms by which ionizing radiation gives rise to unrepaired DSBs and how such damage is coupled to the pathways of cell killing within the moving target of the evolving cancer cell.

DNA DOUBLE-STRANDED BREAK RESPONSE

All cells have become adapted to live in an environment that is more or less mutagenic and have thus evolved responses to permit survival when the genome is damaged.[18] DNA may be damaged during the normal processes of DNA replication and segregation. Within tumor cells, these initial changes become progressively altered because cells compete for survival in the tumor milieu and are subjected to selection by various forms of cytotoxic therapy.[19] The response to DSBs involves two principal components: (1) arrest of cell proliferation to prevent replication and segregation of the damaged DNA and, when possible, (2) repair of the lesion.[19] A third component in the DSB response in multicellular organisms may be altruistic entry of irreversibly damaged cells into the PCD pathways.[20,21] The latter effect is the desired response to cytotoxic therapy. Understanding how the DSB response is regulated at the molecular level may be one of the keys to understanding the differential response to irradiation in individual tumors and the rational design of radiosensitizing drugs. There are several basic questions regarding regulation of this response, including: (1) By which mechanism do tumor cells arrest in the cell cycle? (2) How is the presence of DNA DSBs detected in such cells? (3) What are the major pathways for repair of DSBs? (4) How does the deployment of these pathways affect tumor response to therapy?

Mechanisms of Cell Cycle Arrest: The Cell Cycle and Checkpoints

The cell cycle is a series of molecular programs that read out in a preferred order, leading to duplication of the genome and other cellular components, permitting division into two cells, each with a full set of chromosomes and the organelles required for life.[22] Orderly, high-fidelity, and complete duplication of the genome is required for cell cycle progression. This is achieved through a surveillance system that detects DNA damage or unreplicated DNA and imposes cell cycle arrest at designated checkpoints, blocking the forward progress of the cell cycle engine (Figure 2-1). Because ionizing radiation produces severe damage to DNA, checkpoints are essential for facilitating repair and subsequent cell survival after radiation exposure, and they provide an ultimate target for strategies aimed at sensitizing cells to radiation therapy.

The cell cycle is driven by sequential activation of a series of protein kinases that determine the order and rate of the metabolic events required in each stage. These cell division kinases, or cyclin-dependent kinases (CDKs), are activated by binding proteins originally designated as cell division cycle (CDC) molecules, now known as cyclins.[22] These complexes formed between cyclins and CDK molecules are the master regulators that determine the rates of the individual component reactions regulating each stage of the cell cycle.[23] Phosphorylation of individual cell cycle effector proteins by the cyclin-CDK complexes acts as a series of switches, turning on cell cycle stages in orderly fashion. In mammalian cells, the cyclins regulate individual stages of the cell cycle, and these include the G_1 cyclins (cyclins D and E), S phase-specific cyclins, and G_2-specific cyclins (cyclins A and B), which associate, respectively, with G_1-specific (CDK2, CDK4, and CDK6), S-specific, and G_2-specific (CDC2) cyclin-dependent kinases. The events of G_1 (i.e., synthesis of enzymes and other molecules involved in DNA replication), S phase (i.e., DNA replication), and G_2/M (i.e., chromosome condensation, disappearance of the nuclear envelope, and mitosis) are regulated by the transient accumulation and subsequent degradation of the cyclins.[22-24] Switching off the reactions that characterize individual stages involves targeted degradation of the cyclins by a protein destruction machine called the *proteasome*.[24] Targeted destruction of the cyclins after they have carried out their function ensures unidirectional, irreversible progression around the cell cycle.[23] The timing of the various cell cycle phases under normal conditions is related to the time required

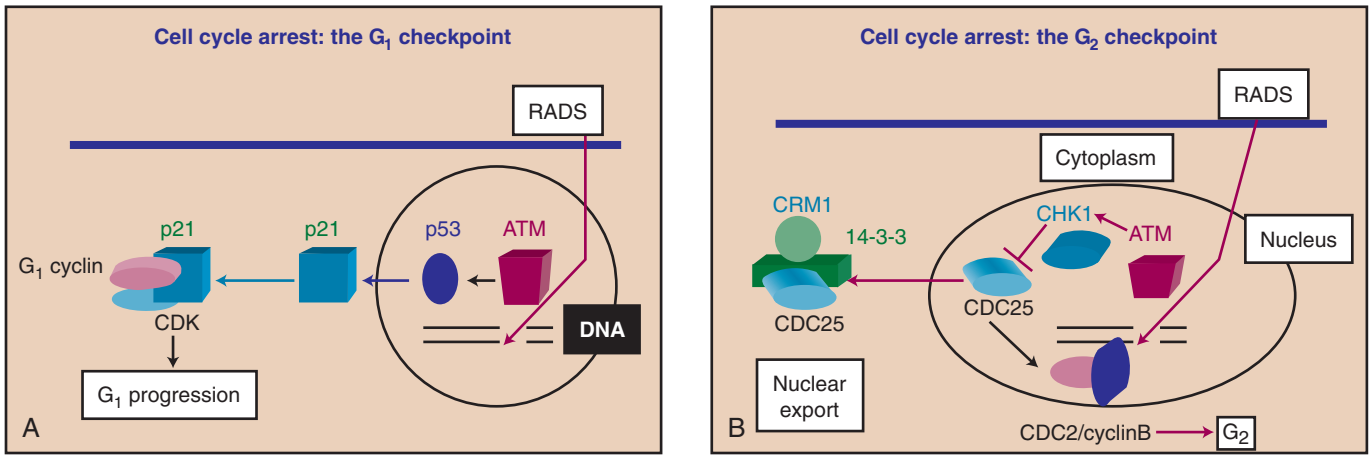


Figure 2-1 Cell cycle checkpoints. **A,** To progress through G_1 to the replication (S) phase, cells require the activity of G_1 cyclins (D, E) and cyclin-dependent kinases (CDK2, CDK4, and CDK6) to phosphorylate substrates such as the retinoblastoma protein (RB1). DNA damage is sensed by the protein kinase ATM, which activates TP53 (p53), leading to transcription of the CDKN1A (p21) protein, a powerful inhibitor of cyclin-CDK complex kinase activity, and to arrest in G_1. DNA damage may be repaired, leading to deactivation of the checkpoint block and progression into S phase. If it is unrepaired, TP53-dependent programmed cell death may occur. **B,** To progress through G_2 into M, the activity of the protein phosphatase CDC25 is required. DNA damage *(red arrows)* also leads to ATM activation, which causes a cascade response as ATM kinase activates the CHK kinases and CHK1 phosphorylates CDC25, leading to recruitment of the activation protein YWHA (formerly designated 14-3-3) and an adapter protein that couples CDC25 to the nuclear export machinery of the cell. Exported from the nucleus, CDC25 is no longer able to mediate dephosphorylation of CDC2 at the G_2/M transition and progression through G_2.

for cyclin-CDK complexes to reach appropriate, critical concentrations and for the phosphorylation of key substrates.[23]

Irradiation leads to prolongation of the cell cycle and arrests in G_1, G_2, and S phases because of checkpoint activation (see Figure 2-1).[25] Although this phenomenon was observed many years ago, it was only later understood at the biochemical and genetic levels. Arrest of cells at the G_1 checkpoint has been particularly well studied (see Figure 2-1, *A*). G_1 arrest is caused by the accumulation of a CDK inhibitory protein, CDKN1A (formerly designated p21 or Cip1), and this molecule prevents the key events that are required for transit through G1, including phosphorylation of the retinoblastoma (RB1) protein and activation of the E2F transcription factors (e.g., E2F1, E2F2, E2F4, E2F6) necessary for accumulation of enzymes required to traverse S phase.[26,27] CDKN1A can be induced at the transcriptional level by TP53 (also known as p53), which accumulates in irradiated cells and binds to the *CDKN1A* promoter, thereby activating transcription. TP53 accumulation depends on the activation by radiation exposure of a DSB sensor molecule, the protein kinase ATM (ataxia-telangiectasia, mutated).[26,27] The exact mechanism involved in detecting accumulation of DSBs and activation of ATM is unclear, although it involves ATM autophosphorylation.[28]

The common mechanism for regulating the G_1 and G_2 checkpoints is inhibition of the CDK components of the interphase cell cycle engine and a block to phosphorylation and activation of effector molecules (see Figure 2-1).[23,27] A variation on this theme is seen at the mitotic spindle checkpoint. Progression through mitosis requires switching off CDK activity through targeted degradation of cyclin B.[29] Arrest in M phase, when the mitotic spindle is compromised, involves the TP53-dependent stabilization of cyclin B. The mitotic spindle checkpoint guarantees that replication is followed by cell division, ensuring prevention of aneuploidy. Not surprisingly, the polyploidy nature of many tumor cells is related to TP53 inactivation.[29] Most evidence indicates that ATM (and its homologues in other organisms) functions as a sensor for DNA damage through a complex series of interactions with the damaged DNA. This ultimately leads to ATM activation and downstream signaling cascades involving the kinases CHK1 and CHK2 (also called CHEK1 and CHEK2), which couple to the cell cycle engine at the level of individual cyclin-CDK complex molecules (see Figure 2-1, *B*).[1,2,19,27,30] The molecular details of these processes are evolving rapidly, and referenced reviews can provide more detailed insight into the mechanisms of DNA damage, sensing, and checkpoint engagement.

TP53: Cellular Triage after Ionizing Radiation Exposure

TP53 is a nuclear phosphoprotein with sequence-specific DNA binding activity. It can function as both transcriptional activator and repressor and plays a triage role in deciding whether to undergo cell cycle arrest and repair or to enter the pathways of PCD or replicative senescence (Figure 2-2).[31,32] When cells are exposed to ionizing radiation or chemotherapeutic agents, the levels of wild-type TP53 protein are increased. TP53 then transcriptionally activates a number of genes, most notably *CDKN1A*, the CDK inhibitor that mediates many of the properties of TP53.[33] In addition to G_1 arrest, genotoxic stress and ionizing radiation can induce TP53-dependent PCD pathways, including caspase-dependent apoptosis.[33] TP53 can transcriptionally activate the proapoptotic *BAX* gene, induce synthesis of JUN kinase, and repress transcription of the anti-apoptotic gene *BCL2*, suggesting that TP53 is a central mediator of PCD processes.[31,34] DNA damage in the presence of wild-type TP53 causes G_1 arrest, followed by a period of DNA repair; if the damage is too great to be easily repaired, the cell is eliminated

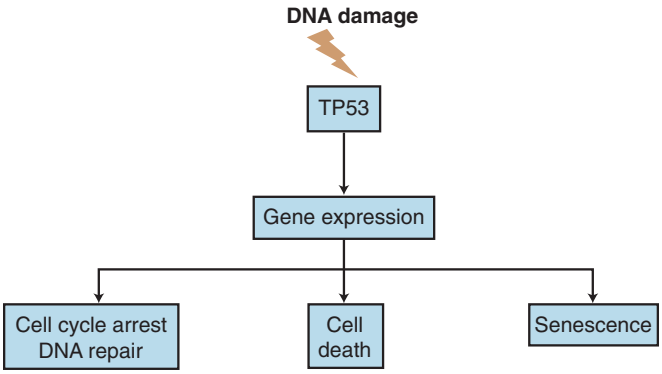


Figure 2-2 TP53 plays a triage role in deciding a cell's fate after exposure to ionizing radiation. TP53 is activated after irradiation, largely through protein stabilization that results from phosphorylation by the protein kinase ATM. Most effects of TP53 are mediated through its transcriptional activity, with some gene products (e.g., CDKN1A [p21]) leading to cell cycle arrest and others (e.g., BID, BBC3 [formerly designated PUMA], PMAIP1 [formerly NOXA]) to programmed cell death. A third fate appears to be senescence, which is mediated largely through CDKN1A. The triage decision appears to be related to radiation dose (i.e., degree of DNA damage), with greater damage favoring the death and senescence pathways.

through TP53-dependent PCD pathways. However, approximately 50% of human tumors possess inactivating mutations in the *TP53* gene.[35] TP53 becomes inactivated in many tumors as a result of selection against its pro-apoptotic properties. The resultant loss of its central function as "sentinel of the genome" may be a type of collateral damage incurred in cells because of the selection advantage for survival accruing from the loss of TP53 apoptotic function.[32,36] The loss of TP53 function is linked to poorer prognosis in malignancies such as lung, breast, colorectal, and hematopoietic tumors.[37] Many tumor cell lines containing mutant TP53, including breast, glioma, and lymphoma cell lines, are more resistant to therapy than their wild-type TP53 counterparts.[38,39]

The loss of wild-type TP53 function in human malignancies may be a key step in the progression of human cancer, and the TP53 status of cells may control the outcome of many tumor types in response to chemotherapy or radiation therapy.[36] Although most of the other DSB response genes have molecular equivalents in yeast, TP53 does not. The TP53 gene appears to be required to determine the fate of damaged cells, which in mammalian cells may be PCD, a sacrifice that contributes to the well-being of the whole organism. TP53 monitors the degree of DNA damage and acts as a master switch, moving the cells from a state of cycle arrest and DNA repair to death or senescence pathways. Loss of TP53 in tumors compromises this critical surveillance and triage function. With the loss of this critical decision-point molecule, damaged and mutated tumor cells may survive to generate new and more malignant phenotypes (see Figure 2-2).

ATM Gene: Master Regulator of the DNA Double-Stranded Break Response

One of the many defects in ataxia-telangiectasia (AT) cells is increased chromosomal instability. Exposure to ionizing radiation also produces an increased number of chromosomal aberrations in AT cells compared with normal cells.[40,41] This effect and the sequence similarity between *ATM* and the DNA repair protein DNA-PK suggested that AT cells might have deficient DNA repair. However, most studies have shown that AT cells do not have gross abnormalities in their ability to repair DNA damage. In general, it does not appear that the radiosensitivity

of AT cells is caused by faulty DNA repair; it more likely results from an inability to detect the presence of DNA damage. Exposure to ionizing radiation causes normal cells to delay at the G_1/S and G_2/M transition phases of the cell cycle, and these checkpoints are thought to allow the cells to repair DNA damage before DNA synthesis or mitosis occurs[27] Both checkpoints are absent in AT cells, suggesting clues to the function of ATM.[27]

Although ATM and TP53 cooperate in radiation-induced apoptosis, there are ATM-independent pathways for the induction of TP53-dependent apoptosis, and many of the downstream effects of ATM are independent of TP53.[27,28] Wild type and knockout mice have been evaluated for acute and late toxicity after whole-body exposure to ionizing radiation. The *ATM*- and *ATM/TP53*-knockout mice had similar severe toxicity profiles, suggesting that TP53 does not play a role in acute radiation toxicity. Both TP53- and *ATM*-knockout mice preferentially developed lymphoid tumors, whereas *ATM/TP53* double knockouts had an accelerated time to tumor formation and a broader spectrum of tumor types. Analysis of the acquired tumors in *ATM*-null/*TP*53-heterozygous mice revealed that three of seven had loss of the remaining *TP*53 allele. These studies showed that ATM and TP53 interact in a complex manner that is specific to cell type and outcome. This interaction most likely relies on a variety of other pathways and will require much additional work before a complete understanding of the ATM/TP53 relationship is obtained.

With isolation of the *ATM* gene it became possible to attempt correction of the cellular defects of the AT phenotype using gene transduction techniques. Several groups have reported that the introduction of ATM into AT cells resulted in reversal of AT defects.[27,41] The transfection of full-length ATM into AT cells reversed DSBs, restored normal sensitivity to ionizing radiation, and decreased the number of chromosomal abnormalities. Transfection of full-length ATM also reversed the defective activation of CDKN1A (p21) and JUN kinase in response to ionizing radiation.[42,43]

Histones and Chromatin Structure

Native DNA exists in the cell in the form of chromatin complexed with a family of proteins called *histones*. Histones are involved in packaging DNA in the nucleus into a compact form. For gene transcription or DNA repair to occur, the histones are altered by posttranslational modifications, most notably acetylation and methylation, that permit decondensation and access of factors to the DNA.[44] The histone acetylase TIP60 is important both in this process and in the modification of ATM itself.[26,45] For effective DNA repair, acetylation of histones by histone acetylases must occur to permit access of repair proteins to the sites of DSBs.[46] DNA is then remodeled by adenosine triphosphate (ATP)-dependent remodeling enzymes to permit repair molecules such as Mre11, RAD50, and NBS1 to access sites of DSBs.[47,48] A novel histone, H2AX, found in low concentrations on chromatin, has been shown to play a crucial signaling role in the response to genomic stresses such as ionizing radiation. H2AX phosphorylation is one of the earliest events occurring after exposure to ionizing radiation, and ATM-dependent phosphorylation of H2AX may be involved in signaling to cell cycle checkpoints and DNA repair enzymes involved in recombination repair.[49,50]

Mechanisms of DNA Repair after Ionizing Radiation

Maintaining undamaged DNA is essential to cell survival. Cells have therefore evolved a wide range of mechanisms to halt cell cycle progression, survey DNA, and repair damage. Radiation causes a number of types of damage either by direct interaction with DNA or indirectly through effects on nearby water molecules and free radical generation. Types of damage include DNA base damage, damage to the deoxyribose sugar backbone, and physical breaks in one or both strands of the DNA. DNA damage induced by ionizing radiation tends to be clustered so that multiple damaged sites are found in proximity along the double helix, known as *locally multiply damaged sites*.[51]

Among the less catastrophic forms of DNA damage induced by ionizing radiation are the singly damaged bases, which can be repaired by base excision repair. This is a process by which the damaged base is recognized and removed by an N-glycosylase, the apurinic or apyrimidinic (AP) site is cleaved by an AP endonuclease, a patch of DNA is excised, DNA is then resynthesized using the other strand as the template, and the repaired strand is ligated.[18,52] In settings in which the base damage is not recognized by the N-glycosylase, another mechanism for repair exists, called *nucleotide excision repair*. In a manner somewhat similar to base excision repair, a damaged section of DNA is removed by incision and excision, a patch is resynthesized using the remaining strand, and the repaired strand is then ligated. Although no naturally occurring mammalian mutants have been identified that are defective in base excision repair, there are a number of different excision repair mutants, which are exemplified by *xeroderma pigmentosum* and Cockayne's syndrome.[18] They are characterized by abnormalities in the repair of damage caused by ultraviolet light, although the clinical spectrum of these repair-deficiency syndromes varies. The abnormal genes are identified by finding the human gene that corrects rodent cell defects, called *excision repair cross-complementing* (ERCC) groups. For a comprehensive review on repair of single-stranded breaks we recommend Friedberg et al.[18]

DNA Strand Breaks

Cellular lethality after radiation involves generation of DSBs.[53-55] Misjoined or unrepaired DSBs lead to chromosome deletions, translocations, and acentric or dicentrics, with lethal consequences for the cell. As with the excision repair defects (e.g., ERCCs), there are several x-ray repair defects in the x-ray cross-complementation (XRCC) groups involved in the repair of DSBs. DNA single-stranded repair is carried out in a manner similar to base damage repair, with the undamaged DNA strand serving as a template. DSB repair is more complicated because there is no adjacent, undamaged template available to form a template for repair of the broken strands. The ends of the broken DNA must be protected, and the damaged site must be reconstituted by the processes of *homologous recombination* and *nonhomologous end joining* (NHEJ).

DNA DSB repair has much in common with the recombinatorial processes involved in immunoglobulin and T-cell receptor gene rearrangement in the immune response. The XRCC groups that have been identified and are involved in DNA DSB repair include genes that produce DNA end-binding proteins XRCC6 (formerly designated KU70 or Ku70) and XRCC5 (formerly designated KU80 or Ku80) and a DNA-dependent protein kinase (DNA-PK). Defects in DNA repair genes are seen in severe combined immunodeficiency (SCID) mice, indicating the importance of recombination in the restoration of DNA integrity after DSBs and in the immune response.[18,53]

Double-Stranded Break Damage and Repair

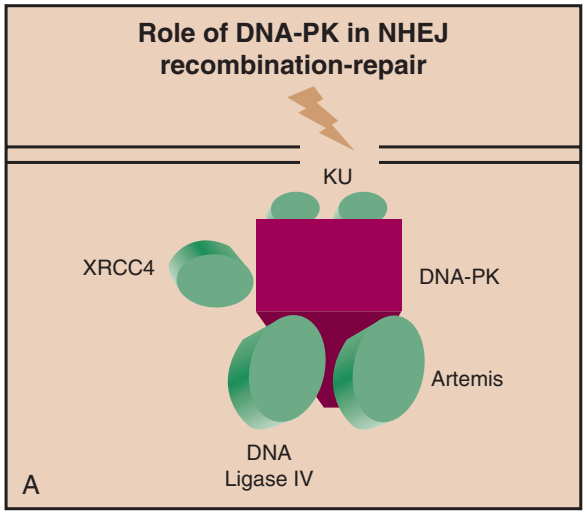
Experiments in yeast and human cells indicate that a single unrepaired DSB can lead to cell death.[53,55] However, cells have the capacity to detect such DSBs and repair them. DSB repair

would be predicted to require three functional components: (1) a mechanism for detecting and gauging DNA damage, (2) a signal transduction system, and (3) an effector system for DNA repair. These components are discussed in the following paragraphs, commencing with the repair component. DSBs can be repaired by a number of mechanisms, but the most prevalent are homologous recombination and NHEJ. Human cells appear to differ from yeast in that homologous recombination predominates in yeast, whereas the opposite is true in mammalian cells.[53,55]

Genetic analysis has revealed the existence of a large number of genes that regulate DSB repair. One essential gene, involved in resistance to cell killing by ionizing radiation and the repair of DSBs, is *XRCC5*, which encodes XRCC5, a protein that binds with high affinity to the ends of the double strands (Figure 2-3, *A*).[1,18] XRCC5 functions in normal cellular processes that require DSBs rejoining, most notably V(D)J rejoining in the immunoglobulin and T-cell receptor genes of immature B and T lymphocytes. XRCC5 exists in cells in a heterodimeric complex with XRCC6, the product of the *XRCC6* gene. The XRCC5/XRCC6 heterodimer is required for the end-binding and repair functions.[56] The XRCC (formerly designated KU) proteins recognize the ends of DSBs and protect them from further degradation before the onset of end-joining reactions required for DSB repair. An associated protein in the complex with important functions in DNA repair is the protein kinase DNA-PK, the product of the *XRCC7* gene.[56]

DNA-PK is a serine/threonine kinase involved in regulating the cellular response to DNA damage.[56,57] DNA-PK is a member of the phosphatidylinositol-3-kinase gene family (*PIK*) that produce a group of high-molecular-weight proteins that contain a conserved kinase domain at the carboxyl-terminal end. PIK family proteins have been identified in yeast, *Drosophila*, and in mammalian cells, and include the human *ataxia-telangiectasia* gene (*XRCC7*) for DNA-PK and the yeast genes *TEL1* and *MEC1*.[56,57] Homology with genes of other organisms can provide a clue to the function of the family of genes in mammalian systems. For example, the *S. cerevisiae TEL1* gene is a homolog of the human *ATM* gene. *TEL1* mutants have shortened telomeres and exhibit chromosome instability. In mice, the SCID mutation results in the loss of expression of functional DNA-PK.[58] SCID mice are deficient in the repair of DNA DSBs, have faulty V(D)J recombination, and are sensitive to radiation.[58] The binding of the XRCC complex (XRCC5 and XRCC6) to DNA-PK activates its kinase activity. The DNA-PK/XRCC complex is involved in recognizing DNA DSBs. Thus in SCID cells, the catalytic subunit for DNA-PK is absent, and its loss may account for increased sensitivity to ionizing radiation, reduced ability to repair DNA DSBs, and the known immune defects.

Genetic evidence indicates the existence of numerous other factors required for efficient DSB repair in human cells.[18,53,55] Among the genes are homologues of the yeast *RAD52* epistasis group, RAD50 and *MRE11*.[26,59-61] RAD50 and MRE11, together with the product of the *XRS2* gene, form a complex in *S. cerevisiae* that is involved in nonhomologous recombination (see Figure 2-3, *B*). RAD50 has been suggested to bind to DNA at the site of DSBs and mark them for repair or recombination. Such a signaling role for RAD50/MRE11 complexes is suggested by studies indicating the formation of nuclear foci containing these proteins in cells after irradiation.[61] The RAD50/MRE11 complexes also contain another important protein, NBN (nibrin; formerly NBS1 or p95), which is inactivated in the Nijmegen breakage syndrome.[26,61] The RAD50/MRE11 foci fail to form in ATM-deficient cells, suggesting a role for this complex downstream of the ATM protein. DSB repair can also be carried out in human cells by homologous recombination, an alternative pathway involving a different



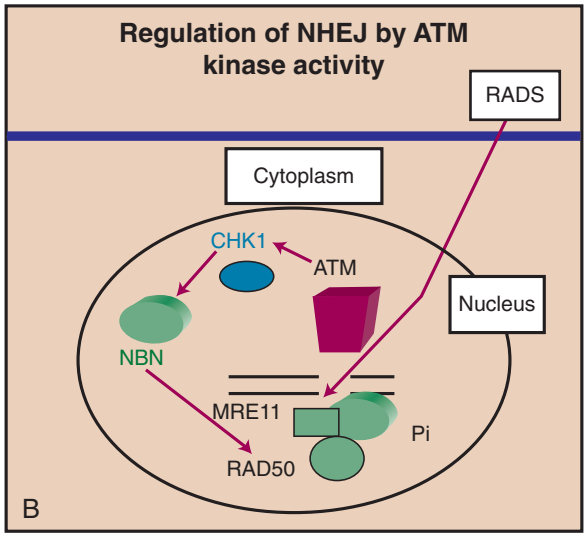


Figure 2-3 **A,** Formation of DNA repair complexes on damaged DNA. Radiation-induced DNA damage causes immediate changes in the vicinity of double-stranded breaks (DSBs). These include rapid phosphorylation of the atypical histone H2AFX and activation of ATM. Protein complexes then begin to assemble on DNA, including the DNA-dependent protein kinase (DNA-PK) complex shown here. This complex is a molecular machine for DNA repair that includes DNA end-binding proteins XRCC6 (formerly KU70) and XRCC5 (formerly KU80); DNA-PK itself, which appears to be a signaling and scaffold protein; and proteins involved in the effector stages of repair. **B,** Another important protein complex mediating DNA DSB repair by the nonhomologous end joining (NHEJ) pathway is the RAD50 complex. The diagram shows the signal transduction pathway leading from ATM, the sensor of DNA DSB, to the phosphorylation of NBN (nibrin, formerly designated NBS1), which induces recruitment of RAD50 and MRE11 into a DNA repair complex at the site of the DNA DSB.

group of genes, including *RAD51* through *RAD57*. RAD51 is the eukaryotic homolog of the bacterial protein RecA and forms structures in meiotic chromosomes containing ATM, suggesting functional coupling between these proteins. The complex also contains TP53 and may be involved in coupling of DNA DSB formation to cell cycle arrest, as well as in carrying out recombination and repair.[62]

The tumor suppressor genes *BRCA1* and *BRCA2* also have function in DNA repair. Although the these proteins have multiple functions, it has been shown that *BRCA1* interacts

with RAD51 and assists in cell cycle arrest through activation of *CDKN1A*, a gene that is normally activated by TP53.[63] RAD51 is thus targeted by three major gene products: ATM, TP53, and BRCA1. Loss of RAD51 leads to cancer development, suggesting that this pathway of DNA repair and replication is crucial in protection of cells from genotoxic stress. That this RAD51 pathway of DSB repair is separate from the RAD50 end-joining pathway is indicated by findings that ionizing radiation causes the formation of nuclear foci containing RAD50 or RAD51 but never both complexes.[64] However, further studies are required to understand the relative contributions of the two pathways to cell survival after exposure to ionizing radiation. As with the RAD50 pathway, understanding of mammalian recombination repair is still preliminary and is difficult to assemble into a fully coherent molecular pathway. *BRCA2* mutant cancer cells are also deficient in DSB repair and have increased radiosensitivity.[63] It is apparent that DNA damage recognition and repair is complex, involving interaction among molecules that can cause cell cycle arrest, apoptosis, and signal transduction. Defects in any of these pathways could lead to radiation sensitivity in normal tissues (and perhaps the corresponding tumor) or to the development of secondary mutations and the mutator phenotype, as with mismatch repair defects. For radiation therapy, the aim of course is to maximize accumulation of DSBs in tumor cells by targeting these pathways.

PATHWAYS OF IONIZING RADIATION-INDUCED PROGRAMMED CELL DEATH

The ability to inhibit the pathways of cell death appears to be a key step in the origin of cancer cells, with the small percentage of cells that are able to evade PCD being the ones most capable of forming tumors.[16] Multiple genetic alterations are involved in escape from PCD, most notably in the *TP53* and *BCL2* families.[16] Radiation oncologists are thus faced with the undesirable situation in which tumor cells are selected for resistance to PCD, whereas normal cells retain these altruistic pathways. Apoptosis and senescence are key PCD pathways with potential roles in cancer induction and resistance to therapy. Excellent reviews have been provided by Edinger and Thompson[32] and Danial and Korsmeyer.[65]

Apoptosis is a normal physiologic process that permits altruistic death of cells during tissue remodeling or the elimination of T-cell populations after the reversal of viral infection.[65] Apoptosis is characterized morphologically by cell shrinkage, membrane blebbing, chromatin condensation, and ultimate fragmentation of the cell into apoptotic bodies. Molecular characteristics include activation of class of proteases (protein degrading enzymes) the caspases. These are involved in intracellular death signaling. Additionally, activation of enzymes that degrade DNA (endonucleases) is seen. In the final stage of apoptosis, the cell corpses exhibit "eat me" signals a process that involves alteration of the cell surface (including expression of annexin V binding sites on the plasma membrane) permitting neighboring cells to remove the apoptotic bodies without the induction of an inflammatory reaction. Apoptosis is mediated by changes in the outer mitochondrial membrane that lead to the release of death signals such as cytochrome c. BCL2 and related family members function as anti-apoptotic factors by blocking pro-death changes in mitochondrial membrane potential or as anti-apoptotic factors by antagonizing the pro-apoptotic factor BAX. The terminal stages involve DNA degradation, which cleaves DNA into 50- to 300-kb fragments and later into smaller fragments by cleavage of the exposed regions of DNA between nucleosomes.[65]

REPLICATIVE SENESCENCE

In addition to vulnerability to overt killing, all somatic cells possess replicative checkpoints that place limits on the number of permitted cell divisions over the lifetime of the cell. For unlimited growth, cells must bypass crisis, the point at which the telomeres on chromosomes have shortened enough to prevent successful future cell divisions. TP53-sensitive (and CDKN1A-sensitive) expression of the enzyme telomerase in tumor cells is sufficient to bypass crisis and permit unlimited growth in some cells (see Figure 2-2). In addition to crisis, cells undergo telomerase-independent forms of senescence, regulated in many cases by the retinoblastoma protein RB1 and the CDK inhibitory protein CDKN2A (formerly designated p16).[66,67] However, TP53 appears to be the primary regulator of senescence and activated this process downstream of DNA damage detected by ATM activation or other pathways.[27] Few experiments have been carried out to examine the role of senescence in responses to ionizing radiation, although in one study, ionizing radiation induced premature senescence that occurred independently of ATM expression.[68]

ACTIVATION OF ANABOLIC SIGNALING PATHWAYS BY IONIZING RADIATION

One of the primary features of cancer is its autonomy in terms of growth signals. There are three operationally defined steps in growth signaling: (1) transmembrane receptor occupation by growth factors and transmembrane signaling, (2) stimulation of cytoplasmic cascades that amplify primary signals, and (3) activation of downstream effector proteins. Step 1 classically involves dimerization and autophosphorylation of receptor tyrosine kinases (RTKs) or recruitment of nonreceptor tyrosine kinases (NRTKs). Such events occur commonly after ionizing radiation, and a generalized activation of the HER1 through HER4 RTKs occurs in irradiated cells (Figure 2-4).[69] Ionizing radiation can induce the release of growth factors such as epidermal growth factor (EGF, TGF-α) and paracrine activation of growth in adjacent cells.[69] Increases in cellular phosphotyrosine levels were observed after exposure to x-rays in a number of cells, and activation of NRTKs has been observed.[69] Of particular importance in step 2 processes are members of the mitogen-activated protein kinase (MAPK) family, which play crucial roles in cell growth and survival. Ionizing radiation stimulates the activity of MAPK members that carry the mitogenic signal (e.g., MAPK1 [formerly ERK2], MAPK3 [formerly ERK1]).[70] The paradigm for step 3 is the activation of factors that bind the promoters of mammalian immediate early genes such as *FOS* and *EGR1* through receptor activation, tyrosine phosphorylation, and MAPK activation. Such transcription factors include serum response factor, ETS domain factors such as TCF62, ELK-1, activating protein-1 (AP1), and cyclic adenosine monophosphate-binding protein (i.e., cAMP response element binding [CREB]).[71] Each of these factors is activated by ionizing radiation, and the promoter of at least one immediate early gene (*EGR1*) is induced by radiation treatment. Therefore, exposure to ionizing radiation could amplify the growth signals already active in cancer cells, suggesting that the RTK-MAPK pathway may be a fruitful target in the selection of radiation sensitizers.[69,72]

Radiation-induced signaling may be secondary to the free radical generation. Radiation produces two main species that combine to kill cells in a clinical setting and that may also double as primary stress signals.[10] These signals are reactive oxygen species (ROS) and DSBs discussed previously. ROS play a role in signal transduction after stimulation by platelet-derived growth factor (PDGF) and phorbol esters.[70,73] ROS

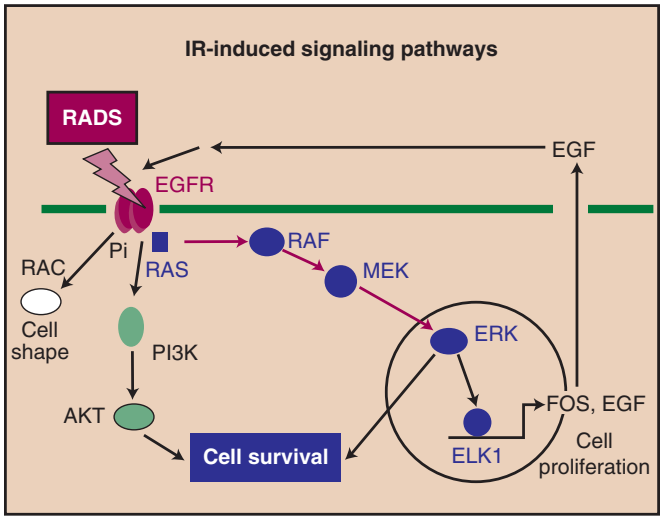


Figure 2-4 Induction of transmembrane signals by ionizing radiation (IR), which directly activates several transmembrane receptors. Free radicals induced in cells by ionizing radiation can activate transmembrane tyrosine kinase receptors such as the epidermal growth factor (EGFR) and HER2, HER3, and HER4 (not shown). Receptor activation gives rise to a network of signals that lead to activation of the powerful prosurvival PI3K/AKT pathway and the growth-mediating RAF/MEK/ERK cascade. Further amplification may take place as a result of transcriptional induction and the release from cells of cytokines with growth factors such as EGF and transforming growth factor-α, which give rise to secondary activation of receptors.

produced by cellular stress, such as peroxide, superoxide, hydroxyl radicals, and nitrous oxide, may feed into this ROS-transduced pathway at a number of places.[74] Cell kill by radiation is closely correlated with the accumulation of DSBs. The dictates of logic and much preliminary evidence strongly suggest a role for DSBs in the sensing and response to ionizing radiation.[27] Cells evidently possess at least one system to sense and respond to radiation, the ATM family of protein kinases, which appear to be situated close to the primary event in DSB-induced signaling as described previously.[27,53] ATM activation leads to phosphorylation of TP53, which couples DSB accumulation to cell cycle arrest in G_1.[30] Vectoral signaling is then coupled to the metronomic events of the cell division cycle. ATM belongs to the lipid kinase family that includes PIK and DNA-PK.[27,40] PIK is activated by ionizing radiation and is required for cell survival during irradiation. DNA-PK is intimately involved in cell responses to radiation, and its ability to sense DSBs in combination with DNA end-binding proteins XRCC6 and XRCC5 suggests that it may be able to function independently of ATM in cell signaling after exposure to ionizing radiation.[56]

Regulatory changes in cells after irradiation may therefore be caused by the aggregate and combinatorial interactions of three distinct types of signaling pathways: classic signal transduction, signaling pathways mediated by ROS, and those initiated in the nucleus by DSBs.

RADIATION AND THE RNA WORLD

Over recent years there has been a revolution in understanding the role of RNA in biology and cancer.[75] In addition to its housekeeping function as mRNA and rRNA, novel RNAs have been shown recently to play key regulatory roles. Small interfering RNA and microRNA play negative regulatory roles in diminishing specific RNA levels and targeting structures in the 3′ and 5′ regions of mRNA.[76,77] Large noncoding RNA plays a role in regulation of transcription, although its regulation of radiation responses is not known.[78] Study of the roles of these molecules in the radiation response has begun.[77,79]

TUMOR MICROENVIRONMENT AND RESPONSES TO IONIZING RADIATION IN VIVO

In addition to malignant cells, tumors contain normal cells and structural elements, including endothelial cells, fibroblasts, extracellular matrix molecules, inflammatory cells, and blood vessels. The tumor microenvironment is abnormal in being largely deficient in nutrients such as oxygen and glucose, and abundant in the waste products of metabolism such as lactic acid and carbon dioxide.[80,81] Thus, the concentrations of nutrients and cell-cell and cell-matrix contacts are abnormal and may be in a constant state of flux because of intermittent perfusion by the microvasculature. The tumor microenvironment is a key determinant of the response to ionizing radiation. Hypoxic cells are markedly radioresistant because of the requirement for oxygen in the formation of the free radicals that mediate radiation-induced DSBs.[10] Defining the tumor milieu and how it is regulated is thus important in understanding the radiosensitivity of tumors.

Hypoxia, Microenvironment, and Radiation Response

The role of hypoxia in radioresistance has been studied for many years.[10,82] Cell killing by radiation is decreased at intermediate- and low-oxygen conditions, and a number of studies have correlated low pretreatment tumor oxygenation with a worse disease outcome.[83,84] Whether there is a direct cause-and-effect relationship between low-oxygen concentration and outcome remains to be resolved, primarily through clinical trials that deliberately attempt to correct the poor oxygenation status of the tumors. In addition to directly inhibiting cell killing by ionizing radiation, hypoxia may amplify the mutator phenotype in the severely hypoxic cells in the central cores of tumors, increasing the rate of evolution of resistant clones and amplifying the malignant phenotype.[85]

Many genes are induced or repressed within the tumor microenvironment.[86,87] The largely unregulated environment found in poorly vascularized tumors could be thought of as resembling the conditions under which many unicellular organisms grow. Survival for these organisms depends on their ability to withstand environmental stresses such as nutritional deprivation, temperature and pH changes, radiation exposure (e.g., ultraviolet light, x-rays), and xenobiotics. Among the molecules induced by hypoxia are members of the unfolded protein response family stress proteins (e.g., glucose-regulated proteins [GRPs], redox enzymes such as heme oxygenase, metallothionein IIA, DT-diaphorase; transcription factors such as JUN, FOS, AP1, TP53, nuclear factor-KB [NF-κB], HIF1) and growth factors or cytokines (e.g., erythropoietin, vascular endothelial cell growth factor [VEGF], EGF receptor, interleukin-1α [IL-1α]).[86,87] HIF1 appears to be of key significance in the response of cells to the microenvironment at the molecular level because this transcription factor regulates expression of many of the factors that mediate angiogenesis.[88]

Tumor Angiogenesis

Another of the hallmarks of cancer is the ability of cancer cells to induce de novo angiogenesis to sustain growth.[36,89,90] Tumors contain multiple angiogenic factors including angiopoietin, acidic fibroblast growth factor (FGF), basic FGF, angiogenin,

PDGF, prostaglandins E_1 and E_2, transforming growth factor-β, tumor necrosis factor-α, and VEGF (also known as vascular permeability factor). The VEGF family has received much attention as potential therapeutic targets. In addition antiangiogenic factors are also expressed and include angiostatin, endostatin, interferon-α and interferon-β, thrombospondin, and tissue inhibitor of metalloproteinase.[90,91] The outcome for vascularization and tumor growth depends on a balance between the factors.

The use of antiangiogenic therapy with local radiation has been investigated in several laboratories.[92,93] One important aspect for combining vascular targeting and radiation therapy and probably also for systemic agents is whether the antiangiogenic therapy increases or decreases tumor oxygenation. The relationship between angiogenesis, antiangiogenic therapy, and the more conventional cancer therapies remains to be elucidated but offers some exciting areas of investigation. The ability to suppress metastases and hold local tumor growth[92,93] offered by vascular targeting may greatly increase the potential role for radiation therapy. However, if antiangiogenic therapy leads to decreased perfusion or hypoxia, the effects are likely to be confounding. Given the role of blood vessels in late radiation injury, the use of antiangiogenic therapy with radiation in clinical treatment will require careful study and assessment of long-term toxicities and late effects.

RADIATION AND THE CELL BIOLOGY OF CANCER

Study of the cell biology of cancer has lagged behind molecular biology studies. However, it is apparent that, rather like normal tissues, tumors contain only a small proportion of cells that can proliferate in the long term. These are known as cancer stem cells by analogy with their normal counterparts. As such cells are resistant to most treatments, targeting them may be important in improving cancer therapy; this is an area of intensive study. In addition to heterogeneity conferred by cell differentiation hierarchies, tumors contain populations of normal cells that confer a growth-promoting niche in the tissue and protect tumor cells by suppressing immunity. Such cells include tumor-associated macrophages and fibroblasts, myeloid suppressor cells, and regulatory T cells. Heterogeneity in terms of cell hierarchy and normal cell infiltration may determine many key features of tumor progression including invasion and metastasis of cancer cells and susceptibility to immune killing. The role of radiation in these processes is under investigation and may be a key area for future development.

TARGETING MOLECULAR PATHWAYS IN THE RADIATION RESPONSE: DISCOVERY OF NEW DRUGS

The accumulated data regarding the signaling circuitry underlying the response of cells to DSBs suggests an opportunity for the development of novel adjuvant therapies. Approaches based on small-molecule inhibitors of specific reactions, RNA interference (small interfering RNAs), and antisense and gene therapy are attractive and follow directly from the basic research available. There is much excitement regarding the potential use of kinase inhibitors in cancer treatment, based on the idea that they work catalytically, are present in small amounts, and often regulate key processes in the cell. The most popular paradigm is a kinase inhibitor, known as imatinib (Gleevec), which has greatly influenced the treatment of hematologic malignancies. Given that the cell cycle checkpoint component of the DNA DSB response is regulated largely at the posttranscriptional level by batteries of protein kinases and phosphatases, many inviting targets are available. Proof of principle that such an approach may work is suggested by studies using agents that inhibit the RAS signal transduction pathway, protein kinase C, or the PIK pathway, which were shown to enhance radiation-induced cell killing.[94,95,96,97,98,99,100] Members of the PIK family may be feasible targets for pharmacologic intervention in the clinic. Loss of function of PIK proteins is usually associated with increased radiosensitivity. Compounds that block the function of these proteins would greatly enhance the efficacy of agents that cause DNA damage, such as radiation therapy, and allow for the treatment of tumors that are particularly radioresistant.

The fungal metabolite wortmannin is a specific inhibitor of the p110 PIK, now designated PIK3CD. Wortmannin forms a covalent adduct with Lys802 of PIK3CD, inactivating the kinase activity.[101,102] This Lys802 is conserved in DNA-PK and AT proteins, suggesting that both would be sensitive to wortmannin. In vitro studies with a wide range of tumor-derived cells, including those of the breast, colon, and prostate, indicate that wortmannin is an effective radiosensitizer of human cells. Wortmannin can inhibit the kinase activity of DNA-PK in vitro and in vivo. DNA-PK also is involved in the activation of TP53 after irradiation of cells, and wortmannin suppresses the activation of TP53 after irradiation. Other studies have shown that wortmannin may exert its primary effect by inhibiting the repair of DNA strand breaks in cells.

In addition to drugs, the development of small interfering RNA approaches offers the promising possibility of "knocking down" selective genes that may mediate resistance.[76] There has been much excitement regarding the use of targeted gene therapy to introduce genes of interest or their antisense partners within viral vectors. Some of the enthusiasm about these approaches has waned because of the potential toxicity of the viral vectors (particularly adenovirus) and a number of other operational problems, such as accurately reaching the target site, achieving sufficient gene production in situ (i.e., drug, enzyme, or toxic molecule) to alter the radiation response, altering the radiation response sufficiently to show an impact on local tumor control, having a positive therapeutic ratio, and ideally, having an impact on survival in addition to enhanced local control. Despite these problems, the approach remains popular, particularly for local expression of products that diffuse from cells, such as cytokines. With the advent of newer, safer vectors for delivery of agents, the approach holds promise.[103]

Previous radiation modifiers in clinical use have been developed based on conventional radiation biology models, such as hypoxia (e.g., radiation sensitizers and enhancers, altered oxygen delivery), the competition model (e.g., thiol depletion and radioprotectors), and increasing susceptibility of DNA to radiation damage (e.g., halopyrimidines).[101,102,104] Although such therapies were not based on the new molecular targets that have more recently been elucidated, much can be learned by studying the relationships between these therapies and the molecular processes. For example, it may be possible to understand how better to use the halopyrimidines in relation to cell cycle checkpoints, hypoxic sensitizers in relation to hypoxia-induced processes, and protectors in terms of specific DNA lesions or activity of repair enzymes.

As mentioned, tumor cells exist in a unique microenvironment that is depleted of oxygen and glucose and rich in carbon dioxide and lactate. Drugs may be designed to prosper in this altered microenvironment and enhance treatment efficacy. Among these more conventional approaches, the bioreductive agents, such as mitomycin C and tirapazamine, require enzymatic activation that occurs preferentially in hypoxic environments.[105]

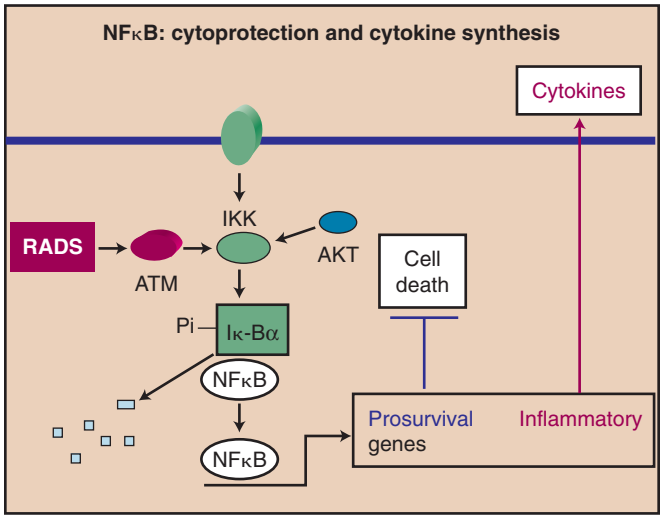


Figure 2-5 Ionizing radiation activates the NF-κB pathway. NF-κB is induced by inflammatory ligands such as bacterial products that stimulate the IKK kinase complex and activate NF-κB through destruction of the inhibitor IK-Bα. This pathway also can be activated by ionizing radiation through a number of mechanisms, particularly IKK activation by the DNA DSB sensor molecule ATM. NF-κB activation has at least two known consequences: increased cell survival through synthesis of death-antagonizing NF-κB products and proinflammatory effects caused by increased expression of cytokines and adhesion factors.

NORMAL TISSUES

Radiation therapy depends for its selective treatment of cancer on tight control of delivery to tumors and avoidance of normal tissues. Most normal tissues that express wild-type TP53 are sensitive to TP53-induced PCD.[106] Renewable tissues such as hematopoietic stem cells and crypt cells in the gastrointestinal tract may be particularly vulnerable.[33] Indirect forms of lethality may occur in whole-body irradiation, leading to the death of hematopoietic stem cells in the bone marrow, or depletion of mature tissues can lead to secondary damage caused by red blood cell depletion, immunosuppression, and gross infection as the gastrointestinal lining is lost.[10,13,14]

Additional changes occur that are thought to be the result of a persistent oxidative state in tissues such as lung, which may lead to chronic inflammatory changes and induction of cytokines and adhesion molecules.[107,108] Changes may result from induction of the transcription factor NF-κB by ionizing radiation in an ATM-dependent manner (Figure 2-5).[109,110] NF-κB, in addition to its role in cytoprotection, plays a broader part in the acute inflammatory response through transcription of a wide range of proinflammatory cytokines and adhesion molecules.[111] Induction of an inflammatory environment in normal tissues may be a side effect of activation of NF-κB in a cytoprotective reaction (see Figure 2-5).

BASIC CONCEPTS AND TECHNIQUES OF RADIATION SCIENCES

Techniques and approaches to molecular and cellular biology in humans and other model organisms, largely developed in the 1960s and 1970s, continue to revolutionize knowledge of basic cancer biology and radiation sciences. The ability to inactivate genes by homologous recombination, which came into frequent use in the 1980s, has permitted the movement of this approach into animal models, allowing study of molecular genetics in vivo. This has permitted us to test the significance of the key genes in the cell cycle, DNA repair, and PCD, which mediate the sensitivity of cells to ionizing radiation and define their role in radiation response. Novel "big biology" approaches, including such genomic techniques as microarray screening, deep sequencing and mass spectrometry permit discovery-based research with the potential for fundamental advances.[112-114] Because of the progress in deciphering human and other genomes in the 1990s, a total readout of expression of all human genes can be undertaken. This has opened the way for identification of signature genes in human cancers that correspond to poor prognosis, treatment resistance, and metastasis. The impact of gene expression profiling on radiation biology is perhaps less than in general cancer biology because most responses to genomic stress occur at the post-transcriptional level. The development of proteomics is being developed, based on advances in mass spectrometry, and this approach allied with deep sequencing may permit the rapid study of critical changes in posttranslational modification, such as phosphorylation, acetylation, and ubiquitination, which mediate many regulatory responses to genomic stress. The increased speed and accuracy of drug development, based on robotic approaches to assaying chemical libraries and in silico design, should also increase the rate of drug discovery and hasten the translation of molecular findings into the clinic.

SUMMARY

The past 20 years have seen an impressive transformation in understanding of the genes that determine the development of the cancer cell, its subsequent response to radiation and chemotherapy, and the signaling circuitry that links the products of such genes to DNA damage response pathways. The rate of accumulation of new knowledge, particularly in the field of DNA sensing and repair, has been so rapid that its future impact on the practice of radiation oncology is difficult to predict. One area of incomplete knowledge is the exact molecular mechanisms of radiation cell death, their link to the DNA damage response pathways, and how they might be altered by the evolving patterns of gene expression in tumor progression. This dilemma is well illustrated by TP53, the factor that in normal cells links the accumulation of genomic damage to cell death by apoptosis, autophagy, and senescence but that is inactivated in most cancers. In contrast, identification of ATM as the master regulator of the response to genomic stress suggests this pathway as one that can be targeted for radiation sensitization. Another interesting possibility for targeting new treatment approaches is that of necrosis, particularly in tumor cells, in which the pathways of PCD have been closed off through alterations in the TP53 and BCL2 pathways. The success of future approaches to cancer treatment and cure will be determined by their ability to inhibit or facilitate normal and adaptive changes in cell physiology to maximize the deleterious effects on the tumor while preserving viability of the surrounding normal tissues.

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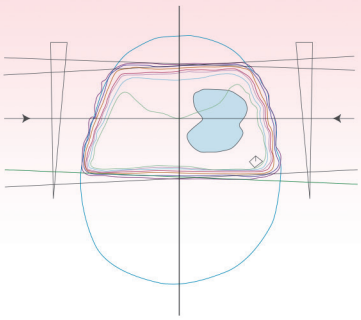
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CHAPTER

3 Dose-Response Modifiers in Radiation Therapy



Michael R. Horsman, Jacob C. Lindegaard, Cai Grau, Marianne Nordsmark, Jan Alsner, and Jens Overgaard

When cancer patients undergo radiation therapy there is a clear dose-response relationship between the dose delivered and the response of the tumor to the radiation. This is illustrated in Figure 3-1. Unfortunately, there is also an increase in normal tissue damage with increasing radiation dose, and it is this complication that limits the total radiation dose that can be given. Substantial effort has been made to try and modify these dose-response relationships and to thus increase the separation between the tumor and normal tissue dose-response curves. The approach has been either to selectively increase the radiation damage in tumors without affecting the normal tissues or by protecting the normal tissues without having a similar protective effect in tumors.

Agents capable of enhancing radiation response include certain conventional chemotherapeutic agents, the halogenated pyrimidines, and treatments that specifically overcome radioresistance resulting from the presence of hypoxic cells that occur as a result of the environmental conditions within most solid tumors. The most widely investigated method applied to the hypoxia problem is radiosensitization of the hypoxic cells with either electron-affinic sensitizing drugs or hyperthermia. Another approach often used to reduce hypoxia—especially in experimental systems—involves increasing oxygen availability (1) by having patients breathe high-oxygen-content gas, (2) introducing perfluorochemical emulsions into the vascular system to increase the oxygen carrying capacity of the blood, (3) modifying oxygen transport or delivery by using agents that affect hemoglobin, (4) using drugs that increase tumor blood perfusion, or (5) a more recent approach of decreasing the oxygen consumption rate of the "nonhypoxic" cell population, thereby increasing the oxygen diffusion distance. Many experimental studies have also demonstrated that hypoxic cells can be preferentially destroyed by bioreductive drugs that are active under reduced oxygen conditions, or again using hyperthermia; each of these hypoxic-cell cytotoxins improve the radiation response of tumors. Another group of agents, which preliminary data suggests have the potential to enhance radiation damage, are the so-called vascular targeting agents. These include drugs that inhibit angiogenesis, the process by which tumors develop their own vascular supply, or agents that preferentially damage the already established tumor vessels.

Radiation protectors fall into several categories based on the timing of their administration in relation to radiotherapy. There are the true "radiation protectors," in particular sulfhydryl compounds, which are used as a prophylactic strategy and administered before radiotherapy and primarily appear to interact with radicals that are formed as a result of radiation exposure. Another group consists of "radiomitigators" that reduce the effects on normal tissues before the emergence of symptoms if given during or shortly after radiotherapy. Finally, there are "therapeutic agents," which are administered after radiotherapy to treat symptoms that have already developed, especially fibrosis.

Radiosensitization by conventional chemotherapeutic agents (e.g., cisplatin, 5-fluorouracil, and mitomycin C), halogenated pyrimidines (e.g., 5-bromodeoxyuridine and 5-iododeoxyuridine), and hyperthermia are discussed in detail elsewhere in this book. In this chapter, the focus will be on hypoxic cell modifiers, vascular targeting drugs, and radioprotectors.

THE HYPOXIA PROBLEM

Importance of Oxygen

In 1909 Gottwald Schwarz,[1] in a simple but elegant experiment, demonstrated that the radiation response of skin was markedly decreased if the blood flow in the irradiated area was reduced by compression. Although he did not acknowledge that the phenomenon was the result of a lack of oxygen, his study was probably the first radiobiologically oriented clinical study implicating the importance of environmental parameters in the outcome of radiotherapy. This finding was used to introduce the concept of "kompressionsanämie" by which the skin was made anemic, thereby allowing a higher dose to be given to deeply situated tumors. Following the work of Schwarz, in 1910 Müller[2] reported that tissues in which the blood flow was stimulated by diathermia showed a more prominent response to radiation. This early study not only demonstrated the importance of oxygen supply in radiotherapy, but it was also the first clinical approach showing how resistance could be overcome by using hyperthermia. Subsequently, sporadic clinical and experimental observations indicated the importance of sufficient blood supply to secure an adequate radiation response. These observations led Gray et al[3] in the early 1950s to postulate that oxygen deficiency or hypoxia was a major source of radiation resistance.

The first clinical indication that hypoxia existed in tumors was made around the same time by Thomlinson and Gray[4] when, from histological observations in carcinoma of the bronchus, they reported seeing viable tumor regions surrounded by vascular stroma from which the tumor cells obtained their nutrient and oxygen. As the tumors grew, the viable regions expanded and areas of necrosis appeared at the center. The thickness of the resulting shell of viable tissue was found to be between 100 and 180 μm, which was within the same range as the calculated diffusion distance for oxygen in respiring tissues. It was thus suggestive that as oxygen diffused from the stroma, it was consumed by the cells and, although those beyond the diffusion distance were unable to survive, the cells immediately bordering the necrotic area might be viable yet hypoxic. In 1968, Tannock[5] described an inverted version of the Thomlinson and Gray picture, with functional blood vessels surrounded by cords of viable tumor cells outside of which were areas of necrosis. This "corded" structure, illustrated in Figure 3-2, is the more typical picture found in most solid tumors.[6] It arises because the tumor blood vessels, which are derived from the normal tissue vessels by a process of angiogenesis, are inadequate to meet the needs of the rapidly growing tumor cells. This hypoxia is more commonly called *chronic hypoxia*.

It was also suggested that hypoxia in tumors could be acute in nature.[7] However, it was not until later that Chaplin et al[8] were able to confirm the existence of acutely hypoxic cells in tumors and demonstrate that these cells were the result of

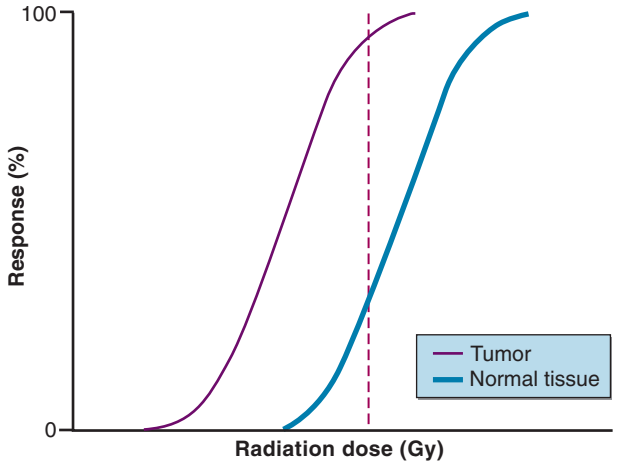


Figure 3-1 Schematic illustration of the proportion of patients cured and patients with normal tissue complications as a function of the total radiation dose received.

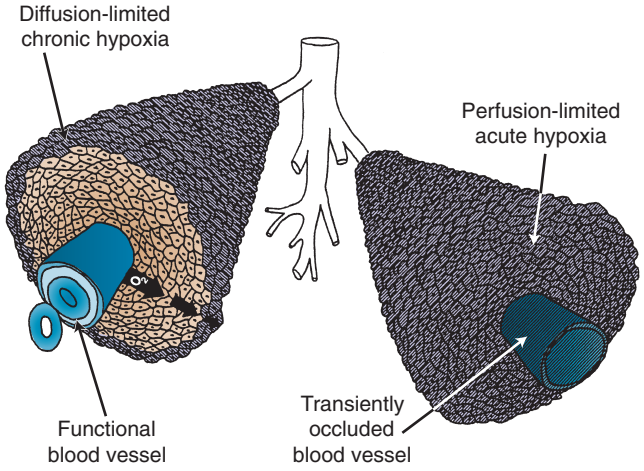


Figure 3-2 Schematic representation of the interrelationship between tumor cells and the vascular supply. On the left, cells are seen growing as a "corded" structure around a functional vessel from which the cells receive their oxygen supply. As oxygen diffuses out from the vessel it is used up, thus the outermost viable cells (shown by the shading) are oxygen deprived or chronically hypoxic. A similar arrangement is seen on the right, but here flow through the vessel is transiently stopped, thus making all the cells oxygen deprived.
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transient stoppages in tumor blood flow (see Figure 3-2). To date, these temporary cessations in blood flow have been observed in mouse and rat tumors, as well as human tumor xenografts, with anywhere from around 4% to 8% of the total functional vessels involved,[9] although the exact causes of these stoppages are not known. The current use of chronic or acute to explain hypoxia in tumors is probably an oversimplification of the real situation. Chronic hypoxia generally refers to prolonged and reduced oxygen concentrations that influence radiation response, but there is evidence that oxygen concentrations that are higher, yet below normal physiological levels, are often found.[10] Furthermore, reduced perfusion can be both partial as well as total,[11] and while cells under the former condition would be oxygen deprived, with the latter they would be starved of oxygen and nutrients, and as such, their survival and response to therapy would be expected to be different.

Evidence for Hypoxia in Tumors

In experimental tumors it is not only relatively easy to identify hypoxia, but one can also quantitatively estimate the percentage of cells that are hypoxic. Three major techniques are routinely used.[12] These are the paired survival curve, the clamped tumor growth delay, and the clamped tumor control assays. All involve a comparison of the response of tumors when irradiated under either normal air-breathing conditions or when tumors are artificially made hypoxic by clamping. Using these procedures hypoxia has been directly identified in most animal solid tumors, with the values ranging from less than 1% to well more than 50% of the total viable cell population.[12] Unfortunately, none of these procedures can be applied to the clinical situation. One therefore must rely on indirect techniques.

Estimating hypoxia in human tumors has generally involved the use of indirect methods.[13] Some of the earliest attempts focused on the vascular supply because it was only via the tumor vasculature that oxygen could be delivered. The endpoints included immunohistochemical estimates of intercapillary distance, vascular density, and distance from tumor cells to the nearest blood vessel[14-16]; oxyhemoglobin saturation determined using cryophotometry, or noninvasively with near-infrared spectroscopy or magnetic resonance imaging (MRI)[17-19]; or measurements of tumor perfusion using MRI, computed tomography (CT), or positron emission tomography (PET).[20-22] With the finding that hypoxia could up-regulate gene/protein expression, it was suggested that endogenous markers could be used to identify hypoxia.[23] The principal markers have included hypoxia inducible factor 1 (HIF-1), carbonic anhydrase IX (CAIX), the glucose transporters GLUT-1 and GLUT-3, and osteopontin (OPN).[24-27] These have been applied either individually or combined with other endogenous markers in gene signatures.[13] More popular techniques involve measurements of the binding of exogenous markers. This can be achieved following immunohistological analysis of biopsied sections, using, for example, pimonidazole or EF5.[28,29] It can also be done noninvasively with PET, single-photon emission computed tomography (SPECT), or MRI analysis of radioactively labeled nitroimidazoles (i.e., [^{18}F] labeled misonidazole or FAZA; [^{123}I] labeled azomycin arabinoside), or PET imaging of [$^{60\text{-}64}$Cu]-ATSM.[30-33]

The most direct method involves determining oxygen partial pressure (PO_2) distributions with polarographic electrodes.[34-39] How this approach can be used to detect hypoxia and relate the measurements to radiotherapy outcome is illustrated in Figure 3-3. In this international multicenter study in head and neck cancer patients, their tumor's pO_2 was measured before radiation therapy and was found to correlate with overall survival, in that those patients with lower tumor oxygenation status, did significantly worse.[40]

Probably the best evidence for the existence of hypoxia in human tumors comes from the large number of clinical trials in which hypoxic modification has shown some benefit.[41] The latter situation constitutes a circular argument: if hypoxic modification shows an improvement then hypoxic clonogenic cells must have been present in tumors. It is, however, likely that even tumors with the same histological makeup and of the same type have substantial heterogeneity with respect to the extent of hypoxia. It must be admitted that today, a century after the first clinical description, the importance of hypoxia and its influence on the outcome of radiotherapy is still the subject of substantial debate. However, we will now discuss in detail how the different hypoxic modifiers have been used to modify the radiation dose response of tumors.

TABLE 3-1 Multicenter Randomized Trials with Hyperbaric Oxygen (HBO)

Site and Study	No. of Patients	Endpoint*	HBO	Air
HEAD AND NECK CARCINOMA				
MRC 1st trial (1977)	294	Control (5 yrs)	53%	30% ($p < 0.01$)
MRC 2nd trial (1986)	106	Control (5 yrs)	60%	41% ($p < 0.05$)
UTERINE CERVIX CARCINOMA				
MRC (1978)	320	Control (5 yrs)	67%	47% ($p < 0.001$)
BRONCHOGENIC CARCINOMA				
MRC; 60 Gy/40 fx (1978)	51	Survival (2 yrs)	15%	8% (NS)
MRC; 36 Gy/6 fx (1978)	123	Survival (2 yrs)	25%	12% ($p < 0.05$)
CARCINOMA OF THE BLADDER				
MRC (1978)	241	Survival (5 yrs)	28%	30% (NS)

fx, *Fractions;* NS, *not significant.*
**Endpoints were control (locoregional control) or survival. See Overgaard[53] for additional information.*

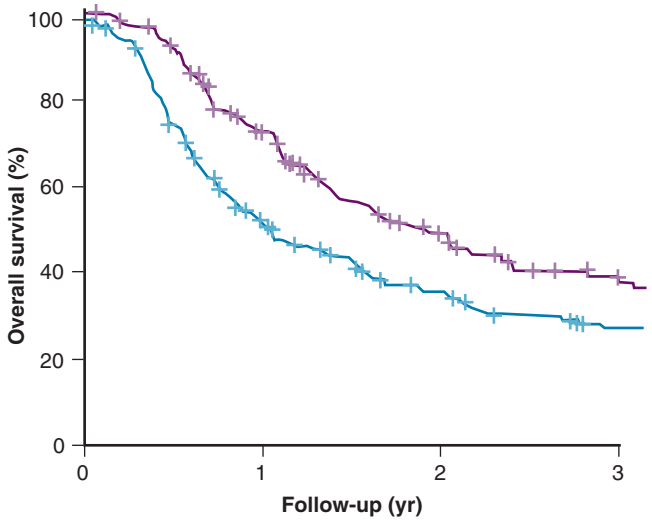


Figure 3-3 Oxygen levels were measured with Eppendorf electrodes before radiation therapy in 397 patients with squamous cell carcinomas of the head and neck. Tumors were stratified by whether the fraction of pO_2 values ≤ 2.5 mm Hg (HP2.5) were above or below the median value for the whole group (i.e., 19%). The lines show Kaplan Meier estimates of actuarial overall survival probability for patients with less hypoxic tumors (HP2.5 ≤ 19%; *red line*) compared with more hypoxic tumours (HP2.5 > 19%; *blue line*), $p = 0.006$.
From Nordsmark M, Bentzen SM, Rudat V, et al: Prognostic value of tumor oxygenation in 397 head and neck tumors after primary radiation therapy. An international multi-center study. Radiother Oncol 77:18–24, 2005, with permission.

OVERCOMING TUMOR HYPOXIA

High-Oxygen-Content Gas Breathing

Because the oxygen supply to tumors is insufficient to meet the needs of all the tumor cells, radiation-resistant hypoxia develops; therefore, an obvious solution to improving the tumor's radiation response would be to increase the oxygen supply. This has been tried, both experimentally and clinically, by simply allowing the tumor bearing host to breathe high-oxygen-content gas mixtures before and during irradiation.

Early experimental studies reported that breathing either oxygen and carbogen (95% O_2 + 5% CO_2) could substantially enhance the response of murine tumors to radiation and that the best effect was generally seen when the gasses were inspired under hyperbaric (typically 3 atmospheres [3 atm]) rather than normobaric conditions.[42,43] This is not surprising because hyperbaric conditions would be expected to saturate the blood with oxygen more than normobaric conditions. However, later studies indicated that the radiosensitizations produced by normabaric oxygen or carbogen were quite substantial;[44,45,46] because it is quicker and easier to breathe gas under normobaric conditions, the use of cumbersome, expensive, and complex hyperbaric chambers is probably not necessary.

Clinically, the use of high-oxygen-content gas breathing, specifically under hyperbaric conditions, was introduced relatively early by Churchill-Davidson et al.[47] Most trials were fairly small, and suffered from the applications of unconventional fractionation schemes, but it appeared that the effect of hyperbaric oxygen was superior to radiotherapy given in air, especially when few and large fractions were applied.[47-49] In the large, multicenter clinical trials conducted by the British Medical Research Council (Table 3-1), the results from both uterine cervix and advanced head and neck tumors showed a significant benefit in local tumor control and subsequent survival.[48,50-53] The same findings were not observed in bladder cancer nor were they seen in a number of smaller studies.[53] In retrospect, the use of hyperbaric oxygen was stopped somewhat prematurely. This was partly the result of the introduction of hypoxic radiosensitizers and partly because of problems with patients' compliance; it has been claimed that hyperbaric treatment caused significant suffering, but the discomfort associated with such a treatment must be considered minor compared to the often life-threatening complications associated with chemotherapy, which is used with less restrictive indications.

The use of high-oxygen-content gas breathing under normobaric conditions to radiosensitize human tumors has also been tried clinically, but it failed to show any dramatic improvement.[54-56] In the most recent study this may have been the result of size limitation,[56] but in previous studies it may have been caused by the failure to achieve the optimum preirradiation gas breathing time.[54,55] Experimental studies have shown that the amount of time is critical for the enhancement of radiation damage and that it can vary from tumor to tumor.[43-45,57]

Hypoxic Cell Radiosensitizers

An alternative approach to the hypoxia problem is the use of chemical agents that mimic oxygen and preferentially sensitize the resistant population to radiation. The advantage of these drugs over oxygen is that they are not rapidly metabolized by the tumor cells through which they diffuse and thus

TABLE 3-2 Multicenter Randomized Trials with Nitroimidazoles

Site and Study	No. of Patients	Sensitizer	Endpoint*	RT and Sensitizer	RT Alone
HEAD AND NECK CARCINOMA					
DAHANCA 2 (1989)	626	MISO	Control (5 yrs)	41%	34% ($p < 0.05$)
MRC (1984)	267	MISO	Control (>2 yrs)	40%	36% (NS)
EORTC (1986)	163	MISO	Control (3 yrs)	52%	44% (NS)
RTOG (1987)	306	MISO	Control (3 yrs)	19%	24% (NS)
RTOG 79-04 (1987)	42	MISO	Control (2 yrs)	17%	10% (NS)
DAHANCA 5 (1992)	414	NIM	Control (5 yrs)	49%	34% ($p < 0.002$)
RTOG 85-27 (1995)	500	ETA	Control (2 yrs)	39%	38% (NS)
European multicenter (1991)	374	ETA	Control (2 yrs)	57%	58% (NS)
UTERINE CERVIX CARCINOMA					
Scandinavian study (1989)	331	MISO	Control (5 yrs)	50%	54% (NS)
MRC (1984)	153	MISO	Control (>2 yrs)	59%	58% (NS)
RTOG (1987)	119	MISO	Control (3 yrs)	53%	54% (NS)
MRC (1993)	183	PIM	Control (4 yrs)	64%	80% ($p < 0.01$)
GLIOBLASTOMA					
Scandinavian study (1985)	244	MISO	Survival	10	10 (NS)
MRC (1983)	384	MISO	Survival	8	9 (NS)
EORTC (1983)	163	MISO	Survival	11	12 (NS)
RTOG (1986)	318	MISO	Survival	11	13 (NS)
BRONCHOGENIC CARCINOMA					
RTOG (1987)	117	MISO	Survival	7	7 (NS)
RTOG (1989)	268	MISO	Survival	7	8 (NS)

DAHANCA, *Danish Head and Neck Cancer study;* EORTC, *European Organization for Research and Treatment of Cancer;* ETA, *etanidazole;* MISO, *misonidazole;* MRC, *Medical Research Council;* NIM, *nimorazole;* NS, *not significant;* PIM, *pimonidazole;* RT, *radiation therapy;* RTOG, *Radiation Therapy Oncology Group.*
**Endpoints were control (loco-regional control) and survival (median survival in months). See Overgaard[61] for additional information.*

the drugs can penetrate further than oxygen and so reach all the tumor cells. In the early 1960s, researchers found that the efficiency of radiosensitization was directly related to electron-affinity[58] and that ultimately led to in vitro studies demonstrating preferential radiosensitization of hypoxic cells by highly electron-affinic nitroaromatic compounds.[59,60] Several of these compounds were later shown to be effective at enhancing radiation damage in tumors in vivo,[61] and as a result, they underwent clinical testing.

The drugs reaching clinical evaluation include metronidazole, misonidazole, benznidazole, desmethylmisonidazole, etanidazole, pimonidazole, nimorazole, ornidazole, sanazole, and doranidazole. Initial clinical studies were with metronidazole in brain tumors and were followed, in the latter part of the 1970s, by a boom in clinical trials exploring the potential of misonidazole as a radiosensitizer.[53,61,62] The results from the multicenter randomized trials are summarized in Table 3-2. Most of the trials with misonidazole were unable to generate any significant improvement in radiation response, although a benefit was seen in some trials, especially the second Danish Head and Neck Cancer study (DAHANCA 2), which found a highly significant improvement in the stratification subgroup of pharynx tumors but not in the prognostically better glottic carcinomas.[63] The overall impression of the "misonidazole-era" was a prolongation of the inconclusive experience from the hyperbaric oxygen trials, namely, that the problems related to hypoxia had not been ruled out indefinately.[61] Therefore, the search for more efficient or less toxic hypoxic sensitizers continues. Furthermore, the experience from the misonidazole trials has been taken into account to select a more homogeneous tumor population in which hypoxia is more likely to be present.

Results from subsequent randomized trials with other nitroaromatic compounds have been conflicting. The European pimonidazole trial in uterine cervix was disappointing,[64] whereas the two other multicenter trials in head and neck cancer, using etanidazole, showed no benefit.[61,65] On the other hand, studies with the low toxic drug nimorazole given to patients with supraglottic and pharynx carcinomas (DAHANCA 5) showed a highly significant benefit in terms of improved locoregional tumor control and disease-free survival rates (Figure 3-4),[66] thereby confirming the result of the DAHANCA 2 study. More recent trials with the 3-nitrotriazole compound, sanazole (AK-2123), in uterine cervical cancer[67] and doranidazole in pancreatic cancer[68] demonstrated significant improvements in both local tumor control and overall survival.

The potential benefit of using hypoxic radiosensitizers to improve radiotherapy is probably best illustrated from a recent meta-analysis of randomized clinical studies in squamous cell carcinoma of the head and neck.[69] These results are summarized in Figure 3-5 and clearly showed that radiosensitizer modification of tumor hypoxia significantly improved locoregional tumor control and overall survival with odds ratios of 0.71 and 0.87, respectively. Although the overall observed gain were small (5% to 10% for local control and 0% to 6% for survival) they are actually relevant. We can conclude that the nonsignificant outcome of most clinical trials (see Table 3-2) is not the result of a biological lack of importance of hypoxia, but in most cases is considered a consequence of poor clinical trials methodology with an overly optimistic study design and an expected treatment gain that goes far beyond what is reasonable. Overall, the results with nitroimidazoles add to the general consensus that if a nontoxic hypoxic modification can be applied, then such treatments may certainly be relevant as a baseline therapy together with radiotherapy for cancers such as advanced head and neck cancer.

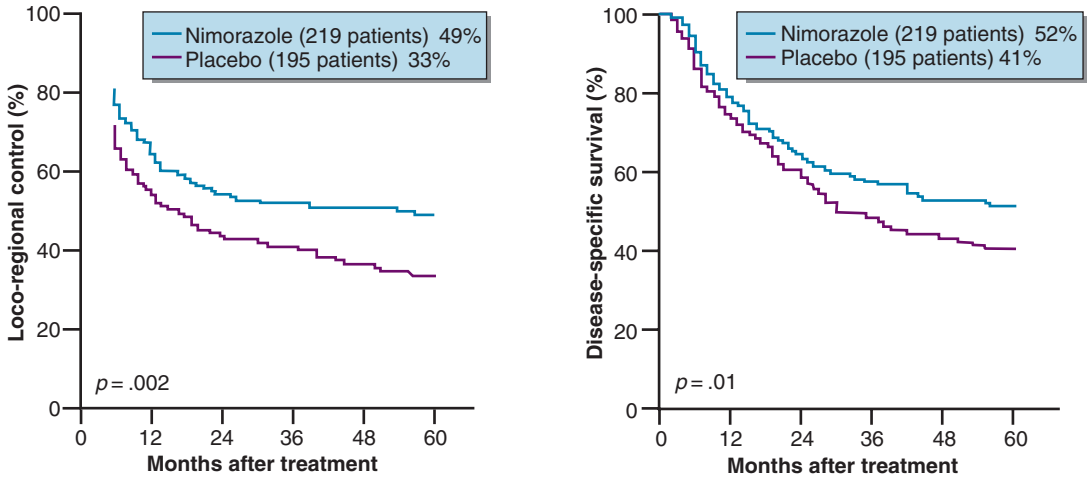
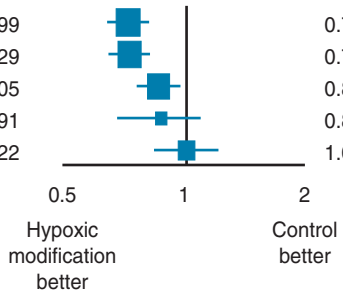


Figure 3-4 Actuarial estimated loco-regional tumor control and disease-specific survival rate in patients randomized to receive nimorazole or placebo in conjunction with conventional radiotherapy for carcinoma of the pharynx and supraglottic larynx.
Reprinted from Overgaard J, Sand Hansen H, Overgaard M, et al: A randomised double-blind phase III study of nimorazole as a hypoxic radiosensitizer of primary radiotherapy in supraglottic larynx and pharynx carcinoma. Results of the Danish head and neck cancer study [DAHANCA] protocol 5-85. Radiother Oncol 46:135–146, 1998, with permission form Elsevier Science.

Head and neck cancer–meta-analysis–summary

Endpoint	Events/Total: Hypoxic Modification	Events/Total: Control	Odds ratio and 95% CI	Odds Ratio	Risk Reduction	NNT**
Loco-regional control	1203/2406	1383/2399		0.71 (0.63–0.80)*	8% (5–10%)*	13
Disease-specific survival	1175/2335	1347/2329		0.73 (0.64–0.82)	7% (5–10%)	14
Overall survival	1450/2312	1519/2305		0.87 (0.77–0.98)	3% (0–6%)	31
Distant metastasis	159/1427	179/1391		0.87 (0.69–1.09)	2% (–1–4%)	57
Radiotherapy complications	307/1864	297/1822		1.00 (0.82–1.23)	0% (–3–2%)	>>



Meta-analysis–hypoxic modification of radiotherapy in HNSCC

*95% confidence interval.
**Numbers of patients needed to treat to achieve benefit in one patients.

Figure 3-5 Meta-analysis of hypoxic modification of radiotherapy in squamous cell carcinomas of the head and neck. Results show summary data from 32 randomized trials (including 4805 patients). Patients received radiation alone or radiation with a hypoxic modifier that included high-oxygen-content gas breathing under normobaric or hyperbaric conditions, or a hypoxic radiosensitizer.
Adapted from Overgaard J: Hypoxic modification of radiotherapy in squamous cell carcinoma of the head and neck—a systemic review and meta-analysis. Radiother Oncol 100:22–32, 2011.

Such a strategy has been adopted in Denmark where nimorazole has become part of the standard radiotherapy treatment in cancer of the head and neck.

Dose Modification Based on Hemoglobin

One of the major factors influencing the delivery of oxygen to tumors is the concentration of hemoglobin. It is, therefore, not surprising that low hemoglobin concentration in general has a negative impact on tumor radiation response. In a review of 51 studies involving 17,272 patients the prognostic relationship between hemoglobin concentration and local tumor control were analyzed, and of these, 39 studies (14,482 patients) showed a correlation, whereas only 12 (2790 patients) did not.[70] However, the relationship between hemoglobin concentration and tumor oxygenation status is not clear because a large (397 patients) international multicenter study in head and neck cancer failed to show a correlation between these parameters.[40]

Although a well-documented causal relationship between hemoglobin concentration, tumor oxygenation, and response to radiotherapy has not been shown, it is likely that such a relationship does exist and there is thus a rationale for investigating the possibility of improving the outcome of radiotherapy in relevant tumor sites in patients with low hemoglobin concentration given curative radiotherapy. This was investigated in two randomized trials using transfusion to raise the hemoglobin levels.[66,71] Despite an initial positive report from the Canadian trial in uterine cervix carcinoma, both studies concluded that the use of such transfusions did not significantly improve treatment outcome. In the DAHANCA 5 study, transfusion was given several days before radiotherapy and

adaptation may have occurred. Based on preclinical data it was hypothesized that any increase in tumor hypoxic fraction induced by anemia will be only transient, with tumors adapting to the lowered oxygen delivery[72]; transfusing anemic animals decreased tumor hypoxia, but this effect also was only transient and the tumors were able to adapt to the increased oxygen level. This suggests that when correcting for anemia it may not necessarily be the final hemoglobin concentration by itself that is important. Rather, an increasing hemoglobin concentration occurring at the time when the tumors are regressing during radiotherapy may be more likely to result in an increased oxygen supply to tumors and a subsequent improvement in response to radiotherapy.

Increasing the hemoglobin concentration by stimulation with erythropoietin (EPO), a hormone normally secreted from the kidney in response to tissue hypoxia and low serum levels, has also been investigated. Several preclinical studies have shown that the induction of anemia in animals could be corrected by serial injection with EPO and that this EPO treatment also overcame the anemia-induced radiation resistance.[73,74] The concept of using EPO to correct for anemia has also been tested in several clinical trials. However, although low hemoglobin can be effectively and safely improved by EPO,[75,76] patients treated with radiation and EPO had a poorer outcome than the control arms not treated with EPO.[77] Although this clearly raises concerns about the use of such agents to improve radiation therapy through a manipulation of hemoglobin levels, it does not make the concept of having a high hemoglobin concentration during radiation therapy an irrelevant issue.

Other "hemoglobin-related" methods for improving tumor oxygenation have been investigated.[78] These include the use of artificial blood substances, such as perfluorocarbons,[79] which are small particles capable of carrying more oxygen than hemoglobin, or by manipulating the oxygen unloading capacity of blood by modifying the oxy-hemoglobin dissociation curve. This can be achieved either by increasing the red blood cell 2,3-DPG content,[80] 2,3-DPG being one of the most important allosteric factors controlling the hemoglobin-oxygen dissociation curve, or using antilipidemic drugs.[81] Although each of these approaches has been shown to improve the oxygenation status of experimental tumors or enhance radiation damage, none of them have yet reached controlled clinical testing; thus, their potential usefulness in the clinic is uncertain.

Changing Oxygen Consumption

A novel approach that is currently receiving attention focuses on reducing tumor hypoxia by decreasing the oxygen consumption of cells close to blood vessels and thereby increasing the oxygen diffusion distance, which makes more oxygen available to the hypoxic cells. This may be achieved using the drug metformin, which has undergone extensive clinical evaluation for the treatment of diabetes and has been linked to decreased rates of certain types of cancer.[82] One preclinical study has clearly shown that high doses of metformin can decrease cellular oxygen consumption in vitro.[83] Additional in vivo data from that study demonstrated that metformin could improve tumor radiation response, but whether or not this was the direct result of reduced oxygen consumption is not entirely known. Further studies in this area are clearly warranted.

Dealing with the Problem of Fluctuating (Acute) Hypoxia

Although several of the procedures used to combat radiation resistance caused by hypoxic cells have met with some success, the results are far from satisfactory. A possible explanation is that most of the procedures used clinically seem to operate primarily against diffusion-limited chronic hypoxia and have little or no influence on fluctuating hypoxia, which is caused by transient variations in tumor blood flow.[9]

Experimental studies have clearly demonstrated that the vitamin B3 analog, nicotinamide, can enhance radiation damage in a variety of murine tumor models using both single and fractionated treatments (Figure 3-6).[9] The enhancement of radiation damage appears to depend on the tumor type, drug dose, and time of irradiation after drug administration.[9] The drug can also enhance radiation damage in certain normal tissues, but generally the effects are less pronounced than those seen in tumors.[9] Nicotinamide seems to primarily prevent or reduce the transient fluctuations in tumor blood flow that normally lead to the development of acute hypoxia.[9] This finding led to the suggestion that the optimal approach would be to combine nicotinamide with treatments that specifically overcome chronic hypoxia. This was subsequently demonstrated with hyperthermia,[84] perfluorochemical emulsions,[85] and carbogen breathing.[57,86-88] Combining nicotinamide with carbogen has undergone testing in a number of European clinical studies, and the results in head and neck[89] and bladder cancer[90] demonstrated an improved response to radiation therapy.

Bioreductive Drugs

The early preclinical studies with electron-affinic radiosensitizers showed that these agents, which were relatively nontoxic to cells under normal oxygenated conditions, were reduced to a more toxic form under hypoxia.[91] This led to the development of various bioreductive drugs that preferentially killed the radiation-resistant hypoxic tumor cell population. Basically, these drugs can be divided into three major groups, as illustrated in Figure 3-7. They are the quinones, nitroaromatics, and N-oxides.[92]

The quinine derivative, Mitomycin-C (MMC), is probably the prototype bioreductive drug.[93] It has been used clinically for many years as a chemo-radiosensitizer, long before it was realized it had preferential effects against hypoxic cells. It is activated by bioreduction to form products that crosslink DNA and therefore produce cell killing. Several randomized clinical trials in patients with squamous cell carcinoma of the head and neck were undertaken, specifically using MMC to counteract the effects of hypoxia, but not all showed a benefit.[94-98] This may not be surprising when one considers that MMC actually has a small differential killing effect between aerobic and hypoxic cells (see Figure 3-7) and was only administered once or twice during the entire course of radiotherapy. Attempts to find more efficient quinones have been undertaken and to that end porfiromycin, RH1, and EO9 were developed.[92] Of these EO9 is currently being evaluated in a phase II trial in bladder cancer.

The finding that misonidazole was preferentially toxic toward hypoxic cells led to numerous efforts to find other nitroimidazoles that were better. The first drug developed was RSU-1069 (see Figure 3-7). This compound has the classic 2-nitroimidazole radiosensitizing properties, but also an aziridine ring at the terminal end of the chain, which gave the molecule substantial potency as a hypoxic cell cytotoxin, both in vitro and in vivo.[99] In large-animal studies it was found to cause gastrointestinal toxicity and a less toxic prodrug was therefore developed (RB-6145), which is reduced in vivo to RSU-1069. Although this drug was found to have potent antitumor activity in experimental systems, further animal studies revealed that this drug induced blindness; this is perhaps not surprising when one realizes that the retina is hypoxic, thus further development of this drug was halted. However, other

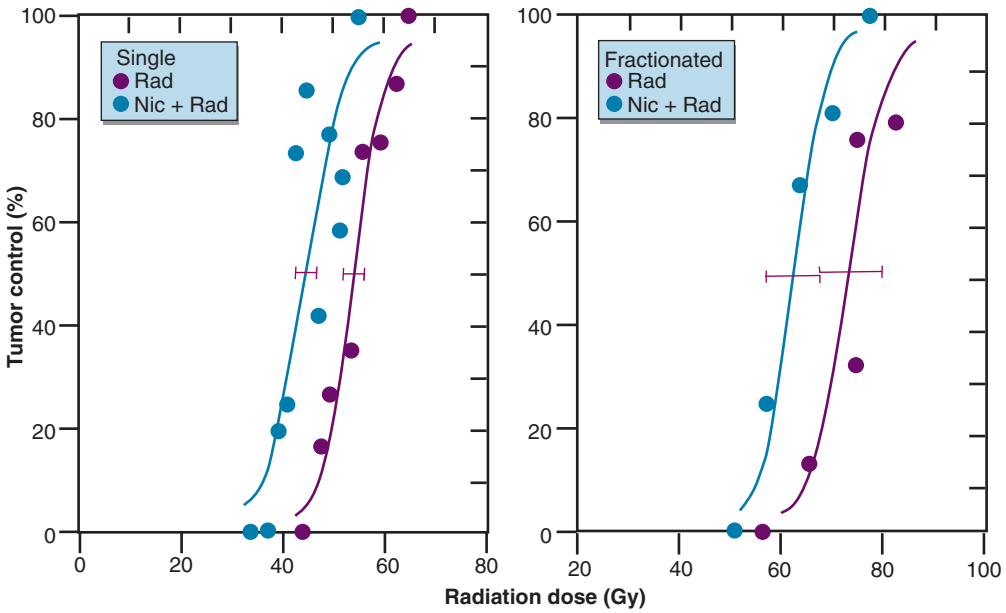


Figure 3-6 Effect of nicotinamide (500-1000 mg/kg) on local tumor control measured as a function of the total radiation dose given either as a single treatment to C3H mammary carcinomas or in fractionated schedule to the carcinoma NT. The drug was i.p. injected 30-60 minutes before irradiation. *Modified from Horsman MR, Chaplin DJ, Overgaard J: Combination of nicotinamide and hyperthermia to eliminate radioresistant chronically and acutely hypoxic tumor cells. Cancer Res 50:7430–7436, 1990, and Kjellen E, Joiner MC, Collier JM, et al: A therapeutic benefit from combining normobaric carbogen or oxygen with nicotinamide in fractionated x-ray treatments. Radiother Oncol 22:81–91, 1991. Copyright 1991, with permission from Elsevier Science.*

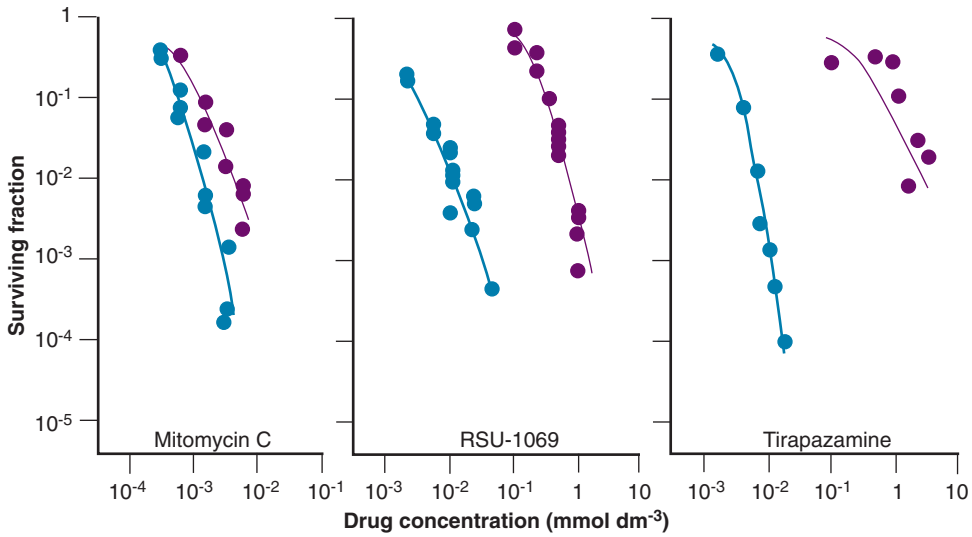


Figure 3-7 Survival of mammalian cells exposed to mitomycin C, RSU 1069, or tirapazamine under aerobic *(red symbols)* of hypoxic *(blue symbols)* conditions.
Adapted from Stratford IJ, Stephens MA: The differential hypoxic cytotoxicity of bioreductive agents determined in vitro by the MTT assay. Int J Radiat Oncol Biol Phys 16:973–976, 1989, and Hall EJ: Radiobiology for the radiobiologist. ed 4. Philadelphia, 1994, JB Lippincott.

nitro-containing compounds have been developed, including NLCQ-1, CB 1954, SN 23862, PR-104, and TH-302,[92] of which the latter is currently under Phase II/III clinical evaluation albeit in combination with chemotherapy.

Perhaps the most promising group of bioreductives is the organic nitroxides, of which the benzotriazene di-N-oxide, tirapazamine, is the lead compound (see Figure 3-7). The parent moiety shows limited toxicity toward aerobic cells, but after reduction under hypoxic conditions, a product is formed that has been shown to be highly toxic and can substantially enhance radiation damage to tumors in vivo.[100] Most clinical studies have involved combining tirapazamine with chemotherapy, although there have been a few trials with radiation with or without chemotherapy.[92] The results from the phase II trials generally showed promise, but in the few randomized trials that have been completed the results were somewhat disappointing. However, it has now been suggested that the benefit of tirapazamine might be achieved if one could select patients who had hypoxic tumors before treatment. Other N-oxides currently under development include chlorambucil N-oxide, SN30000, and AQ4N (Banoxantrone), the latter being combined with radiation in a number of clinical trials.[92]

VASCULAR TARGETING AGENTS

Angiogenesis Inhibitors

The tumor's vascular supply plays a critical role in determining the tumor's microenvironmental factors that influence radiotherapy.[101] This vasculature develops from the normal tissue vessels via the process of angiogenesis,[102] which is a highly complex process triggered by the release of specific growth factors from the tumor cells.[103] These growth factors initiate a series of physical steps, including local degradation of the basement membrane surrounding capillaries, invasion of surrounding stroma by the endothelial cells in the direction of the angiogenic stimulus, proliferation of the endothelial cells, and, finally organization of the endothelial cells into three-dimensional structures that connect with other similar structures to form the new blood vessel network.[103] The importance of this process makes it an attractive target for therapy and numerous approaches for inhibiting the various steps in the angiogenic process have been tested in preclinical models.[104,105] Many of these therapies have now moved into clinical evaluation[106] and, of these, the antivascular endothelial growth factor (anti-VEGF) antibody bevacizumab (Avastin) has been shown to improve outcome in a number of chemotherapy-based trials.[107] Preclinical studies using rodent and human tumor xenografts show that certain angiogenesis inhibitors can be effectively combined with radiation to improve tumor response (Table 3-3),[105] and as a result, a limited number of clinical studies have been initiated combining certain angiogenesis inhibitors with radiation therapy.[106]

The consensus opinion is that the improvement in radiation response found in preclinical studies is the consequence of normalization of the tumor vasculature, resulting in a decrease in tumor hypoxia.[108] Although there are certainly preclinical studies showing an improved tumor oxygenation status with such treatment, there are just as many studies showing no change and even a decrease in tumor oxygenation.[105] These findings not only make it unclear as to the role of vessel normalization in influencing the combination of angiogenesis inhibitors with radiation, but they also indicate that timing and sequencing of the two modalities may be critical for an optimal benefit.

TABLE 3-3 List of Vascular Targeting Agents That Have Been Combined with Radiation

Angiogenesis Inhibitors	Vascular Disrupting Agents
Suramin	Hyperthermia
TNP-470	Photodynamic therapy
Angiostatin	Colchicine
Endostatin	Tumor necrosis factor
Arginine deiminase	Arsenic trioxide
Thrombospondin	Flavone acetic acid
Thalidomide	5,6-dimethylxanthenone acetic acid
Anginex	Combretastatin A-4 phosphate
Anti-VEGF(R) antibodies	AVE 8062
SU 5416	ZD 6126
SU 6668	OXi4503
SU 11248	MN-029
SU 11657	NPI-2358
PTK787/ZK 222584	
ZD 6474	
Metastat	

See Horsman and Siemann[105] for additional information.

Vascular Disrupting Agents

An alternative approach for targeting tumor vasculature involves using agents that can damage the already established tumor vessels.[104,105] This is not a new concept; it was first demonstrated with the tubulin binding agent colchicine back in the 1940s.[109] Since then a number of vascular disrupting agents (VDAs) have been proved capable of preferentially damaging tumor vessels, leading to a reduction in tumor perfusion which results in an increase in tumor ischemia and necrosis, subsequently producing an inhibitory effect on tumor growth.[105] The VDAs include physical treatments (e.g., hyperthermia, photodynamic therapy, and even radiation), chemotherapeutic agents (e.g., tumor necrosis factor, vinca alkaloids, and arsenic trioxides), and small molecule agents (e.g., flavonoid derivatives such as 5,6-dimethylxanthenone-4-acetic acid; tubulin binding drugs such as Combretastatin A-4 phosphate).

As with the angiogenesis inhibitors, several of the VDAs have been combined with radiation (see Table 3-3), and significant improvements in response have been seen in preclinical models.[105] This is illustrated in Figure 3-8 using a C3H mammary carcinoma grown in CDF1 mice. The radiation dose needed to control 50% of treated animals (±95% confidence intervals) following single dose radiation treatment alone was found to be 53 Gy (51-56). This was significantly reduced (Chi-squared test; $p < 0.05$) to 46 Gy (42-49) when tumors were locally irradiated, but 30 minutes later mice were given a single intraperitoneal injection of a large but nontoxic dose of Combretastatin A-4 phosphate (CA4P), the lead VDA in clinical evaluation.[105,107] On its own, in this tumor model, such a drug dose will only slow the growth of the tumors by about 2 days. The enhancement of tumor radiation damage is known to be time and schedule dependent, with the greatest effect seen when the drug is given within a few hours after irradiating.[105] It is also tumor specific with no enhancement of radiation response seen in normal tissues. This has been shown for CA4P in acutely responding normal skin (see Figure 3-8) or late-responding bladder and lung.[105] These differences between the tumor and normal tissue results are entirely consistent with the drugs' ability to induce damage in tumor vessels but not vessels in normal tissue.[105]

RADIATION PROTECTORS

Sulfhydryl-Containing Compounds

More than 50 years ago it was realized that certain amino acids, glutathione, and ascorbic acid were able to modulate radiation induced inactivation of biological material. Based on those observations Patt et al investigated the effect of treating mice with the thiol-containing amino acid, cysteine.[110] They found that administering this compound to mice before whole-body irradiation resulted in a remarkable increase in animal survival (Figure 3-9). In contrast no effect was observed when cysteine was given after irradiation. During the Cold War, this finding led to a large research program at the Walter Reed Army Institute of Research aimed at developing a drug that could protect soldiers from nuclear weapons.[111] Numerous sulfhydryl-containing substances with substantial radioprotective properties were detected, but only WR-2771 (amifostine) was found to exhibit acceptable toxicity. The idea of using amifostine in oncology arose when preclinical studies, performed mainly in the 1970s and 1980s, suggested a selective protection of normal tissue from damage induced not only by irradiation but also from chemotherapy.[112,113] Despite these findings, the interest in amifostine over the years has waxed and waned, although this interest was boosted by commercialization of the drug, US Federal Drug Administration (FDA) approval, and the

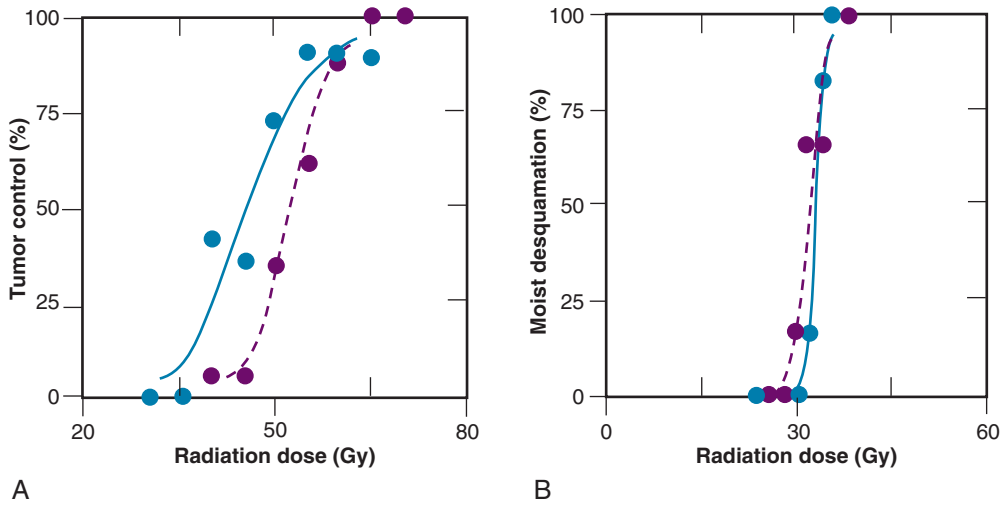


Figure 3-8 Effect of Combretastatin A-4 disodium phosphate (250 mg/kg) on either local control of a C3H mammary carcinoma **(A)** or the development of moist desquamation in the foot skin of CDF1 mice **(B)** following radiation treatment. Radiation was either given alone *(red symbols)* or 30 minutes before intraperitoneal injection of the drug *(blue symbols)*.
Adapted from Murata R, Siemann DW, Overgaard J, et al: Interaction between Combretastatin A-4 disodium phosphate and radiation in murine tumors. Radiother Oncol 60:155–161, 2001.

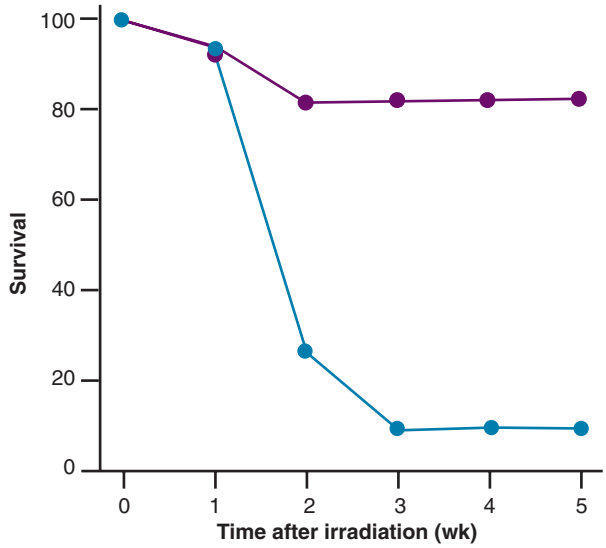


Figure 3-9 Percentage of rodents surviving after whole-body irradiation with 8 Gy. Animals were either control irradiated (blue symbols) or given radiation after injection with 575 mg of cysteine *(red symbols)*.
Adapted from Patt HM, Tyree EB, Straub RL, et al: Cysteine protection against X irradiation. Science 110:213–214, 1949. Copyright 1949 American Association for the Advancement of Science.

establishment of authoritative guidelines.[114] The lack of interest was probably related to the fact that there is no fail-safe modification of traditional radiotherapy.[115] Many normal tissues are dose limiting; therefore, evaluating the therapeutic benefit of a radioprotector requires either that the protector have absolute normal tissue selectivity (and thus fewer complications with an unchanged rate of tumor control for a given radiation dose) or, if selectivity is uncertain, that an increase in radiation dose may be needed to maintain the same rate of tumor control. However, this scenario requires that the protective effect on tumor tissues is predictable and exceeded by the protection offered to all relevant normal tissues. In addition, the "perfect" radioprotector must have an acceptable toxicity profile and must be easy to handle if generalized clinical use is to be expected with routine fractionated radiotherapy.[116-118]

It is not entirely clear how amifostine induces radioprotection. The drug must first undergo dephosphorylation to its active metabolite WR-1065, which is further metabolized to the disulfide WR-33278; the latter metabolite may also afford some protection, although to a lesser extent.[119] Several mechanisms are involved in radioprotection, depending on the quality of the radiation. Protection against sparsely ionizing radiation, such as x-rays, is mainly obtained by scavenging of free radicals[120,121]; such scavenging has also been observed with glutathione, superoxide dismutase and its mimetics, and isoflavones like genistein. Because WR-1065 and WR-33278 react with free radicals in competition with oxygen, the protection obtained by scavenging is highly influenced by oxygen tension (Figure 3-10). Here the protection is maximal at intermediate levels of oxygen (20% to 50% oxygen in the inspired air). At higher oxygen tensions, WR-1065 is counterbalanced by excess oxygen and the protection is gradually lost. The degree of protection is also diminished at low-oxygen tensions where scavenging of free radicals is no longer important because the lack of oxygen by itself provides radioprotection. Additional and complex mechanisms are undoubtedly involved. Some of these may involve hypoxia created locally by direct interaction of thiols with oxygen, chemical repair by thiol-donation of hydrogen, or decreased accessibility of radiolytic attack sites by induction of DNA packaging.[116]

Preclinical studies have shown that many tissues can be protected from radiation damage by amifostine (Table 3-4). However, the protection observed in different normal tissues is unfortunately heterogeneous. Some normal tissues—such as central nervous system, which often is dose limiting in radiotherapy—are not protected because amifostine probably does not cross the blood-brain barrier.[122] In other normal tissues such as salivary glands and hematopoietic system, amifostine affords significant radioprotection. These variations are probably explained by tissue variations in oxygen concentration, dephosphorylation activity, and distribution of amifostine and its metabolites.[119,121,123] To make things even more complicated, tumor protection has been impossible to rule out by preclinical experiments.[115] In addition, large single doses of irradiation have often been used, and relevant

comparison with tumor effects have been absent or difficult to translate into a clinical meaningful context.[116]

On the clinical side there have been far too many publications of phase I-II studies with limited number of patients and a few underpowered randomized studies. In addition, chemotherapy has often been applied together with radiotherapy, making it difficult to evaluate the results (Table 3-5). Despite the long list of preclinical normal tissues studies with a proven effect of amifostine, disappointingly few have been confirmed in the clinical setting. Amelioration of acute radiation toxicity has been observed in studies which often employed various types of treatment intensification like concomitant chemotherapy or accelerated radiotherapy. However, definite confirmation regarding late morbidity such as fibrosis has not been obtained. A pivotal trial by Brizel et al[128] showed that amifostine significantly protected against radiation-induced xerostomia with no apparent loss of tumor control in head and neck cancers. That was followed by amifostine being approved by the US Federal Drug Administration for use in patients undergoing postoperative fractionated radiotherapy in the head and neck region to decrease the incidence of acute and chronic xerostomia. In light of the paucity of relevant clinical data this recommendation seems premature. A later large meta-analysis of published data concluded that amifostine could significantly reduce acute and late side effects associated with radiation therapy.[129] However, that review has since been criticized

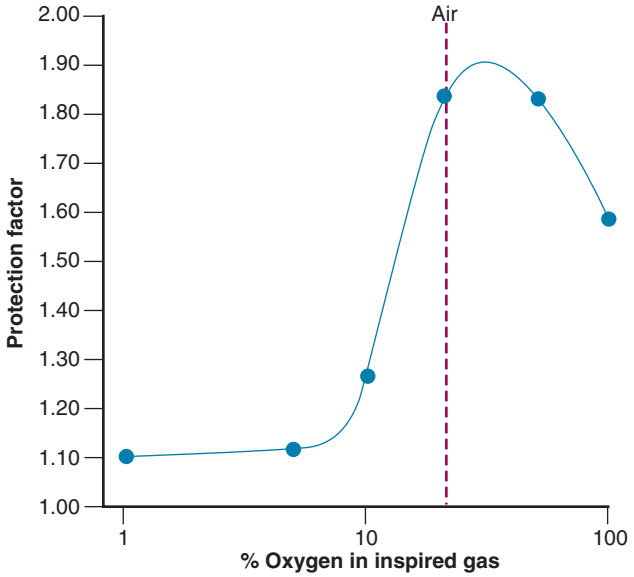


Figure 3-10 The variation in normal skin protection in mice given 400 mg/kg WR-2721 30 to 45 minutes before irradiation in mice that breathed various oxygen concentrations.
Modified from Denekamp J, Michael BD, Rojas A, et al: Radioprotection of mouse skin by WR-2721: the critical influence of oxygen tension. Int J Radiat Oncol Biol Phys 8:531–534, 1982, with permission from Elsevier Science.

TABLE 3-4 Protection Factors Achieved by Amifostine in Different Normal Tissues and Tumors

Tissue	Protection Factor
Salivary gland	2.3-3.3
Bone marrow	1.8-3.0
Jejunum	1.5-2.1
Skin	1.4-2.1
Testis	1.5-1.6
Kidney	1.3-1.5
Bladder	1.3-1.5
Lung	1.2-1.4
Heart	>1.0
Tumor	1.0-2.8

Data from references 115 and 121,123-127.

TABLE 3-5 Randomized Clinical Trials Investigating the Effect of Amifostine on Outcome in Radiotherapy (RT) Administered Alone or with Chemotherapy (CT)

Author	Year	Reference	Site	Treatment	No. Patients
Buntzel	1998	131	Head and neck	RT and Chemo	39
Bourhis	1999	132	Head and neck	RT	26
Brizel	2000	128	Head and neck	RT	315
Momm	2001	133	Head and neck	RT	73
Wasserman	2005	134	Head and neck	RT	303
Buentzel	2006	135	Head and neck	RT and Chemo	132
Anné	2007	136	Head and neck	RT and Chemo	54
Haddad	2009	137	Head and neck	RT and Chemo	58
Antonadou	2001	138	Lung	RT	146
Antonadou	2003	139	Lung	RT and Chemo	73
Leong	2003	140	Lung	RT and Chemo	60
Komaki	2004	141	Lung	RT and Chemo	62
Movsas	2005	142	Lung	RT and Chemo	242
Lawrence	2013	143	Lung	RT and Chemo	243
Bohouslavizki	1998	144	Thyroid	RT (I-131)	50
Liu	1992	145	Rectum	RT	100
Athanassiou	2003	146	Pelvis	RT	205
Kouloulius	2004	147	Prostate	RT	67
Koukourkis	2000	148	Various	RT	140

for publication and classification bias and the quality of the trials included.[130] A more comprehensive meta-analysis found that amifostine did not change radiation-induced overall or progression free survival,[130] thus further studies are needed to explore the potential benefits of amifostine.

Modifiers of the Oxygen Supply

Because hypoxia reduces radiation sensitivity, decreasing the availability of oxygen to tissues may be way to achieve radiation protection. One way to accomplish this might be to modify hemoglobin-oxygen affinity. The most widely studied agents in this context are the substituted benzaldehyde, BW12C, and derivatives.[149,150] These agents preferentially bind to oxy-hemoglobin and so increase the affinity of the hemoglobin for oxygen.[151,152] Consequently this decreases the amount of oxygen available to the tissues. Although this radioprotects some normal tissues,[149,153] there is evidence that in certain normal tissues BW12C can actually increase perfusion,[154] which should increase oxygen delivery. Additionally, experimental studies have also shown that BW12C will significantly radioprotect tumors.[149,150]

Carbon monoxide reduces oxygen transport to tissues by binding to hemoglobin, thereby decreasing the amount available for oxygen transport, as well as causing a left shift of the hemoglobin-oxygen dissociation curve. Therefore, any oxygen that binds to the hemoglobin does so more strongly.[155] This approach to increase hypoxia and reduce radiation response has been well documented in experimental systems.[156,157] Unfortunately, this effect was demonstrated in tumors and not normal tissues. The effect of carbon monoxide in patients has also been observed, as shown in Figure 3-11, which illustrates that patients with head and neck carcinomas who were smokers (and therefore had higher carboxyhemoglobin levels) had a poorer response to radiation therapy than nonsmokers.

Because most modifiers of the oxygen supply already discussed also provide radioprotection for tumors as well as normal tissues, their use in this context must be considered limited. However, this may not be true for pentoxifylline. This is a drug that alters red blood cell deformability and inhibits platelet aggregation and fibrinolytic activity.[158] As a result, red blood cells are better able to transverse narrowed arterioles and capillaries. When given before irradiation, pentoxifylline enhances radiation damage in tumors,[159] presumably because of an improvement in oxygen delivery,[160,161] but it has no effect on the response of normal tissues.[159] However, when administered on a daily basis after irradiation, pentoxifylline had no effect on early skin reactions in mice but did significantly reduce the incidence of late reactions.[162]

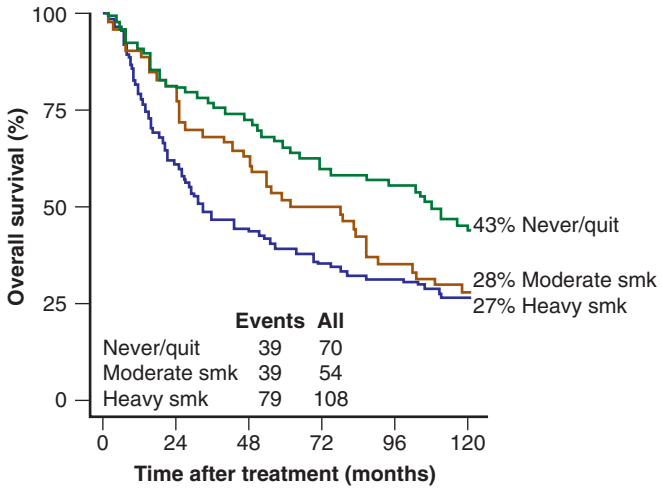


Figure 3-11 Influence of smoking (smk) during treatment on the outcome of radiotherapy in 232 patients with advanced head and neck carcinoma. Results show 10-year survival when comparing nonsmokers and quitters to moderate or heavy smokers (>20 cigarettes or one pack per day).
Redrawn from Hoff CM: Importance of hemoglobin concentration and its modification for the outcome of head and neck cancer patients treated with radiotherapy. Acta Oncol 51:419–432, 2012.

Other Radioprotectors

Various other agents have been reported to be capable of radioprotecting certain normal tissues.[163-165] These include cytokines, such as granulocyte-macrophage colony-stimulating factor, interleukin-1, tumor necrosis factor-α (TNF-α), transforming growth factor-β (TGF-β), and basic fibroblast growth factor.[166-170] Another interesting group of agents inhibit the process of apoptosis. Many tumors have acquired mutations that prevent them from undergoing radiation-induced apoptosis. Proliferating normal cells, however, are often killed by radiation-induced apoptosis, and several apoptosis inhibitors have shown radioprotective potentials in animal models. These include p53 inhibitors (pifithrin-α and pifithrin-μ), growth factors [KGF-1 (palifermin), KGF-2 (repifermin), FGF-20 (velafermin)], activators of NRF2 (triterpenoids), and inhibitors of NF-κB (CBLB502).[163-165] Another recent approach, designed to take advantage of a typically acquired defect in tumor cells, is to induce a G1 cell cycle arrest in normal cells, thereby temporarily arresting them in the relatively radioresistant G1 phase allowing for improved DNA repair (e.g., PD0332991 and 2BrIC).[163-165] Agents are also being developed that target molecular pathways involved in radiation-induced effects, including the TGF-β1/Smad, CTGF/RHO/ROCK, TNF-α, and PDGF/PDGFR pathways.[163-165] Finally, there is a group of miscellaneous inhibitors that include the angiotensin-converting enzyme inhibitor captopril, corticosteroids, prostaglandins, and essential fatty acids.[171-175] However, the mechanisms of action are not entirely clear, nor is there evidence that these agents do not also radioprotect tumors.

SUMMARY

The use of radiation to treat certain types of cancer with curative intent is a well-established and effective therapy, but there is still room for improvement. The additional use of treatments that can either increase radiation damage in tumors without affecting normal tissues, or protect normal tissues without having a similar protective effect in tumors, is clearly warranted. Because the vasculature and microenvironment of tumors differs from those of normal tissues, targeting these parameters should lead to tumor specificity. Many preclinical studies have demonstrated this to be a viable approach. But despite numerous clinical studies confirming the potential of such methods to significantly improve outcome to radiation therapy only one agent has become established in standard radiation therapy protocols. That agent is the radiosensitizer nimorazole, which is only used in Denmark and only in head and neck cancers. The use of radioprotectors is more controversial. Experimentally, several agents have been shown to radioprotect certain normal tissues, but data also demonstrate that some of these agents induce radiation protection in tumors. Results from clinical studies investigating the potential of radioprotectors have also been inconclusive, and until good human data demonstrating radioprotection of normal tissues, but not tumors, become available the use of radioprotectors must be considered experimental.

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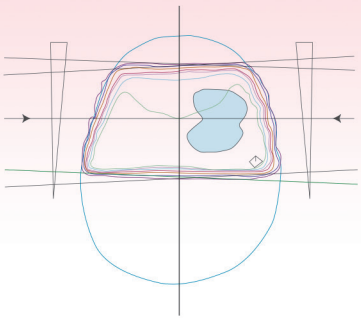
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CHAPTER

4 Interaction of Chemotherapy and Radiation

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Oncology has increasingly become a multidisciplinary field of medicine: (1) Surgery remains the definitive local treatment modality; (2) Chemotherapy remains the definitive systemic treatment modality; and (3) Radiation therapy is the definitive loco-regional treatment modality. Although, historically, these approaches have predominantly been used exclusively of one another, the past 25 years have seen an explosion of both preclinical and clinical efforts that have sought to combine these therapies for improved outcomes, including improved local and regional control, overall survival, cosmesis, and organ preservation. We have learned a great deal about the interactions between chemotherapy and radiation from clinical trials that have combined these treatment modalities in sequential and concomitant regimens. In addition, laboratory investigations have demonstrated key molecular targets and pathways that can potentially be exploited for improved outcome. Indeed, the combination of chemotherapy and radiation has changed the management approach in several disease sites, which are broadly reviewed here.

HISTORICAL PERSPECTIVE

Radiosensitization and chemosensitization are complex concepts that have many different interpretations and have been used to describe many different interactions.[1,2] The use of radiation and chemotherapy for mutual or even simultaneous sensitization adds to the intricacies of these interactions. Indeed, more than 100 years ago, radiation treatment and benzene systemic therapy were combined for leukemia treatment.[3] However, probably the best historical model of chemotherapy and radiation therapy interaction is that of 5-fluorouracil.

5-Fluorouracil

In the 1950s, the halogenated pyrimidine, 5-fluorouracil (5-FU), was combined with external beam irradiation (EBRT) after this class of drug was determined to have anticancer properties.[4] In the last 50 years, 5-FU has been successfully combined with radiation to treat a variety of gastrointestinal cancers, as well as cervical cancer and head and neck cancers.[5] The route of administration and scheduling of 5-FU has been manipulated many times in an attempt to reduce toxicity and maximize tumor control. What began as bolus delivery at the beginning and end of a fractionated radiation treatment course ("Moertel" regimen) has progressed to protracted venous infusion (PVI) and now to twice daily oral 5-FU analog formulations. These approaches have allowed for an increase in cumulative dose of the drug, decreased chemotherapy toxicity, and improved radiosensitization. Indeed, 5-FU has proven to be a staple drug in the armamentarium of medical oncologists and a key radiosensitizer for the radiation oncologist.

RATIONALE

Limitations in Current Therapeutic Approach

Over the past several decades, we have seen the great technological advances in surgery and radiation while novel systemic agents are being developed at a never-before-seen pace. Nevertheless, cancer morbidity and mortality remain major problems. The advent of combined modality therapy has sought to improve on the limitations that surgery, chemotherapy, and radiation carry independently. For several decades, radiation has complemented surgery by improving loco-regional control. Unfortunately, tumor-specific and patient-specific factors limit both surgical and radiation success. In this chapter, we will focus on the multiple ways that systemic therapies are used in an attempt to overcome the shortcomings of radiation treatment. The presence of micrometastatic disease, disease outside of our treatment fields, and the inability to deliver adequate dose to the target region as a result of normal tissue toxicity risk are some of the most frequently cited reasons. In addition, tumors may contain regions of relative hypoxia or subpopulations of cells with intrinsic or acquired resistance to radiation damage. We will briefly review the current understanding of these topics.

Tumor Detection

If ionizing radiation were without normal tissue toxicity, tumor detection would be immaterial, and radiotherapy could be delivered to the entire body much like chemotherapy. Obviously this is not the case, and much like surgeons, we must be able to identify the tumor so that we can precisely and accurately target it with our radiation akin to "carving out" a tumor with a scalpel. Fortunately, advances in radiology have dramatically improved our ability to detect tumor location and extent. Whereas computed tomography (CT) and magnetic resonance imaging (MRI) provide excellent anatomic information, when combined with biological or functional imaging such as positron emission tomography (PET) and single photon emission computed tomography (SPECT), the radiation oncologist can more confidently define tumor vs. nontumor. Emerging MRI sequences including dynamic contrast enhanced and fast imaging employing steady-state acquisition (FIESTA) ultrafast pulse sequence approaches, and MR spectroscopy are providing improved anatomic (and biologic in the case of MR spectroscopy) imaging for surgeons and radiation oncologists. Nevertheless, the resolution of our current techniques (on the order of 5 mm for PET resolution[6]) and high false-negative rates with small tumors still limit our ability to identify microscopic tumor extent and micrometastatic disease. Future technologies such as PET/MRI as well as novel radiopharmaceuticals may provide improvements.

Inherent and Acquired Resistance

We know, empirically, that certain tumors have inherent radiation resistance pathways that manifest with high rates of local failure following radiation. In some cases, such as in pancreatic cancer, it is difficult to deliver adequate doses of radiation to the target because of the limitations in dose tolerance of surrounding bowel, kidney, and liver. However, there are other tumors with extremely high local failures despite dose escalation. A prime example is glioblastoma multiforme, which has local recurrence rates approaching 100%. Biological factors within the tumor or tumor microenvironment also generate resistance. Figure 4-1 summarizes some of the major

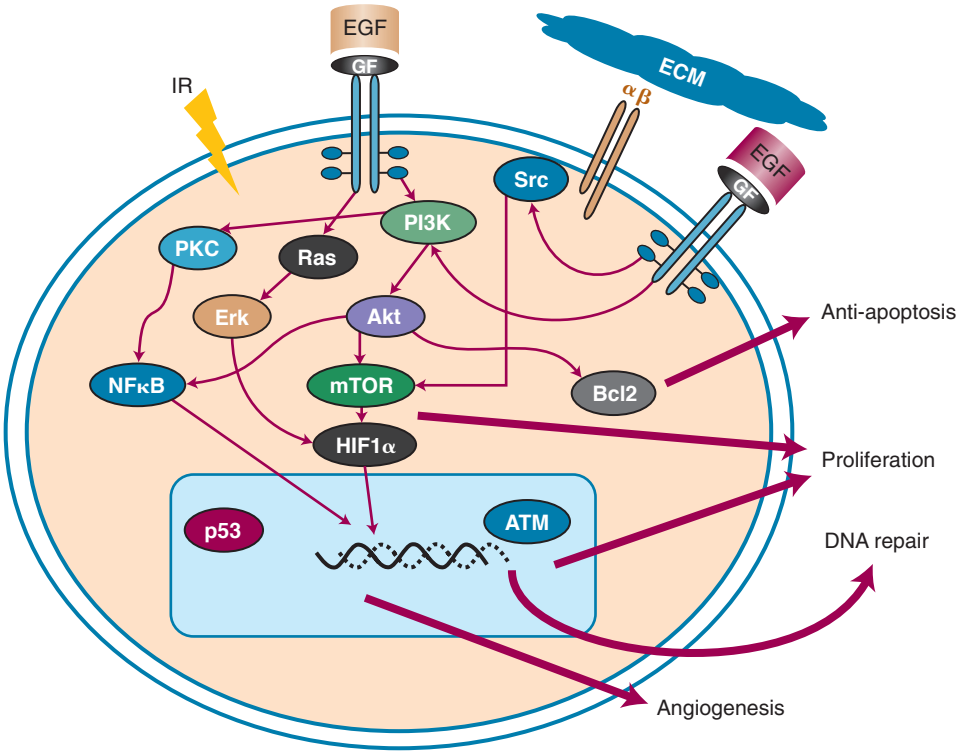


Figure 4-1 Schematic of radiation-induced signal transduction cascades indicating pathways leading to antiapoptosis, proliferation, DNA repair, and angiogenesis.

resistance pathways within tumors. Later in this chapter we will describe how chemotherapeutics can potentially mitigate these resistance pathways.

Increased Toxicity

In the original treatise by Steel and Peckham on combining chemotherapy and radiation,[7] it was assumed that each modality functioned independently in both beneficence and toxicity. However, it is abundantly clear that concurrent chemoradiation has increased toxicity suggesting some level of overlapping toxicity, chemosensitization by radiation, or radiosensitization by the chemotherapy. Because chemoradiation is often used when tumors have wide anatomic extension (thus, precluding surgery), the volume of normal tissue irradiated, and therefore, at risk of toxicity, is larger. In some cases, a patient has comorbid conditions that prevent aggressive therapy as well.

Therapeutic Index

The features described previously generate the need for a metric to determine efficacy relative to toxicity so that newer approaches can be compared. This metric, known as the *therapeutic index* (or therapeutic ratio) refers to the ratio of the probability of tumor control to the probability of normal tissue toxicity. Typically, the ratio is calculated based on the 50% control rate of tumor versus the 50% normal tissue toxicity. These sigmoidal-shaped curves determine the estimated efficacy versus toxicity of treatment. Figure 4-2 depicts an idealized form of these curves. Therapeutic index has been, and will continue to be, the "holy grail" of cancer therapy. For this reason, it is no surprise that it takes careful treatment planning to try to achieve maximal tumor cell kill while also sparing normal tissue in hopes of preserving function. There are a host of technological factors that impact this therapeutic ratio.

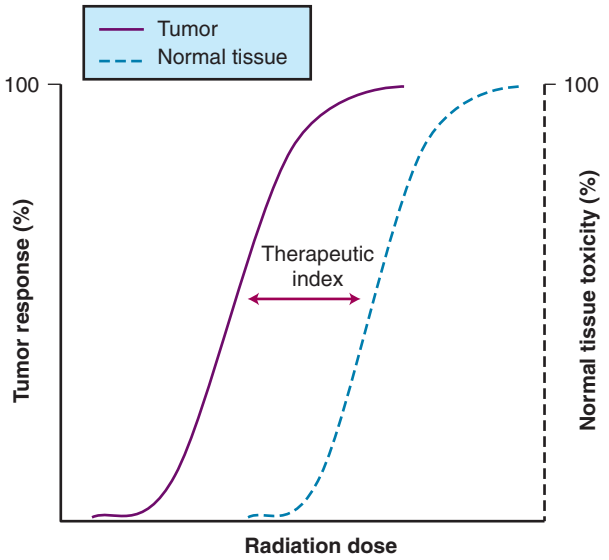


Figure 4-2 Graph of an idealized therapeutic index curve. The therapeutic index is indicated as the difference in probability of tumor response and probability of normal tissue toxicity. The greater the separation of these two curves, the greater the therapeutic index.

Certainly our ability to correctly identify tumor versus normal tissue will affect therapeutic ratio. The expanding use of PET, MRI, and SPECT imaging, as described previously, are allowing radiation oncologists to better differentiate target from nontarget. Obviously, the ability to precisely deliver radiation through techniques such as intensity modulated radiation therapy (IMRT), stereotactic procedures, and proton therapy allow us to avoid normal tissue while targeting tumor.

Moreover, our ability to accurately deliver radiation via image guidance (IGRT) has grown by leaps and bounds, which enables smaller margin expansions and will also limit dose to normal tissue. Nevertheless, based on the anatomical location of the tumor, there are technological limits to what can be accomplished with radiation in and of itself. Therefore, additional improvement will likely rely on the interaction of systemic agents with our technologically advanced radiation delivery methods.

Strategies to Improve Therapeutic Index

The fundamental approach to improving outcomes through combined modality therapy has its basis on the theoretical strategies set forth by Steel and Peckham in 1979.[7] Their seminal paper defined four potential means by which combined therapy could improve the therapeutic index and were described as (1) independent toxicity, (2) normal tissue protection, (3) spatial cooperation, and (4) enhanced tumor response. As will be discussed, the first theoretical concept may not actually function as in the original intent. However, the latter three concepts are relevant for modern strategies of combining drugs with radiation. Additional mechanistic considerations have been identified in recent years that expand on Steel and Peckham's "exploitable mechanisms in combined radiotherapy-chemotherapy" that was described more than three decades ago.[7] These newer concepts of biological cooperation and temporal modulation are impacting current investigative strategies for improving the therapeutic index.

Independent Toxicity

One of the main concepts suggested by Steel and Peckham as a means to improve the therapeutic index is to select a chemotherapeutic regimen with a distinct toxicity profile from that of radiation. This ideal selection of nonoverlapping toxicities could allow for increased tumor cell kill with minimal impact in terms of tissue toxicity. Although this has been pursued in therapy selection, the actual success in finding independent toxicity has been elusive. However, the inverse relationship has been implemented to a great extent. Indeed, the avoidance of drugs with overlapping toxicities is standard of care practice, for instance, avoiding methotrexate with cranial radiation, Adriamycin with breast irradiation, or bleomycin with lung irradiation.

Normal Tissue Protection

The identification of clinically relevant agents that promote normal tissue protection without protecting tumors has provided little in terms of therapeutics. Limited success has been achieved with the free radical scavenging agent, amifostine (WR-2721), which appears to be selectively taken up by normal tissue relative to tumor where it is converted into the active thiol metabolite, WR-1065.[8] Although amifostine has been shown to protect against xerostomia in head and neck cancers treatment (Table 4-1) and to limit renal toxicity from cisplatin, several clinical trials have failed to show an advantage to amifostine use. Undoubtedly, investigations into novel radioprotectors will continue with the potential to impact the therapeutic ratio.

Spatial Cooperation

The concept of spatial cooperation implies that chemotherapy and radiation therapy are independent players with systemic therapy acting systemically, that is, targeting micrometastatic disease, and radiation therapy acting loco-regionally. Because

TABLE 4-1 Possible Drug–Radiation Interactions

Mechanism	Example	Notes
Normal Tissue Protection	Amifostine in head and neck cancers	Reduces xerostomia rates from RT alone
Spatial Cooperation	Early stage breast cancer with adjuvant chemotherapy PCI in SCLC	RT provides locoregional control for breast cancer but no impact on DM SCLC chemotherapy does not effectively cross BBB → RT can effectively treat the brain
Biological Cooperation	Targeted therapies inhibit prosurvival/proliferation pathways within tumors	Kinase targeted agents including tyrosine kinase inhibitors such as dasatinib and sunitinib as well as monoclonal antibodies such as cetuximab and bevacizumab; mTOR inhibitors
Temporal Modulation	Drugs that impact tumor response in between fractions, namely targeting repair, repopulation, reoxygenation, and redistribution.	This is essentially a composite of several of the other mechanisms but requires concomitant delivery of the drug rather than sequential.
Increased DNA Damage	Drugs that incorporate into DNA	5-FU and platinum are classic examples
Inhibition of DNA Repair	DNA intercalators and nucleoside analogs can disrupt repair and enhance radiation cytotoxicity	Alkylators, antimetabolites, platinum, and topoisomerase inhibitors are a few examples
Cell Cycle Effects	Most chemotherapeutics are cell cycle specific (except alkylators) Cell cycle arrest in radiosensitive phases (microtubule targeting agents at M-phase) Elimination of radioresistant cells (S-phase)	Taxanes, epothilones, 5-FU, gemcitabine, and topoisomerase inhibitors are good examples
Targeting Repopulation	Conceivably any systemic agent that has at least cytostatic properties can prevent repopulation	Molecularly targeted agents as well as chemotherapeutics (particularly antimetabolites) can function this way
Hypoxia Targeting	Mitomycin C and tirapazamine selectively targeting hypoxic cells Tumor shrinkage by chemotherapy decreases interstitial pressure and improves oxygenation	Taxanes and other chemotherapies that can produce tumor shrinkage are indirect means (given as induction therapy) whereas mitomycin C and tirapazamine are directly affecting hypoxic cells.
Tumor Microenvironment Targeting	Antiangiogenesis promotes vascular renormalization	Bevacizumab in glioma

5-FU, *5-Fluorouracil;* BBB, *blood-brain barrier;* DM, *distant mets;* PCI, *prophylactic cranial irradiation;* RT, *radiation therapy;* SCLC, *small-cell lung carcinoma.*

these therapies function independently, it could be assumed that a full dose of each will be required to achieve the desired outcome. If the drug and radiation did function completely independently, then concurrent administration should be possible with nonoverlapping toxicities. It is unclear whether a completely independent action can actually be achieved with the chemotherapies that are currently used with radiation treatment, however, because in-field toxicities do occur suggesting some level of localized radiation sensitization. Therefore, sequential therapy is probably the best means to exploit spatial cooperation. Many clinical examples exist for this approach, such as breast cancer with adjuvant chemotherapy followed by radiation, consolidative radiation to bulky disease in lymphoma, or prophylactic cranial irradiation in small cell lung cancer (see Table 4-1).

Enhanced Tumor Response (Cytotoxic Enhancement)

Currently, a tremendous amount of investigative effort is focused on achieving cytotoxic enhancement with combined modality treatment. In other words, the combination of therapies leads to an interaction on some level that generates improved antitumor effect relative to each treatment alone. Interestingly, we have some clinical examples that subtherapeutic, or radiosensitizing, doses of chemotherapy can impact distant disease control suggesting either that increased locoregional control can diminish distant metastatic disease potential or that lower dose chemotherapy can treat micrometastatic disease (i.e., spatial cooperation).

Biological Cooperation

The term, *biological cooperation*, is a newer concept[9] that involves independent targeting of subpopulations of cells within the tumor itself (see Table 4-1). Although similar to the spatial cooperation concept, biological cooperation implies that some portion of the actual radiation target (i.e., in-field) is resistant to radiation, which is the target of the drug given concomitantly. The most prominent example for biological cooperation is hypoxic cell cytotoxins such as tirapazamine. Because hypoxia is a known radiation resistance condition, tirapazamine will target these subpopulations of cells since it is most potent in anoxic conditions. Tirapazamine is discussed in more detail later in this chapter.

Temporal Modulation

The four R's of classical radiobiology, which include reoxygenation, repair, redistribution, and repopulation,[10] refer to factors that are particularly important for fractionated radiation therapy. For example, antiproliferative therapies could prevent accelerated repopulation between fractions, which might not be detectable using single fraction assays, in vitro. Conversely, although DNA damage repair blockade may enhance radiation sensitivity in the tumor, if DNA repair is also inhibited in normal tissue, outcomes may be worse in fractionated therapy.[9] Depending on which factors are most prominent in normal and tumor cells, the therapeutic index can be shifted in either beneficial or detrimental directions. Therefore, temporal modulation implies therapeutics that optimize these four radiobiology factors in between fractionated radiation treatments (see Table 4-1).[9]

POTENTIAL BIOLOGICAL MECHANISMS OF DRUG RADIATION INTERACTION

There are a host of potential mechanisms by which a drug may impact radiation efficacy that are summarized in Table 4-1. Classical definitions of radiosensitizers indicated an enhancement of DNA damage as the critical factor. However, with increased understanding of cancer cell biology, it is apparent that targets other than DNA damage can enhance radiation efficacy. Therefore, a broader defined "radiation enhancer" can impact several potential mechanisms to increase radiation effect.

Increasing Radiation Damage

The classical radiobiology definition of a radiosensitizer implied that the drug would enhance DNA damage. This is accomplished when the drug incorporates itself into the DNA or causes damage to the DNA itself by forming adducts, thereby increasing susceptibility of the DNA to radiation damage. Examples of this type of interaction include 5-FU and cisplatin.

Inhibition of DNA Repair

Cancer cells that can effectively repair DNA damage will have resistance to radiation effect. Therefore, compounds that can interfere with the DNA damage repair signal transduction pathway can potentially enhance radiation damage. Several chemotherapeutics target this process, particularly those that disrupt nucleotide biosynthesis and utilization. Modified nucleotides such as 5-FU, bromodeoxyuridine, gemcitabine, fludarabine, methotrexate, etoposide, hydroxyurea as well as cisplatin fall into this category. Additionally, as will be described, compounds that alter the cell cycle may indirectly inhibit DNA repair.

Cell Cycle Effects

A multitude of preclinical work has identified the G2/M as the most radiation-sensitive and S as the most radiation-resistant phases of the cell cycle.[11,12] In addition, many cytotoxic chemotherapeutics are cell cycle specific. Therefore, agents that can maintain cells in radiation-sensitive phases or eliminate those cells in radiation-resistant phases will cooperate with radiation for enhanced efficacy. Although this is clearly seen in preclinical settings, there is much less direct evidence for this phenomenon in clinical data. Nevertheless, taxanes and nucleoside analogs and modified pyrimidines appear to work in this manner.[13-16]

Repopulation

In normal adult tissue, the rate of cell loss is balanced by that of cell proliferation. When increased cell loss occurs from injury, including radiation treatment, signaling for proliferation occurs resulting in a repopulation. Cancers, however, have an excess of cell proliferation relative to cell loss by their very nature. Therefore, when a subtotal cell loss occurs during fractionated radiation, cancers can also promote increased proliferation. This is known as *accelerated repopulation*. Chemotherapeutics with cytotoxic or even cytostatic effects when given concurrently with radiation, can counteract this repopulation and enhance efficacy.

Hypoxia/Tumor Microenvironment

Solid tumors, particularly those that have grown to any significant size, will contain regions of lower oxygen tension because of the limitations in vascular flow as well as oxygen diffusion within the tumor. Although many tumors trigger angiogenic factors within the tumor, these stimulants manifest as aberrant vasculature often with disorganized architecture. Moreover, larger tumors may have increased interstitial

pressure that leads to further collapse of blood vessels creating hypoxic regions and overt necrosis at times.

Hypoxia is one of the most potent factors of radiation protection known because radiation relies on the production of oxygen free radicals (hypoxia generates two- to threefold less radiation sensitivity).[17] Therefore, drug therapies that mitigate this hypoxia can enhance radiation efficacy. There are four general chemotherapeutic approaches for accomplishing this: (1) chemotherapy can shrink the tumor through cytotoxic action thereby decreasing interstitial pressure. Moreover, because chemotherapy typically targets the fastest proliferating cells, those cells located next to blood vessels are removed bringing the hypoxic regions into closer proximity with the oxygenated region. A good example of this process is demonstrated by taxanes such as paclitaxel.[18] (2) Antiangiogenic therapies such as bevacizumab, an antibody targeting the vascular endothelial growth factor (VEGF), can potentially normalize vascular flow by eliminating the aberrant neovasculature of the tumor. Work by Rakesh Jain[19,20] and others[21,22] provide evidence of this phenomenon. (3) Hypoxic cell targeting agents, such as tirapazamine, can provide biological cooperation by eliminating the most radiation-resistant cells. (4) Hypoxic cell radiation sensitizers can reverse the inherent radiation resistance of the hypoxic cells. Drugs such as misonidazole, a nitroimidazole compound, can mimic the effects of oxygen within the hypoxic regions.[23,24]

Cell Death Pathway Effects

All of the preceding potential mechanisms of drug-radiation interaction display their efficacy through the consequence of cytotoxicity. However, in recent years, it has become clear that there are several ways in which cytotoxicity manifests itself. In 2005, the Nomenclature Committee on Cell Death (NCCD) was created and a classification system based purely on morphological criteria defined four modes of cell death: apoptosis (Type 1), autophagy (Type 2), necrosis (oncosis) (Type 3), and mitotic catastrophe.[25] Although these are distinct forms of cell death, the stimuli and processes involved interrelated. Moreover, there is evidence that ionizing radiation can manifest its cytotoxicity by each type of cell death. Therefore, as our understanding of these cell death pathways improve, novel therapeutics targeting these forms of cell death could enhance radiation efficacy. These cell death mechanisms are briefly described here.

Apoptosis

Apoptosis is the most clearly defined and studied mechanism of cell death. This programmed cell death involves characteristic morphologic changes including chromatin condensation (nuclear pyknosis) and nuclear fragmentation (karyorrhexis). Apoptotic bodies ultimately form and the cell is removed through phagocytosis but without generating inflammatory response. Apoptosis can occur with or without caspase activation[26,27] and does not require DNA fragmentation,[25] although this is a classical hallmark. Apoptosis is considered the major mechanism for chemotherapy-induced cell death. As a mechanism for radiation-induced cytotoxicity, apoptosis occurs readily in "liquid tumors" as opposed to most solid tumors in which apoptosis is a minor component of cell death. As such, drugs targeting the apoptosis pathway may enhance radiation cytotoxicity in solid tumors.

Autophagy

Whereas apoptosis is a clear self-destruct mechanism for the cell, the role of autophagy in cell death is more controversial. Autophagy, literally meaning "self-eating," can provide a protective mechanism for a cell during times of stress (such as nutrient deprivation) because it allows recycling of cellular building blocks through a controlled break down of cytoplasmic components. However, autophagic cell death does occur, which principally differs from apoptosis because of the lack of chromatin condensation.[25]

Necrosis

Type 3 death, or necrosis, is a cell death mechanism in which the cell swells (oncosis), ruptures the plasma membrane, and releases its contents resulting in a local inflammatory response.[25] The best example of this type of cell death is ischemic injury. Large, single fraction radiation, or radio-ablative doses, can produce this type of cell death as seen in stereotactic radiosurgery of brain lesions.

Mitotic Catastrophe

Mitotic catastrophe is a unique form of cell death that involves failed mitotic events.[25] Typically, this is manifest as micronucleation and multinucleation suggesting a series of mitotic divisions occur without cytokinesis that ultimately leads to cell death.

ANALYZING DRUG–RADIATION INTERACTION

Several methodologies for determining the interaction between a drug and radiation have been detailed in the literature. Moreover, several definitions for the possible interactions have also been described. The concept of radiosensitization originated many years ago, and classic radiosensitization has been defined as an increased amount of radiation-induced cell death that results from exposure to a second agent, after correction for the cytotoxicity of this agent. Clonogenic survival assays, that measure all forms of cell death as well as prolonged or irreversible cell cycle arrest, is the most encompassing method of measuring radiation cytotoxicity in vitro (Figure 4-3). Survival curves are generated by plating known quantities of cells on plates and treating them with various doses of radiation or drug and plotting the surviving fraction of colonies formed in a semilogarithmic fashion. Normalization is

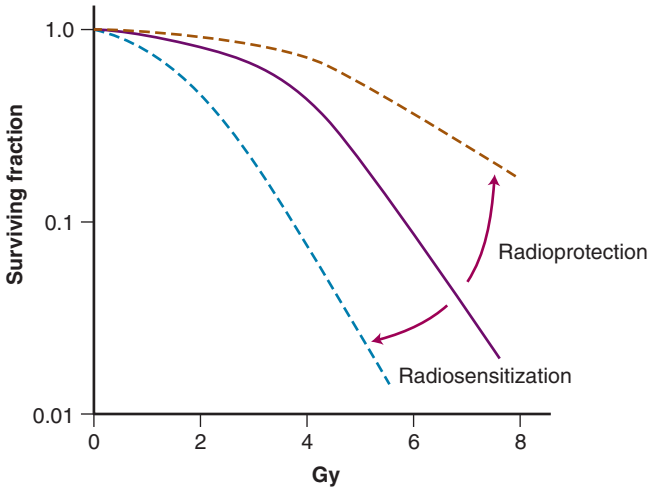


Figure 4-3 Graph of the concept of radiation modulation. The solid line indicates the control clonogenic survival assay plotted as surviving fraction relative to dose in Gy. A combined treatment that causes a rightward shift of the curve indicates a radioprotection effect, whereas a leftward shift of the curve indicates a radiosensitization effect.

performed by dividing the surviving fraction for treated groups by the plating efficiency, which is defined as the surviving fraction of the untreated cells. Modification in radiosensitization, therefore, is demonstrated in clonogenic survival curve data in which a downward or leftward shift of the normalized surviving fraction implies a radiosensitizing interaction, whereas an upward or rightward shift implies a radioprotective shift. Although survival curves can show interaction between chemotherapy and radiation, a better description of radiation modulation is necessary because both chemotherapy and radiation cytotoxicity do not typically follow a linear relationship.

One of the early attempts at providing a more descriptive system was provided by Tyrell,[28] which may be a better starting point for describing various interactions among therapies:

Antagonism: used in all cases in which the action of two treatments is less than would be expected from the addition of the two treatments given independently.
Zero interaction: used when two treatments lead to the effect expected from the addition of the two treatments given independently.
Positive interaction: used in all cases in which the action of two treatments is greater than would be expected from the addition of the two treatments given independently.
Synergism: a special case of a positive interaction; strictly, used when kinetic data are available.

These terms seem to have been supplanted by the "additivity" descriptors including supraadditive, additive, and infraadditive. Once again, the classic paper by Steel and Peckham[7] describes the construction of an "envelope of additivity" for evaluating the interaction of two treatments using isobologram analysis. This envelope of additivity is constructed from cytotoxicity data by calculating a mode 1 curve that assumes that both agents have completely independent mechanisms of action as well as a mode 2 curve that assumes that the two agents have exactly the same mechanism of action. When plotting combination therapy data points on the isobologram, they can either fall between mode 1 and 2 (additive interaction—within the envelope), above mode 1 (infraadditive), or below mode 2 (supraadditive, or synergistic). An idealized isobologram is shown in Figure 4-4 and a step-by-step method for constructing an isobologram is included in the Expert Consult Website.

Additional text available at https://expertconsult.inkling.com/ for a step-by-step method for constructing an isobologram.

Median Dose Effect Principle

A mathematical modeling system that has gained fairly widespread use for interactions of cytotoxic agents is the median effect principle of Chou and Talalay.[29-31] This system was derived from Michaelis-Menten equations and basic mass-action law considerations. This system has been useful for describing competitive enzyme interactions and interactions of cytotoxic agents. The primary relationship of the median effect principle is described by the following equation: $f_a/f_u = (D/D_m)^m$, in which D is dose, f_a is the fraction affected, f_u is the fraction unaffected, D_m is the dose required to produce the median effect (50%), and m is a Hill-type coefficient used to describe the sigmoid nature of the curve. For first-order Michaelis-Menten kinetics, m = 1.

The following manipulation of this equation can be performed, with surviving fraction (SF) substituted for fraction unaffected in the last step:

$$\log(f_a/f_u) = \log[(D/D_m)^m]$$

$$\log(f_a/f_u) = m\log(D) - m\log(D_m)$$

$$\log[(1/SF) - 1] = m\log(D) - m\log(D_m)$$

The general equation is $y = mx + b$.

A plot of log[(1/SF) – 1] on the *y*-axis and log(D) on the *x*-axis results in a line with a slope of *m* and a *y*-intercept of $m\log(D_m)$. The survival curves for the individual agents and for the combination treatment (the individual agents given together in some fashion) can be fitted to the equation for a line by linear regression. If the interaction of two agents is assessed, three lines (i.e., median effect plots) are produced: one for each agent and one for the combination treatment. A graph of the median effect plots for mock individual agents A and B and for the combination of A and B is shown in Figure 4-5. For the combination treatment, D is the sum of the doses of the two agents given concomitantly; it is helpful to perform the experiments with the two agents given together in a fixed ratio of doses (e.g., 1:2). By using various total doses (i.e., the sum), with the agents given in the same ratio, it is possible to determine the contribution of the individual agents to the combination treatment in a later calculation.

This concept can be visualized in Figure 4-5. For instance, in the case of $\log[(1/SF) - 1] = 0$, where SF is surviving fraction, the corresponding log(D), D indicating the sum of the doses of the two agents, can be calculated from the median effect plot for the combination treatment. An example of an actual combination treatment that has been assessed in this manner is radiation followed by a 24-hour exposure to etoposide.[29] In this example, a set of experiments was performed with the dose ratio fixed as 32 Gy to 1 μg/mL of etoposide. In this example, the dose D that resulted in log[(1/SF) – 1] equaling a given value was a combination of radiation and etoposide given in the ratio of 32:1. The radiation and etoposide components could be discerned, from the median effect plot of the combination treatment, by dividing the resulting dose into the appropriate components based on the ratio of delivery of the two agents.

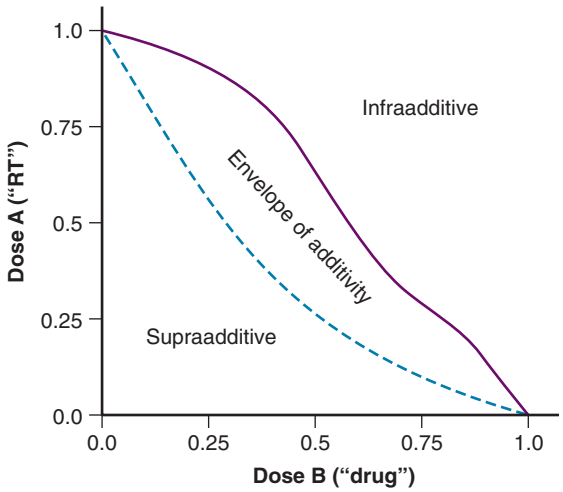
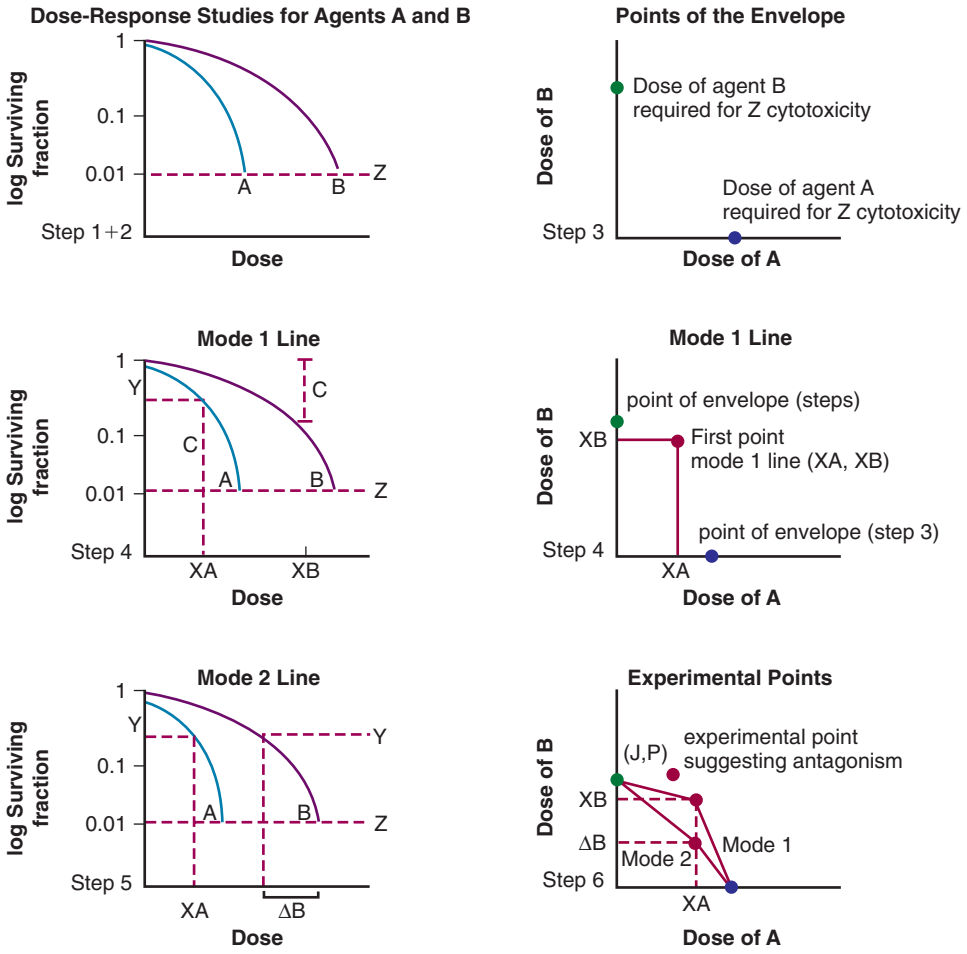


Figure 4-4 Graph of an isobologram for examining the interaction of radiation (RT) and a drug. Isoeffective doses of A (RT) and B (drug) are indicated on the axes. This diagram shows regions of infraadditivity, supraadditivity, as well as an envelope of additivity.



eFigure 4-1 Step-by-step construction of an isobologram to define an envelope of additivity for two cancer treatments. Isobologram analysis is used to evaluate the interaction of two treatments, and it requires the construction of an envelope of additivity that is bordered by mode 1 and mode 2 lines. The mode 1 line assumes that the two agents have completely independent mechanisms of action, whereas the mode 2 line assumes that the two agents have the same mechanism of action.

The following is a step-by-step procedure for calculating isobolograms using Steel and Peckham's method[7,29] (see eFigure 4-1).

Step 1. The investigator must choose to make the assessments at one level of cytotoxicity (e.g., construct an isobologram that represents the interaction of the agents for a cumulative cytotoxicity of 50%, 10%, or 1%). The example in Figure 4-3 depicts the chosen level of cytotoxicity as horizontal line Z: 1% cytotoxicity (0.01 surviving fraction) in this case.

Step 2. Plots are made of dose-response data for both agents. In eFigure 4-1, the dose-response data for the two agents are represented by curves A and B.

Step 3. The extreme points of the envelope of additivity are determined. Initially, a separate cartesian graph is created. The *y*-axis represents the dose of agent B, and the *x*-axis the dose of agent A. The first extreme point of the envelope is placed on the *y*-axis at the dose of agent B alone that causes a specific level of cytotoxicity, as determined by the dose-response curve of agent B, at the intersection of line Z (see eFigure 4-1). The second extreme point of the envelope is placed on the *x*-axis, at the dose of agent A alone that results in that level of cytotoxicity at the intersection of the dose-response curve with line Z (see eFigure 4-1).

Step 4. The mode 1 line is constructed assuming that the agents function independently. The individual dose-response curves are used for this construction. After exposure to dose X of agent A (XA), a level of cytotoxicity is obtained at a point on the dose-response curve that is above line Z. This level of cytotoxicity is identified as Y. Next, the dose of agent B (XB) that is required to produce cytotoxicity equal to the difference in cytotoxicity at line Z and point Y (identified as C) is determined. The cartesian coordinate (XA, XB) is plotted and becomes a point on the mode 1 line. The entire mode 1 line is constructed in this manner by varying the dose of agent A (for a resulting level of cytotoxicity that falls above line Z) and subsequently calculating the appropriate complementary dose of agent B as described.

Step 5. The mode 2 line is constructed assuming that the two agents have the same mechanism of action. As for mode 1 line construction, exposure to dose X of agent A (XA) results in a level of cytotoxicity identified as Y. The dose-response curve for agent B is then examined. The dose of agent B required for cytotoxicity equivalent to Y is determined and identified as YB. The change in dose of agent B that is required to increase cytotoxicity from YB to line Z is determined and labeled ΔB. The cartesian coordinate (XA, ΔB) is plotted. Similar points are calculated for various initial doses of agent A, and the mode 2 line is formed. The mode 2 line varies in shape depending on whether agent A or agent B is selected first for step 5. Generally, the mode

2 line that results in the greatest separation from the mode 1 line is chosen for the envelope of additivity.

Step 6. The two agents are given concomitantly, and a dose-response curve for concomitant treatment is obtained (typically by holding the dose of one agent constant while varying the dose of the other). The doses of the individual agents that result in combined cytotoxicity equivalent to the level represented by line Z are plotted (J, P).

This procedure allows for characterization of experimental data. The experimental point (J, P) represents an antagonistic interaction if the point falls above the envelope of additivity. The effect of the combination treatment is less than would be expected if the agents had completely independent mechanisms of action. An experimental point that falls directly on the mode 1 line suggests that the agents have independent mechanisms of action and the interaction is additive. An experimental point that falls below the mode 2 line suggests a synergistic interaction between the two agents for the particular concomitant treatment used.

The most difficult result to interpret is an experimental point that falls within the envelope of additivity. In some respects, the envelope of additivity is a misnomer because experimental points that fall in this range display an interaction that is greater than the additive effect that is achieved if the agents function by completely independent mechanisms. The interaction between the agents may be positive if the agents have independent mechanisms of action, or it may be negative if they have identical mechanisms of action.

Although the isobologram analysis is useful, it is somewhat limited because interactions in each analysis are investigated at a single level of cytotoxicity. The investigation of interactions at several levels of cytotoxicity requires the construction of several envelopes of additivity. The ambiguity associated with experimental points that fall within the envelope can be disconcerting and may lead to erroneous conclusions, especially if several levels of cytotoxicity are not investigated. Other mathematical modeling systems have been developed to assess the interaction of agents that cause cytotoxicity. These assessments aim to account for the kinetics of cytotoxicity of the involved agents and to assess multiple levels of cytotoxicity.

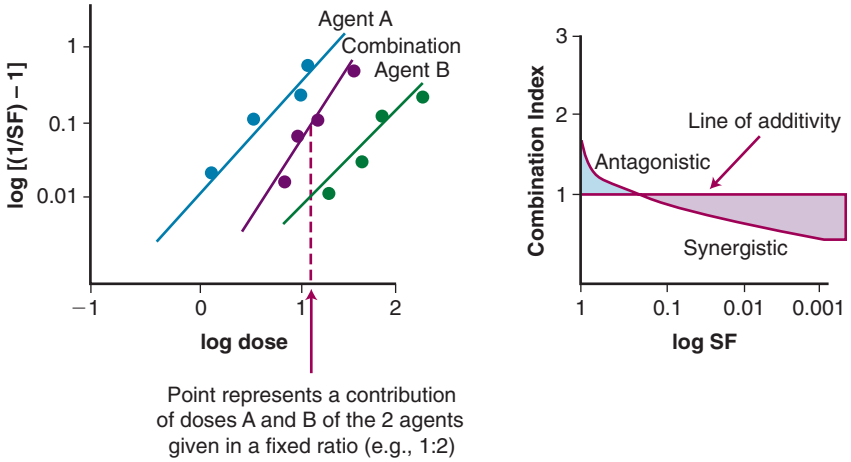


Figure 4-5 The hypothetical graph *(left)* demonstrates the median effect principle analysis for agents A and B given alone or in combination. The combination treatments are given in a fixed ratio so that the individual contribution of each agent to the combined effect can be calculated. The combination index *(right)* is then calculated at various levels of cytotoxicity as measured by surviving fraction (SF). The areas of antagonism, additivity, and synergism are indicated.

Definitions used in the median effect principle include the following:

Mutually exclusive: the agents of interest have similar modes of action and do not act independently.
Nonmutually exclusive: the agents of interest have different modes of action or act independently.
Combination index (CI): the derivation of this index is beyond the scope of this chapter. Calculation of CI allows characterization of an interaction as synergistic (CI <1), antagonistic (CI >1), or a summation (CI = 1). Chou and Talalay[31] provide a full description.

CI can be calculated for any surviving fraction and for mutually exclusive or mutually nonexclusive interactions. For a mutually exclusive interaction,

$$CI = [D_1/(Dx)_1] + [D_2/(Dx)_2]$$

For a mutually nonexclusive interaction,

$$CI = [D_1/(Dx)_1] + [D_2/(Dx)_2] + [D_1D_2/(Dx)_1(Dx)_2]$$

in which

$(Dx)_1 = D_m[(1/SF) - 1]^{1/m}$, solving the general equation for agent 1 given alone in a dose x.
$(Dx)_2 = D_m[(1/SF) - 1]^{1/m}$, solving the general equation for agent 2 given alone in a dose x.
$(Dx)_{1,2} = D_m[(1/SF) - 1]^{1/m1,2}$, solving the general equation for the agents given in combination for dose x, which represents the sum of the doses of the agents given in a fixed combination.
$D_1 = (Dx)_{1,2} \times$ (fraction of the mixture that is agent 1).
$D_2 = (Dx)_{1,2} \times$ (fraction of the mixture that is agent 2).

CI represents the doses of the agents required for a given effect when they are given together, divided by the doses required when the agents are given alone; in this way, CI less than 1 represents a synergistic interaction. A diagram of a CI plot for various levels of surviving fraction is shown in Figure 4-5.

Despite the advent of these robust statistical tools for determining the additivity relationship between treatments, the applicability outside of in vitro models is limited based on time and expense necessary to complete dose response experiments for both drug and radiation. Therefore, preclinical in vivo experimentation typically involves the use of a single drug dose at a concentration that can be achieved clinically.

CHEMOTHERAPY AND RADIATION AND COMBINATIONS OF CYTOTOXIC AGENTS

General Concepts

From the Bench to the Clinic

Occasionally, the process of quantifying interactions of chemotherapy and radiation has frustrated clinicians attempting to interpret in vitro and in vivo laboratory information, as exemplified by Charles Moertel (quoted by Tannock[32]) in his keynote speech at the first International Conference on Combined-Modality Therapy in 1978:

> *Based on the results of various individual studies, I could conclude that it is most ideal to administer the nitrosourea 15 hours before irradiation, 2 hours before irradiation, simultaneously with irradiation, or 6 hours after irradiation. While we will continue to cheer our radiation biology colleagues on from the sidelines, I am afraid that we are not yet at the stage where we can comfortably incorporate their results into our clinical practice.*

This was not meant as disrespect for the radiobiology community but to point out that, at that time, the laboratory models were potentially quite different from the clinical setting. Because it has been difficult to extrapolate from laboratory results to clinical results, many clinicians have used combination treatments on a trial-and-error basis. However, the reverse order of study has occasionally been fruitful, and efficacious combinations of treatment demonstrated in clinical studies have inspired laboratory investigations that revealed interesting molecular bases of interaction.[29,30] Translational research ideally occurs with a concept that arises from laboratory findings and subsequently is shown to have clinical efficacy. However, preclinical model systems have not always allowed investigators to take findings from the laboratory to the clinic, as indicated by the quotation of Moertel and by many of the early hypoxic cell sensitizer studies.

Therapeutic Benefits

Tannock[32] mentioned another problem with translating findings from the laboratory to the clinical setting, emphasizing that investigators must not merely explore combinations of therapeutic agents to find synergistic interactions but must also find interactions that will produce a therapeutic benefit (e.g., provide greater cytotoxicity in tumor cells than in normal cells). To categorize potentially exploitable differences, Tannock[32] described three main categories of biologic diversity between tumor cells and normal cells: tumor cells may display

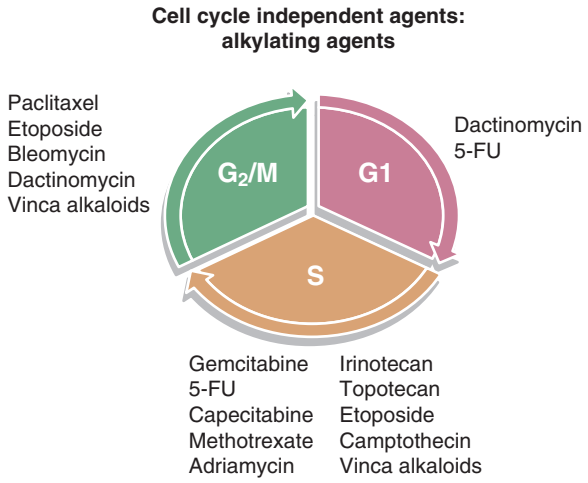


Figure 4-6 Diagram of the cell cycle with the cell cycle phase dependence of various chemotherapeutics.

genetic instability compared with normal tissues; tumor cells and normal cells may be different with respect to cellular proliferation or proliferation that occurs after treatment; and environmental factors such as oxygenation and pH may affect tumor cells and normal cells differently. As findings are translated from the laboratory to the clinical setting, it is important to consider the effects of the host mechanisms on these three areas.

Chemotherapeutic Classes

In the next section, several classes of systemic agents will be presented followed by a brief review of clinical data describing combination treatment of these agents with radiation. There are a host of chemotherapeutic classes that are used in patients that will undergo radiation treatment. Although not all of these agents are used concurrently with radiation, it is helpful to understand their predominant mechanism of action. A brief description of several of the major classes of chemotherapeutics with some information regarding possible means of interaction with radiation follow. In addition, Figure 4-6 summarizes the cell cycle phase specificity of these agents.

Antimetabolites

The origin of antimetabolite chemotherapy dates back to the 1940s when aminopterin was used to treat pediatric leukemia.[33] Since then, a large number of antimetabolite chemotherapeutics have been developed with tremendous success. The targets for these drugs include folate metabolism and nucleoside analogs. The major antimetabolites are presented here.

Fluoropyrimidines: Fluorouracil, Fluorodeoxyuridine, and Capecitabine

The fluoropyrimidines, as the name implies, are halogenated pyrimidines that function as antifolates by inhibiting thymidylate synthesis. As mentioned previously in historical perspectives, 5-FU is one of the most established drugs used in combination with radiation. It has been used in both a bolus infusion as well as a continuous venous infusion when combined with radiation and appears to target the radioresistant cells in S-phase.[16] The two delivery methods have some differences in terms of side effect profile, but both seem to have good efficacy. In a phase III rectal cancer postoperative adjuvant chemoradiation trial, concurrent continuous infusion 5-FU during EBRT was more effective than the bolus delivery.[34] Moreover, data shows that 5-FU plasma levels and intracellular metabolite levels are rather short-lived,[35] also suggesting a need for continuous administration of the drug to be effective with radiation. Because of this, oral formulations have been developed, most notably capecitabine, a fluoropyrimidine carbamate prodrug of 5-FU, which must be converted through the action of thymidine phosphorylase. In addition to the improved patient comfort of taking an oral medication rather than having an infusion pump, another potential advantage of capecitabine in combination with radiation is that it appears that radiation increases thymidine phosphorylase levels in tumors, which allows potential bioaccumulation of active metabolite within irradiated tumor.[36,37]

Gemcitabine

Gemcitabine is an analog of deoxycytidine that specifically functions during the S-phase by preventing the dNTP production. There is both preclinical and clinical evidence demonstrating dramatic radiation sensitizing properties to combined gemcitabine and radiation.[38-41] In fact, a significant amount of toxicity has been demonstrated in clinical trials for pancreatic cancer[42] necessitating either decreased dose of gemcitabine or limited field size for radiation treatment ports.

Antifolates: Methotrexate, Trimetrexate, and Pemetrexed

The antifolate, methotrexate, tightly binds dihydrofolate reductase (DHFR) thereby inhibiting folate metabolism. Through this inhibition, thymidylate synthesis is blocked, and thus, purine biosynthesis. In addition, some amino acid synthesis is impaired through blockade of this enzyme resulting in cytotoxicity.[43] Pemetrexed is a pyrrolopyrimidine that functions as an antifolate that inhibits multiple enzymes including thymidylate synthase, dihydrofolate reductase, glycinamide ribonucleotide formyl-transferase, and aminoimidazole carboxamide formyl-transferase in a cell cycle independent manner. Pemetrexed is effective against many solid tumors and has shown radiosensitizing propertied in preclinical systems.[44,45,46]

Alkylating Agents

Alkylating agents are composed of several classes of electrophilic compounds that share the antitumor characteristic that they form covalent bonds with ("alkylate") DNA bases. Some alkylators interact with a single strand of DNA, whereas others can cross-link two strands. The induced DNA damage leads to the cytotoxicity of these agents. The various classes of alkylators that are potentially used with irradiation are briefly presented here.

Nitrogen Mustard: Chlorambucil and Melphalan

The first of a long series of alkylating agents developed for clinical use, mustard gas was discovered based on clinical observations of people and animals exposed to mustard gas during World War I, particularly the effect on bone marrow.[33,47] Later, nitrogen mustards were developed for lymphoma therapy as mechlorethamine or Mustargen, eventually used in the MOPP (Mustargen, vincristine [Oncovin], procarbazine, prednisone) regimen for Hodgkin's lymphoma. The most commonly used nitrogen mustards are chlorambucil and melphalan (L-phenylalanine mustard) and are principally used for the treatment of chronic lymphocytic leukemia and multiple myeloma, respectively. Because of the bone marrow effect of these drugs, caution should be used when irradiating large volumes of bone marrow.

Oxazaphosporines: Cyclophosphamide and Ifosfamide

The oxazaphosphorines are nitrogen mustard-like compounds that include cyclophosphamide and its structural isomer,

ifosfamide. These agents are used in combination with radiation in both pediatric and adult cancer treatment.

Mitomycin C

Mitomycin C is an antibiotic with alkylating characteristics derived from *Streptomyces*. This agent, is an aziridine ring–containing compound that resembles nitrogen mustard as well. This drug blocks DNA synthesis but also causes cell cycle arrest during G2/M phase transition.[48,49] Mitomycin C has also been shown to function well as a hypoxic cell radiosensitizer,[50] which may help explain why mitomycin C-based chemoradiation is so effective in anal cancer treatment,[51,52] as discussed later in the chapter.

Triazenes: Procarbazine, Dacarbazine, and Temozolomide

Temozolomide has revolutionized the treatment of high-grade gliomas in combination with irradiation. It effectively crosses the blood-brain barrier. (The cerebrospinal fluid [CSF] can achieve 30% of plasma levels).[53] Temozolomide generates DNA damage through methylation of DNA at the O-6 position of guanine. Interestingly, the O-6 methylguanine DNA-methyltransferase (MGMT) is a p53 DNA repair enzyme that can be regulated epigenetically silenced by promoter methylation, which appears to predict for response to temozolomide-based chemoradiation because of the inability of the cancer cell to remove the O-6 methylguanine causing cytotoxicity.[54] Indeed, this DNA alkylation/methylation from temozolomide triggers the mismatch repair pathway with a G2/M phase arrest yielding apoptosis and radiosensitive cells.[55] Ongoing clinical trials are examining the importance of MGMT status and combining temozolomide with other agents.[54,56]

Nitrosoureas: BCNU, Methyl-CCNU, CCNU, and Streptozotocin

Several members of the nitrosourea group of alkylating agents are capable of crossing the blood-brain-barrier and cross-linking DNA. BCNU, or carmustine, has been used to treat brain tumors, predominantly gliomas, but it has also been used for multiple myeloma and high-dose transplant regimens. Gliadel (BCNU impregnated wafer) can be placed in a glioma resection cavity, which biodegrades slowly to release the chemotherapeutic. CCNU, or lomustine, is a related compound with increased lipid solubility also used for brain tumors.[57]

Platinums: Cisplatin, Carboplatin, Oxiliplatin, and Satraplatin

Cisplatin, (cis-Diammine dichloroplatinum[II]), the prototypical and most widely studied member of the platinum family, has been used for decades as an anticancer treatment. Preclinical work in the late 1970s by Soloway et al[58] demonstrated radiosensitization in a murine model of transitional cell carcinoma. Since then, a host of both clinical and preclinical data suggests several mechanisms of interaction between cisplatin and radiation. Potential cooperation between the two modalities can occur at the level of DNA because radiation often causes repairable single-stranded breaks in DNA, which can be converted to lethal double-stranded breaks when they occur close to cisplatin-DNA adducts (intra- and interstrand cross-links). This may also be as a result of the ability of cisplatin to function as a free-electron scavenger that impairs the DNA repair mechanism, thus, "fixing" the radiation-induced DNA damage.[59] In addition, radiation may enhance the uptake of cisplatin into the cell as well as help generate active platinum metabolites.[1] The other family members, carboplatin, oxiliplatin, and the orally active, satraplatin, appear to have similar mechanisms of action though differences among the members may be because of the three-dimensional structure of the DNA adducts that each platinum generates, which influences binding to various polymerases and DNA repair enzymes.[60] For these reasons, the platinums function independent of the cell cycle phase.

Microtubule Targeting

Because microtubule polymerization and depolymerization are critical for spindle formation and chromosome segregation during mitosis, microtubule targeting agents have the ability to enhance radiation effect by creating a cell cycle blockade during M-phase, which is a radiation-sensitive phase of the cell cycle. Moreover, these agents promote apoptosis as well. The three predominant classes of microtubule targeting agents are discussed here.

Estramustine

Estramustine is an interesting hybrid molecule that is derived from both nitrogen mustard and 17β-estradiol. Estramustine effectively blocks microtubules by binding β-tubulin and microtubule associated proteins resulting in destabilization of microtubules. This targets the mitotic spindle and leads to cell cycle arrest during M-phase causing radiosensitization.[61] This drug has been approved for hormone-refractory prostate cancer for almost three decades.

Vinca Alkaloids: Vincristine, Vinblastine, and Vinorelbine

The vinca alkaloids have been used as anticancer agents for more than 40 years and function by targeting microtubules. They are able to force depolymerization of microtubules and, thus, disrupt the mitotic spindle resulting in an M-phase blockade.[62] These drugs have been used for a wide variety of malignancies, both pediatric and adult. In terms of radiosensitization, vincristine, vinblastine, and vinorelbine impact cell cycle effects and DNA damage repair.[9,62]

Taxanes: Paclitaxel, Docetaxel, and Albumin-Bound Paclitaxel

As opposed to the vinca alkaloids, the taxanes stabilize microtubules and promote further tubulin polymerization, which inhibits centrosome mechanics during mitosis. In terms of enhancing radiation effect, the taxanes appear to manipulate several of the factors listed in Table 4-1. First, the taxanes will block the metaphase-anaphase cell cycle checkpoint, which could allow for accumulation of cells in the radiosensitive G2/M phase.[62,63] Furthermore, taxanes can cause tumor shrinkage,[64,65] thereby decreasing interstitial pressure and allowing for improved oxygenation.[18] In addition, taxanes can manipulate signal transduction cascades involved in radiation response.[66]

Epothilones (Epothilone B, Aza-Epothione B [Ixabepilone])

The epothilones are considered next-generation microtubule targeting agents that function similar to taxanes but are derived from mycobacterium. They are able to stabilize microtubules with high potency and halt mitosis similar to taxanes.[62] These drugs were developed to be independent of the p-glycoprotein efflux resistance mechanisms that target taxanes and vinca alkaloids.[62,67] These drugs will likely become a popular choice for concurrent chemoradiation regimens in the future.

Topoisomerase Inhibitors

Topoisomerases are critical enzymes in DNA replication of all cells because of their ability to unwind DNA. There are two major classes of topoisomerases in mammalian cells that are

clinically relevant for oncology therapeutics, topoisomerase I and II. Topoisomerase I (TopI) is involved in DNA replication fork movement and unwinding supercoils during DNA transcription, whereas topoisomerase II (TopII) is important for untangling DNA during transcription and remodeling chromatin.[35,43] These classes are named based on how many DNA strand breaks are created during enzymatic action, a single-stranded break for TopI and double-stranded break for TopII.[43] These breaks are required for TopI and II to unwind and disentangle DNA, but they are temporary because the enzyme will reconnect the broken strands (religation). TopI/II inhibitors have cytotoxicity by disrupting the process and generating DNA double-stranded breaks.

Topoisomerase I Inhibitors (Camptothecins—Irinotecan, Topotecan)

Camptothecin is a naturally occurring alkaloid derived from the plant *Camptotheca acuminata* that was identified in an anticancer drug discovery screen in the 1960s.[68] Camptothecin is believed to form a stable ternary complex that prevents normal DNA religation and a collision of the complex with the replication fork occurs leading to a DNA double-stranded break and cytotoxicity.[69] The S-phase specificity of this drug class provides some of the rationale for radiosensitization. The drug was unsuccessful in the clinic because of severe urinary complications, though camptothecin is still used as a research tool and positive control for cytotoxicity and apoptosis. However, derivatives of camptothecin, notably irinotecan and topotecan, are used as chemotherapeutics. Irinotecan is FDA approved for colorectal cancer, but data related to concomitant administration with radiation has been generated in patients with both small cell[70-72] and non–small cell lung carcinoma.[73,74] Topotecan is approved for ovarian, small cell, and cervical cancer, but it has been combined with radiation in glioblastoma clinical trials.[75,76]

Topoisomerase II Inhibitors

Podophyllotoxins: Etoposide, Etoposide Phosphate, and Teniposide. The plant extract, podophyllotoxin, has microtubule binding activity, yet, the clinically used derivatives do not function through microtubule action but actually are TopII poisons.[77] These epipodophyllotoxins, most notably etoposide and teniposide, are glycoside derivatives that are used in both childhood and adult tumors.[35] In addition, these drugs have been used with radiation in both sequential and concomitant regimens.[78-81]

Anthracyclines: Idarubicin, Doxorubicin, Epirubicin, and Daunorubicin. Anthracyclines are naturally occurring substances that intercalate into the DNA when they target TopII leading to DNA double-stranded breaks.[35,82] These drugs have a wide range of clinical indications, including both liquid and solid tumors. In terms of radiation sensitization, the interaction of doxorubicin and radiation are well known such that concurrent administration is generally avoided. In fact, when doxorubicin is given after radiation, an inflammatory reaction known as "radiation recall" can occur.[83,84]

Others: Mitoxantrone and Dactinomycin. Mitoxantrone is an anthracenedione that was designed to function like an anthracycline but have less cardiotoxicity[85] because it is less likely to form free radicals[35] and may affect calcium release differently.[86] Like anthracyclines, mitoxantrone can intercalate in DNA and poison TopII to form DNA double-stranded breaks. This drug is approved for hormone-refractory prostate cancer. Dactinomycin is a *Streptomyces* derived antibiotic that can intercalate in DNA, block TopII and cause DNA double-stranded breaks.[35] Dactinomycin is used in pediatric sarcoma therapeutic regimens, including rhabdomyosarcoma.

CHEMORADIATION CLINICAL EXAMPLES

An all-encompassing review of the clinical examples of the use of chemoradiation is beyond the scope of this chapter. More comprehensive information regarding disease site-specific trials are included in the individual chapters devoted to each site. What follows is merely a brief account of some of the landmark trials that have demonstrated improved organ preservation, local control, and overall survival in the modern era. Specifically, aerodigestive, genitourinary, gynecological, and central nervous system cancer examples are presented.

Gastrointestinal Cancers

Anal Cancer

A classic example of the evolution of an efficacious interaction of chemotherapy and radiotherapy is combined modality treatment for anal cancer. In the early 1970s, it was discovered that anal cancer could be treated successfully with a combination of 5-FU, mitomycin C (MMC), and irradiation.[52] In 1974, Nigro et al[52] reported on three patients who received variations of these three treatments, with excellent responses to the preoperative therapy (eTable 4-1). This article became a classic in the oncology literature, and the regimen became prominent in the treatment of anal cancer. Because of this regimen, many patients were spared abdominal perineal resection.

After the initial report of Nigro et al,[52] several other groups confirmed the efficacy of chemotherapy and irradiation (without surgery) as the standard treatment for primary anal cancer (Table 4-2).[52,87-89] Subsequently, an intergroup effort was undertaken by the Radiation Therapy Oncology Group (RTOG) and Eastern Cooperative Oncology Group (ECOG) to determine whether MMC could be removed from the regimen because its inclusion resulted in increased toxicity compared with that of 5-FU and radiation without MMC. With 5-FU, however, fewer patients were able to avoid colostomy (see Table 4-2).

Additional attempts at replacing MMC with less toxic concurrent chemotherapy have been undertaken, most notably in the U.S. GI Intergroup study (see Table 4-2) coordinated by RTOG (RTOG 98-11). This trial compared an induction chemotherapy (5-FU and cisplatin) regimen followed by the same chemotherapy concurrently with radiation versus standard concurrent chemotherapy (5-FU and MMC) with radiation. The hypothesis was that the induction chemotherapy would decrease tumor bulk making radiotherapy more effective and thus improving local control and that the additional cycles of induction chemotherapy may improve overall survival (OS) by decreasing distant metastases. However, these hypotheses were disproven because the cisplatin arm not only failed to show a benefit in terms of local control, disease-free survival (DFS), and OS, but was clearly inferior to MMC in terms of colostomy-free survival (CFS).[51] Long-term followup of trial results not only confirmed initial results regarding CFS but, more importantly, demonstrated a statistically significant superior DFS and OS with 5-FU and MMC compared to induction and concurrent 5-FU and cisplatin.[90] Therefore, the combination of 5-FU, MMC, and irradiation remains the standard regimen for anal cancer. IMRT strategies combined with 5FU-MMC based chemoradiation have been investigated by multiple groups and demonstrate a reduction in normal tissue toxicities.[91-93]

Additional text available at https://expertconsult.inkling.com/ for a discussion of how the laboratory investigations followed the clinical data.

eTABLE 4-1 Combined-Modality Treatment for Anal Cancer: A Study of Three Patients

Patient	RT	Chemotherapy	Results
1	34.7 Gy/5 wk	Concomitant 5-FU*/porfiromycin (50 mg)	APR 9 wk after RT, NED
2	30.6 Gy/17 Fx	Concomitant 5-FU*/mitomycin (30 mg)	Clinically free of disease, patient refused APR
3	30 Gy/15 Fx	None	APR 8 wk after RT, NED

Data from Nigro ND et al.[52]

5-FU, *5-Fluorouracil;* APR, *abdominoperineal resection;* Fx, *fractions;* NED, *no evidence of disease;* RT, *radiation therapy.*

**Dose of 1500 mg of 5-fluorouracil in the form of a continuous 24-hour infusion for 5 days.*

The clinical finding of the efficacious combination of 5-FU, mitomycin C, and radiation led to laboratory studies. Dobrowsky et al[94] performed a complex isobologram analysis using the same agents reported by Nigro et al.[52] The assessment by Dobrowsky et al,[94] using an in vitro system of a squamous tumor cell line, illustrated some of the difficulties with the ideal progression of taking laboratory discoveries to the clinic. Two different endpoints were used: colony formation (cells plated after treatment and allowed to form colonies) and viable cells per flask (obtained by multiplying the cell number per flask at 96 hours by the surviving fraction, as stipulated by a standard colony formation assay). In an attempt to duplicate the clinical treatment of Nigro et al,[52] mitomycin C was given as a 1-hour exposure and 5-FU as a 4-day exposure after initial radiation.

The first experiments assessed the interaction of 5-FU and mitomycin C without radiation. Initially, a single dose of mitomycin C (0.5 μg/mL for 1 hour) was combined with various doses of 5-FU. Isobolograms were constructed for the colony formation endpoint at a surviving fraction of 0.04. Isobologram construction showed that the combination treatment resulted in an experimental point below the envelope of additivity at this level of cytotoxic assessment. Isobolograms also were constructed for the viable cells per flask endpoint at the 1% viability level; the experimental point for combined 5-FU and mitomycin C was directly on the mode 2 line. This endpoint was included because it was believed to account for the cytotoxic and cytostatic effects of the treatment.

Because the results of this synergy analysis varied with the endpoint used, the optimal endpoint, whether colony formation or viable cells per flask, is not known. That the use of these slightly different endpoints produced slightly different isobologram results illustrates some of the problems in interpreting in vitro data and in attempting to extrapolate this information to the clinical setting. In the future, it may be possible to assess which endpoints may be most useful for various cytotoxic agents and various tumors on the basis of the relative contribution of cytotoxic and cytostatic effects for a given situation.

On the basis of the experiments without irradiation, specific concentrations of mitomycin C (0.5 μg/mL) and 5-FU (0.15 μg/mL) were selected for subsequent experiments involving radiation[94]; these concentrations resulted in 60% and 80% surviving fractions, respectively. With colony formation as the endpoint, it was discovered that the interaction of irradiation and 5-FU or irradiation and mitomycin C (at the levels of cytotoxicity assessed) produced experimental points below the envelope of additivity. These results corroborated those reported previously by Byfield et al,[95] in which some level of 5-FU cytotoxicity was required for a positive interaction with irradiation. However, the results of radiation in conjunction with mitomycin C were not entirely consistent with those of previous reports, which had suggested that a positive interaction of these agents did not exist.[96]

The previous example illustrates several important points. If the protocol of Nigro et al[52] had been designed on the basis of laboratory studies (if all of the aforementioned studies had existed in 1974), it would have been difficult to assess where to begin. First, the investigator would need to decide which in vitro endpoint would be most relevant to anal cancer (viable cells per flask or colony formation), and this decision would affect whether one believed that 5-FU and mitomycin C interacted synergistically. Second, the investigator would need to decide which assessment of mitomycin C and radiation was most relevant to the treatment of anal cancer because authors disagreed about whether this interaction was synergistic. This example also illustrates the challenges that are faced when interpretations of in vitro or in vivo experimental data are used to guide the design of clinical trials. These challenges can be exciting as we learn more about the significance of various endpoints at the molecular level and how these molecular events may be manipulated in a particular tumor.

TABLE 4-2 Concomitant Radiation and Chemotherapy for Anal Cancer

Study	Regimen	Outcome
Nigro et al[52] (1987), Wayne State University	RT (30 Gy/15 Fx) with CI 5-FU (1000 mg/m^2) for 4 days × 2 cycles and mitomycin C (15 mg/m^2) on day 1	Of 104 patients, 31 required APR
Sischy et al[89] (1989), RTOG/ECOG	RT (40 Gy/20 Fx) with CI 5-FU (1,000 mg/m^2) for 4 days × 2 cycles and mitomycin C (10 mg/m^2) on day 2	Of 79 patients, 8 required APR
Flam et al[88] (1996), RTOG/ECOG	RT (45 Gy/25 Fx) with CI 5-FU during weeks 1 and 4, with randomization to mitomycin C (10 mg/m^2) on days 1 and 29 vs. no mitomycin C	Colostomy-free survival improved with MMC, 71% vs. 59% (p = 0.014)
Bartelink et al[87] (1997), EORTC	RT (60-65 Gy*) alone vs RT plus 5-FU (750 mg/m^2 on days 1-5, 29-33) and mitomycin C (15 mg/m^2) on day 1	Improved event-free survival with RT and chemo compared with RT alone (p = 0.03)
Ajani et al[51] (2008), Gunderson et al[90] (2012); RTOG 98-11 (GI INT)	RT (55-59 Gy) with CI 5-FU CI 5-FU (1000 mg/m^2, for 4 days, wks 1 & 5) and MMC (10 mg/m^2 on days 1 and 29) vs CI 5-FU (1000 mg/m^2) + cisplatin (75 mg/m^2 on days 1 and 29) with induction chemotherapy	(N = 682); Improved DFS and OS at 5 y (67.8% vs. 57.8%; p = 0.006 and 78.3% vs. 70.7%; p = 0.026, respectively) for MMC arm

5-FU, *5-Fluorouracil;* APR, *abdominoperineal resection;* chemo, *chemotherapy;* CI, *continuous infusion;* ECOG, *Eastern Cooperative Oncology Group;* EORTC, *European Organization for Research and Treatment of Cancer;* Fx, *fractions;* GI INT, *gastrointestinal intergroup;* MMC, *mitomycin-C;* N, *total number of patients;* RT, *radiation therapy;* RTOG, *Radiation Therapy Oncology Group.*
**Surgery 6 weeks after initial 45 Gy if no response.*

Esophagus/Esophago-Gastric Junction

Esophageal/esophago-gastric junction cancer remains a challenging cancer to treat, primarily because of the locally advanced stage that is typically found at diagnosis. For nonsurgical approaches to treatment, radiation alone has been shown to be quite limited in terms of controlling the disease. Indeed, chemoradiation has been clearly shown to be the treatment of choice following several landmark trials comparing chemoradiation to radiation alone. The Intergroup trial coordinated by RTOG (85-01) originally published by Herskovic et al[97] and later updated by Cooper et al[98] randomized patients to either 64 Gy radiation alone at 2 Gy/fraction or 50 Gy in 2 Gy/fraction concurrent with 5-FU (1000 mg/m^2/day for days 1-4) and cisplatin (75 mg/m^2 on day 1). In the concurrent arm, the chemotherapy was given every 28 days during radiation and then every 21 days thereafter for two additional cycles. This trial established that radiation alone was inferior to combined modality chemoradiation (5 year OS 0% vs. 26%, p = 0.0001).[98] A meta-analysis by Wong et al[99] confirmed that concurrent chemoradiation was beneficial in terms of survival with a hazard ratio of 0.73, 95% confidence interval of 0.64-0.84, p < 0.0001. Sequential chemotherapy and radiation did not show a statistically significant benefit, however.[99]

The role of trimodality therapy with neoadjuvant chemoradiation followed by surgery has also been investigated. Tepper et al[100] published the results of the U.S. GI Intergroup study (CALGB 9781) that randomized patients to neoadjuvant cisplatin/5-FU/EBRT (50.4 Gy) before esophagectomy versus esophagectomy alone. Although the trial was closed early because of poor accrual, the 56 patients enrolled were analyzed on an intent-to-treat analysis. This revealed a significant difference in median and 5-yr OS with trimodality treatment and surgery alone (median: 54 vs. 21.6 mo.; 5-yr OS: 39% vs. 16%, p = 0.002).[100] More recently, the CROSS group completed a large randomized phase III study of 366 analyzable patients comparing neoadjuvant carboplatin/paclitaxel/EBRT (41.4 Gy) before esophagectomy and esophagectomy alone.[101] Results of this study revealed that preoperative chemoradiation improved OS (median, 49.4 vs. 24 mo.; 5-yr OS 47% vs. 34%; p = 0.003; hazard ratio, 0.657) without significant increases in acute side effects or postoperative complications. Pathologic complete response was noted in 29% of patients with neoadjuvant therapy. A complete resection of the tumor (R0 resection) was accomplished in 92% of patients who underwent neoadjuvant therapy compared to 69% in patients who had surgery alone.

Combining molecularly targeted agents with standard chemotherapies with radiation have also been tested. Most heavily investigated has been the addition of EGFR targeting agents to standard chemoradiation regimens. Results from the SCOPE1 trial, a European multicenter phase II/III trial evaluating the addition of cetuximab to concurrent cisplatin, capecitabine, and radiation (50 Gy), has revealed a lack of benefit and possible detriment with the addition of cetuximab.[102] Initial reports of RTOG 0436, a randomized phase III trial evaluating the addition of cetuximab to concurrent cisplatin, paclitaxel, and daily radiation (50.4 Gy), also confirm these findings with little or no benefit of cetuximab as evidenced by no improvement in OS or clinical complete response.[103]

Gastric

The U.S. GI Intergroup 0116 phase III trial, reported by McDonald et al, compared adjuvant postoperative chemoradiation to surgery alone for patients with resected high-risk gastric or gastroesophageal cancers. Bolus 5-FU/leucovorin was given before EBRT (one 5-d cycle), concurrently with EBRT (2 cycles: 4-d wk 1, 3-d wk 5), and after EBRT (2 additional 5-d cycles). A survival advantage of concurrent chemoradiation was shown (3-yr OS—50% vs. 41%, p = 0.005; 3-yr relapse free survival—48% vs. 31%, p = 0.001),[104] and this treatment has been the standard of care for gastric cancer in the United States. In the United Kingdom, the MAGIC trial established a nonradiation regimen that involves perioperative (neoadjuvant and adjuvant) epirubicin, cisplatin, and 5-FU (ECF) chemotherapy as an appropriate standard of care for resectable gastric cancer.[105] The logical followup study was a postoperative adjuvant U.S. GI Intergroup phase III trial (CALGB 80101) that essentially married the INT-0116 and the MAGIC trial by investigating the role of chemoradiation in the setting of more modern ECF chemotherapy as the experimental arm versus the control arm of GI INT 0116. Although the experimental arm did not improve survival, the ECF regimen had a more favorable toxicity profile.[106]

Rectal

Although rectal cancer is a surgically managed disease, the addition of adjuvant therapy is well recognized as a vital

TABLE 4-3 Randomized Trials of Neoadjuvant Concomitant Radiation and Chemotherapy for Rectal Cancer

Study	Regimen	Outcome
Boulis-Wassif et al[108] (1984)	Preop RT (34.5 Gy at 2.3 Gy/fx) ± 5 FU 10 mg/kg/d day 1-4 followed by surgery	Trend toward improved 5 y OS (59% vs. 46%, $p = 0.06$)
Bosset et al[107] (2006)	4 arm study: preop RT (45 Gy) + S vs. preop CT-RT with 5 FU (325 mg/m^2/d)/LV (20 mg/m^2/day) d1-5, 28-32+ S vs. preop RT + S + adjuvant 5 FU/LV vs. preop CT-RT + S + adjuvant 5 FU/LV	5 y LR was worse in the RT only arm (17.1% vs. 8.7%, 9.6%, and 7.6% in the CT containing arms; $p = 0.002$)
Bujko et al[109] (2006)*	Preop RT (25 Gy at 5 Gy/fx) + S vs. Preop CT-RT (50.4 Gy at 1.8 Gy/fx with 5 FU(325 mg/m^2/d)/LV (20 mg/m^2/day) d1-5, 28-32 + S	No difference in LC, OS, or late toxicity, but CT-RT had more early toxicity (8.2% vs. 3.2%; $p < 0.001$)
Gerard et al[110] (2006)	Preop RT (45 Gy at 1.8 Gy/fx) ± 5 FU (350 mg/m^2/d d1-5 days + LV) followed by S + adjuvant 5 FU (350 mg/m^2/d d1-5 days + LV)	Improved pCR (11.4% vs/ 3.6%; $p < 0.05$) and less LR (8.1% vs. 16.5%; $p < 0.05$) with CT-RT

5-FU, *5-Fluorouracil;* CT, *chemotherapy;* CT-RT, *concurrent chemoradiation;* fx, *fractions;* LR, *local recurrence;* LV, *leucovorin;* pCR, *pathologic complete response;* RT, *radiation therapy.*

**Not a true comparison of adjuvant EBRT ± concurrent chemo as used markedly different adjuvant EBRT regimens*

component of therapy. Four randomized trials[107-110] investigating the addition of chemotherapy to neoadjuvant EBRT in Stage II and III rectal cancer is summarized in Table 4-3 (the Bujko trial did not use the same dose/duration of EBRT so it is not a true comparison of EBRT ± concurrent chemotherapy). Furthermore, a meta-analysis reviewed these four trials.[111] Although this analysis showed improved complete pathological response rate and local control with the addition of chemotherapy to preoperative radiation, no benefit was found in terms of sphincter preservation, DFS, or OS. Of note, preoperative chemoradiation was found to produce increased grade 3 and 4 toxicity compared to preoperative EBRT alone.

The current standard of care approach, however, was defined in the phase III German Rectal Trial.[112] Preoperative chemoradiation was shown to be superior to postoperative chemoradiation in terms of local control, sphincter preservation rates, and toxicity.

As in other disease sites, more recent trials are investigating the addition of molecularly targeted agents to the standard preoperative chemoradiation regimen. The antivascular endothelial growth factor antibody, bevacizumab, has shown promising results in phase I/II trial in which all 32 patients showed tumor regression following neoadjuvant therapy with an actuarial 5-year DFS of 75%.[113] In addition, EGFR targeted agents have shown promise in KRAS wild-type tumors.[114,115] However, these agents remain investigational in this setting.

Head and Neck Cancers

Head and neck cancers management for locally advanced tumors were traditionally managed with surgery and postoperative radiation. However, over the past two decades, an explosion of chemoradiation trials shifted the management toward an organ preservation approach (summarized in Table 4-4). One of the most impressive results for a randomized trial in head and neck cancers was that of Intergroup 0099 (RTOG 8817) originally published by Al-Sarraf et al in 1998.[116] In this trial of patients with nasopharyngeal cancer, radiation alone (70 Gy at 2 Gy/fx) versus radiation with concurrent cisplatin with adjuvant cisplatin/5-FU demonstrated a dramatic 67% to 37%, respectively, 5-year OS advantage in favor of the chemoradiation arm. More than 90 randomized clinical trials have been performed examining chemoradiation in head and neck cancers. Several meta-analyses have been published showing an absolute survival benefit to chemoradiation. Indeed, the most recent update of the MACH-NC in 2009 analyzed more than 17,000 patients in 93 randomized trials and showed an absolute OS benefit of 6.5% at 5 years.[117] Although two large randomized trials of neoadjuvant chemotherapy followed by radiation have shown a benefit in terms of laryngeal organ preservation,[118,119] subsequent studies, including RTOG 9111,[120] and the MACH-NC[117] suggest that concurrent chemoradiation is more effective than sequential administration.

As mentioned previously, the RTOG 9111 was a landmark Intergroup trial for patients with what would currently be staged as T2 and T3 glottic and supraglottic squamous cell carcinomas.[120] This trial randomized patients to one OS was not different between the groups, the DFS and local-regional control favored the concurrent chemoradiation arm.[120] This benefit is not restricted to organ preservation studies. Indeed, two trials published in the same issue of the *New England Journal of Medicine* detailed the RTOG[124] and EORTC[123] trials randomizing patients to postoperative radiation with or without concurrent chemotherapy. Although the two trials had slight differences in their inclusion criteria, they both established the importance of adjuvant chemoradiation in the setting of high-risk postoperative patients. A pooled data analysis from the two trials identified positive margins and extracapsular extension as the two significant risk factors for combining chemotherapy with radiation in the adjuvant setting.[127]

Recently, the question regarding whether induction chemotherapy followed by concurrent chemoradiation is superior to concurrent chemoradiation alone in locally advanced head and neck cancers was addressed in the PARADIGM trial.[128] In this study, patients were randomized to receive either induction chemotherapy with docetaxel, cisplatin, and 5-FU followed by concurrent chemoradiation with docetaxel or carboplatin compared to concurrent chemoradiation using cisplatin. Although the trial was terminated early because of poor patient accrual, results suggest no difference in overall survival between the two groups. However, a greater incidence of febrile neutropenia was noted in patients who received induction followed by concurrent chemotherapy compared to concurrent chemoradiation alone.

In 2006, Bonner et al published the results of a randomized phase III trial incorporating a molecularly targeted therapy with radiation in locally advanced head and neck cancers.[125] This trial used cetuximab, which is a monoclonal chimeric (mouse and human) antibody to EGFR. This trial showed not only a local control benefit but also an overall survival benefit when cetuximab was combined with radiation, including altered fractionation schedules. In addition, the incidence of serious toxicity (other than rash and transfusion reactions) was similar between the groups, which is in stark contrast to chemoradiation regimens that invariably have increased toxicity. These results have held up at the most recently published update[126] showing a 49-month median survival in the

TABLE 4-4 Selected Concomitant Radiation and Chemotherapy for Head and Neck Cancers

Study	Regimen	Outcomes
INT 0099 (1998)[116]	RT (70 Gy) vs. RT (70 Gy) + cisplatin (100 mg/m^2 q3 wks × 3) with adjuvant cisplatin (80 mg/m^2)/5-FU (1 g/m^2/d for 96 h q 4wks × 3)	At 5-yr update, PFS (58% vs. 29%), DFS (74% vs. 46%), and OS (67% vs. 37%) favors the CT-RT arm ($p < 0.001$)
Brizel et al (1998)[121]	RT (75 Gy at 1.25 Gy BID) vs. RT (70 Gy at 1.25 Gy BID) with concurrent cisplatin (12 mg/m^2/d) and 5-FU (600 mg/m^2 days 1-5) on weeks 1 and 6.	3-yr LRC favored CT-RT (70% vs. 44%, $p = 0.01$). 3-yr OS trends in favor of CT-RT (55% vs. 34%, $p = 0.07$).
RTOG 9111 (2003)[120]	3 arm trial of glottic and supraglottic cancer patients: RT(70 Gy) vs. sequential chemo (cisplatin 100 mg/m^2 + 5-FU g/m^2/d for 120 h q3wks × 3) then RT(70 Gy) vs. concurrent ChemoRT (cisplatin 100 mg/m^2 q3wks × 3)	No difference in OS but concurrent arm had superior local control (2-yr: 78% vs. 61% sequential vs 56% RT alone; $p \leq 0.003$) and highest organ preservation rate (88% vs. 75% vs. 70%; $p \leq 0.005$)
Adelstein et al (2003)[122]	3 arm trial: RT (70 Gy) vs. concurrent RT (70 Gy) + cisplatin (100 mg/m^2 q3wks × 3) vs. split course RT (30 Gy with cycle 1 and 30-40 Gy with cycle 3) + concurrent 5-FU (1 g/m2/d for 96 h) and cisplatin (75 mg/m^2) q4wks	The concurrent non-split cisplatin/RT arm had superior 3-ry OS (37% vs. 27% in split course CT-RT vs. 23% in RT alone; $p = 0.014$). Concurrent cisplatin/RT had highest rate of grade 3+ toxicity (89% vs. 77% vs 52%; $p < 0.0001$)
EORTC 22931 (2004)[123]	Postoperative RT (up to 66 Gy) vs. postoperative CT-RT (up to 66 Gy with cisplatin 100 mg/m^2 q3wks × 3) for potential high-risk head and neck cancer patients (Stage III/IV except T3N0 or T1-2N0-1 with +margins, +PNI, +ECE, +VSI, OC/OP primary with + LNs at levels 4-5)	Improvement in 5-yr OS (53% vs. 40%; $p = 0.02$), 5-yr PFS (47% vs 36%; $p = 0.04$), and 5-yr LRC (82% vs. 69%; $p = 0.007$) with CT-RT; Grade 3/4 mucositis was higher in CT-RT arm (41% vs. 21%; $p = 0.001$)
RTOG 9501 (2004)[124]	Postoperative RT (up to 66 Gy) vs. postoperative CT-RT (up to 66 Gy with cisplatin 100 mg/m^2 q3wks × 3) for potential high risk head and neck cancer patients (2 or more +LNs, +ECE, + margins)	Improvement in 2-yr DFS (54% vs. 44%; $p = 0.04$) and LRC (82% vs. 72%; $p = 0.01$) with trend toward better OS (63% vs. 57%, $p = 0.19$); Higher rate of grade 3 or greater acute toxicity in chemoRT arm (77% vs. 34%; $p < 0.001$)
Bonner et al (2006[125] and 2010[126])	Once Daily RT (70 Gy at 2 Gy/d), concomitant boost (72 Gy in 42 fxs) or hyperfractionated (72-76.8 Gy at 1.2 Gy BID) ± cetuximab (given 1 week before RT at 400 mg/m^2 then given weekly at 250 mg/m^2 × 7 wks)	Improvement in MS (49 vs. 29.3 months) and 5-yr OS (45.6% vs. 36.4%) in the cetuximab arm (HR of 0.73; $p = 0.018$). No difference in grade 3 or 4 toxicity, including mucositis, (except acneiform rash and infusion reaction).
MACH-NC meta-analysis[117]	Meta-analysis of 93 randomized trials of CT in head and neck cancer, with 17,346 patients.	Concomitant CT-RT provides absolute 5-yr OS benefit of 6.5% whereas induction chemo showed only 2.4% (HR of 0.81; $p < 0.0001$).

5-FU, *5-Fluorouracil;* BID, *twice per day;* CT, *chemotherapy;* CT-RT, *chemoradiation;* DFS, *disease-free survival;* ECE, *extracapsular extension;* EORTC, *European Organization for Research and Treatment of Cancer;* INT, *intergroup;* LN, *lymph nodes;* LRC, *loco-regional control;* MACH-NC, *meta-analysis of chemotherapy in head and neck cancer;* MS, *median survival;* OC/OP, *oral cavity/oropharynx;* OS, *overall survival;* PFS, *progression-free survival;* PNI, *perineural invasion;* RT, *radiation therapy;* RTOG, *Radiation Therapy Oncology Group;* VSI, *vascular space invasion.*

cetuximab arm and 29.3 months in the radiation alone arm. Five-year OS was 45.6% in the cetuximab group and 36.4% in the radiation alone group (hazard ratio, 0.73; $p = 0.018$).

Several trials are accruing or recently closed combining cetuximab with chemoradiation including the Phase III RTOG 0522 randomizing patients with stage III and IV squamous cell carcinoma of the oropharynx, hypopharynx, and larynx to cisplatin (100 mg/m^2 every 3 weeks) with or without a 1-week pretreatment (400 mg/m^2) and concurrent (250 mg/m^2/week) cetuximab with accelerated fractionation. Initial reports suggest the addition of cetuximab to concurrent chemoradiation does not improve clinical outcomes.[129] Final results should be forthcoming.

The human papilloma virus (HPV) has been implicated as a major cause of head and neck cancers.[130] Interestingly, patients with HPV-associated head and neck cancers have improved outcomes over patients with cancers not associated with HPV. It has been suggested that this may be as a result of an inherent DNA repair defect in HPV-associated head and neck tumors. Thus, efforts by ECOG and RTOG are under way to deescalate therapy in attempts to reduce the morbidities of therapy. The ECOG E1308 is a phase II trial, which tests the efficacy of reducing radiation doses and using concurrent cetuximab rather than chemotherapy in patients who have achieved a complete response to induction chemotherapy. Initial results are promising, with an 86% overall response rate observed in enrolled patients, and more importantly, decreased toxicities compared to historical controls.[131] The RTOG 1016 is a phase III trial randomizing patients to concurrent chemoradiation or cetuximab/radiation. This study is currently nearing completion of accruing the necessary number of patients.

Non–Small Cell Lung Carcinoma

Non–small cell lung carcinoma (NSCLC) is the number-one cause of cancer death in the United States, which is at least partly the result of the late presentation that typically occurs with this disease. As such, most patients will present with stage III disease or stage IV.

The treatment of stage III NSCLC has evolved over the past two decades. For unresectable stage III patients, EBRT alone produced poor 2-year OS, on the order of 20%. A modest improvement (up to 29%) was achieved with more intense radiation schedules such as the continuous hyperfractionated accelerated radiotherapy (CHART) regimen.[132]

To improve on these outcomes, the approach that was most heavily tested was the addition of systemic agents to EBRT, which is summarized in Table 4-5. Three major trials of

TABLE 4-5 Concomitant Radiation and Chemotherapy for Non–Small Cell Lung Cancer

Study	Regimen	Outcome
Dillman et al[133] (CALGB 8433 updated[141])	Sequential cisplatin (100 mg/m^2 d1 and 29) and vinblastine (5 mg/m^2 weekly × 5) followed by RT (60 Gy) vs. RT alone (60 Gy)	Improved MS (13.7 vs. 9.6 mo.; p = 0.012) with CT-RT
Sause et al[134] (RTOG 8808 updated[142])	Three-arm trial: sequential cisplatin (100 mg/m^2 d1 and 29) and vinblastine (5 mg/m^2 weekly × 5) followed by RT (60 Gy) vs. HyperFx RT (69.6 Gy at 1.2 Gy BID) vs. RT alone (60 Gy)	Improved MS (13.2 vs. 12 vs. 11.4 mo.; p = 0.04) with CT-RT
Furuse et al[138]	Chemo of cisplatin (80 mg/m2 on d1 and 29), vindesine (3 mg/m^2 on d1, 8, 29, and 36), and mitomycin C (8 mg/m^2 on d1 and 29) given either concurrently with split course RT (28 Gy × 2, 10 days apart) or sequentially with RT (56 Gy)	Improved MS (16.5 vs. 13.3 mo.; p = 0.03998) with concurrent CT-RT
Curran et al[137] (RTOG 9410)	Three-arm trial: cisplatin (100 mg/m^2) and vinblastine (5 mg/m^2) given before (Arm 1) or concurrently with once daily RT (Arm 2, 60 Gy), or concurrent cisplatin (50 mg/m^2) and oral etoposide (50 mg BID) with HyperFx RT (Arm 3, 69.6 Gy at 1.2 Gy BID)	Improved MS (17 mo.) in concurrent once daily CT-RT arm (arm 2) va. 15.6 mo (arm 3) va. 14.6 mo. (arm 1) (p = 0.038)
Albain et al[143] (INT 0139)	Stage IIIA patients received two cycles of chemo: cisplatin (50 mg/m^2 on d1, 8, 29, and 36) and etoposide (50 mg/m^2 on d1-5 and 29-33) plus 45 Gy. If no progression, they were randomized to surgery or 16 Gy boost. All patients received 2 adjuvant cycles of cisplatin/etoposide	No difference in MS, or 5-yr OS; improved median PFS in trimodality arm (12.8 vs. 10.5 mo.; p = 0.017); in subset analysis, improved OS in patients who underwent lobectomy vs. CT-RT, but CT-RT was better if patient underwent pneumonectomy.
Thomas et al[144] (GLCCG)	Patients received three cycles of cisplatin and etoposide and were randomized to CT-RT with concurrent carboplatin and vindesine followed by S or S followed by RT alone.	Preoperative CT-RT resulted in increased pathological response but no improvement in PFS. For patients requiring pneumonectomy, preop CT-RT had trend to increased Tx-related mortality (14% vs. 6%; p = 0.14)

BID, *Twice daily;* CALGB, *Cancer and Leukemia Group B;* CT-RT, *chemoradiation;* INT, *intergroup;* GLCCG, *German Lung Cancer Cooperative Group;* HyperFx, *hyperfractionation;* mo., *months;* MS, *median survival;* OS, *overall survival;* PFS, *progression-free survival* RT, *radiation therapy;* RTOG, *Radiation Therapy Oncology Group;* S, *surgery;* Tx, *treatment.*

sequential chemotherapy followed by radiation were published in the 1990s that showed improvement with the addition of platinum-based chemotherapy.[133-135] Around the same time, a meta-analysis demonstrated a small, but significant improvement with the addition of chemotherapy.[136] However, because the various trials included many different sequences of chemotherapy and radiation, it was unclear what would be the best regimen. Therefore, several randomized phase III trials compared sequential to concurrent chemoradiation.[137-140] In all but one trial,[140] the concurrent arm showed a significant improvement relative to sequential chemotherapy and irradiation. This established concurrent chemoradiation as the treatment of choice. What was not clear, however, was whether adjuvant chemotherapy could be added to concurrent chemoradiation regimens, and if so, if it was better to administer the chemotherapy neoadjuvantly or adjuvantly.

A phase II trial called the Locally Advanced Multimodality Protocol (LAMP) trial attempted to determine what would be the best approach.[145] The three arms in this trial included (1) neoadjuvant chemotherapy followed by radiation, (2) neoadjuvant chemotherapy followed by concurrent chemoradiation, and (3) concurrent chemoradiation followed by adjuvant chemotherapy. Although the concurrent followed by adjuvant arm had the best outcome, the trial had some limitations including insufficient power to determine the best regimen.[145]

Although concurrent chemoradiation is the standard approach for stage III NSCLC, there are certain instances in which surgery can be combined with chemoradiation in a trimodality approach. Two major randomized trials have been published regarding this trimodality approach, which are also included in Table 4-5 (U.S. Lung Intergroup 0139[143] and the German Lung Cancer Cooperative Group[144] trials). Both trials appeared to show that trimodality therapy was feasible, but that preoperative chemoradiation should be avoided if a pneumonectomy would be performed due to excessive treatment related mortality.

Cervical Cancer

One of the clearest clinical examples demonstrating improved outcomes of combined chemoradiation is in locally advanced cervical cancer. Cisplatin-based regimens have had clear success in a series of randomized phase III trials showing not only improvement in local-regional control but in also OS. This series of clinical trials (summarized in Table 4-6) had differing inclusion criteria and various treatment approaches, yet, these trials presented convincing evidence that cisplatin, when combined with radiation, improves outcome in locally advanced cervix cancer. An excellent review of the historical context and remaining controversies regarding these trials is available,[146] so they will only briefly be discussed here.

The Gynecological Oncology Group (GOG) had three positive trials for chemoradiation as a component of treatment. The GOG 85 trial investigated two different concurrent chemotherapy regimens (hydroxyurea and cisplatin/5-FU) with radiation for patients with locally advanced cervix cancer.[147] This trial demonstrated that concurrent cisplatin/5-FU was superior to hydroxyurea (5-yr OS 62% vs. 50%, p = 0.018). GOG 120 was a three-arm trial that compared radiation alone to two different cisplatin containing regimens (one with cisplatin alone and the other with cisplatin plus 5-FU and hydroxyurea).[148] The two cisplatin-containing arms were superior to the control arm (3-yr OS for both cisplatin based arms of 65% vs. 47%, $p < 0.005$). Since the cisplatin alone arm was less toxic than the 5-FU/hydroxyurea combination, the concurrent cisplatin/radiation approach was preferred. The GOG also

TABLE 4-6 Concomitant Radiation and Chemotherapy for Cervix Cancer

Study	Regimen	Outcome
GOG 85 (1999)[147]	IIB-IVA patients; RT + HU (3 g/m^2 twice per week) vs. RT + Cisplatin (50 mg/m^2)/5-FU(4 g/m^2/96 h)	Improved PFS (RR of 0.79, $p = 0.033$) and improved OS (5-yr: 62% vs. 50%, RR of 0.74, $p = 0.018$) in cisplatin containing arm
GOG 120 (1999)[148]	IIB-IVA patients; three arms: Cisplatin (40 mg/m^2/week) vs. Cisplatin (50 mg/m^2)/5-FU (4 g/m^2/96 h) with HU (2 g/m^2 twice per week) vs. HU (3 g/m^2 twice per week)	Improved PFS (RR of 0.57 and 0.55, $p < 0.001$) and improved OS (3-yr: 65% vs. 47%, RR of 0.61 and 0.58, $p < 0.005$) in both cisplatin containing arms
GOG 123[149]	IB (tumors ≥4 cm) patients; RT ± cisplatin (40 mg/m^2/week)	Improved PFS (RR of 0.51, $p < 0.001$) and improved OS (3-yr: 83% vs. 74%, RR of 0.54, $p < 0.008$) in cisplatin containing arm
SWOG 8797 (2000)[150]	I-IIA patients after hysterectomy with high-risk features (positive nodes, positive margins, or parametrial involvement); RT ± cisplatin(70 mg/m^2)/5-FU(4 g/m^2/96 h)	Improved PFS (HR of 2.01, $p = 0.003$) and improved OS (4-yr: 81% vs. 71%, HR of 1.96, $p = 0.007$) in cisplatin containing arm
RTOG 9001[151]	IB-IIA (≥5 cm), IIB-IVA (or positive pelvic nodes) patients; RT ± cisplatin (75 mg/m^2)/5-FU(4 g/m^2/96 h)	Improved 5-yr DFS (67% vs. 40%, $p < 0.001$) and improved 5-yr OS (73% vs. 58%, $p = 0.004$) in cisplatin containing arm
NCIC[152]	IB-IIA (≥5 cm), IIB-IVA (or positive pelvic nodes) patients; RT ± cisplatin (40 mg/m^2/week)	No difference in PFS or OS

5-FU, *5-Fluorouracil;* DFS, *disease-free survival;* GOG, *Gynecological Oncology Group;* HR, *hazard ratio;* HU, *hydroxyurea;* NCIC, *National Cancer Institute Canada;* OS, *overall survival;* PFS, *progression-free survival;* RR, *relative risk;* RT, *radiation therapy;* RTOG, *Radiation Therapy Oncology Group.*

investigated the importance of chemotherapy with radiation for patients in bulky stage IB treated with hysterectomy in GOG 123. In this trial, the patients were randomized to radiation alone versus radiation plus weekly cisplatin before undergoing hysterectomy.[149] Once again, the cisplatin-containing arm was superior (3-yr OS 83% vs. 74%, $p = 0.008$).

In the 1990s, the RTOG also examined the importance of cisplatin with radiation for patients with locally advanced cervix cancer. RTOG 9001 compared extended field radiation alone to pelvic radiation plus cisplatin and 5-FU.[150] The chemoradiation arm was superior to the extended field irradiation (5-yr OS 73% vs. 58%, $p = 0.004$).

The fifth trial to support concurrent cisplatin/radiation was the Intergroup 0107/SWOG 8797, which tested chemoradiation in the adjuvant setting for patients that underwent hysterectomy with high-risk features at time of surgery including positive pelvic nodes, positive margins, and parametrial involvement.[151] Patients were randomly assigned to receive radiation alone or radiation with cisplatin/5-FU. The chemoradiation group was again superior (4-yr OS 81% vs. 71%, $p = 0.007$).

Only one major trial, from National Cancer Institute of Canada (NCIC), failed to demonstrate an OS benefit for this approach.[152] However, that trial has been criticized because of the small size and wide confidence intervals that may have prevented a difference from being detected.

The next generation of chemoradiation trials is adding molecularly targeted agents, including cetuximab and tirapazamine, to standard cisplatin-based regimens.

Genitourinary Cancer

Chemoradiation is established as the standard bladder preserving management strategy for muscle invasive bladder cancer. Shipley et al[153] published a single institution experience using a neoadjuvant chemoradiation approach similar to the larynx preservation trials discussed previously in which a cisplatin-containing chemoradiation regimen is given (following a maximal transurethral resection of bladder tumor [TURBT]), an evaluation for tumor response is then performed followed by either surgery (for anything less than a complete response) or consolidative chemoradiation. With this approach, the 5-year OS is comparable to surgical series at 54%. Bladder preservation rates without invasive local recurrence are ~50%.

Another genitourinary example involving the use of hormone ablation therapy plus EBRT for high-risk prostate cancer demonstrates a local control, DFS, biochemical DFS, and possibly an OS benefit based on both RTOG[154-156] and EORTC[157,158] experience. It has been postulated that androgen-deprivation therapy used in concomitant radiation regimens not only provides a spatial cooperation interaction but also a biological cooperation function. Currently, the RTOG is investigating the addition of TAK-700 (Orteronel), which suppresses adrenal androgen production, to concurrent EBRT and standard androgen deprivation therapy for high-risk prostate cancer patients (RTOG 1115) in attempts to maximally suppress androgen production.

Glioblastoma

The treatment of glioblastoma has dramatically changed in recent years based on the encouraging findings from the phase III trial from EORTC and NCIC. This trial, first published by Stupp et al in 2005[159] and updated with 5-year data,[160] demonstrated a remarkable improvement in median survival (14.6 vs. 12.1 months) and OS (9.8% vs. 1.9% at 5 years; hazard ratio, 0.63; $p < 0.0001$) with the use of concurrent temozolomide and radiation with adjuvant temozolomide. Prognostic[161-163] and possibly predictive[164] information can be garnered from evaluating the MGMT promoter methylation status because it has been shown that patients whose tumors have MGMT epigenetic silencing as a result of promoter hypermethylation do better.

FUTURE DIRECTIONS

Molecular Prediction

One of the current ideals for the medical field is to develop personalized or "precision" medicine for patients. For the oncology field, the identification of biomarkers for prognosis and response to therapy is of critical importance for achieving this ideal. Perhaps the most promising strategy toward personalized medicine in oncology has been the investigation of synthetic lethal interactions between two distinct pathways, which can be exploited therapeutically.[165] This concept of synthetic lethality is one in which mutation or loss of either of the two pathways individually has no effect on survival; however, mutation or loss of both leads to cell death. To this end, inhibitors of poly(ADP)-ribose polymerase (PARP) have come to the forefront for patients with BRCA-associated cancers.[166,167] PARP is involved in the base excision repair of single-stranded DNA

damage, which if left unrepaired, is converted into a double-stranded DNA break that can be repaired by the homologous recombination repair pathway mediated by BRCA. In patients with BRCA-associated tumors, which are homologous recombination repair defective, inhibition of PARP leads to significant cytotoxicity of tumors while sparing normal tissues, which are proficient in homologous recombination repair. This exciting therapeutic strategy has shown promise in multiple clinical trials and exemplifies the ultimate goal of personalized therapy—that is, to maximize therapeutic ratio.

The predominant investigative tools for biomarker discovery are related to genomics and proteomics, the study of global gene expression and protein expression, respectively. An emerging science is that of kinomics in which global kinase activity is determined. These expression or activation patterns of individual tumors can be correlated to outcomes including treatment response and survival endpoints. The hope is that diagnostic tests can be developed that will guide clinicians in selection of therapy. A brief description of each discovery tool is found here.

Genomics/Transcriptomics

The most actively studied component of molecular prediction uses genomic technology. Genomics refers to the genome-wide evaluation of individual gene expression. Pharmacogenomics refers to the study of genetic information to predict treatment response. There are a host of platforms for analyzing genetic information within a biologic specimen. One means is through evaluation of polymorphisms, which refers to a variation within a gene such that at least two alleles occur in 1% or more of the general population. When the variation occurs at a single nucleotide, this is termed a *single nucleotide polymorphism*, or SNP. Several groups have identified SNPs within DNA synthesis/DNA repair genes that could potentially serve as markers of response to radiation,[168] chemotherapy,[169] or chemoradiation.[170] Genome-wide SNP arrays are commonly used these days and have been applied to translational studies. Historically, though, the most widely used approach has been microarray-based, such as the GeneChip from Affymetrix (Santa Clara, CA). These arrays enable the analysis of relative expression of more than 38,000 genes on a single chip. However, with the advent of next-generation sequencing (NGS or "deep sequencing") ushering in lower costs and higher throughput, NGS approaches are largely replacing microarray-based methods. For example, the RNASeq approach can provide gene expression information (transcriptome) but also provide information about genomic alterations (at least for the expressed genome). Focused exome NGS is being used to identify drug-targetable mutations in patient tumors. NGS approaches are now the methodology of choice for The Cancer Genome Atlas (TCGA) project that is cataloging molecular data on 20 tumor types that has already identified many molecular subtypes among several cancer types.[171]

No matter what platform is used, the identification of genomic/transcoptomic differences between good and poor responders may eventually guide therapy decisions. A significant amount of work has been done in predicting breast cancer response to chemotherapy in vivo.[172] Similar studies for radiation and chemoradiation response are in various stages of development.

Proteomics

Proteomics is becoming an established platform for biomarker discovery. The predominant approach involves mass spectrometry to identify levels of proteins based on peptide fragments generated from enzymatic digestion of all of the proteins within a biologic specimen such as a biopsy, tissue sample, blood, urine, etc. This approach has been used for prognostic purposes in NSCLC[173] as well as prediction of sensitivity to chemoradiation in cervical cancer patients.[174] Miniaturization with nanofluidic assays[175] and novel dynamic-proteomics[176] approaches are providing more information and understanding regarding cellular response to drugs.

Kinomics

Although genomic and proteomic strategies are being used in translational components of several clinical trials with RTOG and other cooperative groups, these technologies have significant difficulty in detecting transient signaling events such as kinase activation. This is as a result of the fact that kinases are predominantly regulated posttranslationally, that is, they are subject to phosphorylation events, conformational changes, subcellular translocation, binding partnerships, etc. Kinomics, thus, refers to the global detection of kinase signaling events within a cell or tissue. There is a tremendous amount of preclinical data that demonstrates robust but transient activation of kinase-based resistance pathways downstream of ionizing radiation and chemotherapy.[177-181] Arguably, the most prominent class of next-generation therapeutics for oncology is kinase-targeted agents. In the near future, there may be a large repertoire of available kinase inhibitors that are available for therapy if we could only identify the patients most likely to benefit from them. Kinomic analysis may help guide therapy by identifying the critical kinase activations that predict for sensitivity or resistance to particular drugs. Although this technology is still in its infancy, kinomics may one day provide a complementary clinical tool to the genomic and proteomic strategies that are making their way into oncology practice. Indeed, the TCGA selected reverse phase protein arrays (RPPA) as their platform technology for functional proteomic evaluation of tumors.[182] Other translational research examples include kinomic profiling of pediatric brain tumors,[183] chondrosarcomas,[184] preclinical xenograft treatment response prediction,[185] chemoradiation response prediction in locally advanced rectal cancer patients,[186] and even for identification of novel radiation modulators.[187]

Patient-Derived Xenografts

One potential strategy to improve molecular prediction is to use better preclinical model systems for combination testing. Patient-derived xenografts (PDX, xenolines, or tumor avatars) have been increasingly used as preclinical model systems. PDX appear to more faithfully represent clinical reality because they are passaged within immunocompromised mice rather than cultured in plastic with high levels of serum. "-Omic" characterization and therapy response data have shown considerable promise leading many pharmaceutical companies and some academic institutions to incorporate PDX into their preclinical testing program. Indeed, several companies specializing in PDX production and therapy testing have emerged in recent years. One potential strategy for integrating PDX into therapeutic development is the concept of a "parallel mouse" clinical trial that can be performed in conjunction with an actual human clinical trial. The incorporation of the parallel mouse trial allows for a larger cohort of tumor specimens to be available for molecular characterization and biomarker development. The potential for PDX-informed clinical decision making could be possible with this approach.

SUMMARY

Multimodality therapy has become the mainstay of the vast majority of solid malignancies. Understanding the interaction between chemotherapy and radiation is, therefore, vital to improving patient care. With the addition of biologically targeted agents to the armamentarium of anticancer therapy, it

may be better to refer to chemotherapeutics and biologics simply as systemic agents. It is expected that clinical investigation will help validate as well as generate novel strategies in the laboratory. In addition, the establishment of useful biomarkers will hopefully usher in a new era of personalized oncologic medicine. In this way, exploitable differences between tumor tissue and normal tissue will be optimized for each patient.

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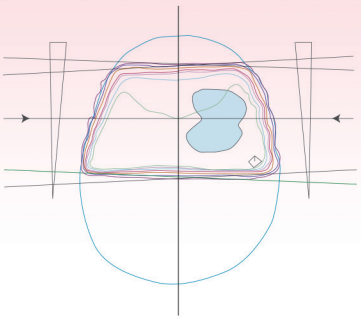
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CHAPTER

5 Biologics and Their Interactions with Radiation



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Over the past decade, radiation oncology researchers have rapidly developed the capability of delivering "targeted" therapy using photon- or proton-based energies with the evolution of intensity-modulated radiation therapy (IMRT) and the incorporation of image-guided motion tracking. During this same decade, advances in molecular pathology have resulted in powerful predictive biomarkers such as KRAS, ALK, and BRAF that have ushered in a new era in cancer therapy, that of personalized cancer therapeutics. Improved understanding of the molecular mechanisms underlying malignant processes has allowed the development of novel therapeutic agents that target specific cellular processes. Molecularly targeted therapeutic agents, or biologics, are a class of agents that have been developed to specifically interfere with functions central to the pathophysiology of the malignant phenotype.

Although initially targeted in the single-agent setting and then with chemotherapy, many of these biologic pathways are also central to the radiation response; this finding raised the likelihood that some biologic agents may be effective radiosensitizers. A radiosensitizing effect has indeed been demonstrated clinically and in model systems. As biologically targeted drugs continue to gain prominence in the cancer therapy landscape, radiation oncologists should be familiar with therapies that their patients are likely to be receiving in conjunction with radiation. Furthermore, the potential for radiosensitization mandates that radiation oncologists become educated regarding the potential for these agents to exacerbate toxicity or improve efficacy in the standard radiotherapy setting. Finally, the potential to take advantage of the new biologics as radiosensitizers offers an exciting opportunity to improve local control for many tumor types treated with radiotherapy.

Before we can move forward we must ask why many of our preclinical studies, that at first glance appear promising, have failed to translate successfully in phase III clinical trials when combined with chemoradiation.[1,2] Over the past decade or so, we have, in fact, only demonstrated success in one phase III trial using an anti-EGFR antibody with radiation alone.[3] Perhaps the optimal preclinical studies were never performed to adequately evaluate optimal sequencing and whether adding a targeted agent to a chemoradiation backbone in fact could be antagonistic. Perhaps some of these targeted drugs might be best used as maintenance therapies after completion of chemoradiation. Perhaps dual targeting of specific pathways might provide improved local-regional control over traditional chemoradiation combinations and should be tested against standard of care. Do we need to dose biologically based approaches in a maximum tolerated drug (MTD) format similar to what we traditionally do with chemoradiation phase I trials? We have even gone as far as adding dual biologics to a chemoradiation backbone with little or no preclinical data to support its clinical translation, resulting in added toxicity.[4-7] These are critical questions that must be answered if we are to realistically move our field forward in a molecular age.

In a previous version of this chapter, the authors emphasized developments in the laboratory and in the clinic related to epidermal growth factor inhibition, antiangiogenesis, proteasome interference, DNA repair inhibitors, mTOR inhibitors, and insulin growth factor receptor inhibitors; and how these factors cooperate with radiation. In this edition, the clinical experience with familiar molecularly targeted drugs and radiation has been updated and streamlined; however, we intend to place an emphasis on selected newer agents that appear promising in a variety of disease sites. These include PI3K/Akt/mTOR pathway inhibitors, PARP inhibitors, and immunomodulating agents. Many additional agents are under investigation including "dirty" biologics, agents such as the multityrosine kinase inhibitors that target multiple pathways, although a detailed discussion of these agents is beyond the scope of this chapter. To provide some perspective, since the previous edition of this chapter was published in 2011, the number of biologics approved by the Food and Drug Administration (FDA) has more than tripled, from ~14 to more than 50 agents (Table 5-1). This update particularly focuses on emerging biologics believed likely to play an increasing role in clinical radiation oncology in the near future. What does the practicing radiation oncologist need to know as we witness a remarkable evolution in our understanding of molecular oncology and develop new insights in to radio-genomics to predict response and toxicity to radiation therapy? Next-generation sequencing is assisting in defining new targets within a cancer to personalize our therapeutic approaches and this information may be valuable in finding the optimal agents to combine with radiation within a specific disease site.

EPIDERMAL GROWTH FACTOR RECEPTOR FAMILY INHIBITORS

Epidermal Growth Factor Receptor Family Biology

The epidermal growth factor receptor (EGFR) family signaling process has captured significant attention clinically over the past 15 years as a targetable pathway that could be used in conjunction with radiation. Why is it important and how does it work? EGFR signaling regulates mesenchymal-epithelial interactions during growth and development, transmitting extracellular cues to intracellular signaling cascades.[10-12] The family has four known members: EGFR, HER2 (erbB2), HER3 (erbB3), and HER4 (erbB4). These membrane-spanning tyrosine kinase receptors contain an extracellular ligand-binding domain, a transmembrane domain, and an intracellular tyrosine kinase domain. These normally quiescent receptors are activated when ligand binds to the extracellular domain of a receptor monomer. Ligand binding induces a structural change that favors dimerization with the same member (homodimer) or a different member (heterodimer) of the family. When dimerized, the tyrosine kinase domains are activated and they phosphorylate key tyrosine residues in the intracellular domain, resulting in activation of several downstream signaling cascades.

The end result of receptor activation, proliferation, differentiation, migration, or survival signaling depends on many factors, including which receptor pairs are formed and for

TABLE 5-1 FDA-Approved Biologic Modifiers[8,9]

Agent	Class	Approved Indication	Key Toxicities
Afatinib[RT] (Gilotrif)	mTKI: HER2, EGFR	Metastatic NSCLC	Skin effects
Aflibercept[RT] (Zaltrap)	VEGFR fusion-protein antibody	Metastatic CRC	Hemorrhage, GI perforation, poor wound healing
Alectinib*	ALK inhibitor	Crizotinib-refractory NSCLC	Fatigue, GI effects
Alemtuzumab[RT] (Campath)	CD52 antibody	B-cell CLL	Cytopenias, infusion reactions
Axitinib[RT] (Inlyta)	mTKI: VEGFR, PDGFR, CKIT	Metastatic RCC	HTN, GI effects, fatigue
Belinostat (Beleodaq)	HDAC inhibitor	Peripheral T-cell lymphoma	Fatigue, GI effects, anemia, fever
Bevacizumab[RT] (Avastin)	Anti-VEGFR antibody	CRC; advanced NSCLC; metastatic RCC; recurrent glioblastoma multiforme; metastatic HER2-negative breast cancer	Hemorrhage
Bortezomib[RT] (Velcade)	Proteasome inhibitor	Multiple myeloma; mantle cell lymphoma	Cytopenias, GI effects, neuropathy
Bosutinib (Bosulif)	Src-Abl TKI	Ph(+) CML	GI effects
Brentuximab vedotin[RT] (Adcetris)	CD30 antibody-drug conjugate	Refractory Hodgkin lymphoma; anaplastic large cell lymphoma	Cytopenias, GI effects
Cabozantinib[RT] (Cometriq)	mTKI: RET, VEGFR, TIE2, MET, TRKB	Metastatic medullary thyroid cancer	Hemorrhage, GI perforation or fistula
Carfilzomib (Kyprolis)	Proteasome inhibitor	Refractory multiple myeloma	Cytopenias, GI effects
Catumaxomab (Removab)	CD3, EpCAM antibody	Malignant ascites	Fever, GI effects
Ceritinib* (Zykadia)	ALK inhibitor	ALK(+) metastatic NSCLC after crizotinib	Fatigue, GI effects, hyperglycemia
Cetuximab[RT] (Erbitux)	Anti-EGFR antibody	Irinotecan-refractory metastatic CRC with KRAS wt; HNSCC	Anaphylaxis, skin rash
CO-1686*	EGFR	EGFR(+) NSCLC with T790M resistance mutation	Hyperglycemia, GI effects, fatigue
Crizotinib[RT] (Xalkori)	ALK inhibitor	ALK(+) locally advanced or metastatic NSCLC	GI effects
Dabrafenib (Tafinlar)	BRAF inhibitor	Advanced melanoma with BRAF mutation	Skin effects
Daratumumab*	CD38 antibody	Refractory multiple myeloma	Cytopenias
Dasatinib[RT] (Sprycel)	mTKI: Src, BCR-ABL, CKIT, PDGFR, TKI	Refractory CML or Ph(+) ALL	Myelosuppression
Denileukin diftitox (Ontak)	CD25-directed diptheria cytotoxin	CD25(+) cutaneous T-cell lymphoma	Infusion reaction, capillary leak syndrome, vision loss
Denosumab (Xgeva)	RANK ligand inhibitor	Bone metastases prevention; giant cell tumor of bone	Musculoskeletal effects
Entinostat*	HDAC inhibitor	Advanced ER(+) breast cancer	Fatigue, neutropenia
Erlotinib[RT] (Tarceva)	EGFR TKI	Chemotherapy-refractory NSCLC; advanced pancreatic cancer with gemcitabine	Skin rash, diarrhea
Everolimus[RT] (Afinitor)	mTOR inhibitor	Advanced RCC; progressive neuroendocrine tumors of pancreatic origin; subependymal giant-cell astrocytoma in tuberous sclerosis; advanced breast cancer with exemestane	GI effects
Gefitinib[RT] (Iressa)	EGFR TKI	Advanced or chemotherapy-refractory NSCLC	Skin rash, diarrhea
Ibrutinib*	Bruton TKI	Mantle cell lymphoma; Waldenstrom macroglobulinemia; CLL	GI effects
Ibritumomab (Zevalin)	CD20 RIT	Relapsed or refractory low-grade or follicular B-cell NHL; follicular NHL with response to first-line chemotherapy	Infusion reactions, cytopenias, mucocutaneous reactions

Continued

TABLE 5-1 FDA-Approved Biologic Modifiers—cont'd

Agent	Class	Approved Indication	Key Toxicities
Imatinib[RT] (Gleevec)	BCR-ABL TKI	Philadelphia chromosome–positive CML or ALL; GIST; dermatofibrosarcoma protuberans; myelodysplastic/myeloproliferative disorders; systemic mastocytosis	Myelosuppression
Ipilimumab[RT] (Yervoy)	CTLA-4 antibody	Advanced melanoma	Autoimmune reactions
Lapatinib[RT] (Tykerb)	mTKI: EGFR, HER2	Refractory HER2 overexpressing advanced breast cancer with capecitabine	Rash, diarrhea
MPDL3280A*	PD-L1	Metastatic bladder cancer	Auto-immune reactions
Nilotinib[RT] (Tasigna)	BCR-ABL TKI	Ph(+) CML	QT prolongation
Obinutuzumab* (Gazyva)	CD20 antibody	CLL	Infusion reactions, cytopenias, PML
Ofatumumab* (Arzerra)	CD20 antibody	Refractory CLL	Cytopenias, GI effects
Palbociclib*	CDK4, CDK6	ER(+), HER2(–) advanced breast cancer	Cytopenias
Panitumumab[RT] (Vectibix)	Anti-EGFR antibody	Irinotecan-refractory metastatic CRC without KRAS mutation	Anaphylaxis, skin rash
Pazopanib[RT] (Votrient)	mTKI: VEGFR, PDGFR, CKIT	Metastatic RCC; advanced soft tissue sarcoma	Hepatotoxicity
Pembrolizumab* (aka lambrolizumab)	PD-1 antibody	Advanced melanoma	Autoimmune reactions
Pertuzumab[RT] (Perjeta)	Anti-HER2 antibody	HER2 overexpressing breast cancer with trastuzumab or docetaxel	Cardiomyopathy, embryo-fetal toxicity
Radium-223 (Xofigo)	Calcium mimetic	Castration-resistant prostate cancer with bone metastases	GI effects
Ramucirumab (Cyramza)	VEGFR	Advanced or metastatic gastric or gastroesophageal adenocarcinoma	GI effects, HTN, headaches
Regorafenib (Stivarga)	mTKI: VEGFR, PDGFR,KIT, RET, TIE2, FGFR, RAF, MAPK	Unresectable or refractory GIST; previously treated CRC	Hepatotoxicity
Rituximab[RT] (Rituxan)	CD20 antibody	Non-Hodgkin lymphoma; CLL	Infusion reactions, tumor lysis, mucocutaneous effects, PML
Romidepsin[RT] (Istodax)	HDAC inhibitor	Cutaneous T-cell lymphoma	GI effects
Temsirolimus[RT] (Torisel)	mTOR inhibitor	Advanced RCC	Rash, asthenia, GI effects
Tositumomab I-131 (Bexxar)	CD20 RIT	Relapsed or refractory follicular NHL	Hypersensitivity, cytopenias
Trametinib[RT] (Mekinist)	MEK inhibitor	Advanced melanoma	Cardiomyopathy, skin effects, GI effects
Trastuzumab[RT] (Herceptin)	Anti-HER2 antibody	HER2-neu overexpressing breast cancer	Cardiomyopathy
Sorafenib[RT] (Nexavar)	mTKI: VEGFR, PDGFR, Raf, c-KIT	Unresectable hepatocellular carcinoma; advanced RCC	Rash, diarrhea, HTN
Sunitinib[RT] (Sutent)	mTKI: VEGFR, PDGFR, c-KIT, Flt3	Advanced RCC; GIST; pancreatic neuroendocrine tumors	Rash, diarrhea, HTN
Vandetanib[RT] (Caprelsa)	mTKI: RET, VEGFR, EGFR	Unresectable or metastatic medullary thyroid cancer	QT prolongation
Volasertib*	Polo-like kinase inhibitor	AML	Cytopenias
Vorinostat[RT] (Zolinza)	HDAC inhibitor	Cutaneous T-cell lymphoma	GI effects
Vemurafenib[RT] (Zelboraf)	BRAF kinase	Unresectable or metastatic melanoma with BRAF mutation	Photosensitivity and other skin effects

[RT]Concurrent trials with radiation are ongoing or have been completed.

ALL, *Acute lymphocytic leukemia;* ALK, *anaplastic lymphoma kinas;* CLL, *chronic lymphocytic leukemia;* CML, *chronic myelogenous leukemia;* CRC, *colorectal cancer;* EGFR, *epidermal growth factor receptor;* FGFR, *fibroblast growth factor receptor;* GI, *gastrointestinal;* GIST, *gastrointestinal stromal tumor;* HDAC, *histone deacetylase;* HNSCC, *head and neck squamous cell carcinoma;* HTN, *hypertension;* mTKI, *multiple tyrosine kinase inhibitor;* NHL, *non-Hodgkin lymphoma;* NSCLC, *non–small cell lung cancer;* PDGFR, *platelet-derived growth factor receptor;* Ph(+), *Philadelphia chromosome positive mutation;* PML, *progressive multifocal leukoencephalopathy;* RCC, *renal cell carcinoma;* RIT, *radioimmunotherapy;* SEGA, *subependymal giant cell astrocytoma;* TKI, *tyrosine kinase inhibitor;* VEGFR, *vascular endothelial growth factor receptor.*

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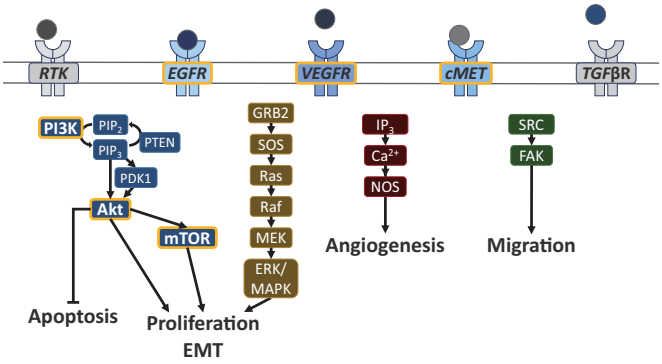


Figure 5-1 General overview of major signaling pathways involved in oncogenesis (many of the molecular targets emphasized in this chapter are outlined in yellow). Cell surface receptors (e.g., EGFR, VEGFR, cMET) normally bind various growth factors and small molecules initiating cell signaling pathways, which lead to maintenance of various cell processes. Mutations involved in up-regulated oncogene or down-regulated tumor suppressor activity lead to inhibition of apoptosis, cell proliferation, epithelial mesenchymal transition (EMT), angiogenesis, migration/invasion, and a variety of additional pro-oncogenic processes.

how long they are activated.[13] This in turn depends on which receptors are predominantly present in the cell and which ligand is involved in activation. There are two ligand families that activate the EGFR family receptors, the EGF-like and heregulin families.[14,15] The EGF-like family includes EGF, TGF-α, amphiregulin, betacellulin, and HB-EGF. The heregulin (neuregulin) family includes many proteins resulting from splice variations of two different genes, all designated as heregulin with different subtypes. The ligands exhibit preference for particular receptors and induce different receptor combinations. HER2 has no known ligand. Instead, HER2 is the favored partner of the other receptors when ligand binds to EGFR, HER3, or HER4.[16] This complex interplay of receptors is important for understanding and interpreting the effect of an inhibitor of a single member of the EGF family.

The effect of receptor activation also depends on which downstream signals are activated involving DNA synthesis and repair, apoptosis evasion, growth factor signaling, and proliferation. EGFR family members signal via a diverse network of signal transduction pathways, including the protein kinase C (PKC), Ras-Raf-ERK, PI3K-Akt, and STAT pathways[17] (Figure 5-1). Furthermore, various receptor pairs recruit different downstream effectors. For instance, HER3 contains multiple PI3K-binding motifs, resulting in strong signaling via PI3K, which plays a role in cell survival, invasion, and proliferation. Interestingly, HER3 alone among the receptors has an inefficient kinase domain, requiring heterodimerization with other family members to become phosphorylated. The need for heterodimerization juxtaposes the PI3K signal emanating from HER3 with the Ras-Raf-ERK or STAT signal emanating from EGFR, HER2, or HER4.

EGFR Family and Tumor Pathogenesis

In 1986, the Nobel Prize was awarded to Stanley Cohen for the discovery of growth factors, resulting from his work in identifying EGF and its receptor.[18] EGFR was first identified as a proto-oncogene because of its homology to the avian erythroblastosis (v-erb) oncogene.[19] Aberrant function of EGFR or HER2 occurs frequently in human tumors; gene amplification results in massive overexpression in a proportion of gliomas and breast cancers.[20-22] Alternatively, dysregulation occurs at more modest levels of expression when the receptor is activated as the result of autocrine stimulation, in which the tumor produces its own ligand to activate the receptor. This type of dysregulation occurs frequently in cancers of the head and neck, gastrointestinal system, and prostate gland.[23-26] Another mechanism of dysregulation is the development of mutations in the kinase domain that render the kinase activity more potent, most clearly demonstrated in lung cancer.[27] Likewise, mutations in the ligand-binding domain can cause the receptor to be constitutively active even in the absence of ligand, as occurs in a significant proportion of gliomas.[28] Dysregulation via mechanisms other than amplification may not always result in overexpression as detected by standard immunohistochemical techniques, raising the issue of how best to identify all tumors in which EGFR dysregulation promotes tumor proliferation and resistance to therapy.

EGFR Family Inhibitors

The frequent dysregulation of the EGFR family in tumors makes the family an attractive target for exploitation. Remarkable progress has been made in the development of EGFR family inhibitors.[29] Many antibodies directed against the extracellular domains of EGFR and HER2 and small-molecule tyrosine kinase inhibitors have now been approved by the FDA for clinical application, and many more are in various stages of development.[8,30]

The first EGFR family–targeted agent to be approved with radiation was cetuximab (Erbitux), an anti-EGFR monoclonal antibody that binds to the extracellular domain of EGFR, interferes with ligand binding and, hence, dimerization and activation.[31] Cetuximab has modest activity as a single agent but gives more encouraging results when it is combined with cytotoxic therapy. Cetuximab is typically given intravenously on a weekly schedule. When combined with radiation therapy, a loading dose is given the week before initiation of radiation treatment. Cetuximab has gained FDA approval for use in treating metastatic colorectal cancer and in locally advanced head and neck cancers. Initial approval for cetuximab in treating metastatic colorectal cancer was based largely on the results of a positive trial including 329 patients randomized to receive either cetuximab and irinotecan or cetuximab alone.[32] Further molecular analysis demonstrated that patients with KRAS mutations in codons 12 or 13 did not respond to cetuximab with survival benefits seen only in patients with wild type KRAS; this is presumably related to alternate activation of signal transduction pathways.[33,34] In head and neck cancers, we have yet to determine biomarkers that predict response to anti-EGFR therapy. This finding underscores the complexity of cancer biogenetics and marks an important turning point toward an era of personalized cancer therapy.

The anti-Her2 antibody trastuzumab and more recently pertuzumab, an antibody that inhibits Her2 heterodimerization, have been shown to improve outcomes for patients with Her2 overexpressing breast cancer.[35-37] These agents are currently recommended for combined use by the National Comprehensive Cancer Network (NCCN) in a variety of stages and settings. Additional investigations are ongoing in other cancers with Her2 overexpressing, including esophageal and salivary duct tumors.

Further discussions regarding the use of EGFR inhibitors alone or with chemotherapy are beyond the scope of this chapter, however, we provide references related to these avenues.[38-44] Our focus is a review of the use of these agents with radiation preclinically and the successes and failures in the clinical arena. One of the most frustrating aspects of this combination is the fact that we still struggle with a lack of predictive biomarkers related to response to EGFR inhibitors. Is it the ligand presence that predicts response? Does the

presence of an EGFR mutation always predict response to EGFR inhibitors in diseases like lung cancer, or do we need to dig deeper?[45] Is it based on gene amplification or high gene copy numbers in EGFR wild type cancers?[46]

Several small-molecule tyrosine kinase inhibitors targeting EGFR have gained FDA approval: gefitinib (Iressa), erlotinib (Tarceva), afatinib (Gilotrif), and lapatinib (Tykerb). These compounds specifically inhibit the tyrosine kinase activity of an EGFR family receptor while relatively sparing the other EGFR family members and related tyrosine kinases. Gefitinib and erlotinib act on EGFR; lapatinib is active against HER2; and afatinib targets both EGFR and HER2. These small-molecule agents have shown modest benefits in patients with advanced malignancies (primarily in patients with EGFR mutations); however, they have yet to demonstrate any significant benefits in phase II/III clinical trials with irradiation. One phase II trial of erlotinib with temozolomide and radiation in patients with newly diagnosed glioblastoma multiforme (GBM) exhibited unacceptable toxicity with multiple treatment related deaths and no evidence of increased efficacy.[47]

The primary toxicity of both gefitinib and erlotinib occurs in the skin, similar to cetuximab, and as diarrhea. However, infrequent cases of serious, life-threatening interstitial lung disease have also been reported for both agents, as well as anaphylactic reactions in approximately 3% of patients treated with cetuximab. Because these reactions can be life threatening, careful monitoring is required with these agents.

EGFR Family and Radiation Response

EGFR family members play an important role in radiation response. Preclinical studies showed that cells made to express v-erb were rendered radioresistant.[48] Similarly, breast cancer cell lines become more radioresistant when made to overexpress HER2, and head and neck cancer cell radioresistance correlates with EGFR expression levels.[49-52]

Clinical studies also suggest that EGFR family dysregulation influences radiation response. A study of 170 gliomas treated with primary radiotherapy demonstrated lower response rates in tumors that overexpressed EGFR; the response rate was 33% in EGFR-negative tumors, 18% in EGFR-intermediate tumors, and 9% in EGFR-positive tumors.[53] In smaller series of patients with head and neck cancers, locoregional recurrence after radiotherapy was associated with EGFR overexpression.[54,55] In breast cancer, a case-control series of patients with in-breast tumor recurrence after breast-conserving surgery and radiotherapy found that the proportion of patients with HER2 overexpression was higher in the recurrence group than in the controls.[56]

Preclinical Studies of EGFR Family Inhibitors as Radiosensitizers

The role of EGFR family members in radiation response was further clarified by studies using newly developed EGFR family inhibitors. In virtually every study, EGFR or HER2 inhibitors demonstrated modest radiosensitization.[57-59] Radiosensitization is more pronounced in vivo than in vitro and with fractionated-dose than with single-dose irradiation. The understanding of the mechanisms underlying enhanced radiosensitization is evolving.[60-62] In every case, the combination of EGFR or HER2 inhibitors and radiation resulted in increased cell cycle arrest, predominately in the G1 phase, but with a substantial decrease in S phase, which translates in vivo to decreased proliferation. Radiosensitization with EGFR family inhibitors also causes decreased angiogenesis. It is not yet clear whether this is an additive result of combined antiangiogenesis effects from both radiation and EGFR inhibitors, or whether the EGFR inhibitors further increase the susceptibility of the vascular elements of the tumor to radiation. The combination of EGFR inhibitors and radiation increases apoptosis in some, but not all, models. Finally, EGFR inhibitors appear to directly interfere with EGFR induced DNA-PK-dependent nonhomologous end joining repair of radiation-induced DNA damage.[63,64] What is lacking in past studies were designs that actually mimicked what we do in the clinic, including comparing chemoradiation to chemoradiation plus an EGFR inhibitor for example in the disease setting to be clinically studied rather than extrapolating from another tumor type. These types of studies, albeit performed in somewhat artificial systems, might have provided valuable information as to the best way to move forward in a clinical trial.

Clinical Studies of EGFR Family Inhibitors as Radiosensitizers

Promising preclinical studies with EGFR family inhibitors have translated into improved patient outcomes in randomized controlled trials when added to radiation alone primarily in patients with locally advanced head and neck squamous cell carcinoma (LA-HNSCC). The most mature of these is a phase III trial that compared the efficacy of standard radiotherapy with standard radiotherapy plus the anti-EGFR antibody cetuximab. In this study, 424 patients with LA-HNSCC of the oropharynx, hypopharynx, or larynx were stratified by T stage, nodal status, and performance status and then were randomly assigned to receive radiotherapy alone or radiotherapy plus weekly concurrent cetuximab. Radiotherapy was delivered using one of three fractionation regimens (stratified): a once-daily regimen (2 Gy × 35 fractions over 7 weeks), a twice-daily regimen (1.2 Gy × 60 to 64 fractions over 5 to 5.5 weeks), or a concomitant-boost regimen (1.8 Gy × 30 fractions with a second daily fraction of 1.5 Gy for the last 12 treatment days over 6 weeks). Concurrent chemotherapy was not allowed. Two-year local control was 56% in the radiotherapy-plus-cetuximab arm versus 48% in the radiotherapy-alone arm, with a median duration of local control of 36 months versus 19 months, respectively ($p = 0.02$).[65] Overall survival was also significantly enhanced with combined therapy. A recent update reported 45.6% 5-year overall survival in the radiotherapy-plus-cetuximab arm versus 36.4% in the radiotherapy-alone arm, with median survival of 49 months versus 29 months, respectively ($p = 0.018$).[3]

Although concern for unwanted normal tissue effects when combining targeted drugs against EGFR and radiation therapy alone is justifiable, the additional morbidity of this approach appears minimal based on the experiences in the clinic to date. In the study by Bonner et al,[65] the improvement in outcome was associated with an increase in acute skin, but not mucosal, toxicity. Furthermore, there were no differences between the groups on standardized quality-of-life assessment scores. Interestingly, a grade 2 or greater acneiform rash correlated with better survival rates (HR 0.49, $p = 0.002$). This correlation, seen in other studies in multiple disease sites, has been hypothesized to be reflective of an anticancer immune response.[66,67] In a separate trial, concurrent administration of adjuvant radiotherapy with trastuzumab in patients with early-stage breast cancer did not increase the incidence of acute radiation toxicity.[68]

Results have been mixed in trials of EGFR inhibitors added to combination chemotherapy and radiation. RTOG 0234, a phase II randomized trial comparing radiation plus cetuximab and either weekly cisplatin or weekly docetaxel in patients with LA-HNSCC, suggest that both regimens are feasible with outcomes superior to results from RTOG 9501 that used high-dose cisplatin on days 1, 22, and 43.[69] Grade 3 to 4 myelosuppression was observed in 28% (cisplatin) and 14% (docetaxel) of patients. Dermatitis was seen in 39% of patients in each

group. The rates of grade 3 or higher mucositis were 37% and 33% in the cisplatin and docetaxel arms, respectively; these rates seem low but are encouraging compared with historical controls. The 2-year distant metastasis rate was 13% in the group that received docetaxel and cetuximab versus 26% with cisplatin and cetuximab. One of the conclusions from this trial is that perturbing growth factor signaling may allow us, under the right circumstances, to reduce administration of high doses of standard chemotherapy and reduce patient morbidity. The addition of cetuximab to the current standard of cisplatin and radiotherapy for LA-HNSCC was evaluated in the phase III RTOG 0522 with abstract only results thus far showing no improvement in progression-free survival (PFS) or overall survival (OS), equivalent overall grade 3 to 5 toxicities, and increased grade 3 or higher mucositis and skin reactions in patients receiving chemoradiation with cetuximab versus chemoradiation alone.[1] In the phase II trial ACOSOG Z4051, 70 patients with locally advanced esophageal adenocarcinoma received preoperative therapy with the EGFR monoclonal antibody panitumumab added to docetaxel, cisplatin, and radiation.[7] Despite 54% of patients showing at least a near pathologic complete response, nearly half of all patients had grade 4 or higher toxicities making this regimen unsuitable for further study. To our knowledge, this type of combination was not studied preclinically to assess its efficacy and safety before going forward into a clinical trial.

An alternative strategy is to evaluate the use of induction chemotherapy before combination EGFR inhibition and radiation. The TREMPLIN study, a phase II randomized trial, directly compared the addition of cisplatin versus cetuximab to radiation for 116 patients with LA-HNSCC of the larynx/hypopharynx with a greater than 50% response following three cycles of traditional induction chemotherapy.[70] Larynx preservation at 3 months, larynx function at 18 months, and overall survival at 3 years demonstrated equivalent outcomes. Local failures were slightly higher in the cetuximab arm (8 vs. 5), but only the patients in the cetuximab arm eventually underwent salvage surgery (7 vs. 0). Grade 3 or higher rates of mucositis were similar between arms, and skin toxicity was roughly doubled in the cetuximab arm; however, acute renal toxicity was substantial in the cisplatin plus radiotherapy arm. This suggests that perhaps by using induction chemotherapy we may be able to study combinations of biologically targeted agents without the added toxicity of conventional chemotherapy agents, assuming the preclinical studies support this approach. An additional trial, the Gruppo di Studio Tumori della Testa e del Collo (GSTCC) trial, employed a 2×2 factorial design for 421 patients with LA-HNSCC randomized with and without induction chemotherapy and randomized to concurrent radiation with either cetuximab or cisplatin.[71] Abstract results showed similar response rates, PFS, and OS between patients receiving cetuximab versus cisplatin. Toxicity rates were also similar between the two groups and patients receiving cetuximab actually required more treatment interruptions with a median radiation therapy (RT) duration of 8 weeks versus 7 weeks in the cisplatin arms. Additional retrospective analyses examining cetuximab versus cisplatin have suggested that cisplatin provides better local control but similar overall survival outcomes.[72,73]

Why the failures to date? As mentioned at the beginning of this chapter, perhaps the optimal preclinical studies were never performed. Often, biologic agents like EGFR inhibitors are combined with radiation in the laboratory and the assumption is made that this will be just as effective, if not more so, when combined clinically with chemoradiation. Preclinical studies must seek to optimize clinically relevant standards to truly understand the optimal sequencing and combinations for integrating EGFR inhibitors with, and perhaps without, radiation, chemotherapy, and additional biologics. Currently, multiple RTOG trials continue to address these issues in head and neck cancers in the setting of intermediate or high-risk postoperative settings (i.e., 0920, 1216) and oropharynx cancers that are positive for human papillomavirus (HPV) (i.e., 1016). Additional RTOG trials examining EGFR targeting concurrently with radiation include RTOG 0839 using panitumumab in locally advanced NSCLC, RTOG 0974 with trastuzumab for Her2 positive breast ductal carcinoma in situ, and RTOG 1010 employing trastuzumab for locally advanced esophageal adenocarcinoma. These are a handful of examples of the ongoing efforts needed to cull out which patients benefit from targeting a particular pathway such as epidermal growth factor signaling and which patients, based on specific mutations, may need interference with Akt, mTOR, or DNA repair pathways in addition to or in lieu of traditional chemotherapy approaches.

ANGIOGENESIS INHIBITORS

Angiogenesis and Tumor Pathogenesis

All tumors require development (or expansion) of blood vessels to promote further tumor growth and nutritional support beyond a 2-mm diameter.[74] Molecules such as vascular endothelial growth factor (VEGF) mediate stimulation of angiogenic signaling and neovascularization. Elevated levels of specific isoforms of VEGF and other indirect markers predict for a worse prognosis in many types of cancer, including those of the gastrointestinal tract, such as pancreatic and esophageal cancers.[75,76] VEGF expression is affected by both the genetic aberrancies of the particular cancer as well as the microenvironmental changes, including hypoxia.

Once VEGF binding activates VEGF-receptor signaling, a cascade of transcriptional signals to promote blood vessel formation is set in motion (see Figure 5-1). Tumors develop a nutritional support system by borrowing existing blood vessels, growing new vessels from surrounding endothelium, and entrapping circulating endothelial stem cells. In contrast to mature vessels, developing tumors display vessels that are immature and chaotic, with a resultant lack of cohesion within the vessel matrix. As a result of increased permeability, blood perfusion through the tumor can be heterogeneous. This can lend itself to areas of hypoxia, which in turn results in activation of pro-angiogenic molecules such as HIF1 and nuclear factor kappa B (NFκB). Transcriptional activation occurs with further production of VEGF and additional pro-angiogenic proteins such as cyclooxygenase (COX)–2, Tie-2, osteopontin, histone deacetylase, and hepatocyte growth factor. An autocrine and paracrine cascade is created to further tumor growth and invasion.

Angiogenesis Inhibitors

Three main strategies under preclinical or clinical investigation exemplify the important concepts underlying angiogenic inhibition: (1) small-molecule tyrosine kinase inhibitors (TKIs) that target vascular endothelial growth factor receptor (VEGFR) signaling, (2) agents that directly target the tumor vasculature, or vascular targeting agents (VTAs), and (3) agents that inhibit VEGF.

Multiple VEGFR-TKIs have now gained FDA approval including sorafenib (Nexavar), sunitinib (Sutent), axitinib (Inlyta), pazopanib (Votrient), regorafenib (Stivarga), vandetanib (Caprelsa), and cabozantinib (Cometriq). Many of these biologics target multiple TKIs in addition to VEGFR signaling. They are indicated for treatment of a variety of cancers including unresectable hepatocellular carcinoma, advanced or metastatic renal cell carcinoma, metastatic colorectal cancer,

gastrointestinal stromal tumors, advanced soft-tissue sarcomas, and metastatic medullary thyroid cancer based on positive results of phase III randomized studies. Vandetanib and cabozantinib are active against VEGFR, EGFR, and more specifically RET kinase, a mutation present in the majority of patients with sporadic or inherited medullary thyroid cancer. These drugs have now been FDA approved for advanced or metastatic medullary thyroid carcinoma following phase III trial results with each significantly prolonging PFS.[76-80]

Agents that target the microtubule formation of intratumoral vasculature, thus destabilizing vessels and causing rapid necrosis within the central part of the tumor, might be effective compounds to combine with radiation. The rationale for pursuing agents that attack intratumoral vessels is based on the premise that endothelial cells in tumors display a different growth pattern than those in normal tissues; it is a chaotic, rapidly expanding pattern. VTAs were developed to take advantage of this differential to selectively occlude or destroy tumor blood vessels. Little progress has been achieved in clinical trials with VTAs, in part because of issues related to cardiac toxicity; however, this remains a potentially promising approach.

An alternative approach, inhibiting VEGF using an anti-VEGF monoclonal antibody is akin to scooping up the keys rather than blocking the lock. Antibodies against VEGF have shown anticancer activity in a variety of preclinical models.[81] Bevacizamab (Avastin) is a recombinant humanized version of the murine antihuman VEGF monoclonal antibody rhuMAb VEGF. Bevacizumab is FDA approved for use in patients with metastatic colorectal cancer when used in combination with 5-fluorouracil (5-FU). Two separate clinical trials demonstrated superior response rates, PFS, and OS in patients treated with combined 5-FU–based therapy with bevacizumab compared with others treated with 5-FU–based therapy alone in either the first- or second-line setting.[82,83] The addition of bevacizumab to carboplatin and paclitaxel also improved overall survival in chemotherapy-naïve patients with metastatic or recurrent, nonsquamous non–small cell lung cancer (NSCLC) and has been approved for use in patients with recurrent GBM, based on trials demonstrating good rates of radiographic response and stable to decreased corticosteroid requirement.[84,85] Improvements in PFS have also been demonstrated in patients with renal cell carcinoma and breast cancer receiving combinations of traditional systemic therapy and bevacizumab.[86] These promising clinical results in the advanced setting have prompted further investigations in the locally advanced setting with radiation.

Preclinical Studies of Angiogenesis Inhibitors as Radiosensitizers

At first glance, one might hesitate to consider blocking angiogenesis from a radiation oncology perspective. If sequencing is not optimal, blocking angiogenesis might to lead to increased hypoxia and reduced tumor control. In fact, the last 10 years have demonstrated the opposite effect: enhanced radiation sensitivity with anti-VEGF agents in the laboratory. Early work by Teicher et al[87-90] demonstrated enhanced radiation cytotoxic effects in a variety of antiangiogenic models. Antiangiogenic agents may enhance the effect of radiation by stabilizing tumor vasculature, thereby enhancing tumor oxygenation.[91] By inhibiting proangiogenic signaling, regulation of antiapoptotic proteins such as amplified NFκB may be improved. Many of these molecules, including VEGF, are activated by radiation, so reversing this process seems logical.

In the clinical trial setting, we have typically combined antiangiogenic agents with chemoradiation; however, we struggle with determining the optimal sequencing. To this end, there have been preclinical studies looking at this issue. ZD6474, a dual VEGFR/EGFR inhibitor, was evaluated with radiation in a xenograft model bearing EGFR-TKI–insensitive NSCLC Calu-6 tumors.[92] Two combined treatment schedules were examined: (1) a concurrent schedule using ZD6474 (50 mg/kg) dosing given 2 hours before the first dose of radiation, and (2) a sequential schedule using ZD6474 dosing given 30 minutes after the last dose of radiotherapy. The sequential approach was superior in terms of the time for treated tumors to quadruple in volume (RTV4) from their pretreatment size ($p < 0.0001$). Importantly, the reduced RTV4 (30 ± 1 day) in the concurrent schedule was also significantly better than either ZD6474 or radiation alone ($p < 0.02$). Nevertheless, clinical trials tend to simply combine these agents concurrently with chemoradiation, ignoring preclinical results.

Similar to studies showing enhanced radiation effects with VEGFR signaling interference, studies combining anti-VEGF antibodies with radiation confirmed that although exposure of human tumor xenografts to radiation promoted induction of VEGF expression, inhibiting VEGF with anti-VEGF antibodies supplanted this effect and resulted in increased endothelial cell killing and synergized antitumor effects in murine tumor model systems.[93]

Clinical Studies of Angiogenesis Inhibitors as Radiosensitizers

Unfortunately limited success has been realized in the clinic. In locally advanced rectal adenocarcinoma, initial phase I studies by Willett et al[94] in rectal cancer brought to light clinical evidence of the vascular normalization hypothesis in which regulation of tumor vasculature may impair entry of metastatic cells into circulation while improving drug delivery and tumor oxygenation for radiosensitization. Multiple subsequent trials have examined the efficacy of either anti-VEGF or anti-EGFR therapies added to standard preoperative chemoradiation regimens for rectal cancer with modest pathologic complete response (pCR) rates ranging from ~10% to 20%.[5,95,96] One recent phase I/II trial examined the combination of bevacizumab and erlotinib with 5-FU and radiation in this setting with an encouraging pCR rate of 33% (9/27) although ~47% of patients experienced at least one grade 3 to 4 toxicity.[5]

In patients with GBM, two recently published major randomized phase III trials examined the addition of bevacizumab versus placebo to standard temozolomide and radiation in newly diagnosed patients.[97,98] Both RTOG 0825 ($n = 637$) and AVAglio ($n = 921$) showed a significant PFS improvement of ~4 months with bevacizumab, but similar overall survival outcomes between arms with a median survival of ~16 to 17 months. MGMT status did not influence response rates between arms in both trials. In the RTOG trial, patients receiving bevacizumab showed higher rates of decline in neurocognitive function and quality of life; whereas in the AVAglio trial, quality-of-life outcomes were improved in patients receiving bevacizumab. Adverse events were modestly increased in the bevacizumab arms of both trials. In the context of these results, the role of bevacizumab in upfront GBM treatment remains unclear.

Results have been more cautionary in combining bevacizumab with EGFR targeting and radiation in lung cancer. Based in part on promising results with bevacizumab and erlotinib in patients with metastatic NCSCL, several phase I/II trials in locally advanced lung cancer have been completed. Bevacizumab and chemoradiotherapy were associated with a concerning incidence of tracheoesophageal fistula and aerodigestive hemorrhage in 3 of 29 patients with small cell lung cancer and NSCLC.[99] A more recent phase I/II trial treated 45

patients with stage III NSCLC with induction, concurrent, and consolidative regimens of bevacizumab and erlotinib with radiation and chemotherapy.[4] Both PFS and OS results were not significantly different from current published results with standard chemoradiation, and on the downside, a significantly higher than expected 29% of patients on this trial had grade 3 to 4 esophagitis. Of note, the radiation in this trial treated elective mediastinal lymph nodes and used three-dimensional conformal radiotherapy to a total dose of 74 Gy (a dose recently shown to have inferior OS when compared to the standard 60 Gy by RTOG 0617); these combined factors likely contributed at least partially to the increased esophagitis rate.[100] The SWOG trial S0533 also attempted to integrate bevacizumab with chemoradiation in a three-step design with administration with docetaxel in the consolidation phase after cisplatin-etoposide and radiation.[101] Because of poor accrual and Cancer Therapy Evaluation Program (CTEP) warnings regarding toxicity, the trial was stopped early. Two of seven patients in the high risk cohort experienced grade 5 hemoptysis.

Bevacizumab as a radiosensitizer has also been studied in cervical cancer with a recently completed RTOG 0417 trial giving the agent every 2 weeks for three cycles during concurrent cisplatin and radiotherapy in 49 patients with stage IB-III disease.[102] With primary endpoints focused on adverse events, this trial noted minimal protocol-defined toxicity with 13 patients (26.5%) having grade 3 toxicities; 5 patients (10.2%) experiencing grade 4 toxicity; and no grade 5 toxicities. The majority of all toxicities were hematologic. In terms of efficacy, 3-year rates showed an 81% OS, 69% disease free-survival, and 23% loco-regional failure.[103] These outcomes are on par with published major trials using standard chemoradiation in cervical cancer.[104]

Thus, in 2014, we are still searching for successful clinical combinations of antiangiogenic agents with radiation in a multitude of disease sites with no positive phase III trials to demonstrate that this strategy is working. Jackson et al[105] further discuss the current use of bevacizumab in combined modality settings with an emphasis on cervical cancer in their recent review, providing the reader with a comprehensive discussion of current and future avenues.

PI3K/Akt/mTOR PATHWAY, INHIBITORS, AND RADIOSENSITIZATION

One of the most important pathways related to cancer cell survival, the PI3K/Akt/mTOR kinase pathway (see Figure 5-1), is a central regulator of cell metabolism, proliferation, and survival by preventing apoptosis. Furthermore, PI3K/Akt/mTOR is up-regulated in many tumors and can also be up-regulated with radiation.[106] Selective and pan-PI3K inhibitors, PI3K and mTOR dual inhibitors, Akt inhibitors, and mTOR inhibitors are all being developed. Given the variety of targets and specificities of these agents, current research has focused on their efficacy, resistance, and toxicity profiles in a wide range of tumors, especially those with pathway alterations (e.g., loss of PTEN, KRAS mutations, and TSC1/2 alterations).[107]

The agents furthest along in development to date are mTOR inhibitors, primarily rapamycin analogs. These include temsirolimus and everolimus, which block signal transduction downstream of mTOR and facilitate apoptosis, suggesting effectiveness as radiosensitizing agents. Currently these two drugs are approved for clinical use in advanced renal cell carcinoma, and everolimus is also approved for pancreatic neuroendocrine tumors, subependymal giant-cell astrocytomas, and advanced breast cancer with exemestane.[108-110] Their clinical role as radiosensitizers is less established but is an active area of research.

To date, preclinical cancer cell models have demonstrated radiosensitizing effects of mTOR inhibitors.[111,112] Temsirolimus is as effective as cisplatin in radiosensitizing HNSCC lines, and triple-combination therapy did not provide additional cooperative effects over temsirolimus with radiation.[112] The in vivo effects were more dramatic partly because of an antiangiogenic byproduct of mTOR inhibition.

The radiosensitizing role of mTOR inhibitors continues to be investigated through clinical studies with mixed results. In a phase I trial of temsirolimus combined with palliative thoracic radiation in patients with NSCLC, dose-limiting toxicities included sudden death, pneumonitis, and pulmonary hemorrhage; however a safe maximum tolerable dose level was achieved.[113] Three separate phase I trials have examined the combination of radiation, temozolomide, and an mTOR inhibitor (i.e., temsirolimus or everolimus) in patients with GBMs, and infectious complications and stomatitis were the primary toxicities.[114-116] These trials have provided the basis for the phase I/II RTOG 0913 trial (i.e., everolimus with radiation and temozolomide up front and in combination with adjuvant temozolomide in GBMs) and the phase II EORTC 26082 (i.e., temsirolimus versus temozolomide in both the concurrent radiation and adjuvant settings for patients lacking methylation of the MGMT promoter with gliomas). In LA-HNSCC, the mTOR pathway has been shown to mediate expression of eukaryotic protein synthesis initiation factor 4E (eIF4E), with elevated eIF4E expression in histologically cancer-free margins associated with increased risk for recurrence. Based on this evidence, Fury et al[117] performed a phase I trial adding everolimus to standard of care concurrent cisplatin and radiation therapy in 13 patients with LA-HNSCC. Three patients experienced dose-limiting toxicities (i.e., two with mucositis, one with failure to thrive), and lymphopenia was the most common grade ≥3 adverse event seen in 12 patients (92%). Overall, a tolerable everolimus dose of 5 mg daily was found, and at 19.4 months follow-up, only 2 patients (15%) had experienced recurrent disease. Translation of these results into phase II and III trials and beyond is anticipated.

The remaining classes of PI3K/Akt/mTOR pathway inhibitors are still in their infancy with many additional phase I/II trials under way.[118] Several investigations are specifically examining their potential as radiosensitizers in both curative and palliative settings including LA-HNSCC, NSCLC, and malignant gliomas. Emerging data in HPV-positive head and neck cancers suggest an increased prevalence of PI3 kinase (PI3K) pathway mutation and copy number alterations.[119] In HPV-positive tumors harboring PI3K mutations mTOR appears activated rather than AKT downstream and thus may be a reasonable target to combine with radiation for this subgroup of patients.[120] A phase I trial of BKM120 or buparlisib, an oral PI3K inhibitor with cisplatin-radiation, is in the process of opening in patients who are HPV positive with locally advanced head and neck cancers.[8] Next-generation sequencing is a powerful tool that continues to deliver new information on the genomic landscape of many cancers including head and neck and should lead to more personalized cancer care.[121]

DNA REPAIR INHIBITORS: FOCUS ON PARP

PARP and DNA Repair

Up-regulated DNA repair within cancers contributes to radioresistance and is a concept across all histologies. DNA damage from radiation or chemotherapy results in a variety of mechanisms that attempt to fix both single- and double-stranded breaks quickly, so cancer cells can continue to replicate and grow. To counteract this repair, one promising strategy incorporates the use of poly(ADP-ribose) polymerase (PARP)

inhibitors. The PARP family consists of 17 proteins with PARP-1, 2, 3, and 4 and Tankerase 1 and 2 playing key roles in posttranslational modification of proteins involved in multiple pathways.[122,123] PARP-1 is the most heavily studied of these enzymes and is activated by base damage, single-stranded DNA breaks, and double-stranded DNA breaks caused by insults, including chemotherapy and ionizing radiation.[124] Activation leads to poly(ADP-ribosyl)ation of PARP-1, nicotinamide adenine dinucleotide (NAD+) consumption, a localized negative charge, and direct enzyme interactions with subsequent interaction of multiple pathways involving DNA repair (especially XRCC1), chromatin restructuring, and cell-cycle check points (Figure 5-2).[125]

Initial interest in PARP inhibition in oncology stemmed from the concept of synthetic lethality in which cancer cells with preexisting deficiencies in homologous-recombination pathways (e.g., BRCA mutations) exhibit selective cytotoxicity to single agent PARP inhibitors. Although many complex interactions occur with PARP inhibition, these cancer cells' susceptibility is in part attributed to their reliance on PARP-dependent DNA repair pathways such as base excision repair.[126] Remarkable activity has been observed in patients with BRCA1/2 mutations in a phase I study using olaparib (AZD2281), an orally bioavailable PARP inhibitor.[127] Importantly, minimal toxicity was observed in doses up to 600 mg twice a day. Objective antitumor activity was reported only in mutation carriers (22/60 patients entered, all of whom had refractory ovarian, breast, or prostate cancer). Two subsequent international phase II trials in patients with metastatic BRCA1/2 mutated breast ($n = 57$) and ovarian cancers ($n = 54$), respectively, treated two cohorts with the oral PARP inhibitor olaparib at doses of 400 mg twice daily (i.e., the maximum tolerated dose) and 100 mg twice daily.[128,129] These trials saw objective response rates of ~30% to 40% in the high-dose groups and ~10% to 20% in the low-dose groups. Both trials reported mostly low grade toxicities with grade 3 to 4 toxicities limited to fatigue, nausea, vomiting, and anemia.

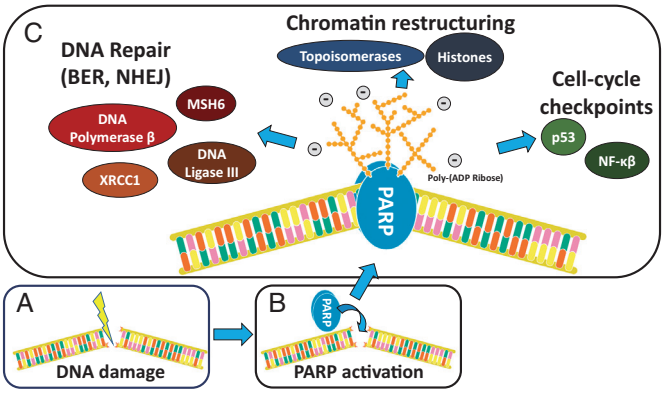


Figure 5-2 Overview of the role of poly(ADP-ribose) polymerase (PARP) activation in response to DNA damage from chemotherapy or irradiation. Activation of PARP triggers various DNA repair pathways, cell cycle regulation, and regulation of gene expression facilitated by chromatin restructuring.

Beyond synthetic lethality, PARP inhibitors show promise as chemosensitizers and radiosensitizers by directly preventing cancer cells from repairing induced DNA damage. In the preclinical setting, many groups have shown the ability of PARP inhibitors to sensitize a variety of histologies, both p53 wild type and null, to radiation in both in vitro and in vivo settings.[130-136] These results are rapidly being translated into the clinic with open phase I and II trial using a variety of PARP inhibitors with radiation and additional systemic agents in sites including central nervous system (CNS), head and neck, breast, lung, esophagus, pancreas, and rectum (Table 5-2).[8] Additional trials have focused on PARP inhibitors with DNA damaging chemotherapies, particularly temozolomide. Specifically, the current RTOG 0929 trial is exploring the use of the oral PARP inhibitor ABT-888 with temozolomide for patients with recurrent GBMs.[137] In development through the NRG (National Surgical Adjuvant Breast and Bowel Project (NSABP), the Radiation Therapy Oncology Group (RTOG), and the Gynecologic Oncology Group (GOG)) cooperative group mechanism is a trial that will evaluate this compound with radiation in patients with newly diagnosed GBM. Of note is the fact that PI3K inhibitors can down-regulate BRCA1/2, suggesting a possible dual targeting approach with these agents and PARP inhibitors to prevent homologous recombination and DNA damage repair.[138]

CHK1 and WEE1

In addition to PARP inhibitors, recent investigations into targeting DNA repair related cell-cycle proteins CHK1 and WEE1 have begun to generate excitement for their role as radiosensitizers. In response to DNA damage, these proteins help mediate both the S and G_2 phase checkpoints.[139] Both CHK1 and WEE1 are up-regulated in P53 mutated cancers, which already bypass the G1 checkpoint.[140] Theoretically, inhibition of either CHK1 or WEE1 would render P53 mutant cancer cells susceptible to DNA damaging treatments such as radiation resulting from critical checkpoint failures, while allowing normal tissues, with intact G1 checkpoints, to remain relatively unaffected. Although lacking preclinical data, several phase I

TABLE 5-2 Select PARP Inhibitors Currently Undergoing Clinical Trials[8,9]

Agent	Manufacturer	Sites
BMN-673	Biomarin	BRCA(+) breast, solid tumors, hematologic malignancies
CEP-9722	Cephalon	NSCLC
E7449	Eisai Incorporated	Advanced solid tumors or B-cell malignancies
Iniparib	Sanofi	Breast, NSCLC
Niraparib	Tesaro	Ovarian, BRCA(+) breast
Olaparib	AstraZeneca	BRCA(+) ovarian, gastric, NSCLC, glioblastoma, esophagus, HNSCC, CRC
Rucaparib	Clovis Oncology	Ovarian, fallopian tube, peritoneal,
Veliparib	Abbott Labs	Pancreatic, ovarian, cervical, breast, NSCLC, DPG, SCLC, liver, prostate, melanoma, metastatic solid tumors, leukemia, myeloma,

CRC, *Colorectal carcinoma;* DPG, *diffuse pontine glioma;* HNSCC, *head and neck squamous cell carcinoma;* NSCLC, *non–small cell lung cancer;* SCLC, *small-cell lung carcinoma.*

trials are evaluating WEE1 inhibitors with concurrent radiation and chemotherapy in patients with recurrent GBMs, cervical cancer, and unresectable pancreatic adenocarcinomas.[8]

IMMUNE TARGETED BIOLOGICS

Cancer and the Immune System

In the past decade, increasing research emphasis has been placed on understanding the role the immune system plays in preventing and controlling cancers and the system's response to radiation. Despite maintaining a multitude of distinctly nonself-antigens among clonal cell populations, many cancers still develop the capability to circumvent the immune system's surveillance of nonself-antigens. Recent research has elucidated that these cancers reach a state of immune tolerance through halting the immune system at immune checkpoints and preventing T-cell activation through alteration of both stimulatory and inhibitory signaling.[141] Two clinically significant regulators of the immune checkpoint are cytotoxic T-lymphocyte associated antigen 4 (CTLA-4), which inhibits initial T-cell activation, and programmed cell death protein 1 (PD-1), which suppresses subsequent T-cell activity in peripheral tissues and tumors.[142-144] Evolving quickly in many different disease sites, we may be entering a new frontier of durable responses never quite seen before in deadly diseases. Can the efficacy of immunologic strategy be amplified with radiation?

CTLA-4 Inhibitors

Ipilimumab, a CTLA-4 antibody, is the first FDA-approved targeted therapy to specifically promote the body's antitumor immune response, rather than directly targeting cancer cells. This human monoclonal antibody's approval for use in unresectable or metastatic melanoma was based on results from two recent phase III trials.[145,146] One trial in 676 patients with metastatic melanoma saw a 3.6-month improvement in median OS from 6.4 months with placebo to 10.0 months with ipilimumab, regardless of whether patients received an additional vaccine that was also part of the study.[145] The 2-year OS nearly doubled for patients on ipilimumab versus placebo (23.5% vs. 13.7%). Regarding toxicity, 14 treatment-related deaths occurred and 10% to 15% of patients had grade 3 to 4 immune-related adverse events. A subsequent trial tested the addition of ipilimumab versus placebo to dacarbazine in 502 patients with metastatic melanoma and again saw a significant improvement in OS.[146] Patients receiving dacarbazine with ipilimumab versus placebo had median OS of 11.2 months versus 9.1 months and 3-year OS of 20.8% versus 12.2%. Although no drug-related deaths occurred, grade 3 to 4 adverse events occurred in 56% of patients in the ipilimumab arm versus 27.5% of those in the placebo arm. As previously seen, this difference was primarily as a result of increased immune-related events including skin, gastrointestinal, and hepatic toxicity. Another CTLA-4 inhibitor, tremelimumab, also underwent multiple phase I-III trials but was not approved because of dose levels inducing unacceptable toxicities and lack of a proven survival advantage.[147]

Ipilimumab, Radiation, and the Abscopal Effect

First proposed in 1953, the abscopal effect has since been elucidated as an immune-mediated systemic cancer response induced by localized radiotherapy.[148,149] Since ipilimumab's FDA approval in 2011, at least four cases have been published linking its use with radiation to the abscopal effect.[150-152] In each case, the patients received ipilimumab either before, concurrent with, or subsequent to stereotactic body radiotherapy or radiosurgery. The high doses of radiation given to each patient have been postulated as necessary to induce sufficient tumor necrosis to allow for an immune response.

A group from Memorial Sloan-Kettering initially reported on a case of a woman with metastatic melanoma who received ipilimumab for four doses followed roughly 1 year later by palliative radiotherapy to a pleural-based spinal para mass to 2850 cGy in three fractions. Following one additional ipilimumab dose 2 months after radiation, the patient was noted to have radiographic regression of both the irradiated lesion and multiple additional distant metastases that were previously progressing.[150] This same group subsequently reported on a patient with metastatic melanoma receiving radiation to an internal mammary lymph node with regression of distant, nonirradiated, left axillary lymph node metastases. In a separate report, a patient with metastatic melanoma received stereotactic radiosurgery to a brain metastasis with concurrent ipilimumab and had a complete clinical response of all metastatic lesions.[151] Notably, his titers of melanoma autoantibodies to melanoma antigen A3 increased from 1:300 to 1:700 following radiation and ipilimumab, supporting a systemic immune response. A Stanford group noted a complete systemic response in a patient with metastatic melanoma receiving stereotactic radiotherapy to two of eight hepatic lesions sandwiched in the middle of four cycles of ipilimumab.[152] Despite the promise of these cases and the growing use of radiation and ipilimumab in patients with melanoma, the abscopal effect remains a rare phenomenon. Ongoing research is investigating the optimal radiation and ipilimumab dosing and timing and the possibility of a biomarker indicating which patients will be most suitable for these treatments. Currently, the National Cancer Institute reports six clinical phase I or II trials hoping to further elucidate the underlying immune mechanisms of the abscopal effect and possibly finding a consistently reproducible method of inducing this phenomenon.[118]

PD-1 and PDL-1 Inhibitors

In a similar but separate immune suppressing vein, the primary effect of PDL-1 binding of PD-1 is suppression of the cytotoxic T-cell response in peripheral tissues and tumors.[153] This mechanism was initially elucidated in the setting of chronic viral infections and inflammatory states, but in the past decade, basic and translational research has shown that PD-1 pathway activation provides an alternative approach to CTLA4 through which cancers can achieve a durable state of immune tolerance.[144,154,155] Notably, cancers have been shown to activate this pathway via two different mechanisms. In one method, a tumor develops constitutive overexpression of PDL-1 on its membrane providing immune suppression regardless of tumor microenvironment. Separately, tumor cells can be induced to express PDL-1 by cytokines (e.g., interferon-γ [IFN-γ]) in a local inflammatory state.[156]

Several molecular therapeutics targeting PD-1 or its ligand PDL-1 are currently under investigation in multiple disease sites with published results appearing promising to date. Three separate phase I studies of more than 600 total patients with advanced cancers of eight separate disease sites receiving an anti-PD-1 or anti-PDL-1 antibody showed objective responses in ~10% to 50% of patients with grade 3 to 4 toxicities in the range of 10% primarily involving immune-related complications.[157-159] In each study, a subset of patients was noted to have durable response off therapy. A recent report notes two patients who achieved eventual durable complete responses lasting more than 3 years off therapy and one patient with 16 months of a stable off-therapy partial response, eventual relapse, and subsequent partial response for at least

16 months following reinduction of anti-PD-1 therapy.[160] In a subset immunohistochemical analysis of tumors for one of these trials, only those tumors expressing PDL-1 by immunohistochemical analysis achieved a response.[159] Based on results of one of these trials focusing on melanoma patients, pembrolizumab (previously lambrolizumab) has gained expedited FDA approval through the FDA Breakthrough Therapies program.[9] In addition, many more trials are ongoing, and further research with these agents is needed to determine optimal dosing and timing; whether patients can be selected for these therapies based on molecular studies; whether these agents can be combined with complementary immunomodulatory biologics such as ipilimumab; and whether these agents have a role in conjunction with radiation including the interesting possibility of an alternative mechanism for generating an abscopal effect. A more in-depth review of immune-targeted biologics by Pardoll et al is provided for reference.[141]

FUTURE DIRECTIONS

Several other classes of agents have not yet received FDA approval but have significant potential as radiosensitizers. The central role of signal transduction, DNA repair, and cell cycle control in radiation response leads to obvious interest in investigating agents that selectively perturb these processes in tumor cells as radiosensitizers.[161,162] Additionally, newer agents targeting cancer stem cells (CSCs) may help impair tumor resistance and relapse following radiation, surgery, and systemic therapies. Here we briefly discuss the bright future of several of these classes.

c-MET

c-MET, another receptor tyrosine kinase, binds hepatocyte growth factor (HGF) and has been associated with a variety of oncogenic pathways including angiogenesis, cell proliferation, DNA damage repair, epithelial-mesenchymal transition (EMT), and the related metastatic capabilities of cell motility and invasion.[163,164] Recent in vitro and in vivo studies have shown that c-MET is up-regulated in many cancer histologies and also up-regulated further in irradiated cells possibly also playing a role in radioresistance.[165,166] At present a variety of these biologics are in varying stages of development as far as phase III trials; however, minimal clinical applications have attempted to use these in conjunction with radiation. Further preclinical investigations examining the radiosensitizing effects of these agents will be necessary before reaching the clinical stage as radiosensitizers.

TGF-β

An intriguing area of anticancer research that is associated with chronic inflammation and potentially tied into the immune-modulating story is the transforming growth factor β (TGF-β) pathway.[167] The TGF-β pathway is found in abundance in solid tumors and is associated with malignant progression through a variety of interactions on the tumor cell and in the surrounding microenvironment. What is its specific mechanism of action? TGF-β1 signaling occurs primarily through a heteromeric complex of type II and type I TGF-β receptors that activates the Smad pathway by TβRI-mediated phosphorylation of Smad2 and Smad3. Subsequent nuclear relocation of receptor-associated phosphorylated Smads bound to Smad4, results in activated TGF-β-driven transcriptional responses.[168] The TGF-β receptor complex can also signal via non-Smad pathways to affect cell survival and EMT.

The paradox lies in the fact that TGF-β actually demonstrates tumor suppressive effects that cancer cells attempt to get around; yet later, TGF-β promotes cancer cell proliferation and invasion once the suppressor activity is blocked (Figure 5-3). Evidence exists that radiation can activate the TGF-β signaling pathway with cross-talk activation of COX-2.[169] This phenomenon has been observed in normal tissue injury in patients treated with radiation.[170] For a wonderful overview of TGF-β signaling and its association with cancer progression as well as opportunities to exploit this pathway for improved anticancer effects we point you to an extensive review by Dancea et al.[171]

Targeting Cancer Stem Cells

In the CSC model, a select group of CSCs drive the renewal, differentiation (including epithelial-to-mesenchymal transition), invasion, and often treatment resistance of an overall heterogeneous population of a cancer.[172] Notch, WNT, and the hedgehog (HH) pathways play central roles in the livelihood

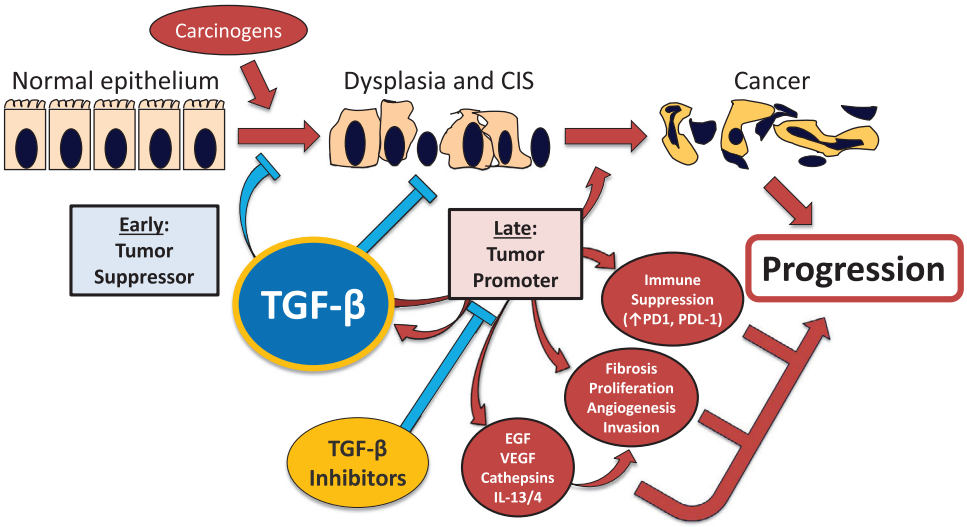


Figure 5-3 The TGF-β pathway exhibits tumor suppressive effects through cell cycle regulation and apoptosis early on in carcinogenesis. Eventually, cancer cells bypass the inhibitory signaling, and TGF-β becomes tumor promoting via a variety of hallmark oncogenic pathways, while concurrently up-regulating TGF-β production.

of these CSCs, offering a handful of promising biologic targets. Multiple phase I and II clinical trials testing inhibitors of these pathways are under way in a variety of solid tumors with early results showing general tolerability but mixed efficacy.[173-175] Furthermore, the potential to impair repopulation makes CSC pathway inhibitors attractive agents as radiosensitizers, especially in the setting of cancers known to exhibit radiation-induced accelerated repopulation such as HNSCC. An early in vivo study presented at ASCO 2014 found that the combination of a HH antibody with radiation in mice with primary cervical cancer xenografts led to better tumor growth delay, reduced lymph node metastasis, increased survival, and had no overt toxicity when compared to radiation alone.[176]

The heterogeneous population of cancers and CSCs may be responsible for the mixed efficacy of biologics previously discussed in this chapter. Nevertheless, this challenge offers an opportunity founded in the hypothesis that cancers may be more vulnerable to combined modality therapies including combinations of complementary biologics, not necessarily limited to CSC pathway inhibitors.[172] In the clinical setting, increased expression GLI-1, a zinc finger protein induced in HH pathway activation, was recently shown to be associated with increased metastasis, progression, and overall survival independent of stage and EGFR expression in a retrospective analysis of HNSCC tumors from patients treated on RTOG 9003.[177] Subsequently, Keysar et al[178] showed that in vitro and in vivo HH pathway inhibition drove HNSCC cells into an EGFR-dependent state thereby preventing cetuximab resistance and significantly impairing tumor growth when combined with cetuximab. A better understanding of such cross-talk signaling pathways among CSCs and the collective cancer cell population will be critical in determining the most clinically effective and tolerable combinations.

Designing Clinical Trials

If the past few years are any indication, we can expect continued exponential growth of targeted therapeutic agents in oncology. With endless permutations of dosing, timing, and combinations of these agents and modern radiation and chemotherapies, increasing emphasis must be placed on careful design and implementation of clinical trials. The NCI and RTOG recently released collaborative strategic guidelines for early stage development of radiosensitizers.[179] The guidelines highlight multiple hurdles in the development of radiosensitizers including difficulties in translating preclinical studies, poor endpoints such as tumor response rates which are expected to occur with radiation alone, and attributing toxicity to an agent versus radiation in a single-arm phase I trial. Furthermore, they provide recommendations for optimizing radiosensitizer trials including rigorous evaluation of preclinical and single-agent clinical data; avoidance of redundant pharmacokinetic studies; efficient methods of dose-escalation; and accurate assessment of expected toxicities. Given the extensive costs of these modern targeted therapies, we must continue to investigate biomarkers for optimal selection of patients whose tumors are most likely to respond to a specific intervention. This sentiment has been echoed by ASCO's recent Choosing Wisely recommendations and recently pursued by large-scale screening efforts.[180,181] Large-scale phase III trials in unselected patients are an inefficient and extremely costly means for scientific progress in our field. A notable alternative to the current trial design paradigm is the concept of the basket study design. In this setting, trials would test targeted therapies in patients with specific mutations regardless of cancer site or histology or within a specific disease site such as lung or rectal cancer with therapy directed based on the mutation status of each patient. Advances in next-generation sequencing will play a central role in making these types of trials feasible.

In addition, and very exciting, is the recent discoveries using cancer personalized profiling by deep sequencing (CAPP-Seq), an efficient and relatively inexpensive ultrasensitive method for quantifying circulating tumor DNA (ctDNA). As an example, Diehn et al[182] at Stanford applied CAPP-Seq for NSCLC with a design covering multiple classes of somatic alterations that identified mutations in >95% of tumors. Subsequently, they detected ctDNA in 100% of patients with stage II-IV NSCLC and in 50% of patients with stage I, with a remarkable 96% specificity for mutant allele fractions down to ~0.02%. Importantly, the measured levels of ctDNA were highly correlated with tumor volume and were accurate in distinguishing between residual disease after radiation and treatment-related imaging changes by computed tomography (CT) or positron emission tomography (PET). ctDNA levels also assisted in determining earlier response to therapy compared to radiographic measurements that can often be difficult to assess. This type of emerging technology offers a glimpse into future possibilities when combining novel agents with radiation and will help us determine if patients are developing resistance to a particular drug. Additionally, integrating radiation into this new framework would need to account for site-specific targeting and toxicity factors (Figure 5-4). With less than 15% of current phase I trials involving radiation, much

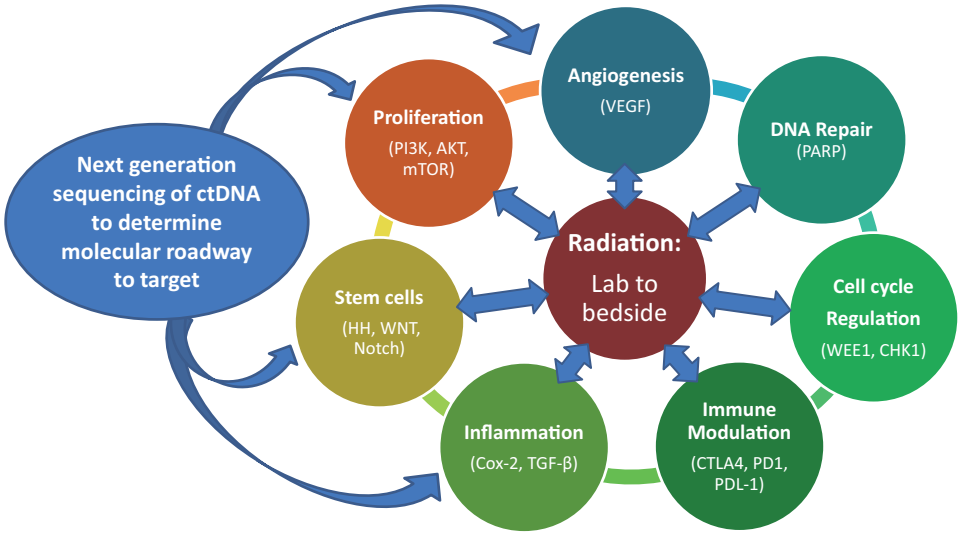


Figure 5-4 Preclinical studies leading to clinical translation using molecular discoveries such as next-generation sequencing to rationally tailor and sequence various biologics during and after radiation therapy for locally advanced disease—getting away from traditional chemoradiation approaches.

work lies ahead for our field toward better understanding the role of targeted therapeutics as radiosensitizers, presenting exciting opportunities to improve treatment results.[118]

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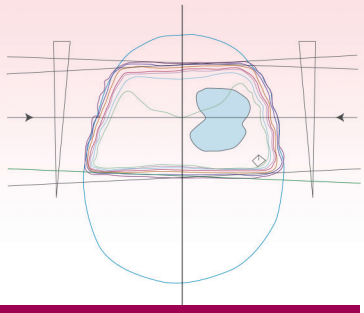
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CHAPTER 6

Radiation Oncology Physics



J. Daniel Bourland

Radiation oncology is a physical medical modality by which radiative energy is delivered to a target volume to effect palliation or cure. An understanding of the particles and processes involved in imparting radiation energy to matter is fundamental to the clinical application of radiation to patients.

In the irradiation of a biologic system, physical and biologic events occur in the following order:

1. *Physical events:* Physical interactions (e.g., photoelectric, Compton, collisional) result in ionizations and radiation dose.
2. *Chemical events:* Ionizations result in broken atomic and molecular bonds or chemical changes.
3. *Biological events:* Changes in the chemistry of molecules mean that there are changes in biological function (i.e., cells have improper or changed function).
4. *Clinical events:* Biologic alteration may result in clinical changes such as tumor regression, cancer induction, and tissue fibrosis.

MATTER AND PHYSICAL DEFINITIONS

Atomic and Nuclear Structure, Particles, and Nomenclature

Matter is made up of atomic and nuclear particles that have interaction and binding energies from 1 to 10 million electron volts (MeV). The smallest structural subunit that retains the character of an element, the atom, has a nucleus consisting of one or more protons and zero or more neutrons and a surrounding cloud of orbiting electrons. In an atom with zero net electrical charge, the number of orbital electrons equals the number of protons. A simplistic representation shows the atom to be neatly arranged with neutrons and protons in the nucleus and electrons in uniform orbits (Figure 6-1). In reality, the atom is a dynamic structure with defined energy states for the electron orbits and the nucleus. Detailed atomic and nuclear models have been formalized.[1,2]

Neutrons and protons are the building blocks of the nucleus; hence, they are called *nucleons.* The two particles have similar rest masses (the mass of the particle at rest, when kinetic energy is zero) but different electrical charges. The neutron, symbolized by *n,* has no charge (neutron for neutral) and the proton, *p,* has a charge of +1. The electron, *e,* has an atomic mass about $\frac{1}{2000}$ that of a proton or neutron and has a charge of –1. Besides the neutron, proton, and electron, other particles exist with unique masses and properties (e.g., spin). These include neutrinos, pions, muons, and others. The neutrino was first proposed as the neutral accompanying particle emitted in beta decay. There has been great interest in determining the mass of the neutrino because the cumulative neutrino mass may account for the "missing mass" in the universe, with great cosmologic implications. More recently it has been determined that the neutrino mass, inferred through observed oscillations in the neutrino state,[3,4] is finite and also small (close to zero). However, even with nonzero mass, the total amount of neutrino mass is estimated to be insufficient to make up for the "missing" mass. The universe is now stated to be made up of matter (4.6% the material "stuff" we are familiar with), dark matter (23%), and dark energy (which comprises more than 70% of the total mass-energy content of the universe).[5] These "dark" components are unknown entities.

Particles are classified by their mass as leptons or hadrons. Leptons, which include the electron and neutrino, are "lightweight" particles with mass comparable to that of the electron and spin of ½. Hadrons are heavy particles with two subclasses called *mesons* (middleweight, spin 0 or 1) and *baryons* (heavyweight, spin ½ or ⅜). Fundamental, or elementary, particles are those that have no subparts and cannot be divided. All leptons are elementary particles; however, the neutron and proton are not and are instead made up of three fundamental particles each, called *quarks,* which have been observed through high-energy physics experiments. Quarks have positive or negative charge in integer increments of ⅓, spin of ½, and other properties with whimsical, quark-deserving names.[1] Combinations of quarks yield the neutron, proton, and all other hadrons. For instance, a proton is made of two up quarks and one down quark, whereas a neutron is made of one up and two down quarks, which explains their similar mass but difference in charge. Antimatter is real, and an *antiparticle* is defined as a particle with identical mass but opposite charge to the particle. An antiparticle for a neutral particle has opposite spin or internal charge (i.e., quark) compared with the particle.

Matter is held together by four fundamental forces that operate over certain ranges and with certain particles. They are the strong, electromagnetic (coulomb [C]), weak (there are two), and gravitational forces, with respective relative strengths of 10^{1}, 10^{-2}, 10^{-13}, and 10^{-42}.[1] Each force acts by exchange of its respective mediator particle: the gluon, the photon, the W and Z particles, and the graviton (which has not yet been discovered). Counting mediators, leptons, hadrons, and their antiparticles, there are about 170 fundamental and composite particles that make up matter.[1] The model in which matter consists of fundamental particles as described previously is called the *standard model.*[1] Table 6-1 summarizes the fundamental particles in the standard model, which are six quarks, six leptons, six antiquarks, six antileptons, and also the four known forces. Of conceptual importance is the 2012 discovery of the "Higgs boson," predicted in 1964 by Higgs, which is a heavy particle (~125 GeV in energy)

responsible for the character of matter we have named "mass." The Higgs boson is placed by itself alongside the other entries to the standard model as the description of fundamental particles that make up matter (Table 6-1). How fundamental particles fit together to make up other particles continues to be studied. A relatively new theory called *string theory* is a descriptor of how quarks and other fundamental particles are assembled with vibration (energy) states for stringlike entities that give each fundamental particle its unique character.[6] However "flexible" they may be, the strings still need additional dimensions called "branes" (after "membranes") to enable their full character to be described.[7,8] Clearly, the fundamental properties of the universe continue to be studied in basic physics research.

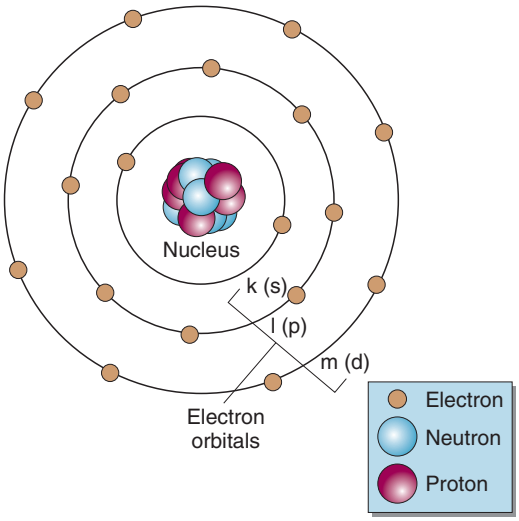


Figure 6-1 The atom has a nucleus composed of protons and neutrons. The nucleus is surrounded by a cloud of electrons in distinct energy levels called *orbitals* named s, p, d, and so on by chemists or called *shells* named k, l, m, and so on by physicists.

TABLE 6-1 The Standard Model of Matter: Fundamental Particles and Mediators

	Generations			
	I	II	III	Mediator (Force)
Quarks	Up	Charm	Top	Photon (electromagnetic)
	Down	Strange	Bottom	Gluons (strong)
Leptons	ν_e	ν_μ	ν_ν	Z (weak)
	e	μ	τ	W+, W– (weak)
Higgs Boson				Responsible for particle mass

Particle mass can be expressed as the atomic mass unit ([amu]; 1/12 of the mass of the carbon nucleus) or in units of energy by conversion with Einstein's formula, $E = mc^2$. Table 6-2 gives the symbol, charge, mass, and stability for the electron, proton, neutron, and other particles of interest.

Combinations of nucleons form a variety of nuclei and determine the physical character of an atom. The number of protons in the nucleus, *Z*, is called the *atomic number* and determines the chemical properties of an atom and the atom's identity as an element. The atomic number also equals the number of electrons in the neutral atom, with one electron per proton. The number of neutrons in the nucleus, *N*, is called the *neutron number.* Whole protons and neutrons constitute the nucleus, and *Z* and *N* have integer values. An atom's mass number, *A*, is the sum of its neutrons and protons. The mass number (an integer) has a value close but not equal to the actual nuclear mass. Their values are similar but must not be confused. Nuclear mass is the noninteger sum of the masses of the individual particles minus their binding energies. Definitions for *Z*, *N*, and *A* are summarized in Table 6-3.

Nuclides and Radionuclides

Nuclides are atomic species made of different combinations of nucleons, and they may be classified by their number of protons, neutrons, or nucleons (*Z*, *N*, or *A*) and by their energy state. Nuclei with the same *Z* but different *N* are called *isotopes* (p for proton), and they exhibit identical chemical characteristics (they are the same elements). Nuclei with the same *N* but different *Z* are called *isotones* (n for neutron). Nuclei with the

TABLE 6-3 Atomic Nomenclature

Symbol	Item	Definition		
Z	Atomic number	Number of protons in the nucleus and the amount of nuclear charge (+Z); also equal to the number of electrons in the neutral atom		
N	Neutron number	Number of neutrons in the nucleus		
A	Mass number	Total number of nucleons: A = Z + N		
Class	**Z**	**N**	**A**	**Examples**
Isotopes	Same	Different	Different	^{1}H, ^{2}H, ^{3}H; ^{125}I, ^{131}I
Isotones	Different	Same	Different	$^{8}He_6$, $^{9}Li_6$; $^{137}Cs_{82}$, $^{138}Ba_{82}$
Isobars	Different	Different	Same	^{60}Ni, ^{60}Co; ^{137}La, ^{137}Ba, ^{137}Cs
Isomers	Same	Same	Same	^{99}Tc, ^{99m}Tc (Δ energy state)

TABLE 6-2 Physical Characteristics of Selected Atomic and Nuclear Particles

Name	Symbol	amu	MeV	m_e	Charge	Lifetime
Electron	e^-	0.000549	0.511	1	–1	Stable
Positron	e^+	0.000549	0.511	1	+1	10^{-6} s
Proton	p	1.007276	938.256	1836.1	+1	Stable
Neutron	n	1.008665	939.550	1838.6	0	12 min
Neutrino	ν, $\bar{\nu}$	0.000000?	0.000?	0	0	?
Muon	μ	0.11320	105.659	206.4	–1	Unstable
Pion	±Π	0.14990	139.578	273.2	(±1	Unstable

amu, *Atomic mass unit.*

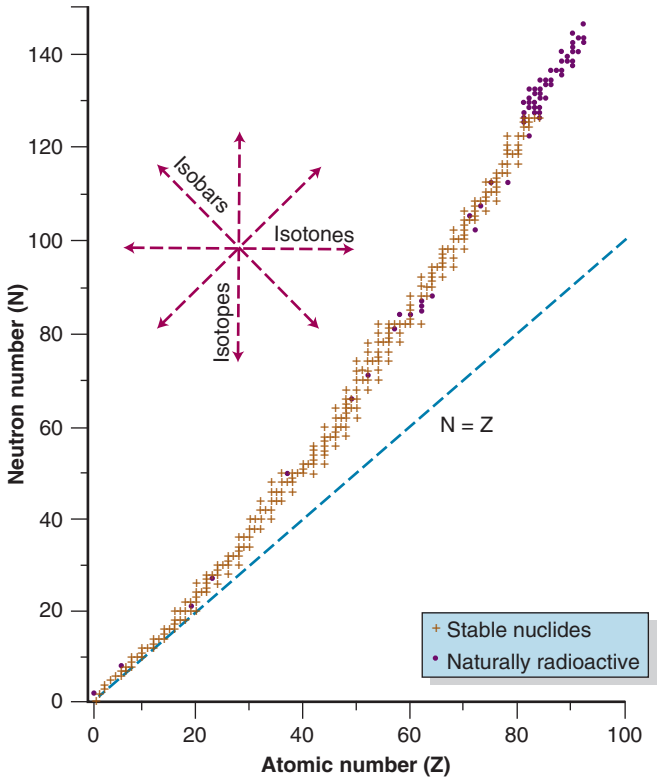


Figure 6-2 Distribution of stable and naturally radioactive nuclides. *Data from Radiological health handbook. Bethesda, MD, U.S. Department of Health, Education, and Welfare, 1970.*

same A but different Z and N are called *isobars*. In a last category, nuclei with the same Z and N, and therefore A, but different nuclear energy states (i.e., excited versus ground) are called *isomers*. Table 6-3 shows these classifications and example nuclides. A nuclide, or nuclear species, X, is denoted as

$$^{A}_{Z}X_{N}$$

in which X is the chemical symbol for the element with atomic number Z, N is the neutron number, and A is the mass number. Because $A = Z + N$, the N value is often dropped to give the following form:

$$^{A}_{Z}X$$

Because the atomic number determines the element's name, represented by the chemical symbol X, the Z is also dropped to give the form ^{A}X. An alternative nomenclature uses the nuclide's name followed by the mass number, such as hydrogen-3 and iridium-192.

Not all combinations of Z and N exist in nature or can be manufactured. Instead, certain combinations are possible, whereas other combinations cannot occur. Figure 6-2 shows the distribution of stable nuclides as a function of the number of neutrons and protons. Notice that at low Z, the ratio of neutrons to protons (N:Z) is about 1.0. Above $Z = 20$, stable nuclides have more neutrons than protons ($N/Z > 1.0$). At higher Zs, the stability of nuclei tends toward neutron-rich nuclides. It has been observed that nuclei with 2, 8, 20, 28, 50, 82, or 126 nucleons (protons and neutrons combined) are stable. These stability "magic numbers" relate to the filling of nuclear energy levels, similar to the complete filling of electron shells. Pairing of like nucleons also results in increased nuclear stability. There are 165 stable nuclei with an even number of both protons and neutrons, 57 stable nuclei with an even number of protons and odd number of neutrons, 53 stable nuclei with an odd number of protons and even number of neutrons, but only 6 stable nuclei with an odd number of both protons and neutrons.

Some nuclides are unstable and eventually transform to stable states by the emission of particles or energy. These nuclides are called *radionuclides* or *radioactive species* because a particle or energy is given off during the nuclear transition. Unstable nuclides lie off the line of stability and will have a neutron or proton excess relative to the stable nuclide. In Figure 6-2, isotopes lie along a vertical axis, isotones lie along a horizontal axis, and isobars lie at 45 degrees to either axis, perpendicular to the line of $N = Z$. Modes of radioactive decay depend on the type of nucleon excess, whether neutron or proton, and are discussed later in more detail.

Stable nuclides include ^{1}H, ^{12}C, ^{33}P, ^{34}S, and ^{59}Co. Radioactive nuclides for these elements include ^{3}H, ^{14}C, ^{32}P, ^{35}S, and ^{60}Co. Other radionuclides of interest to the medical field include ^{99m}Tc, ^{125}I, ^{131}I, ^{137}Cs, and ^{226}Ra.

Photons and Other Definitions

Interactions of ionizing radiation occur at the atomic and nuclear level, where binding energies are small compared with macroscopic realms. Electromagnetic radiation, or photons, are particles that have wavelike qualities with zero mass, which transfer energy from one location to another by propagation of an electromagnetic wave at the speed of light, c ($c = 3 \times 10^{8}$ m/s). Photons are also the mediators of charged particle bonds. A photon has wavelength λ, frequency ν, speed $c = \lambda\nu$, and energy $E = h\nu$; c is the speed of light, and h is Planck's constant ($h = 6.626 \times 10^{-34}$ m^2/kg/s). The electromagnetic spectrum consists of photons with wavelength, frequency, and energy ranges more than 10 orders of magnitude (the range is really infinite). From low to high energy, there are radar waves, microwaves, infrared, light (visible photons), ultraviolet, x-rays, and gamma rays. Photons are named by their wavelength (e.g., radar waves, microwaves), character (e.g., "purple"), and origins (e.g., x-rays from the atom, gamma rays from the nucleus) (Table 6-4).

RADIATION PRODUCTION AND TREATMENT MACHINES

External beam radiation therapy machines produce ionizing radiation by (1) radioactive decay of a nuclide or (2) electronically by the acceleration of electrons or other charged particles such as protons. The basic purpose is to create an intense beam of ionizing radiation with known and predictable characteristics that can be aimed at a patient from a certain distance away (most commonly 100 cm). This beam of radiation with a source outside the patient is the "external beam." The most commonly used radionuclide for external beam radiation therapy has been ^{60}Co. Although once quite common as the first widely used device for external beam radiation therapy, ^{60}Co treatment machines in the United States and other developed nations have been replaced over the past 20 to 30 years by linear accelerators, which produce high-energy x-rays and electrons by electronic means. Basic components of all external beam treatment machines include a radiation source, a collimating system to form and direct a radiation beam, inherent or added shielding for radiation protection, a control system to turn the beam on and off, a light field to delineate visibly the radiation field to be treated, a means to rotate the beam or otherwise change its direction, and a support assembly for the

TABLE 6-4 Physical Definitions

Item	Symbol	Definition
Atom	a	Smallest subunit of an element retaining the character of that element; composed of a nucleus of protons and neutrons and orbital electrons
Electron	e^-	Particle with a charge of –1 and mass of 0.511 MeV; used for radiation treatment when accelerated to energies capable of ionization
Photon	hν, γ, x	Particle with zero charge and mass consisting of electromagnetic radiation; used for radiation treatment at energies capable of ionization
Gamma ray	γ	Photon (electromagnetic radiation) originating from within the nucleus as a result of nuclear transformations
X-ray	x	Photon (electromagnetic radiation) originating from within the atom as a result of atomic transformations
Ionization		Removal of an electron from an atomic shell, leaving the atom with a charge of +1
Ionizing radiation		Radiation of sufficient energy to cause ionization on interaction
Ion	X^-, X^+	Atom of element *X* with an electron deficit, as is formed after ionization, or an electron excess
Nonionizing radiation		Radiation of insufficient energy to cause ionization on interaction
Electron volt	eV	The energy gained by 1 electron when it is accelerated through an electrical field potential of 1 V
Kiloelectron volts	keV	1000 electron volts; used to denote the energy of a monoenergetic particle or photon, as in "100-keV photons" or "10-keV electrons"
Million electron volts	MeV	1 million electron volts; used to denote the energy of a monoenergetic particle or photon, as in "1.17-MeV gamma rays" or "7-MeV electrons" (see Figure 6-7)
Million volts	MV	Million volts; used to denote a spectrum of polyenergetic particles or photons with a maximum energy, as in "18-MV x-rays." In this example, the x-rays have a maximum energy of 18 MeV and a continuous energy distribution of photons from 0 up to 18 MeV (see Figure 6-7).

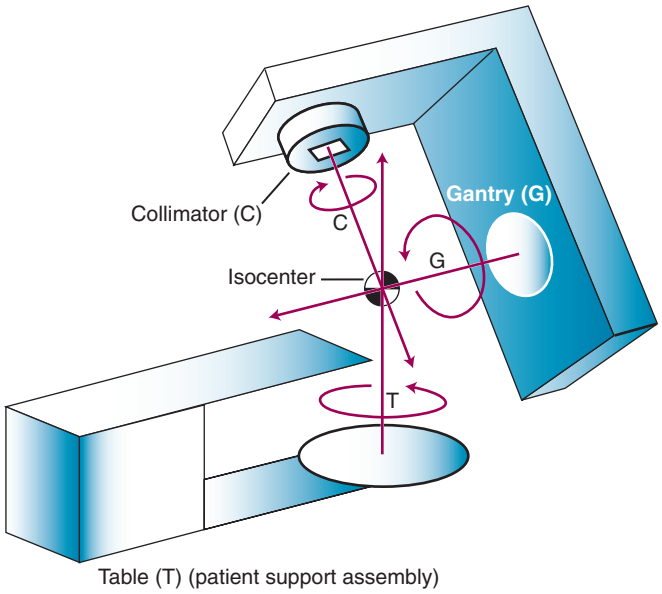


Figure 6-3 Treatment machine geometry for gantry-based linear accelerator or teletherapy unit. Three rotational axes intersect at a point called the *isocenter*. The table surface can translate three directions for a total of 6 degrees of freedom.

patient. These components are assembled for modern conventional treatment machines in an isocentric geometry (Figure 6-3). The isocenter is a point in space at which the treatment machine rotational axes all intersect. Any mechanical rotation is about an axis that passes through the isocenter. With many common components, ^{60}Co teletherapy units and linear accelerators differ primarily in the method of photon production: radioactive source versus electronic source. In current configurations linear accelerators also offer a wide range of sophisticated control systems for control of radiation beam shape, intensity, and trajectory (discussed later).

Radiation Production by Radioactive Decay

Teletherapy is the use of radioactive material, such as ^{60}Co, for production of an external beam of gamma rays for treatment at a distance from the radioactive source (*tele,* meaning "at a distance"). The term is historical and is in contrast to brachytherapy, in which the radioactive source is placed in or on the treatment volume (*brachy,* meaning "close"). Gamma rays are emitted from a daughter nucleus formed after radioactive decay of an unstable parent nucleus. Each gamma ray has a unique energy that relates to the immediately preceding nuclear transformation, and this unique energy can be used to identify the daughter (and therefore the parent). ^{226}Ra, ^{137}Cs, and most commonly ^{60}Co have been used for teletherapy. ^{137}Cs and ^{60}Co are manufactured and became available by neutron activation and as a byproduct of fission after the invention of the nuclear reactor. Use of ^{60}Co as a source of gamma rays for treatment was pioneered by H. E. Johns[9] and represented a major step in obtaining high-energy photons above 1 MeV, "megavoltage" photons. At that time, electronic means of photon production from high-energy x-ray tubes was limited to 300 keV maximum because of electrical arcing at higher accelerating potentials. Specialized particle accelerators were required to produce potentials above 300 keV (e.g., betatrons[10] and van de Graaff accelerators[11]).

Although of historical interest for most readers, ^{60}Co teletherapy units have lower cost and a relatively simple design with lower requirements for their operating environment compared with linear accelerators. For these reasons ^{60}Co teletherapy devices are used worldwide in regions with limited resources for funding and operating infrastructure. A disadvantage is the constantly decreasing dose rate as a result of the decay of the ^{60}Co source and the requirement for eventual replacement of the source. In a conventional ^{60}Co teletherapy unit (Figure 6-4), a cylindrical sealed-source capsule about 3 cm in diameter and 5 cm high contains pellets of ^{60}Co. In each transformation a ^{60}Co nucleus decays to ^{60}Ni, with the prompt emission of two gamma rays at 1.17 and 1.33 MeV each (1.25 MeV average). Typical activity is 6000 to 9000 Ci (2.22 to 3.33 × 10^{14} Bq) for dose rates of approximately 2 to

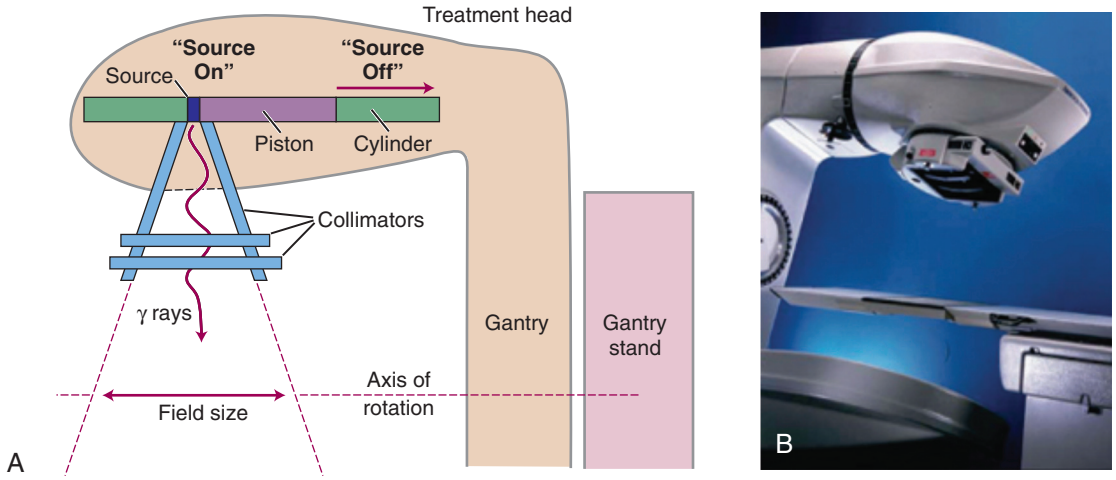


Figure 6-4 In a typical ^{60}Co unit, the source moves from the shielded position (Off) into an unshielded position (On) to produce a treatment beam. ***B,*** *Courtesy Best Theratronics, Ltd., Ottawa, Ontario, Canada.*

3 Gy/min at 80 to 100 cm from the source. The source decays with a half-life of 5.263 years and is replaced every 5 to 7 years when the dose rate becomes "too low"; treatment times may be excessive and radiobiological effect for treatment efficacy may be compromised below 1 Gy/min.

In one of the most commonly available teletherapy unit configurations (Theratron Phoenix, Best Theratronics Ltd, Ottawa, Ontario, Canada) the source is stored in a shielded head of the machine, mounted on the end of a movable piston in a horizontal cylinder (see Figure 6-4). On the initiation of treatment, the source is moved pneumatically to a position over an opening in the shield that allows a treatment beam to exit. A collimator consisting of interleaved bars of a high *Z* material is used to define the field size as the beam exits the shield port. Trimmer bars, additional collimator bars closer to the patient surface, can be used to reduce the beam penumbra, which is large because of the relatively large source size of approximately 1.5 inches. Maximum field size is 35×35 cm^2 at 80 or 100 cm from the source. Irradiation time is measured and controlled by two independent timers. An end effect caused by the mechanical movement of the source, for which the effective irradiation time is less than the timer setting, is inherent and can be measured. Cross-hairs and a field light are used to delineate the central ray and field dimensions. There is a source-to-surface indicator. Source movement is designed so that in the event of treatment termination or device failure the source is automatically returned to the shielded condition. An emergency pushbar (T-bar) can be used to manually return the source to the shielded position, if necessary.

The machine has a rotatable gantry allowing 360-degree rotation of the source and a nominal isocenter position of 80 cm from the source. Later models have a 100-cm isocenter and treatment distance. An additional degree of freedom is provided by a head swivel mechanism that allows the beam direction to be rotated away from isocenter, if desired. A beam stopper may be used to intercept the beam for additional shielding of the exit beam. The beam stop also acts as a counterweight for the head of the machine. There is a patient support assembly (treatment table) with vertical, longitudinal, lateral, and rotation motions. Beam modifiers include custom or standard field blocks and mechanical wedges for producing angled isodose distributions or tissue compensation.

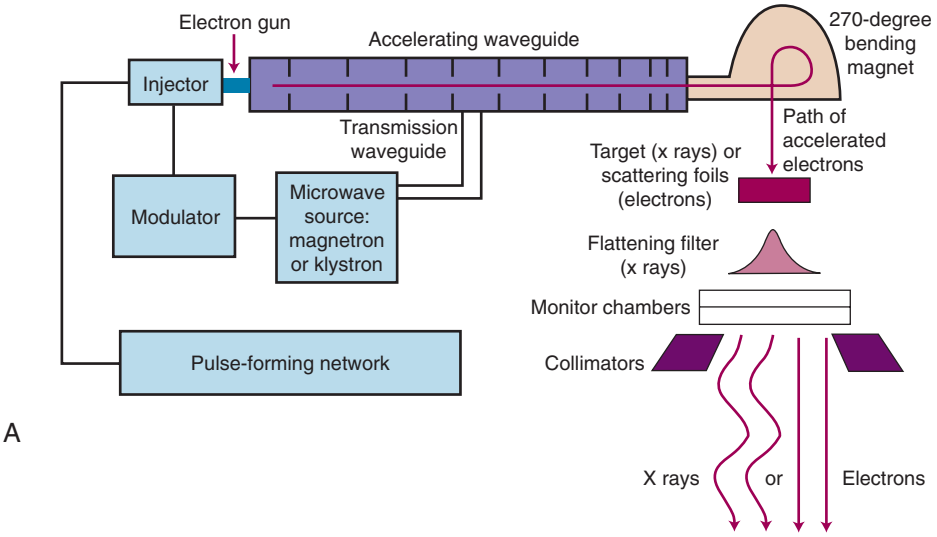
One manufacturer (Best Theratronics, Ltd., Ottawa, Ontario, Canada) states that as of the year 2010 there were 45,000 daily radiation treatments delivered worldwide using this conventional ^{60}Co teletherapy device.

Radiation Production by Linear Accelerators

In a linear accelerator, electrons are accelerated to high energy and are allowed to exit the machine as an electron beam or are directed into a high *Z* target to produce x-rays by the bremsstrahlung interaction. The linear accelerator enables convenient production of megavoltage x-rays in a relatively small device, and its existence is directly related to the invention of the magnetron and the klystron during the development of radar in World War II. Linear accelerators are quite versatile, with x-ray and electron modes, multiple energies, and computer controls. These capabilities have led to the replacement of most ^{60}Co teletherapy machines in the United States with linear accelerators.

The principle of operation for linear accelerators is to accelerate electrons through a waveguide by use of alternating microwave fields.[12] Two basic waveguide designs exist: standing wave and traveling wave. Waveguide length is a function of the maximum acceleration energy (longer is higher energy) and the frequency of the microwave field. The most common frequency for gantry-based linear accelerators (see Figure 6-5, *B*) is 2.998 GHz (S-band microwaves); however, specialized, shorter waveguides are possible at 9.3 GHz (X-band microwaves) that produce megavoltage energies above 6 MeV with acceptable dose rates for treatment. Major electronic components are described in Table 6-5 and are shown in Figure 6-5 for gantry-based linear accelerators, the most common design.

Major mechanical components are similar to those for teletherapy. A rigid, floor-mounted stand holds high voltage, microwave transport guides, cooling and control components, and supports a rotatable gantry holding the waveguide to allow 360-degree rotation of the source at an isocenter of 100 cm to enable multiple beam directions (see Figure 6-3). In an alternative barrel-type design the entire accelerator—including waveguide, high voltage, microwave transport guides, and other components—is contained within a large rigid cylinder and the cylinder and all its contents rotate on a horizontal axis about the isocenter (this design not shown). A set of one or two pairs of high Z collimators ("jaws"), depending on the manufacturer's design, provides at least 99.9% attenuation of the primary beam (0.1% transmission) and defines the length or width of the rectangular x-ray radiation field. A maximum field size of 40×40 cm^2 at 100 cm (isocenter) is common, with 180- to 360-degree rotation of the entire collimator assembly about the isocenter (see Figure 6-3). Collimator settings are continuously variable, and jaw pairs can be



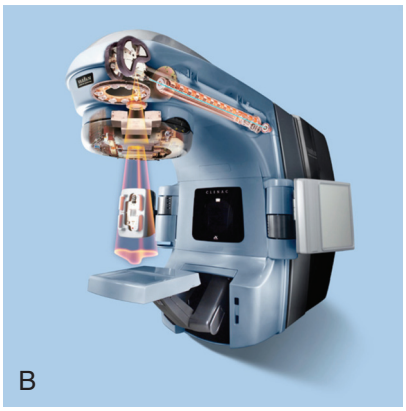


Figure 6-5 Electron linear accelerator schematic. Key components are shown that allow a beam of electrons to be accelerated, producing a treatment beam of electrons or x-rays.
B, *Courtesy Varian Medical Systems.*

TABLE 6-5 Major Electronic and Beamline Components of Linear Accelerators

Component*	Purpose
Electron gun	Source of electrons to be accelerated
Microwave source	Provides accelerating potential and amplitude (power). Typically, magnetrons are used for ≤10 MV; klystrons are used for >10 MV and for most dual-energy machines
Pulse-forming network	Synchronizes electron bunches with microwave phase
Transmission waveguide	Carries microwave power from its source to the accelerating waveguide
Injector	Injects pulses of current to the electron gun (i.e., drives electron gun)
Accelerating waveguide	Location of electron acceleration through multiple coupled cavities in a linear geometry (i.e., the linear accelerator)
Bending magnet	Used in horizontally oriented accelerating waveguides to redirect the electron beam, for electron energy selection, and for beam focusing
Target (for x-rays)	Placed in electron beam for x-ray production on electron impact
Scattering foils (for electrons)	Scatter electrons to produce a uniform beam of electrons for treatment
Flattening filter (for x-rays)	Flattens the highly peaked x-ray beam exiting the target to produce a uniform beam of x rays for treatment
Monitor chambers	Ionization chambers that monitor the amount of radiation in the beam; count dose and turn machine off when set dose is reached; monitor beam flatness and symmetry
Collimators (secondary)	Provide rectangular field shaping for x-rays and set field sizes for electrons
Accessories and beam modifiers† Interlocks†	Define or modify beam shape or intensity. With other control systems, ensure proper operation of linear accelerator for dose assurance and safety

**Components are shown in Figure 6-5.*
†Components are not shown in Figure 6-5.

operated in coupled mode to produce symmetrical and asymmetrical axis. Cross-hairs and a field light are used to delineate the central ray and field dimensions, and there is a source-to-surface indicator.

Although rarely used for linear accelerators, a beam stopper may be used to intercept the beam for additional shielding of the exit beam when facility shielding is limited. Otherwise, internal counterweights provide balance to the gantry to offset the weight of the accelerator waveguide and high-density shielding required around the x-ray target. There is an isocentric patient support assembly (treatment table) with vertical, longitudinal, lateral, and rotational motions. Fine tolerances for the rotational axes and isocentricity of the gantry, collimator, and table are important for accuracy in patient treatments. The combined variation in rotation and coincidence of the three axes is typically maintained within a 1-mm diameter sphere. The patient support assembly is usually the most difficult rotational axis to set for isocentricity.

Accessories and beam modifiers for conventional geometry linear accelerators are important for customizing the external beam field to an individual patient and include custom or standard shielding blocks to shape a patient's treatment fields to minimize the amount of normal tissue treated or protect critical structures; electron applicators for defining electron fields at the patient surface; physical (made of steel) and "virtual" or "dynamic" wedges for producing angled isodose distributions; and compensators for shaping the dose distribution within a patient for desired dose uniformity. Custom block manufacturing for shaping of patient-specific fields was once common, using high Z alloy materials to provide primary beam

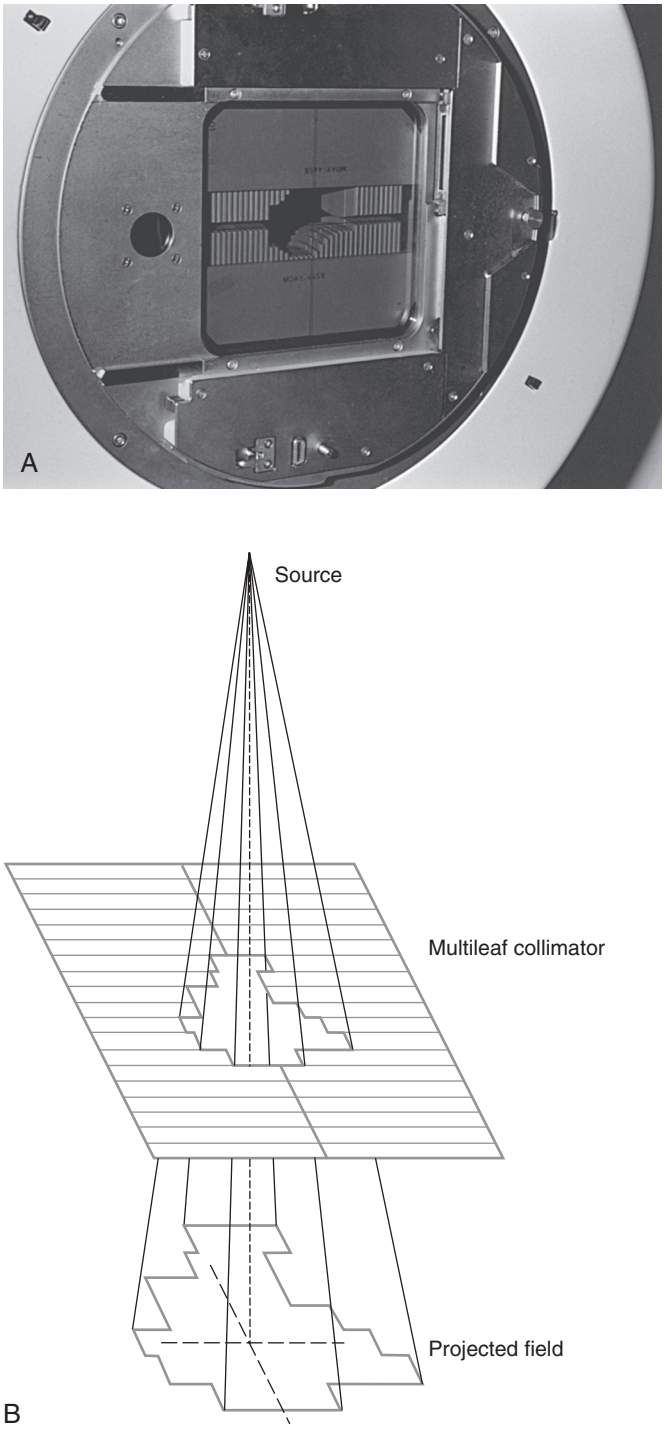


Figure 6-6 The multileaf collimator. **A,** Installed 80-leaf device for a Varian 2100C linear accelerator. **B,** Schematic of beam definition.

attenuation of at least 97% (five half-valve layers). The use of custom blocks has been almost totally replaced by a versatile collimator design called the *multileaf collimator* (MLC), which is now available from all linear accelerator manufacturers (Figure 6-6). The MLC provides field-shaping capabilities, replacing standard manual or custom blocks by the use of a large number of adjustable high *Z* vanes, or leaves. The desired beam outline is shaped as a series of steps by positioning each leaf to approximate a continuous field edge (Figure 6-6, *B*). Different manufacturer's MLC designs include singly and doubly focused leaf ends, where the leaf ends match beam divergence either across the direction of leaf travel (single) or both across and with the direction of leaf travel (double), and projected widths at the isocenter of 3 mm, 4 mm, 5 mm, or 10 mm.[13] MLCs also have capabilities for dynamic treatment, as discussed later for intensity-modulated radiation therapy (IMRT).

Linear accelerators and their supporting technologies have become computer controlled, enabling better-optimized dose distributions, rapid treatment setup, and in-room verification of target location through remote sensing and image-guided approaches. In particular, most modern linear accelerators are hybrid imaging treatment devices fitted with a gantry-mounted kV or MV x-ray imaging device that is coincident with the treatment isocenter. This imaging device provides "in-room" imaging to confirm patient and target position immediately before treatment, in the process termed *image-guided radiation therapy* (IGRT). A wide range of IGRT designs is possible, as discussed later.

Although linear accelerators typically have had an isocentric rotating gantry, there are other commercialized megavoltage accelerator designs available that also have integrated image guidance for treatment. One design, called *tomotherapy*, uses a highly stable computed tomography (CT)-like ring gantry around which an X-band linear accelerator rotates, always pointed toward the rotational center (an isocenter).[14] A binary ("on" or "off") multileaf collimator intensity-modulates a 6-MV x-ray fan beam as the accelerator waveguide is rotated. The treatment table is advanced in a stepwise or continuous motion for either slice by slice or helical fan beam treatment. Another ring gantry design uses a cone beam megavoltage x-ray beam with full MLC, along with kV imaging for image guidance. This entire unit is gimbaled to enable noncoplanar beam geometries outside of the default device orientation.

Another unique geometry uses a nonisocentric format with an X-band linear accelerator fixed on the end of a high-precision robot that is computer controlled for a range of motions with multiple degrees of freedom.[15] This device produces a circular 6-MV x-ray beam that can be pointed at the target from various "nodes" in space—using a relatively large collection of irradiation nodes generates the cumulative dose distribution at the target.

Three differences in radiation sources for teletherapy and linear accelerator devices are fundamental. First, a ^{60}Co teletherapy source is always "on," emitting radiation. Radioactive decay always occurs and cannot be interrupted; to initiate an irradiation the source must be moved from the shielded condition to an unshielded condition (see Figure 6-4). With a linear accelerator, no source is present until the unit is energized; the irradiation is on or off with the flip of an electronic switch initiated by the operator with a key or button at the treatment console. Second, their photon spectra are different (Figure 6-7). In a ^{60}Co unit, two monoenergetic gamma rays are emitted with every decay to produce a discrete spectrum with peaks at 1.17 and 1.33 MeV. In contrast, a linear accelerator produces a continuous x-ray spectrum through the bremsstrahlung interaction. The spectrum has a maximum energy of E_{max} (i.e., accelerating potential) and all other photon energies down to zero. An average x-ray energy of approximately one third E_{max} can be determined and is consistent with theoretical predictions for the continuous bremsstrahlung spectrum (Figure 6-7). Third, a linear accelerator can produce a treatment beam of electrons as well as photons. The accelerated electron beam is allowed to exit the machine under controlled conditions of scatter. Although ^{60}Co gamma rays occur because of an immediately preceding beta decay, the beta particles (electrons) are stopped by the radiation source enclosure, a metallic capsule that contains the radioactive material, and cannot be otherwise harnessed for treatment.

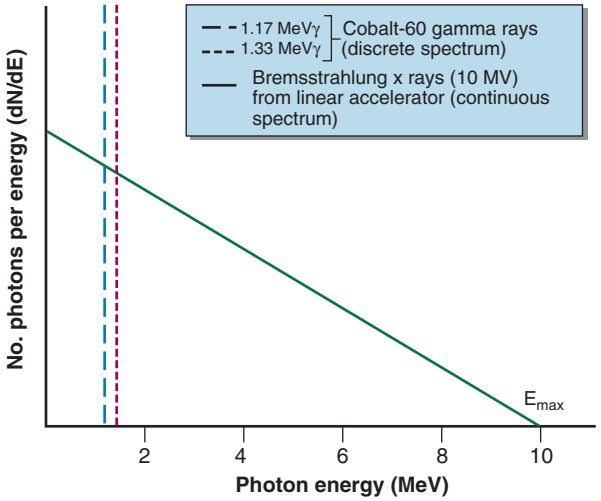


Figure 6-7 Discrete and continuous photon spectra. The discrete spectrum is characteristic of photons emitted by radioactive material. The continuous spectrum is characteristic of polyenergetic bremsstrahlung x-rays emitted by a linear accelerator. E_{max}, 10 MeV.

Radiation Production by Other Accelerators

Other accelerator techniques have been used to produce a variety of high-energy particles such as electrons, protons, neutrons, and higher Z ions. These techniques include the betatron,[10] van de Graaff accelerators,[11] cyclotrons,[16] the racetrack microtron,[17] and accelerators[18] used for high-energy physics experiments.

Among high-energy particles, protons have become the most attractive for therapeutic uses, where proton energies of 230 to 250 MeV yield treatment depths of up to 30 to 40 cm. Although currently an expensive technology to build ($50 to $150 million) and maintain, the use of high-energy protons for treatment is increasing with approximately 15 operating proton facilities in the United States, 50 sites in other nations (including a few for carbon ions), and 40 sites under construction or in the planning stages worldwide.[19] Typically, a large-scale proton facility has a single cyclotron with a beam line that is split to service two to four treatment rooms, each with either a fixed treatment beam or a movable gantry to aim the proton beam. An alternative design includes the use of a smaller (though still large) cyclotron in a single treatment room (one cyclotron per treatment room) that is mounted on a large double-legged gantry system that enables rotation about the patient. Facility designs and technical aspects for proton therapy are available.[20]

INTERACTIONS OF IONIZING RADIATION WITH MATTER

Photon Interactions

Attenuation and Transmission

When incident on matter, ionizing photon radiation undergoes interactions with atomic electrons or nuclei. Interacting photons are removed from the primary beam, an effect called *attenuation.* Photons that do not interact and instead exit the material are called *transmitted photons.* Attenuation and transmission are illustrated in Figure 6-8. A number, N_0, of monoenergetic x-rays or gamma rays is incident to a slab of material, and a smaller number, N, is transmitted. The attenuated photons, numerically equal to $N_0 - N$, are absorbed in the material or scattered in other directions. In narrow-beam geometry, N-transmitted photons alone reach a detector as shown. In broad-beam geometry, scattered photons also reach the detector.

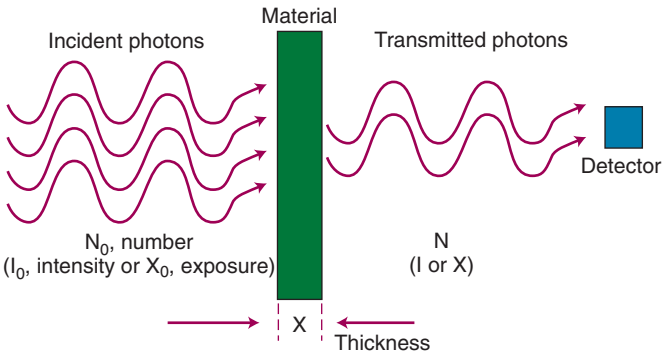


Figure 6-8 Attenuation and transmission. A number, N_0, of monoenergetic x- or gamma rays is incident to a slab of material, and a smaller number, N, is transmitted. The attenuated photons, N_0 and N, are absorbed in the material or scattered in another direction.

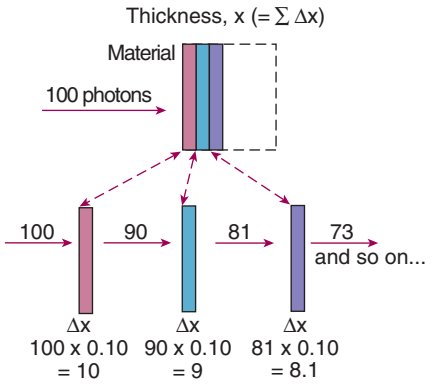


Figure 6-9 Attenuation through successive slabs of material.

Megavoltage photon interaction probabilities are less than 1, typically 2% to 4% per cm in tissue, depending on the incident photon energy, the atomic number of the interaction material, and the interaction type. By physical law, the fractional number of unattenuated photons interacting per unit thickness of a material is constant, such that

$$\frac{\Delta N/N}{\Delta x} = -\mu \quad \text{or} \quad \frac{\Delta N}{N} = -\mu \Delta x \qquad \text{Eq. 1}$$

In the equation, ΔN is the change in the number of photons as the result of attenuation, N is the number of incident photons, μ is a constant that represents the constant fractional attenuation per thickness (called the *linear attenuation coefficient*, with units of length^{-1} [cm^{-1}]), Δx is the thickness traversed by the photons for attenuation ΔN, and the minus sign indicates that the effect is negative, resulting in fewer photons—the attenuation process decreases the number of photons in a beam.

Constant fractional attenuation per unit thickness compounds over successive thicknesses, illustrated in Figure 6-9. This "fraction of a fraction" effect is nonlinear, and the integrated form of Equation 1 yields an important relationship: attenuation in a continuous material is an exponential process:

$$N(x) = N_0 e^{-\mu x} \quad \text{or} \quad \frac{N(x)}{N_0} = e^{-\mu x} \qquad \text{Eq. 2}$$

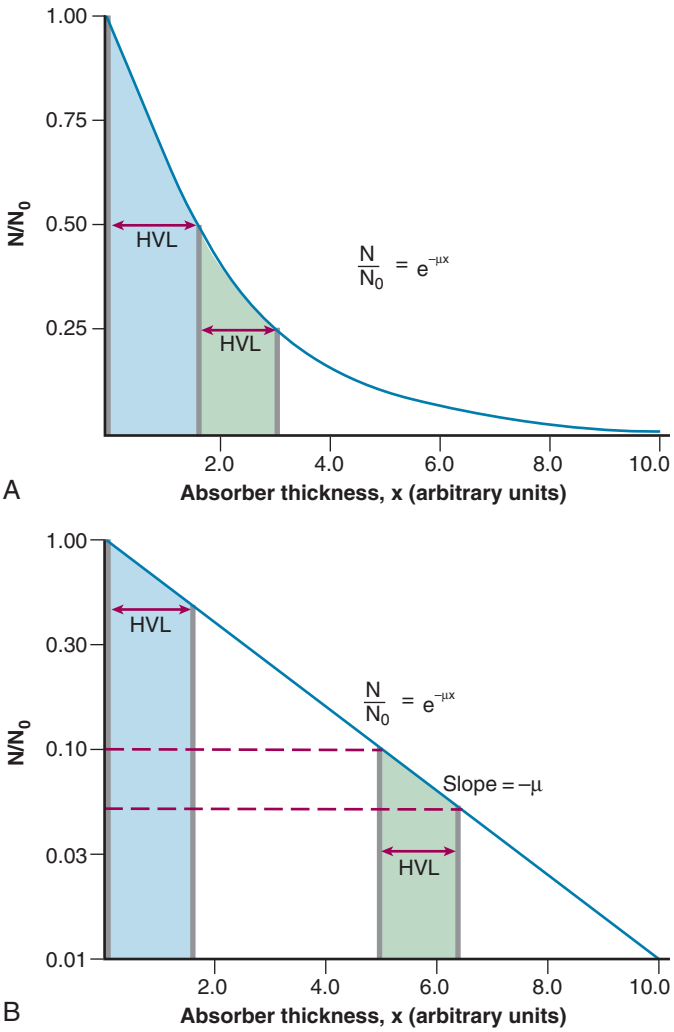


Figure 6-10 Graphic representation of attenuation. **A,** Linear plot. **B,** Semi-log plot. *HVL*, Half-value layer.

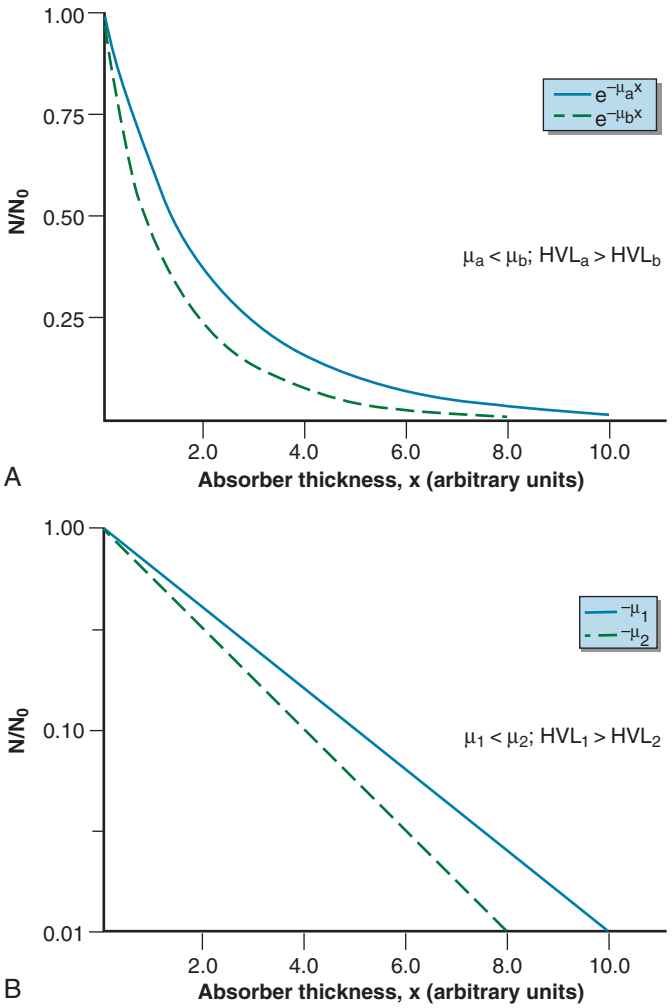


Figure 6-11 Attenuation for two different materials, indicated by the subscripts a and b. **A,** Linear plot. **B,** Semi-log plot. *HVL*, Half-value layer.

In Equation 2, N_0 is the original number of incident photons, $N(x)$ is the transmitted (unattenuated) number of photons, e is Euler's constant ($e \approx 2.7$), μ is the linear attenuation coefficient, and x is the thickness traversed by the photons.

Exponential attenuation is valid for monoenergetic photons and all homogeneous materials in narrow beam geometry and applies to other radiation quantities such as intensity (I) and exposure (X):

$$I = I_0 e^{-\mu x} \quad \text{or} \quad \frac{I}{I_0} = e^{-\mu x} \quad \text{and} \quad X = X_0 e^{-\mu x} \quad \text{or} \quad \frac{X}{X_0} = e^{-\mu x} \qquad \text{Eq. 3}$$

The linear attenuation coefficient is unique for each photon energy and element or material but varies with absorber density. Attenuation coefficients are discussed more fully with radiation interactions.

Equation 2 can be graphed in linear or semi-log form (Figure 6-10). In semi-log form, the attenuation curve is a straight line with a slope of −μ (Figure 6-10, *B*). A smaller attenuation coefficient results in less attenuation and a shallower attenuation curve. Different attenuation coefficients for different materials or different photon energies result in a different amount of attenuation for the same thickness traversed and attenuation curves that differ in their slopes (Figure 6-11).

Beam Quality

Beam quality is a term used to describe the amount of penetration by a photon radiation beam. One indicator of quality is beam energy, defined by accelerating potential, effective energy, or gamma ray energy. Another indicator is the half-value layer (HVL). HVL is the thickness of a material that reduces the transmitted intensity to one half of the original intensity. When $I/I_0 = ½$, the thickness, x, is the HVL, and the attenuation equation becomes

$$\frac{I}{I_0} = \frac{1}{2} = e^{-\mu \text{HVL}} \qquad \text{Eq. 4}$$

Two important relationships come from this equation:

$$\mu = 0.693/\text{HVL} \text{ and } \text{HVL} = 0.693/\mu$$

Thus, given the linear attenuation coefficient, the HVL can be computed, and vice versa. For example, if $\mu = 0.10\ \text{cm}^{-1}$, the HVL = $0.693/0.10\ \text{cm}^{-1}$ = 6.93 cm, and if HVL = 10 cm, μ = $0.693/10\ \text{cm} = 0.0693\ \text{cm}^{-1}$. Notice that the units for HVL are the reciprocal of the units for μ.

Because $e^{-\mu \text{HVL}} = ½$, and given a thickness of material in units of HVL ($x = n$ *HVL*, n equals the number of HVLs), the amount of attenuation can be computed by

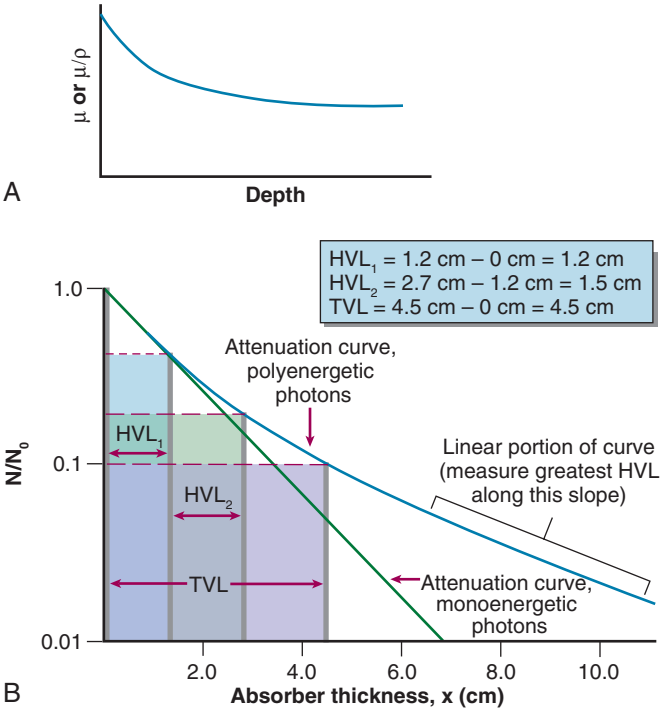


Figure 6-12 Attenuation for polyenergetic photons. **A,** Variation in attenuation coefficient as a function of depth for polyenergetic photons. **B,** Attenuation curve for polyenergetic photons. *HVL*, Half-value layer; *TVL*, tenth-value layer.

$$\frac{I}{I_0} = \left(\frac{1}{2}\right)^n \qquad \text{Eq. 5}$$

In Equation 5, I/I_0 is the fractional transmission, intensity, or exposure and n is the thickness of the material, expressed as the number of HVLs. This equation is valid for positive integer and noninteger values of n (e.g., $n = 1, 2, 5.9, 100.1$, etc).

Similar to HVL, the tenth-value layer (TVL) is the thickness required to reduce the number, intensity, or exposure by a factor of 10:

$$\frac{I}{I_0} = \frac{1}{10} = e^{-\mu TVL} \quad \text{and} \quad \frac{I}{I_0} = \left(\frac{1}{10}\right)^m \qquad \text{Eq. 6}$$

In Equation 6, m is the thickness of the material given in number of TVLs.

HVL can be found graphically from the attenuation curve, whether on a linear or log plot (see Figure 6-10) and for monoenergetic photons can be determined anywhere along the curve because μ is constant; the ratio of the two intensities must be ½. For polyenergetic photons, μ is not constant but instead decreases with increasing depth (Figure 6-12, *A*). The low-energy component of the beam spectrum is attenuated preferentially, compared with high-energy photons because of increased attenuation at low energies. As depth increases, the ratio of high-energy to low-energy photons increases, resulting in increased beam penetration, or "beam hardening." After a large number of low-energy photons are attenuated at depth, additional beam hardening is minimal and μ is essentially constant. The log attenuation curve begins steeply, has curvature, and then becomes linear at depth (Figure 6-12, *B*). Because μ changes with depth, HVL also changes, yielding different first and second HVLs, as defined in Figure 6-12, *B*. The monoenergetic case is shown for comparison. For a polyenergetic beam HVL_1 is always less than HVL_2 because photons incident on HVL_2 have a higher average energy, thus $HVL_1 < HVL_2$. The greatest HVL is found at maximum depth, on the linear portion of the attenuation curve where beam hardening is the greatest. For polyenergetic photon beams, an effective attenuation coefficient (μ_{eff}) can be calculated by determining an effective HVL over a region of interest and then calculating μ_{eff}:

$$\mu_{eff} = 0.693/HVL_{eff}$$

Characteristics of attenuation curves for monoenergetic and polyenergetic photons are summarized in Table 6-6.

TABLE 6-6 Characteristics of Attenuation Curves

Monoenergetic	Polyenergetic
1. Exponential curve on linear scale	1. Complex exponential curve on linear scale
2. Linear curve on semi-log scale	2. Curved on semi-log scale
3. Constant μ	3. Varying μ/μ_{eff} can be determined
4. Constant HVL	4. Varying HVL/HVL_1, HVL_2, TVL, and greatest HVL can be determined

HVL, *Half-value layer;* TVL, *tenth-value layer. See text for other terms.*

Attenuation Coefficients

The linear attenuation coefficient is one representation of photon interaction probabilities. Another form, the mass attenuation coefficient, μ/ρ, is the linear attenuation coefficient divided by the material's density, ρ, and has units of cm^2/g. It is independent of material density and is the form of attenuation coefficient commonly found in physics data tables, presented according to incident photon energy and the attenuating element or material. Its use in attenuation computations requires the density of the material according to

$$\frac{I}{I_0} = e^{-\frac{\mu}{\rho}\rho x} \qquad \text{Eq. 7}$$

Attenuation coefficients can also be expressed in other forms and can be converted from one form to another.[21]

Photon Interactions: X-Rays and Gamma Rays

Attenuation of photon beams is the result of interactions in the intercepting material. There are five most common photon interactions: coherent scattering, photoelectric effect, Compton effect, pair production, and photodisintegration. Each interaction type has an independent interaction probability and contributes to the amount of attenuation. The total linear and mass attenuation coefficients are given by the sum of their components:

$$\mu_{TOT} = \mu_{COH} + \mu_{PE} + \mu_{CE} + \mu_{PP} + \mu_{PD}$$

and

$$\mu/\rho_{TOT} = \mu/\rho_{COH} + \mu/\rho_{PE} + \mu/\rho_{CE} + \mu/\rho_{PP} + \mu/\rho_{PD}$$

In the previous equations, TOT signifies the total coefficient and COH, PE, CE, PP, and PD refer to the respective five interactions. The photoelectric effect, Compton effect, and pair production are the most important interactions for megavoltage photons used for radiotherapy. Detailed presentations of these five interactions have been published.[2,21,22]

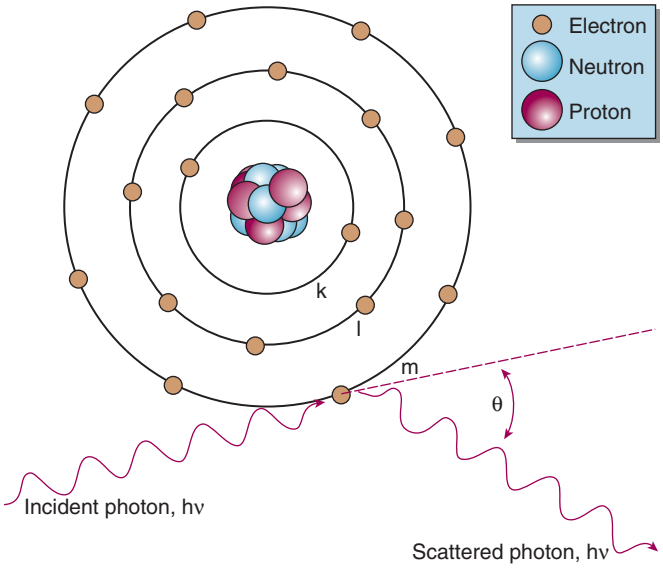


Figure 6-13 Coherent scattering.

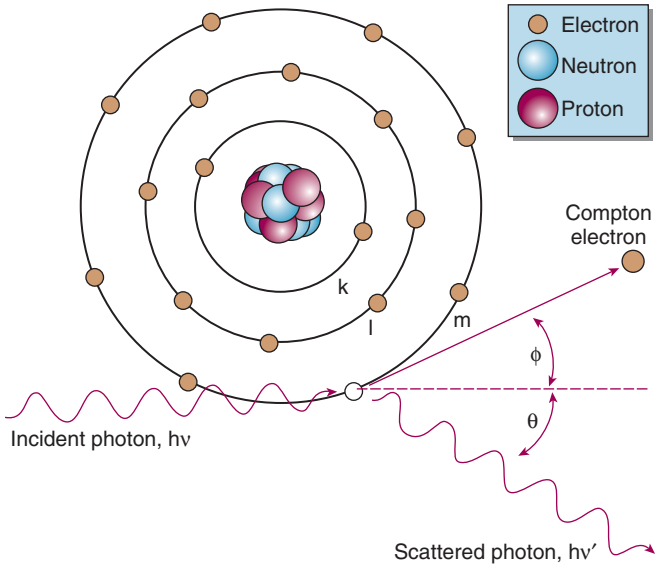


Figure 6-15 Compton effect.

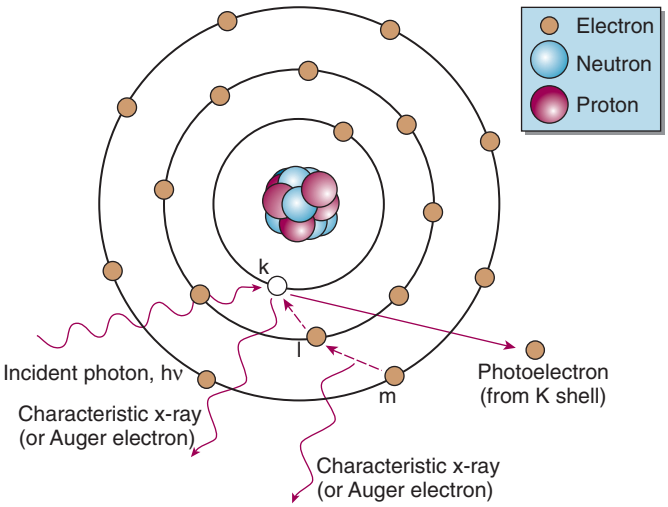


Figure 6-14 Photoelectric effect.

Coherent Scattering

In coherent scattering, a photon is scattered off an outer orbital electron with a change in direction and no change in energy (Figure 6-13). At very low energies (<10 keV), the amount of coherent scattering can be large and attenuation can be high, even though there is no change in photon energy. The amount of coherent scattering is negligible in the diagnostic and therapy energy ranges compared with other principal interactions.

Photoelectric Effect

The following actions occur in the photoelectric effect (Figure 6-14):

1. An incident photon with energy, $E\gamma = h\nu$, interacts with the inner orbital electron with binding energy E_B (most tightly bound). The interaction can occur with other orbital electrons, but the most probable interaction is with the innermost electron.
2. The photon is completely absorbed and no longer exists.
3. The orbital electron, now called the *photoelectron*, is ejected with kinetic energy, E_{pe}, equal to the photon energy minus the binding energy:

$$E_{pe} = E\gamma - E_B$$

If $E\gamma$ is less than E_B, the interaction cannot occur, but the interaction may occur with another orbital electron with a binding energy less than $E\gamma$.

4. Ejection of the orbital electron leaves a vacancy in the inner electron shell. This vacancy is filled by an electron from one of the outer orbitals, with the simultaneous emission of a characteristic x-ray with an energy of E_{cx} equal to the difference of the two electron binding energies (Figure 6-15):

$$E_{CX} = E_{B1} - E_{B2}$$

5. This process leaves a new vacancy in an outer orbital shell, which is filled by an electron from an orbital beyond, with emission of a second characteristic x-ray of lower energy than the first. This cascade of vacancy creation, filling, and characteristic x-ray emission continues until the most outer orbital electron shell has a vacancy that is filled by a "free," or unbound, electron.
6. A competing process to characteristic x-ray emission is the production of an Auger (pronounced "oh-jhay") electron. In this process, the characteristic x-ray energy, E_{CX} , is transferred to one of the nearby orbital electrons with no x-ray emission, and the electron, called an *Auger electron*, is ejected with energy:

$$E_{AU} = E_{CX} - E_{B2} = E_{B1} - 2E_{B2}$$

Characteristic x-rays are so named because their energies are directly related to the unique energy levels of the electron orbits for an element. A material's elemental composition can be determined by detecting its characteristic x-rays. Characteristic x-rays are named for the orbital electron transition that occurred. For instance, a K_α x-ray results in the *L* shell electron filling the K shell vacancy, an M → K transition yields a K_β x-ray, and an M → L transition yields an L_α x-ray.

For an atom with five electron orbitals, the possible electron transitions and their characteristic x-rays after a photoelectric

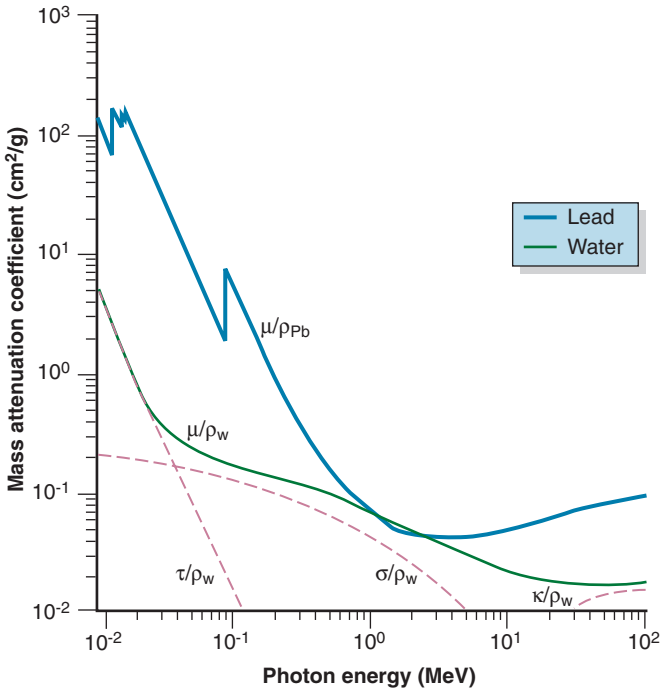


Figure 6-16 Total mass attenuation coefficients for lead and water. Individual interaction coefficients for water *(dashed lines)* also are shown. *Data from Radiological health handbook. Bethesda, MD, U.S. Department of Health, Education, and Welfare, 1970; and Evans RD: The atomic nucleus. Malabar, FL, 1955, Robert E. Krieger Publishing.*

interaction are L → K, M → L, N → M, O → N, M → K, N → K, O → K, N → L, O → L, and O → M. The most probable transitions are those between adjacent orbitals: L → K, M → L, N → M, and so forth. At the same time, Auger electron emission competes with characteristic x-ray emission, at a rate given by w, the fluorescence coefficient.

The photoelectric effect has a strong dependency on photon energy and atomic number of the material. The mass attenuation coefficient varies as $(1/E\gamma)^3$ and Z^3, respectively. Mathematically, this is shown as follows, where CPE is a proportionality constant:

$$\mu/\rho_{PE} = C_{PE} Z^3/(E\gamma)^3 \qquad \text{Eq. 8}$$

These dependencies for water are shown graphically in Figure 6-16. In the photoelectric effect, no interaction is possible until the photon energy is greater than the electron binding energy. After the binding energy is barely exceeded, the probability for interaction increases greatly, leading to a sharp increase in μ/ρ_{PE}, called an *absorption edge*. In Figure 6-16, the *K* and *L* edges for lead are seen, corresponding to photoelectric interactions for the *K* and *L* shell electrons. No absorption edges are shown for water; the binding energies are less than 1 keV and do not show up on the graph.

The dependence on *Z* and E_γ can be used to approximate the photoelectric contribution in a different material, using the formula:

$$\mu/\rho_{PE,2} = \mu/\rho_{PE,1}(E_{\gamma,1}/E_{\gamma,2})^3(Z_2/Z_1)^3 \qquad \text{Eq. 9}$$

If the material *(Z)* is constant but energy is changed, the new photoelectric mass attenuation coefficient is found by:

$$\mu/\rho_{PE,2} = \mu/\rho_{PE,1}(E_{\gamma 1}/E_{\gamma 2})^3 \qquad \text{Eq. 10}$$

If the photon energy (E_γ) is constant but the attenuating material is changed, the new photoelectric mass attenuation coefficient is found by:

$$\mu/\rho_{PE,2} = \mu/\rho_{PE,1}(Z_2/Z_1)^3 \qquad \text{Eq. 11}$$

Compton Effect

In the Compton effect (see Figure 6-15), several events occur:

1. An incident photon with energy, $E\gamma = h\nu$ interacts with a loosely bound, outer orbit electron.
2. The photon is scattered at some angle with reduced energy $E'\gamma = h\nu'$.
3. The orbital electron, now called the recoil or Compton electron, is ejected with kinetic energy, E_{ce}, equal to the difference between the incident and scattered photon energies:

$$E_{ce} = E_\gamma - E'_\gamma$$

4. Because the interaction is with the outer shell electron, which has negligible binding energy, there are no characteristic x-rays or Auger electrons produced.

The distribution of energies and scattering angles for the Compton photon and electron can be described mathematically. The scattered photon has energy $E'\gamma = h\nu'$ given by

$$h\nu' = \frac{h\nu}{1+\alpha(1-\cos\theta)} = \frac{m_o c^2}{1+\left(\frac{1}{\alpha}-\cos\theta\right)} \qquad \text{Eq. 12}$$

In Equation 12, $\alpha = h\nu/m_o c^2$ and represents the ratio of the incident photon energy to the rest mass of the electron, m_o, and θ is the angle of photon scattering as defined in Figure 6-15.

The Compton electron has energy E_{ce} given by the following equation:

$$E_{ce} = h\nu\frac{\alpha(1-\cos\theta)}{1+\alpha(1-\cos\theta)} \qquad \text{Eq. 13}$$

and a scattering angle, ϕ, that depends on the incident photon's energy and its scattering angle, θ:

$$\cos\phi = (1+\alpha)\tan\frac{\theta}{2} \qquad \text{Eq. 14}$$

Selected scattering cases can be considered:

1. The minimum energy transfer occurs for a 0-degree photon scatter; there is no interaction, and the "scattered" photon has the same energy as the incident photon. The electron is scattered at 90 degrees (ϕ = 90 degrees) with zero energy.
2. The maximum energy transfer occurs for a direct hit with a backscattered photon (θ = 180 degrees) and yields a (minimum) scattered photon energy of

$$h\nu' = \frac{h\nu}{1+2\alpha} \qquad \text{Eq. 15}$$

The backscattered Compton photon energy will always be less than and will approach 0.25 MeV (which equals ½ $m_o c^2$) even as the incident photon energy becomes very large. The electron has maximum energy of $E_{ce} = h\nu - h\nu' = h\nu\,(2\alpha/[1+2\alpha])$ and travels in the forward direction.

3. A 90-degree Compton scattered photon has energy:

$$h\nu' = \frac{h\nu}{1+\alpha} \qquad \text{Eq. 16}$$

The 90-degree scattered Compton photon energy will always be less than and will approach 0.511 MeV (which

equals $m_o c^2$) even as the incident photon energy becomes very large. The electron has energy of $E_{ce} = h\nu - h\nu' = h\nu\,(\alpha/[1+\alpha])$, and it travels in a direction that depends on the incident photon energy.

Although isotropically distributed for lower-energy photons, Compton electrons scatter more and more in the forward direction as incident photon energy increases. Their average energy also increases from about 10 keV to 7 MeV as incident photon energy increases from about 100 keV to 10 MeV.[11] The forward-peaked distribution is responsible for the buildup region for megavoltage photon beams, as explained later.

The Compton effect has a slight dependency on incident photon energy, decreasing as energy increases through the megavoltage range, but the interaction probability is essentially constant over most of the megavoltage energy range (Figure 6-16). Compton scattering is independent of atomic number and is dependent on the number of electrons available, or electron density (electrons per gram). The electron density for almost all materials is constant at approximately 3×10^{23} electrons per gram because the N/Z ratio is almost constant. The exception is hydrogen, which with one proton in the nucleus has an electron density of around 6×10^{23} electrons per gram. Except for a small energy dependency and increased interaction probabilities for hydrogen-laden materials, the Compton mass attenuation coefficient is remarkably constant across energy and atomic number, especially for low Z biologic materials such as tissues. Mathematically, this relationship is

$$\mu/\rho_{CE} = C_{CE} \qquad \text{Eq. 17}$$

In Equation 17, C_{CE} is almost a constant.

Attenuation by the Compton effect reduces to the following expression:

$$\left.\frac{I}{I_0}\right|_{CE} = e^{-C_{CE}px} \qquad \text{Eq. 18}$$

For unit thickness of a material, the transmitted amount depends only on material density, not atomic number and photon energy as with the photoelectric effect.

Pair Production

In pair production (Figure 6-17), the following steps occur:

1. An incident photon with energy $E_\gamma = h\nu$ and $E\gamma$ greater than 1.022 MeV passes near a heavy nucleus and spontaneously disappears, creating an electron, e^-, and a positron, e^+, in its place. These two particles are called an *electron-positron pair.* The total kinetic energy of the electron-positron pair, E_{ep}, is equal to the photon energy minus the energy needed to create two electrons, or 1.022 MeV (the rest energy of an electron is 0.511 MeV):

$$E_{ep} = E_\gamma - 1.022\ \text{MeV}$$

   The electron and positron travel off in no particular directions and do not have equal kinetic energies.
2. The electron gradually slows down and is stopped in the material.
3. The positron, the antiparticle of an electron, slows down quickly and annihilates with a free electron, giving off two 0.511-MeV photons (called *annihilation radiation*) that travel in opposite directions (i.e., at 180 degrees).

   The mass attenuation coefficient for pair production varies linearly with atomic number and incident photon energy (when the photon energy is above the threshold of 1.022 MeV):

$$\mu/\rho_{pp} = C_{pp} Z (E_\gamma - 1.022\ \text{MeV}) \qquad \text{Eq. 19}$$

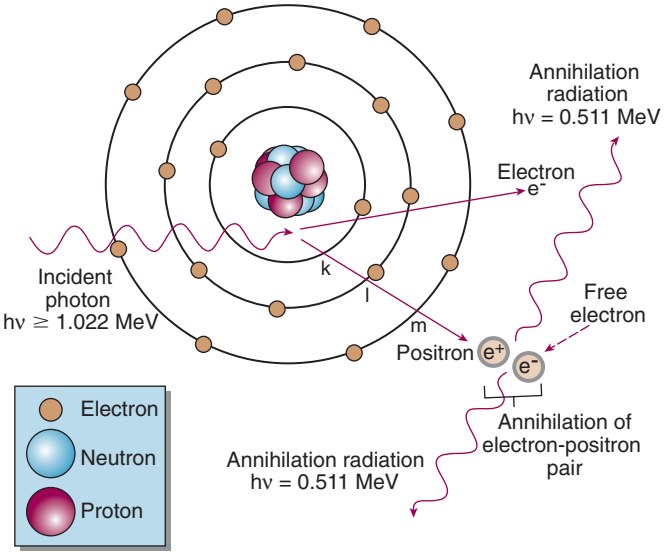


Figure 6-17 Pair production.

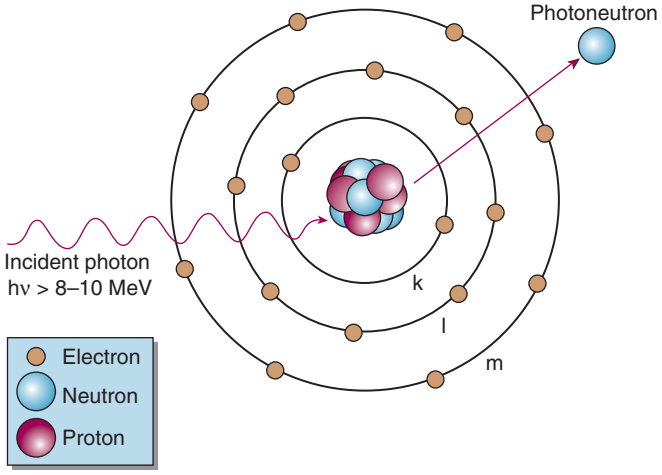


Figure 6-18 Photodisintegration.

Photodisintegration

Several steps occur in photodisintegration (Figure 6-18):

1. An energetic photon of $E\gamma$ greater than 8 to 10 MeV interacts with the atomic nucleus.
2. The photon penetrates the nucleus and is absorbed. The energy deposition results in the emission of a neutron or proton.
3. Neutron emission leaves a fragmented, possibly unstable nucleus (i.e., radioactive), prompting the name *photodisintegration.*

An energy of greater than 8 to 10 MeV is required because the nuclear binding energies for nucleons are 8 to 10 MeV for most materials. Photodisintegration is the interaction responsible for neutron production for photon energies at 10 MeV and greater and can be an important consideration for facility shielding for photon beams of 15 MeV and greater.

Distribution of Secondary Electrons

Electrons released by ionizing photon interactions can travel in any direction from the interaction point and in general have a complex probability for angular spread, depending on incident photon energy and the interaction that occurs. The

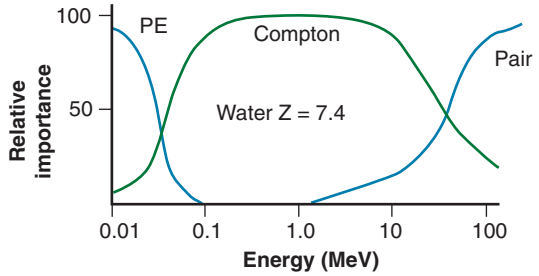


Figure 6-19 Relative importance of photon interactions as a function of photon energy.

probability for forward directions increases with photon energy and is a likely direction for megavoltage photon interactions.[2] As seen later, angular scattering of electrons is responsible for a number of characteristics for megavoltage photon beams, including surface dose, the buildup region, the depth of maximum dose, and the penumbra region.

Total Attenuation Coefficient

Each radiation interaction contributes its part to the total attenuation coefficient. Photons having the same energy can undergo any one of the five interactions when energetically possible. However, the probability for each interaction is different and in a particular energy range a particular interaction will dominate.

In Figure 6-16, the individual interaction and total mass attenuation coefficients are shown as a function of energy for lead and water. Notice the *K* edge in the curve for lead. It can be seen that different energy regions are dominated by particular interactions. For water, the photoelectric effect dominates for photon energies up to 60 keV, the Compton dominates from 60 keV to 10 MeV, and pair production dominates approximately above 10 MeV. For lead, the photoelectric effect dominates up to 700 keV, the Compton effect from 700 keV to 3 MeV, and pair production at 3 MeV and higher. An interaction's region of dominance can be represented graphically to show relative importance as a function of energy (Figure 6-19).

Comparison of interaction dependencies shows why diagnostic energy photons give good contrast for imaging: the photoelectric effect dominates and is quite sensitive to the atomic numbers of the materials being imaged. Materials with even slightly different *Z*s have good subject contrast (and image contrast) because attenuation depends on the cube of the atomic numbers. Radiotherapy portal images, however, have poor contrast because the dominant interaction is the Compton effect. There is no dependence on atomic number, and the effect is constant for most biologic materials (except for hydrogenous materials). Instead of imaging atomic number, the Compton effect images the density of a material, and subject contrast and image contrast are essentially representations of differences in material densities. A comparison of simulator and port images is given later (see Figure 6-49).

Total Absorption Coefficient

Radiation dose relates directly to the amount of energy absorbed at a point, not the amount attenuated, although the two are intimately related. This transfer of energy is done by secondary electrons (photoelectrons, Compton electrons, and the electron-positron pair) that produce a large number of ionizations along their paths until their energy is expended. A portion of the photon energy that is attenuated may escape to other regions as a coherent or Compton scattered photon, an annihilation photon (0.511 MeV), or a bremsstrahlung photon after radiative collision of a secondary electron. The amount of energy absorbed from secondary electrons is less than the amount attenuated as photons, as described by Johns.[21] In a similar fashion to the total mass attenuation coefficient, the total mass *energy absorption* coefficient, μ_{en}/ρ, or simply the mass *absorption* coefficient, describes the energy absorbed resulting from each interaction and is used for computing dose. The value of μ_{en}/ρ is first equal to μ_{TOT}/ρ in the photoelectric region (because all photon energy is transferred to the photoelectron), and then μ_{en}/ρ is less than μ_{TOT}/ρ in the region where the Compton effect dominates (because the Compton scattered photon carries energy away that does not contribute dose to the local region). At very high energies where pair production dominates, μ_{en}/ρ and μ_{TOT}/ρ are almost equal because the fraction of incident photon energy carried off as annihilation photons is negligible compared with the amount transferred to kinetic energy of the electron-positron pair. Over the energy range used for radiotherapy, the amount of absorbed energy at a point in water (tissue) is about one half the amount attenuated at the point. The mass absorption coefficient and dose are discussed more in the next section.

Summary of Photon Interactions

1. Coherent scattering occurs at very low photon energies (<10 keV).
2. The photoelectric effect dominates up to 60 keV in water, with strong dependencies of Z^3 and $1/E^3_\gamma$ for other materials.
3. The Compton effect dominates from 60 keV to about 10 MeV in water, with some dependence on energy or atomic number. Compton scattering depends only on the number of electrons per gram, which is almost constant for all materials ($N_g \approx 3.0 \times 10^{23}$, except for hydrogen, for which $N_g \approx 6.0 \times 10^{23}$).
4. Pair production occurs for photon energies only above 1.022 MeV, dominates above 10 MeV in water, and linearly depends on *Z* and photon energy.
5. Photodisintegration occurs at photon energies above 10 MeV and is responsible for the creation of neutrons in a linear accelerator facility.
6. At diagnostic photon energies, image contrast is determined primarily by differences in atomic numbers of materials being imaged because the photoelectric effect depends strongly on *Z*. Material thickness and density are secondary determinants.
7. At therapeutic photon energies, image contrast is provided by the densities of materials being imaged because the Compton effect depends on the number of electrons per gram, not the atomic number, of a material.
8. The total mass attenuation coefficient describes the amount of attenuation from all processes. A portion of the energy attenuated from the beam is deposited by secondary electrons as dose. The amount of energy absorbed as dose is described by the total mass absorption coefficient, which tracks the total mass attenuation coefficient and is numerically less.

Charged Particle Interactions

Charged particles incident on matter undergo inelastic and elastic interactions with atomic electrons and nuclei, that is, other charged entities.[2,12,13] Inelastic interactions include collisional and radiative processes and result in energy loss by the particle. In an elastic interaction the particle is scattered by an atomic electron or nucleus, resulting in a change of direction for the particle but no energy loss. The interaction probability for charged particles is effectively 1; an incident charged particle interacts at every opportunity. The quotient dE/dx (units of million electron volts per centimeter) is called the *stopping power,* and for charged particles it describes the rate of

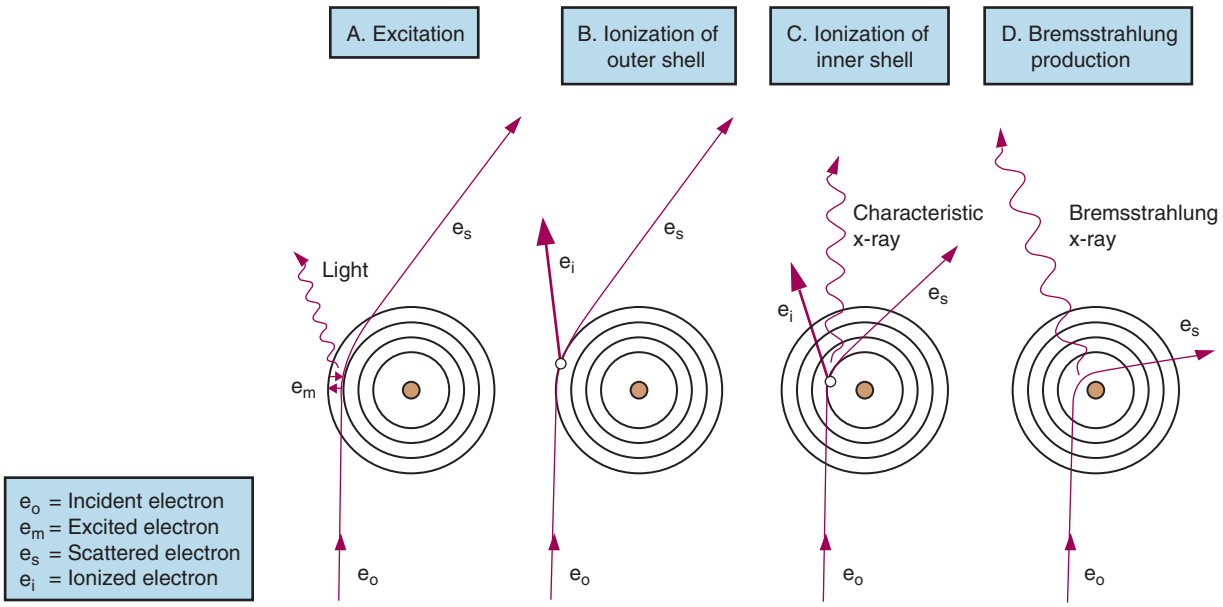


Figure 6-20 Electron interactions. **A,** Excitation. **B,** Ionization of outer shell. **C,** Ionization of inner shell. **D,** Bremsstrahlung production.
Adapted from Johns HE, Cunningham JR: The physics of radiology, ed 3, Springfield, IL, 1978, Charles C Thomas.

energy loss, dE, that occurs over distance traveled, dx, for inelastic collisions. Stopping power is often expressed as the mass stopping power, $dE/\rho dx$ (units of million electron volts per gram per square centimeter), which is independent of the absorber density. Because energy loss is almost continuous and a particle has a particular kinetic energy, E_{KE}, the particle loses this amount of energy and then stops. The distance traveled is finite and is called the *particle range;* the particle can go no farther, and its kinetic energy is zero. For an absorber of density ρ, the particle range, r, can be calculated as follows:

$$r = E_{kE} \frac{1}{\frac{dE}{\rho dx}} \frac{1}{\rho} \qquad \text{Eq. 20}$$

The energy lost through inelastic collisions depends on the particle mass, charge, and kinetic energy and on the mass and charge of the target atom, according to the formula:

$$\frac{dE}{dx} = \frac{2\pi z^2 e^4}{m_o V^2} NZF_Q \qquad \text{Eq. 21}$$

In Equation 21, z is the atomic number of the incident particle of mass M, V is its velocity, e is the electron charge, m_o is the electron mass, NZ is the number of electrons per cubic centimeter in the absorber, and F_Q is a complex function describing energy transfer per interaction.

Collisional energy losses increase by the square of the particle's atomic number and as the incident particle velocity decreases. Increased atomic number results in a greater coulomb force, and decreased velocity increases the amount of interaction time, both leading to increased dE/dx. The energy transfer function, F_Q, is complex and varies with the type of interaction.[2] It accounts for the atomic mass of the absorber, ionization potential, and relativistic effects as V approaches the speed of light.

Light Charged Particle Interactions: Electrons

The electron mass is small compared with any atomic mass, and incident electrons undergo four types of particle interactions with a large amount of scattering.[8] Collisional

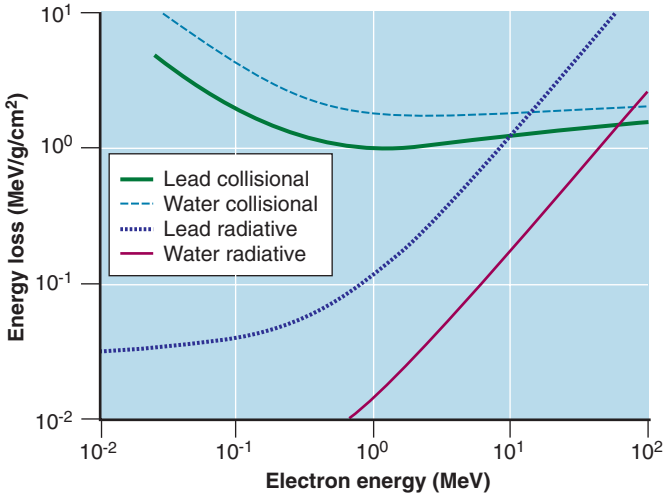


Figure 6-21 Collisional and radiative electron losses as a function of incident electron energy.
Adapted from Johns HE, Cunningham JR: The physics of radiology, ed 3, Springfield, IL, 1978, Charles C Thomas.

interactions result in energy loss of dE_{COL}/dx, causing ionizations or excited states (higher electron orbits) (Figure 6-20). Collisional losses increase as the electron velocity decreases, as stated previously, and decrease as the absorber atomic number increases. The decrease with absorber atomic number results from the decrease in the number of electrons per gram (NZ/ρ) as Z increases. For equivalent mass thicknesses (mass thickness is thickness divided by density, with units of square centimeters per gram), electrons are stopped sooner in low Z than in high Z materials. Figure 6-21 shows these relationships for water and lead.

Radiative interactions result in x-ray emissions. The incident electron penetrates the electron cloud and interacts with the nucleus's positive electrical field, undergoing an abrupt deceleration with energy loss dE_{RAD}/dx and a change in direction (see Figure 6-20, *D*). The energy change, dE_{RAD}/dx, is released in the form of x-rays, called *bremsstrahlung* (or

braking) *radiation.* With an incident monoenergetic electron fluence, a continuous x-ray spectrum is emitted because the probability of any energy loss, large or small, is equal per interaction. Successive bremsstrahlung interactions may occur as the electron loses its energy; a bremsstrahlung x-ray spectrum has a maximum energy equal to the initial electron energy and all other x-ray energies below this maximum to zero (see Figure 6-7). Radiative interactions are important; they are the mechanism by which bremsstrahlung x-rays are produced in diagnostic x-ray tubes and linear accelerators. Bremsstrahlung production increases with incident electron energy and the Z of the absorber (see Figure 6-21).

The probability for collisional and radiative interactions depends on electron energy and the atomic number of the incident material (see Figure 6-21). At electron energies of 100 keV and for high Z absorbers (e.g., x-ray targets), 99% of the interactions are collisional and 1% are radiative (x-ray production), resulting ultimately in heat deposition. At electron energies of 10 MeV, bremsstrahlung is a much more efficient process, and 50% of the interactions are collisional and 50% radiative. At 100 keV, x-ray production is inefficient, whereas at 10 MeV, x-ray production is efficient. Above 10 MeV, bremsstrahlung x-ray production exceeds collisional losses. It has been observed that dE_{COL}/dx increases as electron kinetic energy decreases below 1 MeV (see Figure 6-21). As the electron slows down, it loses energy faster. Above 1 MeV, electrons lose about 2 MeV/cm traveling in water ($dE_{COL}/dx \approx$ 2 MeV/cm). A 10-MeV electron has a range of about 5 cm in water (10 MeV ÷ 2 MeV/cm). Density scaling can be applied for materials different from unit density. For example, a 10-MeV electron travels approximately 3.3 cm in bone of density of 1.5 g/cm^3 (10 MeV ÷ [2 MeV/cm × 1.5]). These relationships use Equation 20 as their basis.

Heavy Charged Particle Interactions

Heavy charged particles, such as protons and alpha particles, experience mainly inelastic collisions. The rate of energy loss is high, resulting in short ranges. Trajectories in water or tissue are in the forward direction with little scattering; the particle mass is similar to that of the interacting material, and few large-angle direction changes occur, in contrast to the large amount of scattering experienced by electrons. Heavy charged particles exhibit rapidly increasing and large energy losses near the end of their ranges because of the dependency on Z^2 and $1/V^2$ discussed previously (see Eq. 21). This increase in energy loss results in a dramatic increase in ionization at the tail of the particle track length after a length of relatively constant loss, a phenomenon called the *Bragg peak.*[2,12,13] Bragg peaks are observable for protons (Figure 6-22) and alpha particles. All charged particles exhibit a Bragg peak, including electrons; however, electrons are light enough such that multiple scatters occur and ionization paths are randomly oriented, blurring any observable effect.

The proton finite range can be modulated through a physical attenuator or other means to decrease the range from the maximum. This process is essentially modulating the incident proton beam energy. If range modulation is done continuously while the beam is on, the Bragg peak will be swept over a range, called the Spread Out Bragg Peak (SOBP), and will produce a high dose plateau (see Figure 6-22). The width of the SOBP dose plateau can be designed to match a tumor size at a certain depth and demonstrates the attractiveness of protons for radiotherapy.

Heavy Uncharged Particle Interactions: the Neutron

Neutrons have no charge and do not undergo coulomb interactions like charged particles. Instead, neutrons interact by inelastic and elastic collisions with nuclei through the strong force. Commonly for lower and middle Z materials, a neutron penetrates the nucleus and is absorbed, followed by the ejection of a proton (the [n, p] reaction). The new nucleus may be radioactive, a process called *neutron activation.* Neutrons may also cause nuclear disintegrations, similar to photodisintegration. For very heavy nuclei, neutrons may cause fission, a reaction harnessed for power production in nuclear reactors. Elastic scattering of neutrons is also common. The type of collision, inelastic or elastic, that a neutron experiences depends on the neutron energy and the absorber atomic number with complex reaction probabilities.[18,21] Neutrons lack charge, thus for higher energy (nonthermal) neutrons their interactions with nuclei are exponential in nature, like photons (see Figure 6-22). Their range can be stated as a mean path length equal to the inverse of the neutron attenuation coefficient.

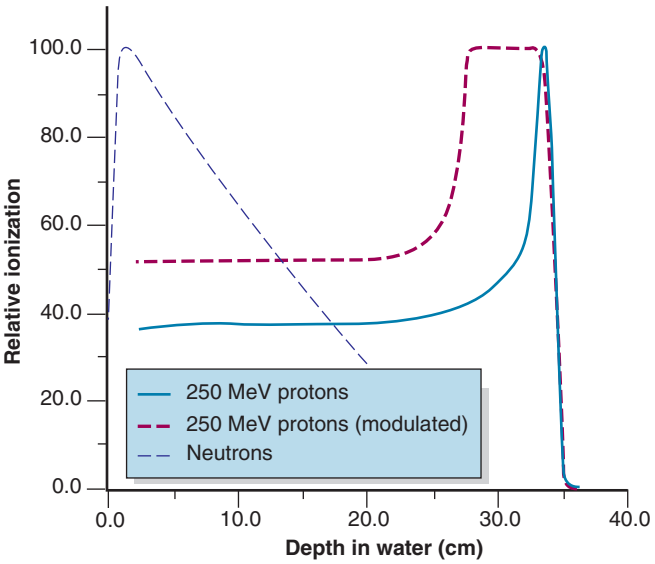


Figure 6-22 Ionization curves for heavy particles. Protons are charged and exhibit a Bragg peak at the end of their range. Neutrons are uncharged and are exponentially attenuated.
Data for protons from Miller DW: Update on proton radiotherapy. In Mackie TR, Palta JR, editors: Teletherapy: Present and future. Madison, WI, 1996, Advanced Medical Publishing.

Summary of Particle Interactions

1. Particles with kinetic energy have inelastic and elastic interactions with an absorbing material. Inelastic collisions result in loss of energy, whereas elastic collisions do not.
2. Electrons experience inelastic collisions through coulomb interactions with the atomic electrons or the nucleus. Collisional interactions with the atomic electrons result in excitation or ionization. Interactions with the nucleus result in production of bremsstrahlung x-rays.
3. For electrons, collisional energy losses dominate at lower energies, whereas radiative losses dominate at higher energies. Interestingly, collisional energy losses are greater per gram of low Z material than for high Z materials. The material of choice for electron shielding is a low Z material because the stopping power per gram is higher and bremsstrahlung production is minimized.
4. In water or tissue, megavoltage electrons lose about 2 MeV/cm traveled. The electron range is finite, and its length in centimeters is found by dividing the energy (in MeV) by 2.
5. Electron interactions result in a large amount of scattering, caused by the light mass of the electron relative to the nuclear mass of any absorber.

6. Charged heavy particles undergo inelastic collisions mainly through coulomb interactions with the atomic electrons, resulting in excitation or ionization. Nuclear interactions occur only at very high energies and do not include bremsstrahlung production.
7. Charged heavy particles have a finite range and experience a rapid increase in energy loss near the end of their track, dumping much of their remaining energy quickly and producing an ionization curve with a Bragg peak. This is of greatest interest for the use of protons for treatment, using range modulation to create an SOBP that covers a target at depth.
8. Neutrons experience inelastic and elastic collisions with nuclei, resulting in nuclear rearrangements that are followed by ionization events. Neutrons do not have a finite range.

RADIATION QUANTITIES AND MEASUREMENT

Ionization and Its Fate

Ionizing radiation is quantified by measuring the amount of ionization produced. The number of ions is directly proportional to the amount of energy imparted to a material. An average of 33.92 eV is required to produce one ion pair (ip) in air.[23] This number is called the *W value* (W = 33.92 *eV/ip* for air), and it is almost independent of the radiation energy. W for other gases is quite similar to that of air, and its uniformity from material to material relates to atomic energy levels and capabilities for transfer of excitation energy.[2] Note that several values for the W value have been determined over time; these variations are small and are responsible for the slight differences in the coefficients used for conversion of exposure to dose, as reviewed later.[22,23]

In four of the five photon interactions, energy is transferred from incident photons to produce ionization or secondary processes. This energy transfer results in radiation dose, and for each interaction it has origins as follows:

1. In coherent scattering there is no ionization. However, the scattered photon might be able to undergo an ionizing interaction.
2. In the photoelectric effect the inner shell electrons are ionized. The photoelectron is ejected and loses its energy by excitation and ionizations. Characteristic x-rays and Auger electrons are energetic enough to cause ionizations.
3. In the Compton effect the outer shell electrons are ionized. The scattered photons and the Compton (recoil) electrons may be energetic enough to cause ionizations.
4. In pair production there is no direct ionization of the atom. However, the electron and positron each have enough energy to cause ionizations, and annihilation radiation is energetic enough to cause ionizations.
5. In photodisintegration there is no direct ionization of the atom. However, the remaining atom (with one fewer neutron) may be unstable and decay by emission of ionizing particles and the ejected neutron may cause activation of other atoms, resulting in nuclear decay and ionizations.

If these ions are collected and measured, the amount of energy deposited can be determined.

Radiation Quantities and Units

Ionizing radiation is quantified using two important quantities: exposure and dose. A third quantity, kerma, is an important concept that relates to exposure and dose.

Exposure

Exposure, *X*, is the measurement of the amount of ionization produced by photon interactions per mass of air (charge per mass of air). The SI unit for exposure is a charge of 1 coulomb (C) per mass of 1 kilogram (kg): $X = C/kg$. The original unit of exposure, *X*, essentially as the first quantitative definition of radiation dose (circa 1933), is the roentgen *(R)*, named after the discoverer of x-rays, Wilhelm Conrad Roentgen:

$$1R = 2.58 \times 10^{-4} C/kg \text{ of air } (= 1 \text{ esu}/cm^3 \text{ in air})$$

In the previous expression, *C* (coulomb) is a unit of charge (or ionization) such that 1 ip = 1.6×10^{-19} C. The original definition of charge per volume, 1 R = 1 esu/cm^3, was based on the *e*lectrostatic *u*nit and is responsible for the odd units of the roentgen as now defined. Use of the roentgen as a radiation quantity remains quite common, particularly within the radiation protection field.

Several important concepts characterize exposure, *X*:

1. It is defined for all ionizations, primary and secondary, when produced and measured in air.
2. It is defined only for ionizing photons (x- and gamma rays), not electrons or other particles.
3. It is properly measured only under conditions of electronic equilibrium, and it is difficult to measure for photon energies higher than 3 MeV. Above this energy the electron range in air becomes too large for electronic equilibrium to be achieved practically.

Electronic Equilibrium

With electronic equilibrium, ionization lost downstream from a volume of interest is replaced by an equal amount from upstream, producing an equilibrium and an accurate ionization measurement. The concept is illustrated in Figure 6-23. After interaction, ionization (electrons) travels away from the interaction point in the direction of the incident photons and a portion actually leaves the volume of interest. To accurately measure the amount of ionization produced, the lost kinetic energy of the escaping electrons must be replaced by an equal amount that enters the volume from upstream (Figure 6-23). This equilibrium of energy flow is called *electronic equilibrium* or *charged-particle equilibrium* and is a required condition for measurement of exposure.

Dose

Dose, *D*, is the measurement of the amount of energy imparted per mass of material (energy per mass).[11] The unit of dose is the gray *(Gy)*: 1 Gy = 1 J/kg. An earlier dose unit is the rad *(rad)*: 1 rad = 100 erg/g = 0.01 Gy; 1 Gy = 100 rad. Although not an official unit, cGy, is often used because of its numerical equivalency to the rad: 1 cGy = 1/100 Gy = 1 rad. Thus, 100 cGy = 1 Gy.

Dose does not have the restrictions of exposure, and the following two statements therefore apply:

1. Dose is valid for any ionizing radiation at any energy (e.g., x-rays, gamma rays, e^-, e^+, n, p, α, Π).

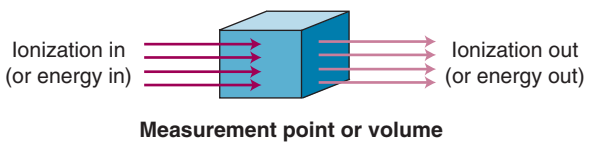


Figure 6-23 Ionization lost downstream from a volume of interest is replaced by an equal amount from upstream, producing electronic equilibrium and an accurate ionization measurement.

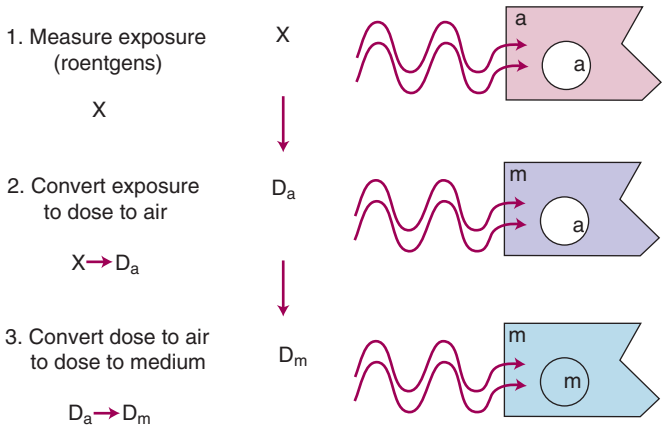


Figure 6-24 The dose measurement process. Exposure to a small mass of air is converted to the dose to medium.

2. Dose is valid for any material and phase: solid, liquid, or gas.

In practice, dose to a medium is determined by measuring exposure and converting it to dose using the W value and the mass energy absorption coefficient, μ_{en}/ρ. The mass energy absorption coefficient is similar to the mass attenuation coefficient, except it describes energy absorbed, not attenuated. The process is illustrated in Figure 6-24 for the following steps, using the original definition of exposure, the roentgen, and with the assumption of electronic equilibrium:

1. Exposure, X, of 1 R is given to a small air-filled cavity contained in a material:

$$X = 1R$$

2. Dose to air in the cavity is computed using the W value and the definition of the roentgen, converting energy units as needed:

$$D_a = WX = 33.92\ \text{eV/ip} \times 1\ \text{R}$$
$$\text{(converting units)} = (33.92\ \text{eV/ip})(1\ \text{ip}/1.6\times10^{-19}\ \text{coul}) \times (2.58\times10^{-4}\ \text{C/kg}/1\ \text{R}) \times (1.6\times10^{-12}\ \text{erg/eV}) \times (1\ \text{kg}/1000\ \text{g})$$
$$\text{(converting to Gy)} = (87.5\ \text{erg/g/R})(0.01\ \text{Gy}/100\ \text{erg/g})$$

so

$$D_a = 0.00875\ \text{Gy/R for an exposure of 1 R} \qquad \text{Eq. 22}$$

The coefficient of 0.00875 Gy/R is called the roentgen-to-gray conversion coefficient and is commonly expressed as the roentgen-to-centigray coefficient of 0.875 cGy/R. The important concept is that an exposure of 1 R, by definition, results in the energy release in air of 0.00875 Gy: 1 R → 0.00875 Gy (in air). This representation of exposure is called "air kerma"; it is the kinetic energies of charged particles released in air. Kerma and the Gray as a unit of dose are discussed later in greater detail.

For X number of roentgens, the dose to air is calculated as follows:

$$D_a = 0.00875\ \text{Gy/R}\ \text{X(R)} \qquad \text{Eq. 23}$$

3. Dose to the material is calculated by converting dose to air, D_a, to D_m. Conceptually, this step replaces the air cavity with an identical volume of the material. It can be shown[21,24] that

$$D_m = Da\left.\frac{\mu_{en}}{\rho}\right|_a^m \qquad \text{Eq. 24}$$

in which

$$\left.\frac{\mu_{en}}{\rho}\right|_a^m$$

is the mass energy absorption coefficient for the material,

$$\left.\frac{\mu_{en}}{\rho}\right|_m$$

divided by

$$\left.\frac{\mu_{en}}{\rho}\right|_a$$

the mass energy absorption coefficient for air.

Combining Equations 23 and 24 yields the following expressions:

$$D_m = \left.\frac{\mu_{en}}{\rho}\right|_a^m 0.875\ \text{cGy/RX(R)} \qquad \text{Eq. 25}$$

and

$$D_m = fX(R) \qquad \text{Eq. 26}$$

in which the f factor, f, is calculated as follows:

$$f = \left.\frac{\mu_{en}}{\rho}\right|_a^m 0.875\ \text{cGy/R} \qquad \text{Eq. 27}$$

For any exposure, $X(R)$, measured in air, the dose to a material substituted at that point can be found by multiplying the f factor by the exposure. In practice, the air-filled cavity is an ionization chamber that is inserted into the radiation beam and the ionization collected in the chamber is converted to dose using exposure-to-dose calibration factors in a prescribed procedure that accounts for the properties of the ionization chamber and particular radiation beam energy and irradiation geometry.

The f factor is an important parameter, and it varies as a function of the material and the photon energy, as shown for water, muscle, and bone in Figure 6-25. By its definition, the f factor for air is always 0.875 cGy/R. Water, muscle, and air have similar f factors because their effective atomic numbers are similar. Bone has a higher atomic number (by a factor of 2) and receives up to four times the dose that soft tissue would receive in the photoelectric region. This effect is responsible for high bone doses received during orthovoltage treatment as well as the contrast seen in diagnostic x-ray images. Notice the decrease in the f factor for fat in the photoelectric region because of its lower Z as a result of its high hydrogen content.

For treatment with ionizing radiation, the amount of energy deposited is quite small per fraction of dose. It takes about 1 million cGy to raise the temperature of 1 cm^3 of water by 1°C. Conversely, for a daily treatment dose of 2 Gy (200 cGy), the

increase in temperature per gram is only 0.0002°C. Thermal effects are non-existent for fractionated and radiosurgical radiation treatment.

Kerma

When photon radiation interacts with a material, energy is transferred to secondary electrons (the photoelectron, Compton electron, pair production electrons) and results in their kinetic energy. This transferred energy is called *kerma* (*k*inetic *e*nergy *r*eleased in *m*edium). Kerma, *K*, is expressed as the amount of energy released per mass of irradiated material and has the same unit as for dose, the gray (J/kg). For example and as reviewed previously, the amount of ionization produced (released) in air for 1 R of exposure is also the "air kerma," with conversion ratios of 1 R = 0.00875 Gy (air kerma) and 1 Gy (air kerma) = 114.3 R. Kerma differs from dose in that kerma is the energy *released* per mass, and dose is the energy *absorbed* per mass. These two quantities may be numerically quite similar, but there are three important aspects to their relationship:

1. The kerma at a point travels (primarily) in the forward direction for megavoltage photons. Secondary particles released at the point deliver their dose downstream from the point, not at the point. Kerma at an interaction point may result in a numerically equal dose at a downstream point of interest.
2. Even if at the same point of interest, kerma will be greater than dose, because secondary electrons may lose some of their energy by the bremsstrahlung process. The bremsstrahlung x-rays carry energy away from the point of interest. $D = K(1 - g)$, in which g is the fraction of energy lost to bremsstrahlung.
3. If electronic equilibrium is satisfied and bremsstrahlung is negligible ($g < 1$), dose equals kerma at the point of interaction. Thus, dose equals kerma, provided there is electronic equilibrium; this concept is key to radiation dose measurements.

Thorough treatments of exposure, dose, kerma, and their relationships are available.[12-14] Much has been studied and written about these and other dosimetric concepts to establish meaningful and consistent definitions. A summary is presented in Table 6-7.

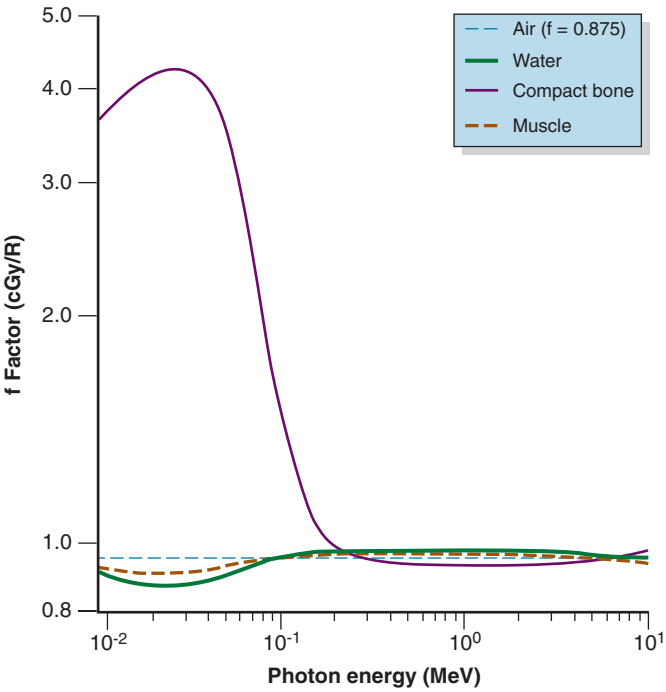


Figure 6-25 The f factor varies as a function of the material and the photon energy.
Data from Radiological health handbook. Bethesda, MD, 1970, U.S. Department of Health, Education, and Welfare.

Radiation Detection and Measurement

There are different types of radiation detection and measurement instruments with particular characteristics that enable measurements of a certain kind to be performed. General classes of instruments are gas-filled detectors, scintillation detectors, other solid-state detectors, absolute dosimeters, and personnel dosimeters.

Gas-Filled Detectors

Gas-filled detectors operate on the basic principle of measuring exposure, that is, collecting ionization in air or a substitute gas. A gas-filled volume is defined as one that contains two oppositely charged plates or wires to collect the charge resulting from ionization in the gas. The reading is in units of charge (coulombs), exposure, or exposure rate. Figure 6-26, *A* shows a simple parallel plate gas-filled detector and its components. As the voltage applied to the electrodes is increased from zero, the amount of charge collected increases (Figure 6-26, *B*). The distinct voltage regions are expanded in Table 6-8. In general, gas-filled detectors require calibration before making radiation measurements.

TABLE 6-7 Radiologic Units

Quantity	What Is Measured	Unit (Symbol)	Value
Exposure	Ionization in air	Roentgen (R)	2.58×10^4 C/kgl_{air}
Dose	Energy absorbed in matter	rad (rad)	100 erg/g
Dose (SI)	Energy absorbed in matter	Gray (Gy)	1 J/kg
Kerma	Kinetic energy released in matter	Gray (Gy)	1 J/kg
Dose equivalent	Biologic effect of energy absorbed	rem (rem)	QF × 100 erg/g
Dose equivalent (SI)	Biologic effect of energy absorbed	Sievert (Sv)	QF × 1 J/kg
Activity	Disintegrations per time	Curie (Ci)	3.7×10^{10} d/s
Activity (SI)	Disintegrations per time	Becquerel (Bq)	1 d/s
Exposure rate constant	Exposure rate per activity	Gamma (Γ)	$R \cdot m^2 \cdot h^{-1} \cdot Ci^{-1}$
Exposure rate constant (SI)	Exposure rate per activity	Gamma (Γ)	$Gy \cdot m^2 \cdot s^{-1} \cdot Bq^{-1}$
Air kerma strength	Air kerma in free space	S_k	$\mu Gy \cdot m^2 \cdot h^{-1}$

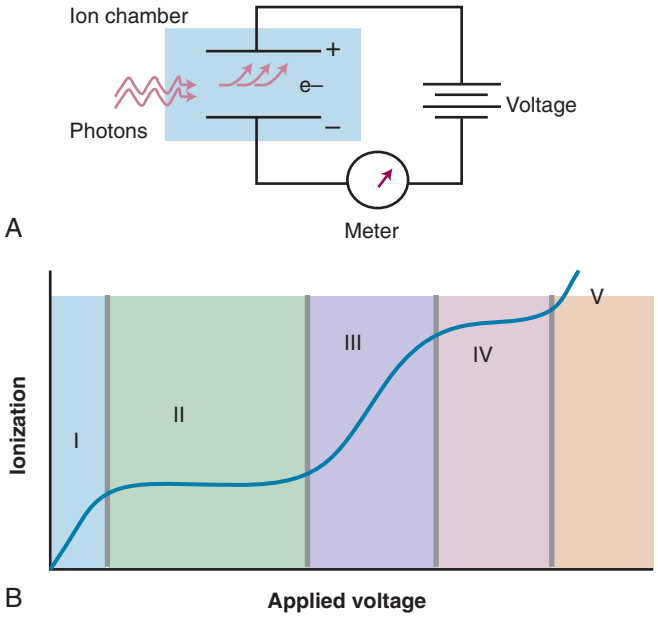


Figure 6-26 Response of a gas-filled detector. **A,** A gas-filled detector collects ionizations from an irradiated volume. **B,** Variation of collected ionization as bias voltage is increased. Regions are explained in Table 6-8.

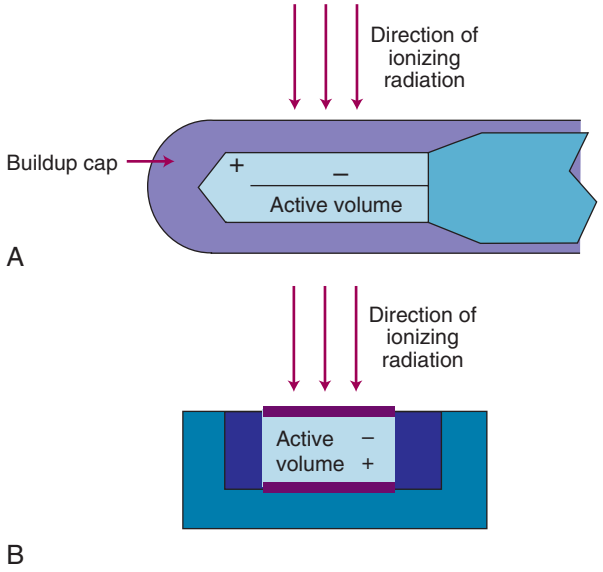


Figure 6-27 Ionization chamber designs. **A,** Thimble chamber. **B,** Parallel-plate chamber. A buildup cap may be added to either chamber to ensure electronic equilibrium, depending on the measurement being performed.

TABLE 6-8 Voltage Regions of Gas-Filled Detectors

Region	Description
I	The recombination region. The voltage is not high enough to separate the ion pairs and recombination occurs.
II	The saturation region. The voltage is high enough to collect almost 100% of the ionization (hence, "saturation"). Also called the ionization region.
III	The proportional, or gas amplification, region. The voltage is high enough to accelerate the ionized electrons to an energy that causes additional ionization, amplifying the actual amount of initial ionization by a factor *M*.
IV	The Geiger-Muller, or GM, region. The voltage is high enough that amplification by accelerated ions proceeds so that the entire gas in the detector is ionized each time a photon hits the detector. Whether low or high energy, the amount of ionization that occurs is the same. Thus, a GM counter emits a "click" for each photon seen and is really a photon counting device.
V	The continuous discharge region. The voltage is high enough to spontaneously ionize the detector gas. Once started, the ionization continues and continues. The detector is not useful at this applied voltage.

Ionization Chambers

Ionization chambers operate in region II (see Figure 6-26, *B*) and are an important type of radiation dosimeter as the principal device used for calibration of radiotherapy beams. The design most commonly used for photon beams is the thimble chamber, also called a *Farmer chamber,* which has a cylindrical geometry with central linear and outer cylindrical electrodes (Figure 6-27, *A*). An active volume of 0.6 mL is convention, although chambers with smaller or larger volumes are available for specialized purposes such as small field dosimetry or low-dose-rate measurements. Parallel-plate chambers are also used and are the recommended chamber geometry for electron beam dosimetry (Figure 6-27, *B*). In general, ionization chambers require calibration before use. Ionization currents produced by radiation beams are very small, on the order of 10^{-9} amperes (A), and require a high-precision device called an *electrometer* for accurate measurement. An ionization chamber and electrometer require calibration before use and with a triaxial connecting cable are required tools for radiation beam calibration. Conditions for radiation beam calibrations are set by national protocols such as the Task Group (TG)-51 from the American Association of Physicists in Medicine[15] and by national or state regulatory bodies. A requirement for operation of all ionization chambers is that the chamber be operated under conditions of electronic equilibrium. In disequilibrium conditions, the amount of ionization measured is incorrect, as will be the exposure or dose calculation.

Solid-State Detectors

Thermoluminescent Dosimeters

In a simple model, crystalline solids have two electron energy levels, called the *valence* and *conduction bands.* The valence band holds bound electrons, whereas the conduction band consists of free electrons. Energy states between these two bands are forbidden. When ionized, a bound electron may gain sufficient energy to jump to the conduction band, leaving a positive "hole" in the valence band. The conduction band electron and the hole can move through the lattice and eventually recombine, with the emission of light on recombination. Because of impurities in the lattice, some crystalline materials have the property of having long-lived "traps" that can hold an electron-hole pair in an excited (or unfilled) state. The electron-hole pair is created and excited into the trap by the

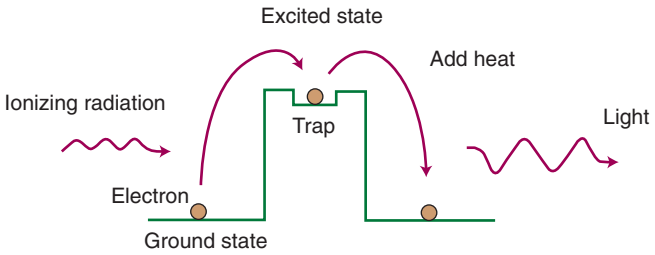


Figure 6-28 Thermoluminescence. Ionizing radiation raises an electron-hole pair to an excited but trapped state. Addition of heat allows de-excitation, which occurs with the emission of light.

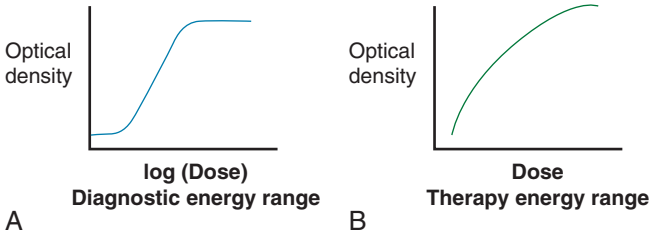


Figure 6-29 Film radiation response varies with film type, photon energy, and dose. **A,** Diagnostic photon energy response. **B,** Therapeutic photon energy response.

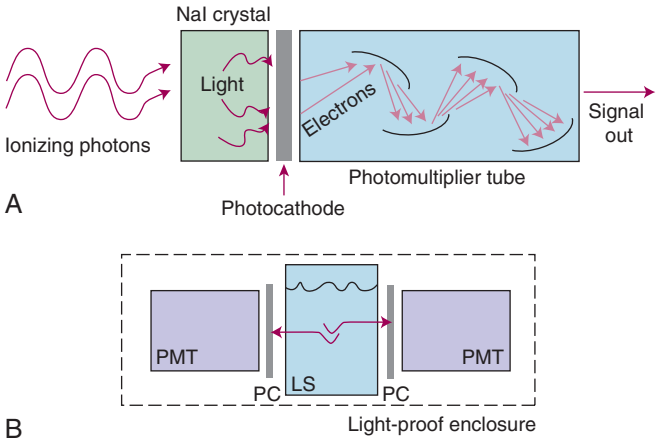


Figure 6-30 Scintillation detectors. Ionizing radiation creates light photons that are converted to electrons and amplified. **A,** Sodium iodine crystal and photomultiplier tube. **B,** Liquid scintillation detection.

absorption of ionizing radiation, which provides the energy to push the pair into the trap (Figure 6-28). Heating the crystal enables the electron-hole pair to leave the trap and return to the de-excited state. With this transition, an amount of light is emitted that is proportional to the amount of radiation dose. Dose is measured by measuring the amount of light emitted. The two most common types of thermoluminescent dosimeter (TLD) are lithium fluoride (LiF, almost tissue equivalent) and calcium fluoride (CaF, not tissue equivalent). A calibration factor must be obtained before use as a dosimeter. TLD is used for in vivo patient dose monitoring during treatment and for personnel monitoring for radiation safety purposes.

Film

Film is a solid-state detector and typically refers to silver-halide films that are sensitive to both light and ionizing radiation. The amount of optical density is proportional to the dose. The response is energy sensitive because film is relatively high Z (the silver content). Response curves are shown in Figure 6-29. Film is used to obtain relative dose distributions (i.e., isodose distributions) for treatment machine quality assurance tests for flatness, symmetry, radiation/light field congruence, and imaging.[16,25] A dose-response curve must be carefully measured, including constant processor control, to enable film to be used to measure actual (not relative) doses. Because of electronic image receptors for digital photography and medical imaging with kV and MV photons (e.g., diagnosis and treatment verification), relatively high cost, and the chemical development process required after exposure, medical uses of silver-halide radiographic film are almost nonexistent, except for specialized imaging applications such as mammography. For physics quality assurance and dosimetry purposes a new type of tissue-equivalent film, called *radiochromic film,* has become a powerful tool. Radiochromic film uses opacity changes from radiation-induced polymerization to indicate dose.[26] This film does not require developing but does have an optimal wavelength of light for reading. A digital flatbed three-channel (color) scanner can be used to read the radiochromic film opacity and through a calibration procedure one- and two-dimensional dose distributions can be obtained. Example uses in therapy beam quality assurance and dosimetry include small beam dosimetry, patient treatment plan verification (such as currently performed prior to a first IMRT procedure), and mechanical and radiologic quality assurance in radiosurgery. Radiochromic film is tissue equivalent and can be used over the full range of x-ray energies. Radiochromic film types are also available for different dose ranges, from 1 Gy up to 50 Gy. Currently, radiochromic film is not an acceptable medical imaging device because of its cost and lack of imaging contrast.

MOSFET Detectors

A semiconductor device called the metal oxide-silicon semiconductor field effect transistor, or MOSFET, can be used as a radiation detector for in vivo dosimetry and physics quality assurance. The p-type device generates electron-hole pairs during irradiation proportional to the dose delivered, and the number of holes, corresponding to dose, can later be read using an appropriate metering device. Advantages include very small size, which enables small field or "point" dose measurements, and the capability for being incorporated into both implantable dosimeters and surface-placed dosimeters for in vivo patient dosimetry.[27] MOSFET dosimeters are primarily used for external beam radiation treatment with photons and require calibration for the photon energy in use. Surface applications require an understanding of the buildup effect for proper assessment of surface dose. Real-time monitoring of brachytherapy dose delivery is also possible.

Scintillation Detectors

Scintillation (light) detectors detect radiation by measuring the amount of light produced in special crystalline materials by the ionizing radiation. The most common material used is sodium iodine (NaI). The NaI crystal is coupled to a photomultiplier tube that amplifies the detection signal coming from the crystal (Figure 6-30, *A*). NaI detectors are extremely sensitive and detect background radiation easily. They are used to detect low-energy or low-activity (dose rate) sources, for instance, in an isotope laboratory within the radiotherapy clinic or a research laboratory using liquid radioactive tracers. These detectors are used in uncalibrated form; a pulse indicates a photon has been detected.

Scintillation materials can also be made in liquid form. With this technique a radiation source (i.e., a sample of radioactive material) is put in direct contact with a liquid scintillator by immersion (see Figure 6-30, *B*). This intimate contact enables

extremely small activities to be detected. Detection limits are in the microcurie and picocurie ranges. This method is used most for detection of very-low-energy beta particles for radioisotope tracer studies, environmental sampling, and isotope analysis of waste or other materials. The liquid scintillator is called a *cocktail* and includes a solvent and the scintillation material. Liquid scintillation detectors require calibration before use, including determination of background count rates.

Semiconductor Detectors: Germanium and Silicon

Germanium (GeLi) and silicon (SiLi) detectors are semiconductor materials that can be used to detect the energies of photons. These detectors are useful only at very low dose rates (i.e., small sample activities or low fluence rates) and are used to measure the photon energy spectrum, not dose.

Absolute Dosimeters

Most dosimeters require calibration in the form of the dose or exposure per reading. Absolute dosimeters *do not* require calibration and instead measure the amount of dose directly.

Calorimetry

All radiation dose, which is energy imparted per mass, eventually becomes heat. If the change in temperature is measured, the amount of dose is known. Temperature changes per gray are quite small as previously stated; thus, a sensitive device called a *calorimeter* is used. Standard-setting bodies, such as the National Institute of Science and Technology, have calorimeters to set the exact calibration factors for radiation beams and instrumentation, and calorimeters are not part of the routine dosimetry instruments used in the radiotherapy clinic.

Chemical or Fricke Dosimeter

The Fricke dosimeter measures chemical changes that are catalyzed by ionizing radiation. The chemical yield of the new product is directly proportional to the radiation dose. The most common reaction used is ferric to ferrous sulfide, such that the amount of Fe^{3+} produced is proportional to the dose delivered. The yield per gray is small, and Fricke dosimeters are typically used in unique geometries and for high dose rates.

Personnel Dosimetry

Monitoring of dose for radiation safety purposes is required for workers who are occupationally exposed to ionizing radiation. Although previously TLD and film have been used, optically stimulated luminescence dosimeters (OSLDs), based on the stimulated luminescence of a thin matrix material of aluminum oxide (Al_2O_3:C) as the dose readout surrogate, is now a primary dosimeter material. The aluminum oxide dosimeter wafer is assembled with other components into a radiation "badge" that is worn at the waist or neck during work. Filters that overlay the dosimeter enable discrimination between electrons or low-energy photons and high-energy photons. Dose readout is accomplished in a light-tight reader and the dosimeter is stimulated with a precision light source to emit light that is proportional to the radiation dose received. Besides personnel dosimeters that must be interrogated with a specialized reader, for high-dose-rate environments there are direct-read dosimeters that can be used for instant readout. Such dosimeters are important for instances of emergency response. Personnel dosimeters are made in holders to enable whole-body and extremity monitoring, based on the work activities being conducted by the user.

References on radiation instrumentation and measurement are available that give detailed theory, design parameters, and operational characteristics for different classes of detectors.[21,22,28]

BUILDUP PHENOMENON

Megavoltage photon beams used for radiotherapy exhibit a phenomenon in which the dose in an absorber is relatively low at the surface but rapidly increases to a maximum during the next few millimeters or tens of millimeters. This region of rapidly increasing dose is called the *buildup region* and is explained as follows. The secondary electrons produced by megavoltage photon interactions travel primarily in the forward direction from the interaction point. The direction and range are represented by the groups of arrows in Figure 6-31. The surface is the first point of interaction, and the dose from these interactions is delivered in the forward direction (point A). Because there are no interaction points upstream from the surface to produce secondary electrons, the surface dose is low. Ignoring attenuation and other small changes to the photon fluence with depth, interactions occur in the next layer of material beneath the surface, with a similar forward dose distribution. These electron tracks overlap (sum) with those from the surface. Additional layers at depth have similar interactions and resulting secondary electron distributions that sum with previous ones. The amount of dose increases rapidly and nonlinearly as successive electron tracks overlap (point B). Given an average, finite secondary electron range, a point is eventually reached where full electron overlap occurs (point D). At this point, the number of summed electron tracks is constant because the electrons being produced match those being lost. A maximum dose, D_m, is reached at a depth called d_m (Figure 6-31), and d_m indicates the average secondary electron range and is the point at which electronic equilibrium is obtained. Because photon attenuation occurs, the number of interactions and resulting secondary electrons decreases with

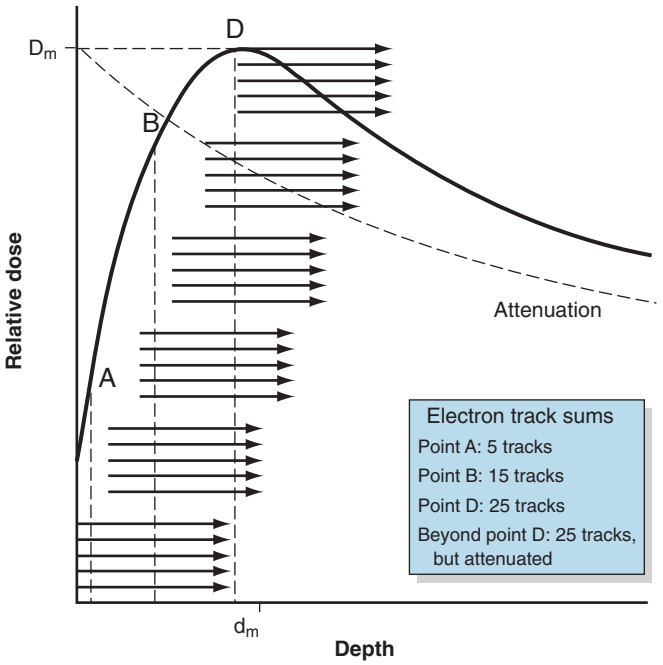


Figure 6-31 Radiation dose buildup. With secondary electrons primarily in the downstream direction, successive electron tracts overlap to produce a rapidly increasing region of dose, called *buildup*. A maximum dose, D_m, reached at a depth called d_m, indicates the average secondary electron range and is the point at which electronic equilibrium is obtained. Because photon attenuation occurs, the number of interactions *(dotted line)* and resulting secondary electrons decreases with the depth from the surface. Attenuation competes with the buildup process, but because buildup occurs more rapidly than attenuation, a net gain of dose results.

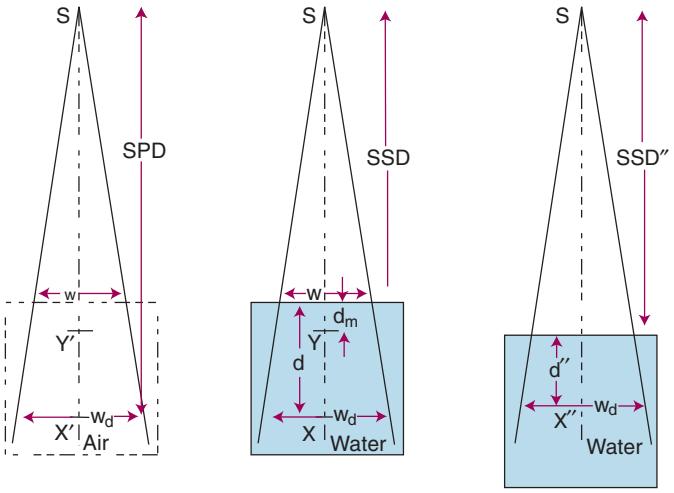


Figure 6-32 Reference irradiation geometries used for measurement of percent depth dose, tissue-air ratio, and tissue-phantom ratio. *Adapted from ICRU Report 24: Determination of absorbed dose in a patient irradiated by beams of x and gamma rays in radiotherapy procedures, Washington, DC, 1976, International Commission on Radiation Units and Measurements.*

depth from the surface. Attenuation competes with the buildup process; however, buildup is more rapid than attenuation, resulting in a net gain of dose. The presence and steepness of a buildup region depend on incident photon energy that governs the type of interaction and the range and distribution of secondary electrons. At higher photon energies, d_m is larger because the average secondary electron range is greater. Beyond d_m, photon attenuation results in transient electronic equilibrium (i.e., energy in is slightly greater than energy out) and a decrease in dose with depth (shown in Figure 6-31 as the dotted line; the difference is exaggerated).

DOSE RELATIONSHIPS FOR EXTERNAL BEAMS

Three mathematical functions that remain important both conceptually and in practice are used to describe the dose characteristics for external radiation beams: percent depth dose (PDD), tissue-air ratio (TAR), and tissue-phantom ratio (TPR).[12,13] These dose functions relate the dose at any point to the dose at a reference point. The irradiation geometry shown in Figure 6-32 illustrates the measurement conditions for the following discussions.[29]

Percent Depth Dose

The PDD is the ratio of the dose at depth, D_d, to the maximum dose, D_m, measured along the central axis of the beam and expressed as a percent. Points X and Y are the locations at depth, D_d and D_m, respectively, in Figure 6-32, *B*. PDD is dependent on the depth, d, reference depth, d_m (the point of maximum dose), beam quality (or energy), E, source-to-surface distance, SSD, and field size at the surface, w. Mathematically,

$$\mathrm{PDD}(d, d_m, E, \mathrm{SSD}, w) = \frac{D_d}{D_m} \times 100\% = \frac{D_X}{D_Y} \times 100\% \qquad \text{Eq. 28}$$

PDD is often expressed as a fraction rather than as a percentage. PDD was the dose function first measured for diagnostic and therapy radiation beams because of the simplicity of measurement, and it remains a basic dose measurement for beam characterization. Inherent in a PDD measurement are the effects of attenuation by the material and the inverse square effect as the distance from the source is changed. PDD is used for photon and electron beams and is often used in tabular form for monitor unit calculations.

Tissue-Air Ratio

Given a fixed irradiation point in space, the ratio of the dose in phantom, D_x, to the dose in air, D_x', at the same point is called the *TAR* (see Figure 6-32, *A* and *B*). TAR indicates how the dose in air is affected when the air is replaced by tissue. The field size at the point and source-to-point distance are constant; the only variable is the depth in phantom:

$$\mathrm{TAR}(d, w_d, E) = \frac{D_X(d, w_d, E)}{D'_X(w_d, E)} \qquad \text{Eq. 29}$$

TAR is essentially independent of SSD because scatter contributions are almost constant for fixed field sizes, regardless of SSD. This independence enables the use of the TAR over a wide range of clinically used SSDs without correction. TAR is used for photon beams only and is not valid for electron beams.

A special case of the TAR, called the *backscatter factor* (BSF), exists when the point of interest is the depth of maximum dose (when $d = d_m$). In this case, the TAR has a maximum value, and

$$\mathrm{BSF}(w_{d_m}, E) = \mathrm{TAR}(d_m, w_{d_m}, E) = \frac{D_Y}{D_{Y'}} \qquad \text{Eq. 30}$$

The BSF takes its name for historical reasons, from a time when low-energy photons were used and the point of maximum dose was on the surface. Any dose scattered to the surface from the phantom or patient was truly backscattered dose.

To determine the TAR and BSF, dose data are acquired at sampled points in phantom and air across and along the radiation beam central axis for the range of field sizes, depths, and SSDs or source-to-axis distances (SADs) clinically relevant.

Tissue-Phantom Ratio

TPR must be used for photon energies above about 4 MV, when in-air measurements required for the TAR are impractical. As with PDD and the TAR, the TPR is the ratio of two doses; however, both doses are made in phantom. The TPR is the ratio of dose D_x, measured at depth d, to dose $D_{x''}$, measured at a reference depth d'' (see Figure 6-32, *B* and *C*):

$$\mathrm{TPR}(d, w_d, E, d'') = D_{X''} \frac{D_X(d, w_d, E)}{(d'', w_{d''}, E)} \qquad \text{Eq. 31}$$

Both measurement points are fixed in space such that the source-to-point distance and field size are the same at each point. The depth of point X is varied to generate TPRs over a range of depths for a particular field size. TPR is essentially independent of SSD because scatter contributions are almost constant for fixed field sizes, regardless of SSD. This independence enables the use of the TPR over a wide range of clinically used SSDs without correction. TPR is used for photon beams only and is not valid for electron beams.

When d'' is the depth of maximum dose, the TPR is called the *tissue-maximum ratio* (TMR). The TPR and the TMR are used in the same manner as the TAR in dose calculations. TMR is the most common data format used for photon monitor unit calculations in second-check computer programs used to

confirm monitor unit results from three-dimensional (3D) radiation treatment planning systems and manual (by hand) calculations.

Primary and Scatter Dose: The Scatter-Air Ratio

Mayneord first proposed that PDD could be separated into primary and secondary (or scatter) components.[12] Later, Clarkson[30] proposed sector integration of scatter components in calculating the PDD at any point inside or outside an irregular field. This concept was later applied by Gupta and Cunningham to the TAR.[31] The concept states that dose at a point is the sum of primary and scatter components. The primary dose results from photons that have interactions at the point of interest. The secondary dose results from photons and electrons that scatter to the point of interest from other interaction points. With this concept, TAR is given by the following expression:

$$\mathrm{TAR} = \mathrm{TAR}_0 + \mathrm{SAR} \qquad \text{Eq. 32}$$

In the equation, TAR_0 is the TAR for zero field size, representing primary dose, and SAR is the scatter-air ratio, representing secondary dose. TAR_0 is found by extrapolation of circular field TARs to zero field size. The SAR is calculated as the difference between the TAR and the TAR_0. For an irregular field, an effective TAR can be found that is the sum of the TAR_0 and an effective SAR for the irregular field:

$$\mathrm{TAR}_{\mathrm{irreg}}(d, W_d, E) = \mathrm{TAR}_0(d, E) + \mathrm{SAR}_{\mathrm{irreg}}(d, W_d, E) \qquad \text{Eq. 33}$$

The irregular field SAR is found by sector integration:

$$\mathrm{SAR}_{\mathrm{irreg}}(d, W_d, E) = \frac{1}{2\pi}\sum \mathrm{SAR}_i(d, W_d, E) \times \Delta\theta \qquad \text{Eq. 34}$$

in which $\Delta\theta$ is the angular increment in radians for each sector. Separation of primary and secondary dose can be applied to any of the dose functions in a similar fashion. For instance, the TMR can be represented as $\mathrm{TMR} = \mathrm{TMR}_0 + \mathrm{SMR}$.

The TAR/SAR and TMR/SMR functions are more commonly used than PDD in dose computation algorithms because fewer inverse square corrections are needed. The TAR and TMR are easily found for isocentric treatment geometries where the size of the treatment field at the isocenter is equal to the treatment field size at the center of the target volume, which simplifies manual (noncomputer) calculations.

Although PDD can be measured with an ionization chamber beyond d_m over the wide range of clinically used photon energies, the TAR cannot be measured when the photon energy exceeds about 3 MV because the range of secondary electrons exceeds the thickness of the buildup cap for the ionization chamber. At these energies, PDD is measured and converted to TPR and TMR by well-known relationships.[21,22] PDD remains the most important and fundamental dose function and performance specification to be measured for almost all physics quality assurance procedures for all external beam treatment devices.

CHARACTERISTICS OF RADIOTHERAPY PHOTON BEAMS

Dose Characteristics

Photon beams used in radiotherapy have dose characteristics that vary primarily as a function of beam energy and treatment machine design. In the standard irradiation geometry (see Figure 6-32, *B* and *C*), PDD measurements are obtained in water along the central axis, beginning at the surface and proceeding to depth. A typical PDD curve shown in Figure 6-33 for megavoltage beams has the characteristics listed in Table 6-9.

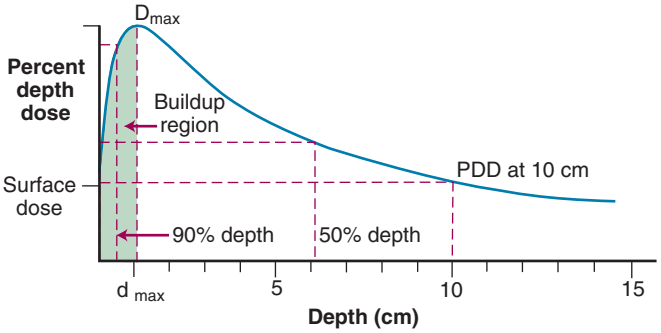


Figure 6-33 A typical photon percent depth dose (PDD) curve is characterized by surface dose, a buildup region, a point of maximum dose, and an exponentially attenuated region. Standard PDD measurements are obtained along the central axis *(dotted lines)*, beginning at the surface and proceeding to depth.

TABLE 6-9 Characteristics of a Typical Percent Depth Dose Curve for Megavoltage Beams

Characteristic	Definition
Surface dose	Nonzero dose at the incident surface
Buildup region	Region between the incident surface and d_{max} where the dose rapidly increase
D_{max}	Maximum dose along the central axis; often used as a reference dose
d_{max}	Depth of maximum dose; often used as a reference point
Percent depth dose	Dose along the central axis of the beam, as a percentage of the d_{max} dose
90% dose depth	Depth from the surface where the dose in the buildup region reaches 90% of D_{max}
50% dose depth	Depth from the surface beyond d_{max}, where the dose falls to 50% of D_{max}
10-cm percent dose	The percent depth dose at 10 cm from the surface, a value often quoted as an indicator of beam penetration

Other important descriptors include an effective attenuation coefficient for depths beyond the maximum depth (d_{max}) and the HVL. The 10 cm PDD in water is most used as an indicator of beam quality, in place of the HVL, because the 10 cm PDD has clinical relevance and the HVL is a better indicator for shielding purposes.

Field size, flatness, symmetry, and sharpness of the beam edge can be measured with a dose profile (Figure 6-34), which is a scanned dose measurement perpendicular to the central axis, across a beam (at a fixed depth, occurring along the horizontal line w_d in Figure 6-32, *B* and *C*). These and PDD measurements are most commonly obtained using a large water phantom with a three-axis scanning system to move a water-immersible ionization chamber or diode detector (Figure 6-35). Dose profiles are normally made at several depths of interest (e.g., d_m, 5 cm, 10 cm, and 25 cm). Beam characteristics from a dose profile are listed in Table 6-10.

The flattening filter and beam steering determine flatness and symmetry in a linear accelerator. Flatness is defined at a reference depth, for instance at a 10-cm depth at the isocenter (SSD = 90 cm). A typical specification is for no more than 3%

dose variation across the useful 80% of the field width (see Figure 6-34). A radiation beam does not have a perfectly sharp edge across the defined beam edge but instead has a gradient from high to low dose with a rounded "shoulder" and "toe." This penumbra region ("penumbra" means "partial shadow") is the result of both the finite source size, "geometric penumbra," and the scattered photons and secondary electrons that cross the beam edge from within the field, "radiologic penumbra." Geometric penumbra can be large because of shadowing of part of the source, as is the case for ^{60}Co teletherapy beams, as a result of a very large (2 cm) physical source size. However, the penumbra region for linear accelerator beams is mostly radiological penumbra because of secondary scatter from within the field and from the collimators. This scattered radiation degrades the beam edge; the dose from the shoulder region scatters outside the beam edge to form the toe. *Penumbra* for radiation fields is defined as the distance over which the dose falls from 80% to 20% of the central axis dose at the same depth, or at the width of the 90% to 10% dose gradient (see Figure 6-34).

Various methods exist to measure a radiation beam along lines of equal dose, called *isodose lines*. In a three-axis water phantom scanner, after determining PDD along the central axis, a certain isodose level is identified in the standard geometry and then tracked to obtain a digital representation of the

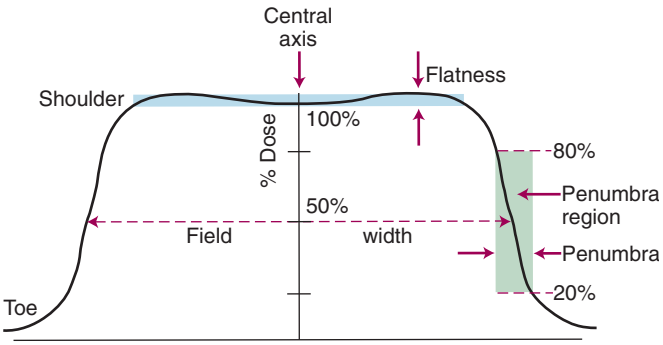


Figure 6-34 The dose profiles of a typical photon beam are characterized by shoulder and toe regions, with definitions for field width, flatness, and penumbra as indicated.

TABLE 6-10 Beam Characteristics From a Dose Profile

Characteristic	Definition
Field size	Distance from field edge to opposite edge at the 50% dose level, with normalization to 100% on the central axis (basically, full-width at half-maximum [FWHM])
Flatness	Deviation in dose level across the width of the field
Symmetry	Deviation in dose level for points symmetrical about the central axis
Penumbra	Dose gradient regions from high to low dose at the beam edge

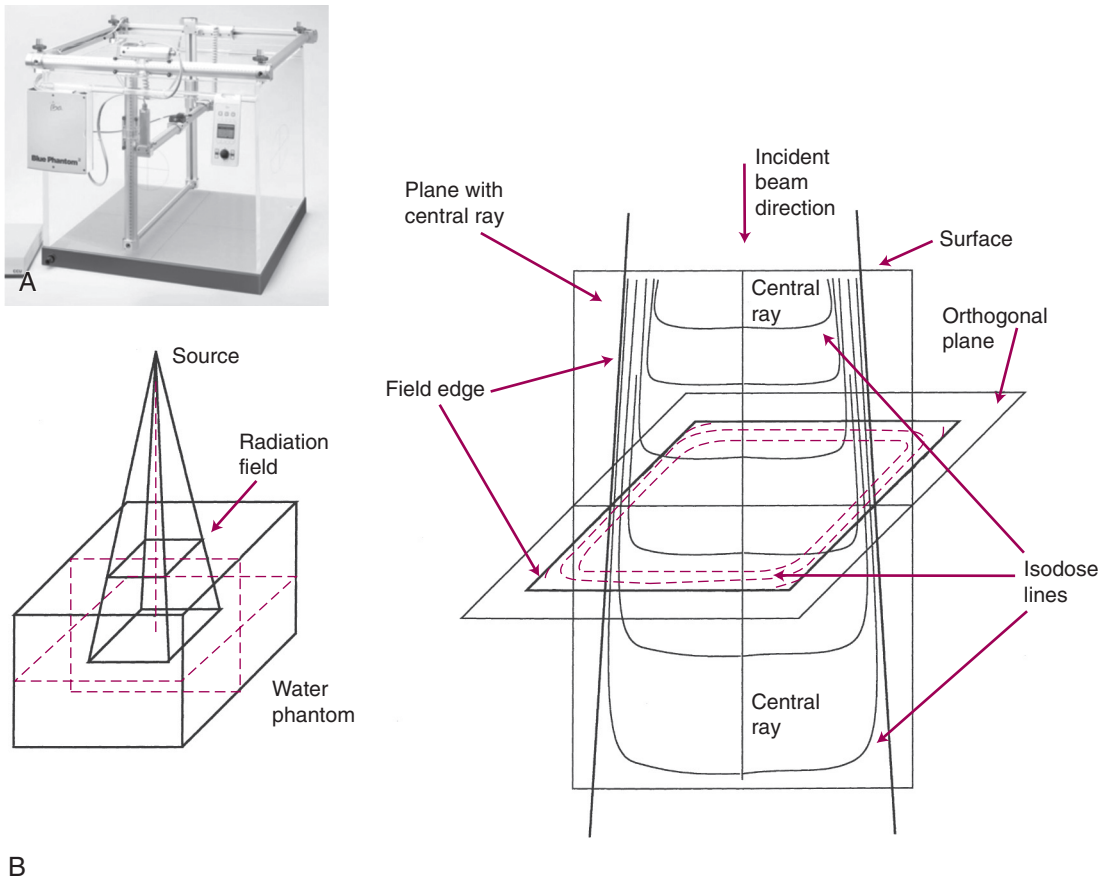


Figure 6-35 Irradiation geometries for isodose measurements. **A,** Beam orientation with phantom. **B,** Planes orthogonal to the central axis and isodose curves.
A, *Courtesy IBA Dosimetry, Schwartzenbruck, Germany.*

TABLE 6-11 Photon Beam Characteristics in Water

Beam Energy	Surface Dose (%)	90% Buildup Depth (cm)	d_{max} (cm)	50% Dose Depth (cm)	10 cm PDD	HVL and Material
60 kVp	100	None	0.0	2	10	1.9 mm Al
120 kVp	100	None	0.0	4	21	5.0 mm Al
300 kVp	100	None	0.0	7	35	3.17 mm Cu
^{60}Co	40-90	0.4	0.5	12	55	11.9 mm Pb
4-MV x-rays	20-40	0.3-0.6	1.2	15	63	14.8 mm Pb
6-MV x-rays	10-30	0.4-0.7	1.5	15	67	15.4 mm Pb
10-MV x-rays	6-30	0.7-1.0	2.5	19	74	16.9 mm Pb
18-MV x-rays	6-30	1.0-1.5	3.2	22	80	16.2 mm Pb

HVL, *Half-value layer;* PDD, *percent depth dose.*

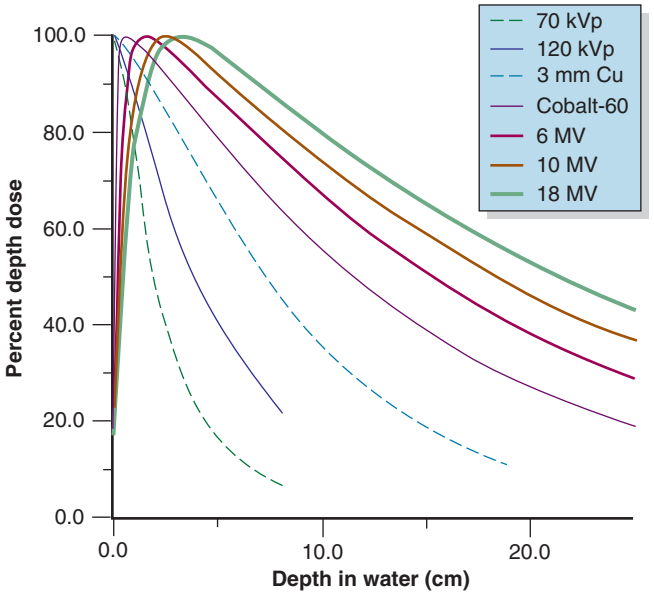


Figure 6-36 Photon percent depth dose curves.
Data courtesy Wake Forest University Baptist Medical Center, Winston-Salem, NC, and the Radiological Health Handbook. Bethesda, MD, 1970, U.S. Department of Health, Education, and Welfare.

dosimetric shape of the beam. Figure 6-35 shows sample isodose curves for a plane containing the central ray of a beam and a plane perpendicular to the central ray. The modern water phantom scanning device is computer controlled and has robust software tools for two-dimensional (2D)- and 3D renderings and analysis of acquired dose distribution data.

Effect of Energy

Photon beam characteristics change with beam energy. Representative beam data are presented in Table 6-11, PDDs in Figure 6-36, and isodose curves in Figure 6-37. Several key observations should be considered:

- PDD increases as energy increases. This effect can be represented by the depth of the 50% dose or the PDD at 10 cm and is consistent with the change in the effective attenuation coefficient.
- Surface dose decreases as energy increases. Scattered radiation is more forwardly directed, away from the surface, as energy increases, reducing the dose contribution at the surface. The breakthrough in achieving megavoltage energies is that surface dose decreased from 100% and d_m moved away from the surface, providing "sparing" of skin and superficial tissues.
- The buildup region has a very steep climb of PDD to D_m. Most therapy beams have reached at least 90% of their D_m dose within 1 cm of the surface.
- The d_m is at or near the surface for low energy beams and increases in depth as energy increases. As incident photon energy increases, the effective electron range (photoelectrons and Compton electrons) increases and the scatter component (secondary electrons and Compton scattered photons) is more forwardly directed. The d_m value is directly related to the average energy of secondary electrons produced in photoelectric and Compton interactions; d_m increases with energy.
- D_m is defined as a point, but as energy increases the PDD curve becomes very broad because of a broader spectrum for the scattered electrons. Strictly speaking, D_m is the one point where electronic equilibrium occurs.
- An effective attenuation coefficient can be found that describes the exponential fall-off in dose with depth.
- HVL, measured in lead at megavoltage energies, increases as peak energy is increased until about 6 MV, and it then falls slightly (see Table 6-11). HVL decreases because an increased amount of pair production increases the attenuation coefficient for photon energies above 6 MV (see Figure 6-16). In tissue or water the attenuation coefficient decreases monotonically and the minimum is reached at very high energies, to the far right in Figure 6-16.
- Linear accelerator photon beams have an effective photon energy of approximately one third of the accelerating potential. For example, an 18-MV photon beam (polyenergetic, bremsstrahlung spectrum) has an effective (monoenergetic) value of 6-MeV photons.
- The central axis portion of a megavoltage beam from a linear accelerator is "harder" than the off-axis region because of the use of a flattening filter that is thicker in the central ray than off-axis (see Figure 6-5). Because the flattening filter is designed to produce a flat field at a depth of 10 cm, not d_m, and the off-axis beam is softer than the central axis, a greater beam intensity off-axis is allowed at the depth of d_m to compensate for the increased attenuation of the off-axis beam component. This greater intensity is exhibited as "horns" in the isodose distribution for off-axis regions near d_m (see Figure 6-37, *A*). This effect is greater for lower-energy megavoltage photons than for higher energies.

Effect of Field Size

Field size determines the amount of scatter present in the beam, with the following observations:

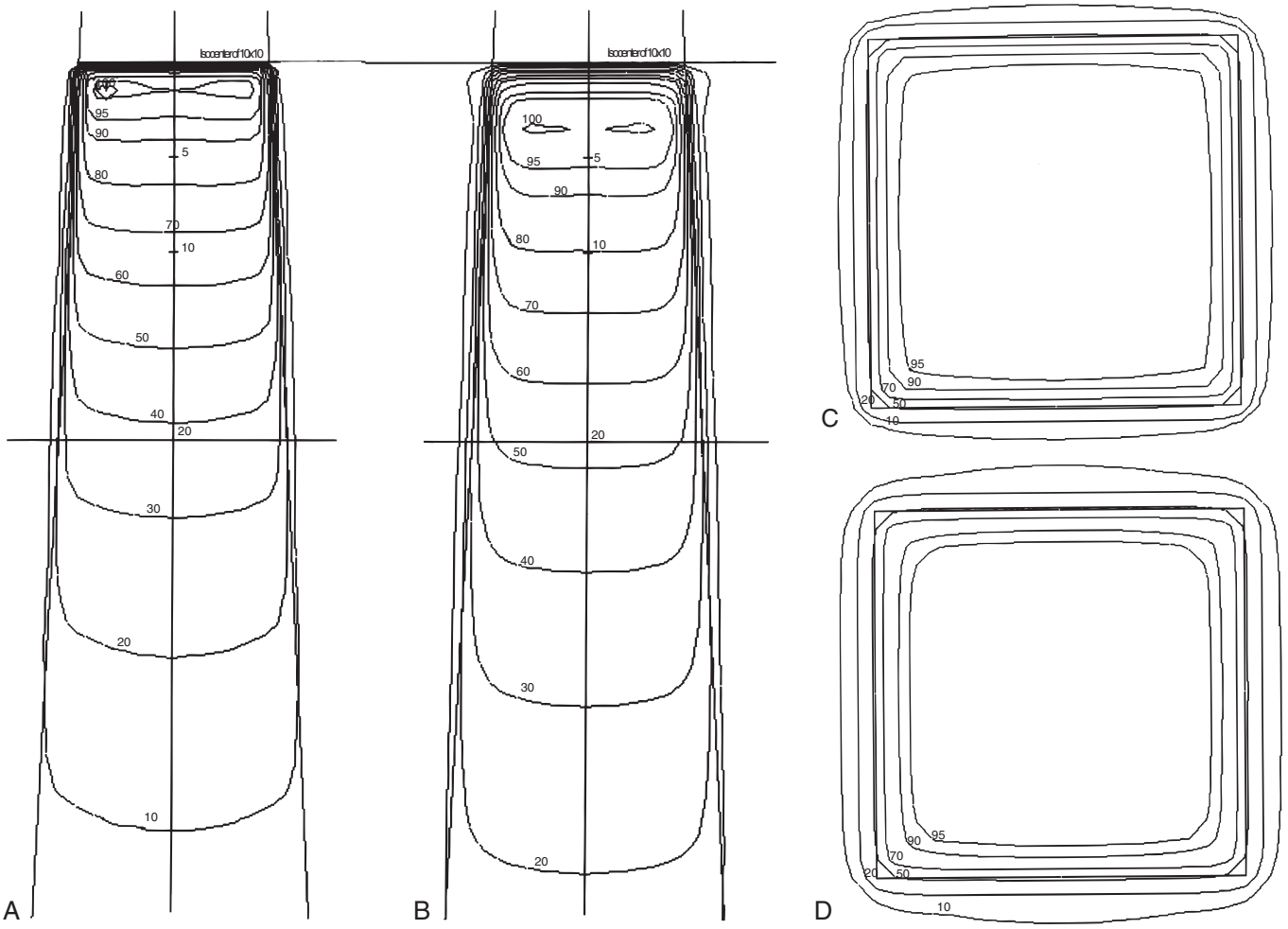


Figure 6-37 Photon isodose curves, 10 × 10 cm² fields. **A,** 6 MV, cross plane. **B,** 18 MV, cross plane. **C,** 6 MV, orthogonal plane. **D,** 18 MV, orthogonal plane.
Data courtesy Wake Forest University Baptist Medical Center, Winston-Salem, NC.

- PDD increases as the field size is increased. The effect results from a differential increase in scatter such that points at depth receive a greater relative amount of scatter than does d_m, leading to an increase in PDD. The increased scatter at depth comes from interactions that occur in the increased irradiation volume.
- Surface dose increases as the field size is increased because the amount of scattered radiation from the collimator faces is increased. This scattered radiation includes secondary electrons and scattered photons of lower energy.
- Absolute dose rate, or beam output, increases as field size increases (Figure 6-38). Output increases because there is increased scatter at d_m from the collimator faces as well as from interactions that occur in the increased volume of irradiated material. Figure 6-38 also illustrates the separation of dose into primary and secondary components.
- In a more subtle effect, d_m decreases as the field size increases because of the presence of an increased amount of lower energy photon and electron scatter.

Penumbra

Beam edge sharpness, or penumbra, is typically 7 to 12 mm in width and varies with the amount and energy of secondary electrons and scattered photons. As the amount of scatter increases, penumbra does likewise:

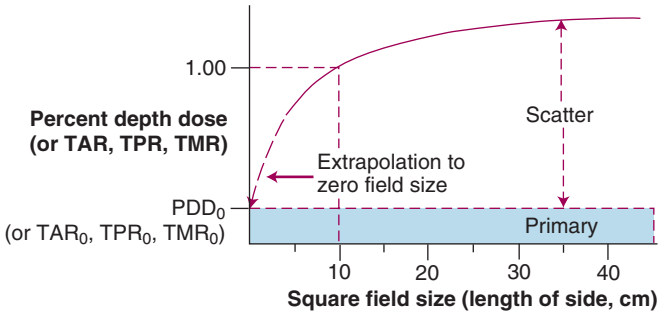


Figure 6-38 Relative dose as a function of photon field size.

- Penumbra increases as depth increases. At depth there is more scatter from the larger irradiated volume upstream, so the penumbra is wider.
- Penumbra increases with field size because of increased scatter from the increased volume of irradiated material and because there is a slight increase in beam divergence (a geometric effect).
- Penumbra increases as SSD increases.
- ^{60}Co has a wide penumbra because the source size is large and the geometric penumbra is large. However, some units have "trimmer" bars that greatly reduce the geometric

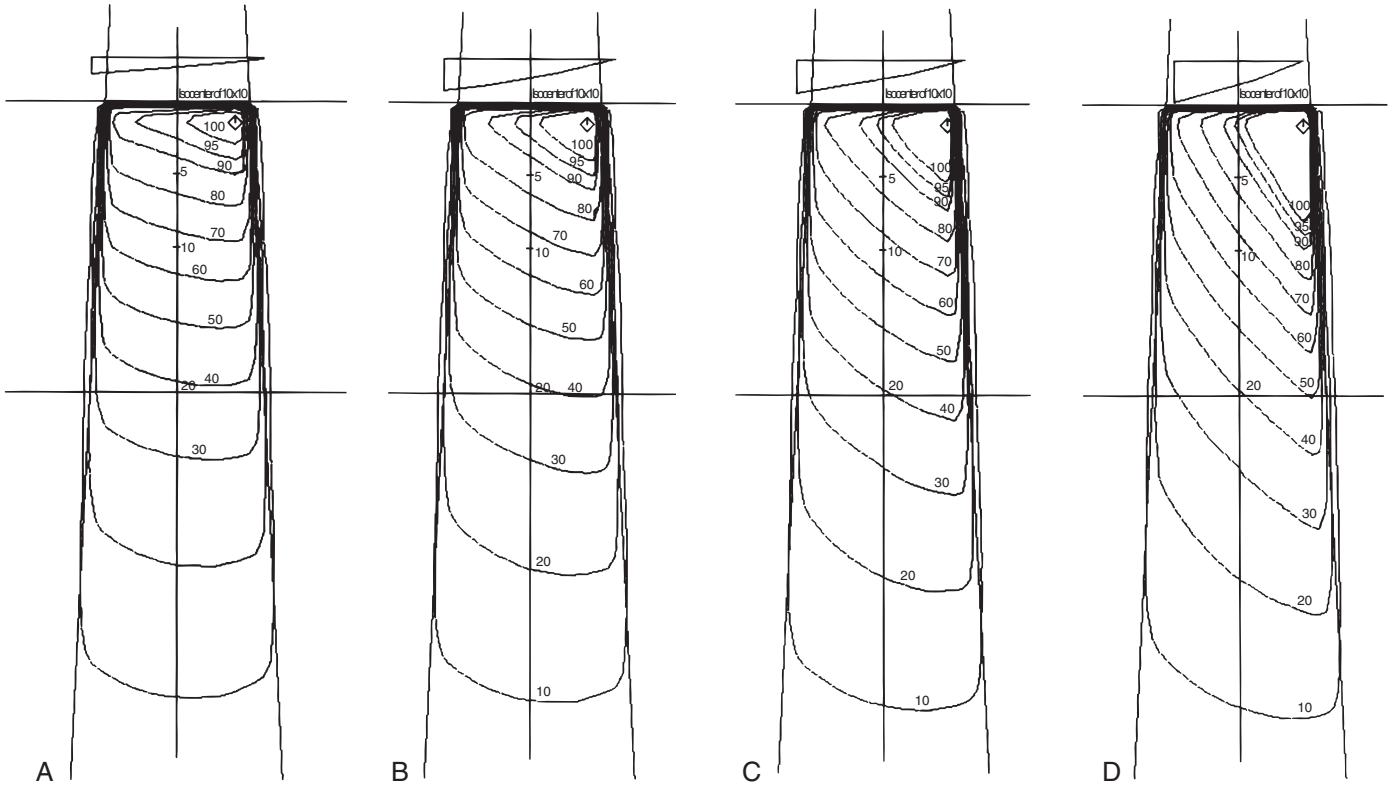


Figure 6-39 Isodose curves with physical wedges, 6-MV photons, and a 10 × 10 cm² field. **A,** A 15-degree wedge. **B,** A 30-degree wedge. **C,** A 45-degree wedge. **D,** A 60-degree wedge.
Data courtesy Wake Forest University Baptist Medical Center, Winston-Salem, NC.

penumbra component, yielding penumbrae comparable to those of linear accelerations.
- Penumbra increases with energy. Scattered electrons and photons that have a higher effective energy have a corresponding higher lateral range of scatter outside the beam edge. This effect is seen as a degradation of the profile (more pronounced shoulder and toe). This comparison is shown in Figure 6-37, *A* and *B*.

Beam Modifiers

Various devices can be put into a photon beam to modify the shape of the beam and its dose distribution. Collimators and custom blocks are used to shape the field, as previously discussed. Their dosimetric effect is to change the irradiated volume and therefore the amount of scatter.

Physical wedges produce skewed isodose lines at fixed angles across the central ray (Figure 6-39) to compensate for beam angle of incidence, tissue shape, or the trajectory of other treatment beams. Historically, wedge angles of 15, 30, 45, and 60 degrees have been available using physical wedges made of steel or lead. Isodoses show the wedge angle is measured from a perpendicular to the central ray, typically at a depth of 10 cm. A physical wedge produces an attenuated beam that is decreased in absolute dose rate and slightly more penetrating resulting from both attenuation and beam hardening by the thickness of the metal wedge in the beam. A commonly available alternative wedging system uses no physical wedge and produces angled isodose lines by scanning one of the independent collimator jaws across the field while the beam is on. This dynamic method does not result in hardening or attenuation of the beam and is called a *dynamic, virtual,* or *soft wedge.* Another method to produce an angled beam intensity is to use one physical wedge with the maximum wedge angle of 60 degrees that is left in the beam for various fractions of time to produce wedge angles from 0 (no time in beam) to 60 (full time in beam) degrees.

Compensators attenuate the beam in desired locations to provide dosimetric shaping. A variety of methods exist that include simple and complex approaches.[13] Compensators have an important role in dose optimization schemes that include static applications as an alternative to dynamic techniques, including IMRT[32] and whole-body irradiations for bone marrow transplantation.

CHARACTERISTICS OF RADIOTHERAPY ELECTRON BEAMS

Dose Characteristics

Electrons differ from photons in that electrons have a *finite range;* electrons travel a certain distance and then stop, and their kinetic energy is zero. PDD measurements are obtained along the central axis in the standard irradiation geometry as for photons (see Figure 6-32). The one difference in the geometry is that an electron cone is used that requires fixed collimator positions in length and width. A typical PDD curve for megavoltage electrons (Figure 6-40) has many of the same characteristics as do photons, including surface dose, a "buildup region," D_m, and d_m. An electron PDD curve also has the characteristics listed in Table 6-12.

Table 6-13 gives several characteristics for megavoltage electron beams as a function of energy. Although electron beams have some of the same features as photon beams, their finite range and the presence of bremsstrahlung contamination are unique.

Field size, flatness and symmetry, and sharpness of the beam edge for electrons can be measured similarly as for photon beams (see Figure 6-34); however, the measurement depth is typically at d_m or at the 95% dose level beyond d_m. Beam steering, scattering foils, monitor chambers, collimator length and width, and electron applicator design all determine flatness and symmetry for electron beams.[33] These design parameters are important for controlling the distribution and amount of electron scatter. Penumbra is the result mainly of electron scattering from within the defined beam and is defined similarly as for photons.

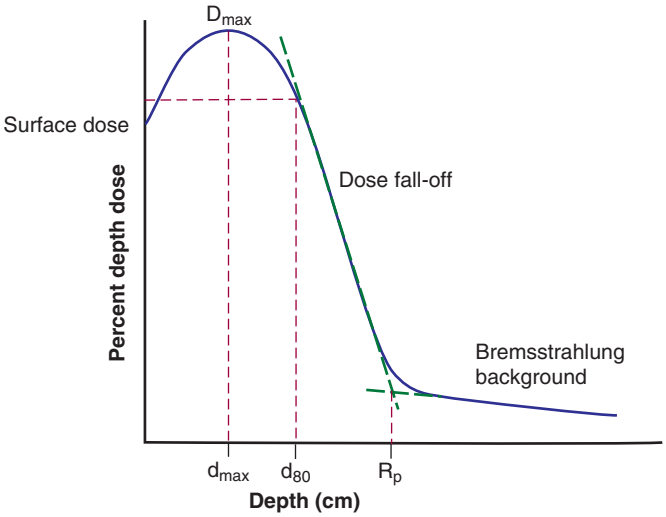


Figure 6-40 A typical electron percent depth dose (PDD) curve is characterized by surface dose, a region of buildup, a point of maximum dose, a rapid dose fall-off, and a tail resulting from Bremsstrahlung background radiation.

TABLE 6-12 Characteristics of an Electron PDD Curve

Characteristic	Definition
Dose fall-off	Region beyond where the dose falls steeply and almost linearly
d_{90}	Depth of the 90% dose beyond d_{max}—a clinically relevant point beyond which dose is not therapeutic
d_{80}	Depth of the 80% dose beyond d_{max}
d_{50}	Depth of the 50% dose beyond d_{max}
R_p	Practical range: the maximum depth to which electrons penetrate; determined by the intersection of the linear part of the dose fall-off curve and the bremsstrahlung background
Bremsstrahlung background	Contamination of the electron beam by bremsstrahlung x-rays created by collisions of the electrons with parts of the machine and with the patient; prevents the dose from going to zero at depth

D_{max}, *Depth of maximum dose;* PDD, *percent depth dose.*

Effect of Energy

Electron beam characteristics change with beam energy. Representative beam data are presented in Table 6-13, central axis PDD in Figure 6-41, and isodose curves in Figure 6-42. Several key observations apply:

- PDD increases as energy increases because the electron range increases with energy. The values for d_{90}, d_{80}, and R_p (see Table 6-12) all increase with energy.
- Surface dose is high, usually in the 70% to 90% range (see Table 6-13), and it *increases* as energy increases (an opposite effect from photon beams) because of changes in the amount of lateral electron scattering and its dose contribution at d_m.
- In general, d_m starts at shallow depths and increases as energy increases because the electron range increases with energy.
- As energy increases, the region around D_m becomes quite broad. In this case d_m is defined at a selected point.
- The steepness of the dose fall-off region lessens with increasing energy. Increased scattering occurs, and a wider

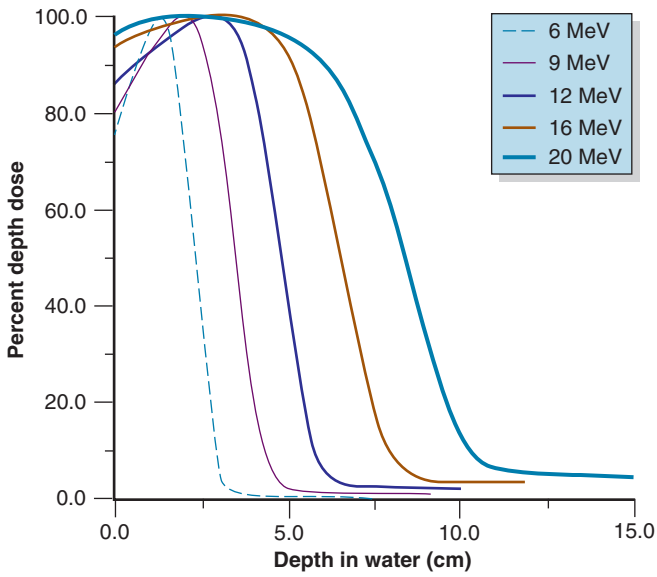


Figure 6-41 Electron beam percent depth dose curves: 6, 9, 12, 16, and 20 MeV.
Data courtesy Wake Forest University Baptist Medical Center, Winston-Salem, NC.

TABLE 6-13 Electron Beam Characteristics in Water

Beam Energy (MeV)	Surface Dose (%)	d_{max} (cm)	d_{90} (cm)	d_{80} (cm)	R_p (cm)
6	78-79	1.2	1.55-1.59	1.74-1.78	2.8
9	83-86	1.5	2.25-2.58	2.59-2.87	4.4
12	84-88	2.0	3.05-3.44	3.50-3.82	5.7
16	89-91	2.0	3.84-4.89	4.53-5.49	8.0
20	91-95	2.0	4.28-5.86	5.15-6.68	9.9

d, *Depth;* d_{90}, d_{80}, *depth of the 90% or 80% dose beyond* d_{max}; max, *maximum;* R_p, *practical range.*

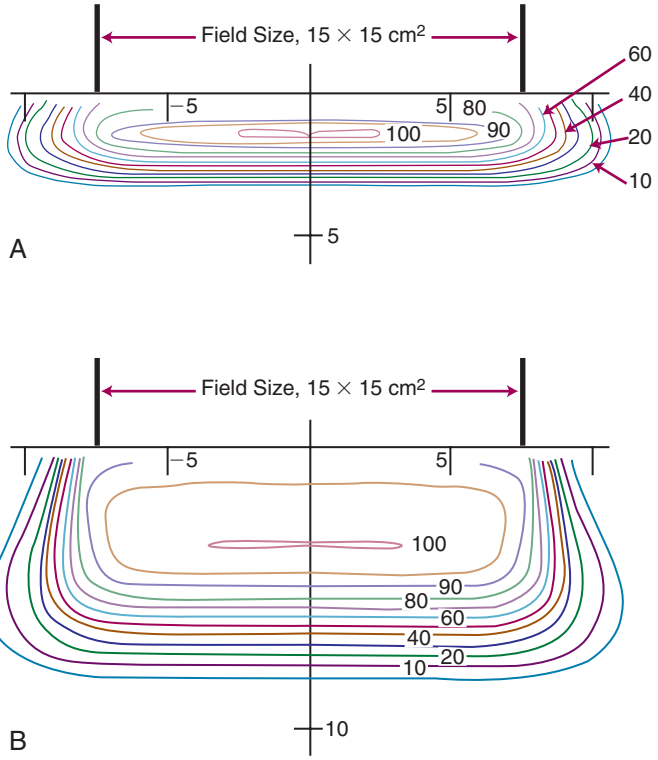


Figure 6-42 Electron beam isodose curves for a field size of 15 × 15 cm². A, 6 MeV. B, 20 MeV.
Data from Hogstrom KR, Steadham RE: Electron beam dose computation. In Mackie TR, Palta JR, editors: Teletherapy: Present and future. Madison, Wlisc., 1996, Advanced Medical Publishing, pp 137-174.

energy spectrum is created with a distribution of electron ranges. The originally monoenergetic electron beam is degraded into a wide spectrum beam with varied practical range.

- The amount of bremsstrahlung contamination increases with energy because the probability for radiative interaction increases with electron energy. Bremsstrahlung contamination can be minimized but not eliminated totally. Structures lying beyond the electron range still receive dose from bremsstrahlung x-rays.
- The approximate d_{80} (depth to the 80% isodose line in centimeters) in tissue can be found by dividing the nominal electron energy (in million electron volts) by 3. The d_{80} of a 9-MeV electron beam is 9/3, or about 3 cm. This number is useful for indicating the largest therapeutic depth, although many clinicians consider the d_{90} as the maximum effective range.

Effect of Field Size

Electron field sizes are changed by using fixed-size applicators to produce square field sizes from approximately 6 × 6 cm up to 35 × 35 cm. Custom cutouts can be used that are inserted into an applicator to provide a shaped field to match a target outline.

- PDD increases only slightly as field size is increased. Scattered electrons have a finite range that is much less than R_p; therefore, for increasing field sizes above 10 × 10 cm or greater, the contribution to the central axis is small. This effect is different from photon beams where scattered photons still have a relatively large mean path length.

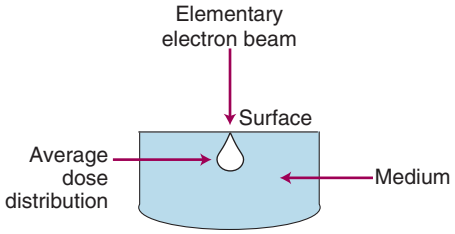


Figure 6-43 Elementary electron scattering kernel.
Adapted from Khan F: The physics of radiation therapy, ed 2, Baltimore, 1994, Williams & Wilkins.

- Surface dose increases slightly as field size is increased because the amount of scattered electrons from the beam path is increased.
- The d_m decreases as field size increases because the amount of lateral electron scatter increases near the surface.
- Absolute dose rate, or beam output, measured at d_m, usually increases as field size increases but can decrease depending on collimator design.

Penumbra

Beam edge sharpness for electron beams varies with measurement depth because of the nature of electron scattering.[22] On interaction at a point, an elementary line of electrons produces a scattering envelope that is teardrop shaped in the forward direction of the beam (Figure 6-43). Electron scattering angles, which initially are primarily in the forward direction, become more randomly oriented at depth.

- Penumbra increases with energy because scattered electrons have a higher effective energy and a corresponding increased range. This effect is seen as a degradation of the profile (enhanced shoulder and toe).
- Penumbra increases as depth increases because of the teardrop shape of electron scattering (see Figure 6-43).
- The field width corresponds to the 50% dose width at d_m, but the shape of the isodose curves changes with increased depth. This effect should be considered during treatment planning.
- Penumbra increases with field size because of increased scatter from the increased volume of irradiated material.
- Penumbra increases as the distance increases from the end of the applicator to the surface. An increased gap allows electrons to scatter laterally before reaching the surface, degrading the field edge.

Other Effects

- Electrons scatter easily, and regions of bone and air greatly change the dose distribution.
- Density scaling can be applied to approximate the electron range in non–unit density materials (see Eq. 20), because mass stopping power is somewhat constant for low Z materials. R_m, the approximate electron range for a material of density p_m, is given by the following equation, in which R_w is the range in water and ρ_W is the density of water (1 g/cm²). For instance, the electron range for a material with a density of 2 g/cm³ is 0.5 times the range in water.

$$R_m = R_w \times \frac{\rho_w}{\rho_m} \qquad \text{Eq. 35}$$

- Electron beams follow the inverse square law, but the reference distance is not the actual source location (i.e., the scattering foil) but instead a virtual source point that is located

along the beam path. This distance is called the *effective source-to-skin distance* (effective SSD) and is usually less than the SAD, for example, 85 cm for a 100 cm SAD linear accelerator. Effective SSD is measured for each energy and applicator and occurs because of multiple electron scatterings along the beam path.

- Use of electron cutouts for field shaping affects scattering conditions and changes output, penumbra, the position of d_{max}, and field homogeneity. These effects are most pronounced when the cutout size is less than one fourth of the applicator dimension or on the order of the electron range.[22] Individual calibration of a cutout or other procedures are required to establish the cutout's dosimetric character when these poor geometric conditions exist.

EXTERNAL BEAM TREATMENT SIMULATION

Purpose

In the "old" days patients were taken to the treatment machine and fields were chosen based on the clinician's general anatomic knowledge and the patient's disease. Diagnostic radiographs were available to help localization. This process is called *clinical setup* because the treatment machine is used with various aids to decide on the beam geometry. Simple fields and manual blocking are used. Clinical setup alone is no longer commonly done, although may be used for emergent palliative treatments. Instead, *simulation* is performed on a special x-ray machine, called a *simulator,* also called a *conventional simulator* (in contrast to a CT simulator). A conventional simulator reproduces all the geometric parameters of the radiotherapy machine and its use has the following advantages:

1. Clinical setup competes with treatment for time on the treatment machine. Simulation on a dedicated simulator does not.
2. Simulators are diagnostic machines with radiographic and fluoroscopic capabilities. Images are of diagnostic quality instead of poor port film quality.
3. The machine can simulate different treatment machine geometries with regard to SSD, SAD, block position, and field size.
4. Simulators are dedicated to the simulation process. Different treatment geometries can be explored without the pressure to turn the room back over for treatment.
5. Simulators can be used to localize and verify brachytherapy implants within the confines of the radiation oncology department (no exposure to outside individuals) and under controlled conditions.

Treatment Setup

There are two basic methods for patient setup: SSD and SAD (Figure 6-44). The SAD technique is most commonly used with today's isocentric treatment devices.

SSD Treatment

If a treatment technique is set up as an SSD treatment, the distance to the patient's skin is recorded in the chart and used as a reference distance for each treatment. The SSD is measured and set to the same point on the patient's surface each time the field is treated. When a different field is treated, the new SSD is set as required before the patient is treated. Each field is independently set and treated. The SSD is standardized to equal the SAD for isocentric machines, so a normal SSD treatment is at 100 cm (80 cm on older treatment machines). The standard SSD is also the distance used for machine calibration. Occasionally, alternative SSDs are used to allow larger field sizes to be used.

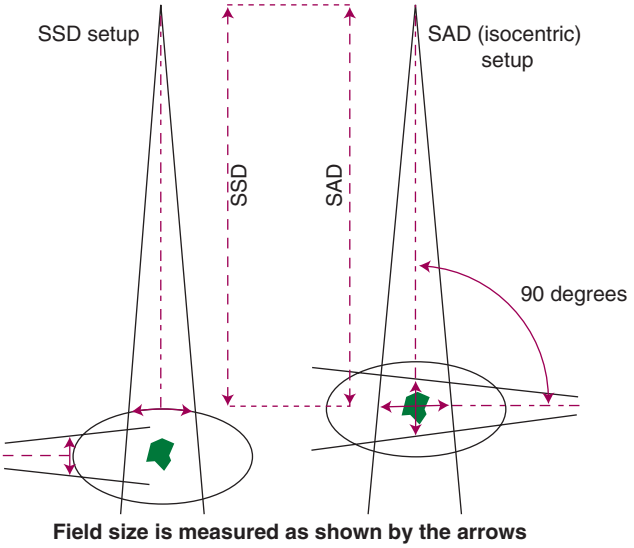


Figure 6-44 Treatment geometries: source-to-skin distance (SSD) and source-to-axis (SAD) approaches.

Compared with SAD treatments, SSD treatments place the target further away from the source. Because the inverse square effect is less, PDDs are greater and larger field sizes may be possible, as when a single field is desired to be used to cover a larger region such as an extremity, the entire spinal cord, or the hemi or whole body. If multiple fields are to be used then the disadvantage is that each treatment field has to be individually set, requiring movements of the treatment couch and patient between successive fields.

SAD Treatment

An alternative to setting the SSD is to set the target volume at the SAD (the isocenter of rotation of the machine). This isocenter is a point in space in the treatment room about which the gantry, collimator, and table all rotate (see Figure 6-3). In this case the SSD is always less than the SAD (SSD < 100 cm). In SAD treatments the target volume always intercepts the beam regardless of gantry, table, or collimator angles.

An advantage is that after one field is set properly, the target is at the isocenter and subsequent treatment fields can be set up rapidly without having to set multiple SSDs. Treatment of a multifield plan therefore is more quickly done because of less setup time, and the target cannot be missed. The disadvantage is that field sizes may occasionally be limited, and there is slightly more inverse square effect.

The advantages of rapid setup and targeting for SAD treatment outweigh those of larger field size and increased PDD for SSD treatments in most cases, and SAD treatments are performed for most patients. This has been especially true because isocenters changed from 80 to 100 cm, providing larger field sizes and less PDD effect, and also because image-guided treatment devices, either orthogonal to or coincident with the central axis of the treatment beam, are designed for rotations around the isocenter, which is most consistent with the SAD treatment technique.

Conventional Radiographic/Fluoroscopic Simulator Description and Components

A conventional radiographic/fluoroscopic (R/F) C-arm simulator unit was originally designed to replicate all of the

mechanical and patient positioning aspects of the radiation treatment unit and has the following components in the geometry shown in Figure 6-3:

1. A fixed gantry stand or base supports the gantry structure that holds the x-ray tube and collimator at one end and the image receptor (flat panel imaging device, film cassette, or image intensifier on the other. The gantry is mounted isocentrically, and the x-ray tube can be positioned to a wide range of SADs or SSDs.
2. The x-ray tube is a diagnostic energy x-ray tube that rides at the top of the gantry. Kilovoltage ranges from 60 to 120 kV(p), and tube current is as much as 1000 mA.
3. The collimator is an assembly that defines the radiographic (image) field size at a given SAD (usually 100 cm). The collimator is isocentric and has field size and rotation capabilities like the treatment machines.
4. Two pairs of field-defining wires are in the collimator, one positioned in the *x* direction and one in the *y* direction. They are used to indicate the size of the treatment field as would be defined by the collimator jaws on the treatment machine. A simulator radiograph shows two radiation fields. The larger field is the actual field imaged as defined by the collimator. The smaller field is the treatment field, indicated by images of the delineator wires. A simulator image shows the treatment field and nearby contextual region.
5. The simulator table is isocentric and has vertical, lateral, longitudinal, and rotational motions. It can be remotely operated from the console, so as to move the patient during fluoroscopy.
6. Hand and console controls allow operation of all of the machine motions from a hand-control unit or the table pedestal in the room, and some of these are duplicated at the control console. All radiographic technique settings are done at the console.

Conventional Simulation Procedures and Immobilization

A patient to be simulated is placed on the conventional simulator table in the treatment position. The supine position is most common, but prone positioning and other geometries are also used. Immobilization devices of various functions and rigidity may be used to maintain patient position, including head holders, thermoplastic face masks, foam molds, cushions and pillows, bite blocks, reflective stereoscopic markers, and vacuum bags. The patient is moved in the treatment position to align the target region or other reference anatomy with the simulator's isocenter. This location is chosen based on available information on the target volume and nearby structures (from planar images, CT, magnetic resonance imaging [MRI], positron emission tomography [PET], clinical examination, surgical reports) or in anticipation of imaging studies for treatment planning. Fluoroscopic imaging or static images are used to determine the location of the isocenter or other reference point in the patient coordinate system. An SSD or SAD setup is chosen, and orthogonal planar images are usually taken to record the patient's position. All geometric information (gantry angle, collimator angle, table position, field size, SSD, SAD) is recorded for each film. Marks are placed on the patient's skin or the immobilization device to indicate the reference field axes.

In conventional simulation, individual treatment field geometries are determined at the time of simulation. All field data are recorded, and simulator images are taken for each field as a record of the intended treatment and for use in designing field shapes. Target and other data are often drawn or annotated on each film or digital image. Images with added contrast agents show certain structures (bladder, rectum). Other data are the clinical examination, surgical reports, surgical clips, markers placed during simulation, and manually transferred contours from CT or MRI images. After the desired data are annotated on the image, a treatment field is drawn that will later be transferred to the shape of the MLC (or custom blocks) for definition of the treatment field aperture on the treatment machine.

Additional geometric information on the patient is needed if treatment planning is to be performed, such as an external contour and the locations of important internal anatomy, including the target, landmarks, and critical structures. For simple 2D planning at least one transverse contour is obtained; however, sagittal and coronal slices (or obliques) can also be obtained. Sources for patient contours include mechanical methods (e.g., solder wire, tracer device), optical methods (e.g., laser grid, light grid, stereo-shift camera), and CT or ultrasound acquisition.[22] In many practices conventional simulation is used for patients who will be treated palliatively, because treatment complexity is low (for instance, one pair of parallel-opposed fields) and patient setup and data acquisition can be done quickly, followed by simple dose calculations, without the need for full 3D representations of the patient anatomy for higher-level dose computations. Thus, institutions with CT simulation capabilities may often retain the "old" conventional simulator for simple cases or for imaging of brachytherapy cases. However, conventional simulation devices are decreasing in number because of the ready availability and maturity of CT simulation, which enables the rapid identification of structures and incorporation of other 3D digital image datasets.

Computed Tomographic Simulation

CT simulation, also called *virtual simulation*[34] or *computer-aided simulation,* uses a CT volumetric image of the patient in treatment position and computer software to perform patient simulation without a conventional simulator. CT simulation is performed on the patient's CT image set, not the patient, hence the name *virtual* simulation. Work flow may vary, depending on clinic preferences for patient flow; however, general principles are to immobilize the patient in the treatment position, obtain CT scout views to verify positioning and to delineate the range of CT scanning, and then acquire the desired CT image sets, which may include noncontrast and postcontrast images. With the patient still in the treatment position in the CT scanner, the CT simulation process then takes place within the computer where the proposed treatment geometry is designed and viewed on screen. Software tools are used to identify and segment anatomic information within the image set (external contour and volumes such as lung, kidney, cord, and tumor) and determine an isocenter for treatment or other identifying reference point. This information is displayed and the treatment beam geometry is reviewed. Once the isocenter has been selected and marked within the CT image set, the isocenter location (or other reference point) is transferred to the (real) patient or their immobilization device, still on the CT scanner, for permanent marking on the patient or immobilization device. Mechanical or laser light technologies exist for a three-point marking that can be replicated on the treatment machine. Importantly, in most software implementations the CT simulation procedure includes virtual simulation only of the proposed treatment geometry and does *not* include dose calculations.

Dedicated CT simulators as turnkey devices, including a CT scanner and simulation software, exist since first in commercial and are in regular clinical use.[35,36] Large aperture CT simulators offer a greatly improved aperture size from a

standard 70 cm up to 85 or 90 cm, depending on the vendor. This increased size greatly improves the image field of view (FOV), allowing bariatric and off-center patients to be CT simulated, as well as enables access for relatively wide or tall immobilization devices.[37] Other readily available CT simulator improvements include multislice and cone-beam CT scanning for rapid acquisition, and four-dimensional (4D) CT-fluoroscopy techniques for assessment of target motion resulting from physiologic processes such as respiration.[38,39]

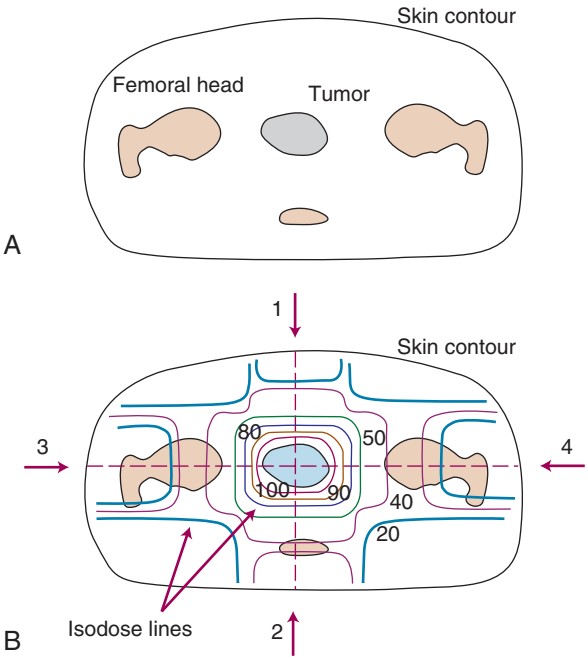
Moving simulation to the digital CT simulation approach has allowed a variety of image processing tools to be applied to the process, such as autosegmentation algorithms and 3D renderings, and has enabled the incorporation of registered multimodality images from MRI, PET, and other modalities. Treatment planning techniques, the next important process after simulation, are discussed in the next section.

EXTERNAL BEAM TREATMENT PLANNING AND DOSIMETRY

Purpose and Procedures

After conventional or computer-aided simulation, the simulator images (if any); CT, MRI, and other digital images; beam geometries; and other patient data are transferred to dosimetry for further treatment planning. During treatment planning, possible beam geometries and combinations are investigated. Simulated beams may be fine-tuned or deleted, or new beams may be created; the beam weights may be adjusted, wedges added, beam energy changed, field sizes adjusted, different normalizations used, and compensation checked. The intent is to produce a treatment plan in the form of a 3D isodose distribution overlaid on the reference CT treatment planning images that can be evaluated by the physician and approved or modified. Treatment plans describe the following characteristics about the patient's treatment, as illustrated in two dimensions for simplicity for the static four-field plan shown in Figure 6-45:

1. Prescription isodose (i.e., the 97% line) or depth (at the isocenter or at 3 cm deep) gives the location where the prescribed dose is to be given.
2. Various tumor, target, and normal tissue volumes as specified according to the International Commission on Radiation Units and Measurement Reports 50 and 62 (ICRU 50 and ICRU 62) recommendations for volumes of interest. This information must be represented in some manner to enable plan evaluation (see later). These volumes may be 3D contours or isodose lines or surfaces.
3. Beam weights indicate the relative dose delivered to the prescription or normalization point by each beam.
4. The presence of beam modifiers (i.e., wedge, custom block, compensation filter, dynamic field shaping, or intensity modulation) is specified.
5. The size and shape of each field (i.e., collimator settings) are specified. If the MLC is used for a shaped field or intensity modulation, each MLC leaf has a specified position as a function of the number of monitor units elapsed.
6. The SSD is specified for each field.
7. "Inhomogeneities" are identified. These are volumes that are not water or soft tissue equivalents (e.g., lung, bone, metal prosthesis) for which dose may need to be corrected. In a CT image set each voxel intensity relates to the average electron density for that voxel and most modern-day treatment planning systems are configured to compute the dose distribution based on the voxel-by-voxel electron density information carried in the CT image.
8. Number of monitor units, or amount of beam-on time, must be set on the machine for each beam.



Beam data
1. AP:18MV x rays, SSD = 92.5 cm, weight = 1.0, field size = 8×10, G:0 C:0 T:0
2. PA:18MV x rays, SSD = 90.5 cm, weight = 1.0, field size = 8×10, G:180 C:0 T:0
3. RLAT:18MV x rays, SSD = 87.5 cm, weight = 1.2, field size = 8×8, G:270 C:0 T:0
4. LLAT:18MV x rays, SSD = 87.5 cm, weight = 1.2, field size = 8×8, G:90 C:0 T:0

Figure 6-45 Typical treatment plan information. **A,** The patient contour and segmented regions of interest. **B,** A treatment plan with superimposed isodose lines. Beam data are shown. *AP,* Anterior-posterior; *LLAT,* left lateral; *PA,* posterior-anterior; *RLAT,* right lateral; *SSD,* source-to-skin distance.

Dose Specification

Components of a dose prescription for a patient treatment course include the patient's name, clinic identification number, treatment site, radiation energy and modality (photons or electrons), prescription point location, dose per fraction, number of fractions, and total dose. These components are recognized standards[40] and are required by most regulatory bodies.[41] The point of prescription defines the location within the patient where dose is to be delivered and therefore defines the geometric point for dose computation. Prescription point selection and additional recommendations for prescribing, recording, and reporting volumes of interest and dosimetric parameters for photon beam treatment are specified by ICRU 50 and ICRU 62.[42,43]

Volumes of Interest

ICRU 50 defines five volumes of interest related to treatment. The following definitions are illustrated in Figure 6-46 for an idealized case:

Gross tumor volume (GTV): The GTV is the volume that contains the gross palpable or visible extent and location of malignant growth. The GTV may be identified on a simple contour, a radiograph, or sectional images.

Clinical target volume (CTV): The CTV is the volume that contains the GTV and any suspected microscopic disease. The CTV is the volume that must receive the prescribed dose to effect cure or palliation.

Planning target volume (PTV): The PTV is a volume that contains the GTV and CTV and that is defined to account for

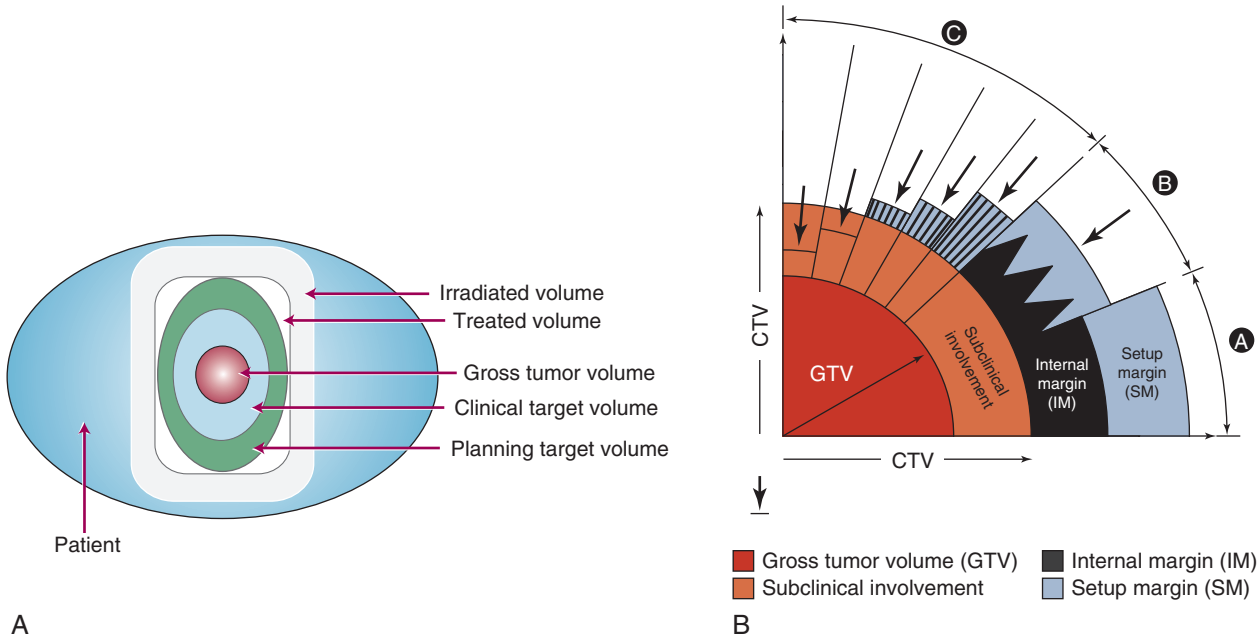


Figure 6-46 **A,** The International Commission on Radiation Units and Measurement Report 50 (ICRU 50) defines five volumes of interest related to treatment. **B,** Schematic representations of the relations between the different volumes (GTV, CTV, PTV, and PRV) in different clinical scenarios. ***A,*** *From ICRU Report 50: Prescribing, recording, and reporting photon beam therapy, International Commission on Radiation Units and Measurements, 1993;* ***B,*** *From ICRU Report 62, Supplement to ICRU Report 50, 1999.*

the irradiation geometry and all uncertainties in treatment, such as organ and patient motions and setup errors. The PTV is a volume that, when covered by the prescription dose, will ensure the delivery of the prescription dose to the CTV. The PTV includes a margin for motion and set-up error but not for microscopic disease. The PTV is a function of treatment geometry, because the number of beams and their orientations may impose limitations on the PTV's shape or scope.

Treated volume (TV): The TV is the volume enclosed by a selected (prescribed) isodose surface and is a function of the treatment geometry required for planning the PTV. For an acceptable plan, the TV is greater than the PTV, although an ideal TV/PTV ratio would be 1.0, indicating perfect conformation (assuming the locations of the volumes were identical).

Irradiated volume (IV): The IV is a volume that receives a significant dose; significance is determined by morbidity or other measures.

ICRU 50 considered radiation target volumes only and did not specify normal tissue volumes that might be relevant for morbidity and avoidance. ICRU 62 addresses this deficiency by specifying organs at risk (OARs) and the planning organs at risk values (PRVs).[43] In ICRU 62 the GTV, CTV, and PTV remain and new defined volumes are the following:

Internal target volume (ITV): The ITV is an expansion of the CTV to account for motion of the CTV, for instance caused by respiratory or digestion motions. Motion may be in a preferential direction such that the expansion of the CTV through internal margins (IMs) may not be isotropic and can be nonuniform.

Organ at risk (OAR): The OAR is a nearby normal tissue or critical structure at risk for radiation-induced morbidity, based on the recognition that normal tissue response is radiation treatment limiting. Thus, relevant OARs are to be identified for purposes of morbidity assessment and assignment of dose constraints. Tissue physiologic organization of OARs as serial or parallel units, or combinations of the two, are considered to aid risk assessment.

Planning organ at risk volume (PRV): The PRV is an expansion of the OAR as a result of possible motion. However, incorporating motion into the OAR can be a challenging process.

Dose Recording and Reporting

The ICRU recommendations for dose include a point for dose computation and indicators of dose homogeneity. The *reference point* is a point within the PTV at which dose is specified. There are several criteria for selecting the reference point:

- The dose at the point is clinically relevant and representative of dose in PTV.
- The point is easily defined by anatomy or geometry.
- The point is a location where dose can be accurately determined.
- The dose gradient at the point is not steep.

With these criteria, suitable point locations include the center of PTV, near the central axis, or where tumor cell density is a maximum. In many cases the isocenter has these characteristics and serves as the reference point, because for nondynamic fields the isocenter is most commonly placed within the target. However, the isocenter may not properly serve as the reference point for IMRT plans because dose constraints for nontarget volumes determine the dose distribution and may result in a nonhomogeneous dose distribution in the target, including a dose gradient through the isocenter.[44]

Dose homogeneity is also to be reported and is represented by the maximum and minimum doses in the PTV. Together, the reference, maximum, and minimum point doses represent the dose to the PTV as well as the variation in that dose.

Dose Reporting for Different Techniques

ICRU 50 demonstrates its recommendations for three levels of complexity: single plane plans, multiple planes, and 3D

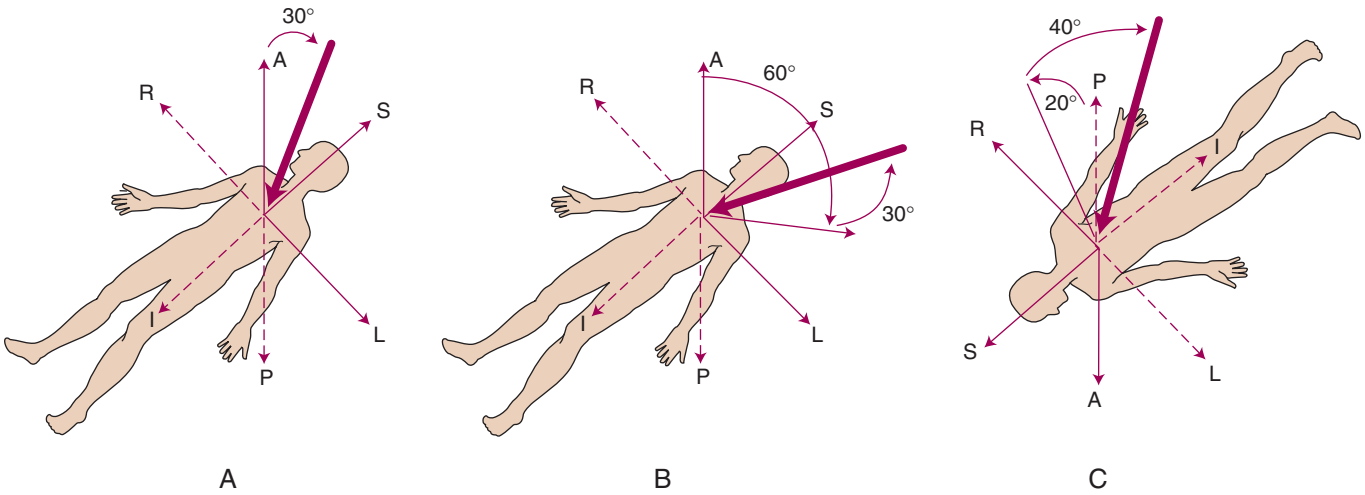


Figure 6-47 Three-dimensional beam nomenclature. Beams are named in reference to the patient coordinate system. **A,** The A30S beam is 30 degrees superior from the anterior axis. **B,** The A60L30S beam is 60 degrees left from the anterior axis and 30 degrees superior. **C,** The P20R40I beam is 20 degrees right from the posterior axis and 40 degrees inferior.

volume studies. In each case the reference point dose is computed and the maximum and minimum point doses are estimated or computed. Isodose distributions are computed if a contour plane or multiple planes are acquired. In the highest complexity, dose evaluation tools such as dose-volume histograms are recommended.

Together the ICRU 50/62 recommendations create a standardized, consistent set of definitions for target and normal tissue volumes, to enable the comparison of treatment plans across institutional and international boundaries. Institutions use the ICRU 50/62 recommendations, and they have been adopted by national protocol groups.

Beam Nomenclature

When using complex field arrangements it can be difficult to describe the precise beam orientation. A system has been developed to allow this description to be done simply.[45,46] The suggested nomenclature defines a coordinate system that corresponds to the patient's anatomic position (Figure 6-47). The axes are labeled *A, L,* and *S* (for anterior, left, and superior) and *P, R,* and *I* (for posterior, right, and inferior). A beam name begins with the closest cardinal axis and then gives the angle of rotation from that axis to the beam central axis. Simple beams with no off-axis rotation are named after their anatomic positions. Examples include *A, P, R,* and *L* for the beam orientations commonly called *AP, PA, right lateral,* and *left lateral*, respectively. Beams with off-axis rotations include the angle of rotation. For instance, A30S indicates an anterior beam that is angled 30 degrees to the superior and A60L30S indicates an anterior beam that is angled 60 degrees to the left then angled 30 degrees superior (see Figure 6-47). This nomenclature is in clinical use in several institutions, and its use removes ambiguities in beam identification. An advantage over naming conventions based on machine coordinates (e.g., the GTC system, for gantry, table, and collimator) is that beam names are reported in the patient coordinate system and can be readily interpreted with respect to the patient position.

Radiotherapy Planning

Two-Dimensional Treatment Planning

Treatment plans such as those shown in Figure 6-45 are the results of 2D treatment planning. The patient contour, whether manually obtained at the time of simulation or obtained from a particular CT slice, must contain the central ray and one collimator axis of the beam; the beam must be coplanar with the contour plane. Beam orientations with central rays outside the contour plane are not permitted. Uses and limitations of 2D treatment planning have been thoroughly discussed[47,48] and very few 2D-only treatment systems are now in use.

Three-Dimensional Treatment Planning

With 3D treatment planning, radiation beam geometries are not constrained to lie in an image plane. Instead, beam trajectories are possible over all solid angles, greatly increasing the number of potential beam paths (see Figure 6-47). Software tools enable target and volume of interest localization/segmentation, image reconstructions, automatic and beam's eye view field designs, 3D dose calculations, and visualization techniques and metrics for plan evaluation. Advantages of 3D treatment include better target localization resulting from image-based planning, more accurate field delineation to include target and exclude critical and normal structures, and improved dose calculation models that consider the 3D shape of the patient and composition. Chapter 16 presents 3D treatment planning in detail, and comprehensive reviews are available.[49-52]

Dose Computation Algorithms

Photon dose calculation methods can be classified as one of four types: (1) empirical or semi-empirical models (e.g., broad beam methods based on the TMR and SMR), (2) analytic models based on first principles, (3) convolution models that use dose kernels and pencil beams, and (4) random sampling or Monte Carlo models that directly calculate the dose. Broad beam methods have been reviewed,[48] and work continues on higher fidelity models.[49,50,53-55] A clinically implemented electron calculation model with acceptable accuracy has been published and further developed.[56] Advances include convolution pencil beams and full Monte Carlo methods, which account for the 3D electron density distribution of the irradiated volume, radiation transport, and the spectral components of megavoltage photon and electron beams.[57] Convolution models for photon beams are well studied and implemented in every commercial treatment planning system. They compute dose based on the electron densities of the individual CT voxels traversed, using "density scaling" across non–unit density voxels. Thus tissue inhomogeneity or other "corrections" are

not needed, as they are for broad beam models, to compensate for inadequacies in the computation model. Physics requirements for dose calculation systems include calibration of the CT scanner intensity values (CT numbers) and proper commissioning of the treatment planning system using measured beam data to confirm dose computation accuracy over the range of irradiation geometries and electron densities clinically encountered. In the relatively near future, photon and electron doses will be computed rapidly, using graphics processing units (GPUs) or other fast hardware, and with the greatest accuracy possible using Monte Carlo algorithms that account for all unique aspects of the patient dataset.[58,59]

Treatment Plan Evaluation and Optimization

Evaluation of a treatment plan to determine clinical acceptability is a process that depends on the patient geometry, target dose coverage, protection of normal structures, and other clinical criteria. A treatment planner (dosimetrist) can provide several "reasonable" plans under physician guidance, but acceptability is a clinical decision by the radiation oncologist. One tool that aids quantitative plan evaluation is the dose-volume histogram (DVH).[60] A DVH represents a treatment plan by graphically indicating the fractional amount of a volume of interest that receives a specified dose (or more). Two histograms are possible: the differential DVH (dDVH) shows the fractional volume receiving a specified dose whereas the cumulative DVH (cDVH) is the integral form and shows the fractional volume receiving a specified dose or more. Both forms are shown in Figure 6-48 for hypothetical target and normal tissue volumes. The cDVH is the form most commonly used. Although DVHs show dose coverage of a volume, a disadvantage is that spatial information of the dose distribution is lost. For instance, inadequate coverage of a target volume may be indicated by the shape of the DVH but the location of the poorly covered region is not indicated; the treatment plan must be viewed to determine the location.

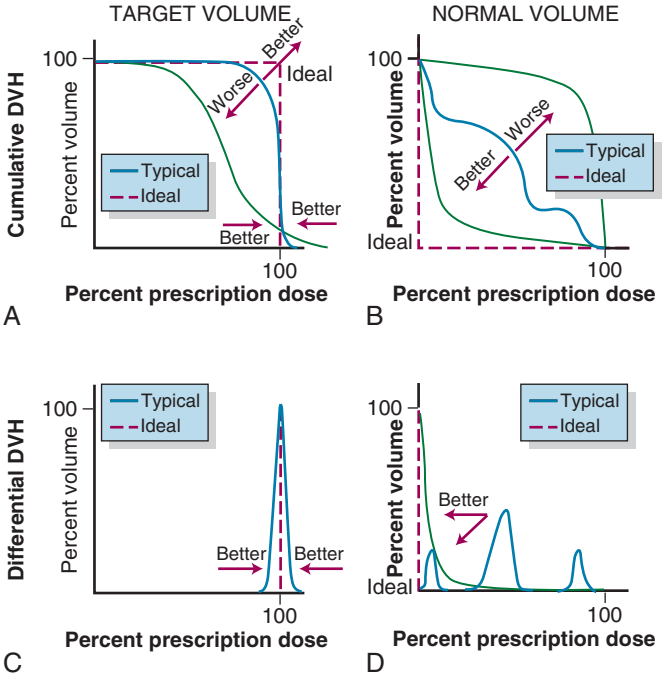


Figure 6-48 Dose-volume histograms (DVHs). **A,** Cumulative DVH for the target. **B,** Cumulative DVH for normal tissue. **C,** Differential DVH for the target. **D,** Differential DVH for normal tissue. Ideal DVHs are shown by the *dashed lines*. Indications for better or worse DVHs are shown.

Optimization of treatment plans depends on quantification of optimization criteria and may include dosimetrics (dose constraints at points or regions), permitted and prohibitive beam geometries, DVH indices, and approximations to biologic response functions such as tumor control probability (TCP) and normal tissue complication probability (NTCP) or other indices.[53,54] Mathematical optimization does not necessarily equate with clinical acceptability; optimization criteria may be improperly selected or otherwise limited. Similarly, rank-ordered, mathematically optimized plans may yield numerous clinically equivalent plans. Continuing work in treatment planning, research, and development requires clinical trials to show efficacy of the techniques. Various trials are under way, as discussed in Chapter 16.

Monitor Unit Calculations

Treatment planning data include beam parameters and weights that indicate the dose contribution of each beam to the prescription point. The setting on the treatment machine that controls dose delivery, either monitor units (MUs) or timer setting, must be computed so that the proper dose for each beam will be delivered. Typically, the MU or timer setting is calculated by the treatment planning system, particularly so for 3D treatment planning systems and for IMRT plans. As an independent check of the planning system and for simple irradiation geometries, the MU or timer setting is validated by performing a second-check calculation using treatment machine data tables of PDD, TMR, and other parameters—a TMR-based algorithm using measured data for each beam is an almost universal practice. Generally, this calculation is based on a broad beam model with homogeneous media (water, based on acquisition of beam data in a 3D water phantom), or the water-equivalent path length for heterogeneous media; thus calculations may give poor agreement (outside of ±5%) for complex irradiation geometries with heterogeneous media, strong surface or interface perturbations or small beams. This simple model is not appropriate for an independent check for IMRT fields without having a model that accounts for the contribution of each beamlet to the prescription point.

In a second-check MU calculation system and for applicable irradiation geometries the MU or timer setting can be calculated with the basic equation:

$$\text{Setting} = \frac{\text{Dose}}{\text{Dose rate}} = \frac{D}{\dot{D}} \qquad \text{Eq. 36}$$

in which the dose, D, is the desired dose (in centigrays) to the prescription point from the beam (target dose), and the dose rate, $\dot{D}$, is the dose per MU (centigrays per MU), or dose per time (centigrays per minute), that the beam delivers to the prescription point. Dose rate is relative to $\dot{D}_0$, the calibrated dose rate of the treatment unit, which is obtained for a reference geometry (depth = d_{max}, 10 × 10 cm^2 field size at 100 cm SAD) and material (water) using a national consensus protocol (in the United States, TG-51, American Association of Physicists in Medicine).

Equation 37 is used for calculation of monitor units (for linear accelerators):

$$\text{MU} = \frac{D(\text{cGy})}{\dot{D}(\text{cGy/MU})} \qquad \text{Eq. 37}$$

Equation 38 is used for timer calculations (for teletherapy devices):

$$T(\text{min}) = \frac{D(\text{cGy})}{\dot{D}(\text{cGy/min})} \qquad \text{Eq. 38}$$

The real work comes in determining the dose rate at the prescription point, $\dot{D}$, for the particular treatment geometry being calculated. $\dot{D}$ (Gy/MU or Gy/min) can be found from the reference dose rate, $\dot{D}_0$, by the following equation:

$$\dot{D} = \dot{D}_0 \times \text{PDD(or TMR or TAR)} \times \text{OF} \qquad \text{Eq. 39}$$

The term *OF* represents *other factors*, including attenuation factors for beam modifiers such as field shapes (use of MLC or custom blocks), wedges, and compensators; output factors for field sizes; off-axis dose rate factors; an inverse square term if needed; transmission and buildup factors for immobilization devices (molded sponges, thermal plastic masks, arm or breast boards, stereotactic frames); and any other devices or parameters that must be considered. As stated, in most cases the beam weight and $\dot{D}$ are computed by the treatment planning system, yielding a completed MU calculation for treatment. As explained here the simple MU calculation is performed as an independent, second check for confirming the treatment planning dose computation. Any MU calculation system must be thoroughly understood and defined to ensure its appropriate application to computation of the correct dose to the patient. MU calculations have been formalized in consensus documents in the United States[61] with similar formats in other countries.

EXTERNAL BEAM TREATMENT VERIFICATION

Treatment Portal Imaging

External beam treatments are verified by validating setup data such as beam geometries, including SSD measurements, and through comparison of simulator and treatment portal images. The use of portal images (originally performed with film) has been shown to have a positive impact on treatment,[62] and common practice is to obtain portal images at the beginning of treatment and for each week thereafter. The image quality of megavoltage port images is poorer than the quality for companion simulator images or kV-equivalent digitally reconstructed radiographs (Figure 6-49) because of poor subject contrast[63] caused by the dominance of the Compton effect. However, improvements to portal image quality have included design of more sensitive films; enhancement of image capture by the use of specifically designed screens, cassettes, or film-screen-cassette systems; combination diagnostic and therapy imaging; image enhancement of digitized portal films; and especially digital acquisition of the portal image, which is the current state-of-the-art.[63-65] Digital portal imaging systems, referred to as *electronic portal imaging devices* (EPIDs) were originally designed with at least five types of EPIDs,[63] depicted schematically in Figure 6-50: mirror-based video systems, fiberoptic video systems, liquid ionization chamber systems, scanning ionization chamber systems, and static solid-state systems—the flat-panel image receptor. This last design, using primarily amorphous silicon (aSi) as the detector element, has become the industry standard and is used by all linear accelerator manufacturers (see Figure 6-5). The use of EPIDs in clinical practice includes simple replacement of film, treatment verification by manual comparison with digital reference films, image enhancement by digital techniques such as adaptive histogram equalization for improved structure recognition, automatic determination of patient positioning to permit or prohibit treatment, dynamic monitoring of conventional treatment, dynamic monitoring of dynamic treatment (e.g., IMRT), and verification of treatment dose delivery.[64] These applications depend on the design and operational characteristics of the devices, such as image sampling and refresh rates (as needed for fluoroscopy), signal-to-noise ratio, detector resolution, detector radiation sensitivity, size of the active imaging area, software for image processing, physical size, and ease of use.

In Vivo Dosimetry

Dosimetric verification of treatment is sometimes required for unique patient geometries or critical situations such as total-body irradiation. Techniques for in vivo dose measurements include the following:

1. Optically stimulated luminescent dosimeters (OSLD) or thermoluminescent dosimeters (TLD) can be packaged in capsules or protective bags and placed in cavities, directly on the skin surface, and under extremities or bolus. Evaluation of results can be challenging for geometries where buildup is not complete. OSLD has replaced TLD as a commonly used method for in vivo dosimetry, although TLD remains a quite valid method.
2. Diode or MOSFET detectors with integral buildup may be placed superficially or intracavitarily. Diode and MOSFET systems can be set up rapidly and results are immediately

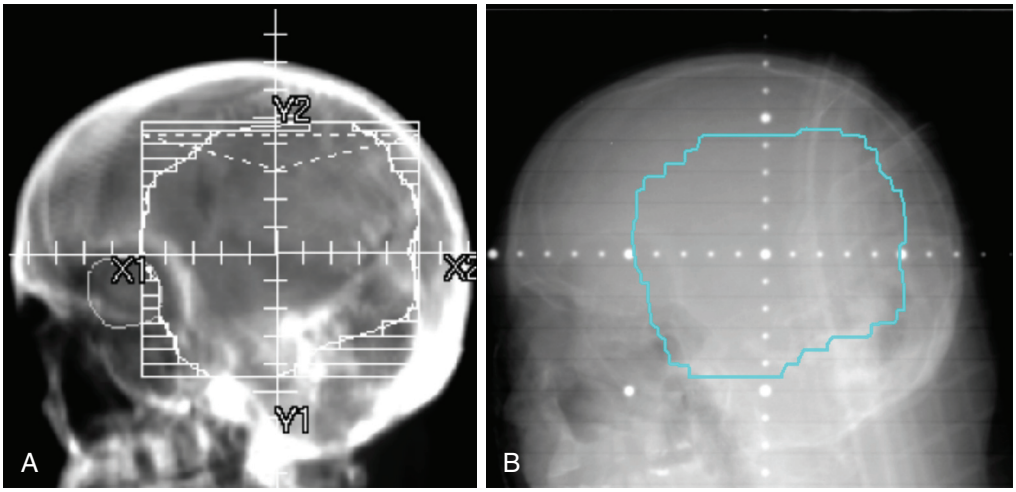


Figure 6-49 Imaging with diagnostic and high-energy photons. **A,** Simulator film of a brain tumor patient, with a block indicated by the outline. **B,** Port film of the patient in **A** shows the blocked area and context around the treatment region. Contrast is much higher in **A** because of increased amount of photoelectric effect. Contrast is poorer and of more limited range in **B** because of dominance of the Compton effect.

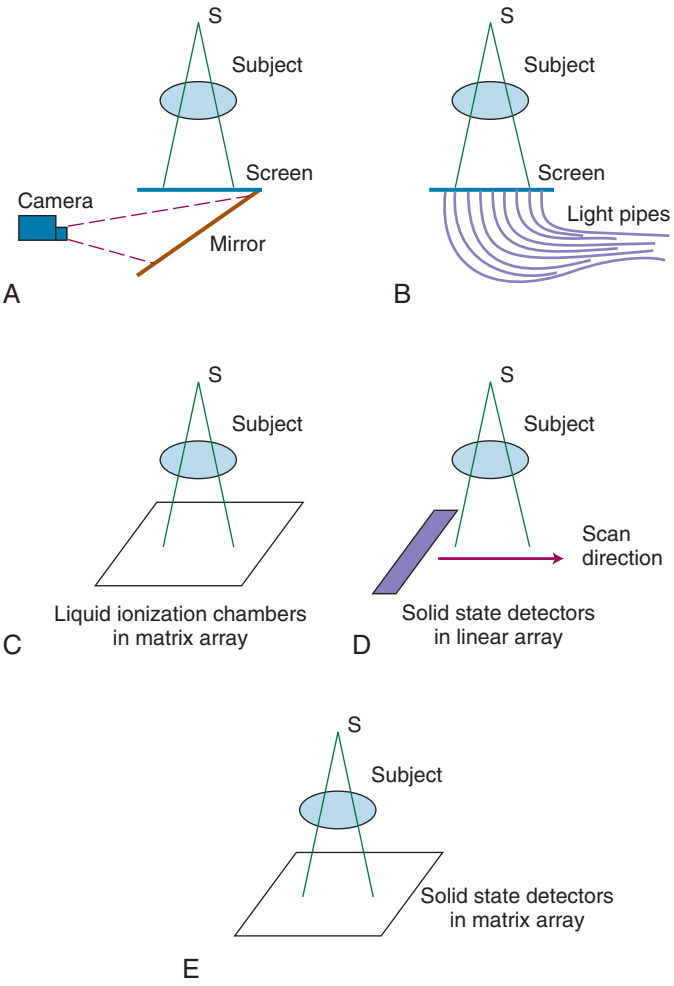


Figure 6-50 Five methods for electronic portal imaging. **A,** Fluorescent screen, mirror, and camera. **B,** Fluorescent screen and light pipe carrier. **C,** Direct irradiation of the matrix array of liquid ionization chambers. **D,** Direct irradiation of the linear array of solid-state detectors, with scanning. **E,** Direct irradiation of the matrix array of solid-state detectors.

available. They have gained popularity because of their ease of use compared with TLD. Designs exist with direct electronic connection to an in-room readout device or detectors alone that after irradiation are inserted into a readout device.

3. Radiochromic film can be used in a patient-equivalent phantom in the replicated patient treatment geometry. Film density is read with a calibrated digital scanner and with a film dose-response curve enables the readout and evaluation of isodose lines to yield a qualitative indicator of the relative dose distribution delivered.
4. A patient-equivalent phantom is tissue equivalent and includes internal structures such as bone, lung, and airways. Some phantoms are sectioned into transverse slabs and can accept radiochromic film, OSLD, TLD, or even ionization chambers at a particular anatomic level. Anatomic phantoms differ in shape or anatomy from the real patient but are useful for studying treatment geometries.
5. Ionization chambers rarely are used for in vivo dosimetry but may be placed with a protective sleeve in vivo superficially or in intracavitary locations, such as for monitoring a high-dose-rate brachytherapy procedure.
6. EPIDs can be used for transmission dosimetry for integrated or real-time measurement of dose when the patient geometry is known. Developing uses include static field and IMRT dosimetry.
7. Remote reporting MOSFET detectors are now available, with primary use in the breast or prostate. These solid-state detectors can be interstitially implanted and interrogated remotely to measure dose in situ. Such devices are biocompatible, relatively small, and can be visualized with kilovoltage imaging.

EXTERNAL BEAM TREATMENTS: GENERAL TECHNIQUES

Target depth, size, anatomic site, and proximity of critical structures all influence the choice of treatment modality (photons or electrons) and the technique to be used. Technique includes the number of beams; beam energy; beam weight (the relative amount of dose delivered by a beam); field shape; irradiation geometry; and use of bolus, wedges, compensators, or other special devices. Treatment planning techniques have been well studied and presented.[66,67] General practice is that photons are almost always used in a combination of two or more fields (i.e., parallel opposed, wedged pair, three field, four field, more field, or arc) and electrons are used as single *en face* fields (perhaps junctioned with other electron fields to cover a larger area). Example photon plans demonstrate these principles for the parallel-opposed, wedged-pair, three-field, four-field, and arc techniques in Figures 6-51 to 6-56. As the number of fields increases, there are two observations: The high-dose region becomes more conformal to the target, and the peripheral dose decreases but the volume of tissue covered by peripheral dose increases.[21] Current-day radiotherapy uses from one field (as delivered in a simple unidirectional treatment) up to effectively several hundreds or thousands, as delivered with IMRT or dynamic arc treatment. Electron treatment planning is less mature than photon planning and even now is often not performed at all, although pencil beam and even Monte Carlo calculation algorithms are available with accuracies that are clinically acceptable.[56,57] Commonly enough, electron treatment plans are based on graphic or tabulated measured data as previously shown (see Figs. 6-42 and 6-43).

THREE-DIMENSIONAL CONFORMAL RADIOTHERAPY

The goal of delivering dose to the target volume and minimal dose elsewhere was not easily approached with the limitations of early treatment technologies, because volumetric images (CT, MRI), beam shaping/modulation techniques, and computerized treatment planning were not available or were primitive. The 3D problem was understood, but tools did not exist to allow solution. Development and maturation of 3D treatment planning tools have rapidly enabled workers to consider the search for an "optimal" treatment plan, reasonably thought of as a plan with a dose distribution that "conforms" to the target volume (Figure 6-57). For many clinical sites conformal radiation treatment is the state-of-the-art, through the use multiple static, shaped fields, static or dynamic IMRT, or other computer-controlled approaches. Conformal radiation treatment is reviewed in Chapter 16.

Conformal radiotherapy plans are realized by using a large number of beams of various weights, sizes or shapes, and orientations to hit the target. If enough beams of the proper kind are used, a dose distribution can be created with a shape

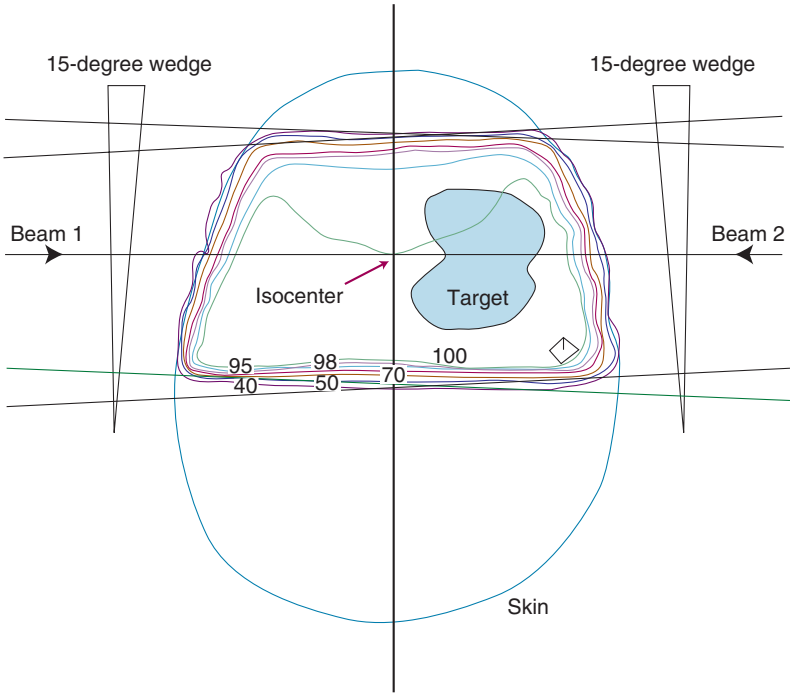


Figure 6-51 Parallel-opposed plan for treatment of a target in the head or neck.

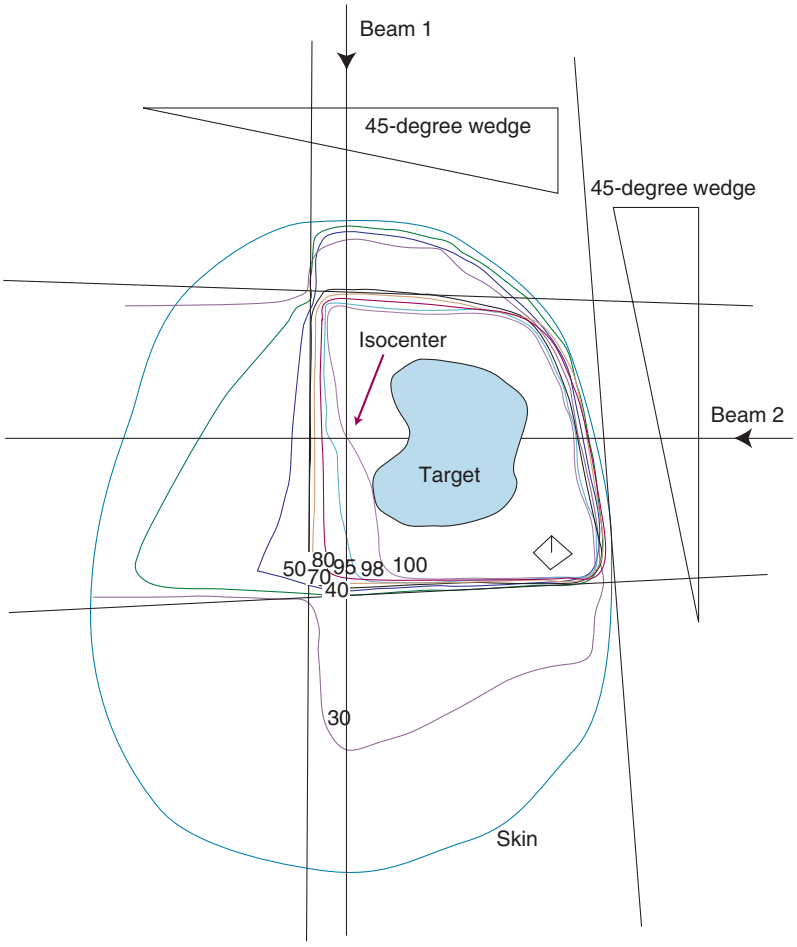


Figure 6-52 Wedged-field plan for treatment of a target in the head or neck.

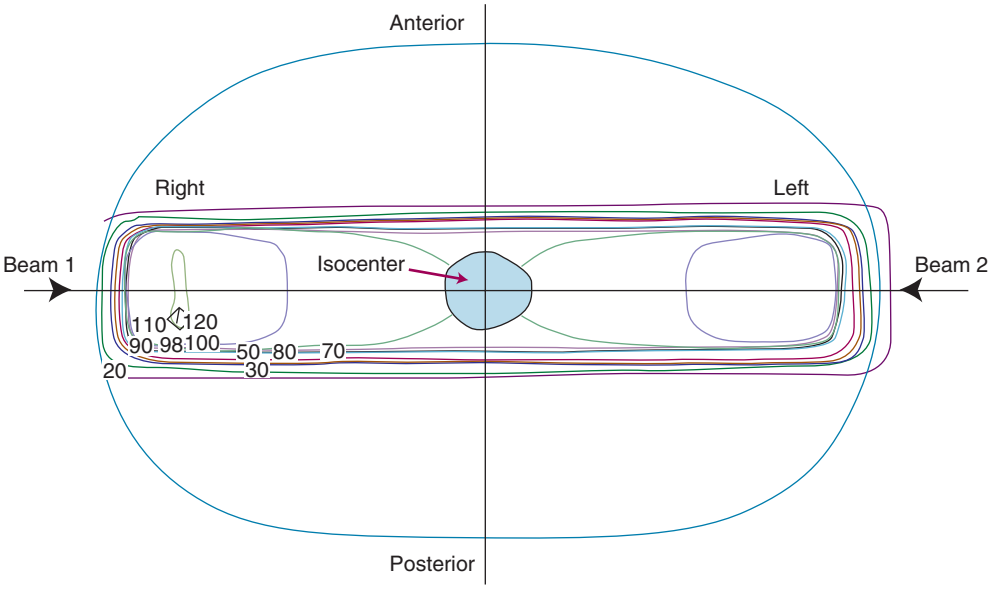


Figure 6-53 Parallel-opposed plan for treatment of a target in the pelvis.

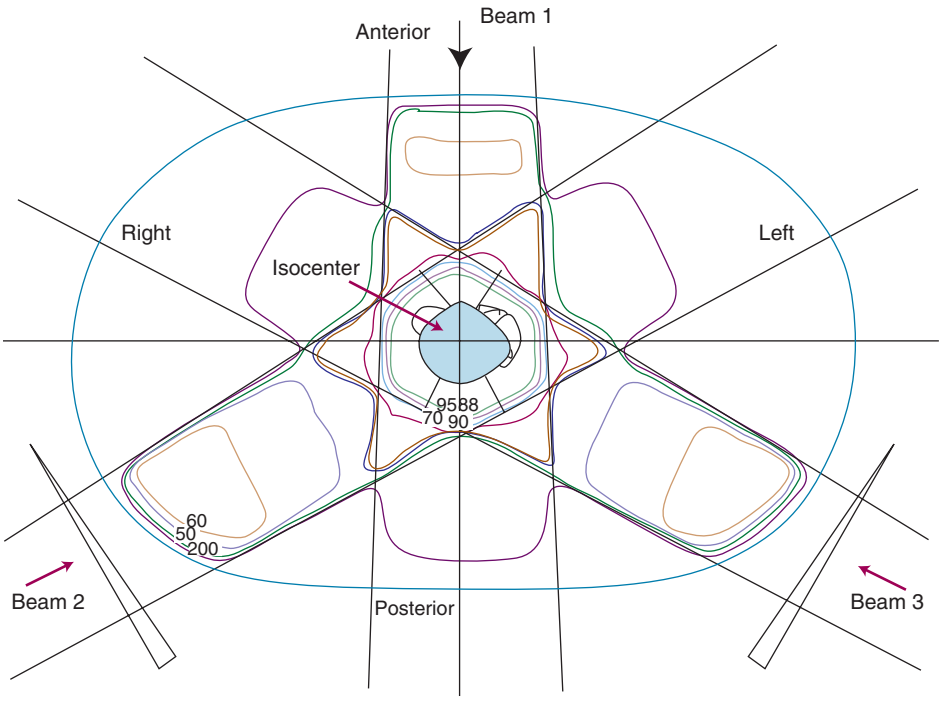


Figure 6-54 Three-field plan for treatment of a target in the pelvis.

that conforms to the target volume. This technique was recognized early[21] and is the reason multiple fields are used. In this regard, all radiotherapy treatment plans are conformal; however, the degree of conformation greatly varies based on the irradiation technique.

Conformal delivery techniques include a variety of approaches. Multiple static fields for 3D conformal radiation therapy (3D CRT) can be shaped by custom blocks, MLCs, miniature MLCs,[68] and custom stereotactic collimators.[69] Dynamic fields using arcs of gantry motion can be delivered using fixed field shapes[70] or variable field shapes[71] for each arc path. IMRT has several delivery approaches and can be delivered using static fields with 3D compensators[32] or by dynamic techniques using a binary collimator[13,72] or MLCs.[73,74] Some of these approaches are used for single-fraction radiosurgery techniques and others for fractionated treatment.

IMRT has become an important treatment approach over the past 15 years for curative treatment as well as for challenging irradiation geometries.[75-77] In IMRT the shaped outline of the radiation beam at a particular gantry angle is subdivided into a large number of beamlets, with the intensity of each beamlet set during an optimization procedure to give a particular dose. Beamlet width is set by the projected width of an individual MLC leaf. With a nonbinary MLC the length of each beamlet is variable and depends on the required dose and dose gradient needed and the technical specifications of the MLC device. The reconstruction of a conformal dose distribution for IMRT is the same process as CT image reconstruction from transmission profiles.[75] If an optimized plan is one that is conformal, solving the inverse radon transform will provide a solution that is optimal. However, it can be shown that a solution cannot be found that will give an exactly

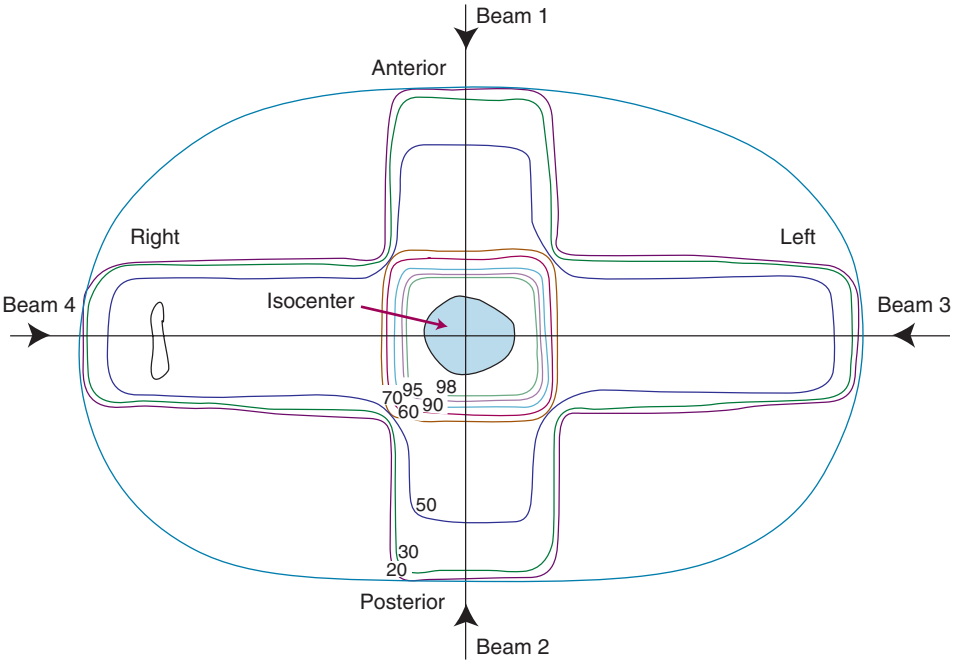


Figure 6-55 Four-field plan for treatment of a target in the pelvis.

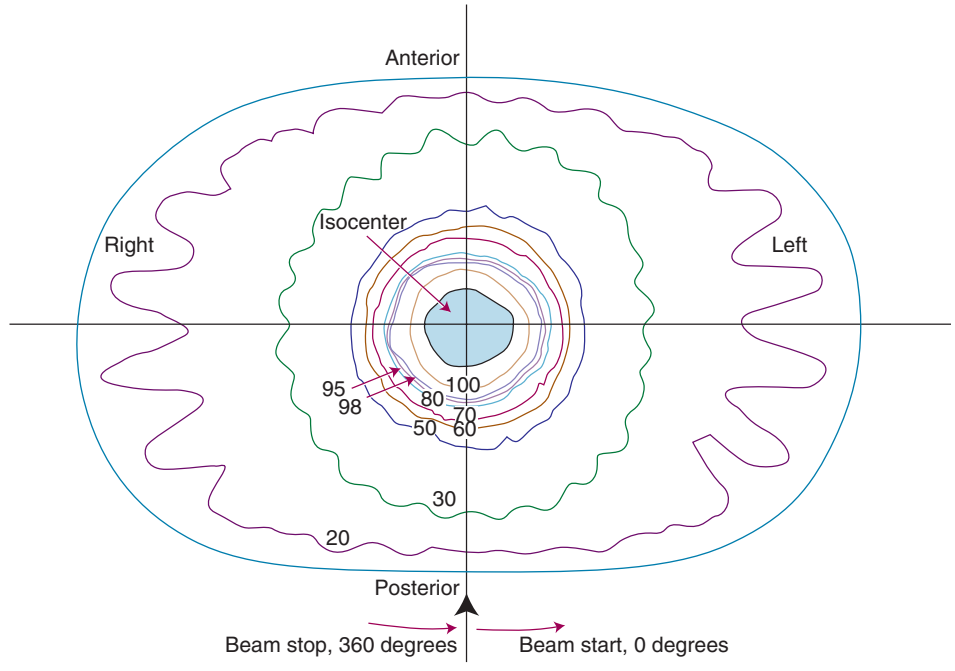


Figure 6-56 Arc plan for treatment of a target in the pelvis.

conforming distribution because negative beam weights (use of negative energy) are required but are not possible. The approach is to find an approximate solution to the inverse radon transform through iterative techniques. Also, importantly, dose constraints are set for both target (minimum dose to a point or volume) and normal or critical structures (maximum dose to a point or volume), and these constraints drive the automated dose optimization process. A thorough review of the conformal problem and its solutions is published,[54] and the field continues to develop with new approaches, faster optimization algorithms, and integrated plan evaluation tools. In a newer technique, rotational IMRT is delivered, using the conventional C-arm linear accelerator design, with simultaneous motions of the MLC leaves and gantry (arc movements). This technique is called intensity-modulated arc therapy (IMAT) or volumetric-modulated arc therapy (VMAT).[78] An intensity-modulated conformal plan is shown in Figure 6-58, and Chapter 16 gives additional information.

IMAGING IN RADIOTHERAPY

Radiotherapy procedures have become image based, and image-guided interventions, whether for surgery, lesion ablations, embolization of vascular defects, radiotherapy, or other therapies, are increasing in number.[56-58,77,78] The contributions of advanced imaging for radiotherapy include two primary areas: imaging for verification of treatment delivery and

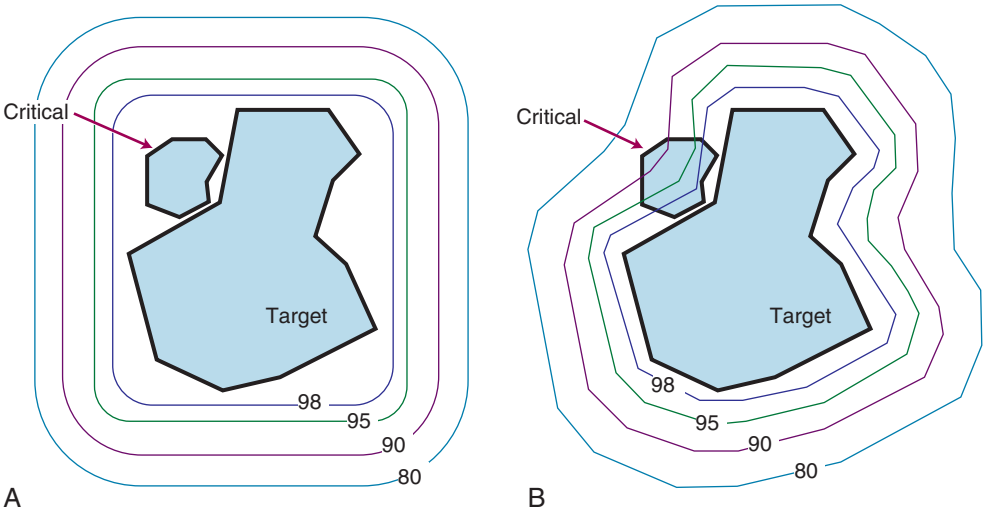


Figure 6-57 The conformal problem. A conventional plan **(A)** treats the target quite well but also treats a nearby critical structure. A conformal plan **(B)** treats the target well and spares part of the critical structure. Is the conformal plan better than the conventional plan?

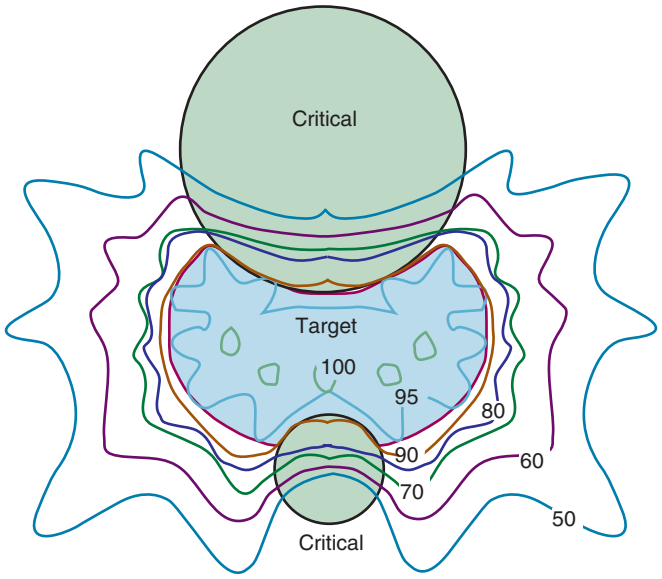


Figure 6-58 Example of a conformal plan. Intensity-modulated plan for a target located between two critical structures.
Adapted from Oldham M, Webb S: A 9-field static tomotherapy planning and delivery study. In Proceedings of the XIIth International Conference on the Use of Computers in Radiation Therapy, Salt Lake City, Utah. Madison, WI, 1997, Medical Physics Publishing.

imaging for better understanding of the biology of cancers and normal tissues.

Image-Guided Radiotherapy

Image-guided interventions have been developed for a multitude of medical procedures, including radiotherapy.[79,80] The main justification has been the development and use of highly conformal radiotherapy plans, which carry risk for their implementation—in general, 3D CRT and IMRT plans use small fields that if delivered with geometric miss to the wrong location increase the likelihood of CTV underdoses. Thus, use of highly conformal radiotherapy techniques has heightened the need for image-based verification of treatment delivery on a more frequent basis than just the weekly portal images. This need has led to IGRT in which daily in-room imaging is performed immediately before each radiation treatment fraction. IGRT approaches that use in-room imaging include isocentric ultrasound imaging, CT-on-rails, radiographic and fluoroscopic projection imaging, kV cone beam CT, MV cone beam CT, and MV fan beam CT.[81,82] These devices are integrated with the MV treatment device to form a hybrid imaging-treatment unit. Implementation issues include image quality, imaging dose, image interpretation, manual versus automated comparison of daily and reference images, revisions to treatment plans based on observed daily variations of position and anatomy compared to a reference treatment plan, and image archival and retrieval.[81-83]

Imaging for treatment simulation and IGRT techniques have made possible the study of target motion, to assess if a target moves outside the radiation field such that a geometric miss might occur.[84] Target motion is primarily because of the respiratory cycle; however, bladder and bowel filling or emptying or other noncyclic motions may also cause target motion. The main approach is to perform a motion study of the target, using (typically) CT and possibly PET, using a variety of image acquisition and reconstruction techniques. A common method is to acquire images at the same time that the respiratory cycle is tracked, over a time period of several respiratory cycles. Each image is correlated with the respiratory phase at the time of acquisition and then rebinned with that corresponding phase. A "playback" of the images over time yields a coherent set of dynamic images on which target motion can be observed and measured as a function of time. This technique is possible for 4D CT and PET imaging modes,[84] with 4D MR under investigation. At the time of treatment planning and treatment any observed target motion can be accommodated by one of several techniques: using a larger treatment field, gating the treatment to match a particular phase of the respiratory cycle, real-time tracking of the target using a surrogate fiducial marker detected by optical means or rapid radiologic imaging, or optical patient surface tracking.[82,84] Motion assessment and compensation techniques continue to be developed, and techniques that use optical and remote monitoring show promise for being fast in detecting motion and changes in patient position.

Although optical methods tend to be limited to detection of visible surfaces, in one technique real-time remote monitoring of target position is performed before and during

treatment, using interstitially implanted glass-encapsulated transponders and an in-room remote readout device.[85] At least three transponders are implanted into the target and their relative positions are determined from the treatment planning CT scan and the remote readout unit, with geometric reference to the isocenter position. Each day patient position is set based on the planning CT scan and then monitored in real-time to ensure treatment delivery to the correct location.[85,86] Accuracy is high, transponder migration is typically small although possible, and imaging modalities should be considered for the best information flow with minimal image artifact.[86,87]

Biologic Imaging

Biologic imaging is imaging of physiologic, metabolic, and functional processes to noninvasively measure the biologic character of tumors or normal tissues. Important biologic aspects of tumors to be imaged include metabolite content, the presence of hypoxia, and cell proliferation. Methods with biologic imaging potential include PET and PET/CT with novel radionuclides and ligands for specific receptor targeting, MR spectroscopy, functional MRI (fMRI), MR diffusion and perfusion imaging, ultrasonography, and optical methods for targeted receptors.[80] Biologic and molecular imaging techniques have increased tremendously over the past 10 years, and their applications include preclinical basic science research, the use of imaging as a biomarker, and studies of clinical responses to radiotherapy. Molecular imaging applications in radiation oncology are in active development.[88]

As a biomolecular imaging example, brain tumors have been studied using magnetic resonance spectroscopy (MRS) to measure the spatial distribution of metabolites that correlate with tumor grade.[59,60,84,85] Choline, creatine, *N*-acetyl-aspartate (NAA), lactate, and other metabolites relevant to the type of tumor (in this case, brain tumors) are determined by MRS. The ratio of choline to NAA is determined by spectroscopic peak height analysis and mapped on a contrast-enhanced MR image (Figure 6-59, *B*). One observation is that the spatial distribution of metabolite values and ratios for brain tumors differ in size and shape from that of (conventional) contrast-enhanced MRI.[89,90] Figure 6-59 shows the problem for targeting with radiation: metabolite ratios or other tumor-specific information from biologic imaging modes will redefine how oncologic targets are determined. Anatomic methods that image endogenous contrast or contrast-enhanced regions will be complemented with advanced biologically based imaging techniques. These multimodality images will be used for targeting. The information is greater than having two different imaging modalities such as CT and MRI; it is the addition of patient-specific imaging to determine tumor character and environment. The validation of these new imaging techniques is important to ensure the understanding of the image information content, that is, the meaning of an intensity value for a voxel and how the image should be used as part of the radiation planning process.[89,91]

Biologic imaging and methods for IGRT will continue to mature over the next decade. Biologic imaging will contribute especially to the understanding of cancer and normal tissue biology. Costs, technologic aspects of implementation, and clinical benefits of multimodality imaging remain to be solved for biologic imaging and its uses in radiation treatment planning and the evaluation of patient response to treatment.[79,92] For instance, dedicated PET/CT and MR simulators have been implemented to facilitate the uses of these advanced imaging modalities for radiation oncology patients.[93] Also, the development of hybrid imaging-treatment devices for IGRT continues with MR-linear accelerator and MR-gamma teletherapy designs now being brought into clinical use.[94,95]

STEREOTACTIC RADIOSURGERY AND RADIOTHERAPY

High accuracy and precision radiotherapy can be performed using stereotactic image-guidance and rigid immobilization or remote monitoring and positioning systems. The *stereotactic* component of these techniques refers to immobilization or fixation of the patient with a rigid or otherwise stable system

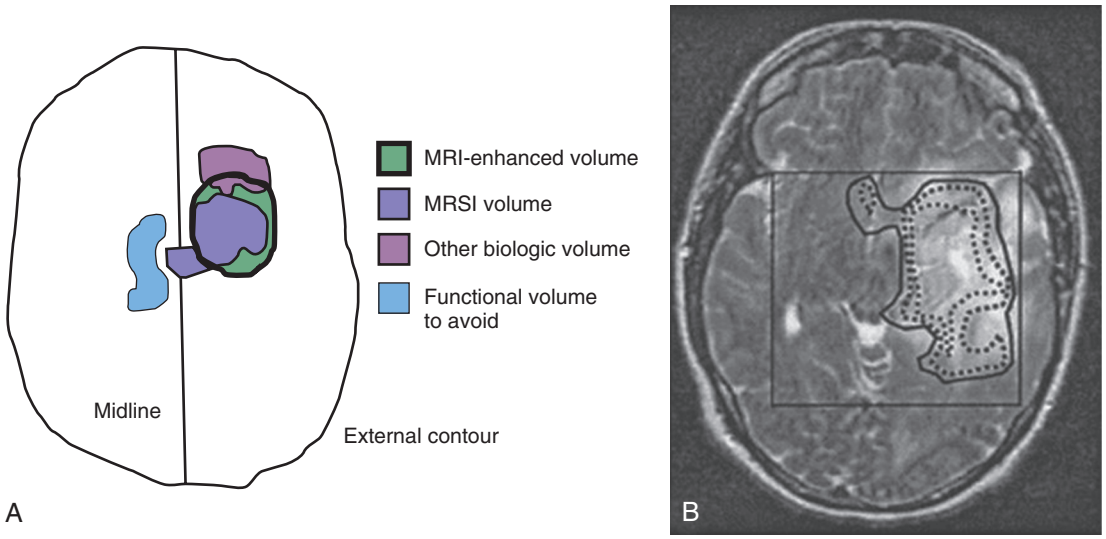


Figure 6-59 Biologic target volumes. **A,** Schematic shows the possible arrangement of three representations of a brain tumor: contrast-enhanced magnetic resonance imaging (MRI, *green*), magnetic resonance spectroscopic image (MRSI, *purple*), and other biologic volume *(violet)*, such as proliferation and receptor density. A region of avoidance *(blue)* is represented as may be obtained by functional MRI. **B,** From inner to outer shells, successive iso-ratio lines for choline-*N*-acetyl-aspartate (NAA) metabolite ratios (cho/ NAA) of 6 *(dotted line)*, 4 *(dotted line)*, and 2 *(solid line)*. Distribution of the metabolite map crosses the midline and differs in size and shape from the (conventional) contrast-enhanced region.
A, *From Bourland JD, Shaw EG: The evolving role of biological imaging in stereotactic radiosurgery. Tech Cancer Treat Res 2:135-140, 2003;*
B, *from Pirzkall A, McKnight TR, Graves EE, et al: MR-spectroscopy guided target delineation for high-grade gliomas. Int J Radiat Oncol Biol Phys 50:915-928, 2001.*

coupled with same-day imaging, to establish a patient-specific image-based coordinate system for the entire treatment process. *Stereotactic radiosurgery* (SRS) refers to the use of single-fraction, small-field, high-dose (12- to 24-Gy margin dose), focal radiation for treatment of relatively small intracranial or extracranial tumors.[96] By two SRS techniques, a gamma radiosurgery unit[97-102] or specially designed linear accelerator systems,[68-70,103-107] a large number of small circular or shaped radiation fields are aimed accurately from multiple directions to intersect a common point at which a target is positioned. In contrast, *stereotactic radiotherapy* (SRT) refers to the use of more than one fraction, typically two to five fractions (hypofractionation), using similar techniques with small fields and relatively high dose per fraction. SRT techniques include noninvasive and replaceable patient fixation,[108] extracranial treatment,[109,110] static or shaped fields,[69,111] intensity-modulated treatment with large- or small-width collimators, treatment with robot-controlled x-ray units,[14,112] shape-based planning,[113] and other optimization algorithms. In particular, stereotactic body radiotherapy (SBRT), which uses a relatively large number (e.g., 7, 9, or 11) of shaped, static fields and hypofractionated dose regimens, has become quite common for small lung targets and liver metastases, possibly including 4D motion accommodation and always using IGRT.[109,110,114,115] Gamma radiosurgery, linear accelerator radiosurgery, and stereotactic body radiotherapy (SBRT) are covered in detail in Chapter 17.

TOTAL-BODY PROCEDURES

Total-body irradiation (TBI) is an irradiation procedure performed as part of bone marrow transplantation and requires special physics measurements for implementation of treatment.[116] The patient is irradiated in the anterior-posterior/posterior-anterior or lateral-opposed directions at an extended distance from the treatment machine using large photon fields to encompass the whole body (Figure 6-60). The goal is to provide dose homogeneity within ±10% of the prescription dose at the patient's midline. Dose compensation for narrow-width regions of the body and protection of the lungs with shielding blocks is required, depending on the technique used. Radiation beam data, such as beam profiles, depth dose or tissue-maximum ratios, and reference dose rates, must be obtained at the extended distance used. Data obtained for conventional treatment at the isocenter may not apply to large fields at extended distances, because of changes in scattering conditions. Higher beam energies are used for lateral techniques, matching the increase in patient thickness compared with anteroposterior geometries.

Total-skin electron treatment (TSET) is similar to TBI except that electrons are used instead of photons. Considerations for this technique, which is used for skin cancers such as mycosis fungoides, have been delineated and include measurement of beam data (e.g., beam profiles, depth dose, and reference dose rate), measurement and any required reduction of bremsstrahlung contamination, and methods for ensuring relatively homogeneous irradiation of the patient surface. In particular, the irradiation geometry must avoid overdoses to thin anatomic regions such as the hands and fingers and prevent underdoses to anatomic regions that might be shielded by skin folds or extremities.[117] Typically, a six-field approach with six different patient positions is recommended. The set up techniques are described in more detail in Chapter 18.

BRACHYTHERAPY

Brachytherapy is a term that comes from *brachy* ("short"), combined with *therapy*, meaning short-distance therapy. The contrast is *teletherapy*, meaning therapy at a distance, as with ^{60}Co or linear accelerator machines, where the radiation source is 80 to 100 cm from the patient. In brachytherapy radioactive sources of small physical size are placed very close to or in the tumor for surface mold, interstitial, or intracavitary treatment. Several terms are defined:

1. *Surface mold:* sources are fixed to an applicator, or mold, that conforms to the patient surface. The surface applicator positions the sources in the desired geometry and is placed on the skin surface to irradiate a superficial target. This technique is not commonly performed, except for purposes of treatment of ocular melanoma.

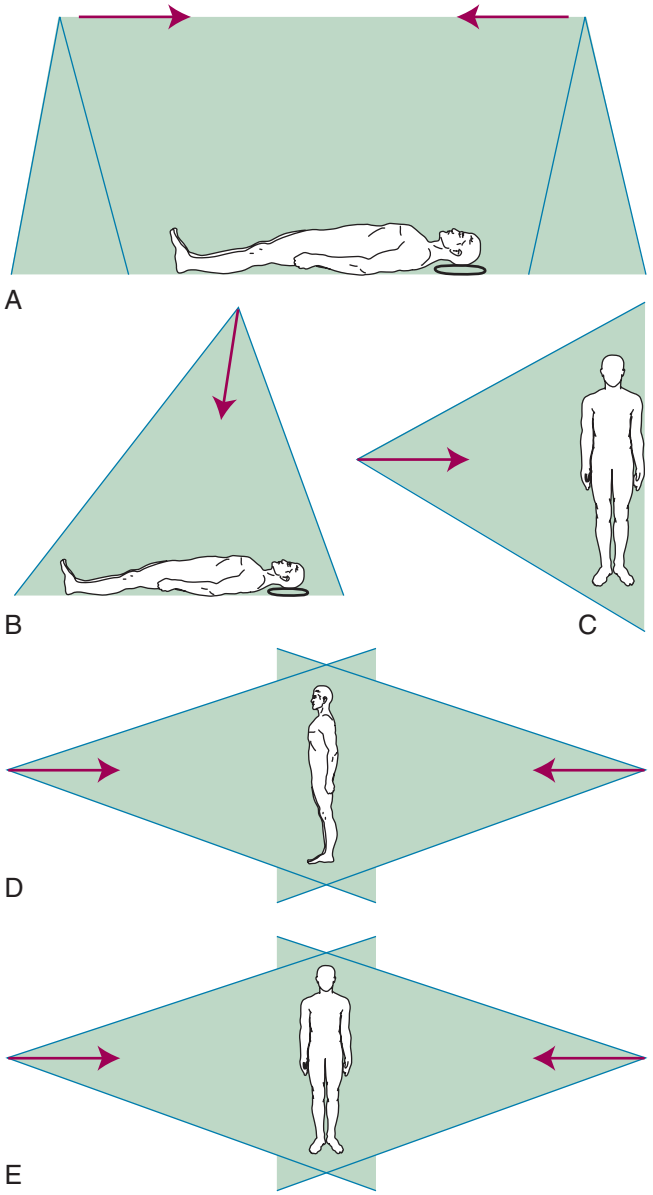


Figure 6-60 Irradiation geometries for total-body irradiation. **A,** Moving-source technique, with the patient on the floor. **B,** Large-field irradiation, with the patient on the floor. **C,** Single, large, lateral field, with the patient erect. **D,** Opposed, large, anterior and posterior fields, with the patient erect. **E,** Opposed, large, lateral fields, with patient erect.
A *to* ***C,*** *From AAPM RTC Task Group 29: Report 17: The physical aspects of total and half body photon irradiation. College Park, MD, 1986, American Association of Physicists in Medicine.*

2. *Interstitial treatment:* sources are implanted in tissues directly or within catheters that are first implanted within the target volume.
3. *Intracavitary or intraluminal treatment:* sources are inserted into body cavities by means of applicator devices. Sites include the oral, rectal, vaginal, and uterine cavities and the tracheal and bronchial lumina.

Brachytherapy has several advantages compared with external beam treatment:

1. The inverse square law dominates the decrease in dose rate and dose as the distance from a source increases. The dose fall-off is steep so that the dose delivered near a source is quite high (thousands of centigrays), whereas a few centimeters away the dose is low (tens of centigrays). The steep dose gradient confines the high-dose region to a small volume.
2. The photons emitted by brachytherapy sources have relatively low energies and greater attenuation in tissue compared with photons used for external beam treatment. This increased attenuation concentrates dose near the source and minimizes dose at a distance.
3. In conventional brachytherapy, prescription dose rates are relatively low, about 0.40 Gy/hr up to 0.80 Gy/hr, and it takes several days to deliver the prescribed dose. This approach may allow treatment of all cells in each phase of the cell cycle for a radiobiologic advantage. High dose rate remote afterloading brachytherapy is now commonly used, with dose rates of approximately 2 Gy/min at the prescription point, comparable to external beam dose rate.

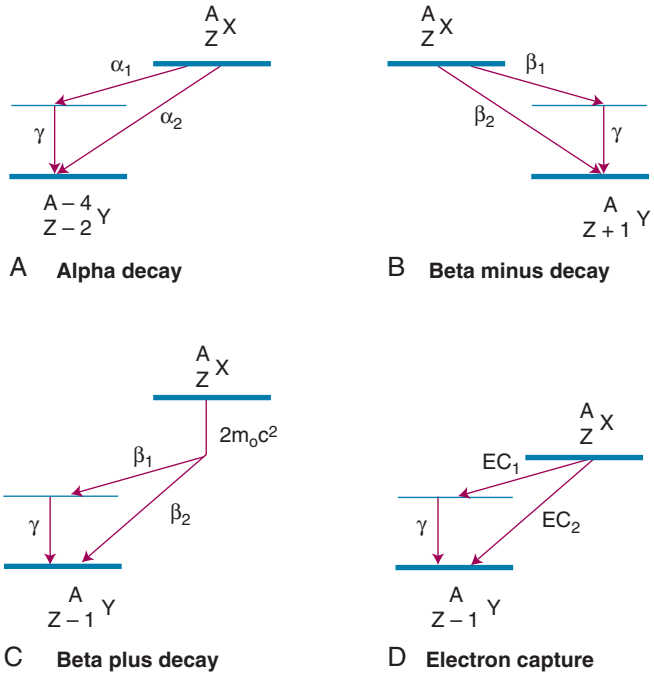


Figure 6-61 Modes of radioactive decay. **A,** α Decay. **B,** β⁻ Decay. **C,** β⁺ Decay. **D,** Electron capture.

Radioactive Decay

The atomic nucleus contains protons and neutrons that prefer certain configurations for stability, as discussed previously. Those configurations that are not stable undergo spontaneous transformation to another nuclear species that may or may not be stable. This spontaneous transformation is called *radioactive decay.* The mode of radioactive decay, meaning the type of transformation and emitted particles, depends on the parent species' nuclear composition. For a particular parent nuclide, a decay mode is allowed or prohibited, and it is one of the following types[2,12,13] (nomenclature is as defined previously, and particles are defined in Table 6-2):

1. In alpha decay (Figure 6-61, *A*), the nucleus gives off an alpha particle, $^{4}\alpha^{2+}$ (2 protons and 2 neutrons—a helium nucleus), resulting in a daughter nucleus of mass A-4 and atomic number Z-2. Alpha particles are monoenergetic and tend to have 4 to 8 MeV in kinetic energy.

$$^{A}_{Z}X \rightarrow {}^{A-4}_{Z-1}Y + {}^{4}\alpha^{2+} + Q \quad 2n \rightarrow 2p + {}^{4}\alpha^{2+} + Q$$

Secondary processes after alpha decay include gamma ray emission (or internal conversion, yielding characteristic x-rays or Auger electrons), which may occur after alpha decay as the daughter de-excites to the ground state. Radionuclides undergoing alpha decay tend to have high Zs and include ^{216}Ra, ^{222}Rn, ^{218}Po, ^{235}U, ^{239}Pu, and ^{241}Am.

2. For beta decay, a single nucleon (neutron or proton) transforms from one type to the other in the nucleus. The nucleus gives off an electron, called a β particle because of its nuclear origin, and a neutrino. There are two types of β particles, one with negative charge, β^-, which is a "regular" electron, also called a *negatron,* and one with positive charge, β^+, the antiparticle to the electron, also called a *positron.* Radioactive decay modes with emission of a β^- or β^+ are possible.
   a. For β^- decay (i.e., negatron decay) (see Figure 6-61, *B*), a neutron transforms into a proton in the nucleus. The nucleus gives off a β^- particle and an antineutrino. The resulting daughter nucleus has the same mass *A* and increased atomic number of *Z* + 1. The β^- particles have a distribution of energies less than or equal to Q (the antineutrino carries off the remainder). The average β^- energy is about one third Q.

$$^{A}_{Z}X \rightarrow {}^{A}_{Z+1}Y + \beta^- + \bar{v} + Q \quad n \rightarrow p + \beta^- + \bar{v} + Q$$

Secondary processes after β^- decay include gamma ray emission (or internal conversion, yielding characteristic x rays or Auger electrons), which may occur after β^- decay as the daughter de-excites to the ground state. The β^- decay occurs for neutron-rich nuclides over all Zs. Example nuclides include ^{3}H, ^{14}C, ^{32}P, ^{60}Co, ^{89}Sr, ^{99}Mo, ^{131}I, ^{137}Cs, and ^{198}Au.

   b. For β^+ decay (i.e., positron decay) (see Figure 6-61, *C*), a proton transforms into a neutron in the nucleus. The nucleus gives off a β^+ particle and a neutrino. The resulting daughter nucleus has the same mass *A* and decreased atomic number of *Z* – 1. The β^+ decay requires that 2 $m_o c^2$, or 1.022 MeV, be available between the parent and initial daughter energy states to be possible. If this energy difference is not available, β^+ decay is prohibited and electron capture may occur. The β^+ particles have a distribution of energies less than or equal to *Q* (the neutrino carries off the remainder). The average β^+ energy is about one third *Q* but is higher than the average β^- energy for the same *Q* because of repulsion by the nucleus.

$$^{A}_{Z}X \rightarrow {}^{A}_{Z-1}Y + \beta^+ + v \quad p \rightarrow n + \beta^+ + v + Q$$

Secondary processes occur after β^+ decay. The positron, β^+, has a short lifetime before annihilation. There is a small chance that the β^+ will hit an electron and annihilate in flight. The greater probability is that the β^+ slows down (through coulomb interactions) and combines

with a free electron. The combined β^+/e^- (or e^+/e^-) species is called *positronium.* Positronium exists for about 10^{-10} seconds before annihilation and the creation of two 0.511-MeV photons (i.e., one photon for each electron mass). A longer-lived state of positronium (10^{-7} seconds) yields three simultaneous annihilation photons. Gamma ray emission (or internal conversion, yielding characteristic x-rays or Auger electrons) may also occur after β^+ decay as the daughter de-excites to the ground state. The β^+ decay occurs for proton-rich nuclides over lower and intermediate Zs. Example nuclides include ^{11}C, ^{15}O (used in positron emission tomography), and ^{22}Na.

3. In electron capture (see Figure 6-61, *D*), the nucleus captures an orbiting electron, increasing the nuclear mass by 0.511 MeV and transforming a proton into a neutron. Electron capture is similar to β^+ decay because the daughter has mass Z-1 and a neutrino is emitted. Most often, the K shell electron is captured. Electron capture occurs for proton-rich nuclides over lower and intermediate Zs when there is not sufficient energy (2 m_oc^2, or 1.022 MeV) for β^+ decay to occur.

$$^{A}_{Z}X + e^- \rightarrow {}^{A}_{Z-1}Y + v + Q \quad p + e^- \rightarrow n + v + Q$$

Secondary processes occur after electron capture. Because an orbital electron is captured, subsequent filling of the electron shell results in the emission of characteristic x-rays after an electron capture event. Gamma ray emission (or internal conversion, yielding characteristic x-rays or Auger electrons) may occur after electron capture as the daughter de-excites to the ground state. Nuclides decaying by electron capture include ^{22}Na, ^{40}K, ^{51}Cr, ^{57}Co, and ^{192}Ir (also with β^-).

The term *Q* in each decay equation represents the total energy given off as kinetic energy of the ejected particles (α, β^-, β^+, $\bar{\nu}$, ν), the remaining nucleus, or both. The neutrino, with a mass of almost zero, was first postulated for existence because of the observed continuous energy distribution for β^- and β^+ energies in beta decay. Without a third reaction product, the β^- or β^+ energies would be monoenergetic and almost equal to Q, reflecting the discrete energy levels in the nucleus.

Secondary Decay Processes

Each of the primary decay modes can leave the daughter nucleus or atom in the ground state or excited state. If an excited state exists, the additional energy is given off in various ways to yield a ground-state daughter.

1. *Isomeric transition by fast gamma emission:* with an excited daughter nucleus, the excitation energy may be given off by photons called *gamma rays.* The gamma ray energy is equal to the difference between the initial and next energy state of the nucleus. Because energy states are fixed for particular nuclei, gamma emissions are fixed and unique for a particular nucleus. Gamma rays identify their nucleus of origin in the same way characteristic x-rays identify their atom. Gamma emission may result in a ground state nucleus by a single gamma emission or by successive gamma emissions through several energy states. The release of energy by gamma emission is fast—the excited state exists for no longer than 10^{-6} seconds—gamma emission is immediate after α, β^-, β^+, or electron capture decay. Although the phrases "^{60}Co gamma rays" and "^{137}Cs gamma rays" are used, these gamma rays are really from the daughter nuclei. Gamma rays from ^{60}Co are really ^{60}Ni gamma rays and gamma rays from ^{137}Cs are really ^{137}Ba gamma rays. However, the terminology is based on the parent nuclide's name.
2. *Isomeric transition from a metastable state:* when an excited nuclear state exists for greater than 10^{-6} seconds before gamma emission, the state is called a *metastable state.* Metastable states sometimes exist long enough to enable the separation of the metastable species from the parent, as is the case for ^{99m}Tc, with a half-life of 6 hours. The "m" refers to metastable. ^{99m}Tc decays to ^{99}Tc (an isomeric transition) by the emission of two gamma rays in succession.
3. *Internal conversion:* an excited nucleus can de-excite without gamma emission by the process of internal conversion. Instead of a gamma ray, the excitation energy is used to eject an orbital electron, usually from the K shell. The ejected electron is called a *conversion electron* and has energy equal to the gamma energy minus the electron binding energy. The usual cascade of characteristic x-rays and Auger electrons follows. Internal conversion competes more with gamma emission as Z increases. The pathways of gamma emission and internal conversion are parallel to the competing processes of characteristic x-ray and Auger electron emission; a photon carries off the excitation energy, or the energy is transferred to an electron that is then ejected.

Radioactive decay is characterized by the following observations:

- All nuclei above $Z = 82$ are radioactive.
- For nuclei below $Z = 82$ some are naturally radioactive (e.g., ^{14}C and ^{40}K).
- High *Z* nuclei tend to undergo alpha decay; their nuclei have an abundance of protons and neutrons that may be emitted as coupled pairs (i.e., an alpha particle).
- Alpha particles tend to have 4 to 8 MeV in kinetic energy.
- Middle-range *Z* nuclei tend to undergo β^- (i.e., negatron) decay.
- Low *Z* nuclei tend to undergo β^+ (i.e., positron) decay.
- In general, if the decay rate is high (i.e., short half-life), the decay particles are energetic.
- In general, if the decay rate is low (i.e., long half-life), the decay particles are low energy.

Radioactive Decay Mathematics

Radioactive decay occurs spontaneously but also with a distinct probability for each radioactive nuclide. The number of transformations occurring per unit time, *A(t)*, is called *activity* and is given by the following equation.

$$A(t) = \lambda N(t) \qquad \text{Eq. 40}$$

in which *N(t)* is the number of atoms of the radioactive species at time *t* and λ is a proportionality constant called the *decay constant.* The SI unit for activity is the becquerel, equal to one transformation per second. The original unit of activity is the curie, which is 3.7×10^{10} transformations per second (3.7×10^{10} s^{-1}), an amount equal to the number of disintegrations occurring in 1 g of ^{226}Ra. λ is called the *decay constant,* which is unique for a nuclide and is equal to ln(2) divided by the half-life, $t_{1/2}$:

$$\lambda = \frac{\ln(2)}{t_{1/2}} = \frac{0.693}{t_{1/2}} \qquad \text{Eq. 41}$$

in which $t_{1/2}$ is the amount of time required for the activity or the number of nuclei to decay to one half of the original value. The relationship between λ and *t* looks like the relationship between HVL and λ.

The half-life, and, hence, the decay constant, is constant and unique for a nuclide, and its measurement can be a means

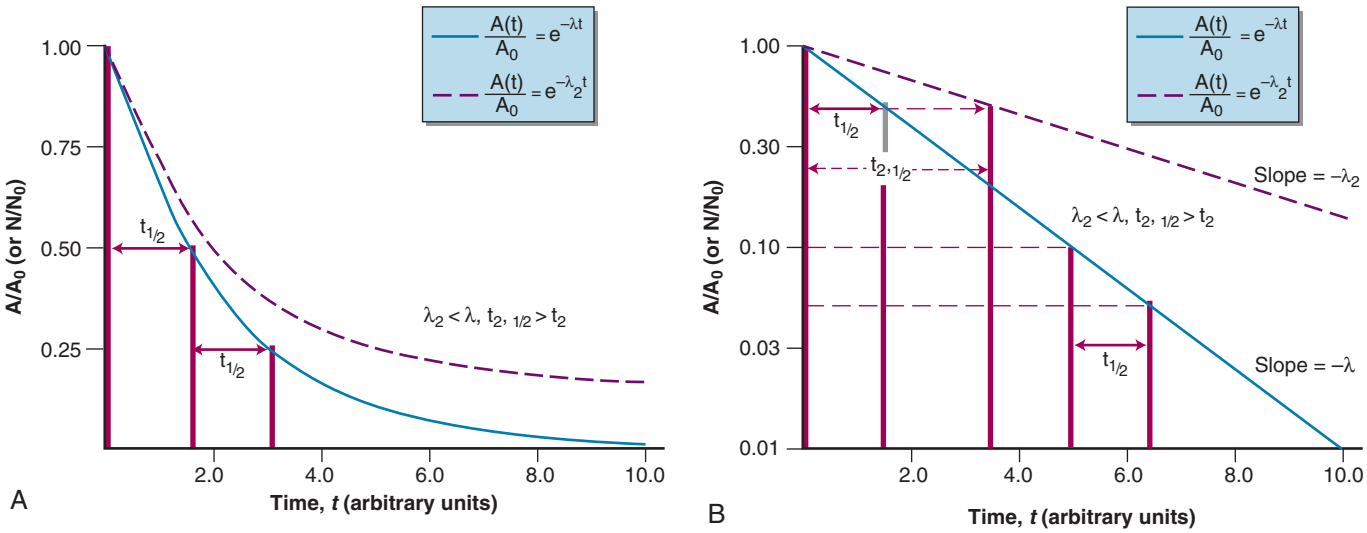


Figure 6-62 Graphic representation of radioactive decay. **A,** Linear plot. **B,** Semi-log plot.

TABLE 6-14 Properties and Applications of Isotopes

Nuclide	Half-Life	Decay Mode	Decay Products*	Physical Form	Γ (R•cm²•mCi⁻¹•h⁻¹)	HVL (mm Pb)	Clinical Application
^{60}Co	5.263 yr	β	β, γ	SSS tubes	13.07	11.9	RA, gyn, H/N
^{103}Pd	17 days	EC	γ, 0.021 $\bar{x}$	SSS seeds	1.48	0.008	IS, prostate
^{137}Cs	30.2 yr	β	β, 0.662 γ	SSS tubes	3.26	5.5	IC, RA, gyn, H/N
^{125}I	60.2 days	EC	0.027 $\bar{x}$	SSS seeds	1.46	0.025	IS, prostate, H/N, pancreas, sarcoma
^{192}Ir	74.2 days	EC, β	β, γ, 0.38 $\bar{\gamma}$	SSS, seeds, wire	4.69	2.5	IC, IS, RA, gyn, H/N, breast, sarcoma
^{226}Ra	1602 yr	α	α, β, γ, 0.83 $\bar{\gamma}$	SSS tubes, needles	8.25	8.0	IC, IS, gyn, H/N, breast
OTHER ISOTOPES							
^{32}P	14.28 days	β	β	LQ			IC (peritoneal)
^{131}I	8.05 days	β	β, γ	LQ	2.2	2.5	OR, thyroid and mets
^{198}Au	2.7 days	β	β, γ	LQ, seeds	2.38	2.5	IC (peritoneal), IS
^{222}Ra	3.83 days	α	α, β, γ	GSS, seeds	10.15	8.0	IS, breast

α, Alpha decay; β, beta decay; EC, *electron capture; γ, gamma emission;* GSS, *glass-sealed source;* gyn, *gynecologic;* H/N, *head and neck;* HVL, *half-value layer;* IC, *intracavitary;* IS, *interstitial;* LQ, *liquid pharmaceutical;* mets, *metastatic;* OR, *taken orally;* RA, *remote afterloading;* SSS, *solid-sealed source.*
**Where a number is given, the units are in MeV. An overlined particle, $\bar{\gamma}$ or $\bar{x}$, indicates that the energy given is an average energy.*

for identifying a species. Depending on the species, the half-life can be large or small and governs the lifetime over which decay occurs. The equation that radioactive decay obeys is:

$$N(t) = N_0 e^{-\lambda t} \text{ or } A(t) = A_0 e^{-\lambda t} \qquad \text{Eq. 42}$$

where $N(t)$ and N_o are the number of nuclei at time t and $t = 0$, respectively, and $A(t)$ and A_0 are the activities (in becquerels or curies) at time t and $t = 0$, respectively. Decay is exponential and can be represented in linear or semi-log form (Figure 6-62).

Properties and Applications of Isotopes

Table 6-14 lists isotopes, their properties, their physical forms, and their therapeutic applications. As seen, brachytherapy sources may be constructed as sealed sources in the forms of needles, tubes, or seeds. The solid radioactive material, in a metallic, stable inorganic or organic chemical form, adsorbed onto a material, or possibly as a liquid or gas, is sealed into a metal source capsule by welds or other means that prevent leakage of the material. Most radioactive sources are beta emitters, and the useful radiations for treatment are the gamma rays or characteristic x-rays emitted after beta decay. Besides containment of the source material, the metal encapsulation stops all beta (or alpha) emissions and allows only the gamma or x-rays to be transmitted. Sources can also be used for their beta emissions when encapsulated in a thin-wall enclosure (i.e., ^{90}Sr) or in unsealed (liquid) form.

Dose distributions from sealed sources have a shape that reflects the rapid fall-off with dose because of the inverse square law, the source energy, the distribution and amount of activity within the source, and the source encapsulation. Source encapsulation in particular affects the apparent activity, active length, and shape of the dose distribution through attenuation by the source capsule walls and ends. Sealed-source dose distributions are anisotropic, not uniform, because of increased encapsulation thickness and self-absorption along the length of the source (Figure 6-63). Investigators have performed measurements and applied Monte Carlo techniques and other models to determine brachytherapy source dose characteristics.[118,119]

Radioactive decay and its energetics are represented by decay schematics (see Figure 6-61). Horizontal lines represent

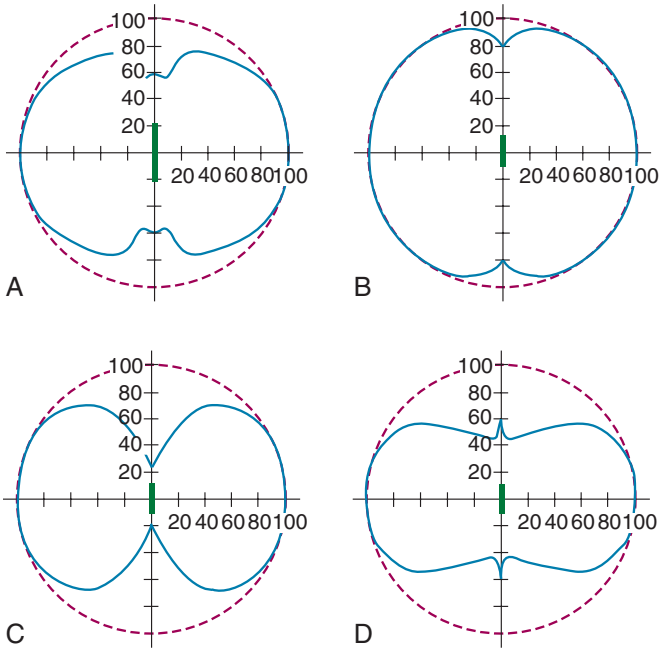
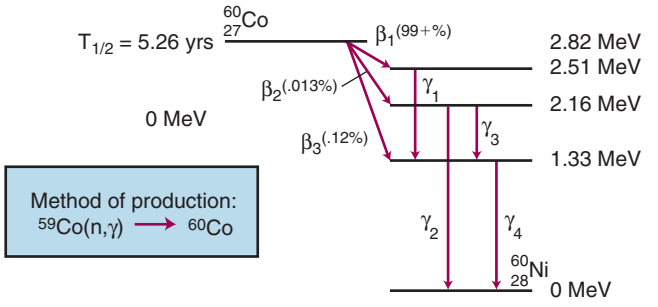


Figure 6-63 Brachytherapy source anisotropy. **A,** Relative dose rate using a 2-cm radius, ^{226}Ra tube, and 1.35 active length. **B,** Relative in-air fluence for ^{192}Ir seed. **C,** Relative in-air fluence for ^{125}I seed, model 6711. **D,** Relative in-air fluence for ^{103}Pd.
***A,** Data from Johns HE, Cunningham JR: The physics of radiology, ed 3, Springfield, IL, Charles C Thomas, 1978; **B** to **D,** data from Interstitial Collaborative Working Group: Interstitial Brachytherapy: Physical, biological, and clinical considerations, New York, 1990, Raven Press.*

the relative nuclear energy levels of the parent and daughters. Branches from the parent to the daughter represent the type of decay, whereas the horizontal spacing of each species represents the atomic number, Z. A branch to the left indicates a transition where Z decreases (α, β^+, or electron capture) (see Figure 6-61, *A* to *D*). A branch to the right indicates a transition where Z increases (β^- decay) (see Figure 6-61, *B*). Elevated horizontal lines above the ground state indicate excited nuclear levels. Vertical arrows from one excited level to a lower one or the ground state indicate gamma emission. Fractional or percentage amount of time a transition occurs is indicated, as are the absolute energies of levels, particles, and photons. Decay schemes for the medical isotopes listed in Table 6-14 are presented in Figures 6-64 to 6-71 and web-only eFigures 6-1 and 6-2, available on the Expert Consult website. It is observed that the nuclear configurations and transitions for these isotopes are simple for some and complex for others. For instance, ^{60}Co decays by β^- decay to ^{60}Ni, which de-excites by the emission of two gamma rays, one at 1.17 MeV and one at 1.33 MeV (see Figure 6-64). ^{125}I decays by electron capture to ^{125}Te, with the emission of one gamma ray (35 keV) and two characteristic x-rays (27.3 keV, 31.4 keV) (see Figure 6-67). After decay, the resulting daughter nucleus itself may be radioactive, resulting in an additional decay or decays. The decay chain for ^{226}Ra has nine decays (and daughters) until stable ^{206}Pb is reached (eFigure 6-2).

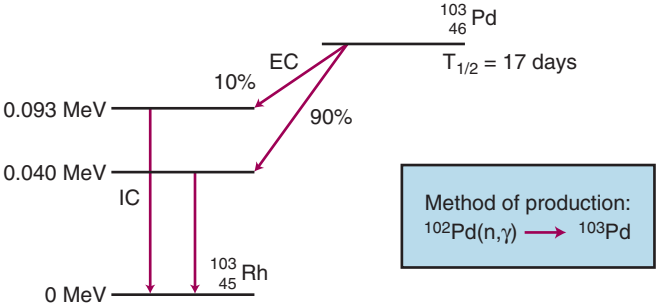
Source Strength

Source strength, that is, the amount of radiation or dose given off per unit time, is an important physical and clinical parameter because dose rate must be known to enable a prescribed dose to be delivered. Source strength has been specified as the amount of milligrams of ^{226}Ra (mg-Ra), the equivalent amount



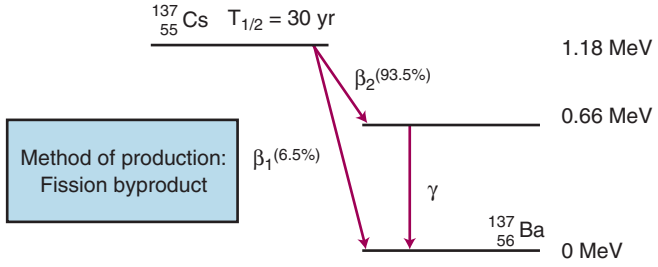
Emitted radiation	Energy (MeV)	Mean number per disintegration
γ ray (Nickel-60 γ rays)	1.173	0.998
γ ray (Nickel-60 γ rays)	1.332	1.0

Figure 6-64 A ^{60}Co decay scheme.
Data from Lederer CM, Hollander JM, Perlman I: Table of isotopes, ed 6, New York, 1967, Wiley & Sons.



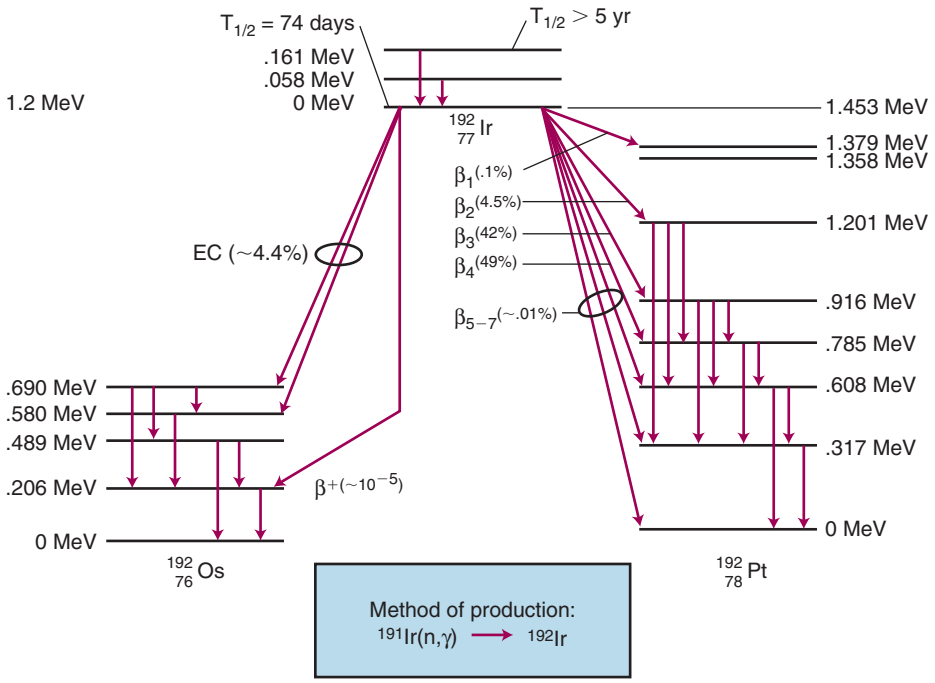
Emitted radiation	Energy (MeV)	Mean number per disintegration
γ ray (Rhenium-103 γ rays)	0.0397	0.001
γ ray (Rhenium-103 γ rays)	0.357	0.001
x-ray, K_α (EC and IC)	0.201	0.656
x-ray, K_β (EC and IC)	0.230	0.125

Figure 6-65 A ^{103}Pd decay scheme.
Data from Lederer CM, Hollander JM, Perlman I: Table of isotopes, ed 6, New York, 1967, Wiley & Sons.



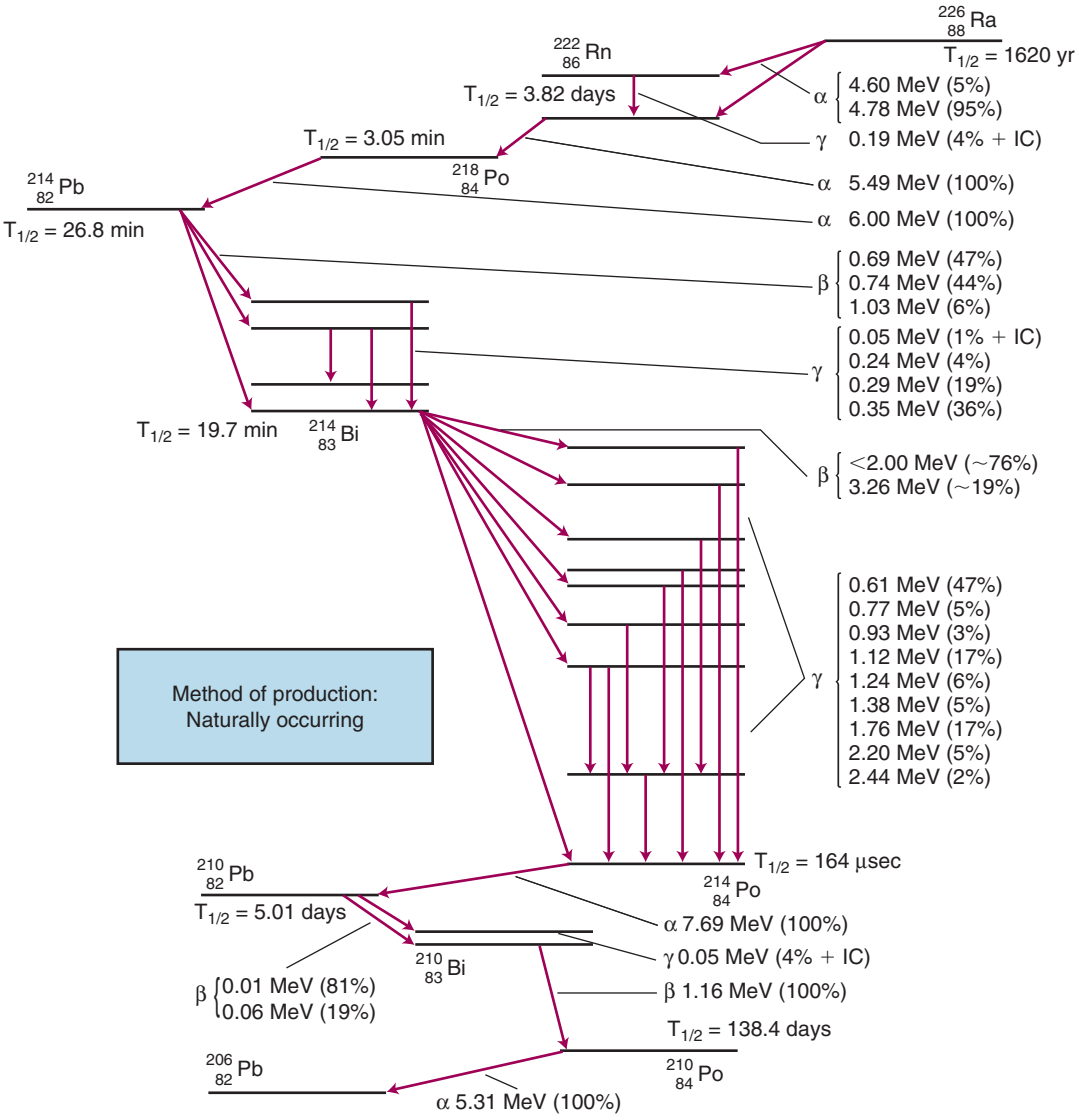
Emitted radiation	Energy (MeV)	Mean number per disintegration
γ ray (Barium-137 γ rays)	0.662	0.85

Figure 6-66 A ^{137}Cs decay scheme.
Data from Lederer CM, Hollander JM, Perlman I: Table of isotopes, ed 6, New York, 1967, Wiley & Sons.



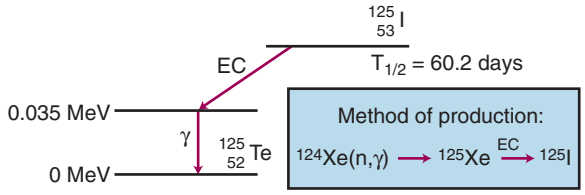
Emitted radiation	Energy (MeV)	Mean number per disintegration
γ ray (Nickel-192 γ rays)	0.296	0.290
γ ray (Nickel-192 γ rays)	0.308	0.298
γ ray (Nickel-192 γ rays)	0.317	0.810
γ ray (Nickel-192 γ rays)	0.468	0.490
γ ray (Nickel-192 γ rays)	0.589	0.040
γ ray (Nickel-192 γ rays)	0.604	0.090
γ ray (Nickel-192 γ rays)	0.612	0.060
γ ray (Nickel-192 γ rays)	Average of ~0.370	Average of ~2.2

eFigure 6-1 A ^{192}Ir decay scheme.
Data from Lederer CM, Hollander JM, Perlman I: Table of isotopes, ed 6, New York, 1967, Wiley & Sons.



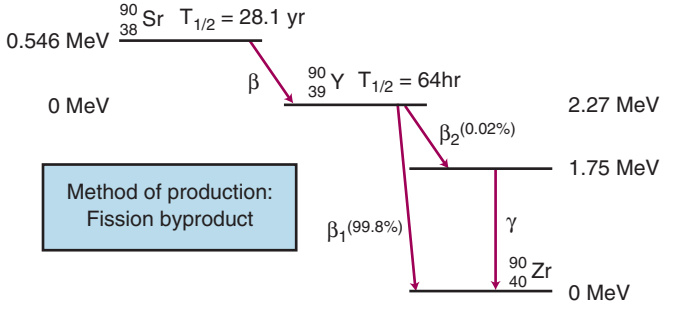
Emitted radiation	Energy (MeV)	Mean number per disintegration
γ ray (Radon-222 γ rays)	0.186	0.040
γ ray (Bismuth-214 γ rays)	0.053	0.020
γ ray (Bismuth-214 γ rays)	0.242	0.075
γ ray (Bismuth-214 γ rays)	0.295	0.210
γ ray (Bismuth-214 γ rays)	0.352	0.380
γ ray (Polonium-214 γ rays)	0.609	0.470
γ ray (Polonium-214 γ rays)	0.769	0.053
γ ray (Polonium-214 γ rays)	0.935	0.033
γ ray (Polonium-214 γ rays)	1.120	0.160
γ ray (Polonium-214 γ rays)	1.238	0.060
γ ray (Polonium-214 γ rays)	1.379	0.048
γ ray (Polonium-214 γ rays)	1.400	0.040
γ ray (Polonium-214 γ rays)	1.728	0.032
γ ray (Polonium-214 γ rays)	1.764	0.170
γ ray (Polonium-214 γ rays)	2.204	0.060
γ ray (Polonium-214 γ rays)	2.435	0.020

eFigure 6-2 A ^{226}Ra decay scheme.
Data from Lederer CM, Hollander JM, Perlman I: Table of isotopes, ed 6, New York, 1967, Wiley & Sons.



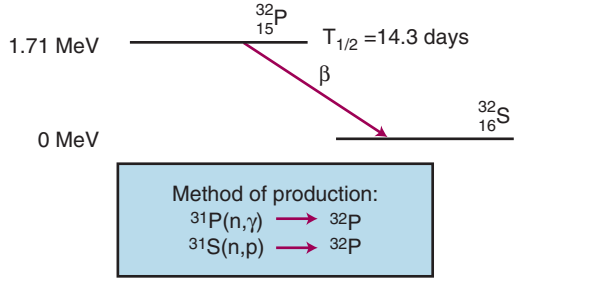
Emitted radiation	Energy (MeV)	Mean number per disintegration
x-ray, K_α (EC and IC)	0.0273	1.126 (0.576 + 0.540)
x-ray, K_β (EC and IC)	0.0314	0.240 (0.124 + 0.116)
γ ray (Tellurium-125 γ rays)	0.0355	0.068
γ ray (Tellurium-125 γ rays)	Average of ~0.0285 (28.5 keV)	Average of ~1.47

Figure 6-67 A ^{125}I decay scheme.
Data from Lederer CM, Hollander JM, Perlman I: Table of isotopes, ed 6, New York, 1967, Wiley & Sons.



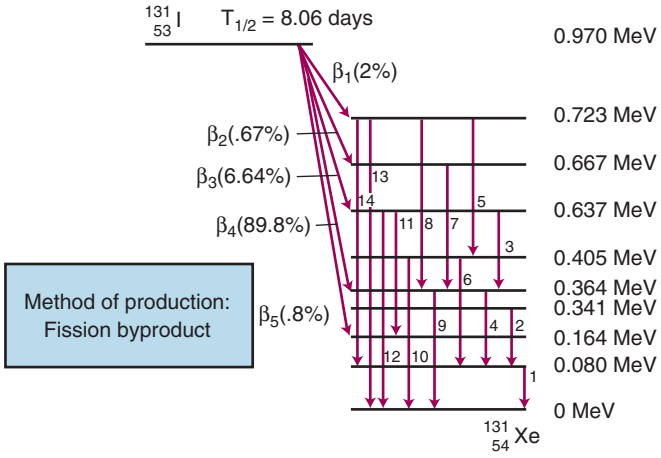
Emitted radiation	Energy (MeV)	Mean number per disintegration
β⁻ (Strontium-90 βs)	0.546 max	1.0
β⁻ (Yttrium-90 βs)	2.268 max, 0.90 average	1.0

Figure 6-68 A ^{90}Sr decay scheme.
Data from Lederer CM, Hollander JM, Perlman I: Table of isotopes, ed 6, New York, 1967, Wiley & Sons.



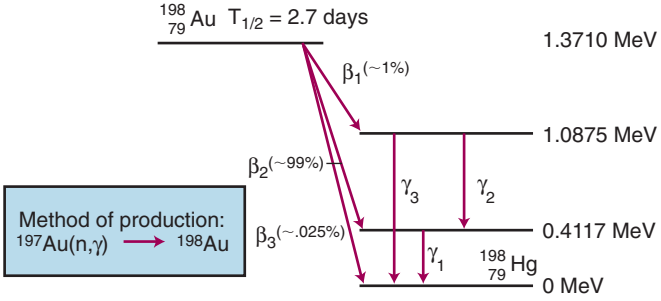
Emitted radiation	Energy (MeV)	Mean number per disintegration
β⁻(Phosphorus-32 βs)	1.710 max, 0.70 average	1.0

Figure 6-69 A ^{32}P decay scheme.
Data from Lederer CM, Hollander JM, Perlman I: Table of isotopes, ed 6, New York, 1967, Wiley & Sons.



Emitted radiation	Energy (MeV)	Mean number per disintegration
γ rays (Xenon-131 γ rays)	0.080	0.026
γ rays (Xenon-131 γ rays)	0.284	0.054
γ rays (Xenon-131 γ rays)	0.364	0.820
γ rays (Xenon-131 γ rays)	0.637	0.068
γ rays (Xenon-131 γ rays)	0.732	0.016

Figure 6-70 A ^{131}I decay scheme.
Data from Lederer CM, Hollander JM, Perlman I: Table of isotopes, ed 6, New York, 1967, Wiley & Sons.



Emitted radiation	Energy (MeV)	Mean number per disintegration
β⁻ (Gold-198 βs)	0.962 max, 0.30 average	1.0
γ ray (Mercury-198 γ rays)	0.4117	0.95

Figure 6-71 A ^{198}Au decay scheme.
Data from Lederer CM, Hollander JM, Perlman I: Table of isotopes, ed 6, New York, 1967, Wiley & Sons.

of milligrams of ^{226}Ra (mg-Ra eq, for ^{226}Ra substitutes such as ^{137}Cs or ^{192}Ir), the actual activity encapsulated, the apparent activity, and the exposure rate at a distance. These historical representations of activity have been replaced by the current day recommended source strength specification of air kerma strength[120] (S_K) with units of μGy/m²/hr. S_K is based on the air kerma rate in free space, $\dot{K}_1$, which gives the kerma rate in air in micrograys per hour at a fixed distance from the source, measured radially from a point source or along the perpendicular bisector for a linear source. Kerma equals dose with

less than 1% difference for brachytherapy photon energies, so $\dot{K}_1$ essentially gives the dose rate in air at the reference distance. Although air kerma strength is adopted as a standard, multiple specifications for source strength are still in use by source manufacturers and treatment planning systems. The same convention of source strength must be used for the radiation source and the planning system to ensure correct computations of dose rate and dose. Additional guidance is available on source strength specification, and other brachytherapy planning issues.[120-122]

Brachytherapy Applicators and Afterloading

When first used in the early 1900s brachytherapy sources were directly implanted into the patient for interstitial or intracavitary treatment. To reduce personnel doses and allow greater flexibility in determining source configurations without having to handle "hot" sources, a technique called *afterloading* was developed in the 1950s, first for intracavitary treatments and later for interstitial applications. With afterloading, the source configuration is determined using nonradioactive "dummy" sources and the actual sources are efficiently loaded at a later time. Afterloading techniques require the use of specialized source applicators to position the dummy sources and allow accurate (re)placement of actual sources. A variety of applicators and techniques have been developed to facilitate implantation of the isotopes shown in Table 6-14, and these are reviewed in a later chapter and elsewhere.[123,124]

Preplanning can be used in brachytherapy to optimize the source locations and activities. For implantation, physical templates may help maintain the intended source geometry and are recommended when possible. Once the applicators are in place, adjustments to the implant geometry are limited to number of sources per applicator, spacing, and activity. Dummy sources are loaded, and each source location is determined by obtaining orthogonal images. These images are best obtained for an applicator(s) that matches the imaging device. Applicators exist that are compatible with either a conventional radiographic/fluoroscopic simulator, a CT simulator, or (more rarely) an MR simulator. A magnification indicator may be needed depending on the imaging method. On the images each source location and anatomic and dosimetry points of interest are identified and digitized. Planning determines the position, activity, and insertion time for each source based on the chosen point of prescription. A plan is represented by isodose distributions that show dose rate (typically, Gy/hr).

Brachytherapy Treatment Planning

Planning for brachytherapy treatments initially was nonexistent, but beginning in the 1920s various systems were developed that provided rules and guidelines for implantation geometries and specifications for prescription. Initially, ^{226}Ra was the only radionuclide used for brachytherapy because of its natural abundance, and systems were developed that were specific to ^{226}Ra source configurations of needles and tubes. Other radionuclides for brachytherapy became available in the 1950s through neutron activation in a nuclear reactor or as byproduct material. The radium systems were modified for the physical characteristics of these nuclear-age radionuclides.

Gynecologic Implants

Three systems using different applicators, source strengths, and treatment times were developed for intracavitary implants of the cervix and uterus.[123] The first two, the Paris and Swedish systems, were modified and became known as the Manchester system, the most widely used brachytherapy system. In the Manchester system, four points of interest are anatomically defined (Figure 6-72):

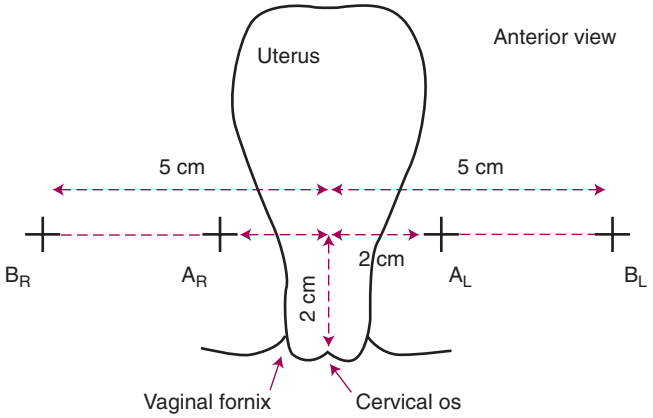


Figure 6-72 Gynecologic anatomy and definitions for points A and B.

1. *Point A* is 2 cm superior to the external cervical os, and 2 cm lateral to midline. Point A is specified on the right and left and indicates the location where nominally the uterine vessels and ureters cross.
2. *Point B* is 2 cm superior to the external cervical os and 5 cm lateral to midline. Point B is specified on the right and left and indicates the presumed location of the obturator lymph nodes.
3. A radiographically defined point indicates the dose of relevance to the *bladder.*
4. A radiographically defined point indicates the dose of relevance to the *rectum.*

The Manchester system prescribes dose to point A using a dose rate of 55.5 R/hr, delivering 8000 R in 144 hours in two 3-day sessions over 2 weeks. Point B gives an indication of peripheral dose at the obturator nodes, and the bladder and rectum points indicate the dose at these dose-limiting structures. The classic gynecologic implant uses three 2-cm sources in a line, or *tandem,* in the uterus and two 2-cm sources, one on either side of the cervix, as shown in Figure 6-75. With activities of 15, 10, and 10 mg (of ^{226}Ra, or mg-Ra eq of ^{137}Cs) in tandem and 15 mg each in the lateral vaginal fornices, for a total of 65 mg-Ra eq, a well-known pear-shaped dose distribution results (see Figure 6-73). Variations to the Manchester system are readily apparent. Implant duration and dose, number of sources, source activity (dose rate), source geometry, applicator design, number of implants, and primary versus boost treatment can all be varied. Gynecologic implant approaches have been reviewed.[123-125]

Interstitial Implants

The Manchester system of implantation rules and dose prescription, also called the Paterson-Parker system after its authors,[126,127] has formed the basis for interstitial implant approaches and was originally developed for ^{226}Ra needles. This system specifies source distribution rules for planar and volume implants. The system is based on the concept of using a relatively uniform distribution of sources having differing linear activities to deliver a dose distribution with homogeneity of ±10% of prescription. Rules include the distribution of activity, that is, the percentage of activity to load in the implant center versus the periphery, for planar targets, and cylindrical, spherical, and cubical implant volumes. A fixed source spacing of 1 cm is specified. The Quimby system was developed and used in the United States and is based on the concept of using a uniform distribution of sources of the same linear activity throughout the implant volume (^{226}Ra needles were available

in the United States with constant linear activity). Source spacing is uniform, with 1- to 2-cm source intervals. The modern Paris system is based on the use of ^{192}Ir wire. Sources are arranged in parallel fashion in planes, the linear activity is constant for all sources, and source spacing is uniform.[128] Target coverage is specified as an isodose surface that encompasses the target volume, relative to a reference point at the implant center. An example of a single-plane implant is shown in Figure 6-74. Combinations of implant planes enable an entire target volume to be treated to a particular dose surface. Table 6-15 summarizes some of the rules for the Manchester, Quimby, and Paris systems. More complete reviews are available and required for complete details for each system.[128,129]

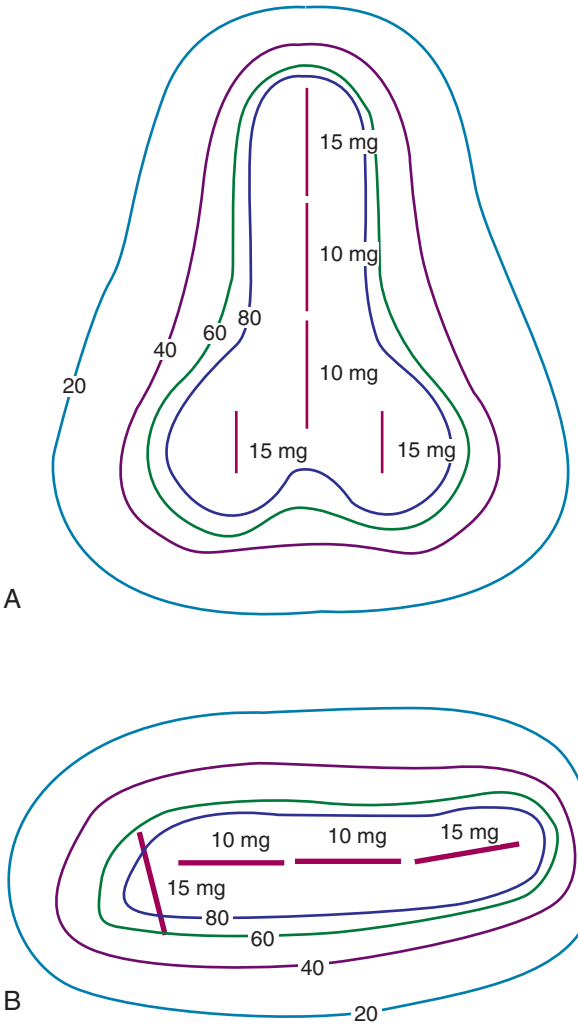


Figure 6-73 Typical gynecologic implant. **A,** Coronal plane. **B,** Sagittal plane. Source arrangement coincides with anatomy shown in Figure 6-73. Isodose values are in units of centigrays per hour.

High-Dose-Rate Remote Afterloading

High-dose-rate (HDR) remote afterloading devices use a single, large activity (10 Ci, ^{192}Ir) source that is stored in a shielded container within the base of the unit and then inserted into implanted applicators or catheters under remote control from outside the treatment room[130-132] (see Figure 6-75). The source position is known continuously and can be moved to various locations within an implanted applicator to build a desired dose distribution. The amount of dwell time in one location

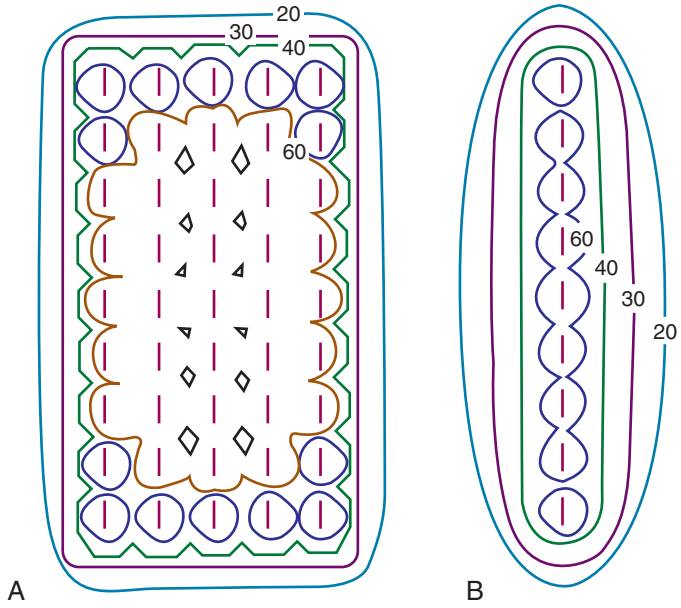


Figure 6-74 Single-plane interstitial implant. **A,** Source plane. **B,** Plane orthogonal to the source plane. Isodose values are in centigrays per hour. *Data from Interstitial Collaborative Working Group: Interstitial brachytherapy: Physical, biological, and clinical considerations, New York, 1990, Raven Press.*

TABLE 6-15 Manchester, Quimby, and Paris Systems

	System		
Parameter	**Manchester**	**Quimby**	**Paris**
Dose	6000-8000 R	5000-6000 R	6000-7000 R
Dose rate	40-60 R/hr	60-70 R/hr	25-90 cGy/hr
Prescription point	10% above absolute minimum	On bisector (planar) or periphery (volume)	85% of minimum central dose
Linear activity	Variable	Constant	Constant
ACTIVITY DISTRIBUTION			
Single plane	Varies with area	Uniform	Uniform
Volume implant	Varies with shape	Uniform	Multiple, uniform planes
Source spacing	Constant at 1 cm	Constant, 1-2 cm	Constant, 0.5-2 cm
Crossing needles	Yes	Yes	No

Adapted from Glasgow GP, Perez CA: Physics of brachytherapy. In Perez CA, Brady LW, editors: Principles and practice of radiation oncology, ed 2, Philadelphia, 1987, JB Lippincott, pp 213-251.

determines the amount of dose delivered. Multiple catheters or applicator connections are possible to enable an entire implant volume to be treated with a single source, in step-by-step fashion. Almost all intracavitary and interstitial implants just described have been replicated using HDR techniques, and primary implant sites are breast, gynecologic, and prostate[130-132] (Figure 6-76). In a novel technique, local, partial breast irradiation is delivered to the breast, using a balloon catheter that positions the HDR source in one or more dwell positions within the postlumpectomy surgical cavity (see Figure 6-76, *A*).

HDR advantages include shorter overall treatment times, opportunities for fractionated treatment, advanced imaging techniques for improved treatment planning, improved treatment planning by customization of the ^{192}Ir source dwell times, and reduced radiation exposure to the implant team. Radiation safety considerations are important for HDR treatment because of the high dose rate of the source. Pre- and post-HDR radiation room surveys must be conducted to ensure proper source storage and radiation safe conditions for both the patient and personnel.[130-132]

Computerized systems have facilitated customized planning for brachytherapy treatments. Planning systems now perform image-based planning and include tools for automated source localization and optimization of the dose distribution. HDR planning systems, in particular, have provided optimization schemes to determine source dwell times to provide a desired dose distribution. A planning system must use the source strength convention for the source being applied (i.e., apparent activity or air kerma strength) and must account for radial and axial anisotropies in the dose distribution,[133] such as the anisotropies shown previously (see Figure 6-63).

Dose Specification

An implant system specifies dose or dose rate at a point or points (e.g., point A) or possibly to a plane or volume of interest that contains the implant. The ICRU has recommended

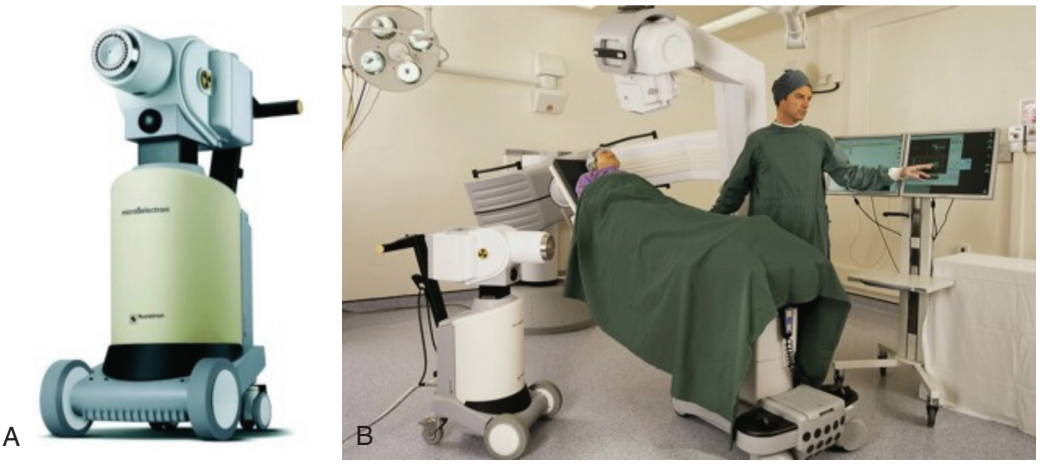


Figure 6-75 High-dose-rate remote afterloading. **A,** Multiport ^{192}Ir remote afterloading device with integrated source shield and head for source path selection. **B,** Integrated HDR brachytherapy procedures suite.
Courtesy Nucletron.

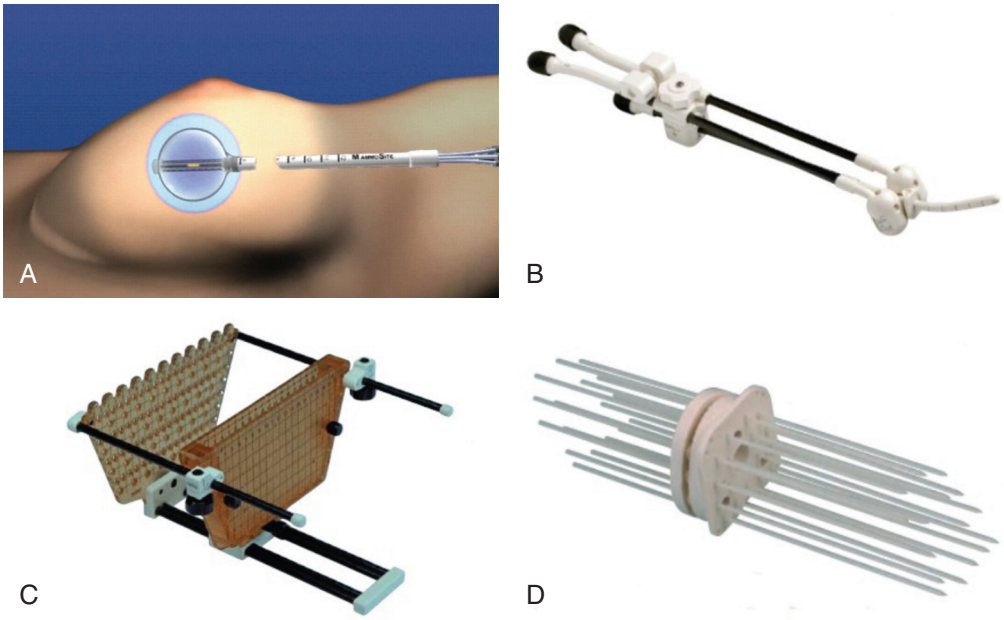


Figure 6-76 Brachytherapy applicators. **A,** Breast HDR balloon catheter, postlumpectomy. **B,** HDR tandem and ovoids. **C,** Kuske interstitial breast template. **D,** HDR prostate. *Courtesy Nucletron.*

TABLE 6-16 Quality Factors for Radiation Protection

Radiation	Quality Factor
X-rays, gamma rays, and electrons	1
Thermal neutrons	5
Neutrons and heavy particles	20

TABLE 6-17 Exposure Limits for Radiation Protection

Exposed Region or Site	Occupational (mSv)	General Public (mSv)
ANNUAL EXPOSURE LIMITS		
Whole body; head and trunk; active blood-forming organs; lens of eyes; gonads	50	1 (frequent exposure) 5 (infrequent exposure)
Hands and forearms; feet and ankles	750	75
Skin of whole body	300	30
ADDITIONAL EXPOSURE LIMITS		
Nonoccupational areas: <0.02 mSv/h (0.02 mSv/h ≈ 50 mSv/yr if exposed year round) <1 mSv/wk (≈ 0.006 mSv/hr for continuous exposure)		
Fetal dose: <5 mSv during the gestation period		
MORTALITY RISK		
Population risk from exposure: risk is approximately 2.5×10^{-2} deaths/person/Sv or 2.5×10^{-4} deaths/person/cSv. There are approximately 2.5 deaths if 10,000 people receive 0.01 Sv (1 cSv) each.		

that dose be reported to a reference volume and points of interest for gynecologic implants and for mean central and peripheral dose for interstitial implants.[134,135] The recommendations are similar to the ICRU's specification of volumes for use in external beam therapy in ICRU 50 and ICRU 62,[42,43] and it is recommended that ICRU's nomenclature be used in clinical practice.[136]

Other Brachytherapy Techniques

Brachytherapy applications have also included molds for ocular melanoma using ^{125}I seeds, biliary stent implantation with ^{192}Ir, ultrasound-guided prostate brachytherapy using ^{103}Pd or ^{125}I, and once popular procedures such as endovascular brachytherapy (^{90}Sr, ^{192}Ir, and other nuclides), and treatment of pterygium (^{89}Sr).[122,137] Development of new radionuclides for specific applications continues, particularly for liquid forms of radionuclides.

RADIATION PROTECTION

Radiation protection practices are important in the radiation oncology clinic for protection of the patient, radiation oncology personnel, ancillary staff, and the general public. Recommendations by international bodies are enacted into law and serve as dose limits for occupationally exposed individuals and the general public.[138] The dose-related quantity of interest for radiation protection purposes is called the *dose equivalent, H*:

$$H = D \times QF \qquad \text{Eq. 43}$$

In the equation, H is the dose equivalent (in sieverts [Sv], with units of J/kg), D is the dose received (in grays, with units of J/kg), and QF is the quality factor (unitless) of the exposing radiation.

The quality factor indicates the biologic effect of the radiation type, relative to x-rays, and varies with linear energy transfer. High linear energy transfer radiations, such as particle radiations, have a high quality factor (Table 6-16). The units of the sievert are still joules per kilogram, as for the gray; however, the meaning of the sievert is different than that of the gray. Given photon and fast neutron exposures of 1 Gy each, the dose equivalent (meaning the biologic effect) for each is different: the photons deliver 1 Sv; the fast neutrons deliver 20 Sv.

Exposure limits for occupational exposure and the general public are given in Table 6-17. A safety factor of 10 is applied to the general public limits compared with the occupational limits for whole-body exposures. However, for annual whole-body exposures the general public is limited to $\frac{1}{20}$ the occupational limit if exposure is frequent. This lower limit (0.1 rem or 0.001 Sv) is the regulatory limit for exposure of the general public in the United States. Exposure limits for occupational radiation protection are based on laboratory studies and observed effects for irradiated human populations and are believed to give equivalent risk as in other safe occupations.

Radiation protection principles are based on three factors: time, distance, and shielding. To reduce any dose, minimize the time of exposure, maximize the distance away from the sources, and maximize the shielding between the sources and the point of exposure. The degree to which each of these principles is exercised for a particular exposure scenario depends on the type of radiation source; its physical properties such as energy, intensity, collimation, and beam orientation; the presence of barriers; distances to points of interest; the potential time of exposure; and the category of individual exposed (occupational or general public). Common protection practices in radiation oncology include the use of heavily shielded vaults for protection of linear accelerator operators and the public, administrative controls that limit access to radiation sources, physical barriers to room entry during exposure, interlocks that prevent irradiation during unsafe conditions, use of long-handled tools when handling brachytherapy sources, afterloading equipment such as source applicators and dummy sources to negate the need to load sources "hot," remote afterloading devices operated under remote control, the use of lead aprons and shielded control consoles during radiographic or fluoroscopic procedures, and assessment of fetal dose for patients or occupationally exposed personnel. A body of literature addresses specific situations that may be encountered.[138-140]

Even though radiation protection exposure limits exist, in general, radiation protection philosophy incorporates the ALARA principle: *as low as readily achievable.* This philosophy holds that although dose rates may be within the legal (acceptable) limits given previously, all exposures should be reduced as much as possible, given practical constraints of money, time, and human and material resources. Examples of ALARA in practice might be the relocation of clerical personnel away from a radiation source storage area, developing a more efficient method for source handling in a busy brachytherapy practice, or the addition of another HVL of shielding to a linear accelerator room ceiling during a time of renovations to further reduce doses to an upstairs pediatric playroom.

Ownership, use, receipt, and transfer of radiation sources are governed by national or state laws and are authorized or licensed under the supervision of institutional committees and state and national regulatory agencies. The Nuclear Regulatory Commission (NRC) regulates radioactive materials only

(e.g., ^{60}Co, ^{137}Cs), and its laws are published in the Code of Federal Register and in regulatory guidance documents.[141,142] These rules apply to all states and U.S. territories. However, the NRC does not regulate electronically produced radiation sources (x-ray tubes and linear accelerators). Some states have agreed to implement the NRC rules as part of their state radiation control program, and these states are called *agreement states*. Radiation users in agreement states are inspected by the state, not the NRC. Radiation users in nonagreement states are inspected directly by the NRC for their radioactive materials. Nonagreement states may have their own state radiation control programs for electronically produced radiation sources. About 75% of U.S. states are agreement states, and the remaining 25% are nonagreement states. Other regulatory agencies with radiation-related regulations include the U.S. Department of Transportation, the U.S. Environmental Protection Agency, and possibly other state or local agencies.

General provisions for radiation sources are specified in a license that is granted to an individual or institution by the appropriate regulatory authority. Radiation source licenses cover a variety of classes of sources and generally require adequate administrative controls by the user. For instance, academic institutions with medical and research uses of radiation sources must have a radiation safety program that specifies items such as educational and experience requirements for users, radiation control procedures, and the administrative chain. Institutional radiation safety programs include a radiation safety committee for oversight and a radiation safety officer for implementation of policy.

Recent events in the United States, where patients were injured or died as a result of overdoses from both radiologic imaging and treatment procedures,[143] have highlighted the need for continued vigilance for radiation safety for patients. The issues relate to the computer-controlled automation of imaging and treatment procedures and the understanding of operators and radiological professionals on the radiation dose and other performance aspects for the equipment being used. The imaging or treatment devices were operated with unknown and incorrect parameters or with a partial malfunction that still enabled radiation delivery. National standards are now being formulated for quality assurance procedures, operator training, and other aspects. Importantly, besides errors in radiologic procedures, a great concern has been stated by the National Council on Radiation Protection and Measurements (NCRP Report 160)[144] about the average collective effective dose in the United States; there has been approximately a twofold increase in the average yearly collective effective dose, from 3.6 to 6.2 mSv over about a 15-year period from 1982 to 2006, owing to a large increase in the amount of dose from radiologic medical imaging, mainly CT, and followed by nuclear medicine imaging. Clearly, the radiologic community must be cognizant of the ionizing radiation dose being delivered by both imaging and treatment procedures, to ensure no dose is given without an intended benefit.

QUALITY ASSURANCE

Radiation machines and sources, beam modifiers, measurement instrumentation, and treatment planning computers must be regularly verified for proper operation and characteristics to ensure quality and consistency of dose. A basic quality assurance program for dose-related items entails daily, weekly, monthly, and annual tests with satisfactory results within specified tolerances. Recommendations and standards for quality assurance exist for machines, sources, instrumentation, and treatment planning computers.[40,145-147] References also are available on the general quality assurance process.[148-150] Dose verification by an independent, accredited radiologic physics center is a desirable service and is required for participation in many cooperative protocol groups.

The age of computerized and automated radiation treatment planning, delivery, and verification presents new challenges for quality assurance of treatment. Treatment processes may now be wholly contained within commercially provided "black boxes" of computer software and automated treatment machines, such that important quality assurance tests may be difficult to design and perform or provide results that are difficult to readily interpret. The radiation imaging and treatment errors mentioned previously are examples of the "black box" syndrome and failed quality assurance procedures. The implication is that high technology approaches to quality assurance will also be needed with redundant methods for ensuring and proving the correct delivery of treatment. Quality assurance and safety in high-technology radiation therapy remain high priorities for those individuals who are prescribing, delivering, and ensuring quality for the benefit of radiation treatment patients.

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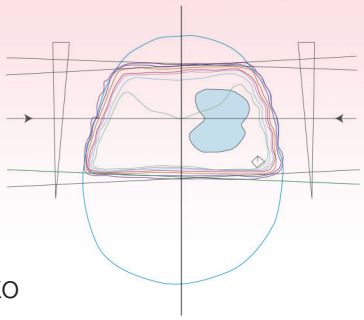
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CHAPTER

7 Radiation Physics: Stereotactic



Timothy D. Solberg, Paul M. Medin, and Brian A. Hrycushko

The field of stereotactic radiosurgery is now more than 60 years old. The intervening decades have seen numerous technical developments, facilitating clinical success in numerous disease sites throughout the brain and body. Yet the fundamental principles remain largely unchanged:

- the delivery of an ablative dose of radiation that is biologically distinct from conventional fractionation;
- the use of many nonoverlapping beams converging on a target from many directions to create a conformal and compact dose distribution, effectively minimizing damage to intervening tissue;
- the assiduous requirement for localization accuracy, facilitated through the use of a stereotactic frame, or more recently, though image guidance; and
- the unique characteristics of radiosurgery beams—small field size, step gradients, loss of lateral equilibrium—that place rigorous demands on beam measurement, commissioning, and quality assurance.

The chapter provides covers the principles of stereotactic localization, the physics associated with small photon beams, selection of appropriate detectors, and the processes for commissioning stereotactic radiosurgery systems.

HISTORY OF STEREOTACTIC IRRADIATION

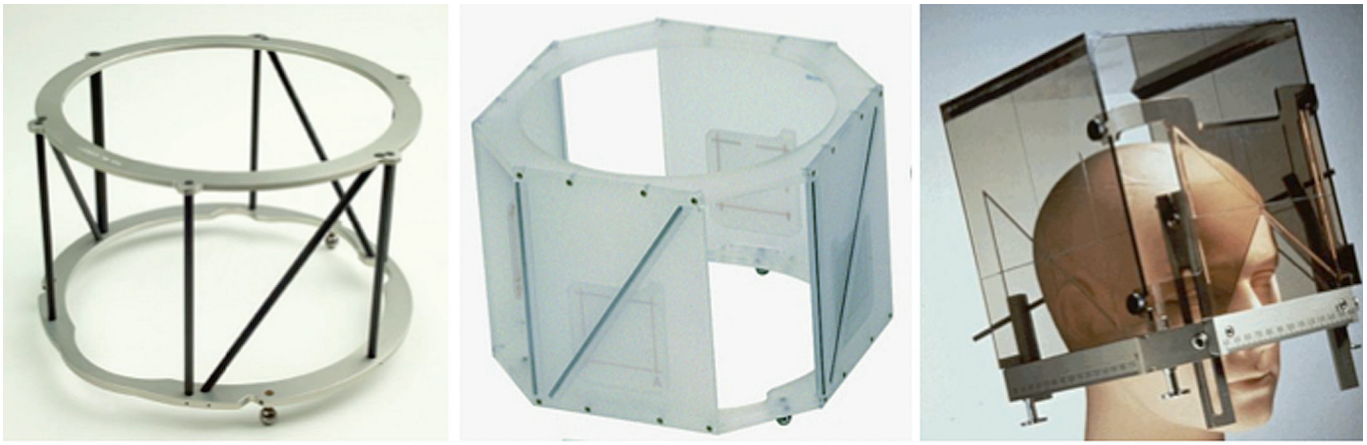
The field of stereotactic irradiation owes its origins to parallel development in two disparate medical disciplines dating back more than a century, stereotactic surgery and external beam radiation. In the late 1800s, surgeons and anatomists began exploring quantitative methods for studying the structure and function of the brain. The methodology, known as stereotaxis, relies on external fiducials to define a three-dimensional frame of reference in which targeting can be performed. Historically the fiducials consisted of a head frame that was rigidly attached to the skull. Because the skull and cranial structures remained fixed with respect to the frame, the external fiducials served as an appropriate surrogate for intracranial localization. The stereotactic method was pioneered by Horsley and Clarke, who devised an instrument for producing lesions at exact locations within the brains of nonhuman subjects.[1,2] Other early efforts included those of Mussen and Kirschner.[3,4] Routine clinical application of stereotactic surgery in humans is credited to the team of Speigel and Wycis.[5] Lars Leksell subsequently developed a frame based on polar rather than Cartesian coordinates, providing maximum flexibility in choosing entry point and trajectory.[6] The commercial Leksell frame (Elekta AB, Stockholm, Sweden) remains identical in function to the 1949 device. Other developments in stereotactic frames included the efforts of Talairach; Narabayashi; Reichert and Mundinger; and Brown, Roberts, Todd, and Wells.[7-14] Brown's modifications to the original Wells-Todd device resulted in the Brown-Roberts-Wells (BRW) coordinate system that is available commercially from Integra Radionics (Burlington, MA) and BrainLAB (Feldkirchen, Germany).[12,14] Examples of commercial stereotactic localization devices are shown in Figure 7-1. In the era of image guidance, the skull serves as its own set of fiducials, and head frames are no longer required.[15-18]

The discovery of x-rays by Wilhelm Roentgen in late 1895 is well known. Throughout the subsequent decades, efforts to increase the penetration ability of x-rays produced with conventional tubes met with modest success, with tube potentials limited to approximately 200 kV. In the early 1950s, Leksell realized that external forms of energy such as ultrasound and ionizing radiation could be coupled to a stereotactic frame. In 1951, Leksell proposed the term *stereotactic radiosurgery* (SRS) to refer to the delivery of a single high dose of radiation accurately directed to an intracranial target. The principles of dose localization require irradiation "through a large number of small portals . . . which all meet and cross in the structure in question."[19] Leksell also appreciated the limitations imposed by low energy x-rays, and his subsequent efforts, as well as those of groups located in Boston, Massachusetts, and Berkeley, California, used beams of protons and other light ions.[20-25] In the mid-1960s, Leksells' colleagues at the Karolinska Institute in Stockholm, Sweden, began efforts on what would become the first dedicated radiosurgery device. The initial Gamma Knife, installed in Sofiahemmet Hospital in 1967, used 179 rectangular-collimated cobalt-60 sources; subsequent commercial versions were implemented with 201 circular-collimated sources.[26,27] The Perfexion unit, consisting of 192 cobalt sources arranged in eight independent sectors, was introduced by Elekta in 2007. Each sector can move to one of four locations to choose between blocked, 4-, 8-, and 16-mm circular collimation.[28] Figure 7-2 shows the evolution of the commercial Gamma Knife, from the Model U to the present Perfexion.

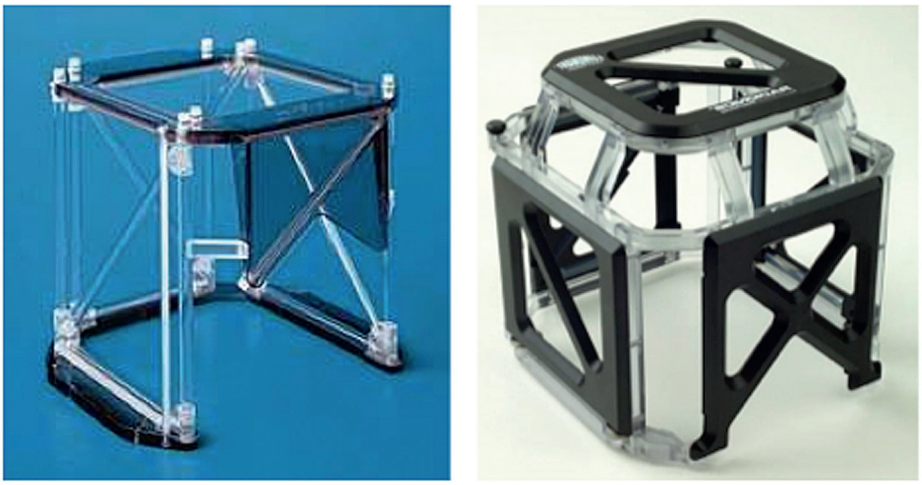
The development of technology for linear accelerator-based radiosurgery began in the early 1980s, with the first radiosurgery patient treated on a modified linac in 1982.[29] All early linac systems used hardware modifications designed to facilitate stereotactic frames and improve targeting accuracy to overcome shortcomings with the treatment couch.[29-31] Subsequent improvement in linac couches allowed the stereotactic frame to be affixed directly to the couch top. Subsequent developments included linacs dedicated for radiosurgery, including the CyberKnife (Accuray, Sunnyvale, CA), 600SR (Varian Medical Systems, Palo Alto, CA), Novalis (BrainLAB AG, Heimstetten, Germany), and C-arm multi-rotation-axis linac (Mitsubishi Electric Ltd., Tokyo, Japan).[32-36] Modern linacs such as the TrueBeam STx and EDGE (Varian Medical Systems, Palo Alto, CA), and Axesse and Versa HD (Elekta AB, Stockholm, Sweden) have localization and dosimetric characteristics that make them well suited for radiosurgery applications. Figure 7-3 shows the evolution of the radiosurgery linacs, including the original Betti device, an early floor stand, the original CyberKnife, and several commercial linac systems.

PRINCIPLES OF STEREOTACTIC IRRADIATION

There are several key principles that make SRS distinct from conventional radiotherapy. First, the procedure involves the delivery of an ablative dose of radiation that overwhelms the capacity of the irradiated cells to survive. The biological processes associated with high-dose delivery are quite different



Radionics CT | BrainLAB CT/Angio | Leksell CT



Radionics MR | Leksell MR

Figure 7-1 Commercial localization devices for defining stereotactic coordinates.

than those occurring at ~2 Gy per fraction, and an increasing number of investigators have alluded to these *threshold effects*.[37] The ablative intent implies that the approach is meant to treat gross disease exclusively and not microscopic extension. The accompanying need for tight margins places demands on both physical and dosimetric accuracy. The superior contrast resolution provided by magnetic resonance necessitates its use in most cranial indications, albeit with careful consideration of potential spatial distortions.[38-41]

Second, the accuracy and precision of both spatial and dosimetric localization is essential. Before the advent of computed tomography (CT), stereotactic localization was performed using a pair of projection radiographs. Fiducials located on the entrance and exit surfaces of the localization device facilitated calculation of both target location and magnification from a pair of radiographs (Figure 7-4). Studies have demonstrated that the target point can be determined to within 0.3 mm over a large range of source-to-target and source-to-image distance and projection angles using such a technique.[42,43] The obvious shortcoming of the approach is that it cannot adequately reconstruct a target volume.

The principle of stereotactic localization based on tomographic images is illustrated in Figure 7-5. The superior-inferior dimension *(z)* is defined by measuring the in-plane distance between diverging fiducials *(y)* and applying simple geometry:

$$z_i = y_i / \tan\theta \quad (1)$$

With modern imaging and head frames, localization accuracy on the order of 1 to 2 mm is achievable.[44-47] There are numerous sources of geometric uncertainty, including mechanical and radiation device isocentricity, imaging resolution, target delineation, as well as the stereotactic frame itself. The report of American Association of Physicists in Medicine (AAPM) Task Group 42 specifies an overall localization uncertainty of 2.4 mm (1σ), providing the planning images use a sufficiently thin slice thickness.[48]

Dosimetric localization requires the delivery of many beams from many directions, overlapping only at the target of interest. Ideally the intensity of any individual beam is sufficiently low that little damage occurs along the beam path, except at the point all beams intersect. Conformality of the high dose and target volumes is essential, as is compactness of the overall dose distribution. Because the intermediate dose volume increases rapidly as a function of target size, single fraction cranial applications are largely limited to lesions smaller than 4 cm.[49]

DOSIMETRY OF RADIOSURGERY BEAMS

Dosimetric integrity, that is, the ability to accurately deliver the intended dose distribution to the desired volume, is a critical element of radiosurgery. Dosimetric integrity begins with



Figure 7-2 Several generations of the Leksell Gamma Knife: **A,** the Gamma Knife Model U; **B,** the Gamma Knife Model B; **C,** the Gamma Knife Model 4C; **D,** the Gamma Knife Perfexion.



Figure 7-3 Evolution of linear accelerator technology for radiosurgery: **A,** the Betti system (Betti and Derechinsky, 1984); **B,** the Philips SRS200 floor stand system, circa 1990; **C,** the original CyberKnife (Adler, 1993); **D,** the Novalis, circa 1997; **E,** the Novalis Tx; **F,** the TrueBeam STx.

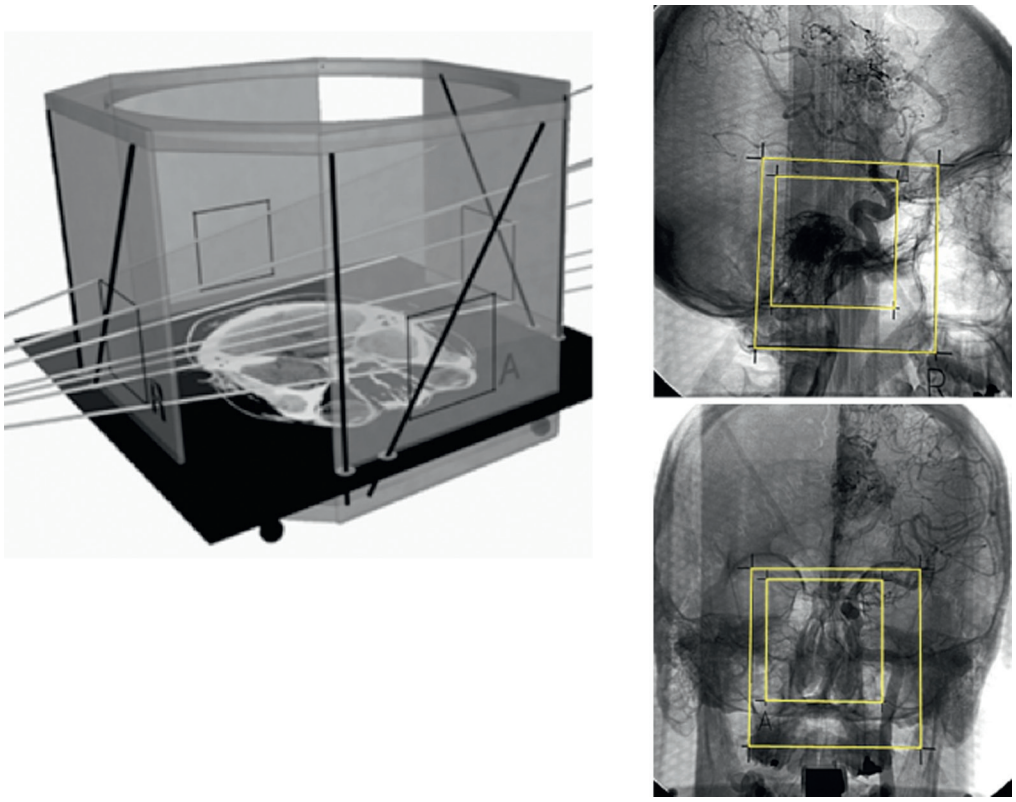


Figure 7-4 Principles of stereotactic localization using biplanar radiography.

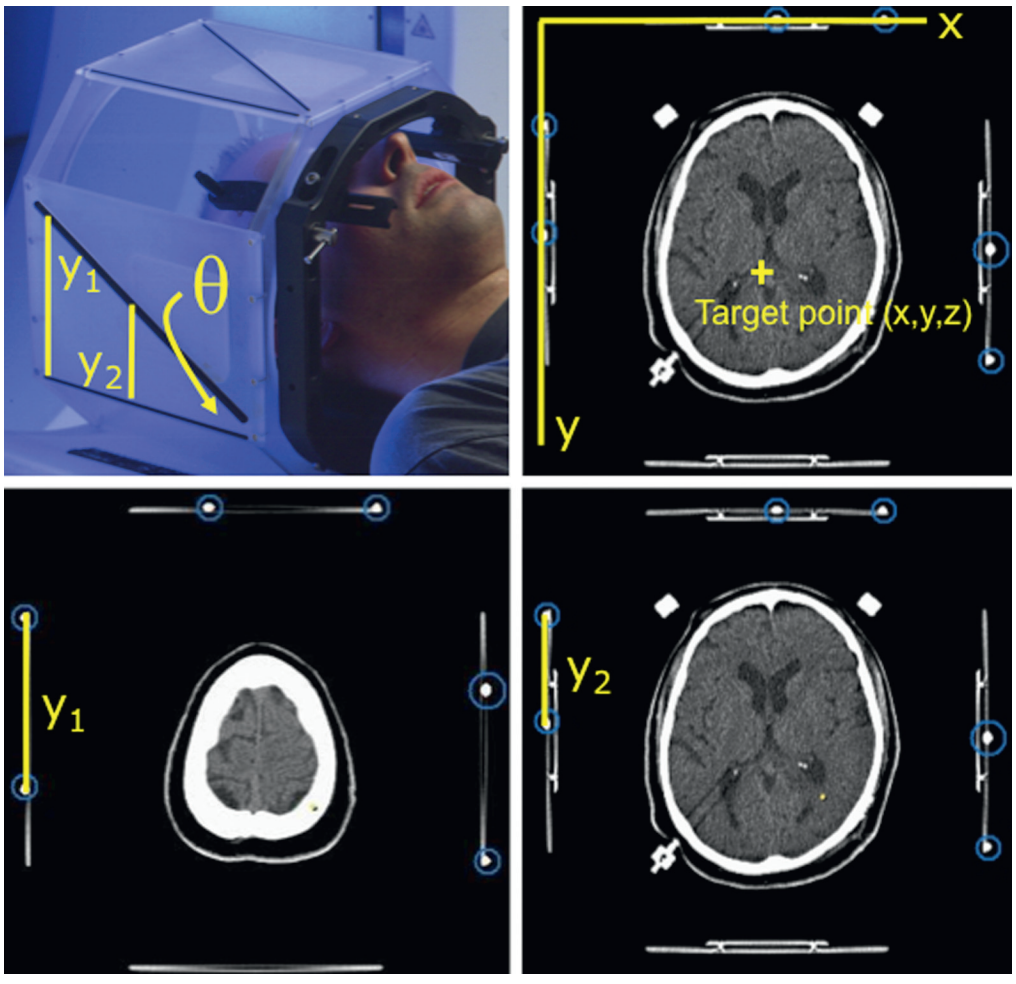


Figure 7-5 Principles of stereotactic localization using computed tomography.

the accurate measurement of photon beam characteristics.[50] In general, SRS planning systems require the measurement of percent depth dose, off-axis profiles, and relative output factors. For systems equipped with a micro-MLC, measurement of leaf transmission and dynamic leaf gap is also required. Historically, radiosurgery planning systems used highly simplistic dose algorithms, ignoring both surface irregularities and tissue heterogeneities.[51,52] For cranial targets, these approximations introduced clinically insignificant errors on the order 1% or less, provided beams are not placed through air cavities.[53,54] Subsequent development of pencil beam algorithms facilitated CT-based dose calculation.[55-57] The current GammaPlan system offers the original water-based dose calculation (TMR10) as well a CT-based convolution algorithm. Modern linac systems provide both pencil beam and Monte Carlo options.[58-63] For commissioning Monte Carlo algorithms, additional beam measurements, including central and off-axis profiles and output factors in air, are often required.[62,64] In-air scans require a brass build-up cap suitable for the beam energy used.

Considerations in Small Field Dosimetry

The measurement of beam characteristics (relative output factors, percent depth doses, and profiles) in small fields is challenging because of their inherent steep-dose gradients. A misunderstanding of detector requirements or misinterpretation of measured beam data can lead to injurious or even life-threatening consequences.[65,66] There is no accepted criterion defining a "small field," but in general, a small field can be labeled so depending on the electron range in the irradiated medium, the detector dimensions, or partial obstruction of the radiation source through collimation.[67]

Lateral electronic equilibrium becomes compromised when the beam radius is comparable in size to the maximum electron range. The maximum electron range depends on the photon beam energy and the irradiated medium composition (i.e., density and atomic number). At this point, electrons leaving the central portion of the field are insufficiently replaced by electrons scattered from the surrounding medium. Output factors for small fields are difficult to measure in these conditions as a result of spectral differences causing stopping power ratios and correction factors to be unclear. AAPM Task Group 65 recommends a general rule of thumb for the lateral electron range being about one third of the forward range, and in a 6 MV x-ray beam, electron disequilibrium has been shown to occur for radii <1.0 cm.[68,69] Below a certain field size, collimating devices can partially block the radiation source from the detector's field of view. Clearly the output from the partially blocked source will be reduced compared to fields in which the detector views the complete source. The partially obscured focus also leads to the field size, as defined by the 50% isodose, to reduce more rapidly than the collimated aperture.[67]

The measurement of small field beam characteristics requires a small detector. The rationale for selection of an appropriately small detector size and the consequences of using too large a detector differ for relative output factor, depth dose, and beam profile measurements. Relative output factors are commonly defined as the ratio of dose for a field size of interest (a small field) over a reference field size (a larger field) at a fixed depth in medium. Relative output factors are specified on the central axis. The detector of choice must be placed on the central axis and must only intercept central-axis fluence. This is easily achieved for a large reference field size with a flat beam profile around the central axis, but much greater consideration is necessary for a small field with steep-dose gradients in close proximity to the central axis. The cross-sectional dimensions of the detector cannot be

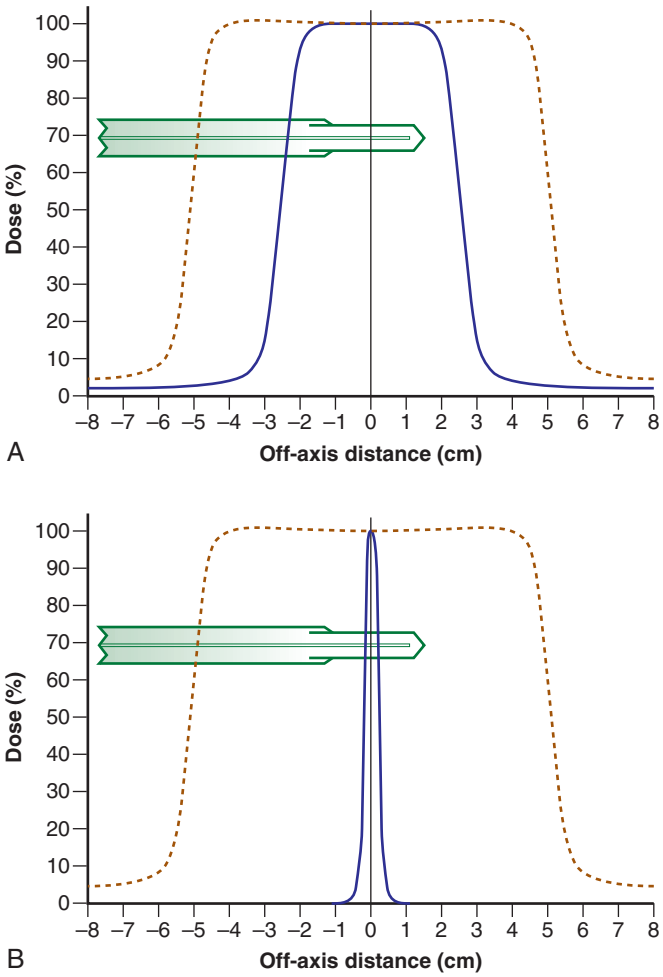


Figure 7-6 A standard air ionization chamber in **(A)** a 5 × 5 cm² field and **(B)** a 0.5- cm diameter circular field relative to a 10 × 10 cm² reference field.

larger than the flat portion of the beam profile (crossline and inline) around the central axis. Appropriate detector selection for a relative output factor measurement of a 5 × 5 cm² field normalized to a 10 × 10 cm² reference field is illustrated in Figure 7-6, *A*. The air ionization chamber fits within the flat portion of the beam profile around the central axis for both fields. Figure 7-6, *B* illustrates an inappropriate detector selection for a relative output factor measurement of a 0.5-cm diameter circular field normalized to a 10 × 10 cm² reference field. The air ionization chamber is much longer than the flat portion of the beam profile around the central axis of the 0.5-cm diameter field and the chamber intercepts the shoulder and tail of the beam profile in addition to the central axis. This results in an output factor measurement that is much smaller than reality and, if used clinically, will result in an overdose to patients. Relative output factors measured with a Farmer-type air ionization chamber and a silicon diode for square fields from 6 to 80 mm are presented in Table 7-1 for comparison. Output factors must be measured for each system independently, and values in Table 7-1 should not be used as a standard. When selecting a detector to measure relative output factors, one should always confirm that the detector dimensions are at least as small as the flat portion of the beam profile around the central axis. For SRS and SBRT beams, AAPM Task Group 101 recommends use of a detector with a maximum dimension of 1 mm.[70]

TABLE 7-1 Relative Output Factors Measured in Small Photon Fields. The Farmer-Type Ionization Is Much Larger Than the Beam, Averaging over the Shoulder and Tail of the Beam Profile in Addition to the Central Axis, and Resulting in Grossly Underestimated Output Factor

Square Field Size (mm)	Output Factor	
	Stereotactic Diode	Farmer-Type Chamber
6.0	0.599	0.126
12.0	0.775	0.420
18.0	0.824	0.647
42.0	0.907	0.900
60.0	0.945	0.940
80.0	0.988	0.975
100.0	1.000	1.000

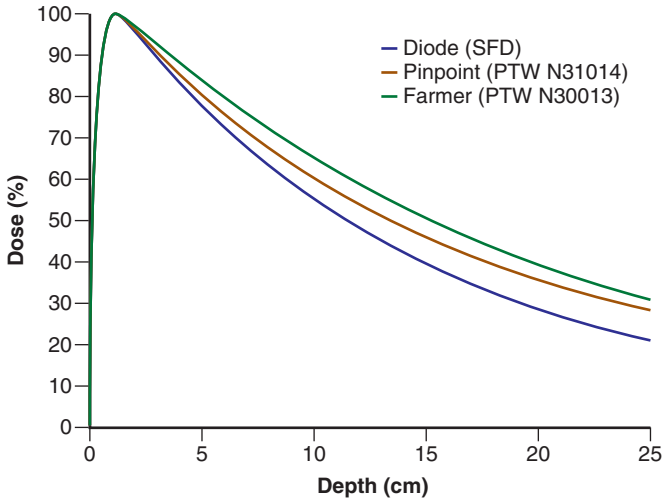


Figure 7-7 Percent depth dose for a 6-mm diameter circular field scanned using a 0.6-cc Farmer-type air ionization chamber, a 0.015-cc pinpoint air ionization chamber, and a stereotactic diode.

Percent depth dose (PDD) measurements for small fields require small detectors because, by definition, PDD describes the change in relative dose with depth on the central axis only. As in the case of relative output factor measurements, a detector wider than the flat portion of the beam profile (see Figure 7-6, *B*) at any depth will give an inaccurate PDD by including the central-axis fluence as well as the shoulder and tail regions. Figure 7-7 shows PDD scans for a 6-mm diameter circular field scanned with, (1) a 0.6-cc Farmer-type air ionization chamber (30013, PTW), (2) a 0.015-cc pinpoint air ionization chamber (31014, PTW), and (3) a silicon diode (SFD, DEB050, IBA Dosimetry). Larger chambers overmeasure the PDD at depth as a result of integration of dose lateral to the central axis.

Small detectors are required to accurately measure beam profiles of small fields to resolve steep-dose gradients in the penumbra region. Figures 7-8, *A* (crossline) and 8B (inline) show beam profiles for a 6.0-mm diameter circular field measured with a Farmer-type air ionization chamber (dashed) and a stereotactic diode (solid). The larger air ionization chamber smears out the profile (penumbra broadening) because it integrates ionization over its 0.6-cc (6-mm diameter, 24-mm length) measurement volume, whereas the diode integrates over its 0.6-mm cross-section. The shape of a beam profile ultimately affects the apparent dose coverage of a target. Over-correcting the shoulder region to achieve target coverage will increase the dose delivered to surrounding tissues.

Detectors for Small Field Measurements

Radiographic and radiochromic film are commonly used in beam data collection for small fields. Film is ideal in spatial dose mapping for relative dosimetry and is recommended for profile measurements with the Gamma Knife radiosurgery system.[48] The superior resolution of radiographic film is inherently limited by the silver halide grain size, typically ranging from 0.1 to 5 µm; however, the practical spatial resolution is limited by the pixel dimensions of the film digitizer. The use of film for small field relative dosimetry is justified as the high spatial resolution provides for a more accurate delineation of the sharp dose gradients within the penumbra region. Although dependencies on irradiation conditions have been observed, reproducible film processor conditions allow radiographic film to be used for output factor corrections for small fields.[71] Radiochromic film has the same benefits for small field dosimetry as radiographic film but exhibits less energy dependence, a greater dynamic range, and no need for film processing.[72]

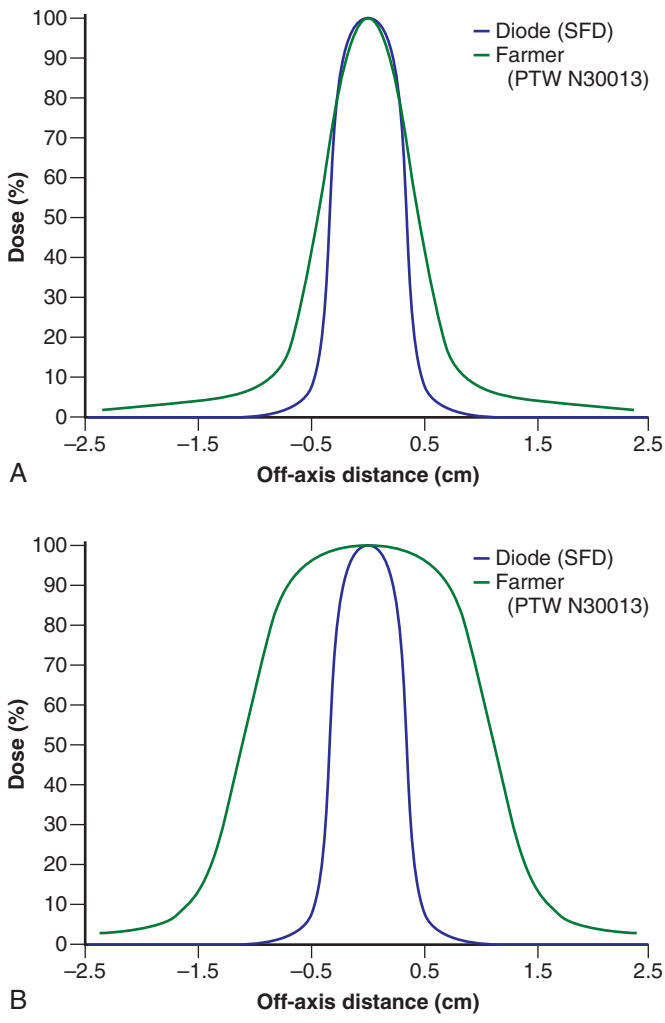


Figure 7-8 Crossline **(A)** and inline **(B)** beam profiles for a 6.0-mm diameter circular field measured using a Farmer-type air ionization chamber *(green curve)* and a stereotactic diode *(purple curve)*.

Semiconductor diamond detectors have been used to characterize SRS photon fields because of their small size.[73] A near soft-tissue equivalence, excellent mechanical stability, and a high signal-to-noise ratio are attractive properties of diamond detectors that are useful for small field dosimetry. The water-to-diamond mass attenuation coefficients and stopping power ratios are relatively constant over the energy range of clinical photon beams making diamond detectors well-suited for relative dosimetry. Measurement of PDD has compared well with diode detectors; however, a significant dose-rate dependence has been observed.[74]

Solid-state silicon diode detectors are the most commonly used detectors for small field dosimetry measurements. Several commercial diode detectors approach the 1-mm maximum dimension recommended by AAPM Task Group 101. P-type silicon diode detectors have the smallest cross-sections among commercially available detectors for radiation therapy applications. Silicon diodes produce approximately 18,000 times the current of an air ionization chamber of equal volume making them useful as a radiation detector at very small sizes (cross-sections from 0.6 to 1.2 mm) while creating sufficient signal.[75] Dieterich et al summarized the physical characteristics and response of seven commercial diode detectors and observed a small interdetector variation that appeared to be systematic with packaging.[76] Diode response has been observed to change with orientation, temperature, radiation damage, energy, and dose rate.[75,77-79] The effect of orientation on response has been investigated with the diode stem oriented parallel versus perpendicular to the beam axis. Although there is the potential benefit of increased resolution with a perpendicularly oriented diode stem, the penumbra width is underestimated because of a decreased electron range in the diode material and skewness can be introduced in profiles, dependent on the scanning direction.[77,78] Scanning with the diode stem oriented parallel with the beam axis is recommended.[77,78] Temperature has been observed to change the response of diodes, but this should not be a significant problem for relative beam data measurements collected in the relatively constant thermal environment of a water bath.[75] Ionizing radiation damages diodes over time, causing a diode's response to decrease as the total dose increases. It is common to preirradiate diodes to minimize the effect of radiation damage.[75] When measuring relative output factors with a diode, it is important to frequently remeasure the output of the reference field to determine if the sensitivity of the device has changed over the course of measurements. Diode response is energy dependent as a result of the atomic number of silicon (Z = 14) and any surrounding high-Z materials (i.e., protective housing or buildup material) being much larger than that of tissue or air. For this reason, diodes may not respond uniformly in fields with nonuniform photon spectra. To minimize the effect of energy dependence in relative output factor measurements, an approach known as "daisy chaining" has been employed in which diode and air ionization measurements are referenced to an intermediate field size. This technique has been described in depth by Dieterich et al.[76] Energy dependence can also affect PDD and profile measurements because of differences in the number of low-energy scattered photons with depth and location within a radiation field. The effect of energy on PDD and profile measurements is dependent on field size and detector design and needs to be verified for a given situation. Heydarian et al measured off-axis factors for circular fields with radii from 7 to 23 mm using a diode and observed good agreement with Monte Carlo simulations.[78] The group also measured PDDs in square field sizes of 10.0, 3.0, and 0.5 cm^2 and observed that the diode produced values less than predicted by Monte Carlo calculations with increasing difference at greater depth. This disagreement was likely predominantly due to a dose-rate effect.

Small Field Beam Data

In Figure 7-9, PDD, off-axis profiles, and relative output factors are shown as a function of field size for both circular and MLC-shaped square fields for a 6 MV beam. The PDD curves exhibit the familiar dependence on field size, that is, the distal slope becomes increasingly shallow at larger field sizes. By overlaying PDD curves for different sized fields on a single plot, errors in detector alignment for small fields will become quite apparent. In addition, a slight shift of the depth of maximum dose (D_{max}) toward shallower depths for the smallest fields can be observed. This is as a result of the absence of lateral electronic equilibrium, which at 6MV occurs for fields smaller than approximately 3.0×3.0 cm^2.[80] For a 6-MV beam with a nominal D_{max} of 1.5 cm at a 10×10 cm^2 reference field, D_{max} may shift to 1.2 cm for a 4-mm diameter circular collimator.

Off-axis profiles are characterized by a sharp lateral falloff. For tapered circular collimators, the 80% to 20% penumbra at 6-MV ranges from ~1.5 to 2.0 mm for 4 to 20 mm in diameter.[81] Measured single beam penumbra on the Gamma Knife have similar values, between 1 and 2 mm.[52] Although the shorter SSD of the Gamma Knife should provide for a smaller penumbra relative to linac systems, the lower energy and finite size of the Co-60 sources act to increase penumbra slightly. Similarly, for micro-MLC the 80% to 20% penumbra at 6-MV ranges from ~2.5 to 5.0 mm for 6 to 30 mm square fields.[81,82]

Relative output is defined as the ratio of dose for a given depth, field size, and source-to-surface distance to that for a reference depth, field size, and source-to-surface distance. Relative output factors are characterized by a decrease with decreasing field size, with a sharp falloff at small fields (Figures 7-9, *C*, and 7-9, *F*, for square and circular fields, respectively). Because there is a greater loss of lateral electronic equilibrium at higher beam energies, relative output decreases with increasing energy, for a given field size.[80] For the same reason, the magnitude of the shift in D_{max} described also increases with energy. These effects are exacerbated at higher energies, thus small field irradiation at energies above 10 MV is not recommended.[48,70,83]

RADIOSURGERY COMMISSIONING AND QUALITY ASSURANCE

Isocentric Accuracy: The Winston-Lutz Test

The Winston-Lutz test is commonly used for assessing isocentric accuracy of linac SRS systems.[30,84] A small radio-opaque sphere is positioned at the isocenter, a series of beams-eye-view images are obtained at various gantry, couch, and collimator combinations (Figure 7-10), and the offset of the sphere is measured relative to the radiation field. For radiosurgery systems that use both circular collimators ("cones") and MLC, the Winston-Lutz test should be evaluated for both field-defining devices. Modern linac systems are capable of results averaging better than 0.75 mm over the full range of gantry, couch, and collimator settings.[64] It is important to perform a Winston-Lutz assessment on a daily basis and after service to the linac or lasers.[66]

End-to-End Target Localization

Although the Winston-Lutz test is essential for characterizing isocentric accuracy, there are various aspects of the treatment process, incorporating imaging, planning, and localization, that must be assessed in an integrated manner. Assessing the ability of the treatment planning system (TPS) to correctly translate the mechanical parameters (i.e., stereotactic coordinates, gantry, couch, and collimator angles, etc.) to the

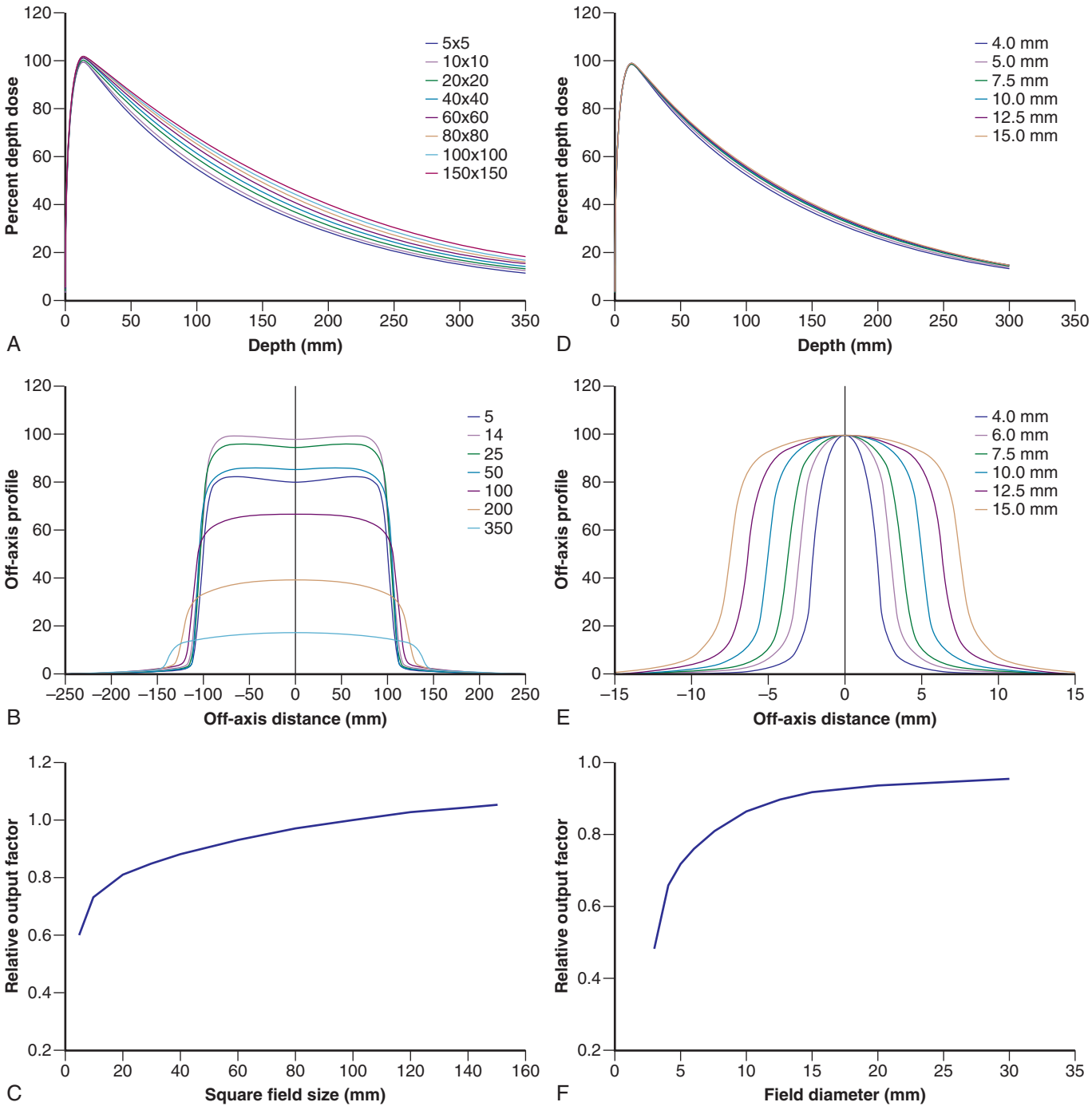


Figure 7-9 Percent depth dose, off-axis profiles, and relative output factors for **(A-C)** MLC-shaped square fields and **(D-F)** circular fields for a 6-MV beam.

treatment device is a critical test of any radiosurgery system. This is illustrated in Figure 7-11 using the Radionics QMP Phantom (Integra Radionics, Inc., Burlington, MA). Within the TPS, an isocenter is placed at the tip of the cone. Using the printed positioning templates, the phantom is localized in the treatment room. If the overall targeting process is working properly, the room lasers should intersect with the tip of the cone.

A hidden target test is also essential for assessing end-to-end capabilities that incorporate imaging, planning and localization aspects. The process of a hidden target test is illustrated in Figure 7-12. In this example, a small, radiopaque ball was placed in an anthropomorphic head phantom, which was in turn fixed in a stereotactic head frame. A CT was obtained and the center of the sphere was identified and defined as an isocenter. In the treatment room, the phantom was aligned to the lasers using templates provided by the treatment planning computer. AP and lateral beams-eye-view films were obtained using a 10-mm circular collimator. Accuracy was subsequently assessed by measuring the offset of the ball within the projection of the field. Hidden target tests can also be used in conjunction with image guidance systems to assess image guided radiotherapy (IGRT) accuracy. Modern systems are capable of end-to-end accuracy on the order of ~1.0 ± 0.5 mm.[46,85-89]

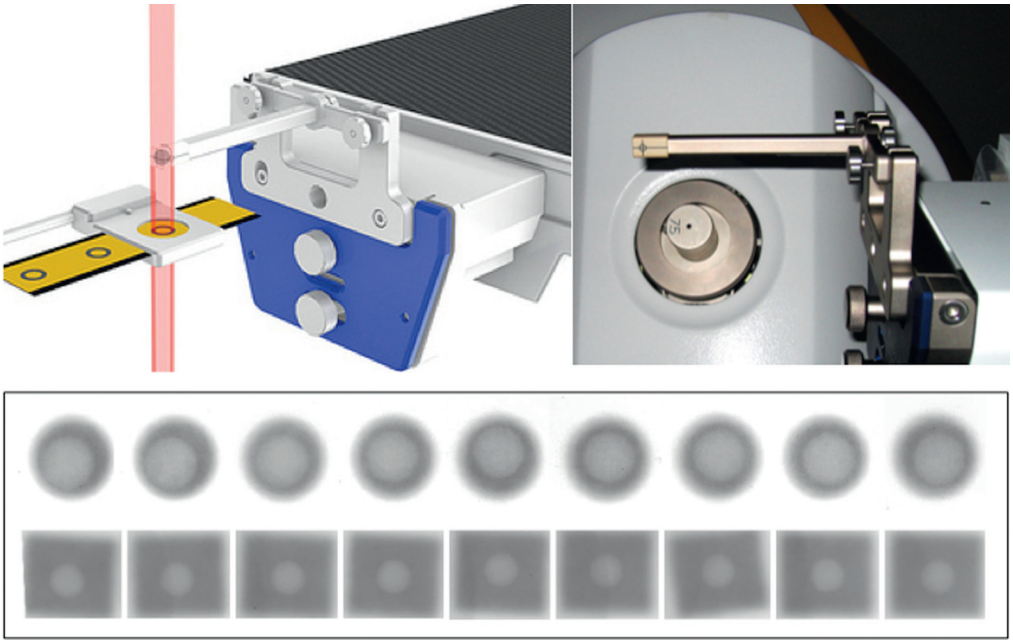
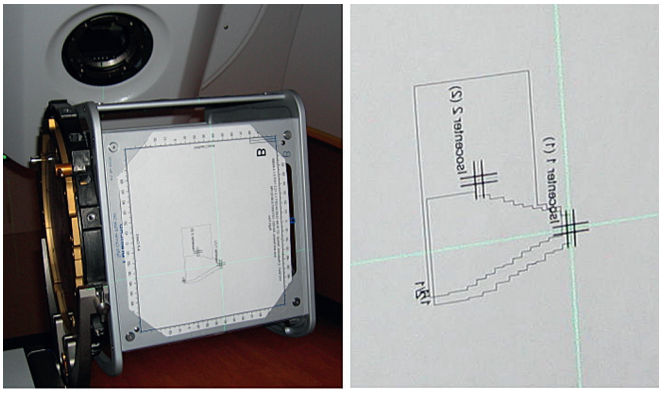
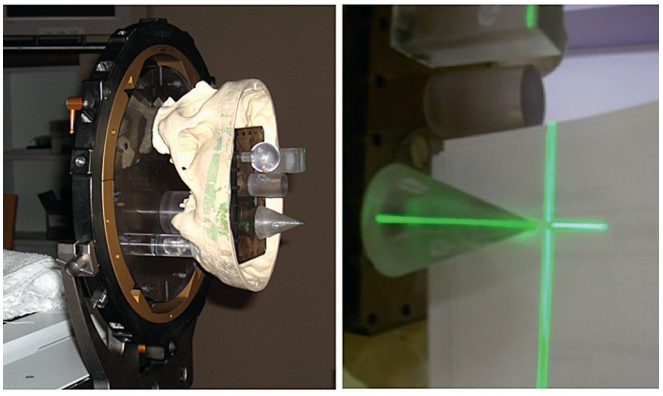


Figure 7-10 Winston-Lutz test of linac isocentric accuracy using both circular collimators and MLC.

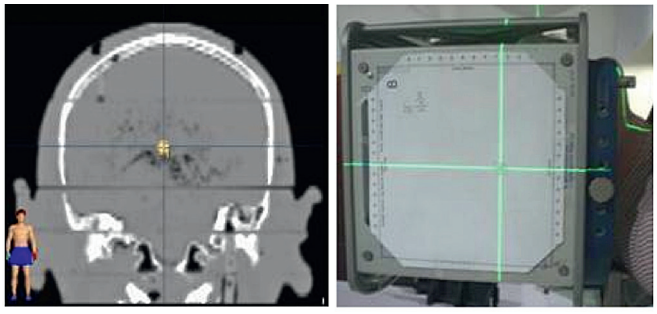


Align target positioning templates with room lasers



Observe laser projection on intended isocenter

Figure 7-11 End-to-end target localization test.



Scan and identify target | Localize on treatment device

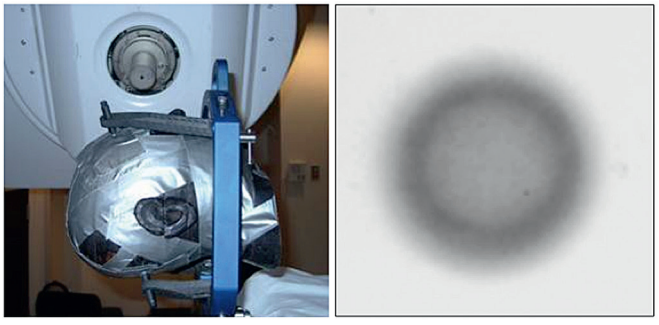


Image treatment beam | Analyze

Figure 7-12 Hidden target test.

Dosimetric Commissioning

Once targeting accuracy has been confirmed, and beam data has been measured and verified, thorough dosimetric commissioning of the radiosurgery treatment planning system must be performed to ensure that the monitor units and other parameters calculated deliver the intended dose within the desired volume. The process of TPS commissioning is a standard radiotherapy task and has been described is several AAPM reports and elsewhere.[90-92] Because radiosurgery has several unique characteristics relative to conventional radiotherapy—for example, large dose per fraction, heterogeneous dose distributions, sharp dose gradients, and use of multiple isocenters—it is important to commission the TPS across a comprehensive range of doses and delivery techniques. This may include arc therapy using circular collimators, regular and irregular shaped conformal beams, dynamic

conformal arcs, IMRT, as well as combinations of these distributed among multiple isocenters. Absolute dose ranging to 20 Gy or higher should be measured using a calibrated or cross-calibrated microionization chamber, whereas dose distributions are typically verified using film or an array detector. The process has been described recently for two newer radiosurgery units.[64,93] Figure 7-13 show examples of film measurements in solid water phantoms, with calculations from the treatment planning system superimposed, for a small field IMRT (top) and multiple isocenter (bottom) delivery. Dosimetric commissioning should also be performed using an end-to-end approach.[70] This can be facilitated using a simple phantom fixed in a stereotactic frame or using an anthropomorphic phantom in combination with image guidance, as illustrated in Figure 7-14. Use of the Radiological Physics Center (RPC) SRS, thorax-lung, spine, and head and neck IMRT phantoms

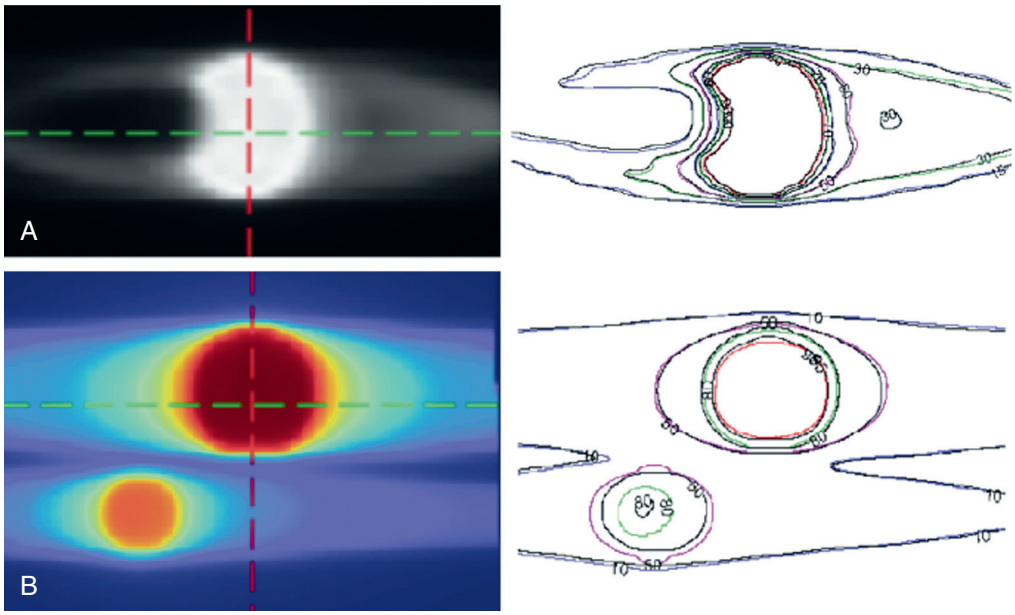


Figure 7-13 Film measurements in solid water phantoms *(left)*, superimposed on calculations from the treatment planning system *(right)*, for a small IMRT field *(top)*, and multiple isocenters *(bottom)*.

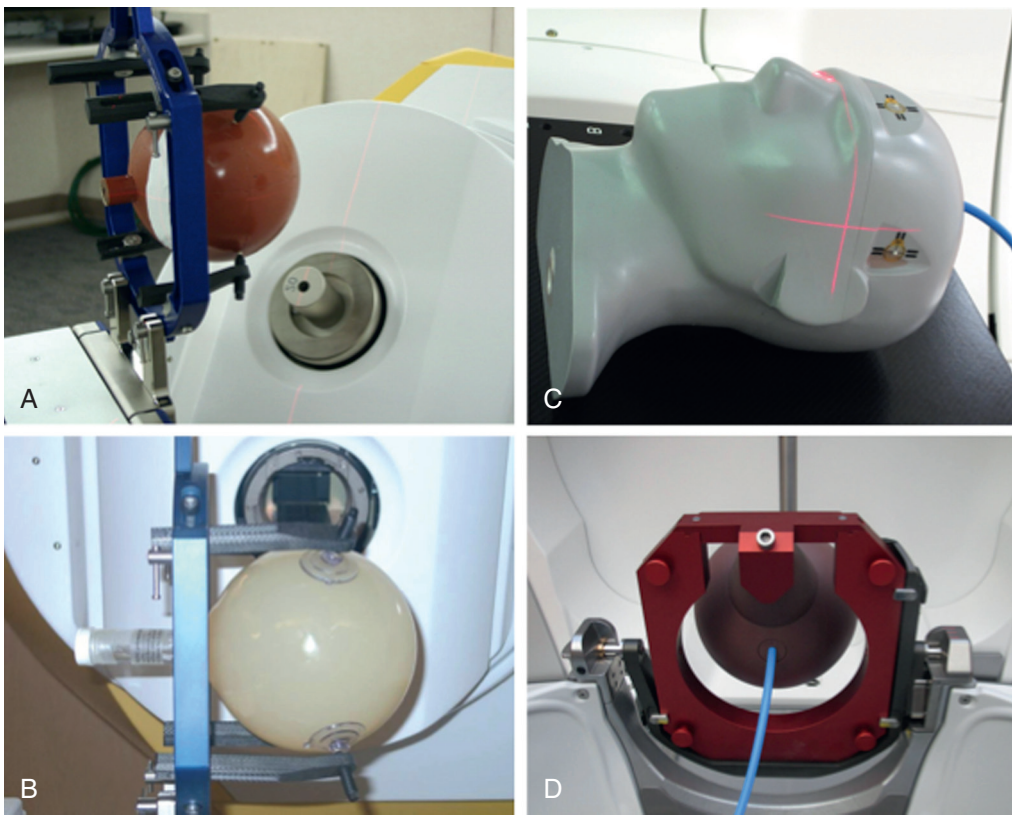


Figure 7-14 End-to-end dosimetric verification on **(A)** a linac system using a solid water phantom, **(B)** a linac system using a BANG-gel phantom, **(C)** a linac system using an anthropomorphic head phantom, and **(D)** a Perfexion system using a solid water phantom.

as an independent means of verification is also highly recommended.[66] Finally, TPS commissioning should always be performed through a record-and-verify system to help detect potential systematic errors that may propagate through the electronic record.

CONCLUSIONS

SRS has become a standard of care in the management of cranial disease and stimulated application in extracranial disease sites. The clinical success of SRS and SBRT has been facilitated in large part through technological development and depends on fundamental understanding of nonequilibrium physics and dosimetry and diligent attention to commissioning and quality assurance.

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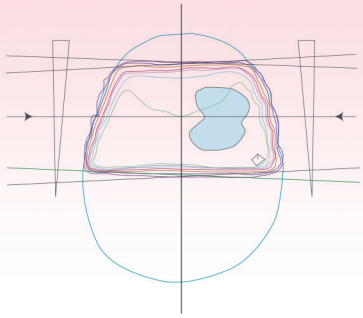
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CHAPTER 8

Surgical Principles



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Surgery remains the central treatment for most cancers. Survival for the majority of patients with solid malignancies is still most dependent on the stage of the tumor and on the physician's ability to resect all of the known tumor. Surgeons help in the diagnosis, staging, curative and palliative therapy, and follow-up of patients with cancer. The surgical oncologist does not act in isolation; instead, interaction with colleagues from other specialties is routine. Because many of the common solid tumors are treated with a combination of therapies, the surgeon usually provides treatment in collaboration with medical and radiation oncologists. This interaction among specialists provides the best chance for patient cure and effective palliation.

Preoperatively, an accurate patient history is obtained and a physical examination plus routine laboratory tests and, when indicated, more specialized evaluations are performed to assess the tumor extent and the patient's ability to tolerate the proposed treatment. The goals of surgical intervention in patients with cancer include providing a histologic diagnosis, disease staging, and disease treatment, either with potential cure or symptom palliation. The role of surgical treatment in the relief of patient suffering is particularly beneficial for visceral obstruction, hemorrhage, perforation, and pain caused by tumor involvement. High-quality radiologic imaging studies such as ultrasonography, computed tomography (CT), and magnetic resonance imaging (MRI) plus three-dimensional reconstructions are instrumental in planning the appropriate operative procedure. A preoperative biopsy of a lesion that appears to be malignant is not necessary for diagnosis but is indicated for a patient receiving preoperative (neoadjuvant) or nonoperative therapy.

The role of the surgical oncologist in the multidisciplinary management of the cancer patient will be highlighted in this chapter. The surgeon's role in multimodality therapies for malignant diseases will be illustrated by the management of cancers of the breast, pancreas, rectum, and retroperitoneum.

HISTOLOGIC DIAGNOSIS

A pathologic diagnosis should be secured before the definitive surgical procedure in some patients. The goal of the diagnostic biopsy is to obtain sufficient tissue for complete analysis with minimal risk for complication. Either cytologic or histologic samples are adequate for most cancers, but a histologic diagnosis is usually preferable. A false-negative cytologic result occurs in 10% to 20% of cancer patients, and false-positive cytologic diagnoses can rarely occur. Biopsies that sample a tumor may underestimate the aggressiveness of a lesion (e.g., atypia or carcinoma in situ instead of invasive cancer) because of sampling error. A diagnostic tissue specimen may be obtained by aspiration cytology, core-needle biopsy, incisional biopsy, or excisional biopsy. A separate biopsy procedure is unnecessary unless it affects preoperative treatment planning. Endoscopically or laparoscopically directed biopsies both allow more accurate staging of intraabdominal malignancies than noninvasive procedures plus provide tissue for diagnosis.

Fine-needle aspiration cytology (FNAC) is widely used to evaluate solitary thyroid nodules. Using a 21-gauge needle and syringe, an aspirate of cellular material or fluid is obtained, differentiating between solid and cystic masses. If a cyst does not completely disappear with aspiration, FNAC examination of any residual solid component is necessary. The success of FNAC depends on the experience of the clinician performing the aspiration and on the interpretation of a skilled cytologist. FNAC of the thyroid enables the pathologist to differentiate most benign from malignant tumors. Papillary, medullary, and anaplastic carcinomas have typical cytologic appearances. Cytology cannot differentiate benign from malignant follicular and Hürthle cell neoplasms. A definitive diagnosis for these thyroid neoplasms depends on histologic examination of the entire excised tumor. The introduction of routine FNAC has dramatically reduced the number of diagnostic surgical operations for benign thyroid masses.

Percutaneous radiograph-directed FNAC has gained great popularity over the past 25 years.[1] Ultrasonography or CT scanning is routinely used to obtain hepatic, renal, pancreatic, and retroperitoneal biopsies. Percutaneous biopsy techniques are particularly useful to confirm the presence of metastases in a patient with a history of malignancy. Adrenal FNAC should be avoided if a pheochromocytoma has not been excluded. If potentially curable metastases (e.g., limited hepatic metastases from colorectal cancer) are present, this diagnostic test is unwarranted and potentially dangerous because of rare tumor seeding. If unresectable cancer is present at exploratory laparotomy, a confirmatory biopsy should be obtained.

The choice of ultrasonographic or CT guidance depends on several factors. In general, ultrasonography is used for superficial lesions. Ultrasonography possesses other advantages, including real-time imaging, which allows constant monitoring of the needle position, and lower costs compared with CT scanning. Ultrasonographic examination is limited by overlying bone and gas. CT guidance is more beneficial for deeper tumors, particularly in the retroperitoneum. Advantages of CT-guided biopsy include better spatial resolution and lack of interference from air or bone. Intravenous contrast provides an estimate of tumor vascularity.

Core-needle biopsy can be performed by hand if the mass is easily palpable and can be stabilized by the operator. Radiographically directed core biopsies, particularly of solid breast masses, are commonly performed preoperatively. Unlike an FNAC, a core biopsy provides sufficient tissue for histologic

analysis. Using local anesthesia, a small (3-mm) incision is made in the skin through which a coring biopsy needle is directed into the center of the lesion. Typically, a 1- × 10- to 20-mm tissue sample is obtained. Core-needle biopsy may also be performed with stereotactic imaging or ultrasonography for nonpalpable breast lesions.

Core-needle biopsies of intraabdominal and thoracic tumors offer the advantages of a histologic diagnosis and greater accuracy than the FNAC. Larger-bore needles can cause complications, most commonly hemorrhage. Some tumors, including many adjacent to major blood vessels, are not safely accessible percutaneously. Core-needle biopsy should not be used for potentially resectable malignancies because of a higher risk of needle track seeding than with FNAC. Intraoperative diagnostic core biopsies are preferable to incisional biopsies when a diagnosis is needed for an unresectable tumor. The decision to resect or not, as in a pancreaticoduodenectomy for painless jaundice, should be based on the clinical and operative findings; a histologic diagnosis is not mandatory before resection.

Incisional biopsy excises more of a tumor mass than needle biopsy. A full-thickness biopsy using a scalpel or punch biopsy tool of a larger skin tumor is a commonly performed incisional biopsy. A full-thickness sampling of the thickest portion of the lesion should be removed to allow accurate tumor staging. Sometimes an incisional biopsy of a sarcoma is performed to provide the diagnosis before proceeding with definitive treatment (e.g., amputation, preoperative chemotherapy, or radiation), but core-needle biopsies are another option. An incisional biopsy of an extremity tumor is preferably obtained through a longitudinal rather than a transverse incision because the longitudinal incision can be more readily incorporated with a wide local excision.[2] Intraoperative incisional biopsies during thoracotomy and laparotomy are rarely indicated; tumor spillage is more likely than with FNAC or core-needle biopsies.

Excisional biopsy of a breast mass illustrates the key principles of a diagnostic surgical biopsy. This procedure can be used for small, palpable lesions amenable to easy complete excision. A diagnostic excisional breast biopsy is now rarely performed. Almost all breast cancers are diagnosed with FNAC or core biopsy preoperatively. If possible, the skin incision should be circumareolar or situated within the elliptical incision that would be used for a mastectomy (Figure 8-1). If the breast mass is believed to be malignant, it should be excised with a 1-cm margin of normal tissue, centering the suspicious lesion in the specimen (Figure 8-2, *A*). The biopsy specimen should be oriented to permit the pathologist to specify which of the resection margins, if any, are histologically involved by tumor. Specimen orientation can be denoted with two sutures (Figure 8-2, *B*) or by painting the specimen with multiple-colored stains. If frozen-section evaluation of the resection margins is available, reexcisions can be performed immediately when necessary. When frozen-section evaluation is unavailable, separate, individually labeled margins may be sent in addition to the primary tumor specimen. Selective reexcision can be performed at a later date if the main specimen has been appropriately oriented with sutures, clips, multicolored inks, or separate margins. Surgical clips left at the base of the biopsy cavity facilitate accurate

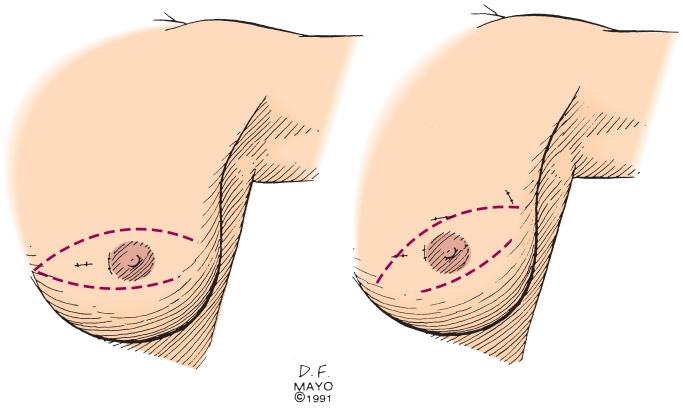


Figure 8-1 Excisional breast biopsy performed within the confines of a mastectomy incision.
Courtesy the Mayo Foundation.

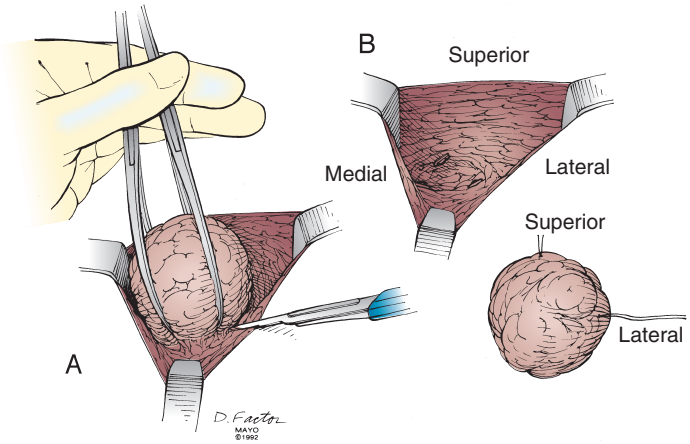


Figure 8-2 **A,** Excisional breast biopsy. **B,** Specimen orientation.
Courtesy the Mayo Foundation.

partial breast or boost-field radiation therapy after breast-conservation surgery. Small titanium clips provide accurate localization for the radiation oncologist with minimal interference on future images, including MRI.

STAGING

The stage of a malignant tumor usually determines the goal of intervention. Symptoms or physical signs frequently alert the clinician to metastatic disease, but diagnostic studies are usually required to confirm distant disease spread. Accurate preoperative staging results in the best treatment because the extent of tumor spread remains the single-most important determinant of patient prognosis.

Clinical and pathologic stages of disease for most cancers have been standardized in the American Joint Committee for Cancer (AJCC) TNM system.[3] In this nomenclature, T refers to the primary tumor, N indicates the status of regional lymph nodes, and M denotes the presence or absence of metastatic disease. For most cancers, the size (e.g., in lung, liver, or breast cancers) or the degree of invasion (e.g., in melanoma or stomach or colorectal cancers) of the primary tumor correlates with the probability of metastases.

Clinical tumor staging is normally determined using combined data from physical examination, a variety of radiologic tests (including plain radiographs, ultrasonography, CT, and MRI), and endoscopic examination. Positron emission tomography (PET)-CT imaging provides more sensitive staging compared with other imaging studies in a number of disease sites. PET-CT can be especially helpful in the diagnosis of unsuspected metastatic disease (e.g., esophageal cancer; melanoma) and in evaluating patients with possible recurrent cancer (e.g., locally recurrent rectal cancer). In symptomatic patients, skeletal metastases can also be diagnosed with a radioisotope bone scan or correlative plain radiographs.

Role of Laparoscopy

The introduction of laparoscopy in general surgical practice has led to more precise staging of many intraabdominal malignancies, particularly gastric,[4] pancreatic,[5] and hepatobiliary cancers.[6,7] Thoracoscopy allows inspection and biopsy of the pleural cavity to assess for intrathoracic tumor spread. When used for diagnosis, laparoscopy allows visualization of peritoneal surfaces; histologic evaluation of peritoneal, omental, or hepatic tumor masses; biopsy of lymph nodes; and collection of ascites or peritoneal washings for cytologic examination. Laparoscopic ultrasonography further improves the staging of pancreatic and hepatobiliary malignancies.[8-10] If the laparoscopic findings confirm metastatic malignancy, the attendant morbidity from tumor resection by traditional or minimally invasive techniques can be avoided. Laparoscopic techniques can be used for cancer therapy to palliate patients with advanced malignancy and curatively resect others.[11]

Staging of Pancreatic Malignancy

Laparoscopy is frequently used to stage pancreatic and periampullary carcinomas because hepatic or peritoneal metastases undetectable by radiographic means occur in up to 30% of patients with tumors believed to be resectable preoperatively.[5,12,13] Recent data[14] show an extended, complete laparoscopic inspection of the abdominal cavity should be undertaken using a 10-mm port at the umbilicus (Figure 8-3). Additional cannulae allow for retraction of the liver to allow observation of all surfaces, plus the lesser sac, omentum, and loops of intestine. Laparoscopic inspection should also include a Kocher maneuver to visualize the paraduodenal retroperitoneum. Inspection of the upper abdomen, looking for small hepatic metastases or drop metastases on the parietal and visceral peritoneum or the greater omentum, is readily accomplished. Any suspicious lesions should be sampled using a biopsy forceps or core-needle biopsy tool. The remainder of the abdomen can be examined, including the peritoneal surfaces, for seeding and dependent areas for ascites. Evidence of direct spread of a pancreatic carcinoma into the transverse mesocolon and small bowel mesentery should be assessed.

With the patient in the reverse Trendelenburg position, limited visualization of the anterior surface of the pancreas may be obtained with a supragastric approach after division of the lesser omentum (Figure 8-4, *A*) or an infragastric approach, entering the lesser sac through the gastrocolic omentum (Figure 8-4, *B*). Biopsy of peritoneal implants within the lesser sac should be obtained. Laparoscopic ultrasonography provides a more accurate assessment of visceral vascular involvement and deep hepatic metastases,[10] although

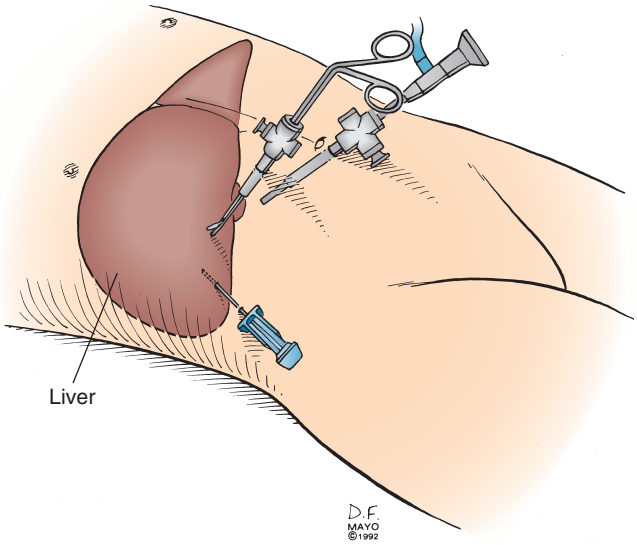


Figure 8-3 Laparoscopic examination of the upper abdominal cavity.
Courtesy the Mayo Foundation.

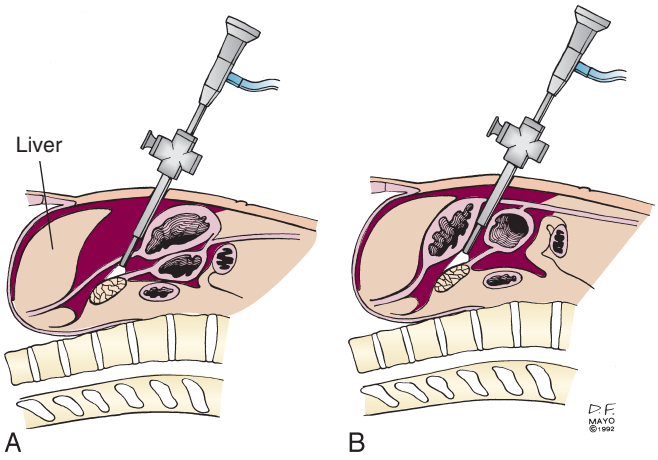


Figure 8-4 Laparoscopic examination of the pancreas: supragastric **(A)** and infragastric **(B)** approaches.
Courtesy the Mayo Foundation.

endoscopic ultrasonography (EUS) provides highly accurate staging in these sites.

GOALS OF SURGICAL INTERVENTION

The primary intent of surgical intervention is curative resection. The surgeon must be familiar with the cancer biology, including modes of spread (i.e., hematogenous, lymphatic, intracavitary, or direct extension). En bloc excision of the tumor is performed for the highest probability of cure (complete resection or R0 resection = no residual tumor). Complete extirpation of the primary tumor with a margin of normal tissue plus a regional lymph node dissection typifies this type of resection. For cancers such as colon carcinomas or retroperitoneal sarcomas, normal adjacent structures directly invaded or adherent to the malignancy should also be resected. Lysis of adhesions between a primary cancer and an adjacent structure can result in residual cancer and tumor spillage. When the local extent of a nonmetastatic malignancy prevents a gross total resection with negative margins, the surgeon should facilitate postoperative irradiation planning by leaving titanium clips at the site of residual microscopic disease (R1 resection = microscopic residual cancer).

Certain intraabdominal malignancies are appropriately treated by surgical debulking (R2 resection = gross residual disease) plus perioperative therapy. Examples include ovarian carcinomas and rare low-grade mucinous adenocarcinomas, known traditionally as pseudomyxoma peritonei, that are usually of appendiceal origin. The goal of operative therapy is to remove as much macroscopic intraabdominal disease as is feasible because patient outcome is improved.

For patients with known metastatic disease who have symptoms or are at risk for complications from locally advanced disease, surgical palliation (R1 or R2 resection) should be considered. Operative procedures should be reserved for well-defined problems amenable to surgical treatment in patients with reasonable performance status and life expectancy. Intestinal obstruction can be corrected by a resection, bypass, or proximal diversion (i.e., ostomy formation). When technically feasible, laparoscopic, laparoscopically assisted (i.e., mobilization using laparoscopic technique and a portion of the procedure performed through a limited celiotomy), and endoscopic stenting techniques are suitable and preferable to a formal laparotomy. Diffuse peritoneal implantation often prevents successful palliation and increases the risk of postoperative complications, including infection and intestinal fistula formation. The surgeon may prevent life-threatening hemorrhage or improve pain by resection of some cancers. Pain can also be alleviated by nerve transection or blockade, such as celiac plexus block for pancreatic carcinoma.

PERIOPERATIVE CARE OF THE ONCOLOGY PATIENT

The cancer patient may develop unique perioperative problems. The surgeon must strive to avoid such problems and must monitor the patient for their occurrence to minimize morbidity and minimize delays in adjuvant therapy. Patients with malignancy have a higher prevalence of postoperative complications because of their neoplastic disease, coincidental comorbidities in older patients, the major surgical procedures patients have undergone, and perioperative and adjuvant therapy-induced immunosuppression. Patients with gastrointestinal malignancies with or without obstruction frequently suffer from substantial weight loss, malnutrition, and resultant immunodeficiency. The hematologic, gastrointestinal, pulmonary, and cardiac toxicities associated with chemotherapy pose additional risks for the patient postoperatively. Before adjuvant therapy is started, sufficient time must be allowed to pass for wound healing and resolution of infectious complications to occur.

The extent and type of operative management must take into account the patient's preexisting and malignancy-induced comorbidities. Cancer cachexia resulting from anorexia is common and results in significant lean tissue loss and immunodeficiency. Because malnutrition significantly increases the risk for perioperative morbidity, the surgeon must carefully assess the degree of preoperative malnutrition. Although retrospective studies evaluating preoperative nutritional support show a reduction in postoperative complications for patients with severe malnutrition,[14] a meta-analysis did not support routine preoperative nutrition for oncologic patients.[15] Total parenteral nutrition should be reserved for patients unable to tolerate enteral nutrition, those unable to take sufficient calories by oral or enteric routes during therapy, and those felt to be unsuitable for operative or combined-modality therapy until their nutritional status improves. Enteral rather than parenteral nutrition should be used whenever possible. Postoperative nutritional support should always be considered, especially in patients with upper gastrointestinal malignancies such as esophageal, gastric, and pancreatic cancers. A feeding jejunostomy catheter placed intraoperatively facilitates delivery of postoperative nutrition.

The oncologic patient has a higher risk for postoperative infection. Immune compromise in patients with cancer occurs as a result of older age, surgical stress, malnutrition, and impaired host defense mechanisms. Neutropenia combined with defective cell-mediated immune responses render malnourished patients especially prone to postoperative complications and impair the patient's response to sepsis. Appropriate perioperative antibiotics and vigilant postoperative observation for infection are critical in reducing the morbidity of postoperative infections.

Older age, the presence of a malignancy, and undergoing operative procedures all increase the incidence of thromboembolic complications. A hypercoagulable state is especially common in patients with pancreatic, prostate, lung, breast, and gastric cancers. Increased factors I, V, VIII, IX, and XI;

decreased proteins C and S; and reduced antithrombin III levels have all been implicated in higher rates of thromboembolic events in patients with cancer. Perioperative subcutaneous heparin (both low-molecular-weight and unfractionated heparin are appropriate treatments), thromboembolic stockings, and sequential compression devices should be used for all patients undergoing oncologic surgery. Patients at high long-term risk for thromboembolic complications (e.g., prior history of deep venous thrombosis/pulmonary embolism [DVT/PE], inherited hypercoagulable trait, debilitated, or those with residual cancer) need to be considered for extended anticoagulation therapy.

Patients with malignancy are often anemic. Blood transfusions result in immunosuppression, including depression of specific cellular immunity, and nonspecific immune responses, including natural killer cell activity and macrophage phagocytosis. Some retrospective studies have shown higher cancer relapse rates in cancer patients receiving blood transfusions, but controlled trials have not demonstrated a poorer disease-specific survival (DSS) rate specifically related to perioperative transfusions.[16,17] Blood transfusion must be administered as appropriate in oncologic patients.

RADIATION THERAPY AND WOUND HEALING

Tissues exposed to radiation therapy develop acute inflammatory changes in proportion to the total dose. Higher-dose fractions may cause more significant changes. Acute radiation injury is manifested by vasodilation (erythema) and tissue edema. Following moderate-dose preoperative radiation (45 to 50 Gy in 1.8- to 2.0-Gy fractions), a 3- to 6-week preoperative recovery period is generally allowed for partial resolution of acute radiation changes.[18] Late radiation changes include atrophy and fibrosis, which result from decreased tissue vascularity.

Wound healing is impaired in irradiated tissue by several factors, including diminished blood supply, impaired collagen formation, and the increased risk of infection resulting in part from decreased leukocyte function. After high-dose irradiation, slow and nonhealing wounds are commonplace. In this situation, nonirradiated tissues, such as vascularized myocutaneous flaps, may need to be transferred into the radiation field to allow proper wound healing.[19] This is preferably done at the time of tumor resection rather than after a nonhealing postoperative wound develops. If partial resection of an irradiated hollow organ (e.g., bowel, bile duct, trachea) is necessary, one side of the anastomosis should be nonirradiated tissue whenever possible. This precaution provides a better blood supply for healing of the anastomosis. This policy will reduce the incidence of early postoperative leak and fistula formation and late anastomotic strictures.

SURGICAL TREATMENT OF BREAST CANCER

The treatment of patients with breast cancer should occur in a multidisciplinary setting. Ideally, patients are evaluated in a breast clinic with treatment specialists, including a surgeon, radiation oncologist, medical oncologist, nurse, and medical geneticist providing preoperative consultation. There should be a focus on patient education regarding the treatment options currently available for both operative and nonsurgical adjuvant therapies.

Most women with breast cancer can now choose breast conservation. Data from multiple mature, controlled trials have demonstrated no significant difference in disease control or survival between patients who elect breast-conservation therapy and those who choose mastectomy.[20-22] Mastectomy is a suitable option if the woman chooses this form of treatment. Mastectomy is preferable for the management of multicentric disease and most large primary tumors (neoadjuvant chemotherapy may allow breast conservation in patients with a sufficient response) and in patients unable to receive postoperative radiation therapy. The majority of patients undergoing mastectomy can have immediate breast reconstruction, if desired. Consultation with a plastic surgeon should be obtained preoperatively to allow the patient to assess the immediate reconstruction options. The timing of breast reconstruction depends partly on patient preference. In addition, if chest wall irradiation is indicated by the breast cancer stage, the immediate reconstruction results are often cosmetically affected.

Early Breast Cancer

Most women with early-stage breast cancer (i.e., stage 0, I, or II breast cancers) are suitable candidates for breast-conservation surgery. The goals of breast-conservation surgery are optimal locoregional control of the breast cancer and preservation of the natural appearance of the breast. All known breast cancers must be excised from the breast and axilla. (It is not necessary to pathologically stage the axilla for most ductal carcinomas in situ.) Radiation therapy must be administered following breast-conservation surgery to reduce the risk of local tumor recurrence, given the high incidence of residual microscopic disease, even with pathologically clear margins. Because radiation therapy is an integral component of breast conservation, patients who are unsuitable for radiotherapy should not undergo this form of surgery. Contraindications to breast-conservation surgery include a history of certain collagen vascular diseases (e.g., scleroderma, polymyositis), the presence of diffuse indeterminate or suspicious calcifications on mammography, a history of therapeutic irradiation to the breast, and positive margins of resection despite wide excision.

Breast-conserving surgery is performed through an incision as close to the primary tumor as possible, whether the lesion is a palpable mass or a mammographic abnormality that has been localized. It is best to remove the entire abnormality with a 1-cm margin of grossly normal tissue to improve the probability of microscopically clear margins. A curvilinear incision in Langer's lines optimizes the cosmetic result in most locations, whereas a radial incision may be preferable in the lower quadrants. Incisions should be positioned to allow them to be included in a standard mastectomy incision wherever possible. After specimen excision, markers (e.g., sutures, clips, dyes) should be placed on the tissue to provide orientation. If frozen-section pathologic analysis is available, evaluation of margins can be obtained intraoperatively. If margin evaluation is performed later, correct specimen orientation will result in less tissue reexcision when the original specimen has tumor involvement of one or more margins. Titanium clips are placed at the base of the biopsy cavity to help target postoperative irradiation. The breast wound is usually closed without approximation of the breast parenchyma. Oncoplastic closures with mobilization of flaps can provide better cosmesis, especially with larger tumor excisions.

Sentinel lymph node biopsy or axillary lymph node dissection is best performed through a separate incision. The axillary incision should be placed between the axillary folds and not cross the lateral border of the pectoralis major muscle (Figure 8-5). Axillary staging aids patient management in determining prognosis and systemic adjuvant treatment. Patients with positive axillary nodes are almost routinely advised to receive systemic treatment, usually combination

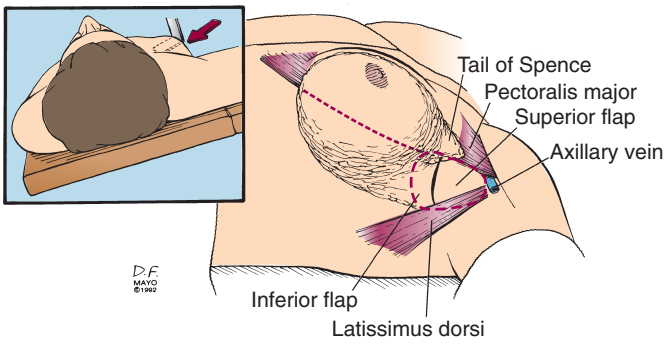


Figure 8-5 Incision of axillary dissection.
Courtesy the Mayo Foundation.

chemotherapy. Postoperative therapy commences after sufficient wound healing has occurred, usually within 4 weeks.

Sentinel Lymph Node Biopsy

Axillary lymph node dissection was once routinely performed in women with invasive carcinoma of the breast. The rationale for axillary lymphadenectomy has shifted from increasing the rate of cure and improved regional disease control to improved staging and appropriate selection of systemic therapy. With the widespread acceptance of the sentinel node biopsy procedure, formal axillary nodal dissection for early breast cancer is limited to patients with pathologic nodal metastasis. Regional metastases are the single-most important prognostic variable for patients who have breast cancer without distant metastases. Because nodal involvement cannot be accurately predicted except with microscopic tissue evaluation, axillary node examination is a necessity.

Minor complications, including seroma development, wound infection, and sensory nerve transection, occur after axillary lymphadenectomy. Although these problems are generally minor, severe and permanent disability from an axillary lymph node dissection may occur. Most commonly this results from upper extremity lymphedema and occasionally from sensory neuropathy. A sentinel lymph node biopsy with limited sampling of the nodes provides an accurate assessment of regional metastasis, with a low prevalence of significant complications. Sentinel lymph node biopsy allows selective completion lymphadenectomy in patients who have documented nodal metastasis.

A sentinel lymph node biopsy identifies and excises the first draining regional node(s). First popularized in the management of cutaneous malignant melanoma, in 1994 Giuliano et al[23] reported their adaptation of the sentinel node technique for patients with breast cancer. Using isosulfan blue to isolate the sentinel lymph node, they identified a sentinel node in 93% of patients with high accuracy for detecting axillary metastases. Given their success with sentinel node biopsy to identify nodal metastases, Giuliano et al[23,24] stopped performing axillary lymphadenectomy for patients with a negative sentinel node biopsy.

To successfully predict nodal metastasis requires an orderly spread of tumor cells in the lymphatics, not a random distribution. The initial draining node or sentinel lymph node is the site of first metastasis. After several confirmatory reports, sentinel lymph node biopsy became standard practice for patients with breast cancer who had no clinical evidence of axillary metastasis.[25-27] The sentinel lymph nodes can be localized with a dye (usually isosulfan blue or methylene blue), a radiolabeled colloid (usually sulfur colloid or human serum albumin), or with both dye and colloid. Through a small axillary incision (2 to 3 cm), the blue-stained lymphatics are frequently located at the lateral border of the pectoralis major muscle and followed to the blue-stained sentinel node. Alternately, a handheld gamma probe allows localization of the radioactive lymph nodes. All nodes stained with dye, those with high radioactivity counts, and those with both staining and high counts are excised and evaluated histologically. Any hard lymph node should also be removed and examined by the pathologist because a tumor-replaced node has no lymphatic flow. Tumor-involved nodes found on frozen-section evaluation allow immediate completion of the axillary dissection. The prognostic importance of minimal tumor involvement of a sentinel node, such as that detected only by immunohistochemical staining (i.e., N0[i+]) and micrometastases (i.e., a tumor deposits less than 2 mm in diameter; i.e., N1mi), remains controversial. Recommendations for complete axillary lymph node dissection and adjuvant treatment based on these limited metastases are still evolving.[28]

MULTIMODALITY THERAPY FOR PANCREATIC ADENOCARCINOMA

Ductal adenocarcinoma of the pancreas is a highly lethal disease with approximately the same number of new cases and deaths each year in the United States. The postoperative mortality rate after major pancreatic resection with curative intent has fallen significantly in major centers over the last three decades. With improved cross-sectional body imaging and endoscopic ultrasonography, preoperative disease staging has dramatically improved. This and new methods of nonsurgical palliation limit surgical intervention in patients with advanced disease that is not curable. Early diagnosis of pancreatic cancer is required to improve the probability of patient survival, but because the symptoms of pancreatic carcinoma are nonspecific and metastases occur early, the diagnosis commonly occurs when the cancer cannot be controlled with local treatments. Specific symptoms do not occur until there is invasion of adjacent structures. Most adenocarcinomas arise in the pancreatic head, with obstructive jaundice being a common presentation. Constant mid-back pain is an indicator of locally advanced cancer with tumor involvement of the splanchnic plexus and the central retroperitoneum. Duodenal obstruction resulting in nausea and vomiting can occur with local progression of the cancer.

Preoperative staging of pancreatic carcinoma should determine if a curative operation is possible. High-quality, thin-cut, spiral CT scanning with oral and intravenous contrast media delineates the primary pancreatic mass, local vascular invasion, and liver metastasis in most patients. EUS and laparoscopy with or without ultrasonography provide more sensitive evaluation of limited metastatic disease.[8-14] With EUS, a high-frequency transducer within the gastric and duodenal lumen is positioned near the pancreas. This technique can detect small pancreatic masses (<1 cm), identify enlarged regional lymph nodes (and allow fine-needle aspiration biopsy of both), and better define the presence and extent of visceral vascular involvement. Laparoscopy for staging pancreatic carcinoma is the best means to detect peritoneal or liver metastases not detected with preoperative imaging.

Only 10% to 20% of patients with carcinoma of the pancreas can be completely resected (R0 resection). Palliation of symptoms to improve quality of life becomes the therapeutic goal for most patients with pancreatic cancer. Obstructive jaundice can be palliated surgically or nonoperatively. Several prospective, randomized studies showed nonoperative biliary

stenting to be as effective in the relief of jaundice as surgical biliary bypass.[29,30] Pain from posterior tumor invasion is effectively treated with a combination of oral analgesics and a celiac plexus block. Operative (laparoscopic or open) gastrojejunostomy or expanding metal endoluminal stents are both reasonable options for the management of duodenal obstruction caused by tumor invasion. Stenting is generally less durable than surgical bypass, requiring multiple procedures when patient survival is lengthy.

The operative results and long-term survival rates after pancreaticoduodenectomy have improved most significantly in medical centers with larger patient experiences. Operative management includes a full abdominal exploration, focusing on inspection of the liver, peritoneum, and omentum for distant metastases. The regional lymph nodes are also palpated to assess for tumor involvement. Periaortic, porta hepatis, small bowel mesentery, or celiac lymph node metastases indicate tumor spread beyond the limits of standard resection. Japanese surgeons have advocated radical lymphadenectomy to improve patient outcome,[31] but randomized trials of extended lymph node dissection have not resulted in improved patient survival rates.[32,33]

Local tumor factors that usually prevent curative resection include retroperitoneal extension to involve the inferior vena cava or aorta or direct involvement or encasement of the superior mesenteric artery or celiac axis. Several centers have shown that en bloc resection of the involved superior mesenteric or portal vein results in patient survival comparable to those of standard pancreaticoduodenectomy.[34,35] After excluding unresectable tumors, the surgeon can proceed with pancreaticoduodenectomy. The classic Whipple procedure, which resects the gastric antrum, or the pylorus-preserving modification provides similar results. Recently laparoscopic and robotic minimally invasive pancreaticoduodenectomy have become reasonable options at select centers with skilled surgeons.

Unfortunately, no more than 25% of patients who have a curative resection for ductal adenocarcinoma of the pancreas will survive for 5 years. Optimal long-term survival is seen with complete resection (R0), no lymph node metastases, small tumor size (<2 cm), and lack of perineural or duodenal invasion. Because survival after curative resection is modest, many nonsurgical therapies have been investigated.

Because approximately 50% of patients have locoregional recurrence after curative resection, adjuvant irradiation could have beneficial effects on patient survival rates.[36] The Gastrointestinal Tumor Study Group[37] first reported encouraging results from a prospective, randomized trial in 1985. The efficacy of adjuvant postoperative irradiation and chemotherapy for adenocarcinoma of the head of the pancreas was evaluated. Forty-three patients were randomized to receive adjuvant therapy with irradiation and 5-fluorouracil (5-FU) or no adjuvant therapy. The median survival time for the 21 patients who received adjuvant therapy was 20 months, and 3 (14%) survived more than 5 years. Among the 22 patients who did not receive adjuvant therapy, the median survival time was 11 months, and only 1 patient (4.5%) survived 5 years.[37] Similar results were noted in a collaborative study from Johns Hopkins Hospital and the Mayo Clinic[38] favoring adjuvant postoperative chemoradiation therapy over surgery alone. A European Study Group for Pancreatic Cancer (ESPAC-1)[39] trial showed benefit for adjuvant chemotherapy, with a deleterious impact of concurrent chemotherapy and irradiation. Major flaws in the ESPAC-1 trial are discussed in Chapter 48, Pancreatic Cancer, in this textbook.

Adjuvant chemotherapy and irradiation are still used in most major treatment centers in the United States for patients with resectable and locally advanced, unresectable pancreatic tumors. Despite improved local control of disease with adjuvant chemoradiation, most patients with pancreatic cancer will succumb to liver or other distant metastases. Pancreatic cancer appears to be a systemic disease at diagnosis in the majority of patients, and death commonly occurs despite clinical presentation with localized disease.

For locally advanced, unresectable pancreatic carcinomas, the use of external beam irradiation (EBRT) plus chemotherapy has been reported to result in a doubling of median survival compared with surgical bypass or biliary stenting. The 2-year survival range increases from 0% to 5% up to 10% to 20% with palliative chemoirradiation. Five-year survivors are rare, and nonprogression of the primary tumor is uncommon. The addition of intraoperative irradiation therapy (IORT) to EBRT with or without 5-FU improves local control, as shown by physicians at the Mayo Clinic and Massachusetts General Hospital.[40-42] This benefit did not translate into an improved patient survival because of liver and peritoneal metastatic progression.

If the full course of adjuvant chemoradiation is delivered preoperatively for patients with locally unresectable or borderline resectable pancreas cancer, this sequence allows restaging 2 to 3 months after treatment initiation.[42,43] The 2-year overall survival appears to be improved with this sequence of treatment followed by IORT. Improvement may result from altered patient selection, however, because the incidence of liver plus peritoneal failure is still excessive.[42,43] Until better systemic therapy is developed, the improved local control of locally unresectable pancreatic adenocarcinoma observed with IORT will not translate into improved survival for patients with locally advanced disease.

THERAPY FOR ADENOCARCINOMA OF THE RECTUM

Despite significant evolution in the multimodality therapy of rectal adenocarcinoma over the past decades, surgical resection continues to be the primary curative modality in these patients. The goal of surgery is to resect all known malignant tissue from the pelvis, thereby optimizing survival and minimizing local failure, while preserving normal bowel, bladder, and sexual function whenever possible. Several patient- and tumor-related factors influence not only the choice of the operation but also the coordination of surgical and nonsurgical treatment modalities. Preoperative clinical tumor staging should assess the level of the tumor from the anal verge, the extent of circumferential involvement, the depth of tumor invasion (T category), and the presence of locoregional adenopathy (N category), and of metastatic disease (M category).[3] Important patient-related factors may include body habitus, preoperative bowel and sphincter function, and the medical conditions that may contraindicate surgical resections due to high operative risk. Additional factors such as performance status, blindness, severe arthritis, or mental incapacity should also be considered before an operation that might result in an ostomy.

Accurate preoperative staging of rectal carcinoma is of central importance for selection of surgical strategy and for determining the need for preoperative therapy. Distant metastatic disease can be detected by CT scanning with 75% to 87% sensitivity. For patients without metastatic disease, preoperative pelvic irradiation with concomitant 5-FU–based chemotherapy remains the current standard of care in the United States for patients clinically staged to have T3-4 or node-positive disease.

Local clinical staging for rectal cancer can be accomplished by either transrectal EUS or by high-resolution pelvic MRI. At present, T and N category are most commonly assessed by

transrectal EUS in the United States. EUS may be preferred to pelvic MRI for tumors of earlier T categories, given the ability for direct inspection of each layer of the rectal wall and perirectal structures. Fine-needle aspiration of suspicious perirectal nodes or extramural lesions can be performed. The reported stage-specific sensitivities and specificities of EUS are T1 (88% and 98%), T2 (81% and 96%), T3 (96% and 91%), and T4 (95% and 98%); corresponding sensitivity and specificity for nodal staging are 73% (95% CI, 71% to 76%) and 76% (95% CI, 74% to 78%), respectively.[44,45] EUS is operator dependent and is of limited value when severe luminal stenosis is present or when EUS is performed in the postirradiation setting because inflammatory changes of the soft tissues reduce the accuracy of EUS.[46] Although nodal staging by CT scanning carries a lower sensitivity (45% to 73%), visible perirectal adenopathy should be suspected as malignant.

High resolution MRI has recently emerged as a preferred method for clinical staging, especially in England and Europe, particularly when the assessment of the circumferential resection margin (CRM) or adjacent organ involvement might be critical. CRM refers to the degree of tumor infiltration of the mesorectal fascia.[47] Preoperative recognition of a threatened CRM where malignant infiltration is present within 1 to 2 mm of the mesorectal fascia allows surgical planning for a resection plane that will result in a negative CRM.[48] In the multicenter Magnetic Resonance Imaging and Rectal Cancer European Equivalence Study (MERCURY),[49] high-resolution MRI accurately predicted the involvement of the mesorectal margin to within 1 mm and extratumoral extension with a specificity of 92%. Using surgical resection specimens as the gold standard, 94% of the patients did have a negative CRM.[50,51] Long-term data after 62 months of follow-up showed high-resolution MRI preoperative assessment of CRM status is excellent for assessing local recurrence risk and disease-free survival.[52] For patients with locally advanced primary cancer or locally recurrent rectal tumor, pelvic MRI or CT are best for assessing tumor involvement or fixation to adjacent pelvic organs, helping the surgeon plan en bloc resection of involved organs for a microscopically negative margin.[48,51] The need for urologic, orthopedic, and plastic surgical assistance can be anticipated preoperatively with pelvic MRI or CT staging.

Surgical resection of curative intent removes the primary tumor, draining lymphatic tissue, and any involved pelvic structures in an en bloc fashion. Proximal, distal, and radial/circumferential resection margins are all key determinant of outcome after standard rectal resection.

The need for adequate distal resection margin is a key contributor to whether the patient is a candidate for sphincter preservation. Sphincter-preserving procedures include low anterior resection (LAR) and proctectomy with coloanal anastomosis, whereas an abdominoperineal resection (APR) results in a permanent colostomy. The choice of the procedure is mainly dictated by whether there is adequate distance remaining between the tumor and the anal verge. The exact location of the tumor is measured in reference to the anal verge or to the top of the anal sphincter complex (i.e., anorectal ring) by digital rectal examination and proctosigmoidoscopy. The adequacy of the distal margin is then assessed to determine the feasibility of sphincter preservation. The operative surgeon should ideally perform this evaluation before the patient receives preoperative adjuvant treatment. Previous studies have shown that tumor deposits in nodal tissue are rarely seen more than 2 to 4 cm distal to the tumor. Thus for tumors in the upper and mid rectum, the ideal adequate distal margin is 5 cm. For tumors located in the very distal rectum where the mesorectal tissue is very thin and has tapered significantly, a 2-cm distal margin is considered adequate because it resulted in no difference in overall survival or local failure rates when compared with a greater distal margin.[53,54] In all rectal operations, proximal ligation of the inferior mesenteric and superior hemorrhoidal vessels and full mobilization of the rectum either to a level well below the gross tumor or to the level of the levator ani muscles are performed. If sphincter preservation is possible, the rectum is transected, usually with a cutting linear stapler. An end-to-end colorectal anastomosis is then created using either a hand-sewn or stapling technique. When the line of rectal transaction is at the level of the anal sphincter, the rectal division may be accomplished transanally. A hand-sewn coloanal anastomosis using interrupted sutures placed transanally is then performed. Although intersphincteric dissection followed by hand-sewn anastomosis has been reported, its role remains highly limited.[55] When sphincter preservation is not possible, an APR is performed. Recently, a "cylindrical" approach to APR has been advocated, with an extended perineal dissection including the origin of the levator ani muscle from the lateral pelvic sidewall. This en bloc resection of the levator muscles results in a more cylindrical specimen and had been associated with less CRM positivity and intraoperative specimen perforation.[56]

When counseling patients for sphincter-preserving procedures, the risk of anastomotic leakage and long-term altered bowel function must be discussed. In an analysis of 5187 patients undergoing LAR in five randomized control trials, the symptomatic anastomotic leakage rate was 9.7%.[57] Leakage was associated with reduced overall survival. A diverting stoma lessened the symptoms of the leakage. Construction of a diverting stoma is prudent with a low rectal anastomosis or in patients who received neoadjuvant chemoradiation or will have adjuvant chemoradiation, or both.[58,59] Sphincter-preservation procedures are also accompanied by altered bowel function, most commonly stool frequency, urgency, and incontinence. Reconstructive techniques, including the colonic J pouch, transverse coloplasty, or side-to-end anastomosis, have been developed. A recent Cochrane review showed that functional outcomes were better with the colonic J pouch than with a straight rectal anastomosis in the short term (18 months). There was insufficient evidence for any long-term benefit.[60] These reconstructive options may not be feasible in patients with a bulky mesentery or narrow pelvis. Therefore, sphincter preservation must be considered in the context of (a) adequate oncologic margin, (b) risk of anastomotic leakage, and (c) altered bowel function.

For tumors confined within the mesorectum, total mesorectal excision (TME) is the optimal technique to minimize the risk of an involved CRM.[61] Popularized by Heald and associates,[62] TME involves sharp dissection of the avascular plane between the visceral covering of the mesorectum and the parietal fascia of the pelvis. The surgical planes between the integral visceral mesentery of the hindgut and the surrounding tissues provide a unique opportunity for defining a surgically achievable "tumor package," and, serendipitously, the field of spread of rectal cancer is commonly limited within this package, or mesorectum.[63,64] TME encompasses virtually every tumor satellite except those in patients in whom the tumor is widely disseminated. The excised specimen includes the entire posterior, distal, and lateral mesorectum to the plane of the inferior hypogastric nerve plexus, which is carefully preserved whenever possible. Anteriorly, the specimen includes the intact Denonvilliers fascia and the peritoneal reflection. The characteristic smooth, bilobed, encapsulated appearance posteriorly and distally reflects the contours of the pelvic floor and the midline anococcygeal raphe. In contrast to the local recurrence rates of 20% to 45% reported with traditional resections, rates between 4% and 7% and 5-year disease-free survival approaching 80% have been reported with TME alone.[63,64]

Several less-invasive surgical approaches for patients with rectal cancer have gained attention in recent years. Transanal local excision, either conventionally or via transanal endoscopic microsurgery, may be an option in select patients with well-differentiated T1 tumors located within 8 cm of the anal verge, less than 3 cm in diameter, occupying less than 30% of the luminal circumference, and without suspicious perirectal adenopathy.[65] Excised specimens should be full-thickness, nonpiecemeal specimens with an adequate margin of resection for pathologic examination. Patients treated in this fashion enjoy minimal morbidity but face increased risks for local failure and, perhaps, decreased overall survival.[66-68] Although laparoscopic-assisted operations for rectal cancer are technically feasible, long-term data demonstrating oncologic equivalence to open procedures are just emerging. Particular concerns of the laparoscopic approach include inadvertent spillage of luminal contents, handling of the tumor specimen, implantation of tumor cells in the pelvis, and the potential for port-site relapse. In the short term, patients have reduced analgesia requirements, ambulate more readily, and appear to have less paralytic ileus.[69] The United Kingdom Medical Research Council trial of conventional versus laparoscopic-assisted surgery in colorectal cancer (UK MRC CLASSIC trial) included a subgroup of 381 patients with rectal cancer who were randomized to open versus laparoscopic procedures.[70] After accounting for a 34% conversion rate, 189 and 87 patients were treated in each arm, respectively. No statistically significant difference was seen in the rates of positive proximal, distal, or circumferential margins; 3-year local recurrence; or overall survival. However, in the subgroup of patients who underwent laparoscopic versus open LAR, the CRM was positive in 12% versus 6% of the open LAR patients (p = 0.19).[70] Finally, robotic surgery for rectal cancer has emerged, and offers the advantages of three-dimensional vision and fine articulation for pelvic dissection.[71] In the United States, the ACOSOG Z6051 trial compared open to minimally invasive surgery for resection of locally advanced rectal cancer, and allowed several minimally invasive techniques in the experimental arm including hand-, laparoscopic-, and robotic-assisted techniques. The initial results of this trial are expected to become available in 2014. Currently available evidence appears to suggest that the number of resected lymph nodes and surgical margins were similar and laparoscopic and open TME had similar effects on five-year disease-free survival.[69]

Despite surgical resection of rectal cancer with curative intent, approximately 20% of the patients develop disease relapse, usually during the first 3 postoperative years. Local pelvic recurrences can be highly morbid, causing pain, bowel obstruction, hemorrhage, and malignant fistulization. The risk of relapse correlates with the T and N category of the tumor, as well as completeness of surgical excision[72] (Table 8-1). Local failure is also more common with a positive CRM.[47,73] Consequently, adjuvant therapy has evolved with the goals of preventing local tumor recurrence, eliminating distant metastases, and increasing both disease-free and overall survival.[74] Both preoperative and postoperative regimens of irradiation or chemoradiation have been developed. Although early trials mainly involved postoperative irradiation, the potential for tumor down-staging, less tissue hypoxia, and less exposure to small bowel in the radiation field has shifted the focus toward preoperative treatment. Two meta-analyzes showed that when compared with surgery alone, the addition of preoperative irradiation to surgery decreased the local failure rate (odds ratio [OR] 0.49; 95% CI 0.38 to 0.62; p<0.001)[75] and that the yearly local failure rate was 46% lower with preoperative irradiation (p<0.001) and 37% lower with postoperative irradiation (p=0.002).[76] In the era of TME surgery, the German Rectal Cancer Study Group trial demonstrated the added benefit of preoperative combination chemoradiation: the local recurrence rate was 6% with preoperative treatments versus 13% with postoperative treatments (p=0.006), although no difference was seen in overall survival.[77] Although a second trial of similar design, NSABP R-03, did not meet its accrual goal, a superior 5-year disease-free survival was observed in the preoperative versus postoperative arm (65% vs. 53%; p=0.011).[78] A 5-year local recurrence rate of 10.7% was reported for both treatment arms. Although preoperative combination chemoradiation has been widely adopted in the United States for nearly all T3-4 and patients with node-positive rectal cancer, its use is more selective in Europe. A recent trial from the Medical Research Council (MRC CR07) compared short-course preoperative irradiation with TME surgery and selective postoperative chemoradiation and demonstrated that preoperative treatment still led to a 6% lower 3-year local recurrence rate, although no difference was seen in overall survival.[79] Finally, based on pooled data from five phase III North American rectal adjuvant trials, selected patients with intermediate-risk rectal cancers (T1-2N1 and T3N0) might not need radiation therapy as a component of adjuvant treatment.[72] An ongoing trial ALLIANCE N1048 is investigating the feasibility of omitting pelvic radiation in select intermediate risk upper rectal cancers (treatment arms of preoperative chemotherapy versus preoperative chemoradiation).[80] Ongoing research continues to focus on finding the optimal treatment regimen that provides oncologic benefit but spares potential toxicities.

MANAGEMENT OF RETROPERITONEAL SOFT-TISSUE SARCOMA

Soft-tissue sarcomas constitute less than 1% of all malignant tumors in the United States. Approximately 15% of sarcomas arise in the retroperitoneum.[81] Retroperitoneal sarcomas provide a challenge for the surgical oncologist. Most patients with retroperitoneal sarcoma eventually die of their disease, despite never developing disease outside the abdomen. The locally invasive growth pattern, the lack of anatomic boundaries in the retroperitoneum, and the large size of most sarcomas at presentation make complete R0 resection difficult. The rate of complete gross tumor resection (R0 and R1), which was

TABLE 8-1 Rectal Cancer: Overall Survival and Risk of Relapse by TN Category

Risk for Relapse	TN Category	5-Year Local Recurrence (%)	5-Year Distant Metastasis (%)	5-Year Overall Survival (%)
Low	T1-2N0	≤5	10	90
Intermediate	T3N0, T1-2N1	7-9	15-20	65-73
Moderately high	T4N0, T3N1,T1-2N2	8-12	28-37	48-58
High	T4N1, T3-4N2	14-23	39-53	30-36

approximately 50% in major centers,[81] has increased to 67% to 75%.[82,83] The local recurrence rate at 5 years after complete surgical resection ranges from 40% to 50%.[82-85] Among patients who are disease free at 5 years, 40% will experience a relapse by 10 years after their operation.[86] Uncontrollable local recurrence is the most common cause of death from retroperitoneal sarcoma. Retrospective analysis of more than 1000 patients with retroperitoneal sarcoma found primary tumor size; tumor fixation to nerve, vessels, or bone; regional lymph node involvement (rare); presence of metastatic disease; and tumor grade predictive of survival.[87]

The most common presentation for retroperitoneal sarcoma is an abdominal mass or pain, or both. An abdominal CT scan establishes the extent of tumor, the relationship of the sarcoma to normal organs, the presence or absence of tumor necrosis, and the presence of liver metastases. CT scanning of the chest is performed to rule out pulmonary metastases. Diagnosis of a retroperitoneal sarcoma can be made by a needle or rarely incisional biopsy if preoperative treatment is planned. A limited biopsy to exclude metastatic testicular cancer or lymphoma is indicated before primary surgical resection when the diagnosis is in doubt.

The surgical treatment of retroperitoneal sarcomas consists of en bloc resection of the tumor plus adjacent organs invaded by or adherent to the sarcoma. Recent reports recommend removal of any adjacent organs regardless of apparent tumor involvement.[88,89] This is feasible for some sarcomas but not for others.[90] This policy has not been shown to give better results in a controlled study.[87] Most retroperitoneal sarcomas involve left- or right-sided retroperitoneal structures, with few arising in the midline. Because of their large dimensions, en bloc resection often requires ipsilateral nephrectomy and colectomy, partial small bowel resection, distal pancreatectomy, and splenectomy. Less frequently, a partial gastrectomy, pancreaticoduodenectomy, major hepatectomy, or vascular resection may be indicated. Any adherence of the sarcoma to an adjacent structure must be assumed to be malignant in nature. These structures should be excised en bloc whenever feasible. If extensive venous collaterals are present from vena caval occlusion, the inferior vena cava may be resected without reconstruction; a prosthetic graft reconstruction is indicated in other patients. An aortic resection and prosthetic reconstruction should be considered for a sarcoma encasing the aorta when the sarcoma can be completely excised. When a retroperitoneal sarcoma has an extensive volume of necrotic tissue, care must be used during mobilization to avoid tumor rupture.

Resection of a large retroperitoneal sarcoma en bloc is presented in Figures 8-6 and 8-7. This patient reported pain and had an abdominal mass. A preoperative CT scan image appears in Figure 8-6. The sarcoma filled the left upper quadrant, displacing the spleen and distal pancreas anteriorly. On abdominal exploration through a midline incision, the tumor was found to be limited to the left retroperitoneum. The stomach was not involved by tumor. After opening the lesser sac, the stomach was reflected cephalad. The splenic flexure of the colon was also uninvolved. It was retracted caudad, providing excellent exposure of the distal pancreas, spleen, left kidney, and anterior surface of the sarcoma (Figure 8-7, *A*). The neck of the pancreas was divided, allowing ligation of the splenic artery and vein (Figure 8-7, *B*). To minimize intraoperative bleeding, the vascular supply along the medial aspect of the sarcoma was ligated before the sarcoma was mobilized and en bloc resection was performed. The left renal artery and vein were then exposed and ligated (Figure 8-7, *C*). The resected retroperitoneal sarcoma with the distal pancreas, spleen, and left kidney are shown in Figure 8-7, *D*.

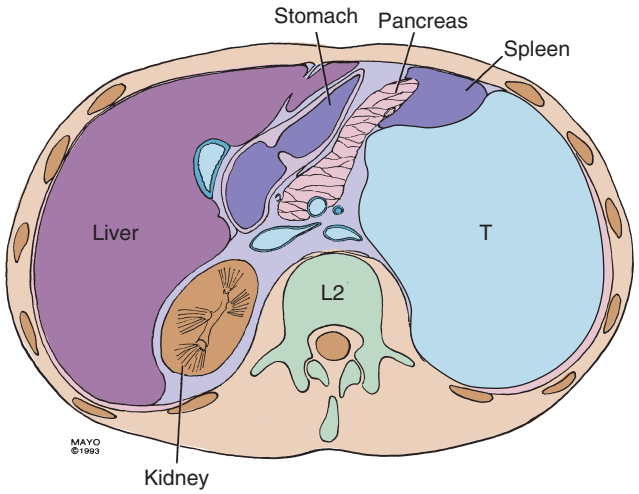


Figure 8-6 Appearance of left upper quadrant mass on CT scan. *T*, Tumor.
Courtesy the Mayo Foundation.

Because local tumor recurrence is the most common pattern of treatment failure, radiation therapy should theoretically improve results. Some retrospective series have suggested an improvement in the local control and survival of retroperitoneal sarcoma patients with adjuvant irradiation.[91,92] The large-field radiotherapy needed to treat the resection bed following retroperitoneal sarcoma excision can cause significant complications. IORT plus EBRT has been considered a better alternative to full-dose EBRT because of less toxicity to normal tissues. A prospective, randomized clinical trial performed at the National Cancer Institute compared IORT plus postoperative low-dose EBRT with postoperative high-dose EBRT alone. This study showed no statistically significant difference in survival rates between patient groups, but the pattern of disease failure differed between the two groups. Patients receiving IORT plus EBRT had significantly better local disease control within irradiation fields and a significantly lower prevalence of small bowel toxicity.[93] A trial sponsored by the American College of Surgeons Oncology Group to study whether adjuvant EBRT improved local control and survival rates compared with resection alone for patients with retroperitoneal sarcoma closed prematurely because of poor patient accrual. Currently, there is no proven survival benefit for the use of either adjuvant radiation therapy or chemotherapy for retroperitoneal sarcomas.

SUMMARY

Surgery is still the single-best treatment for most solid tumors in adults. The surgical oncologist must understand the biology of the particular malignancy. Accurate preoperative tumor staging is crucial in treatment decisions. The goal of surgical intervention may be potential cure or palliation. Adjuvant radiotherapy and chemotherapy should be used whenever evidence-based data show that they confer additional survival time or palliative benefit. The physiologic status of the patient must be established and maximized preoperatively to minimize surgical morbidity or mortality. The principles of surgical oncology, including complete en bloc tumor resection, should be followed whenever possible. Adequate postoperative healing must occur before adjuvant therapy starts. The survival of patients with most surgically treated cancers will likely improve as the result of improved nonsurgical treatments rather than more radical surgical procedures.

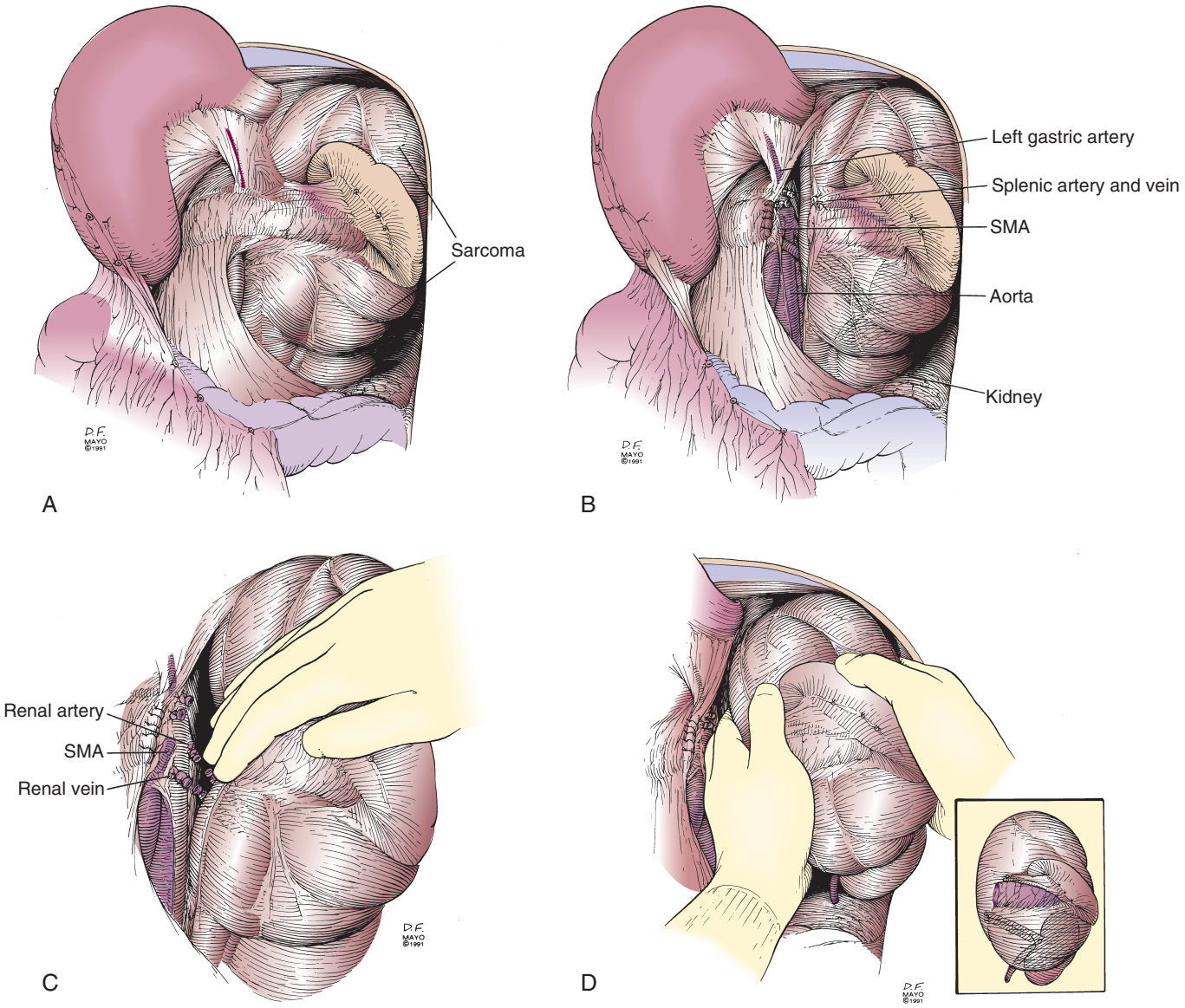


Figure 8-7 **A,** Mobilization of the transverse colon and stomach with exposure of retroperitoneal structures. **B,** Division of the neck of the pancreas and ligation of the splenic artery and vein. **C,** Ligation of the left renal artery and vein. **D,** En bloc resection. *Inset,* Specimen consisting of the sarcoma, spleen, distal pancreas, and left kidney. *SMA,* Superior mesenteric artery.
Courtesy the Mayo Foundation.

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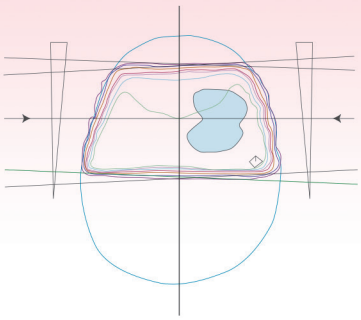
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CHAPTER

9 Principles of Chemotherapy



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A BRIEF HISTORY

In the history of medicine, cancer was initially regarded as a localized disease, and engaged the primary attention of surgeons and radiation oncologists. Metastatic disease was regarded as untreatable. With the arrival of cancer chemotherapy in the form of alkylating agents, in the post–World War II era, it became possible for the first time to entertain the use of drugs to improve local control of cancer, to prevent distant recurrence after surgery, and even to cure systemic disease, as in childhood acute leukemia and choriocarcinoma. With the introduction of adjuvant therapy of breast cancer in the late 1960s the concept of even apparently localized cancer as a potentially systemic disease, which demands systemic therapy, was integrated into the thinking of cancer management in its earliest stages. However, progress in drug discovery was slow. At the time of the publication of the first trials of melphalan for adjuvant therapy of breast cancer in 1971, only a handful of agents were available for treatment of cancer and were primarily drugs developed for the treatment of leukemia. The addition of anthracylines, taxanes, and platinum analogs, and most recently targeted agents, has since that time vastly expanded the effectiveness and the range of uses of chemotherapy.

The history of cancer drug development begins with the initial trials of *alkylating agents* at Yale University, as first reported in 1946.[1] The Yale experiments proved that a systemically administered agent could cause regression of murine leukemia and ultimately a human tumor—in this case a mediastinal mass in a patient with Hodgkin disease. The conceptual basis for clinical studies of nitrogen mustard was the observation that mustard gases used in military campaigns produced lymph node depletion and bone marrow aplasia. Although it was known at the time that these compounds were highly reactive with proteins, nucleic acids, and other electron-rich molecules, the specific intracellular targets on nucleic acids were not identified until more than a decade later, and we are only now beginning to understand the reasons for the somewhat selective action of alkylating agents on tumor cells.

This early experience with alkylating agents led a number of bold investigators to undertake an alternative approach and search for compounds (antimetabolites) that would act as fraudulent counterparts of natural metabolites known to stimulate cancer cell growth. Among these metabolic targets, folic acid and nucleic acid bases proved most vulnerable (Figure 9-1). In the late 1940s, scientists from American Cyanamid synthesized analogs of folic acid, a vitamin known to stimulate the proliferation of cancer cells in culture and in humans. Sidney Farber, a pathologist, found striking but short-lived responses to the first antifolate, aminopterin, and its closely related analog, methotrexate, in children with acute lymphoblastic leukemia (ALL). Prospects for the treatment of leukemia with drugs escalated in the following decade, as new antimetabolites were discovered. Hitchings and Elion at Burroughs Wellcome successfully developed purine analogs, 6-thioguanine and 6-mercaptopurine. Soon afterward, corticosteroids, first used as antiinflammatory agents, were found to kill malignant lymphocytes in children with ALL and in adults and children with lymphoma. In response to the success of combination chemotherapy in childhood ALL, large-scale screening systems for anticancer drugs were initiated at the National Cancer Institute in 1955. These initial attempts at drug discovery tested random chemical libraries and natural product extracts against transplantable murine leukemias and later murine solid tumors, leading to the isolation of new cytotoxic compounds. The newly discovered compounds fell into four primary classes: agents that formed adducts with DNA, agents that blocked mitosis, agents that blocked the function of topoisomerases (DNA unwinding drugs), and antimetabolites.

Combinations of these drugs successfully overcome resistance to single agents and were able to cure childhood ALL and lymphomas. Solid tumor chemotherapy advanced more slowly. Through the discovery of 5-fluorouracil (5-FU), an analog of thymine and a highly potent inhibitor of thymidylate synthase, breast and colon cancer proved modestly responsive. Platinum analogs with potent DNA damaging activity were discovered to have antitumor activity in the early 1970s and, in combination, led to the cure of testicular cancer and to effective combination therapy of ovarian and colon cancer. In addition 5-FU and the platinum drugs were found to be radiosensitizers and improved local control in many tumors of the aero-digestive tracts.

Equally rewarding efforts in the field of natural product chemistry yielded valuable new anticancer drugs with unique mechanisms of action. Scientists at Eli Lilly discovered the antimitotic and antitumor properties of the vinca alkaloids. Shortly thereafter, analysis of fermentation broths led to the discovery of DNA damaging drugs such as mitomycin C, a novel alkylating agent; bleomycin, a DNA-cleaving peptide; and inhibitors of topoisomerase (anthracyclines, and camptothecins); and from natural product screening, even more potent antimitotic agents (paclitaxel and eribulin). Various drug combinations have become standard therapies for most metastatic tumors, and when combined with radiation treatment and surgery as adjuvant therapy, improved the 5-year survival of patients with cancer from 30% in 1950 to more than 60% in the year 2000.

The beginning of the 21st century has witnessed a major breakthrough for cancer treatment with the arrival of targeted therapies (Table 9-1).[2] The development of highly efficient technology for gene sequencing led to the identification of molecular alterations that cause malignancy and shifted the field of drug discovery from cytotoxics to therapies that selectively target oncogenic driver alterations. These driver mutations produce gene products that transform otherwise normal cells and create a tumor dependent for its survival on the specific activated pathway, a conditioned termed *oncogene addiction*. Inhibitors that shut down the target and its pathway lead to death of the cancer cell.

The goal of targeted therapy is not to induce DNA damage but is rather to inhibit specific signaling pathways that control proliferation, cell survival, invasion, metastases, or angiogenesis. A growing number of these agents are available and run the gamut from highly potent small molecules that inhibit

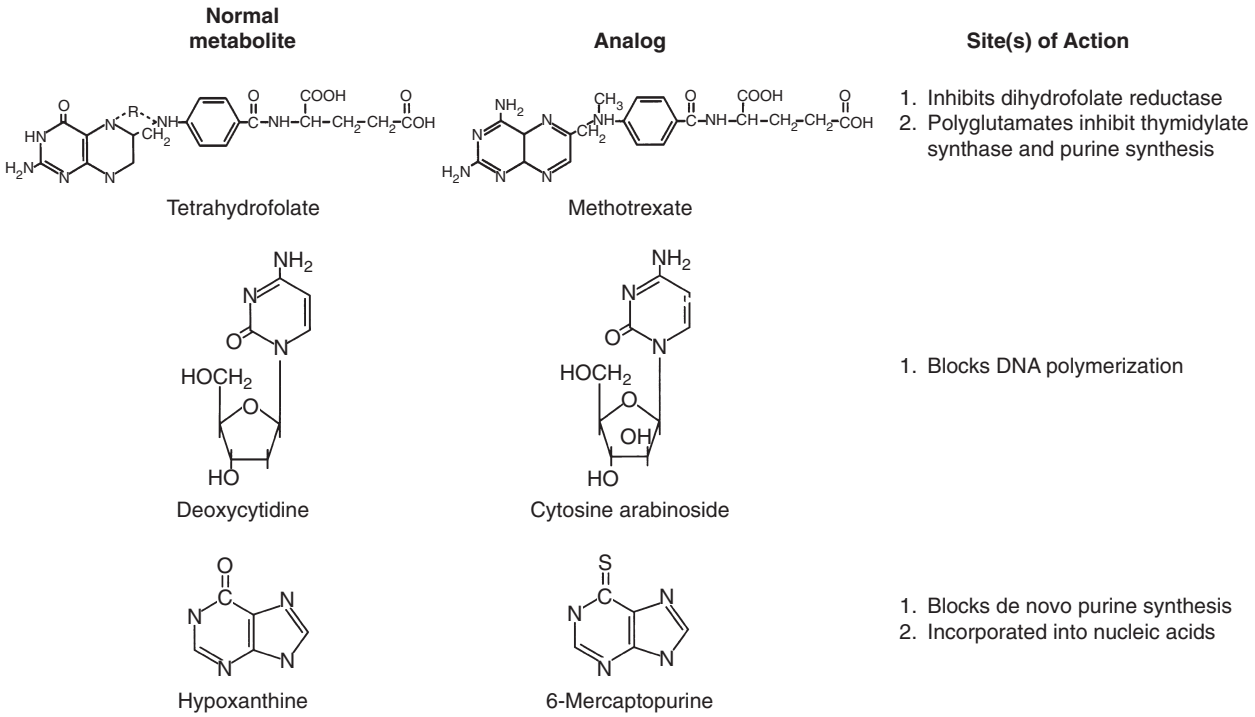


Figure 9-1 Examples of chemotherapy drugs that are analogs of natural metabolites.

TABLE 9-1 FDA-Approved Targeted Cancer Therapies

Drug	Class	Target	Application
Imatinib (Gleevec)	Benzamide	BCR-ABL, C-KIT	CML, GIST
Dasatinib (Sprycel)	Carboxamide	BCR-ABL, SRC, C-KIT, PDGFRβ	CML, Ph + ALL
Nilotinib (Tasigna)	Benzamide	BCR-ABL, PDGFR, C-KIT	CML
Ponatinib (Iclusig)	Benzamide	BCR-ABL (including T151I), PDGFR, C-KIT, SRC, RET	CML, Ph+ ALL
Bosutinib (Bosulf)	Quinolinecarbonitrile	BCR-ABL, SRC, LYN, HCK	CML
Omacetaxine mepesuccinate (Synribo)	Cephalotaxine	Unclear	CML
Gefitinib (Iressa)	Quinazolinamine	EGFR-TKI	NSCLC
Erlotinib (Tarceva)	Quinazolinamine	EGFR-TKI	Colorectal, NSCLC
Afatinib (Gilotrif)	Butenamide	EGFR, HER2, HER4	NSCLC
Crizotinib (Xalkori)	Pyridin-2-amine	ALK, ROS1, MET	NSCLC
Dabrafenib (Tafinlar)	Sulfonamide	BRAF, CRAF	Melanoma
Trametinib (Mekinist)	Acetamide	MEK1 and MEK2	Melanoma
Vemurafenib (Zelboraf)	Carboxamide	BRAF	Melanoma
Ipilimumab (Yervoy)	Recombinant human monoclonal antibody	CTLA4	Melanoma
Cetuximab (Erbitux)	Chimeric monoclonal antibody	EGFR extracellular domain	Colorectal, ENT
Panitumumab (Vectibix)	Human monoclonal antibody	EGFR extracellular domain	Colorectal
Regorafenib (Stivagra)	Carboxamide	RET, VEGF receptor 1-3, PDGFR, FGFR, and others	Colorectal
Bevacizumab (Avastin)	Humanized monoclonal antibody	VEGF	Colorectal, NSCLC, breast, glioblastoma
Ziv-Afilbercept (Zaltrap)	Fusion protein (VEGF-binding portion of VEGF receptors 1 and 2 fused to human IgG1)	VEGF1 and 2	Colorectal
Trastuzumab (Herceptin)	Humanized monoclonal antibody	HER2 extracellular domain	Breast
Lapatinib (Tykerb)	Quinazolamine	HER2 and EGFR-TKI	Breast
Pertuzumab (Perjeta)	Humanized monoclonal antibody	HER2	Breast
Rituximab (Rituxan)	Chimeric monoclonal antibody	CD20	Lymphoma
Tositumomab (Bexxar)	131I murine monoclonal antibody	CD20	Lymphoma

TABLE 9-1 FDA-Approved Targeted Cancer Therapies—cont'd

Drug	Class	Target	Application
Ibritumomab (Zevalin)	111In murine monoclonal antibody	CD20	Lymphoma
Brentuximab (Adcetris)	Antibody-drug conjugate (IgG1, MMAE and a linker)	CD30	Lymphoma
Ibrutinib (Imbruvica)		BTK	Lymphoma
Vorinostat (Zolinza)	Phenyloctanediamide	HDAC	Lymphoma
Romidepsin (Istodax)	Bicyclic depsipeptide	HDAC	Lymphoma
Dentileukin Difitox (Ontak)	Recombinant fusion of diphtheria toxin and IL-2	IL2-receptor(s)	Lymphoma
Bortezomib (Velcade)	Modified boronic acid	26S proteasome	Myeloma
Carfilzomib (Kyprolis)	Carboxamide	26S proteasome	Myeloma
Obinutuzumab (Gazyva)	Humanized monoclonal antibody	CD20	CLL
Ofatumumab (Arzerra)	Human monoclonal antibody	CD20	CLL
Alemtuzumab (Campath)	Humanized monoclonal antibody	CD52	B-CLL
Gemtuzumab (Mylotarg)	Calicheamicin linked to human monoclonal antibody	CD33	AML (CD33+)
Sunitinib (Sutent)	Butanedioic acid	VEGFR, C-KIT, PDGFR, RET, FLT3	Renal, GIST
Sorafenib (Nexavar)	Carboxamide	BRAF, FLT3, C-KIT, VEGFR, RET, PDGFRβ	Hepatocellular, renal
Everolimus (Afinitor)	Rapamycin derivative	mTOR	Renal
Temsirolimus (Torisel)	Macrolide	mTOR	Renal
Axitinb (Inlyta)	Benzamide	VEGF receptor 1-3	Renal
Pazopanib (Votrient)	Methylbenzenesulfonamide	VEGF receptor 1-3, PDGFR, FGFR1, C-KIT	Renal, sarcoma
Vandetanib (Vandetanib)	Quinazolin-4-amine	EGFR and VEGF	Thyroid
Vismodegib (Erivedge)	Benzamide	Smoothened (Hedgehog pathway)	Basal cell
Capozantinib (Cometriq)	Carboxamide	RET, MET, PDGFR, FGFR	Thyroid

AML, *Acute myelocytic leukemia;* B-CLL, *B-cell chronic lymphocytic leukemia;* CML, *chronic myelogenous leukemia;* GIST, *gastrointestinal stromal tumor;* NSCLC, *non–small cell lung cancer.*

specific targets such as receptor tyrosine kinases (RTKs), to monoclonal antibodies that block the same receptors, initiate immune responses against tumor antigens, carry cytotoxic payloads, or block tumor blood vessel formation. Monoclonal antibodies such as trastuzumab, cetuximab, and bevacizumab also enhance the effectiveness of chemotherapy, and cetuximab, an inhibitor of the epidermal growth factor receptor (EGFR), synergizes with irradiation (see Chapters 4 and 5). The role of targeted drugs in the overall management of cancers is continuously evolving. Targeted drugs used in sequence with or in conjunction with irradiation and chemotherapy are under active investigation in most solid tumors, lymphomas, and leukemia.

THE BASIS OF CHEMOTHERAPY: CANCER CELL BIOLOGY

Every phase of chemotherapeutic research, from discovery to clinical application, is based on our improved understanding of cancer cell biology (see Chapter 2). Cancer cells have unique properties that distinguish them from their normal counterparts and that form the basis for treatment. Among these properties are continuous and excessive proliferation, defective repair of DNA leading to high mutation rates and great population diversity, reduced rates of apoptosis (i.e., programmed cell death), altered metabolism to enhance lipids and nucleic acid synthesis, induction of nutrient vessels, ability to escape immune surveillance, and ability to invade neighboring tissues and to metastasize.[2] Many of these properties have been the starting point for successful drug discovery efforts.

Most cancer cells display defects in DNA repair that allow the rapid generation of a diversity of subclones, thus increasing their adaptation to adverse environments (low pH, poor nutrients), and increasing the probability of drug resistance. With a few notable exceptions, the successful cytotoxic drugs have attacked only the first of these properties, proliferation. The new generation of targeted agents is expanding the horizon for cancer treatment by addressing the full circle of biological changes in human tumors.

MODELS FOR CHEMOTHERAPY

In parallel with the discoveries of new drugs in the period from 1946 to 1970, Skipper and colleagues[3] at the Southern Research Institute and at the National Cancer Institute developed and characterized transplantable murine leukemias, notably L1210 and P388, as well as murine solid tumors such as sarcoma 180 and B16 melanoma. Their model systems allowed reproducible, quantitative experiments with chemotherapy and radiation therapy in mice. They established a rational basis for understanding the kinetics of cell kill, evaluating efficacy of drug combinations, and studying mechanisms of drug resistance. From their experiments emerged the theoretical basis for combination chemotherapy:

1. *Fractional cell kill.* Each dose of chemotherapy kills a constant fraction of the tumor cell population. Pharmacokinetic parameters correlate with cell killing. For example cell kill by alkylating agents increases linearly with dose and

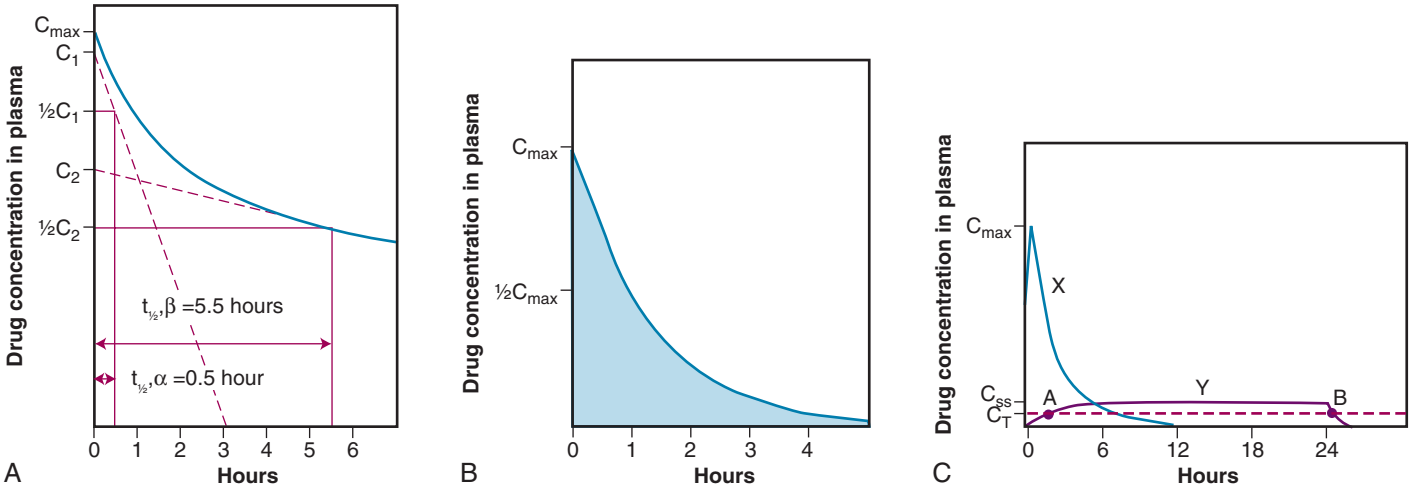


Figure 9-2 Drug elimination from plasma. **A,** The *solid blue curve* illustrates a semilogarithmic plot of drug concentration versus time after a rapid intravenous injection. The *dashed red line* intercepting the *y*-axis at C_2 represents an extrapolation of the log-linear terminal phase. The *dashed red line* that intersects the *y*-axis at C_1 is obtained by subtracting the extrapolated values of the log-linear terminal phase from the observed drug concentrations. Maximum drug concentration in plasma (C_{max}) = $C_1 + C_2$. The initial (α) phase half-life ($t_{1/2,\alpha}$) is the time for C_1 to decay to $\frac{1}{2}C_1$. The terminal (β) phase half-life ($t_{1/2,\beta}$) is the time for C_2 to decay to $\frac{1}{2}C_2$. This biphasic behavior results from distribution of the drug among rapidly and slowly perfused regions of the body, as well as its elimination. **B,** Drug concentration in plasma versus time is plotted on linear axes. The *blue shaded area* is the area under the curve (AUC); it represents the integral of drug concentration over time. The AUC is a measure of total systemic exposure to the drug. **C,** Linear plots of drug concentration versus time are illustrated for a rapid intravenous injection *(X)* and a 24-hour continuous infusion *(Y)* of the same total dose of drug (the AUCs are equivalent). Notice that the duration of drug concentrations above the threshold for cytotoxicity (C_T) is much longer with the continuous infusion (represented as B-A) than with the bolus administration. Conversely, the maximum plasma concentration achieved by bolus administration (C_{max}) is much larger than that of the continuous infusion (C_{SS}).

peak drug concentration, whereas for most other drugs, kill depends on the area under the curve describing drug concentration over time (or $C \times T$) (Figure 9-2). For other drugs, such as paclitaxel and for most of the targeted therapies, the *time of exposure above a threshold concentration* determines the cytotoxicity for tumor and for normal target tissues. For drugs that depend on continuous inhibition of the target, such as the receptor tyrosine kinase inhibitors, it is important to maintain a constant receptor-inhibiting drug concentration in plasma.

2. *Importance of dose intensity (dose per unit time).* During the time period between cycles of treatment, tumor cells resume proliferation. Short rest periods between treatment cycles, and higher doses of drug produce the best results.
3. *Drug resistance.* Exposure of tumors to single-agent chemotherapy rapidly results in outgrowth of drug-resistant cells. Biochemical studies of these drug-resistant cells disclosed a number of changes, including decreased drug uptake (methotrexate), increased drug export (anthracyclines and taxanes), enhanced DNA repair (alkylating agents and platinum analogs), mutations or amplification in the drug target (methotrexate and 5-FU), or loss of intracellular pathways required for drug activation (many nucleoside and base analogs such as 5-FU and fludarabine require phosphorylation). Combinations of drugs with different mechanisms of action and different mechanisms of resistance were able to cure lymphomas and leukemia that readily become resistant to single agents.
4. *Cell cycle dependency of cell kill.* Most anticancer drugs, particularly the antimetabolites, have their greatest effect on actively proliferating cells. Drugs that act on DNA synthesis damage cells during periods of DNA synthesis (S phase), whereas mitotic inhibitors produce cell kill through exposure of cells during mitosis (M phase) (Figure 9-3). The rate of cell proliferation slows and the number of nonproliferating cells increases with expansion of the tumor mass. Other factors such as poor perfusion and increased oncotic pressure discourage nutrient and drug entry into large, poorly vascularized tumor masses. Chemotherapy is most effective when the tumor burden is lowest and cell proliferation is most active, as in the adjuvant setting.

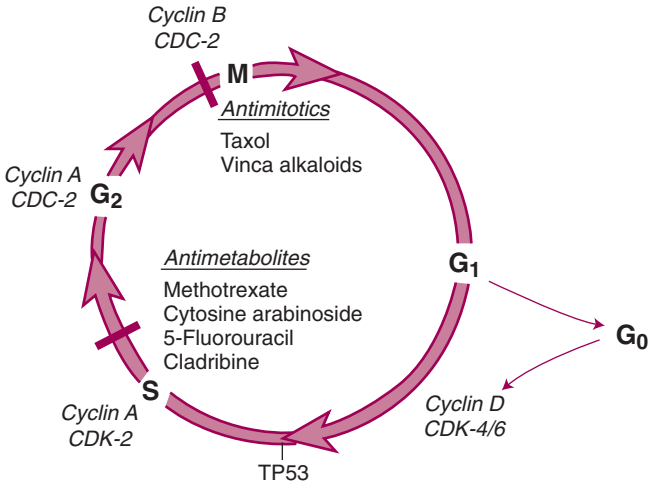


Figure 9-3 The cell cycle, its controls and checkpoints, and the site of action of cell cycle phase-specific drugs. The cell cycle phases are G_0 (nondividing cells), G_1 (resting phase), S (DNA synthesis), G_2 (gap between S and M), and M (mitosis). Transitions between phases are controlled by the appearance of specific cyclin proteins that complex with and activate cyclin-dependent kinases. The G_1/S transition is also controlled at a checkpoint by proteins such as TP53, which monitor DNA integrity. Other proteins monitor the G_2/M checkpoint.

These principles expounded in mouse models profoundly influenced all aspects of clinical chemotherapy, including regimen design, the use of drugs in combination, adjuvant

chemotherapy, and high-dose chemotherapy. Relying on these principles, the cure of ALL was accomplished through development of effective combination therapy. However, other measures were required to prevent relapse: the institution of intrathecal methotrexate and neuro-axis irradiation to eliminate central nervous system (CNS) leukemia, refinement of drug dosage and schedule to maximize drug efficacy, the implementation of maintenance methotrexate and 6 mercaptopurine,[4] and supportive care with platelets and antibiotics. Each of these insights, further refined by the use of new antinausea medications and bone marrow colony-stimulating factors, has become a basic component of modern chemotherapy.

SOLID TUMOR CHEMOTHERAPY

The principles enumerated have been applied with greatest success to the treatment of aggressive and rapidly proliferating tumors such as leukemias and lymphomas. The development of drug therapy for the more common solid tumors has taken a slower and more tortuous course. Drugs identified in mouse leukemia screening systems have been less effective against most solid tumors, notable exceptions being choriocarcinoma and testicular cancer, which can be cured with repeated cycles of intensive chemotherapy. However, new chemotherapies have improved survival of metastatic cancer: 5-FU, beginning in the 1950s, doxorubicin and cisplatin in the early 1970s, etoposide and paclitaxel in the late 1980s, the antimetabolites pemetrexed and gemcitabine in 1990s, and since 2000, a new antimitotic, eribulin[5]; a unique alkylator, bendamustine[6]; and an albumin encased taxane, abraxane.[7]

An important breakthrough in solid tumor chemotherapy was the proposal to employ drugs in the adjuvant setting after removal of the primary tumor in patients at high risk for relapse. Drugs that produced only partial responses in advanced disease could prevent disease recurrence in a significant fraction of women with Stage II (node positive) localized breast cancer. The conceptual basis for this strategy derived from experimental chemotherapy models that revealed that tumors are most susceptible to chemotherapy when the tumor burden is small and cells are actively proliferating. Cytotoxic drugs now have a firmly established role in the adjuvant treatment of lung, breast, and colorectal cancers either before or after surgery (see Chapter 4).

Newer concepts aimed at improving local control of otherwise inoperable tumors have led to so-called neoadjuvant, or induction, therapy.[8] In this strategy, drugs are used alone or in combination with radiation therapy, before surgery, in the initial treatment of locally advanced tumors of the breast, head and neck, bladder, rectum, and lung (see Chapter 4, Tables 4-2 to 4-7). This preoperative therapy reduces the size of otherwise unresectable tumors to a point where total surgical removal is feasible, less morbid and organ preserving, or, in some cases, such as anal cancer, even unnecessary. A new paradigm for drug approval has been established with the Food and Drug Administration's (FDA's) accelerated approval of the monoclonal antibody, pertuzumab, for neoadjuvant therapy of HER2+ breast cancer, based on improvements in the pathological complete remission rate at the time of surgery.[9]

Advances in bone marrow stem cell harvesting from peripheral blood, their storage, and reinfusion after high-dose chemotherapy has allowed escalating drug dosage and increasing dose intensity. In this setting, high-dose chemotherapy followed by marrow stem cell infusion is remarkably safe and reliably cures a significant minority of patients with relapsed lymphomas and relapsed or high-risk leukemia and a fraction of patients with relapsed testicular cancer. As they become safer to use, high-dose regimens may be employed in earlier stages of disease to enhance the cure rate of otherwise incurable cancers in patients, although the value of this approach for most solid tumors is unproven

DRUG INTERACTIONS WITH IRRADIATION

Because most patients with cancer now require multimodality therapy, even for early-stage tumors, it is important to understand the potential benefits and risks of drug interaction with irradiation.[10] The biological basis for these interactions and the rationale for current regimens are presented in Chapters 4 and 5. To be effective, irradiation requires the presence of oxygen to produce toxic oxygen radicals and is countered by the cell's attempts to scavenge the radicals and repair DNA damage. Radiosensitizers can act by increasing oxygenation, creating new DNA breaks, depleting scavengers of oxygen free radicals, or blocking repair of DNA breaks. Each of these properties has been the subject of intensive clinical investigation. The most favorable of these interactions identified thus far stem from the radiosensitizing properties of three drugs, often used in combination with irradiation: 5-FU, a drug that inhibits thymidylate synthase and thereby blocks DNA synthesis; platinum analogs, which form adducts with DNA, create DNA breaks, and deplete free radical scavengers such as sulfhydrils and glutathione; and mitomycin C, which forms free radicals and DNA adducts in hypoxic environments. Other drugs, particularly gemcitabine, doxorubicin, and bleomycin, are extremely potent radiation sensitizers, and generally should not be used simultaneously with irradiation for fear of serious toxicity to heart, lungs, and other normal tissues. The potential value of combining irradiation with antivascular endothelial growth factor (anti-VEGF) therapies, which normalize tumor blood vessels and improve oxygenation and drug deliver, is reviewed in Chapter 5 and is again intriguing, but unproven.

Most recently, inhibitors of DNA repair have entered clinical trial. Oliparib blocks the function of polyadenosyl ribose polymerase (PARP), a central component of base repair; it has antitumor activity in patients harboring breast cancer or serous ovarian cancer with defects in homologous DNA repair due to BRCA 1 or BRCA 2 mutations, and has interesting, but unproven potential for enhancing radiation damage to DNA in tumors with DNA repair defects such as BRCA 1 or 2 mutations (see Chapter 4).

Drugs and irradiation may share common mechanisms of tumor cell resistance. Increased proficiency of repair of double strand breaks may impair the response to both irradiation and to several classes of antitumor drugs, including alkylating agents, platinum analogs, and topoisomerase inhibitors (see Chapter 4). Cells with defects in apoptosis and checkpoint function (TP53 mutation) fail to initiate apoptosis in radiation resistant tumors. Stem cells, both cancer related and normal varieties, are inherently resistant to reactive oxygen damage and overexpress the multidrug resistance (MDR) transporter.[11] Tumor stem cells are quiescent regarding cell cycle progression and may reside in hypoxic niches within tumors. The epidermal-to-mesenchymal phenotypic transition (EMT), with distinctive cell surface markers[2] and a drug-resistant profile similar to that seen in stem cells, appears to be a common event in drug- and radiation-resistant tumors. New drugs designed to reactivate apoptotic pathways (BCL2 inhibitors) and cell checkpoint function (HMD2 inhibitors), and inhibitors of the PI3 kinase cell survival pathway are of particular interest in reversing EMT changes.

Because drugs have become an integral part of the initial therapy of many patients with cancer, it is essential that the medical oncologist, surgeon, and radiation oncologist understand the principles of chemotherapy and the specific features of the commonly used agents.

THE CYTOTOXIC DRUGS: TARGETING DNA SYNTHESIS AND MITOSIS

The cytotoxic drugs in current clinical use act directly on the synthesis or integrity of DNA. These drugs may inhibit synthesis of DNA or its precursors, block cell division, inhibit necessary changes in DNA topology, or covalently bind to DNA, causing strand breaks or miscoding. All such drugs affect the integrity of DNA, and in the presence of the normal machinery (TP53) for monitoring DNA integrity, they induce apoptosis. Unfortunately, they are also cytotoxic toward normal cells. The reasons for their somewhat selective toxicity for malignant versus normal cells, as is apparent in the cure of lymphomas and leukemias, are poorly understood. The process of malignant transformation may enhance sensitivity to DNA damage by virtue of defects in DNA repair, although at the same time these same defects expand tumor cell diversity and encourage drug resistance. Many of the defective genes responsible for inherited cancer syndromes, such as *BRCA1* and *BRCA2* genes, mismatch repair genes, *TP53*, and nucleotide excision repair defects, create sensitivity to irradiation and to agents that inhibit aspects of DNA repair.

In designing clinical regimens, the relationship of drug action to the cell cycle is of particular importance because this knowledge serves as the basis for combining drugs and sequences in clinical practice and influences their use in combination with radiation therapy. The cell cycle and its primary controls are shown in Figure 9-3. Antimetabolites such as methotrexate, 5-FU, cytosine arabinoside, gemcitabine, and the purine antagonists kill cells that are actively synthesizing DNA; therefore, they are cell cycle dependent. Nucleoside analogs, including cytosine arabinoside, fludarabine phosphate, and cladribine, must be incorporated into newly synthesized DNA to be cytotoxic. Alternately, other agents such as the camptothecins, etoposide, and doxorubicin produce DNA strand breaks at any stage of the cell cycle, and are less dependent on cell cycle events for cytotoxicity, although these breaks may become lethal only as the cell crosses a checkpoint and enters DNA synthesis. Antimitotic agents, constituting a separate class of drugs, block the formation of the mitotic spindle and thereby prevent separation of chromosomes to the daughter cells. Drugs of this class are therefore effective against cells during the mitotic phase of the cell cycle. Still others, such as alkylating agents and platinum compounds, bind covalently to DNA and produce strand cross-links and strand breaks. Their toxicity seems less dependent on cell cycle stage.

Once it has been damaged through its encounter with a cytotoxic drug, the cancer cell has several options, and its eventual viability depends on which pathway it takes. If the normal monitors for genomic integrity (including most prominently the product of the *TP53* gene) are intact, the cell may halt further progression in the cell cycle while its DNA is repaired. If the damage is sufficiently extensive, TP53 may initiate apoptosis. If, however, TP53 function is absent, cell cycle progression may continue past the G1-S checkpoint despite drug-induced DNA damage, and the cell may prove viable. In most experimental settings, lack of wild-type TP53 is associated with drug and irradiation resistance. Paradoxically, some DNA repair defects, as found in mismatch repair (colon cancer), are associated with resistance to thio-purine analogs, platinum analogs, and alkylating agents, perhaps as a result of a failure to respond to DNA adducts and to initiate apoptosis.

From a theoretical viewpoint, it is understandable that rapidly dividing tumor cells, such as those found in acute leukemia, high-grade lymphoma, and choriocarcinoma, may be exquisitely sensitive to antimetabolites and cell cycle–specific drugs. How do these drugs kill the more slowly dividing solid tumors? Many of these tumors have long cell cycles (4 to 5 days). Many cells are in the G0 phase (nondividing state), and at any moment, only 1% to 3% of cells are in S phase. Cell kinetic factors diminish the effectiveness of chemotherapy, and the disordered vascularization of tumors may also contribute by limiting drug entry into areas of slow blood flow. Despite these disadvantages, solid tumor chemotherapy produces meaningful responses. Several factors, including pharmacologic, pharmacokinetic, and tumor cell-specific factors likely contribute to solid tumor killing by cycle specific or cycle sensitive drugs:

1. Drugs such as paclitaxel and doxorubicin clear slowly from the blood stream and the extracellular space. Alternative regimens, such as prolonged drug infusion, seem to increase the activity of 5-FU and paclitaxel, compared with the results of bolus administration.
2. Other drugs, such as methotrexate, which forms an intracellular polyglutamated species, and gemcitabine, which forms a long-lived intracellular triphosphate, persist inside the cell long after their disappearance from plasma.
3. As mentioned, tumor cells may be less able to repair DNA and more susceptible to cell death induced by DNA damage than their normal counterparts. For example, transformed mouse embryo fibroblasts have a heightened sensitivity to cancer drugs compared with their nontransformed parent, provided they have wild-type *TP53* genes.[12]
4. Underlying the tumor proliferation rate is a significant death rate that results from a number of factors, such as hypoxia, nutrient deprivation, disordered DNA synthesis, and mitosis, and, in general, a high-background rate of mutation that affects genes essential for cell integrity and survival. A small shift in the balance between cell proliferation and cell death may lead to regression of a tumor, despite its low growth fraction

DRUGS THAT INDUCE DIFFERENTIATION

Although differentiation inducers have long attracted interest for cancer drug development, only a small number of compounds have reached clinical evaluation. 5-aza-cytidine and its close congener, 5-aza-2′deoxycytidine are both approved for treatment of myelodysplastic syndrome. They induce differentiation by irreversibly inhibiting DNA methyl transferase. They are modestly myelosuppressive but induce the production of both myeloid and erythroid lineages and reduce transfusion dependence in MDS.[13]

A more compelling example of differentiation induction is provided by all trans-retinoic acid (ATRA), which binds to the mutated retinoic acid receptor created by the RAR-PML translocation in acute promyelocytic leukemia (APL), thereby inducing differentiation and remission. Its primary toxicity is a syndrome of pulmonary failure resulting from clogging of small vessels by the mature leukemic granulocytes. Arsenic trioxide is a second agent capable of induction of differentiation in APL. It promotes degradation of the translocated fusion protein, produces free radicals, and has antiangiogenic properties as well. Its toxicities include the pulmonary failure syndrome seen with ATRA, prolongation of the PR interval, arrhythmias that are accentuated by potassium (K+) and magnesium (Mg+) depletion, and hyperglycemia.

IMMUNOTHERAPY

Immunotherapies have been the object of much research attention, but only in the past decade have drugs of this kind proved useful. Monoclonal antibodies have clearly won a place in the standard regimens for treatment of lymphoma

(brentuximab for Hodgkin disease and rituximab for B-cell lymphomas), breast cancer (traztuzumab, pertuzumab, and TDM1 for Her-2 positive tumors), and cetuximab and panitumumab for colorectal cancer. Their mechanisms of action may simply be engagement and inhibition of a receptor necessary for survival, but auxiliary actions such as antibody dependent cellular cytotoxicity may play a role. The newest additions to immunotherapy include anti CTLA-4 and anti-PD1 and antiPDL-1 antibodies, which release autoimmune antitumor responses; these have shown remarkable long-term responses in melanoma, kidney cancers, and adenocarcinoma of the lung.[14-17] Even more impressive are the massive antitumor effects of chimeric antigen receptor T cells in which T-cell receptors are engineered to recognize the CD-19 auto-antigen antigen and destroy all B cells, physiological and malignant, including B-cell lymphomas and leukemias.[18]

TARGETED THERAPIES: SIGNAL TRANSDUCTION INHIBITORS

Expanding knowledge of the biology of cancer cell growth and death and the processes that regulate differentiation has provided a new set of targets for cancer treatment. Excessive proliferation of tumor cells has many causes; observations of tumor biology in model systems and in well-studied human cancers have shown that the proliferative drive may result from mutations that stimulate cell division as, for example, mutated growth factor receptors, whereas other mutations free the cancer cell from normal cell cycle controls through loss of suppressor functions such as mutations in the cell cycle checkpoint, TP53, or mutations in the retinoblastoma pathway. Still other mutations promote cell survival as occurs with activating mutations in the PI3-kinase pathway and activation of antiapoptotic proteins such as BCL-2 (see Chapter 2).

Drug discovery efforts have targeted specific activated pathways and mutations that promote proliferation and cell survival (see Table 9-1).[19] Inhibiting the function of a dominant gene product is a classic problem in cancer drug discovery. In the late 1980s, the first efforts at targeted inhibition led to development of inhibitors of the K-RAS protein, a signal transducer that links growth factor receptors to the MEK-ERK downstream cascade. K-RAS is mutated in 80% to 90% of pancreatic cancers and provides the proliferative drive in subsets of patients with non–small cell lung cancer (NSCLC), acute myelogenous leukemia, and colorectal cancers. The K-RAS protein is activated by an enzymatic step that attaches a lipid tail (a farnesyl group) to its near-terminal cysteine. Although inhibitors of farnesylation caused regression of experimental K-RAS-driven tumors, these drugs failed in clinical trials because the inhibitors lacked specificity for farnesylation of K-RAS, and alternative pathways for lipid modification of K-RAS circumvented the inhibition. New K-RAS strategies now focus on blocking a unique binding pocket in the G12C mutation, or downstream inhibition of the MEK-ERK pathway activated by mutant K-RAS.[20]

The first successful targeted small molecule emerged from studies of the BCR-ABL kinase in chronic myeloid leukemia (CML). In 1998, Druker introduced imatinib, an adeno triphosphate (ATP) competitive inhibitor that produced molecular remissions in a high percentage of patients who had progressed on standard chemotherapy. Imatinib produces long-term disease control, with normalization of both blood counts and cytogenetics in more than 90% of previously untreated patients in the chronic phases of the disease. Newer inhibitors, nilotinib, busotinib, and dasatinib, kill CML cells with mutations that confer resistance to imatinib. The newest and most potent BCR-ABL inhibitor, ponatinib, has sustained activity against virtually all resistant cell lines, including T315I, and was approved for the treatment of resistant CML and Philadelphia chromosome positive ALL.[19]

The success of imatinib has spawned an ever-increasing number of successful targeted agents (see Table 9-1). A parallel development in chronic lymphocytic leukemia (CLL) has led to the success of ibrutinib, an inhibitor of the Bruton tyrosine kinase, a key mediator of B-cell receptor signaling and early B-cell proliferation. The drug is approved for second line CLL and mantle cell lymphoma.[21] Its toxicities are limited to diarrhea, rash, and mild hepatic enzyme elevations. It does not produce profound immunodeficiency, as compared to the highly immunosuppressive anti-CD20 antibody, rituximab.

Imatinib also inhibits the KIT (CD117) receptor and proved to be the first targeted small molecule effective in the management of a solid tumor, in this case metastatic gastrointestinal stromal tumor (GIST). The presence of specific activating mutations within the *KIT* gene predicts for response in patients with GIST (see Table 9-1). The multitargeted tyrosine kinase inhibitor, sunitinib, has demonstrated benefit in patients with imatinib-refractory GIST, even in those with *KIT* mutations that are typically resistant to imatinib.[19]

Downstream of RTKs, other phosphorylation steps, when constitutively activated by mutation, may lead to malignancy and may be successfully targeted by small molecules. A striking example is presented by B-RAF inhibitors for melanoma. More than 50% of advanced stage melanomas carry a mutation of *B-RAF*, most commonly resulting from V600E or V600K mutations (BRAFV600E or BRAFV600K), which are transforming alterations that produce constitutive activation of the downstream MEK/ERK pathway and cancer cell proliferation. Vemurafenib, a selective inhibitor of the mutated BRAF protein, with limited inhibition of the wild type enzyme, produced an unparalleled 80% antitumor response rate in patients with advanced melanomas. A subsequent study showed that the combination of another BRAF inhibitor, dabrafenib, with a MEK inhibitor, trametinib, was superior to monotherapy with dabrafenib. The response rate in the cohort receiving combination therapy was 76% and a progression-free survival of 9.8 months compared with 5.8 months in the monotherapy groups, leading to approval of both new drugs in 2013.[22] It is noteworthy that the same mutation in *B-RAF*, V600E, found in melanoma also occurs in subsets of colorectal cancer, thyroid cancer, and NSCLC. Although lung and thyroid cancers with B-RAF mutations do show sensitivity to B-RAF inhibition, colorectal cancers of this type are unresponsive, indicating that the tissue context of the mutation may be important in determining response.[19]

RECEPTOR TYROSINE KINASES AS TARGETS

Mutations or translocations in genes coding for RTKs cause epithelial cancers arising in subsets of patients with lung, colon, thyroid, and breast tumors. These RTK mutations constitutively activate the kinase function of EGFR, EML4-ALK, and ROS-1 in NSCLC, C-KIT in melanoma and gastrointestinal stromal tumors, and RET in medullary thyroid cancer. The net effect is to create a cell under constant proliferative stimulus. Cells with these mutations become addicted to the aberrant signal and die when the signal is interrupted. Most clinically effective kinase inhibitors target the ATP binding pocket of the RTK.

EGFR inhibitors have proved useful in NSCLC. EGFR is overexpressed in many solid tumors and plays a critical role in activating downstream molecules that control cell cycle

progression, proliferation, angiogenesis, and survival. Subsequent trials have revealed that this new class of drugs is highly effective for the 10% of patients with NSCLC with tumors that harbor *activating mutations* in EGFR, but there is no clear benefit in the 40% to 80% of NSCLCs that overexpress *nonmutated* EGFR. Activating mutations caused by deletions or base substitutions clustered around the ATP-binding pocket of the tyrosine kinase domain of EGFR. Seventy percent of EGFR-mutated tumors respond initially to erlotinib. The median duration of response is 10 months, exceeding the results of chemotherapy by 3 to 4 months. The benefits of erlotinib and gefitinib are offset by important toxicities, including acneform rash and diarrhea. Resistance arises through further mutations in the ATP-binding pocket of the receptor, or by activation of the c-MET pathway. A second-generation EGFR inhibitor, afatinib, with greater potency of binding, produced a highly significant improvement in response rate and progression-free survival, compared to conventional chemotherapy for relapsed patients. Third-generation inhibitors from Astra-Zeneca and Clovis, which irreversibly bind to mutant EGFR and specifically block the mutant receptor, remain active against EGFR-resistance mutations such as T790M, have much reduced toxicity to bowel and skin, and produce clinical responses in patients resistant to erlotinib, according to early clinical experience.

Cetuximab, a chimeric IgG1 monoclonal antibody targeting the extracellular portion of the EGFR, is not active against lung adenocarcinoma with wild type or mutated EGFR, but is approved for the treatment of chemotherapy-refractory colorectal cancer. The addition of cetuximab to irinotecan results in nearly doubled response rates, as compared to irinotecan alone.[19] Panitumumab, another monoclonal antibody targeting the EGFR, improved progression-free survival rates compared with placebo in patients with chemotherapy refractory. Responses are more frequent in patients who develop the typical acneform rash associated with these agents. More importantly, patients who have activating mutations of K-RAS or BRAF derive no benefit from these EGFR antibodies. Cetuximab enhances local disease control with irradiation in squamous cell carcinoma of the head and neck.[23]

Other subsets of NSCLC contain unique RTK translocations that have been successfully targeted. The *EML4-ALK* translocation activates the anaplastic large-cell kinase RTK in 4% of patients with NSCLC. In a phase I/II trial of the MET/ALK inhibitor, crizotinib, patients possessing the ALK fusion protein exhibited a 53% clinical response rate, with an additional 20% of patients having stable disease for prolonged periods, findings confirmed in a phase II trial. This agent also has activity against other *ALK* driven tumors, including anaplastic large cell lymphoma and inflammatory myeofibroblastic sarcomas.[19] Resistance to crizotinib develops in the form of mutations in the ATP-binding site of the fusion kinase. A series of second-generation inhibitors, insensitive to these crizotinib-resistance mutations, have strikingly high response rates in *EML4-ALK* mutated tumors and will likely displace crizotinib as primary therapy (Shaw, A. New Engl J Med, in press). Crizotinib is also active against kinases associated with an activating translocation of the ROS-1 RTK,[24] found in 1% of NSCLC.

HER2-DIRECTED THERAPY

HER2 (EGFR 2 or ERB B-2), is a RTK activated by heregulin. It lacks the ability to signal downstream but promotes proliferation and survival through dimerization with one of the other EGFR receptor family members, preferentially HER3. As a dimer, it signals through both the MAP kinase and PI3K/AKT pathways. About 25% of breast cancers demonstrate amplification of the *HER2* gene, resulting in ligand-independent cancer cell proliferation and survival. *HER2* amplification is associated with a more aggressive phenotype and worse clinical outcomes. Trastuzumab, a monoclonal antibody against HER2, is approved for the treatment of metastatic HER2-positive breast cancer. Although monotherapy with traztuzumab shows modest efficacy, its combination with taxanes or other chemotherapies in HER+ breast cancer results in improved response rate, disease-free survival, and overall survival and decreased recurrence in adjuvant therapy, as compared with chemotherapy alone.[25] Trastuzumab also shows efficacy with chemotherapy for *HER2* amplified gastric adenocarcinomas.[26]

A newer antibody, pertuzumab, blocks HER2 dimerization with HER 3 and prevents signaling through HER3. In combination with trastuzumab and docetaxel, pertuzumab improved progression-free survival (18.5 months versus 12.4 months) and overall survival in metastatic disease[27] and yielded an improved pathological complete response rate in presurgical treatment of breast cancer (neoadjuvant therapy). A growing number of targeted therapies are being tested, with the aim of gaining accelerated approval by demonstrating improvements in pathological CR rates in neoadjuvant trials of early breast cancers.

Small molecules that compete with ATP are also effective in blocking HER2 signaling. Lapatinib, a selective HER2 and EGFR inhibitor, proved effective with capecitabine in the treatment of HER2-positive breast cancer, after progression on traztuzumab.[19] In combination with traztuzumab and a taxane, lapatinib enhances time to progression in first-line therapy.[25]

Trastuzumab has also been used as a carrier of a highly toxic maytansine derivative, emtansine. Trastuzumab-DM-1 (TDM-1), approved in 2013 for the treatment of HER2-positive breast cancer after progression on trastuzumab, produced superior progression-free survival (9.6 months versus 6.4 months) and overall survival (30.9 months versus 25.1 months), as compared with lapatinib plus capecitabine.[9]

PI3 KINASE AS A TARGET FOR CANCER THERAPY

Intracellular regulatory pathways have attracted the interest of drug discovery programs. The phosphatidylinositol-3-kinase (PI3K) pathway (Figure 9-4) receives signals from a number of RTKs; these signals activate proliferation and exert prosurvival effects through down-regulation of the intrinsic pathway of apoptosis. Multiple components of this pathway, especially the PI3K alpha (breast, endometrial, lung, and colon cancer) and delta (lymphomas) iso-enzymes, display amplification or mutations in human cancer. The PTEN phosphorylase, a suppressor of the pathway, is frequently inactive or deleted in breast cancer and other tumors. Inhibitors of sequential components of this pathway, including PI3CA inhibitors for metastatic breast cancer and the PI3K delta inhibitor idelalisib, used with rituximab for chronic lymphocytic leukemia,[28] have shown promising activity in early trials.

mTOR occupies a central position in the downstream signaling pathway for PI3K. It forms multiprotein complexes that signal for proliferation, survival, and angiogenesis and modulate intermediary metabolism. mTOR inhibitors specific for the TORC1 complex have been approved for cancer indications, including the immunosuppressive rapalogs, temsirolimus for patients with high-risk renal cell carcinoma, and everolimus for the same disease refractory to immunotherapies. Everolimus is also approved for mantle cell lymphoma and for carcinoid and peripheral neuro-ectodermal tumors, and in combination with examestane for hormone refractory breast cancer. The mTOR inhibitors cause interstitial lung

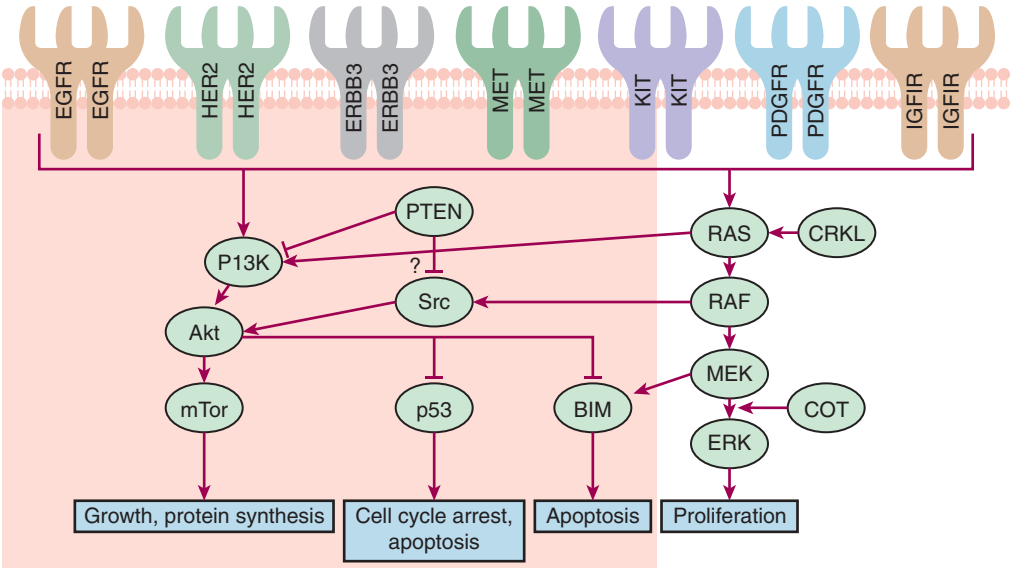


Figure 9-4 Physiology of major transmembrane tyrosine-kinase receptors and associated intracellular pathways. Receptors are displayed as homodimers. Note that most of these receptors may form heterodimers to activate the same intracellular pathways. The blue background highlights intracellular tyrosine kinases of the PI3K/AKT pathway; the yellow background highlights the RAS/RAF/ERK pathway. There is crosstalk between both pathways on multiple levels, three of which are displayed, including RAF-dependent Src-activation, MEK-dependent BIM-activation and RAS-dependent PI3K activation.

disease as a major complications, along with rash, diarrhea, and hepatic toxicity and may augment myelosuppression as a result of chemotherapy.[19] Newer mTOR inhibitors block both TORC-1 and TORC-2 complexes, as well as upstream kinases, and may show improved therapeutic effects.

PROTEASOME INHIBITION

In 2003, the FDA approved bortezomib, a proteasome inhibitor, for patients who have progressed while receiving prior therapy for multiple myeloma. It blocks the chymotryptic activity of proteasome degradation of key proteins and thereby blocks activation of nuclear factor kappa B (NFκB), a potent survival factor for cancer cells. It is currently approved for first-line therapy for multiple myeloma in combination with dexamethasone, and second-line therapy of mantle cell lymphoma. A more potent successor molecular, carfilzomib, also a proteasome inhibitor, has impressive antimyeloma activity and less neurotoxicity in second-line treatment.[19] Their other toxicities are occasional myelosuppression and diarrhea.

ANGIOGENESIS ANTAGONISTS

Although most drug discovery efforts are aimed at pathways and targets that govern the balance of cell proliferation and cell death, other unique aspects of cancer biology have attracted notice, particularly tumor blood vessel formation, Angiogenesis has been traced to tumor cell secretion of factors such as basic fibroblast growth factor, angiopoeitins, and VEGF. Specific inhibitors of this process, such as anti-VEGF antibody (bevacizumab) (see Table 9-1) and anti-VEGFR small molecules (sunitinib, pozatinib, vandetanib, and sorafenib), are now approved for multiple clinical indications.[19]

In 2004, the humanized monoclonal antibody bevacizumab was approved for the first-line treatment of metastatic colorectal cancer in combination with chemotherapy and subsequently with chemotherapy for first-line treatment of ovarian and lung cancer and for recurrent glioblastoma multiforme after first-line therapy. Compared with chemotherapy alone, the addition of bevacizumab to chemotherapy in metastatic colorectal cancer and metastatic cervical cancer improved the response rate, progression-free survival rate, and overall survival rate.[29,30] Bevacizumab also extends progression-free survival as a single agent in renal cell carcinoma, and in combination with temozolamide and radiation therapy in glioblastoma multiforme but does not extend overall survival for those indications. Bevacizumab has multiple effects on tumor perfusion and drug access. A study of neoadjuvant 5-FU combined with radiation therapy for T3 rectal cancer demonstrated a decrease in tumor perfusion, vascular volume, microvascular density, and interstitial fluid pressure after administration of bevacizumab.[31] As a class effect, the antiangiogenic drugs reduce interstitial pressure and improve oxygenation to enhance irradiation effects, and improve delivery of cytotoxic chemotherapy to the tumor, enhancing the radio- and chemosensitizing properties of the drug.

Other antibodies target EGFR by using a decoy receptor. Ziv-afilbercept, a recombinant fusion protein of IgG and VEGFR, binds circulating VEGF. Added to FOLFIRI, it doubled the response rate and marginally improved survival in refractory metastatic colorectal cancer, as compared to FOLFIRI alone.[19]

Small molecules effectively inhibit VEGFR by competing with ATP for the intracellular kinase site on the receptor molecule. Many of these compounds inhibit other tyrosine kinases. Sunitinib inhibits VEGFR2, c-KIT, and platelet-derived growth factor receptor (PDGFR). In a phase III trial comparing sunitinib with interferon-alfa in patients with metastatic renal cell carcinoma, sunitinib produced a superior response rate and progression-free survival. Sunitinib improved time to tumor progression in patients with GIST resistant to imatinib therapy and lengthened survival in patients with unresectable or metastatic peripheral neuro-ectodermal tumors. It received approval for these three indications.[19]

Other antiangiogenic compounds have been approved for clinical use. Sorafenib, an inhibitor of B-RAF kinase and VEGFR2, is approved for unresectable hepatocellular carcinoma on the basis of an improvement in overall survival.

Sorafenib also improved survival rates when compared with placebo in patients with metastatic clear cell carcinoma of the kidney. Axitinib produced longer progression-free survival than did sorafenib as second-line therapy for renal cell carcinomas.[32] Pazopanib has also won approval for renal cancers and soft-tissue sarcomas.[19]

It is notable that the antiangiogenic drugs produce significant toxicity: hypertension with occasional congestive heart failure, proteinuria, rare episodes of intestinal perforation (usually in patients who have undergone abdominal surgery), thrombosis, and hemorrhage, and for the oral compounds, diarrhea, fatigue, and hepatic enzyme elevations.[19]

Thalidomide and its analogs, also called immunomodulatory derivatives (IMIDs) have defied categorization with respect to their mechanism of antitumor activity. Originally used as a sedative and then as a the treatment for erythema nodosum leprosum, thalidomide and its IMID analogs have antiangiogenic and anticytokine properties, suppressing TNFα, IL-12, IL-6, and NFκB. Analogs are known to destabilize cyclin D complexes and promote ubiquitination of key lymphocyte transcription factors, IKZF1 and IKZF.[33] More potent and less sedating derivatives, lenalidomide and pomalidomide, are highly active in multiple myeloma and mantle cell lymphoma, and have notable activity in other lymphomas and chronic leukemias. Lenalidomide produces hematologic remissions in the 5q-forms of myelodysplasia. The side effects of the IMIDS include peripheral neuropathy, diarrhea or constipation, and venous thrombosis, especially when used in combination with dexamethasone, and lenalidamide is associated with an increased rate of second malignancies when used with melphalan.[34]

EPIGENETIC MODIFIERS

Epigenetics is a rapidly expanding area of research that examines the control of gene expression by histones and by DNA methylation. Histones couple with DNA and, in their unmodified state, block access by polymerases and transcription factors. Methylation, acetylation, or phosphorylation of histones decompacts chromatin, increases gene expression, and can induce differentiation and apoptosis in tumor cells. Histone deacetylase inhibitors (HDACs) are a new class of antitumor drugs that can induce cell cycle arrest and differentiation. They may cause hyperacetylation of nonhistone proteins as well, including TP53, HSP90, RAF, AKT, HER2, and BCR-ABL. Through their effects on acetylation of histones and key oncoproteins, they exert valuable antitumor activity in cutaneous and peripheral T-cell lymphomas. They may also serve as radiation sensitizers.[35] Two agents of this class, vorinostat and romidepsin, are FDA approved for patients with cutaneous T-cell lymphoma. Their most common side effects are diarrhea, fatigue, nausea, and loss of appetite, but they may also prolong the cardiac QT interval and may induce arrhythmias. They are currently being studied in combination therapy of multiple solid tumors.

OPTIMIZING CLINICAL CHEMOTHERAPY: PHARMACOKINETICS AND PHARMACODYNAMICS

In the treatment of patients with cancer, the ultimate effectiveness of drug therapy is determined by three factors[1]: the inherent sensitivity of the tumor,[2] the ability to deliver drug to its site of action in therapeutic concentrations, and the limitations of host toxicity.[3] It is generally not possible to measure drug concentrations in tumor, although new imaging techniques such as positron emission tomography (PET) and nuclear magnetic resonance imaging (MRI) do allow noninvasive tracking of the distribution and transformation of some drugs in humans in experimental settings.[36] The pharmacokinetic profile of drug in plasma, or change in drug concentration over time, represents the closest correlate of tumor exposure accessible to measurement in the usual clinical setting. In the initial clinical trials of new agents, pharmacokinetic studies are critical for determining whether cytotoxic drug concentrations are achieved and for adjusting the route and schedule of drug administration to achieve an optimal profile, as suggested by preclinical models. In phase II and III trials, pharmacokinetics can yield important additional information on the effects of age, gender, drug interactions, and organ dysfunction on drug clearance.

Anticancer drugs are cleared from the body by one mechanism or a combination of several mechanisms, including renal excretion, hepatic metabolism, chemical decomposition, or metabolic alteration at extrahepatic sites (Table 9-2). Considerable variation is often found among individuals in their ability to clear anticancer drugs, which may necessitate dose adjustment for patients with renal or hepatic dysfunction. Other factors, such as gender, age, serum albumin concentration, lean body mass, nutritional status, and performance status, can influence the pharmacokinetic behavior and pharmacologic effect of a drug, but their quantitative impact on drug disposition is difficult to predict in individual patients. Inherited defects (polymorphisms) in metabolic capability may lead to severe unexpected toxicity for drugs such as 5-FU (i.e., dihydropyrimidine dehydrogenase deficiency) and 6-mercaptopurine (i.e., thiopurine methyltransferase deficiency).[37] Genetic variation in the UDP*-glucuronosyltransferase 1A1 gene (UGT1A1 gene), which is associated with Gilbert syndrome, results in severe toxicity, primarily neutropenia, in patients receiving irinotecan because of the inability to conjugate and clear the active compound, SN-38.

Virtually all targeted small molecules and natural products (taxanes, vincas, and anthracyclines) are cleared through metabolism by hepatic microsomes and require dose reduction in the presence of abnormal liver function. A smaller number of cytotoxic drugs, including methotrexate, pemetrexed, fludarabine, hydroxyurea, and bleomycin, are excreted unchanged in the urine (see Table 9-2) and depend primarily on renal function. Adjustments in dose are required in the presence of renal dysfunction.

Correlations between pharmacokinetic and pharmacodynamic endpoints, such as organ toxicity and therapeutic outcome, are more difficult to establish, but some important insights into these relationships have been identified for several anticancer drugs (Table 9-3). For antimetabolites, most natural product drugs, and platinum compounds, pharmacodynamic endpoints such as antitumor effects and toxicity to bone marrow and intestinal epithelium correlate best with the area under the plasma concentration time curve (see Figure 9-2). For other drugs, such as paclitaxel, the duration of time above a threshold plasma concentration (0.05 to 0.1 μM) correlates best with toxicity to marrow, and there is preliminary evidence that duration above a threshold level also correlates with antitumor effectiveness (Figure 9-2).[49] For alkylating agents, which display a relatively simple relationship between peak plasma concentration and toxicity, dose rather than drug concentration over time correlates best with toxicity and tumor cell killing.

Pharmacokinetic studies can also reveal the existence of drug interactions, which are common for drugs that depend on hepatic microsomal clearance. Inducers of metabolism such as phenylhydantoin, or inhibitors such as imidazole antifungal drugs, can alter clearance, leading to toxicity or ineffective therapy (Table 9-4).

TABLE 9-2 Clearance Mechanisms of Anticancer Drugs

Primary Clearance Mechanism	Drug	Dose Modification for Organ Dysfunction
Hepatic metabolism	Busulfan, taxanes, vinca alkaloids, irinotecan, anthracyclines, imatinib, nilotinib, bosutinib, dabrafenib, pazopanib, axitinib, lapatinib, vandentanib, bortezomib	Y
	Chlorambucil, cyclophosphamide,* ifosfamide,* thiotepa, ponatinib, dasatinib, erlotinib, gefitinib, crizotinib, sorafenib, sunitinib, ibrutinib, regorafenib, cabozantinib, vismodegib, carfilzomib, romidepsin	N
Reduction	Mitomycin C*	N
Deacetylation	Trametinib	N
Conjugation	Etoposide, vorinostat	N
	6-Mercaptopurine	Y†
Soluble enzymes	Ara-C, gemcitabine, omacetaxine mepesuccinate, cyclophosphamide metabolites, ifosfamide metabolites	N
	5-Fluorouracil	Y‡
Nonenzymatic hydrolysis	Camptothecins, BCNU,* mechlorethamine, melphalan	N
Renal excretion	Bleomycin, carboplatin, deoxycoformycin, etoposide, fludarabine, hydroxyurea, methotrexate, topotecan, imatinib, vandetanib	Y

Y, *Yes;* N, *No.*
**Enzymatic and spontaneous chemical reactions required for drug activation, aldehyde dehydrogenase inactivates.*
†Methyltransferase deficiency.
‡Dihydropyrimidine dehydrogenase deficiency.

TABLE 9-3 Pharmacodynamic Relationships of Chemotherapeutic Agents in Cancer Patients

Drug	Clinical Effect	Pharmacokinetic correlate	References
Busulfan	Hepatotoxicity	AUC	38
Carboplatin	Thrombocytopenia	AUC	39
Cisplatin	Nephrotoxicity	C_{max} (unchanged drug)	40
Doxorubicin	Cardiotoxicity	C_{max}	41
Etoposide phosphate	Myelosuppression	AUC (etoposide)	42
Fludarabine phosphate	Leukopenia	AUC	43
5-Fluorouracil	Risk of toxicity	AUC	44
Methotrexate	Response Bone marrow suppression	$C_{max,}$ C × T: (C over 10 μM)	45,46
Paclitaxel	Neutropenia	Time above threshold C_p	47
Topotecan	Neutropenia	AUC (total drug)	48

AUC, *Area under the plasma concentration–time profile;* C_{max}, *maximum plasma concentration;* C_p, *plasma concentration;* GSH, *glutathione.*

TABLE 9-4 Examples of Pharmacokinetic Drug Interactions Involving Anticancer Agents

Chemotherapeutic Agent	Interacting Drugs	Effect on Anticancer Drug Clearance	Probable Mechanism	References
Cyclophosphamide	Phenobarbital	↑	CYP450 enzyme induction	50,51
Doxorubicin	Cyclosporine	↓	Inhibit P-glycoprotein–mediated biliary excretion	52,53
Methotrexate	Aspirin, penicillins	↓	Inhibit tubular secretion	54-56
	Cephalosporins	↑	Inhibit tubular resorption	
Paclitaxel	Verapamil	↓	Inhibit CYP450 metabolism or biliary excretion, block MDR pump	57
Vinblastine	Erythromycin, imidazole antifungal drugs	↓	Inhibit CYP450 metabolism	58

CLINICAL SCHEDULES OF DRUG ADMINISTRATION

Cancer drugs are given in repetitive cycles of administration interrupted by rest periods that facilitate the recovery of normal tissues, particularly bone marrow and gastrointestinal mucosa. With the availability of myeloid stimulatory factors such as granulocyte colony-stimulating factor, it is possible to shorten the period between cycles from the traditional 4-week interval to 2 weeks. The ability to provide such dose-dense therapy with the aid of growth colony-stimulating factor may result in improved outcome without an increase

in toxicity.[59] The theoretical basis for cyclic chemotherapy was established by animal models, which showed that for any given drug schedule and dose, a specific fraction of tumor cells is killed. Repeated cycles of treatment are therefore required for curative therapy. Whether it is necessary to eliminate the last tumor cell to cure the disease is still in doubt. Molecular markers for residual disease may be present for years after remission induction in children with acute leukemia.

Although peak drug plasma concentration, area under the curve (AUC), and time over a threshold level have been correlated with response and toxicity for selected chemotherapeutic agents, clinical investigators lack pharmacokinetic data and further, lack correlations of pharmacokinetics with pharmacodynamic effects for most combination therapy regimens. A greater effort has been made to develop such correlations for targeted drugs, but the information is usually imprecise. The practical endpoint in combination clinical studies is typically to maximize dose intensity (drug administered per unit time) of the individual agents. For cytotoxic drugs, clinical data support a strong relationship between dose intensity and response in the treatment of lymphomas, breast, ovarian, and colon tumors.[60] Taken to its extreme, high-dose chemotherapy with bone marrow stem cell replacement yields the highest dose intensity and the highest response rates in patients who have otherwise refractory tumors, but at a high dollar cost and at the risk of fatal toxicity. In clinical practice, most oncologists administer full doses of drug, aiming at achieving reversible and readily tolerated toxicity as their clinical endpoint.

In designing a combination chemotherapy regimen, the clinical investigator must choose from a range of options regarding route, schedule, and sequence of drug administration. A number of factors determine the final choice of schedule of administration.

1. *Pharmacokinetics of the individual agents in humans.* Specific factors, such as peak drug concentration and clearance from plasma, desired AUC, and duration of drug concentration above a threshold, are central considerations for individual agents (see Figure 9-2). In general, clinical investigators attempt to reproduce a profile of drug concentration and duration of exposure that mimics optimal conditions in experimental systems.
2. *Cell cycle kinetics and cell cycle phase specificity of the agent.* If the agent in question exerts its effects only against cells in a specific phase of the cell cycle, the schedule must be planned to ensure a maximum duration of drug concentration above the threshold. In practice, the best example is the prolonged infusion of antimetabolites (i.e., 5-FU or cytosine arabinoside given by continuous infusion). Most dividing cells in a tumor that is growing relatively rapidly, such as acute myelocytic leukemia, are exposed to drug during their DNA synthetic phase if the infusion of cytosine arabinoside lasts for 7 days.
3. *Drug interactions.* Interactions that alter pharmacokinetic behavior or enhance or inhibit cytotoxicity (Table 9-4) may dictate the use of a specific schedule or sequence of drug administration.
4. *Drug interactions with irradiation.* The growing interest in combined-modality treatment for solid tumors stems from the expectation that many cancer drugs act as radiosensitizers. In most instances, the maximum radiosensitization is realized if the drug is present during the exposure of tumor to irradiation. Continuous drug infusion or daily administration is favored, although rigorous proof that one schedule is better than another is often lacking.
5. *Toxicity.* Most chemotherapy regimens are developed to allow rapid and complete recovery of normal tissues between cycles of treatment. Ultimately, toxicity limits the dose of drug employed and the duration of administration. If drugs are used in combination with other treatment modalities, further limitations of schedule and dose may be imposed. For example, the radiosensitizing effect of 5-FU or cisplatin-based chemotherapy on mucosa or bone marrow may limit the dose of radiation therapy and chemotherapy if the two modalities are given concurrently and particularly if the field of irradiation includes the marrow, gut, or other epithelial surfaces.
6. *Convenience and cost.* Oral drug administration is the easiest and least expensive way to give drugs. However, because of variable and often limited oral bioavailability of cancer drugs, few cytotoxic drugs are given by this route. Intravenous administration guarantees entry of the full dose into the bloodstream. Intermittent bolus schedules are usually favored, although pharmacokinetic or cell cycle kinetic considerations can pose strong arguments for prolonged infusion schedules. An example of such a cell cycle phase-specific drug is the antimetabolite 5-FU. An improved response rate and less toxicity result when 5-FU is administered as a continuous infusion for 48 hours, rather than the daily times five schedule.[61] Oral therapies represent a further advance in terms of convenience and cost, provided they are equally effective. Capecitabine, an oral prodrug of 5-FU, appears to be equally active as infusional 5-FU when combined with oxaliplatin in patients with metastatic colorectal cancer.[62]
7. *Targeted drugs* are usually administered on a schedule that ensures long-term, continuous exposure to the agent. Monoclonal antibodies administered every 3 to 4 weeks provide prolonged exposure because of their very long plasma half-life (2 to 3 weeks), whereas the daily oral dosing of targeted drugs is required to produce trough levels of drug in plasma above the minimum inhibitory concentration.

The Special Problem of Drug Sanctuaries

Although drug distribution from the bloodstream into most tissue compartments occurs with relative ease, certain "sanctuary" sites present special barriers to penetration. In general, tumor blood vessels proliferate in response to the needs imposed by rapid tissue proliferation, but the resulting vessels tend to be unusually permeable, allowing permeation of protein into the extracellular space and resulting in an increased interstitial pressure, sluggish flow, and poor drug penetration. These changes are corrected by antiangiogenic therapies such as bevacizumab and small-molecule VEGFR inhibitors (see later discussion) and may allow better penetration of oxygen and small molecules.

Other tissue sites tend to exclude many drugs. Most chemotherapy agents achieve low concentrations in the testes, vitreous humor of the eye, and the brain when administered systemically. The brain is protected by blood-brain barrier, a compact alignment of microvascular endothelium, which limits the passage of large molecules and hydrophilic drugs. In addition, there are active MDR export pumps in the vascular endothelium of the brain.[63] Disruption in the barrier by tumor vessels associated with metastases or primary brain tumors allows for greater penetration of drugs into the CNS, but the barrier seems to be maintained at the infiltrating edge of tumor. Although radiation therapy is the most effective means of treating many types of brain metastases, systemic chemotherapy or immunotherapy may benefit patients with CNS tumors. Temozolomide, a highly lipophilic alkylating agent, extends the survival time of patients with malignant glioma when it is used in conjunction with irradiation. Other drugs clearly reach intracranial tumors.[64]

EGFR inhibitors and second-generation ALK inhibitors have demonstrated activity against brain metastases resulting from NSCLC.[19] High-dose methotrexate is the preferred mode of treatment for primary CNS lymphomas, although the ratio of cerebrospinal fluid (CSF) to blood concentration of drug is less than 0.1.[65,66] Even antibodies, such as ipilimumab may be effective against intracranial tumors. The VEGF inhibitor bevacizumab depletes a systemically circulating growth factor. It is approved for second-line treatment for patients with glioblastoma multiforme with tumor progression after temozolomide and radiotherapy.[67]

PREDICTING TUMOR RESPONSE

Pharmacogenomics may enable the clinician to determine which drugs will be poorly tolerated by an individual and may allow more rational selection of a particular antineoplastic agent in the individual patient. For example, a high level of thymidylate synthase, in some tumors, the result of a polymorphism in tandem repeats in the gene's promoter region, predicts for resistance to 5-FU in patients with colorectal cancer.[68] Genomic polymorphisms in the DNA repair genes *ERCC1* (formerly designated *XPD*) and *XRCC1* may be prognostic factors in patients with NSCLC treated with cisplatin.

Transcriptional silencing may alter gene expression and affect the outcome of chemotherapy. O-6-methylguanine-DNA methyltransferase (MGMT) is an enzyme responsible for DNA repair following alkylating agent chemotherapy. The gene may be silenced in tumors by methylation of its promoter, creating vulnerability of the tumor cell to DNA damage. MGMT gene silencing occurs in about 20% of glioblastomas and is associated with a high response rate to the alkylating agent temozolomide in patients with glioblastoma and neuroendocrine tumors.[69]

As discussed previously, it is now possible to predict which patients with NSCLC, melanoma, or colorectal cancer are more likely to benefit from a particular targeted therapy. In the case of NSCLC, those patients whose tumors possess an activating mutation in the ATP-binding pocket of the RTK are more likely to benefit from the use of an EGFR-TKI or an inhibitor of the ALK receptor tyrosine kinase. Similarly, patients with colorectal cancer whose tumors possess a mutation in either KRAS or BRAF, resulting in their constitutive activation, are unlikely to benefit from a monoclonal antibody inhibiting EGFR.

DRUG RESISTANCE

The fractional cell kill hypothesis must be modified to incorporate concepts of drug resistance. In practice, the response to an initial cycle of chemotherapy may be much greater than to subsequent doses, and in many solid tumors, such as breast cancer and lung cancer, tumors may again grow rapidly after an initial response. The explanation for this finding lies in the problem of drug resistance and the ability of cancer drugs to select for drug-resistant cells. Mechanisms of resistance may affect any of the steps necessary for drug action: entry of drug into tumor cells by means of active transporters, enzymatic drug activation, action at a molecular target within cells, and even the processes in the cell that trigger cell death. Although many examples of drug resistance have been characterized in model systems, the understanding of resistance in clinical practice remains incomplete. Some of the more common mechanisms in model systems, and evidence for the same mechanism in the treatment of human tumors are given in Table 9-5.

TABLE 9-5 Drug Resistance Mechanisms in Cancer Therapies

Molecular Mechanism	Example	Drugs Affected
Decrease in cellular uptake	Deletion of folate transporter Deletion of nucleoside transporter	Methotrexate, pemetrexed Ara-C, gemcitabine
Increase in cellular efflux	Increased multidrug resistance (CD116) expression or gene amplification	Vinca alkaloids, anthracyclines, taxanesl, etoposide, topotecan
Alteration of target protein	Mutant dihydrofolate reductase Mutant topoisomerase I Mutant tubulin BCR-ABL mutations or amplification EGFR mutations EML4-ALK mutations BRAF splicing variants or BRAF amplification KIT mutation, KIT amplification, or PDGFR alterations	Methotrexate Topotecan Vinca alkaloids, paclitaxel Imatinib, dasatinib, nilotinib Gefitinb, erlotinib, cetuximab, crizotinib Crizotinib Vemurafenib Imatinib
Alternative pathway activation	Multiple mechanisms (see reference 19 for details)	Gefitinib, erlotinib, crizotinib, cetuximab, panitumumab, imatinib (GIST), vemurafenib, bevacizumab, trastuzumab
Deletion of target protein	Deletion of topoisomerase I Deletion of topoisomerase II	Topotecan Anthracyclines, etoposide
Decreased activation of drug in tumor	Deoxycytidine kinase deficiency Decreased folylpolyglutamate synthetase	Ara-C, fludarabine, cladribine Methotrexate, pemetrexed
Increased detoxification	Increased glutathione or glutathione transferase	Alkylating agents, platinum analogs
Enhanced DNA repair	Increased nucleotide excision repair Increased O-6-alkyl-guanine alkyl transferase	Platinum compounds, alkylating agents, Procarbazine, temozolamide Nitrosoureas
Defective recognition of DNA adducts	Mismatch repair defect	Platinum compounds, 6-mercaptopurine, nitrosoureas
Alteration of apoptosis pathways	Mutant TP53, BCL2	Alkylating agents, antimetabolites, EGFR inhibitors, RAS/RAF/MEK pathway inhibitors

With few exceptions, single-agent treatment of cancer produces only temporary responses. This rule applies as well to the targeted agents, where resistance to agents such as EGFR inhibitors develops through mutation in the binding site of the target protein or through activation of an alternative proliferation pathway (C-MET). Resistance likely antedates exposure to the drugs but is a spontaneous product of the underlying genetic instability of tumors. Although the sensitive fraction of cells is killed with each dose of drug, drug-resistant mutants proliferate and replace their sensitive counterparts under the selective pressure of drug. Based on the experience of antibiotic treatment of bacterial infections, it was logical to combine drugs that had different mechanisms of resistance. If the frequency of mutation to resistance is 1 cell of 10^{-6}, the chances of any cell being simultaneously resistant to two drugs would be the product of these probabilities, or 10^{-12}. Goldie et al have argued convincingly that the best strategy for chemotherapy is to employ as many non–cross-resistant agents as early as possible in the treatment regimen.[70] In addition, the use of radiosensitizing chemotherapy with irradiation can have major benefits for local control of tumor and for reducing local morbidity related to surgery in tumors of the aerodigestive tract and have the added potential of synergistic DNA damage.[71-74]

In using drug combinations, certain qualifying considerations have to be kept in mind:

1. Drug resistance mechanisms, such as the overexpression of the MDR transport system, may confer resistance to multiple drugs, as may defects in cell death pathways, enhanced DNA repair, poor tumor blood flow, or other biological factors[2]
2. Simultaneous administration of multiple agents may lead to overwhelming toxicity, unfavorable drug interactions at the molecular target, or unwanted pharmacokinetic interactions. Because of negative interactions, multiple agents may be given sequentially rather than simultaneously, with more favorable outcome.

COMBINATION CHEMOTHERAPY

With few exceptions, multiagent therapy has proved more effective than single-agent therapy in the treatment of most human cancers. In general, the choice of drugs for combination therapy is made on the basis of mechanistic, pharmacokinetic, and toxicologic considerations. The most important criteria for including drugs in a combination regimen are the following:

1. single-agent activity in the disease to be treated;
2. nonoverlapping toxicities, allowing full doses of each drug to be used;
3. different mechanisms of action; and
4. nonoverlapping mechanisms of resistance.

These are not hard and fast rules. There are numerous examples of clinical regimens that use multiple alkylating agents, multiple natural products (despite their shared cross-resistance), or combinations of myelotoxic drugs. Often, these choices are dictated by impressive single-agent activity in the tumor being treated and the uncertainty of knowledge about clinical mechanisms of drug resistance. For example, individual alkylating agents differ in their mechanisms of activation, transport, and adduct formation. Their DNA adducts are repaired by a variety of enzymatic pathways. It is not clear which of these factors contributes to clinical drug resistance (see Table 9-5). Although these agents belong to the same class of drugs, in the absence of more complete knowledge about resistance, it is possible to construct a reasonable argument for combining different alkylating agents.

The development of targeted drugs has greatly expanded opportunities to address resistance to cytotoxic chemotherapy. Drugs such as bevacizumab and trastuzumab have significantly enhanced the effectiveness of cytotoxic chemotherapy of colon and breast cancers, respectively. Trastuzumab blocks signaling through the MEK-ERK and PI3K pathways that promotes proliferation and survival, whereas bevacizumab normalizes tumor vasculature and improves access of cytotoxics to poorly perfused tumor cells. The further development of targeted drugs in combination may allow successful inactivation of multiple resistance pathways, as exemplified by the joint use of B-RAF and MEK inhibitors in melanoma, a strategy that holds great promise for cancer treatment. To implement this strategy, it is necessary to perform molecular profiling of tumor samples on a routine basis, a capability not widely available in current practice, and one must be able to combine drugs without experiencing excessive toxicity.

SUMMARY

The potential for cancer chemotherapy to cure of metastatic cancer has been fully realized in only a few clinical circumstances, primarily those in which a rapidly proliferating hematologic cancer has been treated aggressively with a multiagent regimen. Solid tumor chemotherapy with curative intent must be given early in the course of disease, carefully interdigitated with irradiation and surgery, and administered in maximal doses. Because of the likelihood of serious side effects and drug–irradiation interactions, such regimens are difficult to design and implement. Thus far, the key drugs for such combinations have been 5-FU and cisplatin or carboplatin. The development of optimal chemoradiotherapy regimens must take into account the advantages and disadvantages of sequential versus concurrent combined-modality approaches. To maximize therapeutic synergy and minimize toxicity, protocol planning must pay careful attention to potential drug–irradiation interactions, drug pharmacokinetics, and drug–drug interactions. The patient population being treated (often, elderly patients with associated conditions such as heart disease or hypertension and other evidence of organ dysfunction) may have limited ability to tolerate the rigors of combined-modality treatment. Advances in cancer biology, particularly in the areas of angiogenesis and metastasis, will lead to newer, more tumor-specific, less-toxic approaches to cancer control. Recent strides in molecular profiling of an individual's tumor may lead to a more rational, tailored design of a patient's treatment, and ultimately beneficial therapy, while sparing the unnecessary toxicity and expense of treating with an ineffective drug.

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A full list of cited references is published online at www.expertconsult.com.

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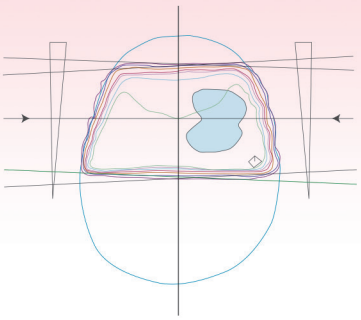
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CHAPTER

10 Imaging in Oncology



Ersan Altun, Valerie S. Jewells, and Julia R. Fielding

Computed tomography (CT) has been the mainstay radiologic modality for detection of primary malignant disease and metastatic disease for many years. Advantages of CT include the speed, patient comfort, and high spatial resolution. The technology of CT scanners has improved dramatically for the last 15 years. The present generation of scanners can obtain a larger volumetric data during each turn of gantry by using single tube (single source) or double tubes (dual source). The state-of-the-art single source scanners can obtain 320 to 640 slices and dual-source scanners can obtain 256 slices per gantry rotation allowing image acquisition of the whole body in seconds. These sophisticated scanners enable the reconstruction of multiplanar reformatted (MPR) images including, but not limited to, the coronal and sagittal planes; MPR maximum and minimum intensity projection images as well as three-dimensional (3D) images including volume rendering (VR), surface shaded display (SSD), or fused 3D-MPR images of any desired organ or structure. These scanners are also capable of performing dynamic time-resolved or four-dimensional (4D) angiography and perfusion imaging, which can demonstrate the entire circulation and perfusion of the desired vessels, structures, or organs in seconds. Additionally, fluoroscopic and kinematic images of the desired organs and structures can be acquired. CT is the best technique for the evaluation of lungs and vessels. CT is also successful for the evaluation for the neck, mediastinum, abdomen, and pelvis.

Disadvantages of CT include exposure to ionizing radiation. The average effective dose for the chest is 7 to 15 mSv, abdomen 8 mSv, and pelvis 6 mSv. Patients must also often drink barium or iodine-based contrast material.

Visceral organ and vascular assessment require the intravenous injection of relatively large volumes (50 to 100 mL) of iodine-based intravenous contrast agent.[1] Contrast agents increase the conspicuity of tumors and enable the visualization of vessels allowing for accurate surgical, interventional, and therapeutic planning. In rare cases contrast injection results in allergic-like reactions, ranging from urticaria to shock.[2-9] The overall incidence of allergic-like reaction is 0.2% and the incidence of serious acute allergic-like reactions is 0.04%.[2,3] The mortality rate is 0.9/100,000 to 2.1/1,000,000 injections.[2,5,6] These rates are lower than those for the administration of the antibiotic penicillin. Active asthma or a history of multiple allergies to food, drugs, or the environment increase the risk of an allergic reaction to iodine-based intravenous contrast minimally.[9] However, the history of a prior reaction is the best indicator of a future adverse event. The likelihood of a recurrent reaction is in the range of 8% to 25%.[9] These patients can be premedicated with steroids to decrease the risk.[9]

Another possible adverse outcome is that of contrast media–induced nephropathy. This is an important consideration because renal impairment is present in a significant proportion of oncology patients. In general, patients with serum creatinine levels of less than 1.5 mg/dL can undergo intravenous contrast-enhanced CT without significant risk of nephropathy.[10] For those patients with elevated serum creatinine levels, vigorous oral and intravenous hydration for several hours before and after the examination can significantly decrease the risk of renal damage.[9]

The now widespread use of F-18 fluorodeoxyglucose (FDG)–enhanced fused positron emission tomography/computed tomography (PET/CT) images allows for localization of metabolically active sites of disease accurately with the help of fused CT images. The most important advantage of PET/CT examination is the capability of whole body imaging enabling metabolic and anatomic information. It is particularly helpful in primary lung and esophageal cancers and lymphoma. Although FDG is the most commonly used agent, new specific agents may be used routinely in the near future.

Magnetic resonance imaging (MRI) has become the preeminent tool for the evaluation of the central nervous system and musculoskeletal system since its introduction into routine clinical practice. It has been also used extensively for head and neck imaging. Over the past 15 years, MRI has also been widely used for body imaging including the thorax, abdomen, and pelvis. Thus, MRI has become important in staging cancers in every part of the body because of its higher soft-tissue contrast resolution and improved identification of normal anatomy. MRI is the most accurate and sophisticated technique for the evaluation of central nervous system, musculoskeletal system, and head and neck tumors. MRI has also become the most accurate technique for the evaluation of mediastinum, diaphragm, chest wall, and pelvis. However, the motion artifacts, which are the most important drawback of MRI, may especially limit interpretation of chest and abdomen studies and the visualization of gastrointestinal tract. Despite these limitations, with the use of proper techniques and motion-resistant protocols, MRI has been proven to be a successful method for evaluation of the solid organs of the abdomen.

The lack of available protons in the air-filled lungs makes MRI of limited value in the detection of pulmonary nodules, airways, and lung cancer. MRI is the most accurate and safe method for the evaluation of primary and secondary tumors involving the heart chambers, pericardium, and great vessels. MRI is also successful for the evaluation of large and medium sized arteries and veins. However, because of its lower spatial resolution compared to CT, evaluation of small vessels is not as successful. CT remains the test of choice for the evaluation of patients with trauma and in intensive care because it provides comprehensive information in seconds without any motion artifacts.

Most oncology studies done on MRI use an intravenous contrast material composed of a gadolinium chelate. The incidence of acute adverse events is 0.08% and the vast majority of them are mild.[11,12] The incidence of anaphylaxis is 0.001% to 0.01% and the overall death rate according to Food and Drug Administration is less than one case per million injections.[12,13] In healthy patients, the risk of nephrotoxicity is virtually nonexistent. However, in 2006, a new disease entity called

nephrogenic systemic fibrosis (NSF) was associated with the use of gadolinium-based contrast agents in patients with acute renal failure and stage 4 and 5 chronic renal insufficiency with an estimated glomerular filtration rate <30 mg/dL/1.73 m^2.[14] NSF is a systemic fibrosing disorder, which may be fatal, and no effective treatment has been identified.[14] NSF has been particularly associated with the use of specific type of gadolinium chelates having low stability including gadodiamide, gadopentate dimeglumine, and gadoversetamide.[14-17] These agents are now contraindicated in patients with acute renal failure and stage 4 and 5 chronic renal insufficiency.[14] Cautious use of all gadolinium agents in patients with renal insufficiency, including the implementation of lower dose policy and preferential use of more stable agents, decreased the incidence of NSF significantly in the last 5 years.[14,18]

Intravenous contrast volumes used in MRI are in the range of 1 to 20 mL in adults and pediatric patients depending primarily on the weight of the patient. Patients must be cooperative and be able to lie supine for 10 to 20 minutes. The presence of ferromagnetic implants, including cardiac pacemakers, ocular implants, and aneurysm clips prohibits performance of MRI.[19] Surgical clips, artificial joints, and heart valves can be safely imaged.

MR-PET systems, which have the ability to combine the morphologic imaging features of MRI with metabolic imaging data of PET, have recently begun to be used in clinical practice. Although the clinical role of this imaging modality has not been established, the combination of functional and anatomic imaging may play an important role in the evaluation of treatment response.

In the following sections, the imaging appearances of common primary and metastatic cancers in the head, neck, chest, abdomen, and pelvis will be demonstrated using CT, MRI, and, in some cases, PET/CT images obtained with standard imaging protocols. Imaging of primary breast cancer is omitted because it is generally performed using mammography and ultrasound.

MRI of the head and neck including central nervous system, spine, abdomen, and pelvis usually consists of T1-weighted (black fluid), T2-weighted (bright fluid), and contrast-enhanced images obtained sequentially using T1-weighted images in multiple planes. In addition to the body coil, surface coils are available for each part of the body, increasing both signal to noise and spatial resolution. Most tumors have increased T2 signal compared with adjacent normal tissue and demonstrate characteristic enhancement patterns. Bone imaging often requires fat saturation to demonstrate marrow changes as well as comparison with plain radiographs.

Picture archiving and communications systems (PACS) allow the images to be viewed at multiple sites simultaneously by radiologists and clinicians.

IMAGING OF THE BRAIN

The goal of imaging is to stage tumor extent and assess for tumor type. Therefore, all patients with brain tumors will need imaging for extent of disease, to aid surgical and radiation therapy planning, and determine tumor type/prognosis.[20] Evaluation of primary and metastatic brain tumors is best performed with postcontrast MRI because postcontrast CT is less sensitive for lesion conspicuity and assessment of disease extent.[21] In addition to conventional MR techniques, multiple nonconventional MRI techniques have proven to be useful for assessment of tumor type and grade as well as therapeutic response. These include diffusion weighted imaging (DWI), perfusion imaging (PI), and MR spectroscopy (MRS) and have shown promise particularly when combined for separation of tumor grades II and III at least with oligodendrogliomas.[22]

Using conventional MRI, malignant potential is related to lesion size, extent of T2/FLAIR abnormality, enhancement, and necrosis. The T2/FLAIR abnormality needs to be assessed because in many tumors it reveals more about tumor extent than contrast enhancement as the tumor infiltrates beyond the mass lesion into the brain structures and often also even beyond the extent of the T2/FLAIR abnormality. On conventional MRI, necrosis and enhancement are features that are consistent with higher grade of primary brain tumors based on the World Health Organization (WHO) grading criteria. However, be aware that conventional MRI simply assesses morphologic criteria.[23] By WHO criteria, those tumors that are lower grade (i.e., grades I and II, do not necrose, and are less likely to enhance). One tumor that does not appear to follow these rules is the pediatric pilocytic astrocytoma (grade I), which often presents in the posterior fossa and enhances with cystic areas that can be misinterpreted as necrosis.

Brain tumors in adults are divided into intraaxial and extraaxial tumors. Extraaxial tumors are typically dural meningiomas (grade I) or less commonly atypical meningiomas (grades II to III) that are more commonly in patients older than 65 in nonskull base regions, are the second-most common intracranial tumor, and are most commonly seen at the cerebellopontine angle regions and vertex. Higher grade, extraaxial tumors such as angiosarcomas and malignant meningiomas usually cannot be definitively differentiated by conventional imaging before surgery, although obvious infiltration portends a poorer prognosis (Figure 10-1, *A*). However, apparent diffusion coefficients have recently shown some promise in differentiating lower and higher-grade meningiomas.[24] Other dural-based disease processes in the differential include metastases, leukemia, lymphoma, sarcoidosis, Wegener's, tuberculosis, and meningitis.

Intraaxial adult brain tumors are most frequently derived from astrocytes or oligodendrocytes and are most commonly high grade (i.e., glioblastoma multiforme; Figure 10-1, *B*) and gliomatosis cerebri (WHO grades III and IV). In order of descending frequency are astrocytomas (grades I to II), oligodendrogliomas (WHO grades II to III), lymphomas and gliomatosis cerebri (WHO grades III to IV). Factors that result in reduced enhancement and therefore an incorrect assumption of lower grade or better tumor response include steroid administration[25] and antiangiogenesis chemotherapies.[26]

Also impacting on appropriate diagnosis are similar appearance patterns with different tumor types. For example, GBM and lymphoma both have a tendency to cross the corpus callosum and enhance/necrose, which makes differentiation difficult. Generally, lymphoma is found in patients who are HIV+, has a significantly better prognosis, and different assessment needs for pathologic diagnosis. MRI features that may help distinguish between GBM and lymphoma are dark T2 signal and restricted diffusion on DWI (Figure 10-1, *C-E*) as a result of dense cellularity.

An additional method of nonconventional tumor assessment is MRS, which can assist determination of tumor grade and differentiation of a single metastasis from a primary brain tumor. Because primary brain tumors are infiltrative in nature, their edges will be less well defined with regard to changes in metabolites unlike metastatic disease (Figure 10-1, *F-G*).[27] MRS measures 1 cm cubes or voxels which, when performed together as many voxels adjacent to each other as multivoxel MRS, can assess metabolite concentrations over the entire tumor and adjacent regions.

Other discriminating factors for a metastatic lesion include typical peripheral location at the gray-white matter junctions, significant surrounding edema, and multiplicity. Using MRS, higher-grade tumors will have lower N-acetyl-acetate (NAA) levels in correlation with the number of neurons and axons in

the voxel being destroyed (Figure 10-1, *H-J*). Higher-grade tumors will demonstrate higher choline (Cho) levels secondary to rapid cell turnover. Typically, values of NAA and Cho are assessed with regard to creatinine (Cr) concentrations, as NAA/Cr and NAA/Cho ratios as Cr levels typically remain stable. However, a more accurate method of absolute metabolite quantification can be performed with programs such as the LC model.[28] Other MRS markers of higher-grade malignancy are lactate and lipid, commonly seen in GBMs and consistent with anaerobic metabolism and myelin destruction respectively.[29] Occasionally, MRS will assist in the differentiation of GBM and tumefactive multiple sclerosis (MS) by assessing other regions of the brain for lipid levels. Also, for differentiation of tumefactive MS, one looks for a broken ring of enhancement[30] and assesses other regions for T2/FLAIR lesions in typical locations for MS including the corpus callosum (radiating outward as Dawson fingers) or in other typical locations including the periventricular white matter and subcortical regions. If still uncertain and MS is suspected, follow-up imaging to identify new lesions over time may avert unnecessary biopsies. Also within the differential are infectious lesions/abscesses. In general, abscesses will show restricted diffusion unlike primary brain tumors and they may also exhibit the presence of "daughter" or secondary lesions that are adjacent to the larger "mother" lesion. Another type of metastatic disease that the clinician needs to be aware of is leptomeningeal metastases (Figure 10-2, *A*-C) that can coat the brain surfaces and because of free cerebrospinal fluid (CSF)

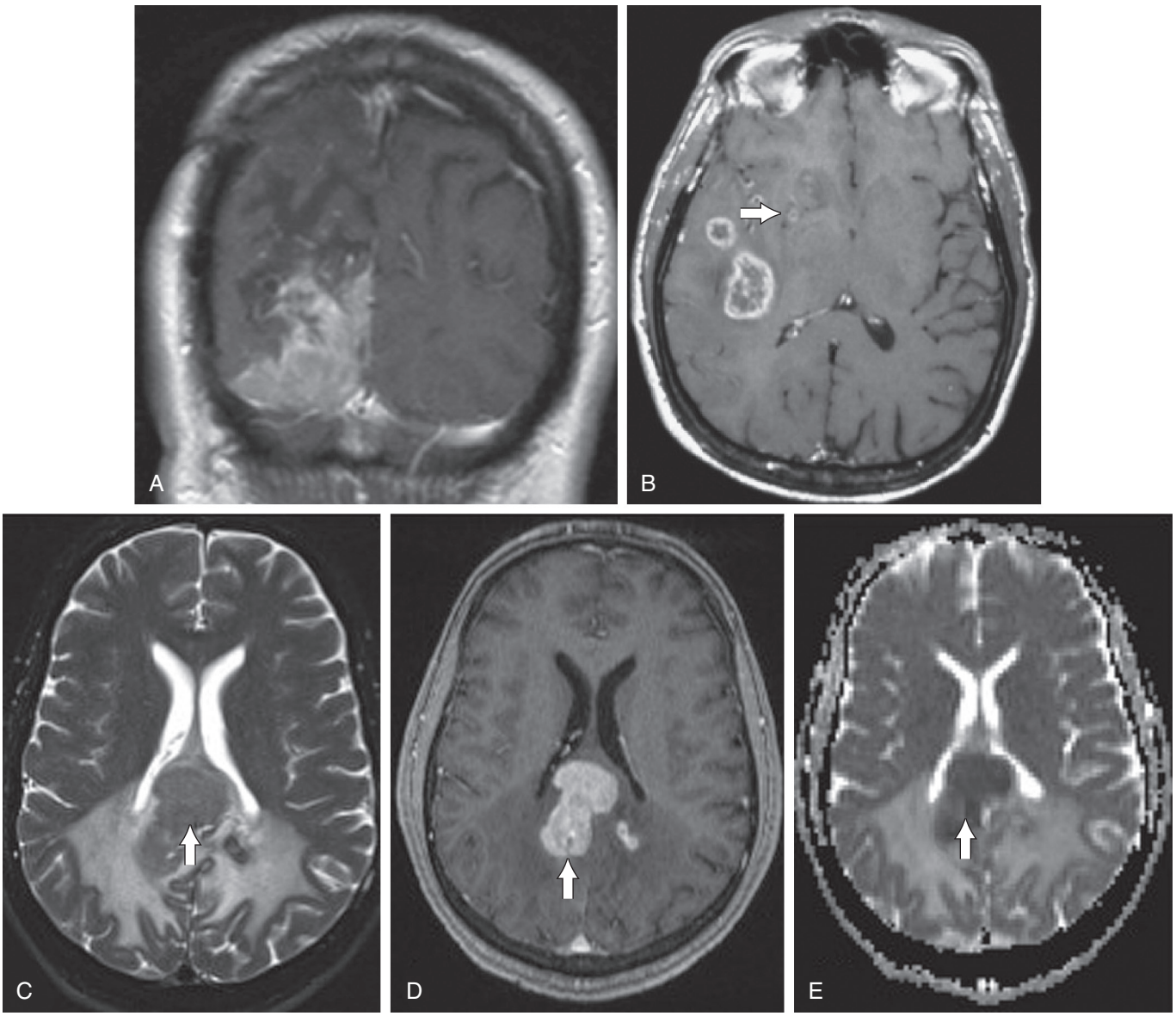


Figure 10-1 **A,** Meningiomas are extraaxial tumors whose margins are usually well defined. This meningioma is atypical and has poorly defined margins that can mean higher grade and more difficult resection **B,** This glioblastoma multiforme GBM demonstrates typical necrosis and enhancement and is centered in the white matter not at the gray-white matter junction as is typically seen with metastases. **C-E,** This case reveals perivascular spread *(arrow, b)* a poor prognostic indicator. Lymphoma can be difficult to differentiate from GBM because both tumors will exhibit increased T2/FLAIR signal **(C),** enhancement **(D),** and be in a butterfly distribution across the corpus callosum. Also commonly seen is low T2 signal (**C,** *arrow*) and low signal on the apparent diffusion coefficient (ADC) map consistent with restricted diffusion (**E,** *arrow*) in lymphoma.

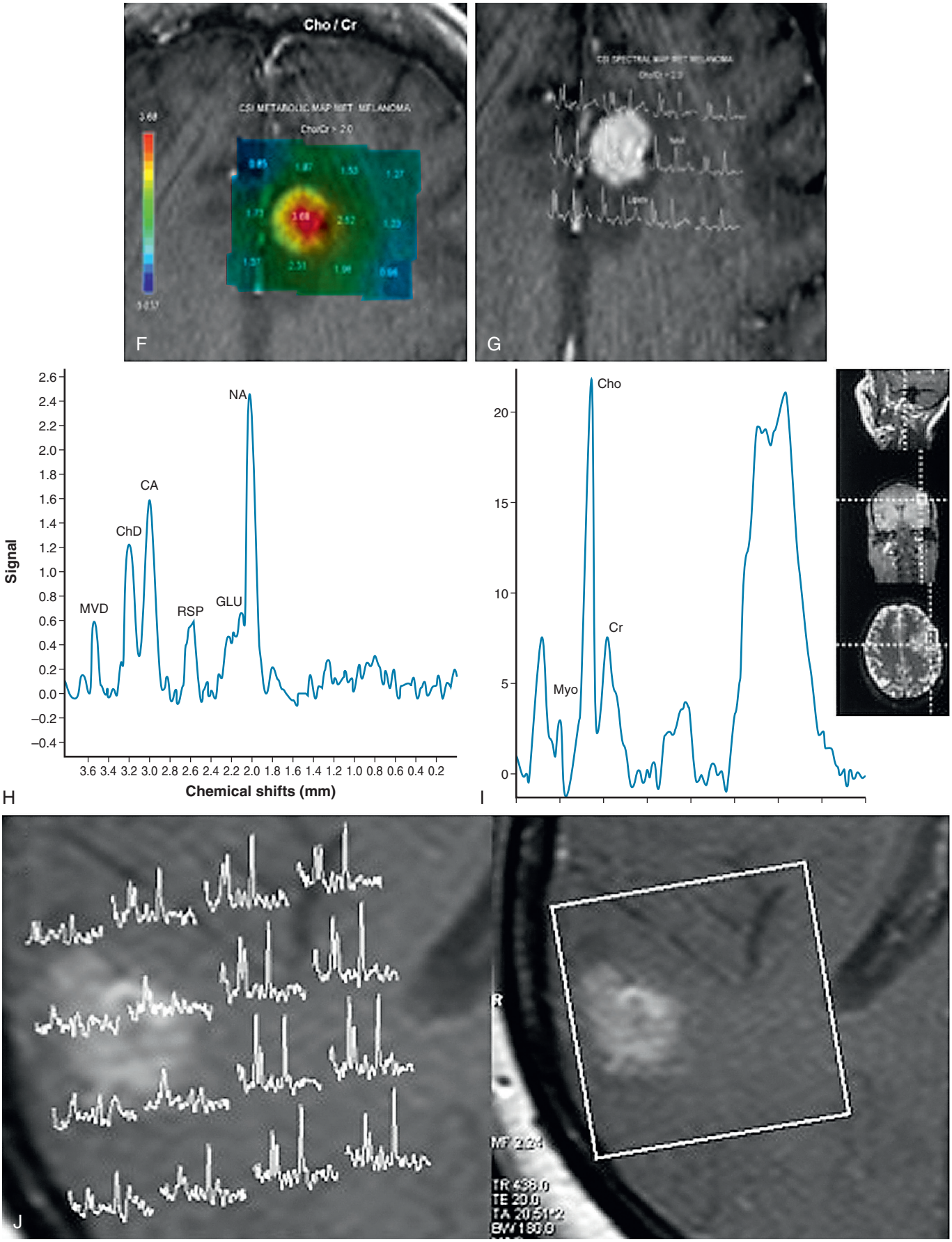


Figure 10-1, cont'd **F-J,** The above gray-white matter junction metastatic melanoma lesion demonstrated an abrupt cut off in of MR spectroscopy. A normal spectrographic pattern **(H)** while versus a typical tumor pattern **(I)** of elevated choline (*Cho*) from increased cell division, depressed N-acetylaspartate (NAA) from neuronal loss, and elevated lipids in a GBM.

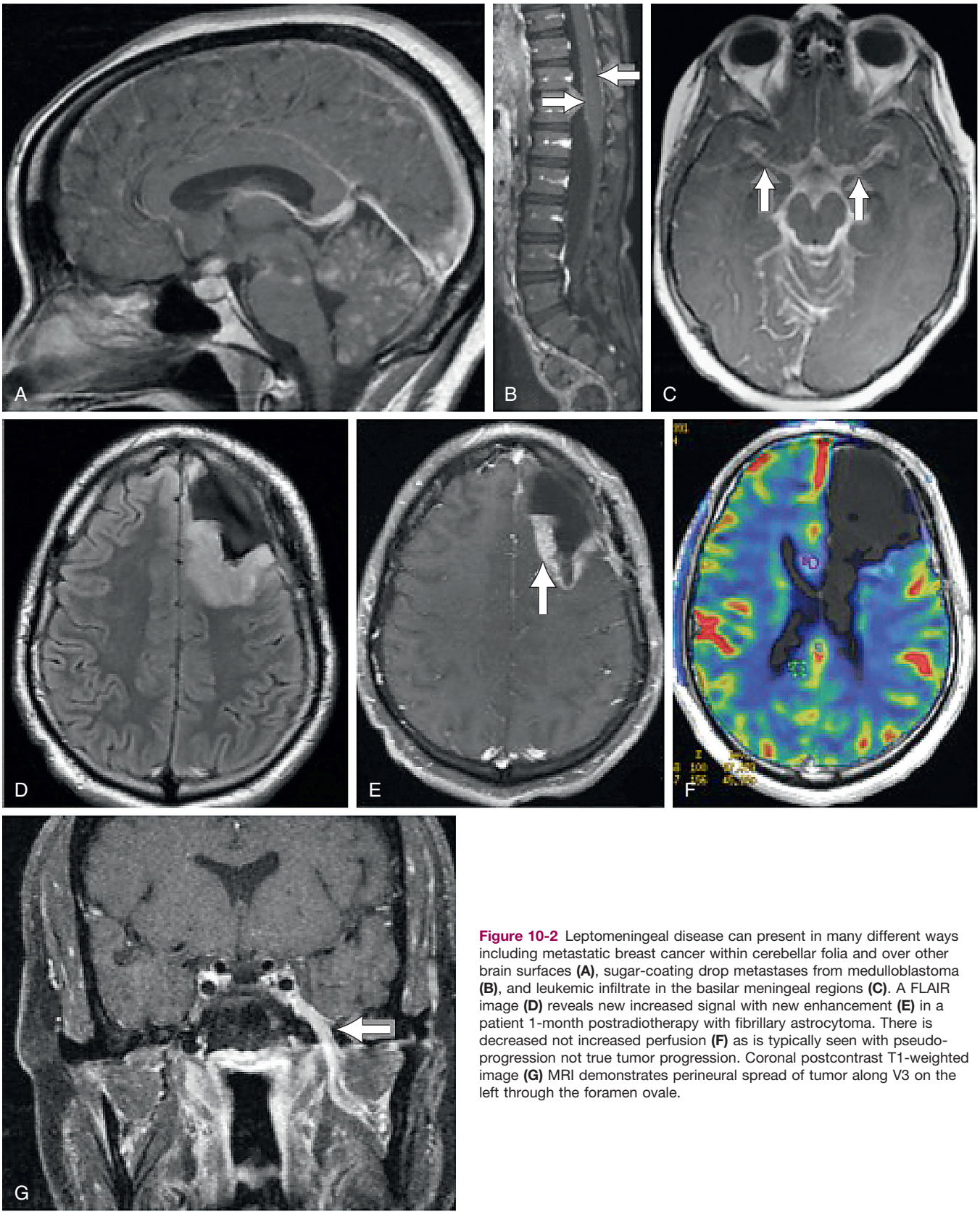


Figure 10-2 Leptomeningeal disease can present in many different ways including metastatic breast cancer within cerebellar folia and over other brain surfaces **(A)**, sugar-coating drop metastases from medulloblastoma **(B)**, and leukemic infiltrate in the basilar meningeal regions **(C)**. A FLAIR image **(D)** reveals new increased signal with new enhancement **(E)** in a patient 1-month postradiotherapy with fibrillary astrocytoma. There is decreased not increased perfusion **(F)** as is typically seen with pseudo-progression not true tumor progression. Coronal postcontrast T1-weighted image **(G)** MRI demonstrates perineural spread of tumor along V3 on the left through the foramen ovale.

flow tumor cells can also be deposited on the surface of the spinal cord (Figure 10-2, *C*).

PI, another nonconventional MRI technique determines tumor grade using time to peak (TTP), mean transit time (MTT), cerebral blood flow (CBF), and cerebral blood volume (CBV), which correlate with tumor grade and angiogenesis properties seen in higher-grade tumors.[31] However, the greatest use of PI is for the exclusion of residual or recurrent disease compared to pseudo-progression. Posttreatment brain tumors can be difficult to assess because of a process called pseudo-progression. In pseudo-progression there is mass-like enhancement or necrosis mimicking an active or recurrent tumor that is actually a result of tumor necrosis. Therefore, there will not be increased perfusion as occurs in recurrent or residual tumor[32] (Figure 10-2, *D-F*). MRS has also been useful for determination of pseudo-progression.[33]

IMAGING OF THE HEAD AND NECK

Typically, patients with head and neck cancers are initially imaged with CT. CT is more convenient for patients with large neck masses who may have respiratory compromise. However, the use of MRI is often advocated in children to reduce radiation dose. In performing neck CT, we use 75 mL of contrast with a 45-second delay for axial scanning and then reconstruct the coronal and sagittal planes for assessment of tumor extent. The contrast delay is needed for optimal tumor and mucosal enhancement. Also, employment of butterfly images through the oral cavity will help avoid dental artifact. In general, CT is preferred over MRI to identify the primary head and neck tumor extent if imaging in the oropharngeal, laryngeal, and hypopharyngeal regions is performed in all three planes, because of swallowing and respiratory artifact.[34]

However, MRI is better for perineural spread along cranial nerves (CNs) V (Figure 10-2, *G*) and VII as well as for tumor localization in patients who cannot receive contrast.[35] MRI is also helpful for assessment of dural involvement with intracranial extension and has accuracy rates of 84% for determination of dural involvement.[36] MRI also demonstrates better definition of the skull base structures including the pharyngobasilar fascia, sinus of Morgagni, cartilaginous Eustachian tube, and levator veli palatine muscles. Therefore, for nasopharyngeal carcinoma including sino-nasal undifferentiated carcinoma (SNUC) and esthesioneuroblastoma, or cases of malignant parotid masses, MRI is the preferred study. Our standard protocol for skull base assessment includes axial 4 mm T1/T2/3D MPD rage postcontrast axial and coronal images through the entire brain as well as 0.7 mm isotropic T2 weighted CISS in the axial plane through the region of the skull base.

For assessment of cartilaginous involvement of the larynx, MRI and CT are equally accurate.[37] With regard to nodal assessment CT is slightly superior to MRI,[38] unless SPIO particles are added to the neck MRI protocol.[39] Abnormal nodes will not uptake SPIO particles and will not be dark on T2. Therefore, with SPIO, MRI will surpass CT and likely also PET for assessment of nodal involvement, but it is not approved by the Food and Drug Administration for use in the United States. Ultrasound (US) with color Doppler can also be used to assess benign and malignant nodes and be used for biopsy guidance of suspicious nodes and is equal to CT for malignant nodal detection.[40] US is the preferred method of guidance for thyroid biopsy. PET/CT for head and neck cancers staging is most cost effective in cases of unknown primary, T3/T4 stage and multiple bilateral neck nodes because distant metastases are more likely. It is also useful for the N0 neck to forgo neck dissection and to help with the decision-making process in cases in which surgical resection would be extensive and the patient may be best treated with chemotherapy and radiation therapy. PET/CT is further discussed in Chapter 11.

IMAGING OF THE SPINE

If a primary or metastatic tumor is suspected in the spine, imaging is best performed with pre- and postcontrast MRI in axial and sagittal planes. In general, primary tumors of the cord (i.e., intramedullary) include astrocytomas (40%), ependymomas (50% to 60%), and hemangioblastomas. Because ependymomas arise from ependymal cells lining the central canal, they are typically central in location and are more common in the cervical than thoracic regions followed by the filum. Filar ependymomas are usually myxopapillary type, can seed the subarachnoid space, and are more likely to recur than other types of ependymomas,[41] suggesting that long-term follow-up is necessary. Eighty-four percent of ependymomas exhibit cyst formation and a hemosiderin cap from hemorrhage is seen in nearly half of the cases. Spread can be retroperitoneal as well as inferiorly into the sacro-coccygeal region.

Astrocytomas occur in children as well as adults in the third to fifth decades and are more common in males than females (1.3:1). Astrocytomas are more common in the thoracic than cervical regions, are more infiltrative, associated with a syrinx, eccentric in location, and up to 30% may not demonstrate enhancement.[42] Therefore, astrocytomas are in the differential diagnosis of nonenhancing cord lesions. Hemangioblastomas another primary spinal cord tumor are low grade, capillary rich, and seen in young women sporadically or males with Von-Hippel Lindau syndrome. Although typically in the thoracic, cervical, lumbar, sacral regions; respectively, hemangiomblastoma are also often within the cerebellum. These lesions typically have a cystic component with a mural enhancing nodule. Extramedullary tumors include meningiomas, schwannomas/neurofibromas, and metastases, often leptomeningeal (Figure 10-2, *B*) and often drop metastases from brain tumors, or directly extending from bone metastases. Metastases to the cord are uncommon. We have found the use of diffusion tensor imaging for determination of tumor resectability to be useful, and this is a technique you may wish to add to your preoperative assessment.[43-45]

IMAGING OF THE CHEST

Primary Tumors of the Lung

Lung cancer is the leading cause of cancer-related death in the United States and the world. Malignant neoplasms of the pulmonary parenchyma and bronchi mainly consist of two histologic types: (1) non–small cell type (80% to 85%) and (2) small cell type (15% to 20%).[46-49] Non–small cell cancer includes three different subtypes: (1) squamous cell, (2) large cell, and (3) adenocarcinoma.[46-49] Treatment strategies mainly differ depending on the non–small cell and small cell type. The three subtypes of non–small cell group have similar treatment options and a better prognosis compared to small cell type when the disease is localized.

Imaging Strategies

Radiologic studies are used for the diagnosis, staging, and evaluation of treatment response.

Lung cancer is most frequently discovered on chest radiographs. When there is a suspicion of lung cancer either clinically or on a chest radiograph, contrast-enhanced CT scanning is the technique of choice for the detection and characterization of a primary mass. Contrast-enhanced CT enables limited local staging with the identification of additional nodules, assessment of size and location of lymphadenopathy, and

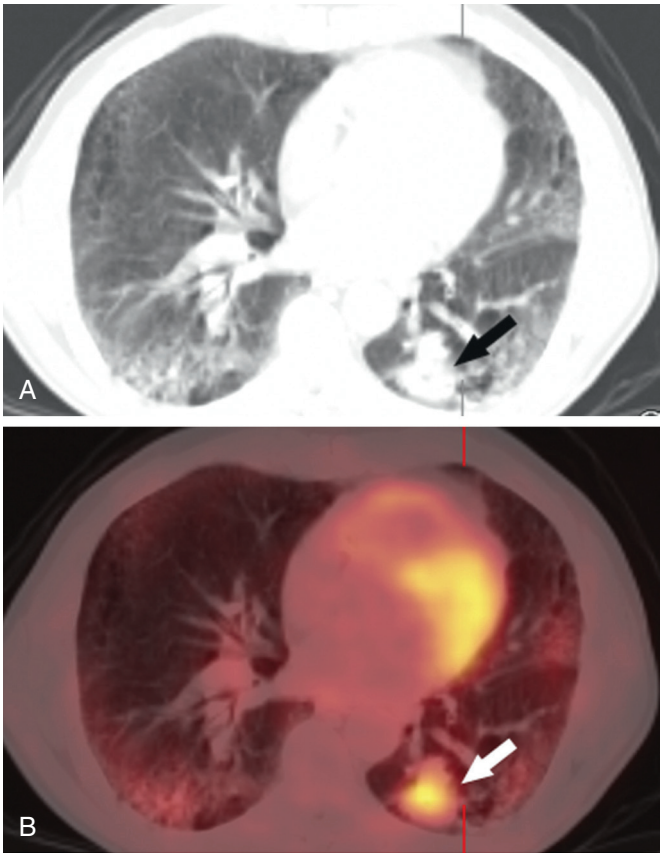


Figure 10-3 Male, age 56 years, with treated lung cancer. Axial CT scan **(A)** demonstrates a residual mass within the left lower lobe *(arrow)*. Corresponding fused PET/CT image **(B)** reveals increased avidity for FDG, similar to the heart, and indicative of residual disease *(arrow)*. PET imaging should be performed approximately 8 weeks following radiation therapy to minimize false-positive results because of inflammation of the targeted tissues.

detection of lung, adrenal, or soft-tissue metastases. Lymph nodes larger than 1 cm in the short-axis are considered pathologic on CT.[48,49] However, the sensitivity and specificity of this criterion is low. PET/CT examination allows for the addition of metabolic information to anatomic or morphologic information and is generally used as the next step in the workup including identification of involved lymph nodes and metastases to the whole body including the adrenal glands, bones, and liver.[48,49] MRI can also be used as a problem-solving technique in certain situations such as the evaluation of chest wall, mediastinum, and major vessel or brachial plexus invasion.[48,49] In most cases, CT or PET/CT is used to follow response to chemo- or radiotherapy and surgery and to diagnose their complications (Figure 10-3).[48-50]

Tumors may be visible as central or peripheral masses on imaging studies. Central tumors may be obscured by associated atelectasis or postobstructive pneumonitis. The distribution of parenchymal findings depends on the tumor location and may range from a subsegmental atelectasis to collapse of an entire lobe or lung. A solitary pulmonary nodule may be a finding of lung cancer and certain characteristics including size, calcification, shape, edge characteristics, cavitation, contrast enhancement, and growth rate may help differentiate between a benign and malignant lesion. Certain types of calcifications including lamellated or central calcifications in granulomas; the popcorn pattern in hamartomas are highly specific for benignity. Dystrophic calcifications may rarely be seen in primary and secondary tumors. A smooth peripheral margin is more frequently associated with benign lesions whereas lobulation, spiculation, and the presence of a pleural tag are worrisome findings. Cavitation may be seen in malignant lesions and thick-walled lesions and irregular internal margins are more frequently associated with malignancy.

The absence of growth over a 2-year period is the most reliable indicator of benignity because the doubling time varies between 30 and 490 days (mean value 120 days).[51] Intrathoracic involvement is not limited solely to mediastinal and hilar lymph nodes. The pleura, chest wall, heart, great vessels, diaphragm, and phrenic and recurrent laryngeal nerve are additional structures that can be involved secondarily. Pleural involvement may be seen as a pleural effusion with or without an associated mass.

Local extension and resectability may also be evaluated with imaging. Although the extension and invasion of tumor can be visualized in the chest wall and mediastinum, subtle invasion may be difficult to detect. Less than 3 cm contact with the chest wall and mediastinum, less than 90 degrees contact with the aorta and presence of fat between the mass and normal structures suggest technically feasible resectability, although the opposite findings are not reliable for either invasion or unresectability.[48] The most frequent distant metastases are bone, brain, contralateral lung, liver, adrenals, soft tissue, and skin.[48,49]

Non–small Cell Cancers

Adenocarcinoma accounts for 30% to 40% of lung cancers.[47] These tumors are typically small, round, smoothly marginated, and peripherally located. However, central location does not exclude the diagnosis of adenocarcinoma. When the primary mass is located peripherally, hilar and mediastinal lymph node metastases are present at diagnosis in 18% and 2% of cases, respectively. When the primary mass is located more centrally, hilar and mediastinal lymphadenopathy is present in 40% and 27% of cases, respectively.[52] Calcifications are rarely present in primary lung adenocarcinomas.

Broncheoalveolar carcinoma (BAC) is considered a subtype of adenocarcinoma. Approximately 60% of BACs presents as a solitary peripheral pulmonary nodule.[53] Other common presentations include multiple nodules (15%) and alveolar filling pattern mimicking pneumonia (10%).[54] These opacities may present a diagnostic challenge because they can remain unchanged in size for several years and are generally not hypermetabolic on PET/CT imaging. Mediastinal lymphadenopathy is present at diagnosis in 18% of patients.[54]

Approximately 10% of lung cancers are large cell carcinomas.[47] These typically present as large, peripherally located masses. Cavitation and calcification are uncommon findings. Hilar and mediastinal lymphadenopathy is found in 30% and 10% of cases, respectively.[53] Large cell carcinomas are characterized by a rapid growth pattern with early lymphatic and hematogenous metastases.[54,55] Large cell carcinomas can be histologically difficult to differentiate from poorly differentiated adenocarcinomas and squamous cell carcinomas.[47]

Squamous cell carcinomas (SCCs) make up 30% to 40% of lung cancers.[47] Although SCC often presents as a centrally located mass, it is peripherally located in a third of cases and may occur as an endobronchial mass that is associated with bronchial obstruction.[53] Cavitation of the primary mass occurs in 10% to 20% of patients. Most apical tumors, or Pancoast tumors, are SCC.[54] Pancoast tumors may extend superiorly and invade the subclavian artery and brachial plexus. Radiologic findings may include apical mass, prominent apical cap, bone destruction, and clinical findings may include arm pain and Horner syndrome as a result of involvement of brachial

plexus and stellate ganglion, respectively. Brachial plexus involvement, apical chest wall, vertebral bodies, and neural foramina are best examined with MRI.

Small Cell Cancers

Approximately 90% of small-cell carcinomas are located centrally and tend to spread longitudinally along submucosal and intramural portions of the bronchial walls and in the supporting tissues and lymphatics. They often have extensive mediastinal or hilar lymphadenopathy and may encase mediastinal structures. This histologic subtype is composed of neoplasms arising from neuroendocrine cells. Distant metastases occur early.[53]

Staging of Lung Cancer

The distinction between T1 and T2 is generally easy as it depends on size criteria; however, the diagnosis of chest wall, diaphragm, pleural, or mediastinal invasion may be difficult. MRI may be helpful in these situations.[48,49] Assessing the mediastinum for nodal metastases is important for staging. Unfortunately, morphologic criteria on MRI and CT are not effective in characterizing lymph nodes. Using the 1-cm short-axis criteria, CT has been reported to be 41% to 67% sensitive and 79% to 86% specific for detection of nodal metastases.[46] Oftentimes, enlarged nodes are hyperplastic because of infection or inflammation, particularly in the setting of postobstructive pneumonia. PET/CT is useful in differentiating benign from malignant lymphadenopathy in patients without superimposed infection. If an enlarged node discovered by CT does not show 18-Fluoro deoxyglucose (FDG) avidity, it will be free of metastases with nearly 100% certainty.[56,57] PET/CT has a high negative predictive value for small (T1), peripheral tumors with low FDG uptake and no significant activity in the hilar lymph nodes.[48,49] Problems remain with detection of lung nodules less than 5 mm in diameter and superimposed or concurrent infection, which also shows increased uptake. PET/CT examination is also effective for the detection of distant metastases and in the absence of symptoms the negative predictive value is usually 90% to 95% for liver, brain, adrenal gland, and bone. However, small liver metastases may not be detected on PET/CT and benign adrenal nodules may be FDG avid.

Follow-up of Lung Cancer

CT and PET/CT are used for the evaluation of treatment response; however, there are no commonly accepted follow-up criteria.[48] Metabolic imaging is helpful for the evaluation metabolic activity in tumors that do not show any change in size or show increased necrosis despite increase in size.

Screening for Lung Cancer

The National Lung Cancer Trial (NLST) in 2011 found a mortality benefit of at least 15% in long-term smokers who underwent annual screening with low-dose CT screening. Although, based on this finding, the U.S. Preventive Services Task Force issued a draft recommendation in favor of CT lung cancer screening, the debate over cost continues.[58]

Lymphoma

Lymphoma is a malignant disease of hematopoietic cells of specific lineage including T and B cells and histiocytes. The lymphocytes located in the lymph nodes, organs, and bone marrow may develop into lymphomas, which may involve any part of the body. Lymphoma is mainly composed of two groups: Hodgkin disease (HD) and non-Hodgkin lymphoma (NHL). More than 80% of patients with HD have intrathoracic involvement at presentation consisting of enlarged anterior mediastinal and paratracheal lymph nodes.[59] NHL is a more heterogeneous group of diseases, and thoracic lymph node involvement is present in 45% of cases.[60] The prognosis and treatment vary according to the type of NHL. The paratracheal and anterior mediastinal lymph nodes are the most commonly involved sites. Large mediastinal lymphadenopathy (>10 cm) is associated with an increased risk of relapse and usually requires aggressive combination therapy.[61] Lung nodules are uncommon in both HD and NHL.

NHL and HD may also be seen in patients with posttransplant lymphoproliferative disorder (PTLD).[62] PTLD may involve various sites in the body and present most commonly as a pulmonary mass or nodules in the lungs.[63,64] PTLD may be divided into two groups according to its pathogenesis including Epstein-Barr virus–dependent type and Epstein-Barr virus–independent type, in which the underlying etiology is unclear.

In addition to CT and MRI, PET/CT (Figure 10-4) provides metabolic information, which is especially critical for the early evaluation of viable tumor in patients undergoing chemo- or radiotherapy without significant change in the size of the lesions.

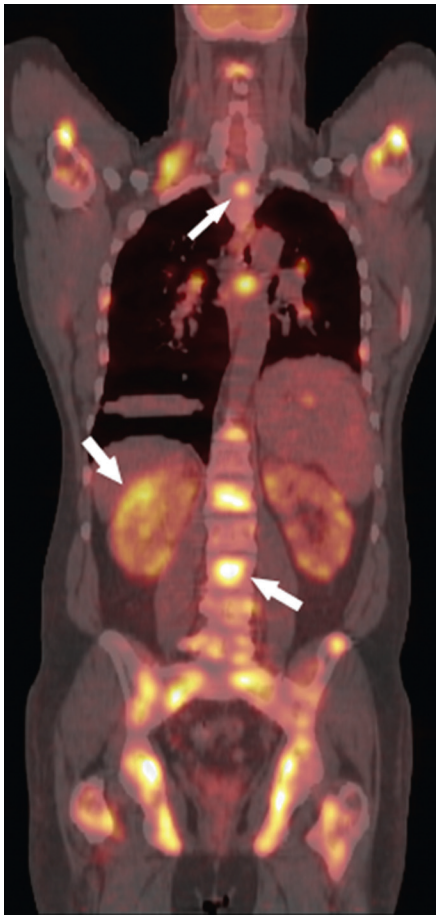


Figure 10-4 Male, age 44 years, with known lymphoma. Coronal fused PET/CT image shows multiple regions of increased uptake, including the kidneys, bones, and thyroid gland *(top arrow)*.

Metastatic Disease to the Chest

CT scan is the test of choice for identification of metastatic disease and response to therapy. Many cancers secondarily

involving the lungs will present with multiple nodules. In the case of SCC and adenocarcinomas, nodules may be cavitary. Response to therapy is often determined based on an increase or decrease in the size and number of nodules. It is prudent to compare the current scan with the most recent prior scan and the most remote scan to avoid overlooking slow-growing disease. Other manifestations of metastatic disease include enlarged mediastinal, hilar, or axillary lymph nodes, nodular pleural thickening, pleural effusion, and, particularly in the case of lung or breast cancer, chest wall invasion. Osteolytic or osteoblastic bone metastases can be identified. Three-dimensional reconstructions can be of particular value in identifying central lung nodules abutting vessels, chest wall masses, and rib or spine lesions. Maximum intensity projection (MIP) reconstructions are especially helpful for the detection of small pulmonary nodules.

CANCERS OF THE ABDOMEN AND PELVIS

Primary Tumors of the Gastrointestinal Tract

Primary Esophageal Tumors

Esophageal carcinoma is the thir-most common gastrointestinal tract malignancy. Surgical resection after preoperative radiation therapy and chemotherapy is currently the best curative treatment for patients without distant metastases. Accurate preoperative staging and evaluation of response to neoadjuvant therapy is critical for the therapeutic approach. The diagnosis is generally made with endoscopy.[65,66] The tumor may spread via direct extension, lymphatic, or hematogenous routes. SCCs predominately affect the proximal two thirds of the esophagus and the majority of adenocarcinomas affect the distal third and together constitute more than 90% of the tumors.[65,67] Because the esophageal mucosa lacks a serosa, which may behave like a barrier to the spread of disease, the tumor easily spreads to adjacent structures in the neck and mediastinum.

The esophagus has an extensive lymphatic drainage and therefore mediastinal, perigastric, and celiac lymph nodes can be involved. Additionally, lymphatic spread may result in discrete mucosal implants. Hematogenous metastases most commonly involve the liver, lungs, and bones.[65] Initial screening includes the use of three modalities: CT, endoscopic US, and PET/CT.[65-67] Endoscopic US is the most accurate technique for the differentiation of T stage and has overall 75% to 95% accuracy for these stages.[65,67] The exclusion of T4 disease is the most important role of CT. Staging accuracy using combined endoscopic ultrasound and contrast-enhanced CT reaches 85% to 90%.[68] PET/CT is the most accurate technique for the evaluation of lymph node involvement (Figure 10-5) and is helpful for the detection of distant metastases. PET/CT is sometimes used to follow therapy and more commonly used to determine late recurrences.[68,69]

Primary Stomach Tumors

Gastric adenocarcinoma is the second-most common gastrointestinal tract malignancy and usually identified at an advanced stage.[70] Endoscopy is the gold standard for the diagnosis of gastric adenocarcinoma. Endoscopic US is used to assess the depth of invasion into the gastric wall and has higher accuracy (78% to 93%) compared to cross-sectional imaging techniques for the determination of T staging.[70] Cross-sectional imaging is used for staging of lymph nodes and distant metastases.[70-73] PET/CT is particularly important for the demonstration of involvement of small morphologically normal appearing lymph nodes in FDG avid tumors.[70] CT and MRI are superior in the identification of lymph nodes increased in size and number and distant disease including parenchymal metastases or peritoneal involvement.[74,75] MRI has higher accuracy for the detection of small metastases, especially in solid organs. The combination of cross-sectional techniques is used for the evaluation of treatment response.

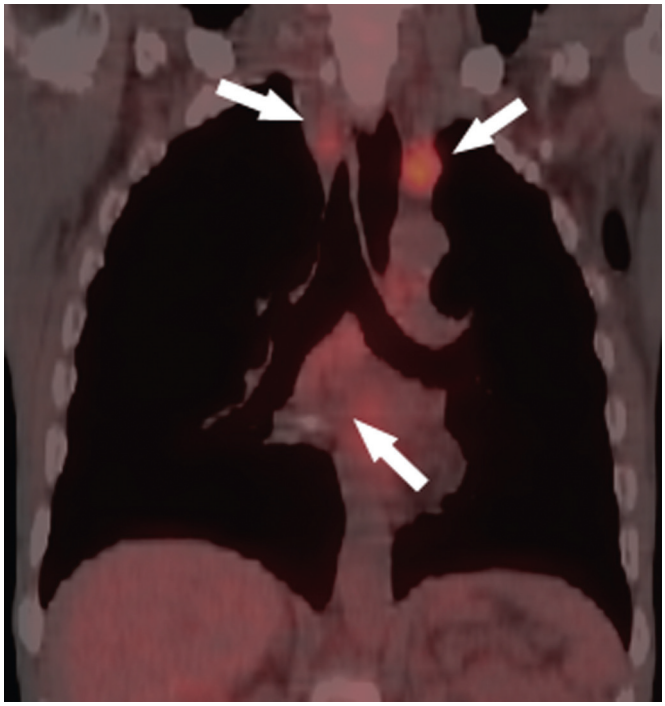


Figure 10-5 Male, age 67 years, with known esophageal cancer. On CT scan, multiple enlarged nodes involving nearly all mediastinal sites were identified. Coronal fused PET/CT image shows increased avidity in the paratracheal and subcarinal lymph nodes *(arrows)*, indicative of carcinoma.

The most common finding of adenocarcinoma is the gastric wall thickening, which may be focal or diffuse. Ulceration is common. Differential diagnosis includes gastrointestinal stromal tumor (benign or malignant), metastatic disease, and lymphoma. For tumors located in the gastric cardia or fundus, lymph node involvement patterns are similar to those of distal esophageal tumors and include the gastrohepatic ligament and periaortic spaces.[70-73] Distal cancers often drain along the lesser curvature of the stomach.[70-73] Reformated images are usually helpful for the detection of small asymmetrical wall thickening and lymph nodes.[76]

Primary Small Bowel Tumors

Small bowel tumors constitute less than 5% of all gastrointestinal tumors.[77] Tumors are more common in the duodenum compared to the jejunum or ileum. Tumors may manifest as nodules, annular lesions, excavating masses, or stricturing lesions. The most common malignant neoplasms include adenocarcinoma (40%), carcinoid (20% to 25%), lymphoma (10% to 15%), and gastrointestinal stromal tumors (GIST) (10%). Adenocarcinoma occurs most commonly at the duodenum near the ampulla, whereas carcinoid tumors originate most often in the ileum. Adenocarcinomas present as soft-tissue mass causing annular or eccentric luminal narrowing and obstruction. Carcinoid tumors may vary from small submucosal lesions to large ulcerating lesions with a prominent desmoplastic reaction and homogeneous enhancement. Lymphomas

usually present as circumferential or cavitary mass. CT is the most commonly used and available technique for diagnosis.[78] The use of conventional small bowel imaging with barium under fluoroscopy has dramatically decreased after the evolution of CT and MR enterography or enteroclysis techniques.[77-83] CT and MR enterography/enteroclysis techniques have similar accuracy and have increased the accuracy of detection of small bowel tumors compared to CT or MRI alone.[77-83] Metastastases to the small bowel are uncommon. Staging is performed with CT or MR, which often demonstrates extension to mesenteric lymph nodes, the liver, and peritoneum.[82,83]

Primary Tumors of the Colon and Rectum

Primary colorectal tumors are usually discovered during colonoscopy. Occasionally, an obstructing colonic cancer will be identified on a CT scan of the abdomen. Wall thickening is the most common presentation and may be associated with colonic obstruction and advanced disease.[84] The primary use of cross-sectional imaging is for identification of locoregional and distant metastatic disease. Patterns of spread are primarily lymphatic and hematogenous. Direct extension occurs when a tumor perforates the serosa and invades adjacent tissue. Lymphatic spread may occur into the ischiorectal fossa and perianal space (rectum/anus) or along the mesenteric vessels (left and right colon). A common final pathway for many tumors is the nodal region adjacent to the origin of the inferior mesenteric artery. Enlarged nodes may also be seen in the porta hepatis. Lymph nodes greater than 1 cm in short-axis diameter are considered suspicious for metastatic disease. Unfortunately, size is not a good indicator of tumor involvement. Lymph nodes greater than 1 cm in size harbor cancer in only 65% of cases.[85] Hematogenous spread yields liver or lung metastases. MRI is the best technique for the evaluation of the liver and staging of rectal cancer.[86,87] Advanced disease may consist of pulmonary nodules, widespread lymphadenopathy, and solid tumor masses within the mesentery and pelvis because of direct extension of disease. PET/CT has high accuracy for intraabdominal and extraabdominal staging ranging between 92% and 99%, respectively.[86]

Metastatic Disease to the Gastrointestinal Tract

Metastases most commonly affect the serosa and develop secondary to direct extension or peritoneal dissemination. Gynecologic malignant neoplasms (ovarian) and gastrointestinal malignant neoplasms (colon, gastric, and pancreatic) are the most common tumors. Most serosal metastatic implants distort and narrow the small and large bowel, sometimes leading to obstruction. Rarely, hematogenous or lymphatic metastases to the bowel wall may occur. Cross-sectional imaging including CT and MRI can be used for the diagnosis although CT is more commonly used and especially helpful for the evaluation of bowel obstruction.

Primary Tumors of the Liver

Hepatocellular carcinoma (HCC) is the most common primary malignancy of the liver and occurs most commonly in patients with cirrhosis and chronic liver disease.[88,89] The nodular regeneration and fibrotic network of chronic liver diseases make detection of HCCs difficult. Excluding HCCs, three focal nodular lesions are specifically seen in patients with chronic liver disease: regenerative nodules, low-grade and high-grade dysplastic nodules.[88,89] Regenerative nodules and low-grade dysplastic nodules are benign lesions.[88,89] High-grade dysplastic nodules may be premalignant.[88,89] HCCs may develop de novo or may develop in high-grade dysplastic nodules.

MRI is the most accurate imaging technique for the detection and characterization of focal liver lesions including hepatocellular carcinoma.[88,89] The use of dynamic postgadolinium imaging, including hepatic arterial dominant, hepatic venous, and interstitial phases, are critical. Although high-grade dysplastic nodules demonstrate arterial enhancement with fading, HCCs show arterial enhancement with wash out and capsular enhancement on later phases.[88,89] HCCs show variable signal intensities on T1- and T2-weighted sequences.[90,91] HCCs may have fat content or contain hemorrhage. Subcapsular lesions may cause subcapsular or intraperitoneal hemorrhage. HCCs are usually focal lesions; however, diffuse infiltrative HCCs are uncommonly seen and generally associated with portal or hepatic venous tumor thrombosis (Figure 10-6).[88,89]

Metastatic Disease to the Liver

MRI is the most accurate technique for the detection and characterization of metastases in the liver.[92,93] Metastases may be hyper- or hypovascular. Adenocarcinoma metastases are the most common cell type and vary in vascularity depending on the primary site. The most common hypovascular adenocarcinoma metastasis is secondary to colon adenocarcinoma (Figure 10-7), and the most common hypervascular adenocarcinoma metastasis results from breast cancer (Figure 10-7). Typical hypovascular adenocarcinoma metastases appear as lobulated masses with intensely enhancing borders and minimal central enhancement on CT and MRI. Typical hypervascular adenocarcinoma metastases appear as oval lesions showing thick ring enhancement or homogeneous enhancement. Adenocarcinoma metastases are of increased signal intensity on T2-weighted images but are less bright than cysts or hemangiomas. Another common and typical pattern of metastatic disease is rapid, complete enhancement with later washout, which is a characteristic feature of hypervascular metastases including carcinoid or neuroendocrine tumors. Hemorrhagic or melanin containing metastases (malignant melanoma) demonstrate high signal on T1-weighted images (Figure 10-7). Cystic metastases may be seen with epithelial ovarian cancers. Using MRI, it is usually possible to identify benign lesions with confidence when they exceed 10 mm in diameter.

Primary Tumors of the Retroperitoneal Organs

Primary Pancreatic Tumors

The most common pancreatic malignancy, adenocarcinoma, usually occurs in the head of the pancreas (Figure 10-8) and may occlude the pancreatic duct, common bile duct, or both.[94,95] This can lead to the classic (although rare) presentation of painless jaundice with a distended, palpable gallbladder. MRI combined with Magnetic resonance cholangiopancreatography is the most accurate technique for the evaluation of pancreatic adenocarcinoma when the tumor is confined to the pancreas. CT is advantageous in evaluation of vascular encasement of the superior mesenteric artery, a sign of unresectable disease.[94] Endoscopic US has been reported to be comparable to MRI for local staging.[94] Although endoscopic US is limited because of its invasive nature, the ability to do biopsy under ultrasound is an important advantage. Diagnostic accuracy is high, ranging from 88% to 94%.[96,97]

Staging is best done using the combination of MRI-MRCP and PET/CT.[94] Dynamic MR imaging including hepatic arterial and venous phases depicts vascular encasement and invasion with a high degree of accuracy and plays a critical role not only for the determination of resectability but also

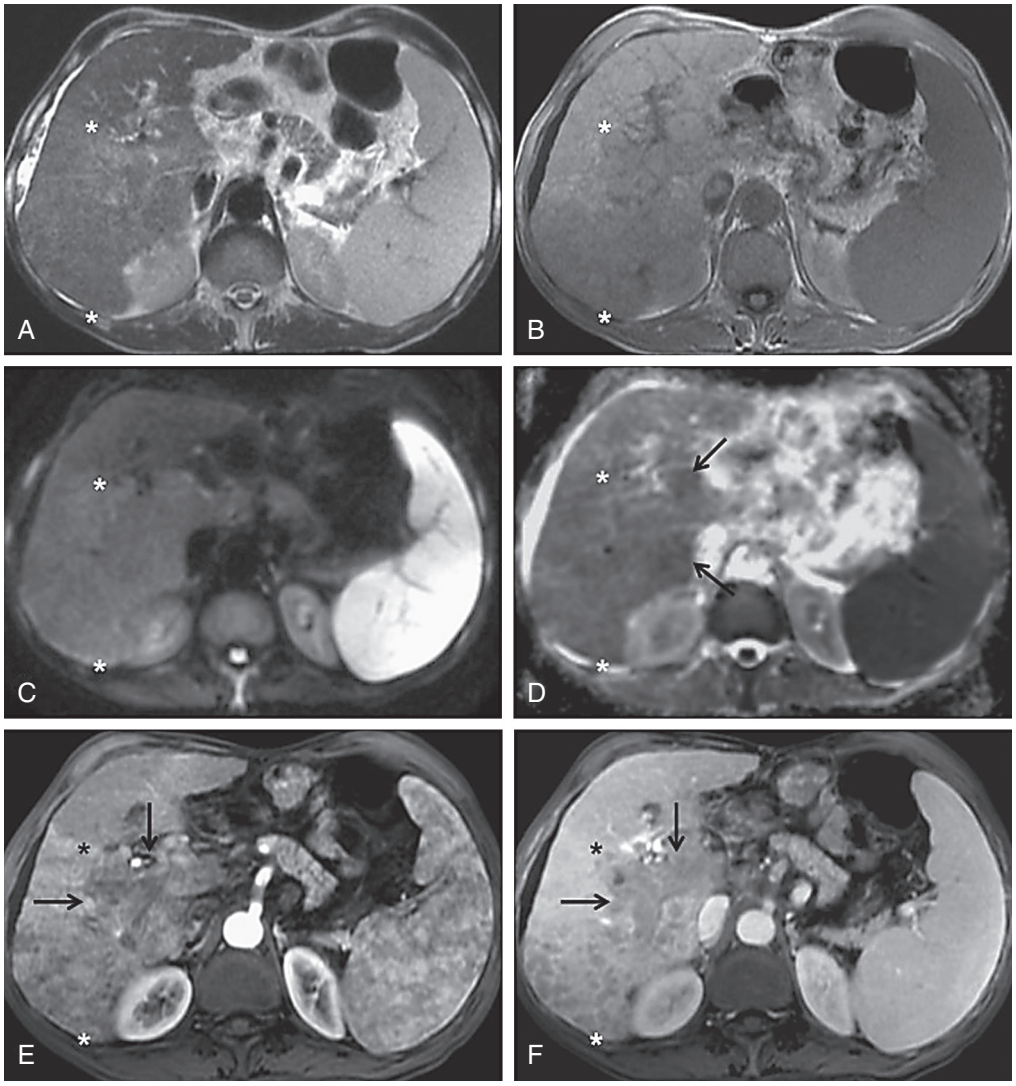


Figure 10-6 Male, age 60 years old with chronic liver disease secondary to Hepatitis C infection presents with very high alpha fetoprotein (AFP) levels and jaundice. A diffuse hepatocellular carcinoma (anterior and posterior borders are marked with asterisk on images) replacing the right lobe of the liver and part of the left lobe shows is shown with mild to moderate high signal on transverse T2-weighted SS-ETSE **(A)** and diffusion weighted **(C)** images. The lesion shows partially low signal on T1-weighted 2D-GE image **(B)**. The lesion shows areas of diffuse restriction *(arrows)* adjacent to the thrombosed portal vein on apparent diffusion coefficient (ADC) map **(D)**. Please note that the portal vein could not be differentiated on precontrast images. The lesion and associated tumor thrombosis *(arrows)* demonstrates early heterogeneous enhancement **(E)** with later heterogeneous washout **(F)** on postgadolinium images.

for treatment planning.[94] Local lymph node enlargement and liver metastases are accurately identified. MRI is more accurate compared to CT in the detection of small tumors, small liver metastases, and peritoneal metastases.[94] MRI is slightly more accurate or comparable in the determination of local invasion. MRI can detect pancreatic lesions at 1 cm range although CT can detect the lesions at 2 cm range. Unfortunately, identification of very small (<1 cm) pancreatic cancers remains difficult. Pancreatic ductal dilation with abrupt cutoff may be a sign of small neoplasms.[94] The second most common solid malignant neoplasms of the pancreas are hypervascular tumors including neuroendocrine tumors (Figure 10-8).

Primary Tumors of the Kidney

Renal cell carcinoma is most often identified serendipitously, usually on a CT scan or ultrasound study performed for symptoms unrelated to the genitourinary tract. Once a solid, vascular mass is identified, treatment is surgical removal or ablation, barring significant medical comorbidities. Staging may be performed with contrast-enhanced CT or MRI, which have similar high accuracy, although contrast-enhanced CT is more commonly used (Figure 10-9).[98,99] MRI may be preferred in patients with severe allergy to iodinated contrast media, whereas CT may be preferred because of the concerns of nephrogenic systemic fibrosis. PET/CT is usually not used for the initial staging. Tumor size, location, and vascular supply are critical in determining whether the patient is a candidate for laparoscopic or partial nephrectomy.[100] Multiplanar imaging or reformatted images fully depict the vascular and urinary tract anatomy.[101] Extension into the renal vein, the presence of enlarged perihilar lymph nodes, involvement of the ipsilateral adrenal gland, and invasion of adjacent organs can also be assessed.[98]

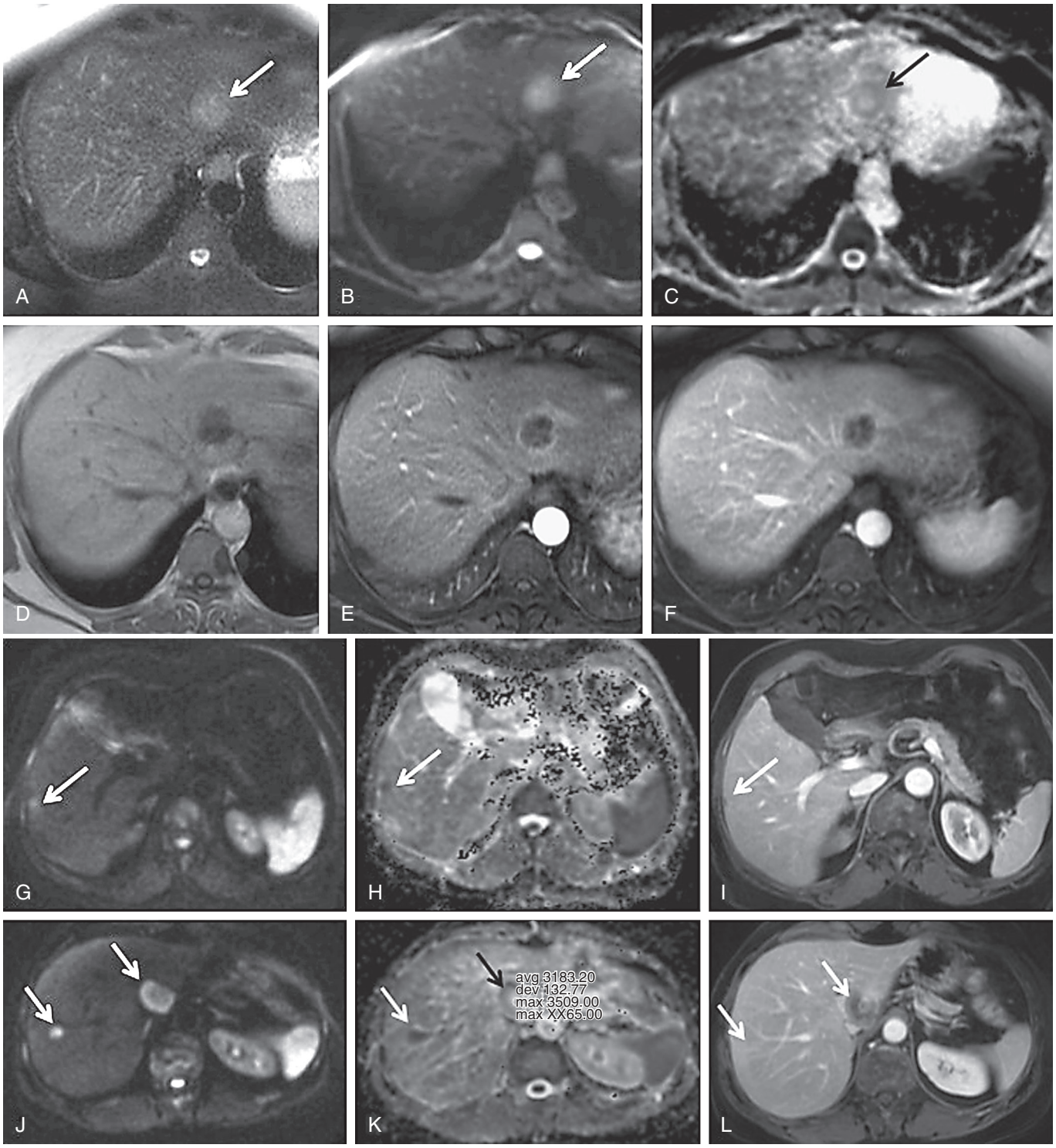


Figure 10-7 Male, age 51 years old with a solitary liver metastasis secondary to colon cancer. The lesion *(arrows;* **A-C***)* is located in the left lobe of the liver and shows mildly high T2 signal on T2-weighted transverse SS-ETSE image **(A),** mildly high signal on diffusion weighted (DW) image **(B)** and peripheral low signal on apparent diffusion coefficient (ADC) map **(C),** which represents peripheral diffusion restriction. The central high signal on ADC map represents central necrosis. The lesion shows typical mildly lobulated appearance on T1-weighted in-phase image **(D)** and predominant peripheral enhancement on contrast-enhanced images **(E** and **F)**. Female, 55 years old with liver metastases secondary to invasive ductal carcinoma of the breast. A small lesion *(arrow)* with high signal on DW image **(G)** shows low signal representing diffusion restriction on ADC map **(H)**. It is difficult to visualize the lesion *(arrow)* on postgadolinium image **(I)** because of its similar enhancement due to background liver. Female, 48 years old with liver metastases secondary to invasive ductal carcinoma of the breast. Two lesions *(arrows)* with high signal on DW image **(J)** are noted. The smaller lesion *(white arrow)* shows low signal representing diffusion restriction on ADC map **(K)** while the larger lesion *(black arrow)* with indicated measurements on ADC map **(K)** demonstrate peripheral low signal suggesting peripheral diffusion restriction. The smaller lesion shows similar enhancement compared to the background liver and is difficult to visualize on postgadolinium image **(L)** whereas the larger lesion shows predominantly peripheral enhancement **(L)**.

Continued

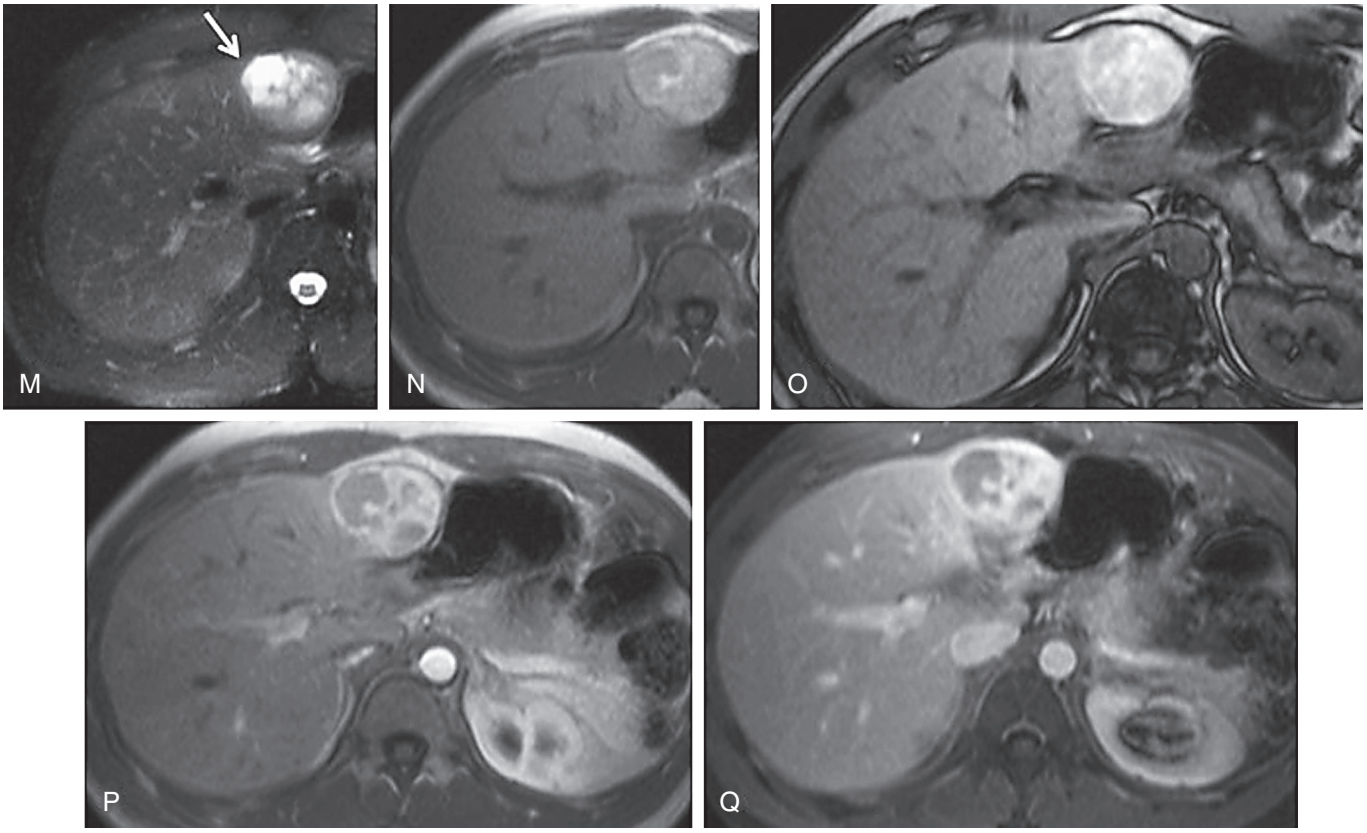


Figure 10-7, cont'd DW imaging may be particularly helpful for the better demonstration of small liver metastases, especially if they are located peripherally or treated with chemotherapy. Male, 35 years old with liver metastasis secondary to malignant melanoma. A metastasis *(arrow)* with heterogeneous high signal on transverse T2-weighted SS-ETSE image **(M)**, high signal on both in-phase and out-of-phase T1-weighted 2D-GE images **(N** and **O)** and heterogenous enhancement on postgadolinium images **(P** and **Q)** is seen in the left lobe of the liver. High T1 signal is typical for malignant melanoma metastasis because melanin shows high signal on T1-weighted images.

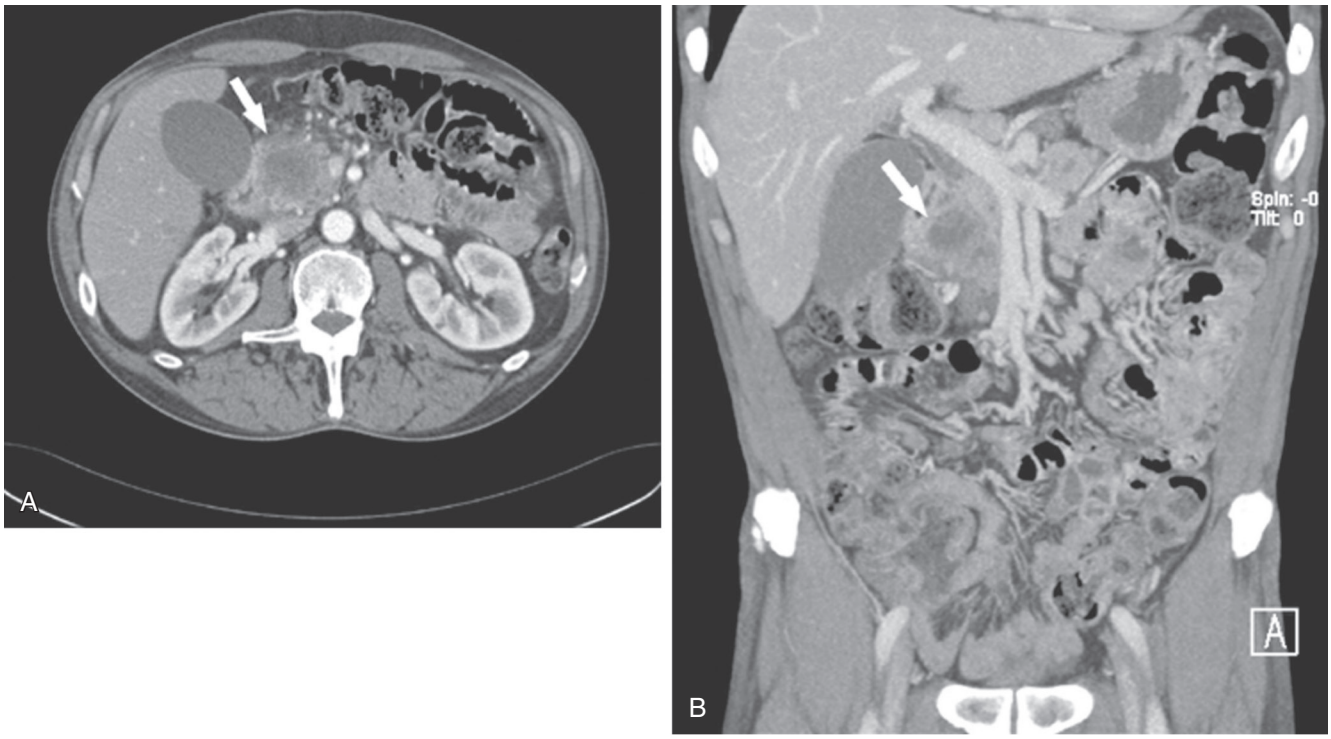


Figure 10-8 Female, age 67 years, with pancreatic cancer. Axial contrast-enhanced CT image **(A)** shows low-density mass arising from pancreatic head and encasing the superior mesenteric vein. Coronal reformatted image derived from the axial CT data **(B)** shows the relationship of the tumor *(arrow)* to the adjacent vasculature and gallbladder. No liver metastases or enlarged local lymph nodes were identified. Male, 45 years old with pancreatic neuroendocrine tumor and liver metastases.

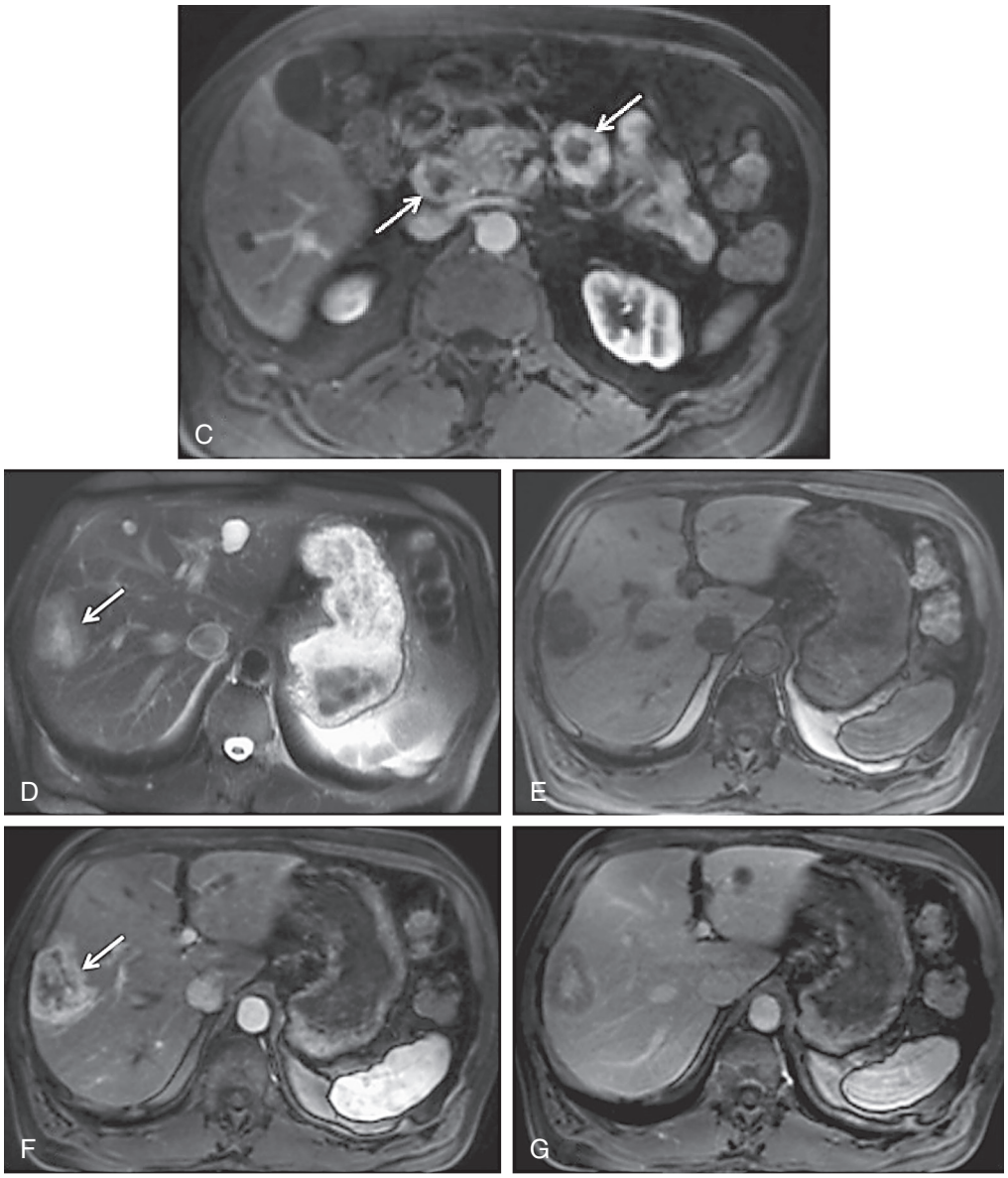


Figure 10-8, cont'd Two peripherally enhancing hypervascular lesions *(arrows)* are detected in the pancreatic head and body of the pancreas on the hepatic arterial dominant phase on postgadolinium 3D-GE image **(C)**. A hypervascular metastasis *(arrows)* is noted in the right lobe of liver demonstrating mildly high signal on transverse T2-weighted SS-ETSE image **(D)** and low signal on T1-weighted 3D-GE image **(E)**. The metastasis shows intense peripherally dominant heterogeneous enhancement on the hepatic arterial dominant phase **(F)** and later peripheral wash-out with central wash-in on the hepatic venous phase **(G)**. Please note that additional hypervascular small metastases and small cysts are also seen in the liver.

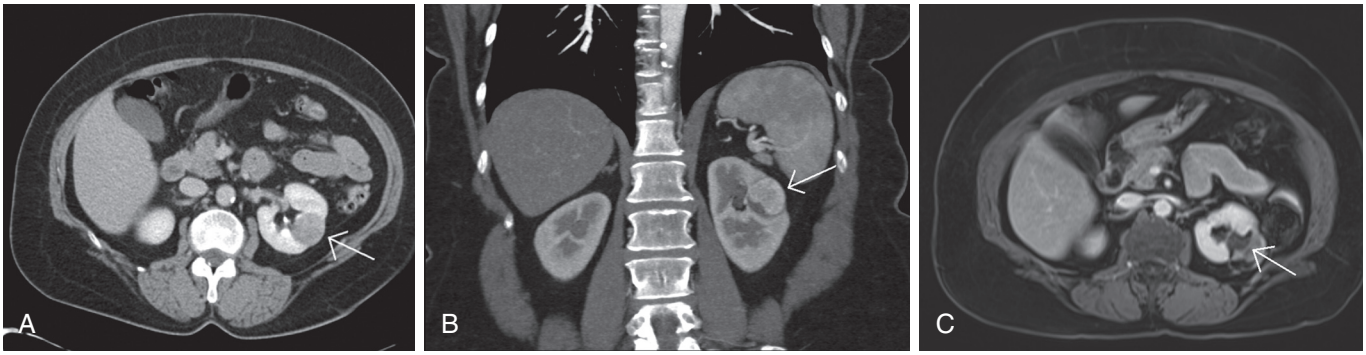


Figure 10-9 Female, age 65 years, with renal cell carcinoma. Axial contrast-enhanced CT image **(A)** and coronal reformatted contrast-enhanced CT image **(B)** demonstrate an enhancing mass involving the left kidney *(arrows)*. The patient subsequently underwent percutaneous radiofrequency ablation (RFA). Axial contrast-enhanced MRI image **(C)** demonstrates no suspicious enhancement *(arrow)* following RFA, and surrounding hematoma at the RFA site.

Urothelial carcinoma is staged primarily using CT urography, in which delayed multiplanar images are reconstructed to visualize the urinary tract with high resolution. Three-dimensional delayed images can also be acquired with this approach similar to an intravenous urogram.[101,102] A synchronous bladder or upper tract lesion can be staged with CT urography, eliminating the need for an additional test. Alternatively, MR urography can be used in younger patients to evaluate the urinary tract, without the radiation exposure of CT scanning.

Primary Tumors of Other Retroperitoneal Organs

Large masses of the retroperitoneum are often sarcomas. They may arise from the inferior vena cava (IVC), renal capsule, muscle, or fat. MRI and CT can successfully be used for the diagnosis and staging although CT is more commonly used.[103,104] MRI may be more advantageous for the evaluation of vascular invasion or superficial organ or body wall invasion, whereas CT may be more advantageous for bowel involvement. MRI can also better evaluate the internal structure of the tumor including fat content, necrosis, or hemorrhage. Liposarcomas are the most common type of retroperitoneal sarcomas, and CT and MRI demonstrate the fat content successfully. Retroperitoneal sarcomas most commonly metastasize to the lungs and liver.

Primary and Secondary Adrenal Tumors

Nonfunctioning adenomas are the most common adrenal lesions, whereas metastastases are the most common malignancy. It is critical to definitely identify adenomas to avoid overstaging of a primary neoplasm, particularly lung cancer. When an adrenal lesion measures less than 10 HU on an unenhanced CT scan, it contains intracytoplasmic lipid and is reliably benign. Unenhanced CT with a cutoff value of 10 HU has 71% sensitivity and 98% specificity for the differentiation of benign lesions from metastatic lesions.[105-107] Lipid poor benign lesions cannot be reliably identified with unenhanced CT. The measurement of washout on contrast enhanced CT can be employed because benign lesions demonstrate increased washout of contrast material on delayed images acquired at 15 minutes, compared to metastatic lesions.[105-107] An absolute percentage washout of 60% or higher has reported sensitivity of 86% to 88% and specificity of 92% to 96% for the diagnosis of adenoma.[105] Chemical shift imaging (CSI) MRI is based on the detection of signal loss on T1-weighted images determined with slightly different parameters. The decrease in signal intensity arises from the different precession frequencies of fat and water protons and is indicative of a benign adenoma.[105,107,108] CSI-MRI has 81% to 100% sensitivity and 94% to 100% specificity for the differentiation of adenomas from metastases.[105] PET/CT is a reliable technique for the identification of hypermetabolic metastases to the adrenal gland that are more than 1 cm in size. PET/CT has 100% sensitivity and 98% specificity for the differentiation of adenomas from metastases.[105]

Adrenal cortical carcinomas and pheochromocytomas are other rare retroperitoneal tumors that can be diagnosed with CT and MRI. Pheochromocytoma is usually a clinical diagnosis based on physical findings and increased urinary excretion of vanillymandelic acid. MRI is used to locate the source of the tumor.

Primary Tumors of the Pelvic Organs

Primary Testicular Tumors

Testicular tumors are diagnosed with US with high accuracy.[109] MRI has high accuracy for the diagnosis and differentiation of testicular and extratesticular tumors and is used for the diagnosis in equivocal cases.[109,110]

Following the standard treatment of orchiectomy, contrast-enhanced CT scans of the abdomen and pelvis are performed to search for nodal involvement and metastatic disease.[111] The lymphatic drainage of the testicles follows the gonadal veins.[111-113] Therefore, for right-sided testicular tumors, the sentinel nodes are those in the aortacaval and pre- or paracaval lymph nodes at the level of L2; whereas on the left paraaortic and preaortic lymph nodes just below the left renal vein are of greatest importance.[112,113] Right-to-left crossover of lymphatic involvement may be seen following the normal drainage to the cisterna chyli and thoracic duct. Left-to-right crossover may be seen more frequently (20% of cases).[112,113] The involvement of contralateral nodal metastases is rare (less than 2% of cases) without the involvement of ipsilateral nodes.[112,113] The iliac chain lymph nodes may be involved because of the spread from the sentinel nodes if the tumor burden is high.[112,113] The pelvic and inguinal lymph nodes may also be involved if the normal lymphatic drainage pathways are disrupted due to previous pelvic or scrotal surgery or orchiectomy.[112,113]

Involved lymph nodes are of soft-tissue density with moderate to prominent enhancement. Enlarged lymph nodes from nonseminomatous germ cell tumors including teratoma may contain cystic areas. Unfortunately, node density does not correlate with the degree of cell kill following chemotherapy. Residual nodes often undergo surgical resection to maximize potential for cure. On follow-up scans, all nodes greater than 5 mm are considered suspicious for metastasis. Enlarged nodes may encase the renal vessels and compress and occasionally invade the inferior vena cava (IVC). MRI has similar accuracy for the diagnosis of lymph node involvement and it may be preferred not only because of the concerns of allergic reaction to iodinated contrast, but also because of the concern of radiation because testicular cancer is most common in young men. PET/CT is also successful for the evaluation of metabolic activity of large residual solid lymph nodes, which do not decrease in size following therapy.

Primary Tumors of the Prostate Gland

Transrectal image–guided biopsy is still the gold standard for the diagnosis of prostate cancer. MRI has been increasingly used for prostate imaging over the last 10 years. MR imaging is usually performed with endorectal and surface phased array coils using a high field strength 1.5 T magnet. Endorectal coils may not be necessary using a 3.0 T magnet because of its higher signal-to-noise ratio. Small field-of-view high-resolution T2-weighted MRI imaging is the standard mainframe for prostate imaging. On T2-weighted images, prostate cancer usually appears as a region of low to intermediate signal.[114-118] Direct extension of disease through the low T2-signal capsule is indicative of extracapsular extension and seminal vesicle or neurovascular bundle invasion and enlarged lymph nodes can be detected.[114-118]

Multiparametric MR imaging including T2-weighted imaging, diffusion-weighted imaging, dynamic contrast-enhanced imaging, and MRS detect tumors in approximately 70% to 75% of cases. (Figure 10-10).[114-118] Diffusion weighted imaging may be particularly helpful for the differentiation of fibrosis and benign prostatic hypertrophy from adenocarcinoma.[117] This is especially helpful in detection of cancer in the central and transitional zones. Combined diffusion weighted and T2-weighted imaging has better sensitivity and specificity (70% and 83%) compared to T2-weighted imaging alone.[117] Additionally, multiparametric MR imaging has a sensitivity of 93%, positive predictive value of 57%, and an overall accuracy of 92% in patients with low prostate-specific antigen (PSA)

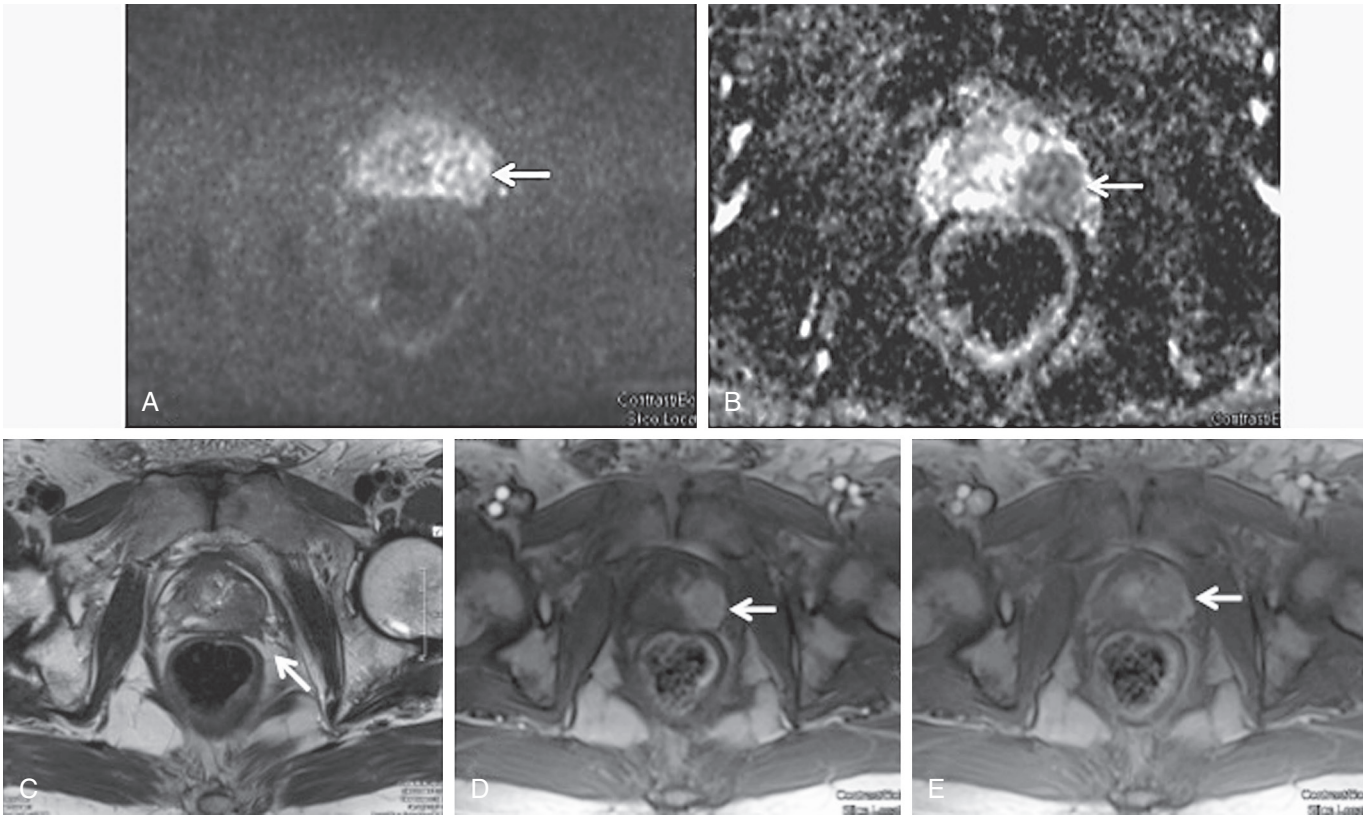


Figure 10-10 Male, age 63 years old man with prostate adenocarcinoma. The lesion *(arrows)* shows high signal on diffusion weighted (DW) image **(A)** and low signal on apparent diffusion coefficient (ADC) map **(B)** representing diffusion restriction. The capsular invasion and extracapsular extension (*arrow*, **C**) is detected on high-resolution T2-weighted turbo spin echo (TSE) image **(C).** On raw postgadolinium perfusion images **(D** and **E)** of prostate gland, the lesion (arrows) shows early increased enhancement **(D)** and late washout **(E)**.

levels and Gleason scores who are undergoing active surveillance.[119]

In most institutions, no pelvic imaging is performed before radical prostatectomy. CT or MR scans of the abdomen and pelvis are ordered before the onset of radiation therapy to identify soft tissue and bony landmarks for planning. In advanced disease (PSA > 20 ng/mL), in patients with high-risk histopathology and in patients with biochemical recurrence, CT or MRI can be used to image the pelvis to identify enlarged pelvic and retroperitoneal lymph nodes. These images are fused with projected radiation fields to optimize dose to the tumor. PET/CT and bone scans are also helpful for the detection of distant organ metastases and bone metastases, respectively. Finally, although US remains the standard, MRI has begun to be used for the evaluation of rising PSA levels in patients with negative US-guided biopsy results, for targeted biopsies, and radiation seed placement in the treatment of prostate cancer.

Primary Bladder Tumors

About 90% of bladder tumors arise from urothelial cells and are primarily transitional cell carcinomas.[120] SCC accounts for 6% to 8% of bladder cancers.[120] Adenocarcinomas typically arise from the urachus. Urothelial tumors are classified as invasive or noninvasive based on extension into and through the muscle.[120] Initial evaluation for painless hematuria, which is the clinical presentation in 80% to 90% of patients with urothelial tumors, includes CT urography and cystoscopy. Cystoscopic staging is the essential part of pretreatment planning and biopsy of the lesions is performed to assess the pathology, grade, and depth of invasion.

CT urography has a more than 90% sensitivity and specificity for the diagnosis of bladder cancer.[120] However, the accuracy for T staging is low (40% to 60%), and CT is especially important for the detection of disease involving the perivesical fat.[120,121] MRI has comparable accuracy for the diagnosis of bladder cancer and may be more accurate especially for the diagnosis of invasion of adjacent organs and T staging (75% to 92%).[120,122,123] It has been reported that MRI may be more accurate for the identification of T2 disease because the detrusor muscle is better visualized with high-resolution T2-weighted sequences, and differential enhancement of tumors and bladder wall is better appreciated with MRI (Figure 10-11).[120,122] Because urothelial carcinoma is often multifocal, CT or MRI should be performed to evaluate the entirety of the urothelial tract for the detection of additional masses, although CT urography is more commonly used for the evaluation of ureters and renal collecting systems with the help of multiplanar and 3D imaging. MR urography is performed with coronal heavily T2-weighted and postgadolinium 3D-GE T1-weighted sequences. Urine appears bright, with or without the use of gadolinium-based contrast agents. CT and MRI have similar accuracy of 70% to 90% for lymph node staging.[120] However, disease involving small lymph nodes less than 10 mm cannot be detected and enlarged lymph nodes may be reactive. Therefore, specificity is limited. Obturator lymph

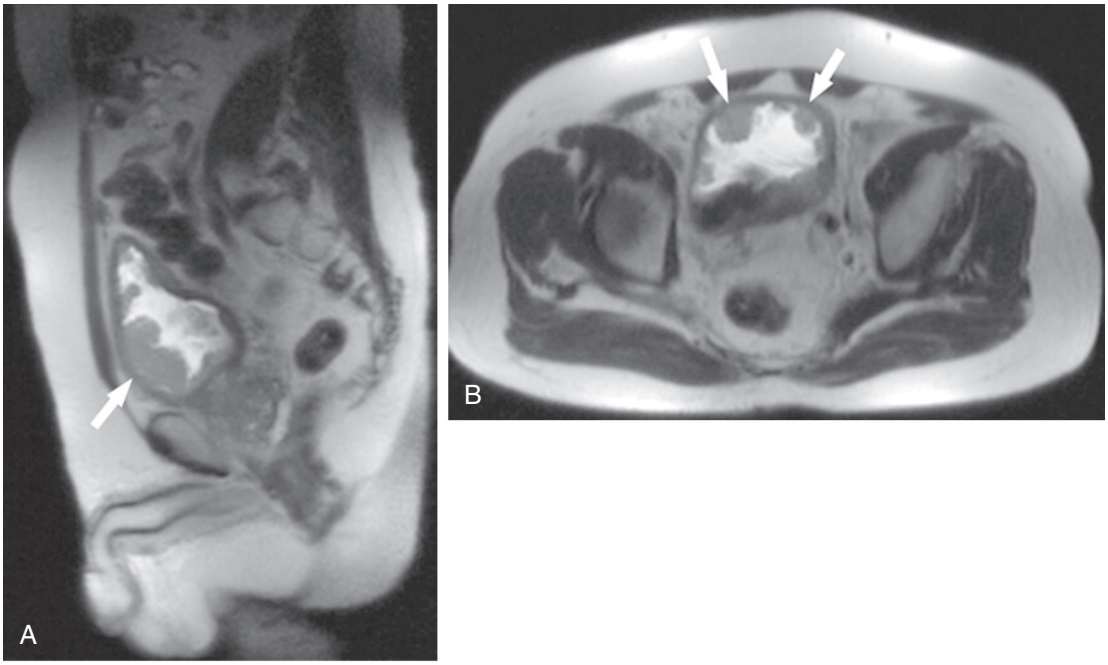


Figure 10-11 Male, age 82 years, with transitional cell carcinoma of the bladder. Sagittal **(A)** and axial **(B)** T2-weighted MRI images show multiple nodules *(arrows)* arising from the bladder wall surrounded by high-signal urine. There is no evidence of invasion of the low-signal muscular wall.

nodes, iliac, and retroperitoneal lymph nodes are the most commonly involved. In general, patients with enlarged lymph nodes are treated with chemotherapy before surgery.

Primary Gynecologic Tumors

Using either CT or MRI imaging, it is best to approach gynecologic cancers in a systematic way. The goals of abdominal and pelvic imaging are to identify the source of the mass whenever possible, locate findings indicative of extension such as peritoneal implants and ascites, assess lymph nodes for increased size and number, and determine whether there is renal compromise. Hydronephrosis will often need to be treated before chemotherapy can begin.

Primary Cervical Tumors

Cervical carcinoma is the third-most common gynecologic malignancy in the United States and the most-common gynecologic malignancy worldwide. The revised FIGO staging system recommends CT or MRI when available. CT has lower accuracy compared to MRI for local staging although CT is able to depict extensive disease, enlarged lymph nodes, hydronephrosis, a fistula into the bladder or rectum, and distant metastases.[124] MRI has higher accuracy than CT for the identification of important prognostic factors including tumor size, parametrial involvement, pelvic wall invasion, and bladder or rectal invasion. MRI has 93% accuracy for determination of tumor size.[125,126] MRI has similar accuracy for the detection of lymph nodes and can also depict ureteral involvement and hydronephrosis.[125,126] Tumor size less than 4 cm, with preservation of low signal intensity cervical stromal ring excludes parametrial invasion with a negative predictive value of 94% to 100%, MRI has 88% to 97% accuracy for the detection of parametrial invasion, which is a contraindication for surgery.[125,126] Dynamic contrast-enhanced imaging and diffusion weighted imaging may be helpful for the detection of small tumors or involvement of adjacent structures.[125]

MR imaging is used for the local staging of tumors at stage IB or higher. MRI can exclude local invasion into the adjacent organs with a negative predictive value of 100% and has 71% to 100% sensitivity and 88% to 91% specificity for bladder or rectal invasion.[125]

The presence of pelvic lymph node metastases does not change the FIGO staging but is a sign of poor prognosis. MR and CT have similar accuracies (85% to 90%) for lymph node detection and are both limited by size criteria.[125] PET/CT is especially helpful for the evaluation of lymph nodes and distant metastases and for the demonstration of posttreatment response. In western countries it has become the test of choice before surgery. MR-PET using the morphologic information from MRI and metabolic information from PET is a promising technique for the diagnosis and follow-up of cervical carcinoma.

Primary Uterine Tumors

Endometrial carcinoma is the fourth-most common malignancy in females and the most common gynecologic malignancy in the United States.[125-128] Adenocarcinomas comprise 90% and sarcomas 2% to 6% of endometrial neoplasms.[125-128] Adenocarcinoma with squamous cell differentiation and adenosquamous carcinoma form the remaining histologic types.[125-128]

On US examination of a postmenopausal woman, the thickness of the endometrium should not exceed 4 to 5 mm. Women with thickened endometrial linings on ultrasound examination may merit biopsy. However, even in the presence of vaginal bleeding, endometrial thickness of less than 4 to 5 mm usually excludes endometrial cancer. MRI has higher accuracy for the diagnosis and staging of endometrial carcinoma compared to CT. MRI plays significant role for the determination of prognostic factors including depth of myometrial or serosal invasion; involvement of cervix, vagina, adnexa, pelvic side wall, bladder, and rectum; and lymph node involvement.[125-128]

Surgical staging of endometrial cancer is done according to FIGO system.[128]

MRI is especially helpful for the evaluation of large tumors, and small tumors of intermediate and high risk. High-resolution T2-weighted images including the sagittal plane are essential for the evaluation of endometrial cancer. Diffusion weighted imaging may be helpful. Dynamic contrast-enhanced images including early and late phases are helpful for the determination of invasion of the tumor because the tumors show early increased enhancement compared to endometrium and myometrium and are prominently hypointense compared to myometrium on the late phases.[125-128]

MR and CT have similar accuracies (85% to 90%) for lymph node detection and are both limited by size criteria.[125,128] In cases in which pelvic lymphatic pathways are blocked by tumor, extension via the processus vaginalis to the inguinal nodes may occur. PET/CT may be especially helpful for the evaluation of lymph nodes and distant metastases and for the demonstration of posttreatment response.

Primary Ovarian Tumors

Ovarian cancer is the leading cause of death from gynecologic cancers in the United States and the majority of cases have advanced disease at the time of diagnosis with a 5-year-survival rate of 30% to 73%.[129] These lesions not infrequently are detected incidentally.[130] The risk of undergoing surgery for incidentally found adnexal masses is 5% to 10%.[129] Benign adnexal lesions are common even in the postmenopausal period.[129,130] Because the imaging features of benign and malignant ovarian neoplasms often overlap, the purpose of imaging is to differentiate benign lesions from indeterminate and malignant lesions and to stage malignant lesions.[129,130] Surgery, despite its risks, is the preferred diagnostic and therapeutic approach for indeterminate lesions rather than follow-up.

US and CT are usually the first modalities used for the evaluation of adnexal masses.[130,131] US has variable sensitivity (85% to 100%) and specificity (52% to 100%) levels for the detection of ovarian malignancies.[129,130] The sensitivity and specificity of CT for the diagnosis for indeterminate masses detected on US is 81% and 87%, respectively.[129,131] CT can successfully diagnose advanced ovarian cancers and may be used for presurgical or pretreatment evaluation and staging (Figure 10-12). PET/CT is not recommended for primary detection or diagnosis because of low sensitivity (52% to 58%) and specificity (76% to 78%) because borderline tumors and low-grade or small tumors may result in false-positive results, whereas inflammatory conditions including hydrosalpinx, endometriosis, and physiologic hypermetabolic uptake in premenopausal women may cause false-positive results.[129,132] However, PET/CT is successfully used for follow-up.[132] Although MRI has high sensitivity and specificity in the diagnosis of ovarian malignancy and staging of ovarian malignancies, it is not as commonly used as CT, primarily because of the time required to acquire and review images.[129,133]

Epithelial ovarian neoplasms constitute 90% of ovarian cancers and arise from the surface epithelium. These tumors, including serous, mucinous, clear cell, endometrioid, and Brenner tumors, are classified as benign, borderline malignant, or malignant. Epithelial malignant tumors typically present as cystic lesions with solid components, mural nodules, thick walls, and septae. Ascites, hydronephrosis, and omental and peritoneal implants are common accompaniments. Enlarged lymph nodes are less common but do occur. Borderline tumors usually present without ascites, peritoneal implants, or involvement of lymph nodes. Fat and fibrous tissue are present in benign ovarian tumors including dermoid tumors and fibromas, respectively.[129,133]

Metastatic Disease to the Pelvis

MRI and CT may both be used to identify tumors within the pelvis. With either technique it can be difficult to separate enhancement caused by inflammation or fibrosis from irradiation or surgical therapy from recurrent disease. Although the presence of a mass lesion abutting the peritoneal surface is indicative of a metastasis (Figure 10-13), the follow-up is important for the detection of small metastases. Enlarged lymph nodes are also usually an ominous sign. PET/CT is especially helpful for the evaluation of response to therapy and the detection of small metastases or metastatic lymph nodes during the follow-up and is usually used in combination with MRI. MR/PET may also be more helpful for the detection of early small volume disease.

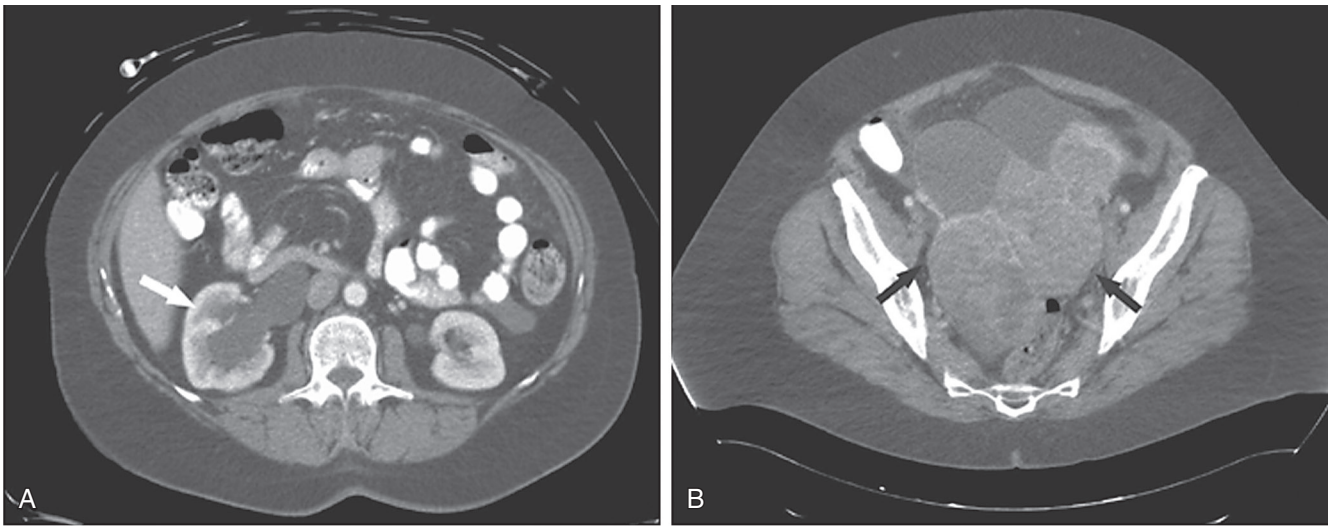


Figure 10-12 Female, age 57 years, with a pelvic mass. Axial contrast-enhanced images at the level of the kidneys **(A)** and pelvis **(B)** show an obstructed right kidney *(white arrow)* and bilateral pelvic masses with cystic and solid components *(black arrows)*. Upon resection this mass was found to consist of bilateral ovarian cystadenocarcinomas.

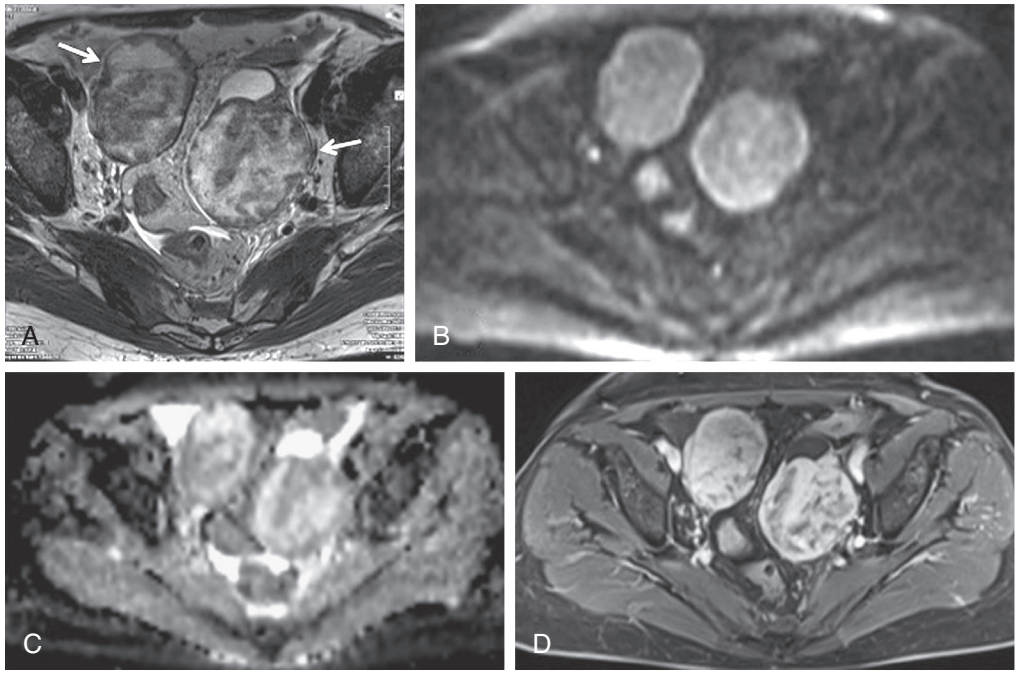


Figure 10-13 Female, age 40 years old with gastric adenocarcinoma with bilateral ovarian metastases (Krukenberg tumor). Both enlarged ovaries *(arrows)* with heterogeneous signal are seen on transverse high-resolution T2-weighted turbo spine echo (TSE) image **(A)**. The enlarged metastatic ovaries show increased signal on diffusion weighted (DW) image **(B)**, partially low signal on apparent diffusion coefficient (ADC) map **(C)** representing restricted diffusion and heterogeneous increased enhancement on postgadolinium image **(D).**

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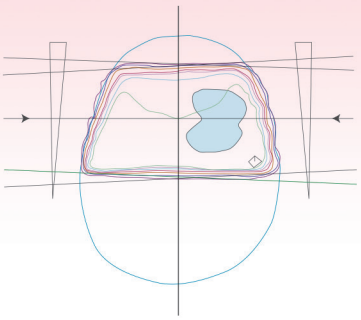
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CHAPTER

11 Nuclear Medicine



Terence Z. Wong, Amir H. Khandani, and Arif Sheikh

Molecular imaging techniques such as nuclear medicine are playing an increasingly important role in oncology. In particular, hybrid imaging modalities such as positron emission tomography/computed tomography (PET/CT) and single photo emission computed tomography/computed tomography (SPECT/CT) frequently provide more accurate initial staging and follow-up in oncology patients. Moreover, metabolic changes to therapy almost always precede anatomic changes, and functional imaging can be useful to assess early response to therapy.

Because CT is used routinely for radiation treatment planning, adding the metabolic information provided by PET or SPECT tracers provides a natural opportunity for selectively targeting tumor subpopulations. Adaptive treatment plans based on PET imaging are currently being investigated.

POSITRON EMISSION TOMOGRAPHY (PET)

Despite the exquisite spatial resolution of CT and magnetic resonance imaging (MRI), the physiologic aspects of disease processes are generally not revealed by these anatomically based modalities. Anatomic modalities also have shortcomings in assessing the early response to treatment and in distinguishing responders from nonresponders.

Over the past half-century, a variety of nuclear medicine probes have been used to evaluate disease processes at the cellular level. Nuclear medicine is the only clinical discipline using intracellular contrast agents in imaging, and it is therefore more sensitive than anatomic modalities in detecting disease processes. The concentration of tracer needed (picomolar levels) for PET imaging is many orders of magnitude less than needed to measure enhancement using MR or CT contrast agents (millimolar levels). On the other hand, nuclear medicine imaging techniques have generally suffered from low specificity and low spatial resolution, the latter being associated with the physics of single-photon-emitting radiotracers. Hybrid imaging (SPECT/CT, PET/CT, PET/MRI) affords the opportunity to combine the strengths of both anatomic and functional imaging.

PET is a nuclear medicine modality that uses positron emitters such as ^{18}F, ^{15}O, ^{13}N, and ^{11}C. The fact that these nuclides are components of common biologic molecules makes PET particularly suitable for visually capturing a wide range of biologic pathways. With the exception of ^{18}F these radionuclides have a relatively short half-life and generally require an on-site cyclotron for availability. The longer half-life (110 min) of ^{18}F has enabled ^{18}F PET tracers to be produced commercially at centralized cyclotron facilities and distributed widely for PET imaging.

Currently, the most widely used PET tracer is the glucose analog 2-deoxy-2-[^{18}F]fluoro-D-glucose (fluorodeoxyglucose [FDG]). FDG-PET has proven applications in staging and restaging a variety of malignancies. Currently, clinical investigations are under way using FDG-PET to evaluate early response to therapy, and some trials are incorporating adaptive treatment strategies based on the metabolic response. Although there is keen interest in developing additional PET tracers, FDG has proven to be a versatile general-purpose radiopharmaceutical and will likely remain a "workhorse" oncology tracer in the foreseeable future.

BASIC PHYSICS OF POSITRON EMISSION TOMOGRAPHY

The radioisotope portion of the molecule used in PET imaging emits a positron (i.e., positively charged electron), which travels a distance of a few millimeters in tissue before it collides with a negatively charged electron. This collision annihilates the entire mass of the positron and electron, generating two photons with energy of 511 KeV each. These two photons travel at the speed of light in exactly opposite directions (i.e., 180 degrees apart). Coincident detection of these two photons by two oppositely positioned detectors in the PET scanner results in images with a much higher resolution compared with the conventional, single-photon nuclear medicine studies.

PET/CT allows metabolic information from PET to be combined with the anatomic information from CT. PET/CT increases the diagnostic accuracy compared with stand-alone PET. In PET/CT, the patient undergoes a CT scan, followed by a PET scan, without changing the patient's position. PET for most oncologic indications is acquired from the base of the skull through the upper thighs. In some instances, such as in melanoma patients, PET is acquired from the vertex of the skull through the toes. The CT portion of PET/CT is acquired within seconds, whereas the PET acquisition time for each bed position (about 15 cm) is several minutes; the total PET acquisition time in newer machines is 15 to 25 minutes.

In addition to delivering anatomic information, the CT portion of PET/CT is used to measure the attenuation of the x-ray photons traveling through the patient to produce the so-called attenuation map and correct the PET data for tissue attenuation. During PET acquisition, photons from structures deep in the abdomen or pelvis are more strongly attenuated than those from superficial structures and the chest. The intensity of uptake in deeper structures is underestimated on nonattenuation-corrected PET images; the intensity of uptake in the deeper structures is normalized to the intensity of uptake in the superficial structures on the attenuation-corrected PET images (Figure 11-1). Attenuation correction of the PET data is also a prerequisite for quantification of radiotracer uptake in PET/CT scans.

Spatial alignment between the PET and CT scans is crucial both for correct anatomic localization and for accurate quantification. Misalignment may be caused by the changed position of a body part (e.g., neck, legs) or physiologic changes in the position of an organ (e.g., respiratory movement) between the CT scan and PET scan. The most commonly encountered problem occurs at the lung bases because CT is obtained over a short time interval and PET images are acquired with the patient quietly breathing. This respiratory misregistration can be minimized by acquiring the CT scan with respiration suspended in quiet end-expiration. Because the degree of misalignment and resulting mislocalization can be significant, the

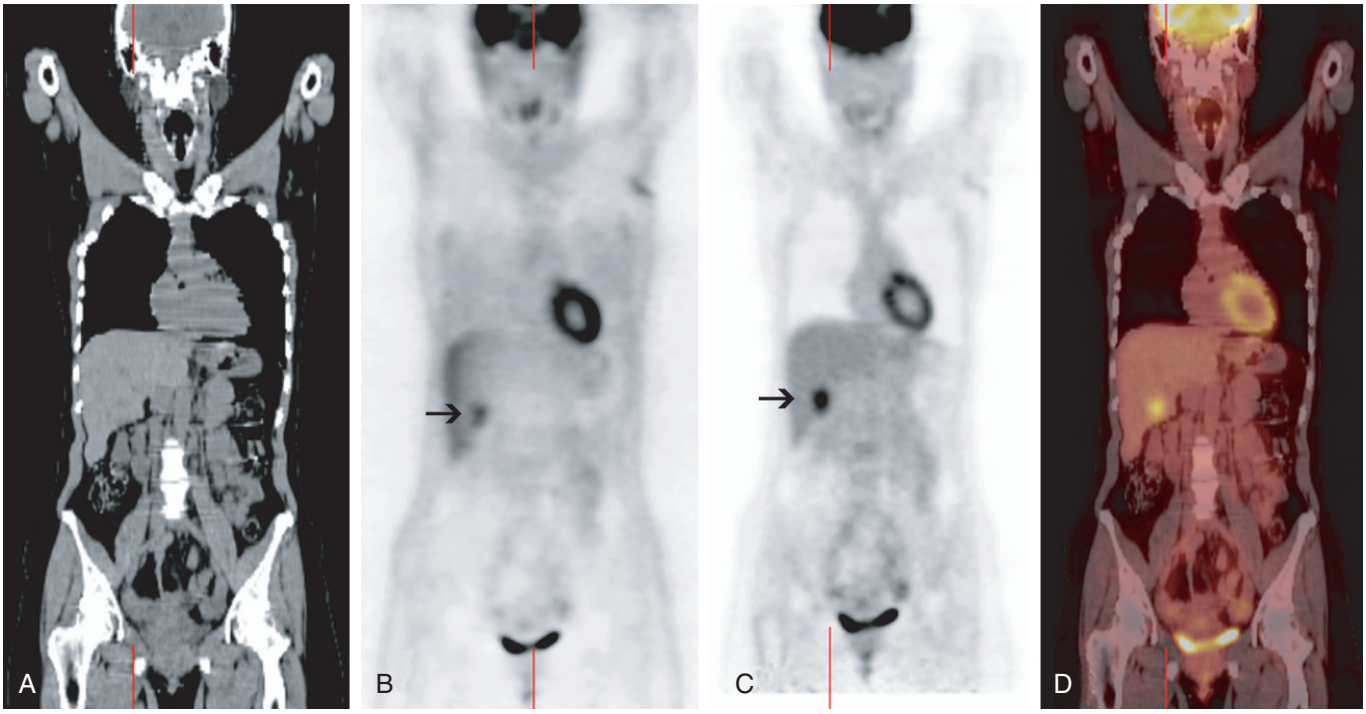


Figure 11-1 CT **(A)** provides diagnostic information (morphology), anatomic localization **(D)**, and photon attenuation data to equalize the intensity of uptake between deeper and superficial structures on the PET scans. In this example, the metastatic liver lesion *(arrow)* is better appreciated on the attenuation-corrected PET image **(C)** than on the nonattenuation-corrected PET image **(B)**.

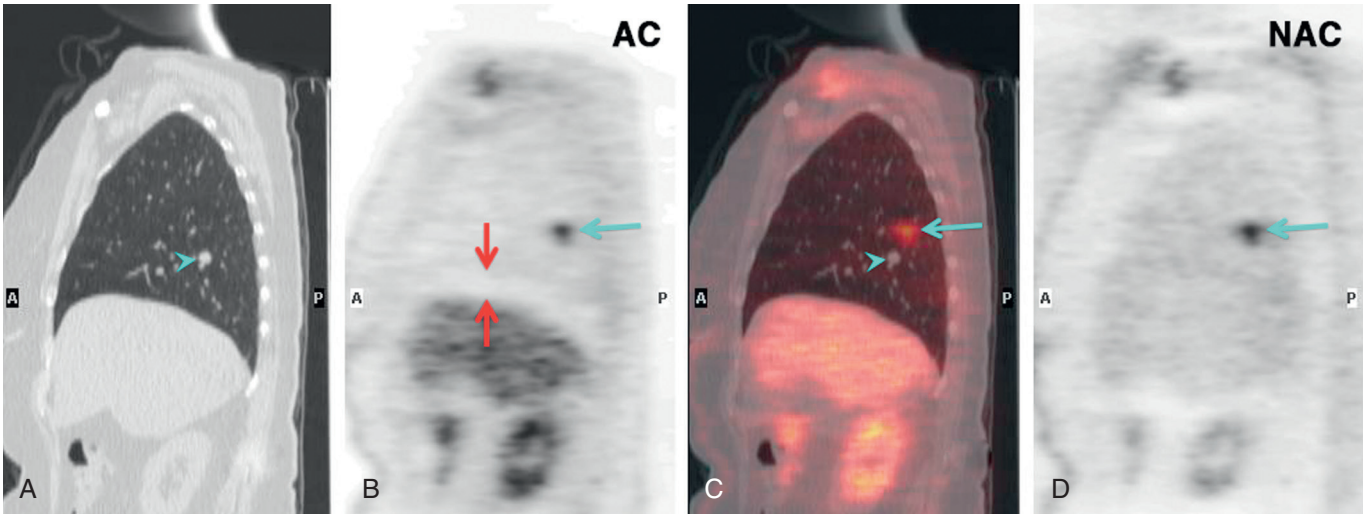


Figure 11-2 Respiratory misregistration. Patient took a full inspiratory breath during the CT scan **(A)**, while FDG-PET imaging (NAC = without attenuation correction) was obtained with the patient quietly breathing **(D)**. Consequently, the lung nodule on CT *(blue arrowhead)* does not correlate with the hypermetabolic focus *(blue arrow)* on PET, as illustrated on the fused PET/CT image **(C)**. On the attenuation-corrected (AC) PET images **(B),** a photopenic rim is noted at the lung base reflecting diaphragmatic misregistration *(red arrows)*. Because the CT scan is used for attenuation correction of the PET images, standardized uptake value (SUV) measurements made on misregistered lesions may not be accurate.

radiologist must be cautious when interpreting or quantifying the attenuation-corrected PET/CT images or using PET/CT images for radiation therapy planning. The magnitude of this misalignment can be assessed by using the fusion display of the nonattenuation-corrected PET images with CT. In case of significant misalignment, the nonattenuation-corrected PET images should be reviewed without fusion with CT, and the metabolic findings on PET should be correlated side by side with the anatomic findings on CT (Figure 11-2).

Current PET/CT scanners are equipped with multidetector CT (MDCT) and have full diagnostic CT capabilities that are equivalent to stand-alone CT scanners. This enables comprehensive PET/CT examinations to be performed that combine PET with fully diagnostic contrast-enhanced CT.[1] MDCT allows reconstruction to be performed using isotropic voxels, enabling multiplanar display of CT images with full spatial resolution. This provides optimal definition of target lesions as well as morphologic characterization and therefore can maximize the diagnostic capabilities of combined PET/CT imaging.

PET-MR has been introduced clinically relatively recently, which offers the ability of obtaining PET images with MRI,

and fusion of that information. MRI provides superior soft-tissue contrast compared to CT. In addition, advanced imaging sequences such as diffusion-weighted imaging (DWI) and dynamic contrast enhancement (DCE-MRI) permit quantitative physiologic information to complement the PET radiotracer information. MRI is also used to calculate attenuation correction for the PET images. Because MRI is limited in its ability to visualize bone and does not use photons, quantification of uptake on PET images may be less accurate compared to PET/CT. However, MRI has diagnostic advantages over CT in evaluating the brain, head and neck, and pelvis, and clinical applications for PET/MRI are currently being developed. Another advantage of MRI is that there is no associated ionizing radiation, so PET/MRI may have additional applications in the pediatric population.

GENERAL ASPECTS OF TUMOR VISUALIZATION ON FDG-PET

FDG is currently the most commonly used radiotracer in clinical PET imaging. Tumor imaging with FDG is based on the principle of increased glucose metabolism of cancer cells, which are more dependent on anaerobic glycolysis (Warburg effect). Like glucose, FDG is taken up by the cancer cells through facilitative glucose transporters (GLUTs). Once in the cell, glucose or FDG is phosphorylated by hexokinase to glucose-6-phospate or FDG-6-phosphate, respectively. Expression of GLUTs and hexokinase, as well as the affinity of hexokinase for phosphorylation of glucose or FDG, is generally higher in cancer cells than in normal cells. Glucose-6-phosphate travels farther down the glycolytic or oxidative pathways to be metabolized, in contrast to FDG-6-phosphate, which cannot be metabolized. In normal cells, glucose-6-phosphate or FDG-6-phosphate can be dephosphorylated and exit the cells. In cancer cells, however, expression of glucose-6-phosphatase is usually significantly decreased, and glucose-6-phosphate or FDG-6-phosphate therefore can become only minimally dephosphorylated and remains in large part within the cell. Because FDG-6-phosphate cannot be metabolized, it is trapped in the cancer cell as a polar metabolite, and it constitutes the basis for tumor visualization on FDG-PET scans.

The intensity of a malignant tumor on PET is dependent on the histology and number of malignant cells in the tumor mass. Hodgkin lymphoma and melanoma are markedly intense on FDG-PET, whereas other tumors such as bronchioloalveolar lung cancer, mucinous adenocarcinomas, or mucosal-associated lymphoid tissue (MALT) lymphomas may have only modest FDG activity. In addition, FDG is also taken up in benign processes such as infection and inflammation because white blood cells and fibroblasts are highly avid for FDG. The major causes for false positive and false-negative FDG-PET activity are summarized in Box 11-1.

Radiation therapy can elicit a chronic accumulation of metabolically active macrophages that are avid on FDG-PET scans. The time course is variable and is dependent on the tumor site, but FDG activity may persist for months in the radiation treatment field. An example of evolving postradiation therapy changes in lung cancer is shown in Figure 11-3. Interestingly, FDG-PET may be obtained during chemoradiation therapy to evaluate early response in patients with non–small-cell lung cancer, suggesting that this inflammatory activity may be delayed until some time after therapy.[2,3] In contrast, radiation therapy may result in false-positive FDG activity when evaluating early response to neoadjuvant therapy in esophageal cancer, and FDG-PET is typically used to evaluate early response to the chemotherapy alone prior to adding radiation therapy.

BOX 11-1 Potential Pitfalls in Oncologic Imaging with FDG-PET

I. FALSE-POSITIVE UPTAKE

1. Variant physiologic activity
   a. Cardiac
   b. Thyroid
   c. Gastrointestinal tract
   d. Genitourinary tract
   e. Brown fat, muscle
2. Nonmalignant conditions
   a. Inflammation, particularly chronic
   b. Atypical infection, including fungal
   c. Granulomatous diseases, sarcoidosis
   d. Pneumoconioses
   e. Benign neoplasms (adenomas)
   f. Reactive lymph nodes
3. Posttreatment changes
   a. Prior radiation therapy
   b. Talc pleurodesis
   c. Postsurgical

II. FALSE-NEGATIVE UPTAKE

1. Variable FDG metabolism
   a. Prostate adenocarcinoma
   b. Renal cell carcinoma
   c. Neuroendocrine tumors, carcinoid
   d. Adenocarcinoma in situ (bronchoalveolar)
   e. Lobular breast cancer
   f. Mucinous neoplasms
   g. Mucosa-associated lymphoid tissue lymphoma (MALT)
   h. Hepatocellular carcinoma
   i. Sclerotic osseous metastases
   j. Necrotic tumors and nodes
   k. Small or superficial lesions
   l. Sentinel lymph nodes
2. High adjacent FDG background activity
   a. Cerebral cortex
   b. Gastrointestinal tract
   c. Genitourinary tract
   d. Cardiac

PATIENT PREPARATION FOR FDG-PET

To minimize FDG uptake in the muscle while maximizing its uptake in tumor, patients are instructed to fast for at least 4 hours and avoid excessive physical activity for 24 hours before the PET appointment. Glucose-containing drinks and intravenous glucose should be avoided at least 4 hours before FDG injection. The fasting state lowers the serum level of glucose so that FDG has less competition for uptake by the tumor, whereas muscle uptake is minimized by fasting (by lowering the serum insulin level) and by avoiding excessive physical activity; low FDG uptake in the muscles improves the tumor-to-background ratio and the image quality.

High glucose levels in diabetic patients can decrease the image quality. Although a normal glucose level in diabetic patients before FDG injection is desirable, it often cannot be achieved. Most institutions perform PET for diabetics after one or two attempts to reduce the serum glucose level below an empirically set level of 200 to 250 mg/dL. Although the positive predictive value of the findings on such a scan remains high, the negative predictive value may be reduced. In patients with diabetes, the image quality (i.e., muscle and soft-tissue uptake) should be assessed before interpretation and mentioned in the report.

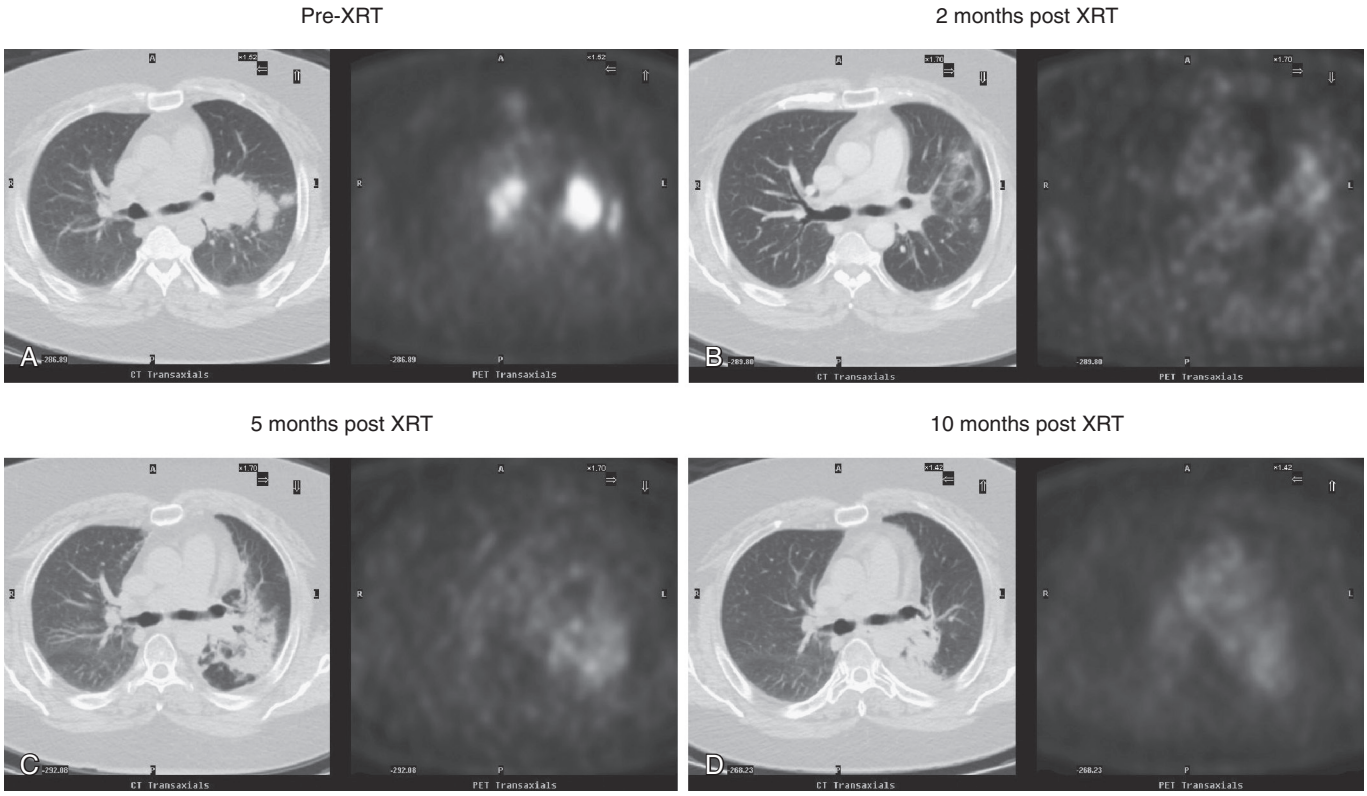


Figure 11-3 Evolution of posttreatment changes in the lung following radiation therapy. Pretherapy PET/CT scan **(A)** demonstrates bilateral hilar masses, predominantly on the left. PET/CT at 2, 5, and 10 months following radiation therapy **(B-D)** include evolving atelectasis and bronchiectasis on CT, with associated mild homogeneous FDG accumulation. The geographic distribution and absence of focal FDG accumulation are characteristic of expected postradiation changes.

FDG uptake in the brown fat in the neck and supraclavicular regions may obscure pathologic findings in these areas. FDG uptake in brown fat is even more extensive in pediatric patients, and it can be seen in the mediastinum, paraspinal region, and upper abdomen. Diazepam administration can reduce the FDG uptake in brown fat.

PET QUANTIFICATION

As previously mentioned, one of the advantages of PET imaging with attenuation correction is the ability to measure activity within target lesions. The standardized uptake value (SUV) is a semiquantitative measure of the tracer uptake in a region of interest that normalizes the lesion activity to the injected activity and a measure of the volume of distribution (usually total body weight or lean body mass). For FDG-PET, it is generally accepted that SUV alone is not reliable to differentiate malignant from benign processes and that other factors, including lesion location, size, CT morphology, pattern of contrast enhancement, and symmetry contribute to this evaluation. In addition, there are many technical and biological factors that can influence the observed SUV, such as the patient's serum glucose, the time between tracer injection and image acquisition, the detector technology of the PET scanner, attenuation-correction map, imaging field of view, and the image reconstruction parameters.[4] Nonetheless, SUV may be useful as a measure to follow the metabolic activity of a tumor over time within the same patient and to compare different subjects within a research study under defined conditions. For FDG-PET, the magnitude of early response to therapy varies with tumor histology. Most malignancies responding to therapy exhibit a 20% to 35% reduction in SUV early in the course of therapy, and these changes have prognostic significance.[5] On the other hand, Hodgkin lymphoma and gastrointestinal stromal tumors (GIST) have a dramatic response on FDG-PET soon after initiation of therapy, which can be assessed visually. Several clinical trials are investigating the ability of PET to direct therapy based on metabolic response early in the course of therapy. Currently, SUV measurements are not sufficiently standardized between PET/CT scanners, and the baseline and follow-up scans should be performed on the same PET/CT scanner for reliable assessment of early response to therapy.

MOST COMMON INDICATIONS FOR FDG-PET/CT IN ONCOLOGY

Lung Cancer

FDG-PET/CT (referred to hereafter as PET) has an overall sensitivity higher than 90% and specificity of about 85% for diagnosing malignancy in primary and metastatic lung lesions; the sensitivity and specificity of PET for small cell lung cancer are similar. The sensitivity of PET for bronchioloalveolar lung cancer and carcinoid of the lung is about 60%, and the specificity of PET for lung cancer is lower in areas with a high prevalence of granulomatous lung disease. PET is particularly useful in patients with a low (5% to 20%) or intermediate (20% to 70%) risk of lung cancer, as determined by an evaluation of symptoms, risk factors, and radiographic appearance. In these cases, PET is helpful in moving the patient to the very-low-risk (<5%) or high-risk (>70%) category.[6] It is expected that the use of PET for diagnosing malignancy in indeterminate lung nodules will continue to grow as more patients are diagnosed

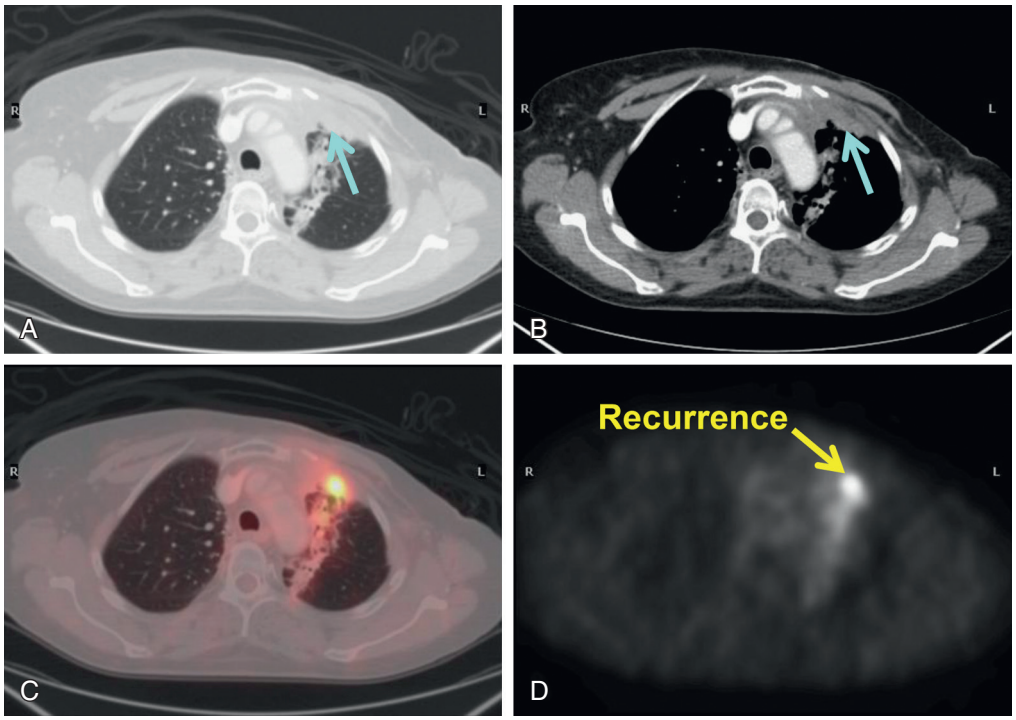


Figure 11-4 Recurrence following radiation therapy. Contrast-enhanced CT (with lung **(A)** and soft-tissue **(B)** windows) demonstrates opacity in the left upper lung in a geographic distribution consistent with postradiation therapy changes. Fused PET/CT **(C)** and PET **(D)** images reveals expected mild activity within the radiation treatment field, but superimposed focal activity *(arrow)* on FDG-PET corresponding to a focal area of nodular pleural thickening on CT *(light blue arrows)* which was subsequently shown to represent recurrent tumor.

with nodules on CT performed for other indications or as a screening test. Most of the current PET scanners are capable of detecting lung lesions as small as 4 to 5 mm.

In mediastinal staging of non–small cell lung cancer (NSCLC), patients with clinical stage I and II disease have by definition a radiographically negative mediastinum. However, in patients with central tumors, adenocarcinoma, or N1 lymph node enlargement, the false-negative rate of CT for mediastinal involvement is 20% to 25%. It is unclear whether PET should be used instead of mediastinoscopy in staging the disease of these patients. In mediastinal staging of clinical stage III tumors, positive results of PET need to be confirmed by tissue diagnosis because of a relatively high false-positive rate (15% to 20%). The false-negative rate of PET and mediastinoscopy in assessing enlarged mediastinal lymph nodes is 5% to 10%, and some authorities therefore do not pursue biopsy in the case of a negative PET result for disease in the mediastinum, whereas others argue that mediastinoscopy can detect "microscopic" metastases, and they are not comfortable accepting a negative PET result.[7] Practically, in larger centers, patients with stage III tumors undergo both PET to assess for distant metastases, and mediastinoscopy, but a strong argument for staging of the mediastinum with PET can be made in communities without an experienced mediastinoscopy service. In any case, it should be noted that the term *microscopic* is not well defined, and that routine pathologic tissue processing may be a limiting factor in detecting microscopic disease.

For patients with clinical stage I peripheral tumors, most authorities do not request mediastinoscopy before surgery because the rate of mediastinal or systemic involvement is very low (about 5%). Among patients with clinical stage II tumors, the rate of metastatic disease is higher, and there is a debate about whether PET is warranted in these patients to assess for systemic disease. For stage III tumors, the false-negative rate of clinical evaluation for systemic disease is about 15% to 30%, and PET therefore is justified instead of a battery of other tests (e.g., bone scan, CT, MRI) to assess for distant metastases.[7] According to the most recent recommendations of the American College of Chest Physicians, in patients with a normal clinical evaluation and no suspicious extrathoracic abnormalities on chest CT who are being considered for curative-intent treatment, PET is recommended to evaluate for metastases.[8] PET is more sensitive (90% versus 80%) and more specific (90% versus 70%) than bone scan in detecting bone metastases from NSCLC; PET has a sensitivity and specificity of greater than 90% in detecting adrenal metastases from NSCLC. Brain CT or MRI is still needed because PET cannot reliably detect brain metastases because of physiologically intense brain uptake of FDG. For patients with stage IV tumors, PET can potentially indicate the best accessible site for biopsy.

PET is also useful in restaging NSCLC. In particular, PET appears to be more sensitive than CT in differentiating postirradiation change from local recurrence, although differentiating these two entities remains a challenge. The postirradiation change in the chest can remain intense on PET for up to several years. In differentiating local recurrence from postirradiation change, the intensity of uptake and its shape should be taken into account (Figures 11-3 and 11-4).

Head and Neck Cancers

Most patients with head and neck cancers present for PET with a known diagnosis. However, cervical lymph node metastases from an unknown primary constitute about 5% of newly diagnosed head and neck cancer cases; CT and MRI can identify up to 50% of the primary tumors in patients with no findings on physical examination. The overall PET detection

rate in patients with negative results of physical examination, CT or MRI, and endoscopy is about 25%. However, this number is probably higher if PET is performed before endoscopy. In one prospective study, patients underwent PET prior to endoscopy but the results were first not revealed to surgeons performing the procedure under anesthesia. The surgeons were able to find the primary site of the disease in only 5 out of 20 patients. When PET information was revealed to the surgeons during the procedure, they were able to find the primary site of the disease in another 6 patients, which improved the detection rate to a total of 11 out of 20 patients.[9] It should be noted that knowledge of the variable benign and physiologic uptake patterns in the head and neck region is essential to minimize false-positive interpretations.

In initial staging of head and neck tumors, PET has a sensitivity and specificity of about 90% for nodal staging, and PET therefore is more sensitive and specific than CT or MRI. A weakness of PET is its low sensitivity (30%) for nodal disease in patients with clinically N0 necks. Given the high specificity of PET in nodal staging, it appears reasonable to perform neck dissection in patients with a positive PET result, whereas those with a negative PET result may be able to undergo sentinel node localization and biopsy.[10] In addition to local staging, PET can detect synchronous malignancies and distant metastases. In initial staging of head and neck malignancies, a PET scan is overall most helpful in patients with locally advanced disease because these patients have a risk of 10% or greater for distant disease. Furthermore, PET has been playing an increasingly important role in planning of radiation treatment in patients with head and neck cancers because it helps to better delineate the primary tumor from surrounding tissue and differentiate between metastatic and benign lymph nodes.

For restaging of head and neck tumors after radiation therapy, PET is highly sensitive but should be performed at least 3 months after irradiation to avoid false-positive findings. Patients with a negative scan at 3 months after irradiation can be followed without intervention (i.e., high negative predictive value), but those with a positive scan need to undergo further evaluation and probably biopsy.[10] For follow-up of the patients with a negative FDG-PET 3 months after completion of radiation therapy, there are currently no definitive data to indicate the time interval and total duration of the follow-up, and this should depend on the patient's individual risk factors.

Lymphoma

Hodgkin disease and high-grade non-Hodgkin lymphoma are mostly markedly avid for FDG and almost always visible on PET, whereas low-grade non-Hodgkin lymphoma may be only mildly intense and, in rare cases, completely invisible on PET. FDG-PET is superior to CT in staging of lymphoma and is recommended by the International Harmonization Project (IHP) for staging of Hodgkin lymphoma and aggressive non-Hodgkin lymphoma because of their consistent FDG avidity and potential curability. Furthermore, it is reasonable to use FDG-PET in all lymphomas except chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL), marginal zone lymphoma (MZL), and some peripheral T-cell lymphoma (PTCL)[11]; however, there is no definite evidence that PET changes the initial management in a significant number of patients with lymphoma. Other controversial issues related to the initial stating of lymphomas with PET include the sequence of imaging tests to avoid redundant testing and the routine use of contrasted CT after PET/CT. Contrasted CT is definitely helpful to better delineate intraabdominal disease and for reliable measurement of lymph node size.[11]

The normal spleen shows mild uptake, whereas the uptake of the normal bone marrow can be variably intense. Intense spleen uptake (i.e., more intense than the liver) before chemotherapy is a reliable indicator of its involvement, but spleen involvement by lymphoma cannot be excluded with normal uptake. PET can be used to identify areas of bone marrow involvement although the impact of this on the overall staging is unclear because most patients with clearly visible marrow involvement on PET have other sign of stage IV disease. The relevance of PET in this setting remains controversial. Activation of hematopoiesis after chemotherapy or by bone marrow stimulating factors can cause intense uptake in the bone marrow, spleen, or thymus, which can persist for a while after the termination of the chemotherapy or stimulating factors.

The most promising role of PET in lymphoma management appears to be in therapy monitoring: early prediction of response to chemotherapy (i.e., interim or midway PET) and evaluation of a residual mass for active lymphoma at the completion of chemotherapy (i.e., end-of-treatment PET). The decrease of uptake associated with effective chemotherapy seen on interim PET precedes the anatomic changes seen on CT by weeks to months. At the completion of chemotherapy, CT demonstrates a residual mass at the initial site of disease in as many as 50% of patients. On the end-of-treatment PET, these patients demonstrate increased FDG uptake in the area of residual lymphoma in contrast to those without active lymphoma. The positive predictive value of residual uptake at the completion of chemotherapy is more than 90%. The negative predictive value is likely lower and associated with microscopic remnant disease. Generally, patients with non-Hodgkin lymphoma and stages III and IV Hodgkin disease and negative PET results at the completion of chemotherapy should undergo repeat PET at least once at about 6 weeks after the last cycle of chemotherapy.

In follow-up of patients in remission, PET is more sensitive than CT in detecting recurrent disease. However, there are no guidelines as how often follow-up PET scans should be performed. Follow-up PET scans are often performed, depending on the individual risk factors, as frequently as every 3 months.

Colorectal Cancer

PET plays no role in the screening or diagnosing of colorectal cancer, and neither the depth of the tumor nor the local lymph nodes status can be assessed by PET. However, PET is highly sensitive in detecting distant hepatic and extrahepatic metastases. A meta-analysis of the literature on detection of hepatic metastases from colorectal, gastric, and esophageal cancers by ultrasound, CT, MRI, and PET found that in studies with a specificity higher than 85%, the mean weighted sensitivity was 55% for ultrasound, 72% for CT, 76% for MRI, and 90% for PET. Results of pairwise comparison between imaging modalities demonstrated a greater sensitivity of PET than ultrasound ($p = 0.001$), CT ($p = 0.017$), and MRI ($p = 0.055$). The conclusion was that at equivalent specificity, PET is the most sensitive noninvasive imaging modality for the diagnosis of hepatic metastases from colorectal, gastric, and esophageal cancers.[12] Considering the higher sensitivity of PET in detecting distant metastases and the introduction of intravenous contrast to the CT portion of fused PET/CT, it is conceivable to use PET/CT in preoperative staging of colorectal cancer; the contrast-enhanced CT portion of PET/CT can be used instead of conventional CT or MRI for evaluation of anatomic resectability of liver metastases. PET plays an important role in restaging of colorectal cancer. PET can visualize the site of the local and distant disease when recurrence is suspected based on the clinical findings, findings on other imaging modalities, or an increasing carcinoembryonic antigen level with sensitivity and specificity higher than 90% (Figure 11-5).

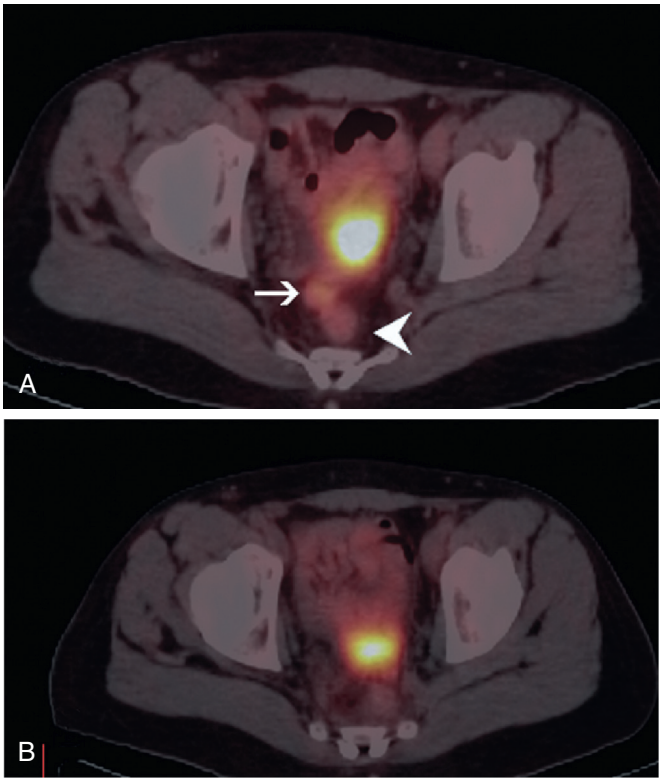


Figure 11-5 PET/CT for differentiating local recurrent from scar in a patient with colon cancer, status after low anterior resection. Recurrent disease was suspected based on increasing carcinoembryonic antigen (CEA) level. CT is not able to differentiate between scar and local recurrence. **A,** FDG-PET indicated an intense focus *(arrow)* suspicious for malignancy. A second mild focus was interpreted as scar *(arrowhead)*. **B,** The diagnosis was confirmed surgically and the recurrent tumor was removed.

Breast Cancer

PET can increase the detectability of small primary breast cancers and may be useful especially in evaluating patients with dense breasts. In evaluating the axillary lymph nodes, PET does not play any role because of its low sensitivity (60%) despite relatively high specificity (80%).[13] In contrast, PET is relatively sensitive (85%) and specific (90%), and it is superior to CT (sensitivity of 54%, specificity of 85%) in evaluation of the internal mammary chain lymph node for metastases. The main role of PET in breast cancer lies in the investigation of distant metastases and response monitoring. Compared with CT, PET has a higher sensitivity (90% versus 40%) but lower specificity (80% versus 95%) in detecting metastatic disease. Overall, PET has the same sensitivity as bone scan in detecting bone metastases (both about 90%), but PET appears to be somewhat more sensitive than bone scan for osteolytic lesions and somewhat less sensitive than bone scan for osteoblastic lesions. PET has a higher specificity than bone scan in detecting bone metastases (95% versus 80%). This may be explained by the fact that PET captures the metabolic activity of the tumor cells independently of changes in the bone, whereas bone remodeling seen on bone scan can result from metastatic disease and benign causes. Overall, priority should be given to FDG-PET over ^{99m}Tc bone scan for staging purposes not only because FDG-PET can detect both bone and soft-tissue metastases.

In patients with advanced breast cancer undergoing neoadjuvant chemotherapy, PET differentiates responders from nonresponders as early as after the first cycle of therapy. This may help improve patient management by avoiding ineffective chemotherapy and supporting the decision to continue dose-intensive preoperative chemotherapy in responding patients although universal criteria for assessing response have not been established. PET has great efficacy in cases of suspected recurrence and surpasses conventional imaging (including bone scan) for whole body evaluation.

FDG-PET/CT Applications in Other Malignancies

In esophageal and gastric cancer, PET is useful to assess for distant disease. In esophageal cancer, PET has the potential to be used for monitoring the effect of neoadjuvant therapy. In ovarian, uterine, and cervical cancer, PET is used to assess for recurrent disease. In cases of cervical cancer, because of its greater sensitivity than CT and MRI for detecting paraaortic nodes, PET plays an important role in nodal staging and radiotherapy planning. In malignant melanoma, PET is used to evaluate the presence of distant metastases at the time of initial diagnosis and to assess for recurrent disease after initial treatment in high-risk patients. In sarcoma, the most intense areas on PET have usually the highest grade and should be considered for biopsy.

Targeted Imaging in Nuclear Medicine

From its inception, nuclear medicine has used specific physiologic and biophysical targets for imaging and therapy.

Because nuclear imaging techniques have had high sensitivities with known lower specificities, agents with greater specificity are being developed. Even though there may be some trade-off in sensitivity compared with other nuclear modalities, they have proved to be better than general radiologic modalities for many indications, and in some cases, they can be used for targeted radionuclide therapies. Newer imaging technologies have been developed that greatly enhance molecular imaging.

Traditionally, nuclear imaging involves planar imaging using single photon emitters, such as technetium-99m (^{99m}Tc), indium-111 (^{111}In), iodine-123 (^{123}I), among many others. However, it is also possible to do tomographic—or SPECT—imaging of radiotracers, providing overall greater accuracy of lesion diagnosis and detection. Compared to PET imaging, SPECT imaging has lower resolution, and can be further limited in large patients because of inherent attenuation. In the last few years, however, there have been substantial advances using concurrent CT imaging—as in PET/CT—for both attenuation correction as well as anatomic localization. The result has been the development of SPECT/CT that has provided a great leap forward in disease evaluation and the continued development of molecular imaging independent of PET/CT.

In the realm of radiopharmaceutical development, some agents rely on targeting using antibodies or their fragments, peptides, or are receptor or even gene specific. Although established procedures like FDG-PET imaging are clearly superior to most of these newer methods at the present time, they remain clinically important in sites where PET may not be available. Nevertheless, radiopharmaceutical development in both the PET and SPECT side show promise in the evaluation of disease, and the evolution of molecular imaging.

Bone Scanning

Bone scanning is the most basic oncologic imaging procedure in nuclear medicine. Its utility has long been proven in multiple diseases in both detection of osseous metastases and in follow-up. Traditionally, the study is done using planar whole

body studies using ^{99m}Tc-labeled bisphosphonates, most commonly methyl diphosphonate (MDP) and hydroxyethylene diphosphonate (HDP). Multiple additional limited planar or SPECT views can also be obtained by focusing in on the body part of interest. The procedure allows a rapid skeletal survey and an overall assessment of disease.

There are drawbacks to this modality. MDP and HDP accumulation is related to the osteoblastic phase of bone remodeling, so planar bone scintigraphy is relatively insensitive for the detection of lytic lesions. In addition, bone remodeling occurs in many conditions, including arthritis, inflammation, trauma, benign and malignant neoplasms, and metastatic disease, reducing the specificity of the study. SPECT and SPECT/CT imaging can improve both the sensitivity and specificity of the study; however, a single SPECT acquisition can take 15 to 30 minutes and only covers a selected area of the body. Some have advocated whole-body SPECT studies, which could take more than 90 minutes of scan time.

^{18}F-sodium fluoride (NaF) was one of the first radiopharmaceuticals used for skeletal scintigraphy, but it fell out of favor with the development of ^{99m}Tc tracers and improved gamma camera technology. However, there is now renewed interest in bone imaging with NaF utilizing PET/CT technology.[14] Additional advantages of NaF-PET/CT compared to ^{99m}Tc bone scans include shorter uptake time (1 hour versus 2 to 4 hours) and the ability to obtain diagnostic contrast-enhanced CT scans along with the NaF-PET images. Although NaF is FDA approved, NaF PET scanning is currently being evaluated by CMS at the time of writing this manuscript for potential reimbursement as a routine clinical procedure.

Antibody-Based Imaging Agents

One of the more successful antibody-based agents is ProstaScint (capromab pendetide), an antibody against prostate membrane surface antigen, a type II membrane glycoprotein strongly associated with prostate cancer. The usual indication is a rising prostate-specific antigen (PSA) level in a patient who has had a prostatectomy but who has no obvious location for a metastatic focus as determined by CT or MRI. These modalities have sensitivities of disease detection of only 5% to 20%, although they have much higher specificities. The accuracies for capromab imaging are about 70%, although it is much less sensitive than bone scan for skeletal metastases. Absence of extrapelvic disease on capromab and other studies may allow for radiotherapy to the pelvis.

Carcinoembryonic antigen scans use a labeled murine antibody fragment (^{99m}Tc-arcitumomab) to detect recurrent colorectal and breast cancer. OncoScint (^{111}In-satumomab pendetide) is another antibody also used for detection of recurrent colorectal and ovarian carcinomas. The sensitivity of extrahepatic disease recurrence detection for satumomab is 97%, whereas for CT scan it is 72% for colorectal malignancy. For liver metastases CT is better, but when the two modalities are combined, the sensitivity is approximately 90%.[15] Although FDG-PET outperforms these modalities and is the scan of choice, the antibodies may be of clinical value if FDG-PET is not available.

Clear cell renal cell carcinomas can constitute up to ~55% to 60% of histologies of incidentally discovered renal masses, and methods to identify this aggressive malignancy early and preoperatively could be useful. A recently developed agent—^{124}I-cG250 (Girentuximab)—a radiolabeled chimeric antibody against the carbonic anhydrase IX (CA IX), is reactive in >95% in immunohistochemical assays on fresh frozen tissues and can be used with PET/CT imaging. A phase I trial for this agent showed more than 90% accuracy for the detection of primary clear cell renal carcinoma, although the accuracy for metastatic disease detection was not studied.[16] This agent is still undergoing review for clinical approval as an imaging agent.

Cellular Imaging

Various agents being developed build on the newer understanding of cellular physiology, including angiogenesis, apoptosis, and other ideas. Some are routinely used clinically, but others show potential for future development and may revolutionize the way cancer is approached.

^{18}F-fluorothymidine (^{18}F-FLT) is a thymidine analog and a PET tracer, which is phosphorylated by thymidine kinase-1 (TK1) to FLT-monophosphate. FLT uptake correlates with TK1 activity and cellular proliferation. FLT may be more suitable than FDG to monitor the effect of chemotherapy and radiation therapy. Another important area of current PET tracer research concerns cell-cell and cell-matrix interaction. Tracers such as ^{18}F-galacto-GRD (glycosylated Arg-Gly-Asp) enable the noninvasive determination of integrin $\alpha_v\beta_3$ expression and are being evaluated for use in assessing angiogenesis and metastatic potential of tumors.

Annexin-V shows great promise for evaluating apoptosis, and it is available as a single-photon and PET agent. Highly apoptotic areas in tumors may be more likely to be sensitive to irradiation or chemotherapy, and there is the potential for evaluating therapy response or overall disease prognosis with such agents. Similarly, the field of tumor hypoxia is central to the understanding of tumor response to irradiation. PET agents such as ^{18}F-fluoromisonidazole (^{18}F-MISO) and Cu-labeled diacetyl-bis (*N*(4)-methylthiosemicarbazone (Cu-ATSM) can be used to detect intratumoral hypoxia. Although still in the evaluation phase, these agents could potentially be used to evaluate areas of hypoxia for targeting radiation delivery.[17]

Recently, ^{11}C-choline has obtained clinical approval in the United States for imaging prostate cancer. Tumor cells produce abundant quantities of choline because it is a precursor of phosphatidylcholine, a major constituent of membrane lipids, which along with proteins, are synthesized during cell proliferation. Choline kinase is upregulated in malignancy, which leads to incorporation and trapping of choline into lecithin. The limitation for this tracer is that its use requires proximity to a cyclotron given its short half-life. A recent study showed an accuracy of 99% when ^{11}C-choline PET is used in a hybrid PET-MRI scanner.[18] ^{18}F-fluorocholine (FCh)[19] and ^{18}F-FACBC (1-amino-3-fluorine 18-fluorocyclobutane-1-carboxylic acid)[20] are also being evaluated for evaluating prostate cancer, and will also likely benefit from the combination of PET/MRI.

Neuroendocrine Tumor Imaging

^{111}In-octreotide is a peptide that is routinely indicated for neuroendocrine tumors, including carcinoids, tumors associated with the multiple endocrine neoplasias, meningiomas, and lymphomas (i.e., Hodgkin disease and non-Hodgkin lymphoma). Increased activity can be seen in benign disease such as sarcoidosis and other inflammatory processes. ^{111}In-octreotide has the highest affinity for somatostatin receptor (SSTR) subtypes 2 and 5, with weaker affinities for others. This agent is still relevant in the era of PET because many of the well-differentiated lesions will not take up FDG. Even so, many diseases do not have appropriate receptor expression and therefore have limited detection on such scans. A similar agent, ^{99m}Tc-depreotide, has greater affinities for SSTR 2, 3, and 5 and therefore has the potential for greater sensitivities for tumors with various SSTR expressions and uptake in a broader number of malignancies, including lung cancers.

Routine imaging of neuroblastoma and pheochromocytomas involves metaiodobenzylguanidine (MIBG), a

norepinephrine analog taken up by the uptake 1 mechanism in receptors. It has uptake in many of the same malignancies as octreotide, although not with the same frequency. For imaging, MIBG may be labeled with ^{131}I, ^{123}I, or ^{124}I, a positron emitter. The sensitivity for lesion detection can exceed 90%, and specificity approaches almost 100% for single photon imaging.[21] Nevertheless, as tumors de-differentiate or metastasize to other sites, specifically the bones, MIBG becomes less sensitive in detecting disease, in which case a bone scan is useful. With the advent of ^{124}I-MIBG used in PET/CT, it is unknown whether the increased resolution will allow better detection of disease, obviating the need for bone scans.

There is growing interest in being able to use newer tracers such as 3,4-dihydroxy-6-^{18}F-fluoro-phenylalanine (^{18}F-FDOPA) and PET in neuroendocrine imaging, which use neurohumoral pathways of uptake, and trapping similar in concept to that of FDG to concentrate in relevant areas. Many studies show that this tracer has far greater accuracy for disease detection than either octreotide analogs or MIBG.[22] Unlike the SPECT counterparts, the PET imaging can be done within an hour after injection, with PET quality images. Still, ^{18}F-FDOPA is most useful in the well-moderately differentiated tumors, with FDG being superior for the more poorly differentiated ones. Additionally, octreotide based positron tracers labeled with ^{68}Ga—such as [1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid]-1-Nal3-octreotide (^{68}Ga-DOTANOC), and others—are undergoing review, with at least one of these forms expected to be approved in the near future for imaging.[23]

Other Modalities

Breast-specific gamma imaging (BSGI) is gaining interest in breast imaging. The limitations and controversies surrounding mammography are well known. Single photon gamma devices have now been developed for specifically imaging breast. These use ^{99m}Tc-Hexakis (2-methoxy-2-methylpropylisonitrile), also known as sestamibi, a tracer which has been used for imaging in malignancies before the rise of FDG PET or where PET was not readily available. The modality may be particularly useful in denser breasts where traditional mammographic evaluation is more limited. Recent publications have shown good ability to evaluate lesions, with an overall accuracy of about 91%.[24]

Positron emission mammography (PEM) similarly uses breast-specific PET imaging technology with FDG. Again, this holds promise in mammography, demonstrating significant improvement in diagnostic accuracy. Studies have demonstrated a similar performance as compared to breast MRI, providing complementary information in the evaluation of breast cancer. Still, even combining these modalities show some limitations in the initial surgical management of disease.[25]

TARGETED RADIONUCLIDE THERAPY

Imaging agents are valued more for their sensitivity, but for targeted therapy, it is the specificity that is essential. Many imaging agents are specific enough for therapeutic purposes. Treatment of well-differentiated thyroid cancer, radioimmunotherapy, and bone metastases pain palliation are discussed elsewhere in this text. The following sections provide examples of selected therapies used in other clinical settings that show promise for development in the near future.

Thyroid Diseases

Thyroid diseases are the most successful clinically relevant application of targeted therapy. The thyroid's unique ability to metabolize elemental iodine to synthesize thyroid hormones is fortuitous because it is a highly specific but easily targeted process with radioactive iodine. Treatment is effective, is virtually definitive, and has minimal side effects. There are practically no long-term sequelae from appropriate radioactive iodine administration for benign thyroid disease. Generally, radioactive iodine treatment in benign disease is reserved for hyperthyroid conditions, such as Graves disease or toxic and multinodular goiters. Radioactive iodine is used when the disease cannot be controlled medically, and it is often a first-line option in clinically hyperthyroid patients. Surgery is reserved for instances in which radioactive iodine may be contraindicated (e.g., pregnancy, marrow suppression, etc.) or when there may be compressive findings of the enlarged thyroid on critical structures, such as the trachea.

Patients with thyroid cancer have traditionally undergone 4 to 6 weeks of L-thyroxine withdrawal before radioiodine scanning and treatment to stimulate tumors to take up iodine. The introduction of recombinant human thyroid stimulating hormone (rhTSH) has revolutionized thyroid malignancy evaluation. rhTSH is injected intramuscularly to stimulate residual thyroid cells to take up radioiodine. This avoids the prolonged hypothyroid state that patients traditionally had to go through, and can be used in those who would otherwise be unable to tolerate hormone withdrawal. When used before therapeutic radioiodine in post-surgical remnant thyroid ablation for low-risk disease groups, prospective studies show equivalent efficacy in short-term outcomes.[26] Retrospective studies show similar efficacy between hormone withdrawal and rhTSH in longer-term outcomes in even moderate-higher risk patients.[27]

Octreotide Derivatives in Neuroendocrine Malignancies

A novel application is to use octreotide in targeted radionuclide therapy. ^{111}In-octreotide has been used in clinical trials and initial results were encouraging, although objective response rates were a meager 0% to 8%, with 42% to 81% with stable disease and 12% to 38% showing disease progression. The octreotide molecule has subsequently been modified to increase its specificity for tumor targeting, decrease its affinity for nontargeting areas in other organs, and in an effort to improve its toxicity profile. ^{111}In-octreotide has been altered to create [^{90}Y-DOTA^{0}]- Tyr^{3}-octreotide (DOTATOC) and [^{177}Lu-DOTA^{0}]-Tyr^{3}-otreotate (DOTATATE), with some improvement in their target to nontarget ratios. The DOTATOC trials showed improved objective responses ranging from 7% to 33%, stable disease in 52% to 81%, and disease progression in 9% to 19%. Trials with DOTATATE also showed similar objective response rates. Aside from marrow toxicity and myelodysplasia, nephrotoxicity was the other most significant long-term sequela, which could be decreased with infusion of amino acids before therapy. As in most targeted therapies for solid tumors, hematotoxicity was seen in these patients.[28]

The success of DOTATOC and DOTATATE likely results from their better targeting of tumor compared with octreotide. The radiobiology of the beta emitters ^{90}Y and ^{177}Lu appears to be superior to the Auger emitter ^{111}In. The newer trifunctional, somatostatin-based derivatives have prolonged cell retention, and they are internalized into the cell nucleus, making them optimal for Auger therapy, such as ^{111}In.[29] Future trials with such compounds are of great interest in developing targeted radionuclide modalities.

Metaiodobenzylguanidine Therapy in Neuroendocrine Malignancies

MIBG has been used therapeutically as ^{131}I-MIBG in neuroblastomas in children and pheochromocytomas. Objective

responses have ranged from 47% to 80% as a single agent in neuroblastoma. The main toxicity was hematologic, and subsequent trials are being conducted with autologous stem cell reconstitution. Studies have also been conducted combining MIBG with chemoradiotherapy.[30]

Other Targeted Radionuclide Therapies

Polycythemia vera was frequently treated with ^{32}P-phosphorous in the past, but with the advent of modern chemotherapy, this has become uncommon. Although the median survival was improved, there was an increase in the incidence of secondary blood dyscrasias. This therapy is used in patients who cannot tolerate hydroxyurea and other treatments, or who have symptoms that do not respond to other therapeutic maneuvers.

Radiocolloids such as ^{198}Au-gold colloid or chromic phosphates labeled with ^{32}P or ^{90}Y have been used as palliative regimens in malignant ascites in ovarian carcinoma, pleurodesis for pleural effusions, intracavitary injections for cystic brain tumors, and even for radiosynovectomies in benign inflammatory arthritic diseases. Other therapies have included using ^{35}S-thiouracil for ocular melanoma. Despite being effective treatments, they have been replaced by modern medical management, although they are still rarely used when other therapies fail. Interest in radiosynovectomy is growing as an alternate to surgical management, or delaying surgery when medical management is no longer adequate.

Some newer therapies involve using microspheres embedded with ^{90}Y for palliation in hepatocellular carcinoma, as well as other malignancies such as colorectal carcinoma and neuroendocrine malignancies that have metastasized to the liver. Following arterial access by an interventional radiologist, the ^{90}Y microspheres are injected selectively into the hepatic artery to the site of diseased liver, where they will reside in the vascular space, delivering lethal radiation doses locally. Because the product is not systemically delivered, side effects are well tolerated and less severe than other therapeutic options. Palliative benefits are clear, and some initial evidence suggests promising survival time compared to systemic options.[31,32] Its role compared to bland embolization or chemoembolization is not well defined. Similarly, ^{131}I-Lipiodol is also emerging as a candidate for similar indications, and has undergone trials with cisplatin showing a well tolerated toxicity profile.[33] In the future, newer therapies may use liposomes to deliver therapeutic radionuclides to micrometastases in various other malignancies to complement antibody mediated therapies.[34]

Therapy-Enhancing Strategies

Therapy enhancement basically relies on trying to boost radionuclide uptake and prolong its cellular retention for improving efficacy, or improving tumor sensitivity to make them more susceptible to the effects of targeted radiation. In thyroid cancer, lithium has been shown to have a modest increase in free iodine retention and raising the dose delivery to tissue.[35] There is some evidence to suggest that medications like rosiglitazone, SAHA and others may improve radioiodine uptake in tumors with decreasing ability to take it up, but no clear clinical benefit has yet been demonstrated.[36] Whereas newer agents—such as sorafenib and sunitinib—have demonstrated some activity against tumors independent of radioiodine, no studies have been done to see whether combined modality therapies are any more effective in the treatment of advanced thyroid cancer.

Conversely, the addition of gemcitabine to an yttrium-90 radiolabeled antibody—^{90}Y-hPAM4—has shown some promise in pancreatic cancer in improving therapeutic efficacy of targeted therapy, presumably by acting as a radiosensitizer.[37] Currently, a Phase III trial is under way in evaluating this combination as a potential future clinical therapy.

Some of the newer antibody therapies use genetically engineered antibodies or altered pharmaceuticals and attach radionuclides with more favorable characteristics to improve tumor-specific targeting and possibly therapeutic efficacy. Other methods employ multistep targeting, all of which are experimental, but they hold promise. Such results have prompted their use in conjunction with external beam therapy and chemotherapy. This could help to bring targeted radionuclide therapy into general clinical practice.

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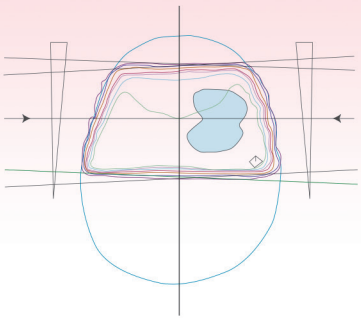
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CHAPTER

12

Health Services Research in Radiation Oncology: Toward Achieving the Achievable for Patients with Cancer



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WHAT IS HEALTH SERVICES RESEARCH?

Medical research may be considered as a continuum of four overlapping domains: basic or biomedical research, clinical research, health services research (HSR), and population health research. HSR aims to create the knowledge required to improve population health by improving the delivery of health services. Although there is some overlap between the domains of clinical research and HSR, their purposes are distinct. *Clinical research* describes the natural history of diseases, it investigates their pathophysiology, and it seeks to discover more effective treatments. *HSR* describes how health systems work, it investigates how they go wrong, and it seeks to discover better ways to deliver health services. The results of clinical research are primarily intended to guide physicians' decisions about the care of individual patients, whereas the results of HSR are intended to guide the decisions of managers and policy makers about the design and implementation of healthcare programs.

Need for Health Services Research in Radiation Oncology

Clinical radiation oncology is a mature science. It has a sound theoretical basis, in both biology and physics. We have a universal language for describing the diseases treated, the treatments used, and the outcomes achieved. Much is now known about the factors that influence outcomes in the individual case. There is a well-established process for evaluating the efficacy of treatment, and a large body of empirical information now permits evidence-based decisions about the use of radiotherapy (RT) in the majority of cases.

In contrast, the science of HSR in radiation oncology is at a much earlier stage of development. There is no comparable universal language for describing the performance of RT programs. There is only limited information available about the factors that influence the performance of RT programs in the population at large. There is no well-established process for measuring the effectiveness of RT programs at the population level. In the absence of empirical evidence, most decisions about the design and management of RT services are guided only by theory and expert opinion, and their consequences are unpredictable. Given that we would no longer tolerate this unscientific approach to decision making in the care of individual patients, it is anomalous that it should still be used in making decisions about health systems that may affect tens of thousands of patients.

The challenges for the HSR community in radiation oncology are to create the knowledge required for evidence-based management of RT programs and to promote the use of evidence in the design and management of RT programs.

How Can Health Services Research Help to Improve the Outcomes of Cancer?

At any point in time, the state of scientific knowledge and technological development sets an upper limit on what is *achievable* for patients with cancer. What is achievable in any particular society is also limited by how much that society is able and willing to spend on cancer care. However, what is actually *achieved* depends not only on what would be achievable if we made optimal use of the available knowledge, technology, and resources, but also on how close we get to attaining the achievable, which is a quantity we have termed the *attainment factor*.

$$\text{Attainment Factor} = \text{Achieved outcome} / \text{Achievable outcome}$$

The achieved and the achievable outcomes are measured in units that correspond to the outcome of interest. Attainment can have any value between 0 and 1 or may be multiplied by 100 and expressed as a percentage. The equation may be rewritten as

$$\text{Achieved outcome} = \text{Achievable outcome} \times \text{Attainment factor}$$

Cancer outcomes can be improved by increasing the *achievable* or by increasing the *attainment factor*. Biomedical and clinical research aim to improve outcomes by increasing the *achievable*. HSR aims to improve outcomes by increasing the *attainment* of what is already potentially achievable within the limits of existing knowledge, technology, and resources.

What Is the Scope of Health Services Research?

Health system performance has three dimensions: accessibility, quality, and efficiency. Together these determine the extent to which we attain the achievable in health care. *Accessibility* describes the extent to which patients are able to get the care they need, when they need it. *Quality* describes the extent to which the right care is delivered in the right way. *Efficiency* describes the extent to which accessibility and effectiveness are optimized in relation to the resources expended. HSR is concerned with measuring these quantities, understanding the factors that influence them, and discovering and evaluating ways of enhancing them.

The scope of HSR in oncology covers the entire continuum of cancer care. In a systematic cross-sectional study of 1,113 HSR publications from 2009, the majority of HSR focused on active treatment (32%), with fewer studies addressing survivorship (19%) or screening (16%), and even fewer than that focused on diagnosis/assessment (10%), palliation (8%), or

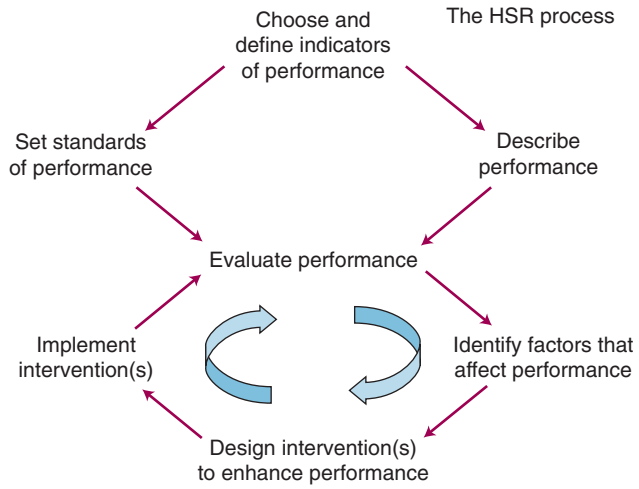


Figure 12-1 A general scheme for research on health system performance.

BOX 12-1 The Dimensions of Healthcare Accessibility

AVAILABILITY

Total system capacity in relation to total needs
Total resources, efficiency, and flexibility

SPATIAL ACCESSIBILITY

Distance, travel times, and costs of transportation

ACCOMMODATION

Hours of operation
Transportation services
Lodges/hostels

AFFORDABILITY

Prices in relation to patients' ability and willingness to pay
Indirect costs

AWARENESS

Physicians' awareness of patients' needs and of potentially useful services
Patients' awareness of needs and services

prevention (4%)[1] Across this continuum, the focus of HSR was most commonly on quality of care (56%), with fewer studies focused on accessibility (25%), efficiency (5%), or general well-being of subjects (14%).[1]

Figure 12-1 shows a general framework for a program of HSR aimed at improving some specific aspect of health system performance. The first step is to select, define, and validate appropriate indicators of the aspect of performance that has been targeted for investigation. The next two steps are to: (1) develop methods of measuring system performance in terms of the chosen indicator(s) and (2) prescribe standards or targets for system performance in terms of the chosen indicators. These two steps, which often involve the use of different methods, can sometimes be undertaken in parallel. Once standards have been set and methods for measuring performance have been established and validated, it becomes possible to evaluate the performance of the system against the standards. This in turn permits further explanatory studies aimed at identifying factors that are associated with better or worse performance. This information can be used to design interventions aimed at improving performance. The interventions may then be implemented and systematically evaluated. Interventions may be refined through further cycles of improvement before they are suitable for dissemination and incorporation into routine practice.

STUDIES OF THE ACCESSIBILITY OF RADIOTHERAPY

Concept of Healthcare Accessibility

The term *accessibility* was originally used narrowly to describe the ability of patients to obtain entry into the health system.[2] It is now used more broadly to represent the overall "degree of fit between the clients and the system."[2,3] Accessibility can be seen as having a number of dimensions that determine that overall degree of fit (Box 12-1). *Availability* describes the total volume of the service available in relation to the total number of clients that would benefit from it. Availability depends on the adequacy of supply of healthcare workers and on the adequacy of facilities and equipment. For any given level of resources, availability also depends on the degree of efficiency in production of services. *Spatial accessibility* describes the geographic relationships between the places where services are provided and the places where potential clients reside. The term *accommodation* describes the extent to which the system is designed and operated to facilitate clients' access to service, for example, by operating at convenient hours or by providing transportation for patients who may need it. *Affordability* describes the relationship between the cost of health services and clients' ability and willingness to pay. It depends not only on the direct cost of services, but also indirect costs, for example, loss of earnings during a protracted course of treatment. *Awareness* describes the extent to which those who need the service know that it is available and that they might benefit from it. In the context of a specialized service such as RT, patients' awareness of the potential benefits of RT depends largely on their attending physician's awareness of the indications for RT.

Need for Studies of Access to Radiotherapy

There are compelling reasons for doing research aimed at optimizing the accessibility of RT. In To achieve optimal cancer outcomes at the population level, it is necessary to make effective treatments accessible to every patient who needs them. RT is known to be effective in many clinical situations and the World Health Organization (WHO) recognizes RT as a key component of any overall program of cancer control. In its 2005 declaration on Cancer Control, the WHO states that "recognizing that the technology for treatment of cancer is mature and that many cases of cancer can be cured …, all nations should improve access to appropriate technologies."[4] Many nations aspire to providing adequate and equitable access to health care for all of their citizens, but there is remarkably little information available about how successful they are in achieving this laudable goal with respect to RT. In reality, the widespread reports of waiting lists for RT in the medical literature and news media and the limited supply of radiotherapy equipment and personnel in many developed and developing countries suggest that access to RT remains suboptimal in many parts of the world.

Waiting Lists for Radiotherapy

Long waiting times for RT were first identified as a cause for concern in the medical literature in a report from Norway more than 20 years ago.[5] Waiting lists for RT have since been

reported in many other countries including Australia,[6] the United Kingdom,[7] Canada,[8] New Zealand,[9] Denmark,[10] Germany,[11] Spain,[12] and Italy.[13] In countries affected by waiting lists of RT, they have been a major concern for both patients and the providers. The problem of waiting lists for RT is an ongoing challenge for health services researchers in radiation oncology; but the first step in dealing with the problem is to learn how to measure waiting times for RT.

Measuring Waiting Times for Radiotherapy

Different methods are available for quantifying waiting times and waiting lists for RT, including mail surveys, retrospective reviews of preexisting administrative data, and prospective collection of information about delays as patients pass through the system.

Mail and e-mail surveys can provide a lot of information about waiting times from multiple institutions and can also be used to compare waiting times between different centers within one country or compare waiting times between different countries. In the 1990s, a survey of heads of radiation oncology at comprehensive cancer centers in the United States and Canada showed that waiting lists for RT were widespread throughout Canada but revealed no evidence of similar problems anywhere in the United States. Median waiting times for a range of indications for RT were two to three times longer in Canada than in the United States.[14] Figure 12-2 shows, for example, that at almost every Canadian center, patients with laryngeal cancer waited longer for RT than they did at almost any U.S. center. However, the validity of such surveys may be questioned because they rely on the veracity of self-reports and because the primary information on which each report is based may differ from center to center.

Retrospective analysis of data that have been gathered for other purposes can provide more objective information about waiting times for RT. This may be an important first step in addressing this type of problem. At the beginning of the 1990s, reports of long waiting lists for RT in Ontario were frequently in Canadian news media. Health system managers felt that these reports were unduly alarmist and at first denied that there was any systemic problem.[8] To clarify the situation, we undertook an analysis of waiting times for RT based on computerized electronic records of all visits to the province's radiotherapy centers over the preceding decade. Once these administrative records had been linked to the province's cancer registry, we were able to describe waiting times for RT for various specific conditions.[8] For example, Figure 12-3, *A* shows that waiting times from diagnosis to start of radical RT

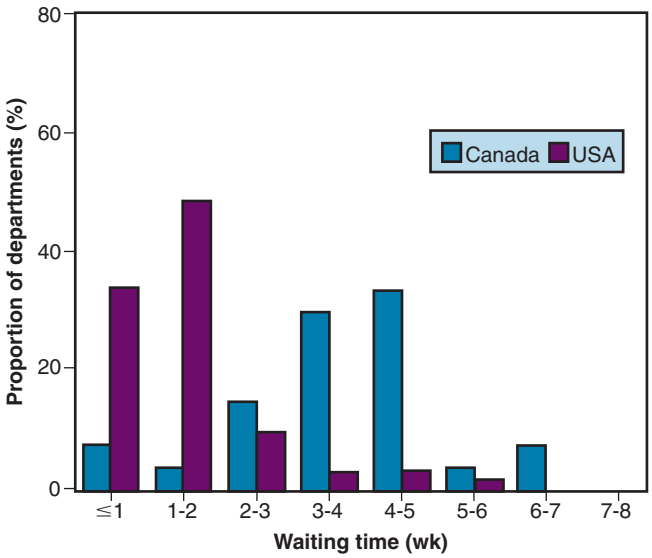


Figure 12-2 Waiting times for RT for carcinoma of the larynx in Canada and the United States. The frequency distributions illustrate the time from referral to initiation of RT for a T2N0M0 carcinoma of the larynx in Canada and the United States based on the results of a mail survey. *(Adapted from Mackillop WJ, Zhou Y, Quirt CF: A comparison of delays in the treatment of cancer with radiation in Canada and the United States. Int J Radiat Oncol Biol Phys 32:531–539, 1995.)*

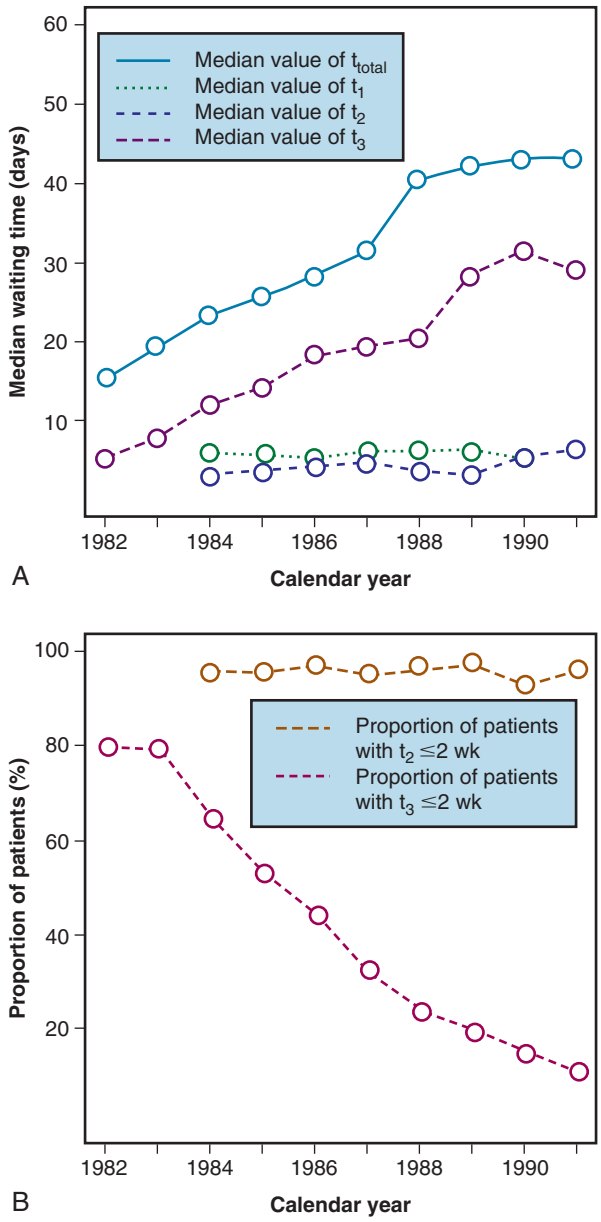


Figure 12-3 Waiting times for RT for carcinoma of the larynx in Ontario. **A,** Temporal trends in median waiting time for RT in Ontario, for which t_{total} is the interval between diagnosis and start of RT, t_1 is the interval between diagnosis and referral to RT, t_2 is the interval between referral and consultation, and t_3 is consultation and start of RT. Data needed to measure t_1 and t_2 were available only from 1984. **B,** The proportion of patients meeting the standards of the Canadian Association of Radiation Oncologists, which states that patients are to be seen in consultation within 2 weeks of referral (i.e., $t_2 < 2$ weeks) and started on RT within 2 weeks of consultation (i.e., $t_3 < 2$ weeks). *(Adapted from Mackillop WJ, Fu H, Quirt CF, et al: Waiting for radiotherapy in Ontario. Int J Radiat Oncol Biol Phys 30:221–228, 1994.)*

for laryngeal cancer increased dramatically through the late 1980s and early 1990s. Similar large increases in waiting times were found in many other clinical situations. Further, as shown in Figure 12-3, *A*, the observed increases in overall waiting time between diagnosis and treatment were entirely the result of increases in the waiting time between the first visit to a radiation oncologist and the start of RT. There was no increase in the interval between diagnosis and referral to radiation oncology or between referral and consultation. These findings pointed to rate-limiting problems in access to planning or treatment machines. It is useful, whenever possible, to report observed waiting times in relation to standards or guidelines. At the time of this first report, the Canadian Association of Radiation Oncology (CARO) had already set standards for acceptable waiting times for RT: the maximum acceptable delay between referral to, and consultation by, a radiation oncologist was deemed to be 2 weeks, and the maximum acceptable delay between consultation and the start of RT was deemed to be 2 weeks.[8] Although these standards were based only on expert opinion, they provided a useful framework for comparison. Figure 12-3, *B* shows trends in compliance with these standards over time. Most patients met the CARO standard for prompt consultation throughout the study period, but the proportion of patients meeting the CARO standard for prompt start of RT fell from 90% to 10%. This simple study, which merely quantified the magnitude of the problem in the community, was useful because it led to public recognition of the seriousness of the problem.[8] This proved to be an important first step in promoting the reinvestment in the infrastructure of the provincial RT system.

There are limitations to the retrospective analysis of waiting times. First, this approach is blind to patients who dropped off the waiting list before they were treated because it starts by identifying patients treated with RT and then follows them backward to measure waiting times from date of diagnosis or some other milestone. Secondly, it is unlikely that any database created for other purposes will provide all the information necessary to identify the rate-limiting step in the RT process. The date of the decision to treat with RT, for example, is an important milestone that signals the transition from pretreatment assessment to planning, and this is collected only in systems designed specifically to monitor flow through the RT process. Administrative databases may also lack information about other elements of the patient's care that are necessary to interpret waiting times for RT. For example, planned deferral of the start of postoperative RT because of delayed wound healing is indistinguishable from unscheduled delay unless the date when the patient is ready to be treated is recorded prospectively. Finally, the retrospective approach does not provide the real-time information needed to fine-tune the performance of an RT program. Prospective collection of the pertinent information is the preferred approach for tracking patients through the system. This approach has now been adopted by the Ontario RT system (see "A Canadian Case Study" in this chapter).

Causes of Waiting Lists for Radiotherapy

Kinetics of Waiting Lists

When demand for RT exceeds supply, waiting times inevitably increase and a waiting list for RT starts to grow. In theory the waiting list will then continue to grow for as long as demand continues to exceed supply. In reality, waiting lists for RT do not grow indefinitely. When waiting times for RT become longer than the referring physicians believe is acceptable, they may begin to offer their patients alternative treatments in circumstances in which RT would normally have been their first choice. For example, when long waiting lists for RT developed in Ontario in the early 1990s, there was a significant decline in the use of primary RT in the management of head and neck cancers, followed by a rebound when waiting lists decreased after a major reinvestment in facilities.[15,16] It has also been shown that there is a significant negative association between the prevailing waiting time for RT and the proportion of patients receiving postoperative RT following a partial mastectomy for breast cancer.[17] Furthermore, tumor progression or deterioration in patients' general condition during the delay may render them ineligible for RT that would initially have been appropriate, and these cases drop off the list. Decreasing referrals and increasing drop-offs from the waiting list serve to reduce demand for RT. As demand declines, the balance between supply and demand is eventually restored; the waiting list then ceases to grow, waiting times stabilize at a higher level, and RT utilization rates stabilize at a lower level. This phenomenon has been referred to as *implicit rationing* because it limits utilization without explicitly limiting access to care.[18]

Even when average supply is equal to average demand for RT, random fluctuations in referral rates may produce transient peaks in demand that exceed supply, and this may be sufficient to cause a substantial waiting list.[19] This risk can be reduced by forward planning that provides a buffer of reserve capacity or by building flexibility of capacity into the system. The smaller the functional unit, the greater is the impact of random fluctuations, and the more reserve capacity is required to avoid a waiting list.[19]

Even in the absence of any shortfall in supply, quite long delays may develop in a complex process such as RT planning, simply because of the many serial steps involved. Process mapping and redesign can be useful in streamlining health systems and can reduce delays in some situations. For example, a French proton therapy center applied such an approach to reduce average wait times by 4 or more weeks and to increase the annual number of treatment sessions from 4000 in 2007 to 4500 in 2009.[20] Investigators at the University of Michigan examined streamlining the referral to treatment process for patients requiring palliative radiation for bone and brain metastases. They standardized processes and cut the number of individual steps to begin treatment from 27 to 16. The proportion of patients receiving consultation, simulation, and treatment within the same day was increased from 43% to nearly 95%.[21] However, no amount of fine-tuning will have any impact on waiting times for RT if total demand exceeds total supply.

Consequences of Waiting Lists for Radiotherapy

Delays in starting RT are a source of great concern both to the patients and to those involved in their care. Box 12-2 summarizes the potential adverse effects of waiting list for RT. Delays have both direct and indirect effects on the well-being of patients, and waiting lists also have broader economic and social consequences. It is useful to classify the direct effects of delay on the well-being of individual patients as *nonstochastic* or *stochastic*.[22] We use these terms as they have been used in the field of radiation protection, in which they provide a useful distinction between the effects of radiation that depend on chance and those that do not. The nonstochastic effects of delay include the psychological distress resulting from the delay and the physical symptoms as a result of the untreated cancer. They occur in most cases and often increase in intensity with time, although they may not occur at all before some initial threshold period has been exceeded. The stochastic effects of treatment delay include the development of metastases and failure to achieve local control with radiation. These are all-or-nothing phenomena. Their probability increases as a function of time, but their severity is independent of time,

BOX 12-2 The Effects of Waiting Lists for Radiotherapy

DIRECT EFFECTS OF DELAY IN RT ON THE WELL-BEING OF PATIENTS

- 1.0 Nonstochastic effects
  - 1.1 Persistence or worsening of symptoms while waiting for treatment
  - 1.2 Psychological distress
- 2.0 Stochastic effects
  - 2.1 Decreased probability of local control
  - 2.2 Increased probability of spread beyond the irradiated field
  - 2.3 Decreased probability of cure because of 2.1 and 2.2
  - 2.4 Increased probability of complications due to compensatory increases in dose and/or volume

INDIRECT EFFECTS OF WAITING LISTS FOR RT ON THE WELL-BEING OF PATIENTS

- 3.0 Decreased probability of being referred for RT when it is appropriate
  - 3.1 Omission of necessary RT
  - 3.2 Exposure to less effective or more toxic alternatives to RT
- 4.0 Re-referral to a distant center for RT with loss of continuity of care
- 5.0 Decreased quality of practice of radiation oncology
  - 5.1 Risk of cutting corners to treat more patients (e.g., hypofractionation)
  - 5.2 Decreased quality of personal care because of the imperative to maximize technical productivity
  - 5.3 Decreased scope for innovation

ECONOMIC EFFECTS OF WAITING LISTS

- 6.0 Decreased efficiency of RT programs
  - 6.1 Decreased net benefits of RT (see 1.0 and 2.0)
  - 6.2 Increased costs associated with care for patients during delay
- 7.0 Decreased overall efficiency of cancer treatment programs
  - 7.1 Decreased benefits of RT because of treatment delayed or denied
  - 7.2 Increased costs because of the requirement for additional care during delay or use of more expensive alternatives to RT

OTHER SOCIETAL EFFECTS OF WAITING LISTS

- 8.0 Legal liability of providers for failure to provide adequate access to care
- 9.0 Decreased public confidence in the healthcare system

and there is no lower limit of waiting time below which they will not occur. Waiting lists may also have indirect adverse effects on patient care, mediated by changes in medical practice. In addition to their effects on health outcomes, waiting lists have important economic and societal implications.[22]

Measuring the Direct Effects of Delays in Radiotherapy

Some of the direct effects of delays in RT are self-evident. Delays in cancer treatment cause psychological distress and patients who are symptomatic wait longer for relief. There are also good reasons to believe that delays may adversely affect the long-term outcomes of RT. Delays provide an opportunity for tumor progression. There is abundant evidence that the probability of local control decreases as tumor volume increases and that the risk of metastasis increases over time.[23] These arguments are probably sufficient to persuade most radiation oncologists that unnecessary delays in RT should be avoided. However, in a publicly funded health system, in which waiting lists are endemic and widespread, many different specialties may each use their own waiting list problems to try to lever additional funding from a limited overall pool. In this context, direct evidence that delays in RT have an adverse effect on clinical outcomes is necessary to ensure that the needs of the RT sector are given appropriate priority.

Given the scant direct evidence that was available about the impact of delay on outcomes in the early 1990s, we initially used a mathematical modeling approach to estimate the risks of treatment delay.[22] The model was based on radiobiological principles that had been validated in experimental systems, and it incorporated the best available clinical information about tumor doubling times and the relationship between tumor volume and local control in the context of cancer of the tonsil.[22] The model predicted a decrease in local control rates of between approximately 10% per month of delay in the start of RT. Others have since made similar predictions.[24,25] However, although this approach was credible to radiation oncologists, it was not readily understood by those outside the field and had no impact on public policy. To make the case for increased resources, we therefore needed to provide direct clinical evidence of the adverse effects of delay.

Measuring the magnitude of the stochastic effects of treatment delay is not straightforward. It is inherently difficult to measure the risk of treatment failure as a result of delay because local failures caused by delay are absolutely indistinguishable from treatment failures resulting from other causes. The problem is analogous to that of defining the risk of carcinogenesis associated with low-dose radiation. One cannot simply count the cancers resulting from radiation because they are usually indistinguishable from the many other cancers that may occur because of causes other than radiation. Rates of failure must, therefore, be compared in groups of patients who have been exposed to longer and shorter delays, and the challenge is to ensure that those groups are comparable with respect to all other relevant prognostic factors. A randomized trial would be the best way of creating truly comparable groups, but it would be unethical to randomize patients to timely RT versus delayed RT, because there is no conceivable benefit in delay. Comparisons of the outcomes of RT in nonrandomized groups of patients who have waited longer or shorter periods of time are subject to all the biases that may affect any retrospective observational study. However, in this context, such studies are important because they represent the best available direct source of information.[25,26]

Recent systematic reviews have identified a growing number of observational studies that have investigated the association between treatment delay and the outcome of radiotherapy in certain clinical situations.[27] Figure 12-4 summarizes the results of the 20 high-quality studies included in a recent published meta-analysis.[27] Most of these studies had been done in the context of head and neck cancers and breast cancer. In these two disease groups, meta-analysis have showed a significant increase in the risk of local recurrence in patients who waited longer for RT.[27] A large population-based outcomes study, not included in this meta-analysis, recently confirmed that delay was associated with a higher risk of local failure following postlumpectomy RT for breast cancer.[28] We found no evidence of a threshold below which delay was free of risk. Moreover, although there was less evidence of an association between delay and local control in sites other than breast and head and neck, there was insufficient data available to conclude that delay in RT is free of this risk in any situation. We found no significant association between delay in RT and

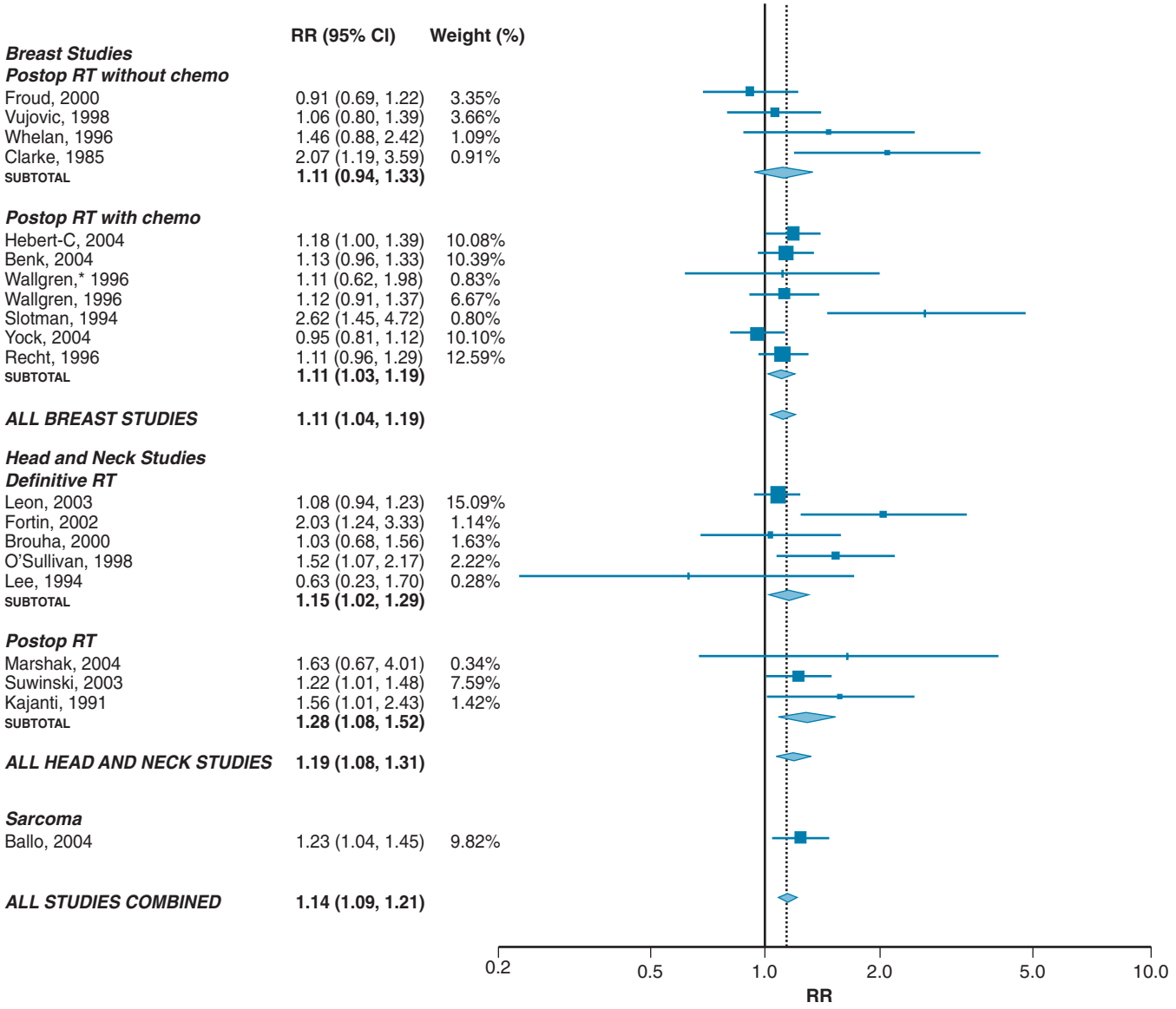


Figure 12-4 The association between delay in RT and the risk of local recurrence. The plot shows the results of a meta-analysis that included 20 high-quality studies that compared rates of local recurrence following RT.
(From Chen Z, King W, Pearcey R, et al: The relationship between waiting time for radiotherapy and clinical outcomes: A systematic review of the literature. Radiother Oncol 87:3-16, 2008.)

the risk of distant metastasis, although there was less information available about this outcome.[27] There was a small but significant decrease in survival with increasing delay in head and neck cancers.[27]

The relative risk of local recurrence of 1.1 per month of delay in starting postoperative RT for breast cancer translates into an absolute increase in recurrence rate of about 1% per month of delay in a population with a baseline rate of local recurrence of 10%.[27] Although this is a small risk for any individual it has the potential to cause an important increase in the number of recurrences at the population level. The increase in the relative risk of recurrence by 1.15 per month of delay in patients undergoing definitive RT for head and neck cancers translates into an absolute increase in risk of recurrence of 3% in a population with a baseline risk of failure of 20%, or an absolute increase of 6% in a population with a baseline risk of failure of 40%.[27] Interestingly, these findings are consistent with those predicted by the mathematical models described previously.[22,24] Thus, a few weeks delay in RT may have an adverse effect on outcome that is sufficient to cancel out all the improvements in outcome achieved by advances in the practice of RT over the last 20 years.[24,25] Given that there is no theoretical reason to believe that there is a threshold below which delay is safe, we have recommended that it would be prudent to adopt the principle that delays in RT should be as short as reasonably achievable (ASARA), modeled on the ALARA principle that guides risk management in the field of radiation protection.[25]

Indirect Effects of Waiting Lists for Radiotherapy on Patient Care

Box 12-2 summarizes the indirect effects of waiting lists on patient care and population health. The phenomenon of implicit rationing by which waiting lists reduce the use of RT

has already been described and the consequences of underutilization of RT will be discussed later in this chapter. Waiting lists may also increase the use of alternative treatments that may be less effective, more morbid, and more expensive than RT. There is evidence that long waiting lists may cause radiation oncologists to modify the way they prescribe RT. A study from the Queensland Radium Institute, for example, showed a significant negative correlation between waiting times and the number of fractions prescribed per course, as a result primarily of decreases in palliative fractionation as waiting times increased.[29] We have found a similar association between prevailing waiting time and the choice of fractionation for bone metastases in Ontario.[30] There are obviously serious risks in deviating from accepted practice in radiation oncology for the sole purpose of getting more patients treated. However, in circumstances in which randomized trials have demonstrated that shorter courses of RT are equivalent to longer courses of treatment, adoption of the more parsimonious approach has the potential to reduce overall workload and greatly increase the availability of RT, without adversely affecting outcomes.[31] The challenge is to ensure that shorter-than-standard courses of RT are used only in circumstances in which they have been shown to be medically appropriate. Explicit standards of care are required to prevent deterioration of quality in an attempt to maintain accessibility.

Societal Effects of Waiting Lists for Radiotherapy

Waiting lists for RT are potentially costly (Box 12-2). Patients require both care and counseling during delays and the costs of alternative treatments may be considerably higher than those of RT. Waiting lists have sometimes caused patients to be referred to distant centers for RT with loss of continuity of care and support for patients and added costs to the health system. The inability to provide timely RT may also be frustrating and distressing for the staff of RT programs. Waiting lists also expose RT providers to legal liability. In Quebec, a class action suit was launched against the hospitals responsible for providing RT, on behalf of approximately 10,000 women who had to wait long periods for adjuvant RT following surgery for breast cancer. At trial, the judge accepted the evidence that delay was associated with an increase in the risk of local failure and the case was ultimately settled with financial compensation for women who had waited for longer than 12 weeks to begin postoperative RT following lumpectomy.[32] Chronic waiting lists for RT and other important medical services eventually became an important political issue. Waiting lists are often used as evidence of the need for change, both by advocates of privatization of the health system and by those who favor reinvestment in the public system. By the early 2000s, public opinion polls showed that "wait times" for medical care had become the greatest concern of most Canadian voters, and there were increasing demands that government should set waiting time standards.

A Canadian Case Study

Why did waiting lists for RT become such a widespread problem around the world in the 1990s? Was there an increase in demand or a decrease in supply or both? Ontario's experience serves as a useful case study. Analysis of historical data showed that three different factors conspired to cause a huge increase in demand for RT over the critical period.[16] First, the incidence of cancer increased inexorably by approximately 3% per year, resulting primarily from the aging of the Ontario population.[16] Second, there was a dramatic increase in the number of patients referred for RT for breast cancer (consistent with the evidence-based trend toward breast conservation surgery[16]), for rectal cancer (consistent with the evidence-based adoption of postoperative RT and chemotherapy[31]), and for prostate cancer (as a result of a large increase in the number of early cases detected following the widespread adoption of prostate-specific antigen [PSA] screening[16]). Third, there was a significant increase in the average number of fractions prescribed per course of RT. This was driven by an increase in the number of fractions per curative or adjuvant course, which outweighed a concomitant but smaller decrease in the number of fractions per palliative course of RT.[16] There was no decrease in treatment capacity. In fact, the number of treatment machines in the province increased faster than the incidence of cancer.[16]

The demographic trends responsible for increasing cancer incidence and the changing patterns of practice that were responsible for Ontario's waiting list crisis are international phenomena, which explains why waiting lists developed more or less simultaneously in many other countries at the about same time. Countries where most or all of the RT system was publicly funded were hardest hit. The fact that the United States did not experience similar problems probably reflects the much greater reserve capacity available in the large private sector in the United States and also its ability to increase capacity rapidly in response to increased demand. In the private sector, increased demand represents an opportunity to increase revenues. When demand begins to outgrow supply, providers titrate additional resources into the system until demand is once again saturated. In contrast, in a publicly funded system operating on a fixed global budget there is rarely any reserve capacity, and it may be impossible to expand capacity rapidly. Increasing capacity often requires expanding facilities and acquisition of new equipment, and approval processes for new capital projects in publicly funded systems may take years to complete. These built-in delays may make it impossible ever to catch up on a growing problem once it becomes established. Only accurate forecasting of the future need for RT, linked to a proactive planning process for facilities, equipment, and personnel, can provide a way of avoiding similar problems in the future in slow-to-react public systems.

In Ontario, additional steps were used to prospectively monitor waiting times for radiotherapy as an indicator of quality of care. Prospective data collection was required to overcome the limitations to the retrospective analysis of waiting times, because such analyses are "blind" to patients who dropped off the waiting list before they were treated. Further, the data used in retrospective analyses may lack the information necessary to define the rate-limiting steps in the RT process or may lack information about other elements of the patient's care that are necessary to interpret waiting times for RT or to fine-tune the performance of an RT program. Prospective collection of the pertinent information is the preferred approach for tracking patients through the system. Figure 12-5 illustrates how this approach was adopted by the Ontario RT system using the framework presented previously (see Figure 12-1). Definitions were developed for overall wait times (and by waiting period) as indicators of performance, and the CARO definitions were used to set standards of performance as described. Methods were developed to prospectively collect wait-time data for each treating center, and proportion of patients meeting performance standard were routinely monitored and publicly reported. To improve wait times, investment in infrastructure was made. Further, each cancer center evaluated its treatment processes relevant to wait times and implemented process improvements (e.g., by running appropriate processes in parallel rather than sequentially). Patients with delays that were medically indicated (e.g., delayed wound healing) or with personal circumstances requesting delay were identified prospectively and accounted for in the analyses. As a result, analyses now reveal that the vast majority of patients meet wait-time standards across the province.[33]

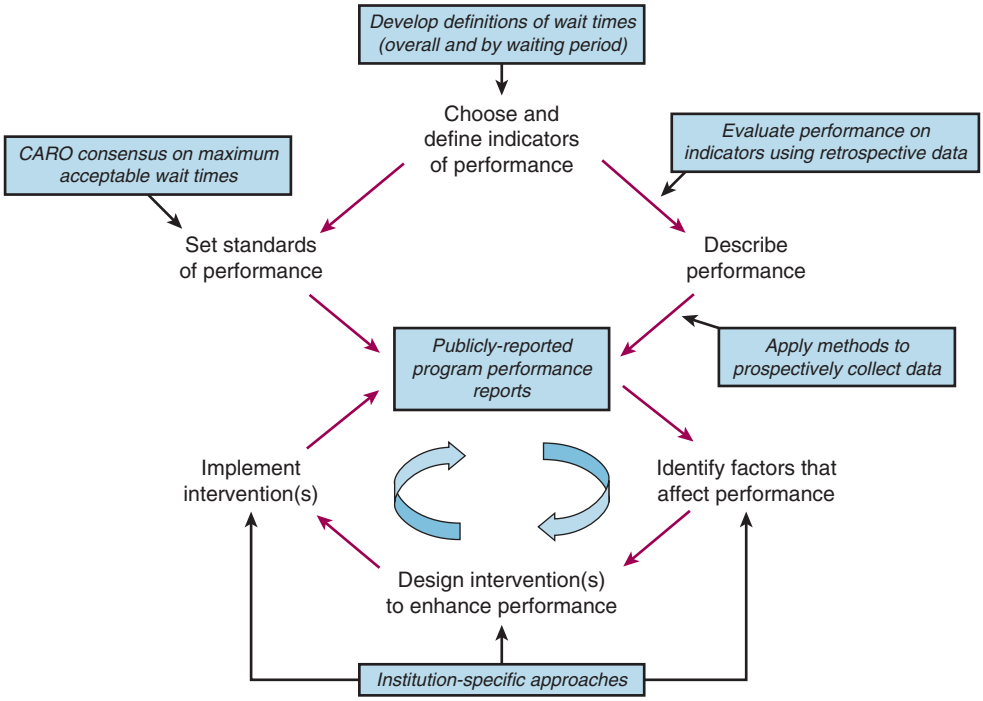


Figure 12-5 An illustration of the use of HSR to improve quality of care with regard to radiation wait times.

Measuring Access to Radiotherapy

Limitations of Waiting Times as an Indicator of Access to Radiotherapy

The existence of a long waiting list for RT is a symptom of inadequate access to RT. The duration of the waiting time for RT may be directly related to the probability of an adverse outcome, and waiting times may therefore serve as a quantitative measure of the quality of care. The length of a waiting list, however, provides no information about the magnitude of the shortfall between supply and demand, and waiting times cannot, therefore, serve as a quantitative measure of accessibility. The absence of a waiting list does not mean that access is optimal. Waiting lists develop only in response to supply-side problems in the availability of services. Waiting times are entirely insensitive to demand-side problems with respect to spatial accessibility, accommodation, affordability, or awareness (see Box 12-2). Problems in those dimensions of accessibility in fact reduce demand and may serve to reduce or avoid waiting lists. Thus, the absence of a waiting list does not imply that access is optimal. To ensure appropriate access to RT, it is also necessary to monitor RT utilization rates.

Defining Accessibility of Radiotherapy

The best quantitative measure of the accessibility of any service is the rate of its appropriate utilization, that is, the proportion of patients that need a service who actually receive it. The term *need* is used here as defined by Cuyler,[34] who states that "the need for medical care exists when an individual has an illness for which there is effective and acceptable treatment."

$$\text{Accessibility} = \frac{\text{Number of patients who need and receive treatment}}{\text{Total number who need treatment}}$$

Accessibility can have any value between 0 and 1, where 1 corresponds to optimal access. These values can also be multiplied by 100 and expressed as a percentage. Thus, to determine the accessibility of RT directly, we must measure both the utilization of RT and need for RT in the cancer population. In practice, the number of patients in a population who receive RT is relatively easy to determine, but the number who need RT is usually unknown. Proxy measures of need therefore have to be chosen.

Measuring Accessibility of Radiotherapy

The *incidence* of cancer (i.e., number of new cases diagnosed in the population of interest, over the period of interest) may be used as the denominator for describing the rate use of RT in the initial management of the disease. The best way to establish the proportion of cases that are treated with RT is to follow all of them forward in time from the date of diagnosis and find out if and when the patient received RT. The approach was first used in the Netherlands,[35] and we subsequently used it to describe the use of RT in Ontario.[15] The estimated rate of use of RT in the initial management of cancer depends on the cutoff point in time used to define initial RT. If a short cutoff point is chosen to define initial RT (e.g., RT within 3 months of diagnosis), the indicator will miss some patients who receive adjuvant RT following surgery. If a longer cutoff point is chosen (e.g., RT within 1 year), the indicator will include almost all patients who receive RT as part of their initial management, but it will also wrongly include some patients who are actually receiving RT for an early recurrence following primary surgery. The best cutoff point depends on the specific disease under consideration. For practical purposes, we have chosen to use the proportion of incident cases treated within 1 year of diagnosis to describe the initial use of RT in the general cancer population.[15] Figure 12-6, *A* describes variations in the use of RT in the initial management of cancer in Ontario in terms of this indicator ($R_{1\ year}$).

The incidence of cancer is a less suitable denominator for describing the utilization of palliative RT because a high proportion of incident cases will never develop indications for palliative RT, and many of those who ultimately do need

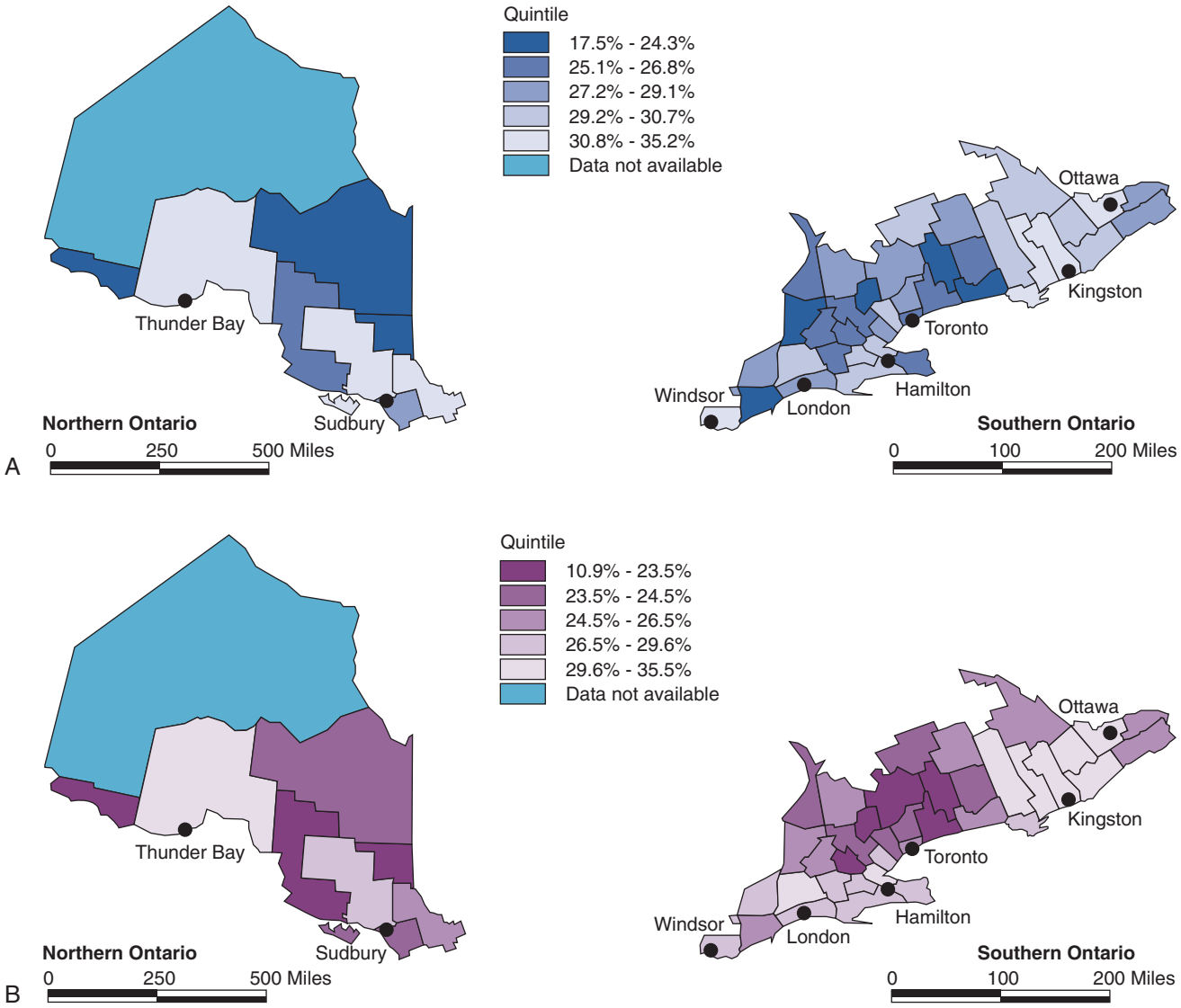


Figure 12-6 Geographic variations in the use of RT in Ontario. **A,** Intercounty variations in the rate of use of RT in the initial management of cancer within 1 year of diagnosis. **B,** Intercounty variations in the use of palliative RT in the last 2 years of life among patients who died of their cancer. The location of the provincial RT centers is shown for comparison.
*(**A,** Adapted from Mackillop WJ, Groome PA, Zhou Y, et al: Does a centralized radiotherapy system provide adequate access to care? J Clin Oncol 15:1261–1271, 1997; **B,** adapted from Huang J, Zhou S, Groome P, et al: Factors affecting the use of palliative radiotherapy in Ontario. J Clin Oncol 19:137–144, 2001.)*

palliative RT will not require it until years after the diagnosis. It is preferable to describe the use of palliative RT among patients who die of their cancer. This can be accomplished by identifying patients who died of their disease in a population-based cancer registry and following them back in time to identify those who received RT within a defined interval before death.[36] Figure 12-6, *B* describes variations in the use of palliative RT in the last 2 years of life among patients who died of their disease in Ontario. The same approach lends itself well to the description of the rates of use of other types of care in the terminal phase of the illness.

What Factors Affect the Rate of Radiotherapy in the General Cancer Population?

Figure 12-6 illustrates geographic variations in the rate of use of RT in Ontario, with the highest rates being observed in the counties where RT facilities are located.[15] It has generally been found that rates of RT use are higher in urban than in rural areas,[37] and that proximity to an RT facility is associated with higher utilization rates.[15] Taken together, these observations suggest that spatial accessibility is an important determinant of the accessibility of RT.

In studying geographic variations in practice, it is obviously important to be able to distinguish systematic variation from variations because of chance alone. Modeling techniques have been developed that can be used to isolate the systematic component of variation.[15] Multivariate analysis is helpful in distinguishing the impact of health system-related factors from other factors that are legitimately involved in determining patients' eligibility for RT. These include differences in cancer incidence, stage distribution, evolution of evidence supporting use of radiotherapy, patient functional status, and patient preference. Patient functional status and preference are important factors but are usually not available in administrative health data. Patient preference plays a significant role in observed rates of RT in cases in which there is more than one

TABLE 12-1 Factors Affecting the Use of Palliative Radiotherapy in Ontario*

	Odds Ratio	95% Confidence Interval
MEDIAN HOUSEHOLD INCOME		
Low, <Can $20,000	1.00	—
Medium, Can $20,000-$50,000	1.09	1.04-1.15
High, >Can $50,000	1.17	1.11-1.24
RT DEPARTMENT IN DIAGNOSING HOSPITAL		
No	1.00	—
Yes	1.35	1.30-1.40
PROXIMITY OF PATIENT'S HOME TO NEAREST RT CENTER		
No RT center in county of residence	1.00	—
RT center in county of residence	1.24	1.21-1.27
REGION		
Northeast Ontario	0.84	0.79-0.90
Toronto	0.88	0.84-0.92
Windsor	0.90	0.84-0.97
Ottawa	1.00	—
London	1.02	0.97-1.07
Northwest Ontario	1.04	0.96-1.13
Kingston	1.17	1.11-1.26
Hamilton	1.20	1.14-1.26

**From a logistic regression that controlled for age, sex, and primary site.*

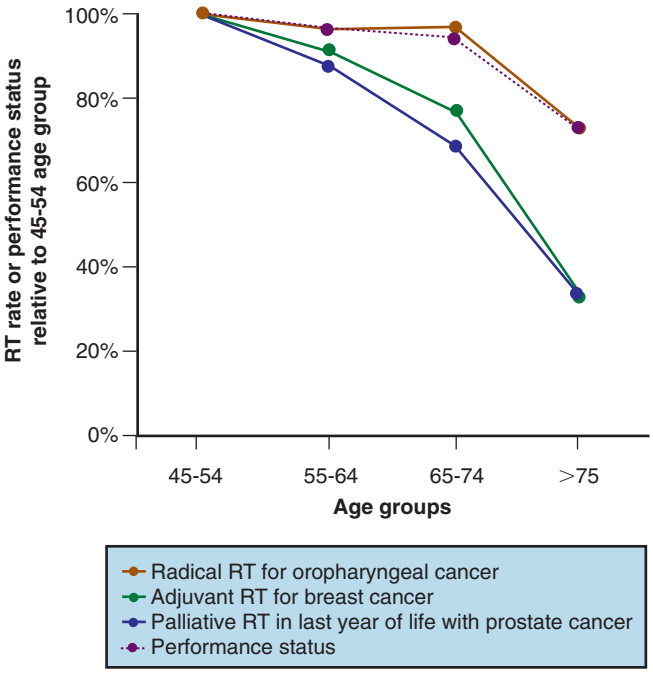


Figure 12-7 The effect of age on the use of RT. The proportion of patients who received RT for specified indications is shown for older age groups and compared with the rate observed in patients between 45 and 54 years old. The expected decline in performance status with increasing age is shown for comparison.
(Adapted from Tyldesley S, Zhang-Salomons J, Groome P, et al: Association between age and the utilization of radiotherapy in Ontario. Int J Radiat Oncol Biol Phys 47:469–480, 2000.)

standard-of-practice treatment. An example is treatment of low-risk prostate cancer.

Measurements of RT use have revealed unexpected inequities in access to care. One example is from a study investigating factors associated with use of palliative RT among patients who died of their cancer in Ontario (Table 12-1). In multivariate analysis, rates of use of palliative RT proved to be significantly lower among patients in whom the diagnosis was made in a hospital without an RT facility,[36] which confirms the concern of others that lack of awareness of the indications among other health professionals for RT may also be a significant factor in determining accessibility.[37] Additionally, even in the context of a publicly funded health system, the socioeconomic status of the patient influences the likelihood of receiving palliative RT. Figure 12-7 shows that rates of use of palliative and adjuvant RT decrease with increasing age and that this decrease is far greater than can be explained due to declining performance status.[38]

Measuring the Need for Radiotherapy

Given that the use of RT varies widely, it is important to ask what proportion of patients with cancer need RT. In the past, it was often stated that approximately 50% of patients with cancer should receive RT at some point in the course of the illness, but that recommendation was based almost entirely on expert opinion.[39] Two more objective methods have since been developed for estimating the need for RT.

Evidence-Based Requirements Analysis

Evidence-based requirements analysis (EBRA) is an objective method that has been used to estimate the need for RT. The indications for RT are first identified by systematic review. Next, an epidemiologic approach is used to estimate how frequently each indication for RT occurs in the population of interest. Finally, the results of the systematic review and the epidemiologic analysis are combined to estimate the overall need for RT. In this context, the term *need* can be equated with the *appropriate rate* of utilization of RT,[34] and the two terms may be used interchangeably. Tyldesley et al discovered this method and used it first to estimate the need for RT in patients with lung cancer.[40] We have subsequently refined the method and used it in several other major cancer sites.[41] The strengths of the method are: (1) that it is transparent in that all the assumptions involved are explicit; and, (2) that it is flexible, and models can be adapted to reflect the case mix in any community of interest or to explore the implications of changes in the indications for RT. The main weaknesses of the approach are that it is complex and time consuming and like any other type of modeling, its results are only as good as the information on which it is based. EBRA can be expected to produce valid results when it is applied to major cancers where the indications for RT are well defined and there is sufficient epidemiologic information available to estimate the frequency with which each indication occurs. Delaney et al extended the use of this method to measure the need for RT across the whole spectrum of malignant disease, and it is now being widely used to predict requirements for RT equipment.[42]

Criterion-Based Benchmarking

An alternative way of estimating the appropriate rate of the use of RT is to use a series of observations to derive a "benchmark." In the business world, *benchmarking* has been defined as "measuring products against the toughest competitors or those recognized as industry leaders."[43,44] In the field of health care, the equivalent is to measure outcomes against the best achieved anywhere or against those achieved in recognized centers of excellence. The same concept may be applied in setting benchmarks for the appropriate rate of utilization of any given treatment. The rate observed under certain specific conditions may be equated with the appropriate rate of

utilization—in other words, with the need for treatment. Benchmarks for the utilization of RT should be set in communities in which there is unimpeded access to RT and expert decision making about the use of RT. To ensure unimpeded access, there should be no financial barriers, referring physicians should be aware of the indications for RT, and patients should have convenient access to a nearby RT center that has sufficient capacity to provide prompt treatment. To ensure optimal decision making, decisions about the use of RT should be made by experts practicing in a multidisciplinary setting, and ideally the decision to treat should not affect their remuneration. If these criteria are met, it is reasonable to expect that the observed rate of utilization of RT will approximate the appropriate rate. We call this approach criterion-based benchmarking (CBB).[44]

We have been able to select a few communities in Ontario that meet most of the listed criteria and have used them to set benchmarks for the appropriate rate of utilization of RT for lung cancer.[44] Figure 12-8 shows that in this context, estimates of the appropriate rate of RT generated by this method are similar to those derived from the evidence-based approach. The CBB method has several strengths: (1) It is an inductive method that is grounded in observations in the real world; (2) it is applicable to both rare and common cancers because it does not require an accurate, comprehensive catalog of indications for treatment or detailed information about case mix; (3) it is relatively inexpensive and can be repeated easily if the indications for treatment change; and (4) it can be validated by replication in different communities. It also has several weaknesses: (1) It assumes that optimal structures and processes are associated with optimal practice, and this has not been proved; (2) the structures and processes that support optimal access and optimal decision making are not well defined; and (3) it requires a detailed knowledge of the structures in place in communities that are candidates to be benchmarks and this information may not readily be available. This CBB approach has been adopted by Ontario's provincial cancer agency and is now used for RT system planning. It is also used in the ongoing evaluation of the performance of the RT system performance by the Cancer Quality Council of Ontario which routinely reports on rates of RT use in relation to benchmarks established for the major malignant diseases.

Once utilization and need have been measured, it is straightforward to calculate the level of unmet need. Consider the data shown for lung cancer in Figure 12-8. It was estimated that approximately 41.6% of cases of lung cancer need RT as part of their initial management but the observed rate of RT use was only was 32.5%. Thus, only 32.5/41.5 = 78.3% of cases who needed RT actually received it. The ~22% shortfall between the observed rate and the appropriate rate represents an important opportunity for improving outcomes of lung cancer.

The Consequences of Underutilization of Radiotherapy

Adequate access to RT is a necessary component of any comprehensive cancer control program. At present, many patients who might benefit from RT have no access to the treatment that they need. This is a global problem that affects both developed and developing countries, but it is most prevalent and severe in low-resource settings where RT services are either nonexistent, or so limited as to be essentially nonexistent[43,45] (see discussion later in this chapter).

The consequences of lack of access to RT are most devastating for patients who have a radiocurable condition for which no other curative treatment is available (e.g., those with locally advanced cervical cancer). In situations such as this, the lack of access to RT inevitably translates into an avoidable and often unpleasant death. In contrast, failure to provide adjuvant RT when it is indicated, does not make death inevitable but does increase the risk of local recurrence and may also compromise long-term outcomes. Many patients who do not get palliative RT when they need it to relieve their pain or other symptoms will continue to suffer, whereas others who are more fortunate, must accept the lesser benefits and perhaps greater toxicity of alternative treatments.

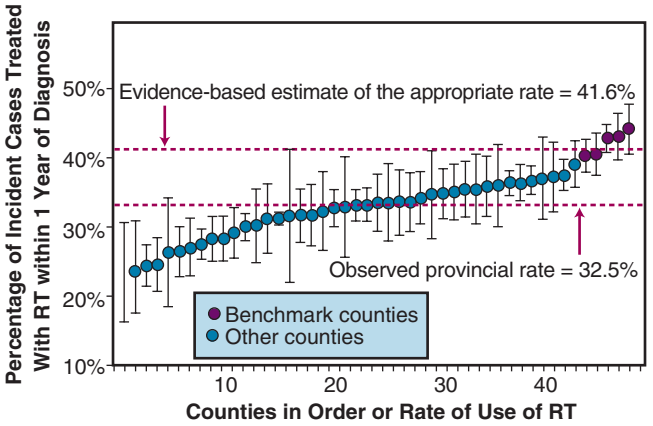


Figure 12-8 Evidence-based estimates and benchmarks of the appropriate rate of use of RT in the initial management of lung cancer. The rates of RT in the initial treatment of lung cancer are shown for each county in Ontario. The *error bars* represent the 95% confidence limits for these observations. Benchmark counties are those where cancer centers with relatively short waiting lists were located. The evidence-based estimate of the appropriate rate and the overall provincial rate are shown as *horizontal lines*; the distance between the lines represents the unmet need for RT.
(Adapted from Barbera L, Zhang-Salomons J, Huang J, et al: Defining the need for radiotherapy for lung cancer in the general population: a criterion based, benchmarking approach. Med Care 41:1074–1085, 2003.)

Beyond its effects on the patients themselves, the lack of access to RT may have serious consequences for their families and their communities. The unnecessary death of a young man or woman may have devastating economic as well as social consequences for their surviving family. The broader economic consequences of failure to use RT vary depending on the patient's condition and the socioeconomic status of the community. In rich countries, in which a range of other services are more readily available, failure to use RT when it is indicated may lead to the increased use of other, less cost-effective treatments, with a consequent overall increase in the cost of care. Even in poor countries where no alternative treatments are available, it may ultimately cost more not to treat a curable young patient than it would have cost to provide the necessary RT because failure to treat him or her results in the loss of a productive member of society.

STUDYING THE QUALITY OF RADIOTHERAPY

This section introduces the concept of quality in health care, describes what HSR has taught us so far about the quality of RT, and identifies what we still need to learn.

Concepts of Quality and Effectiveness in Health Care

In the field of HSR, the term *efficacy* is used to describe the extent to which a treatment achieves its objectives in the controlled setting of a clinical trial. The term *effectiveness* is

reserved for describing the extent to which a health program meets its stated objectives in the real world. The term *quality* is used to describe the effectiveness of the care provided, relative to the effectiveness of the best possible care. In this context, the term *quality* is therefore synonymous with the term *attainment factor* as defined previously.

Almost 40 years ago, Donabedian[46] defined *quality* as "a property of, and a judgment upon, some definable unit of health care, and that care is divisible into at least two parts: technical and interpersonal." The quality of technical care is measured by the extent to which "the application of medical science and technology maximizes its health benefits without correspondingly increasing its risks." The quality of interpersonal care is measured by "how well the physician-patient interaction meets the socially defined norms of the relationship."[46] Although others may define it somewhat differently today, there is universal agreement that quality is a multidimensional concept that embraces both the technical and personal elements of care.

Donabedian[46] also provided an approach for evaluating and improving quality, which Kramer and Herring soon astutely recognized as being appropriate for use in radiation oncology.[47] Donabedian's approach was to analyze the quality of programs in terms of *structure*, *process*, and *outcome*. The term *process* is used here to describe the way that care is delivered. In the context of radiation oncology, it includes pretreatment assessment, medical decision making, planning, delivery of RT, and supportive care during RT, and so on. The term *structure* is used broadly to include facilities, equipment, human resources, and organizational structures. The term *outcome* is used here, as in clinical practice, to describe the consequences of the care that has been provided. It is reasoned that: (1) optimal *process* is necessary for optimal *outcome*; (2) adequate *structure* is necessary, though not sufficient, for optimal *process*; and (3) *outcomes* may be enhanced by identifying and correcting deficiencies in structure, or deficiencies in process. This became the philosophy of the U.S. Patterns of Care Study that was established by Kramer in 1970. It operates on the premise that practice variations exist, differences in process and outcome can be measured, and deficiencies can be corrected.[47] The Patterns of Care Study (PCS) continues this important work today under the new title of Quality Research in Radiation Oncology (QRRO).

Studies of the Structure of Radiotherapy Programs

Two different types of research are being undertaken in this area. First, there are descriptive studies of the physical and organizational structures that prevail in RT programs around the world. In some instances, the observed structures are compared with predetermined standards. In others, the description of structures has been linked to studies of process and outcome with the goal of establishing which types of structure are associated with the best results. These studies may rely on mail surveys or involve on-site visits, but they are all cross-sectional or retrospective in design. Second, there is the field of technology evaluation, which is essentially prescriptive rather than descriptive in intent. It seeks to establish prospectively the usefulness of new technologies in patient care and thus contributes information that is important in setting standards for equipment in an RT program.

Descriptive Studies of the Structure of Radiotherapy Programs

In a highly technical specialty like radiation oncology, optimal care can be provided only when the necessary technological infrastructure is in place, including the correct mix and quantity of equipment and the correct mix and quantity of personnel. Nationwide surveys of RT facilities have now been done in many different countries. In the United States, the PCS/QRRO has taken the lead in describing the basic structural characteristics of radiation oncology facilities for the entire country. Its comprehensive survey of the structure of U.S. facilities serves as the starting point for national surveys of treatment processes and outcomes and permits stratified sampling of different types of facilities.[48] In addition to evaluating equipment and personnel, PCS/QRRO has described the structure of RT facilities in the following terms: (1) whether they have resident training programs or not, (2) volume of new cases treated per annum, (3) whether they were headed by a full-time or part-time radiation oncologist, and (4) participation in clinical trials.

In Europe, a variety of government,[49] agencies,[50] and individual investigators[51] have conducted national surveys of RT program infrastructure, primarily as a basis for planning. Most national surveys reveal considerable diversity with respect to the level of technology and expertise that is available in different RT centers, particularly with respect to brachytherapy. The European Society for Radiotherapy and Oncology (ESTRO) has more recently taken the lead describing and comparing the infrastructure of RT programs across Europe in a project called Quantification of Radiation Therapy Infrastructure and Staffing (QUARTS), funded by the European Commission.[52] QUARTS involves an international survey of equipment and personnel, the establishment of guidelines for levels of staffing and equipment, and the estimation of future needs based on projected incidence and estimates of the need for RT.

International comparisons of radiotherapy structure have been performed by the International Atomic Energy Agency (IAEA). These studies have covered Europe, Asia, Africa, and Latin America.[53-56] A common theme has been wide variation in the supply of RT resources with undersupply a common international problem, especially in low-income (gross national income [GNI] per capita US$1,035 or less) and middle-income countries (GNI per capita US$1036-$12,615).[53-55,57] A strong relationship exists between a lower national economic status and the degree of greater undersupply of RT equipment.[58] At its extreme, 29 of 52 African countries, with a total population of 198 million people, have no known external beam RT facility.[53]

The concept of program structure embraces not only physical infrastructure but also organizational structures including systems of funding, management, and governance. These elements of structure in radiation oncology may also have important effects on processes, but they have generally received less attention than the physical elements of structure. Funding arrangements at European RT centers listed in the ESTRO directory were investigated as part of an international study of palliative RT.[59] A broad range of funding mechanisms for RT departments is described, including a global budget, per-case payments, fee-for-service, and all possible combinations thereof. RT centers in Spain, the United Kingdom, and the Netherlands were mainly funded by a global budget plus or minus per-case payments, whereas the majority of centers in Germany and Switzerland received most of their funding through a fee-for-service arrangement.[59]

Prescribing Technology Assessment

New technologies are being developed rapidly, and our specialty needs to develop better ways of evaluating them and of determining their appropriate place in routine clinical practice.[60,61] Wherever possible, new treatment techniques should

be evaluated in randomized clinical trials, but it is clear that this approach only lends itself to the study of relatively common presentations of relatively common diseases. A large component of the practice of radiation oncology, however, is directed toward patients who have one of the many less common cancers or one of the infinite range of unusual presentations of a common cancer. In neither of these situations is there ever going to be "level 1 evidence" to guide our practice, and it would be impossible for a new approach to treatment to achieve their full potential if we demanded level 1 evidence for its use in every situation. On the other hand, if we choose to make our decisions about the acquisition and use of new technologies based only on the manufacturers' claims of enhanced precision, we may expose our patients to added risks and added costs without real benefits.[60]

Studies of Process in Radiotherapy

The term *quality assurance* (QA) is used to describe processes intended to avoid error in medical care, that is, to ensure that every patient gets the right treatment delivered the right way. Much of what has been written about QA in radiation oncology concerns the avoidance of error in delivering RT, but avoidance of error in case selection for RT deserves equal attention. The term *error* is used here to describe a deviation from appropriate care. Operationally, deviations from appropriate care can only be identified when the boundaries of appropriate care have been defined. Any QA program therefore falls into two parts: setting standards (i.e., deciding what is appropriate) and ensuring compliance with standards (i.e., making sure that every patient is treated appropriately). Some processes in a RT program have the potential to affect every patient, whereas others concern specific groups of patients. We deal first with research in the area of general QA before considering the process of care for specific groups of patients with cancer.

Research on Quality Assurance Processes in Radiotherapy

The RT community has long recognized the importance of routine QA because of the potential for a malfunctioning or wrongly calibrated machine to cause systematic errors in the treatment of a large number of patients. Detailed guidelines and protocols have therefore been developed for commissioning, maintenance, and calibration of treatment machines.[61] However, neither the existence of such guidelines nor an organizational commitment to adhere to them is sufficient to guarantee patient safety. A seminal study undertaken some years ago by Horiot et al on behalf of the European Organization for Research and Treatment of Cancer (EORTC) revealed that some centers made systematic errors in radiation dosimetry.[62] It also showed that feedback of the results of the initial survey diminished the frequency of such errors when the study was later repeated.[63]

Although QA on equipment reduces the chance of systematic error, the requirement for individualization of treatment plans creates the added risk of random error caused, for example, by lapses in human judgment or miscommunication. It has been shown that although well-defined care paths or intervention-specific guidelines can minimize the frequency of this type of error, it does not eliminate them. Real-time audit is necessary to avoid rare but potentially serious errors in the context of routine practice,[64] and even in the controlled setting of clinical trials.[65] The general rule that emerges from these analyses is that human errors cannot all be avoided, but the vast majority can be detected before they have any adverse impact on the patient. Understanding why errors occur is now recognized as the key to development of better processes for their avoidance in future, and the epidemiology of medical errors is therefore a growing field of study.[66] Because actual errors are rare, it is important also to investigate near-misses[67] and this is the approach that is now widely being used in the field of RT.[68,69] Although several recent accidents have heightened awareness of the dangers of RT,[70] serious errors that result in harm to patients are exceptionally rare in comparison to error rates in other fields of medicine.[71] The low error rates in RT were not achieved by chance; they reflect a long-standing awareness of the dangers of RT and a tradition of commitment to QA that antedates the intense media attention directed to medical error over the last decade. Nonetheless, new technologies bring new risks of error and there is a need for continuing research in field of QA in RT.

Research on Practice Patterns in Radiotherapy

During the past 30 years, there have been numerous studies of patterns of care in radiation oncology using methods primarily developed by the PCS.[72] Many different clinical situations have been studied. Most work has been done in the major sites in which RT plays an important role in curative treatment, but there have also been a number of studies of the practice of palliative RT, particularly in the context of bone metastasis. Striking variations in practice have been discovered in every situation that has been studied in detail. Practice has been shown to vary at many different points in the pathway of care: in pretreatment assessment; in fundamental aspects of the RT prescription, including target volumes, treatment techniques, and dose and fractionation; in decisions about adjunctive systemic treatment; in the planning process; in treatment delivery; in the way that treatment details are recorded; in supportive care during and after treatment; and in arrangements for long-term follow-up.

Why Study Practice Variations in Radiotherapy?

Practice variations have been identified in every field of medicine where anyone has taken the trouble to look for them. As we have seen, radiation oncology is no exception. In the era of evidence-based medicine, practice variations represent a threat to the credibility of any medical specialty; it is difficult to defend variations in patient care except insofar they reflect variations in the needs of individual patients or unavoidable variations in the availability of resources. Practice variations in radiation oncology represent not only a threat but also an opportunity for improving practice and outcomes. The opportunities to improve the quality of care depend on the state of knowledge in the particular clinical situation under study. If optimal practice has already been established or can be established for the purposes of the study, deviations from the optimal represent opportunities for improving quality of care. It then becomes important to understand why practice deviates from the optimal, to design interventions that will improve practice. If, on the other hand, optimal practice has not yet been established, practice variations represent an opportunity for learning. Studies of practice patterns may identify controversies that should be addressed in clinical trials. In certain specific circumstances, it may be possible to explore the relationship between treatments and outcomes to determine which approach is superior. The scope and limitations of this type of study are discussed in Relating Structure and Process to Outcomes.

Why Does Practice Vary in Radiation Oncology?

In an ideal world, cancer treatment would be guided only by precise classification of the case and the application of scientific knowledge about the optimal treatment of that class of cases, taking into account the patient's personal values and preferences. In the real world, however, other environmental

factors may influence patient care. Treatment options are often constrained by the resources available. Scientific knowledge is variably disseminated and may be interpreted differently by individual physicians, depending on their training, experience, and work environment. Moreover, financial considerations have the potential to influence medical decisions, whenever there is more than one defensible treatment option available. We now review what is known about the impact of each of these factors on the practice of RT.

Impact of Program Structure on the Practice of Radiotherapy. Consistent with Donabedian's concept, there is abundant evidence that physical and organizational structures determine processes in RT (see Figure 12-12). If the total availability of personnel and equipment is not adequate to permit prompt access to RT, referring physicians may choose alternative forms of treatment. Many studies have revealed that radiation oncologists' choices of investigations, treatment techniques, and fractionation schemes are influenced by the resources available. The PCS has consistently found significant associations between the structural characteristics of facilities and the quality of processes involved in patient care. For example, in a now-classic study of work-up and treatment procedures in head and neck cancers,[73] the PCS found significantly poorer compliance with its criteria of appropriateness of assessment, treatment, and other aspects of care among patients treated at facilities headed by a part-time, rather than a full-time, radiation oncologist (Figure 12-9, *A*), and at nontraining facilities compared with training facilities (Figure 12-9, *B*).

Impact of Scientific Evidence on the Practice of Radiotherapy. Practice varies most where there is least evidence available. Decision making about the use of RT has been shown to be highly variable in the context of adjuvant RT. This is most evident where the value of RT has not been confirmed in randomized trials. Although many indications for RT are supported by the results of randomized trials, there have been far fewer formal comparative studies of the details of RT prescriptions and techniques. Not surprisingly, technical practice of RT is even more variable than clinical decision making in radiation oncology. Even in situations in which there have been several consistent published reports that appear to indicate that one approach is superior to another, it has been shown that physicians may interpret these data differently and therefore may still vary widely in their treatment recommendations.[74]

There has been much interest in enhancing the practice of medicine through the synthesis and dissemination of scientific knowledge in the form of treatment guidelines. Guidelines are clearly valuable for reference purposes, but it is not clear to what extent they have actually succeeded in modifying practice in the general population. For example, we observed no impact of a provincial guideline promoting shorter fractionation for postlumpectomy RT over and above changes attributable to prior reports of randomized trial evidence supporting this practice.[75] Changes in practice have sometimes been reported after the introduction of treatment guidelines, but it is usually impossible to conclude that the guidelines themselves were responsible for those changes.[76]

The existence of treatment guidelines does not guarantee appropriate clinical decision making. Misclassification of patients may lead to selection of an inappropriate care path or treatment plan. This may be caused by inadequate or inaccurate pretreatment assessment or misinterpretation of the results of an adequate assessment. If QA is directed only at the avoidance of errors in delivery of RT, patients remain at risk of receiving the wrong treatment, albeit flawlessly delivered. Clear specification of eligibility criteria for RT and real-time audit of compliance with those criteria is required to avoid this type of error.

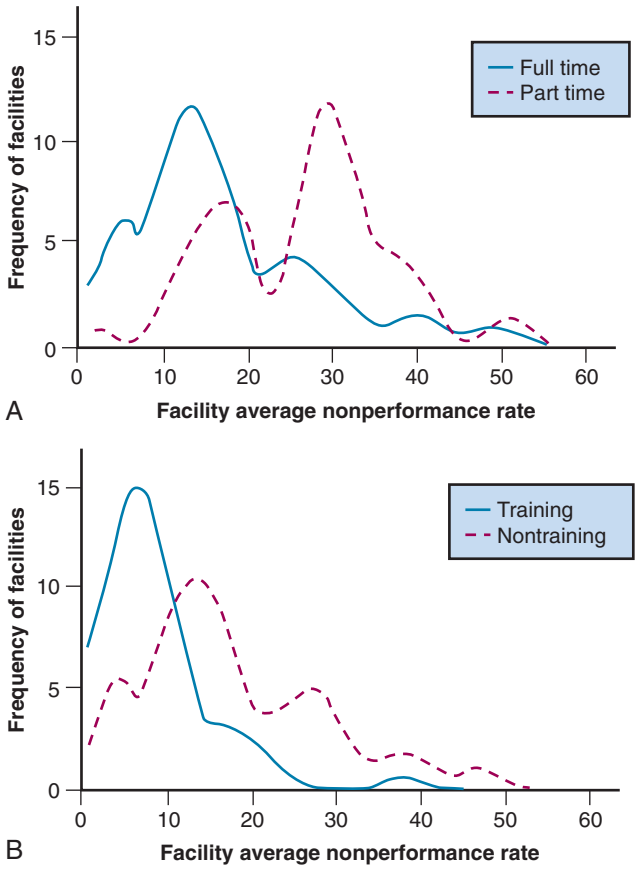


Figure 12-9 Relationships between the structural characteristics of RT programs and quality of practice. **A,** Nonperformance rates for part-time and full-time facilities. **B,** Frequency polygons of nonperformance scores for training and nontraining facilities.
(Adapted from MacLean CJ, Davis LW, Herring DF, et al: Variation in work-up and treatment procedures among types of radiation therapy facilities: the patterns of care process survey for three head and neck sites. Cancer 48:1346–1352, 1981.)

Scientific evidence appears to vary in its impact depending on the practice environment and also on the demographic characteristics of the patients. In 2001, the U.S. Commission on Cancer reported that breast-conserving surgery was still used in less than 50% of U.S. patients with stage 1 and 2 breast cancer and that variations in its use were not consistent with existing practice guidelines.[77] Breast conservation was more rapidly and completely adopted in urban than in rural areas and there were large geographic variations in its adoption across the United States, with much higher rates in the northeast than elsewhere. Older patients and patients from lower socioeconomic groups were less likely than others to have a partial mastectomy, and those who did were less likely to receive postoperative RT. There is also evidence that the characteristics of physicians and their type of practice influence the extent to which they rely on guidelines or other published information in reaching treatment decisions. Reliance on published information in decision making is greater in academic centers and decreases the longer the physician has been in practice.[78] Local policies may affect practice more than national guidelines. A study from the United Kingdom, for example, showed that much of the variation in the use of postoperative RT for breast cancer was attributable to variations in the local management protocols of surgical units.[79]

Impact of Physicians' Beliefs on the Practice of Radiotherapy. There is abundant evidence that physicians' beliefs

about appropriate treatment are shaped by factors other than universal knowledge. Physicians' views about the indications for RT are strongly influenced by their training and experience. Because the key decisions about referral are usually made by surgeons, the views of the surgical community are a major determinant of the role that RT plays in cancer care at the population level. It has repeatedly been shown that surgeons are less likely to recommend RT than radiation oncologists, particularly when a choice has to be made between primary RT and primary surgery. For example, in comparison to radiation oncologists, urologists are less likely to recommend primary RT for prostate cancer,[80] and otolaryngologists are less likely to recommend RT for laryngeal cancer.[81] Medical oncologists today have acquired a significant role in initiating referrals to radiation oncology, but their views about the indications for RT also differ significantly from ours.[74]

Impact of Financial Incentives and Disincentives on the Practice of Radiotherapy. There is evidence that funding mechanisms may affect case selection for RT. For example, a study based on administrative claims data from Pennsylvania showed that the patient's health insurance status was associated with the chance of receiving RT following partial mastectomy. Postoperative RT was given in only 45% of patients with Medicaid compared with greater than 75% of patients with private insurance and Medicare and similar observations have been made elsewhere.[82] Funding arrangements have also been shown to influence choices of fractionation in some studies. Lievens has explored the effects of funding on patterns of palliative RT in Belgium.[83] She found that fractionated courses of RT were prescribed more frequently than single treatments for bone metastases, at least in part because the funding mechanism in place at that time penalized the use of single fractions. In 2001, a new mechanism of funding of palliative RT was introduced in Belgium, which removed the disincentive to single treatments. Since that time, there has been a trend to reduce the number of fractions prescribed in all except 3 of the 23 centers that responded to her most recent survey. Many of those centers reported that the change in the fee schedule was a significant factor in their decision to change practice.[83] Lievens et al have also shown significant associations between funding models and the practice of palliative RT in an international survey of RT centers across Europe. They found that centers funded by a global budget or per-case payment used a significantly lower number of fractions per course and were less likely to use shielding blocks than were centers funded by fee-for-service. The growing evidence that funding may shape the way that RT is practiced suggests that it may be possible to improve practice by appropriately manipulating reimbursement systems. However, there is also a high risk that poorly designed fee schedules may compromise quality of care.[84] It has also been pointed out that, under per-case funding arrangements, profits may be inversely related to quality, making it important to set clear baseline quality standards.[85]

Role of Quality Indicators in the Practice of Radiotherapy

Assessment of quality of care allows healthcare providers to examine their clinical performance against established standards of care, allows payers to assess the quality of care they are purchasing, and is an increasingly important area of HSR.[86] As described previously, the general framework (see Figure 12-1) for a program of HSR describes how quality indicators may be used to assess quality of care and to improve health system performance. Quality indicators may be selected, defined, validated, and applied to target observed variations in practice by evaluating actual practice against targeted performance and to conduct explanatory studies aimed at identifying factors that are associated with better or worse performance.

Quality indicators specific to radiation oncology have been developed across the framework of structure, process, and outcome domains of quality of care and across a spectrum of clinical settings.[86-88] A recent comprehensive review by Albert and Das summarizes the current scope of quality indicator development and application in radiation oncology.[89]

The setting of radiation utilized in the curative management of prostate cancer can be used to illustrate these general principles of quality measurement. Prostate cancer has a high incidence and is commonly managed with either external-beam radiotherapy or brachytherapy as definitive treatment. The RT is highly technical, and continuous advances in technology require consideration in the definition and application of quality indicators in this setting.[88] In Canada, RT is delivered exclusively in 37 publicly funded cancer centers across the country, staffed by approximately 400 radiation oncologists. A Canadian HSR team undertook a modified Delphi process to identify existing candidate quality indicators for measuring the quality of technical medical care and to develop consensus on a suite of quality indicators based on best available evidence.[88] This process identified a suite of 25 quality indicators covering all aspects of prostate cancer radical RT management: pretreatment assessment, external beam RT, brachytherapy, androgen deprivation therapy, and follow-up.

These selected quality indicators were then used as criteria in an audit of patterns of practice, and to develop benchmarks of performance in highest-performing centers.[90] Thirty-two of 37 RT centers (84%) participated, providing 810 cases in total. Analysis of these cases revealed that compliance with 12 pretreatment assessment indicators varied considerably across indicators: from 56% (sexual function documented) to 96% (staging bone scan obtained in high-risk patients). For cases treated with external-beam radiotherapy (EBRT), 100% of EBRT cases were treated using three-dimensional conformal radiotherapy (3DCRT) or intensity-modulated radiotherapy (IMRT) techniques with computed tomography (CT) or magnetic resonance imaging (MRI) planning, whereas 81% of planned cases recorded dose-volume histograms for planning target, rectum, and bladder volumes. For patients treated with conventional fractionation, the dose to the prostate was >70 Gy in 100% of low-risk patients, was >70 Gy in 92% of high-risk cases, but was >74 Gy in only 78% of intermediate-risk patients treated without androgen ablative therapy (ADT). ADT therapy was used in 92% of high-risk cases. Figure 12-10 illustrates that centers varied with regard to how many indicators they were fully compliant on; no center was fully compliant on fewer than 4 of 16 indicators, and no center was fully compliant on all indicators.[90] Given that each quality indicator was selected as representing a minimum standard of care,[88] these data suggest room for improvement in quality of care, particularly for indicators such as dose, in which variation can affect cancer outcome.

Studies of Outcomes in Radiotherapy Programs

It is important to appreciate that although outcomes may seem to be the ultimate measure of quality, one cannot fine-tune the operation of a cancer program by measuring the long-term outcomes by which we usually judge the success of cancer treatment. It may take a decade to measure the 5-year recurrence-free rates associated with a particular pattern of practice. Any feedback from audit of outcome comes far too slowly to permit optimization of the program performance. Quality improvement programs in oncology largely have to operate on the principle that if you get the structure and the process right, the outcomes will look after themselves. That being said, there is some value in measuring outcomes and the opportunity to do this should not be overlooked.

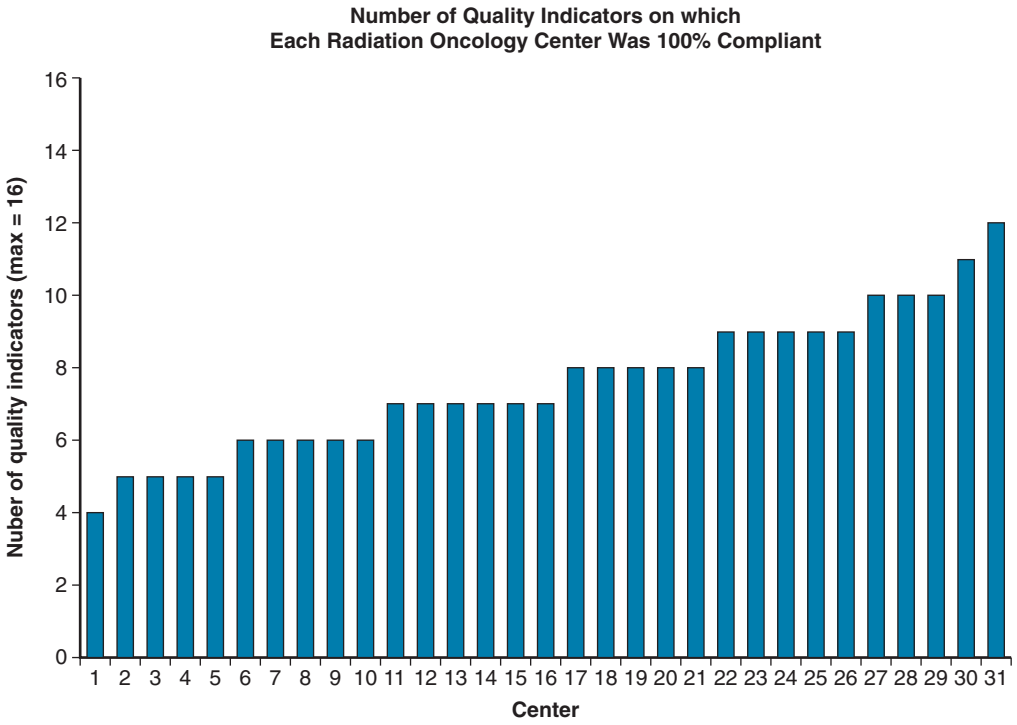


Figure 12-10 Center performance on a suite of 16 quality indicators across Canadian radiotherapy centers. The graph shows the number of indicators on which all cases sampled from that center met the specific quality indicator (demonstrating 100% compliance on that indicator). *(Data taken from Brundage et al: Radiother Oncol, 107:339–345, 2013.)*

Surprisingly, it may be easier to measure outcomes than processes in the general population. Accurate information about vital status is usually available in cancer registries, and it may be quite straightforward to measure survival at the population level. Hospital records and billing files may provide information about subsequent surgical procedures that can sometimes provide surrogate measures of local control by RT. For example, survival without subsequent laryngectomy has been used as a surrogate for local control in measuring the success of radical RT for laryngeal cancer, and survival without subsequent cystectomy has been used as a surrogate for local control after radical RT for bladder cancer (Figure 12-11). The high statistical power of population-based studies also makes it possible to detect and quantify rare but serious late effects that it might be impossible to detect based on the analysis of experience of any individual institution.[91]

Large variations in outcome have been observed among different countries and among different regions, demographic groups, and institutions within the same country. The challenge lies in distinguishing the component of variation in outcome attributable to differences in quality from the inevitable variations in outcome due to differences in case mix.

International variations in cancer outcomes are inevitably multifactorial in origin, and it is difficult to attribute them to any individual aspect of health system performance. Nonetheless, such comparisons have proved to be useful.[92,93] Figure 12-12 shows international variations in cancer survival as a function of proportion of gross domestic product spent on health care. It demonstrates a remarkably clear relationship between investment in health care and cancer survival. It is impossible to determine whether the worse outcome observed in countries that spent less on health care was the result of more advanced stage of disease at diagnosis, higher levels of comorbidity, poorer access to care, or poorer quality of care. However, despite these uncertainties the message is clear that you get what you pay for. These results had a direct influence on public policy in the United Kingdom and were used to justify an expansion in the budget of the National Health Service's cancer programs by almost $1 billion, permitting a massive expansion in the equipment and staffing of its radiation oncology programs.

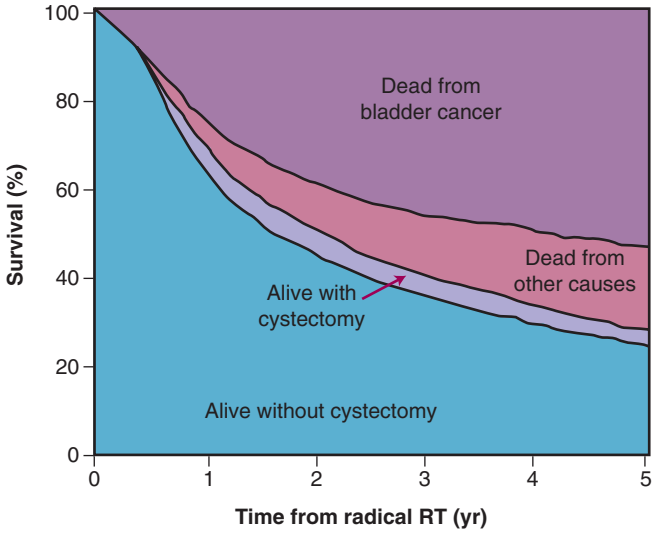


Figure 12-11 Outcome of radical RT for bladder cancer in Ontario. The graph illustrates the results of a population-based study of the outcome of radical RT for bladder cancer in Ontario. The curves show the probability of survival and cystectomy-free survival in 1370 patients who received radical RT for bladder cancer between 1982 and 1994. Deaths from cancer are differentiated from deaths from other causes. *(Adapted from Hayter CRR, Paszat LF, Groome PA, et al: A population-based study of the use and outcome of radical radiotherapy for invasive bladder cancer. Int J Radiat Oncol Biol Phys 45:1239–1245, 1999.)*

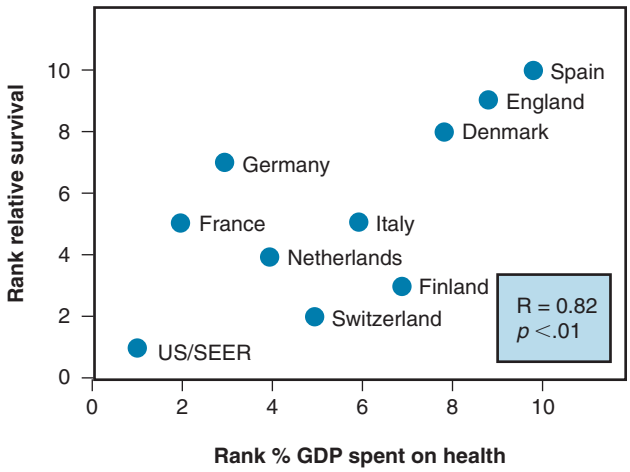


Figure 12-12 Correlation between relative survival and expenditure on health care. The scatter plot shows the relationship between relative survival for all cancer in female patients and the percentage of gross domestic product (GDP) spent on health care in 10 developed countries. *(Adapted from Evans BT, Pritchard C: Cancer survival rates and GDP expenditure on health: A comparison of England and Wales and the USA, Denmark, Netherlands, Finland, France, Germany, Italy, Spain, and Switzerland in the 1990s. Public Health 114:336–339, 2000.)*

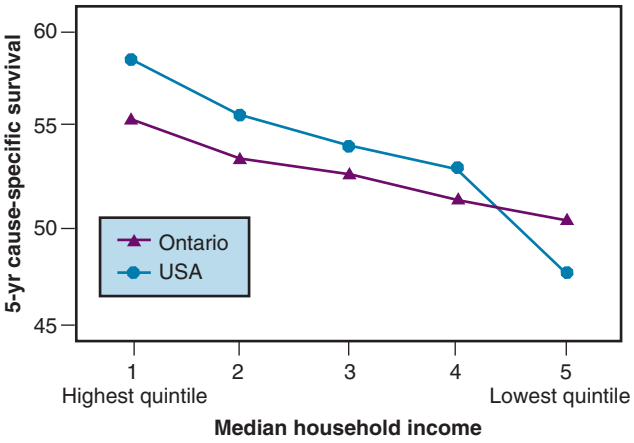


Figure 12-13 Associations between socioeconomic status (SES) and cancer survival in the United States and Canada. The graph shows 5-year, cause-specific cancer survival as a function of SES for all cancers combined (excluding prostate) in the Canadian province of Ontario and in the regions of the United States covered by the Surveillance, Epidemiology, and End Results (SEER) cancer registries. *(Data from Boyd CJ, Zhang-Salomons J, Groome PA, et al: Associations between community income and cancer survival in Ontario and the United States. J Clin Oncol 17:2244–2255, 1999.)*

It has also been shown that cancer outcomes are worse in residents of poorer communities than in residents of richer communities within the same country.[92] Figure 12-13 shows variations in 5-year survival among patients from richer and poorer communities in Canada and the United States. There is a clear gradient in survival across socioeconomic strata in both countries. Some, but not all, of the observed variation is the result of more advanced stage at diagnosis among the poorer groups, probably reflecting differences in access to care.[92] Differences in quality of care may be responsible for some of the observed differences in survival not explained by differences in stage mix. These differences in outcome represent potential opportunities for improving overall outcomes at the population level.

Before we can develop strategies for reducing these disparities, further studies are needed to explore their causes. Although the socioeconomic status–survival gradient is steeper in the United States, there is still a significant difference in outcome among residents of richer and poorer communities in Canada. This may seem somewhat surprising because Ontario has a single-payer, universal healthcare system with no parallel private healthcare sector, and in theory the rich do not have better access to care or quality of care than the poor. Clearly, however, the removal of financial barriers to access to care does not in itself abolish differences in outcome between rich and poor.[92]

Interregional comparisons within the same country may also be informative. When dissimilar populations are compared, it is necessary to control for differences in case mix, but in the absence of any major interregional variations in socioeconomic status, systematic variations in case mix are unlikely. Under these circumstances, variations in outcome, which exceed those expected because of chance alone, may reasonably be attributed to variations in access or quality. Figure 12-14 shows the observed 5-year survival for several major cancer sites in eight different regions of Ontario. Once the observed variations are reduced to take account of the expected variation because of chance alone, the best observed outcomes may be used as a benchmark for the achievable outcome. Figure 12-14 shows that, after adjusting for variation because of chance alone, there were no residual geographic variations in the outcome of cancers of the pancreas, colon, or cervix, but there remained important geographic variations of survival for head and neck cancers, Hodgkin disease, and testicular cancer. Table 12-2 shows the observed 5-year survival for the province as a whole compared with the estimated achievable survival for several diseases in which geographic variation in outcome exceeded that because of chance alone. Although such studies can demonstrate the potential to improve outcome by improving quality, they do not reveal where the defects in quality lie. Further studies are required to identify specific defects in the underlying processes and structures.

Relating Structure and Process to Outcomes

Whether you begin with variations in outcome and work back to try to find their causes or begin with variations in process and work forward to try to identify their consequences, there are significant problems that must be addressed before a causal relationship between process and outcome can be established. We will discuss these problems and describe how they should be addressed in the context of outcomes research.

Limitations of "Outcomes Research"

Studies that examine treatment and outcome in the context of routine care are often today referred as "outcomes research." This type of study should *not* generally be used to try to evaluate the efficacy of treatment. It is notoriously difficult to control for bias in retrospective reviews of institutional experience.[94] Comparisons of outcomes achieved in contemporaneous groups of patients who have received different types of treatment at the same institution are inevitably confounded by "treatment selection bias." Comparisons of outcomes between groups of patients who received different treatments more or less contemporaneously at different institutions are less subject to treatment selection bias but are vulnerable to "referral bias" resulting from interinstitutional differences in case mix.[94,95] The use of "historical controls" (i.e., the comparison of outcomes between patient groups who have received different treatment at different points in time) is also fraught with hazard.[96] Case mix may change systematically over time; investigations may change, resulting in "stage migration"; and collateral aspects of care may also change. It is possible to

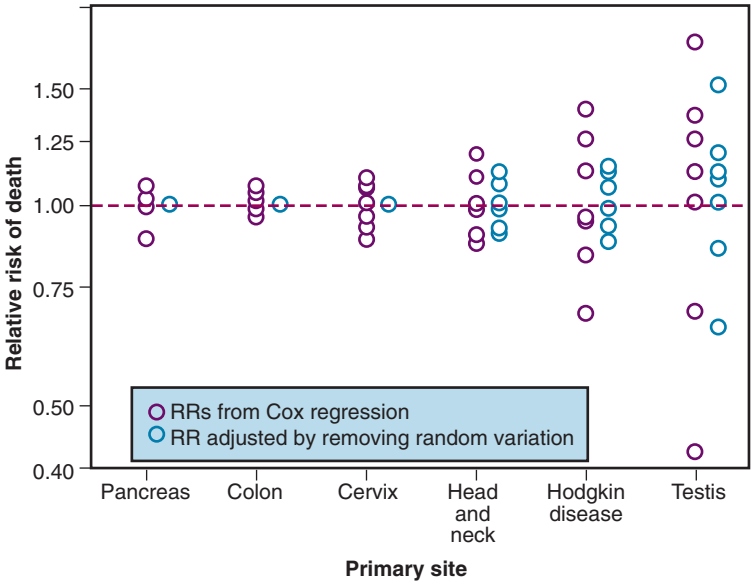


Figure 12-14 Interregional variations in cancer survival in Ontario. The scatter plot shows the relative risk of death from cancer in seven geographic regions of Ontario derived from a Cox regression that controlled for age, sex, and socioeconomic status. The *purple circles* represent the observed variations in survival. The *blue circles* represent the remaining variation after subtraction of the expected random component of variation. *(Adapted from Zhang-Salomons J, Groome PA, Mackillop WJ: Estimating the best achievable cancer survival by eliminating regional variations in Ontario. Clin Invest Med 363[Suppl 22], 1999.)*

TABLE 12-2 Observed versus Achievable 5-Year Survival for Selected Cancer Sites in Ontario*

Primary Site	Achievable 5-Year Survival Rate (95% Confidence Interval)	Observed 5-Year Survival Rate (95% Confidence Interval)	
		All Ontario	Worst Region
Head and neck	64% (63-65)	60% (59-61)	54% (49-59)
Hodgkin disease	88% (86-90)	86% (84-87)	81% (73-89)
Testis	97% (97-98)	95% (94-96)	92% (89-95)
Central nervous system	32% (31-34)	28% (27-29)	27% (24-30)
Rectum	52% (51-54)	50% (49-51)	48% (45-51)
Stomach	21% (20-22)	20% (19-21)	15% (12-17)
Lung	18% (18-19)	15% (15-16)	12% (11-13)
Ovary	49% (47-51)	46% (44-47)	40% (33-48)
Prostate	77% (76-77)	75% (74-75)	71% (69-72)
Bladder	74% (72-75)	73% (72-74)	68% (65-71)

**The best achievable survival was estimated from the highest observed survival in any of the seven regions in Ontario, by subtracting deviations from the provincial average that are expected, as a result of random variation. Cox regression was used to control for age, sex, and socioeconomic status. This model assumes that there are no systematic variations in case mix among the regions.*

reduce the impact of these types of bias by controlling for known prognostic factors, but these usually leave much of the variance in outcome unaccounted for. For these reasons, none of these types of retrospective, observational studies can substitute for prospective, experimental studies (i.e., randomized controlled trials) in the evaluation of efficacy of treatment. The credibility of our discipline is weakened to the extent that we rely on these less valid methods in situations in which a randomized trial is possible.

Legitimate Roles of "Outcomes Research" in Evaluating Effectiveness

It is important to recognize that there are some aspects of medical practice that cannot be evaluated in randomized trials and must be explored using observational methods.

There are some important aspects of treatment that cannot and should not be studied in a randomized trial. It may be important, for example, to know how much outcomes are affected by deviation from standard practice, such as by delay in initiation of RT, protraction of overall treatment time, the use of lower-than standard doses, or reliance on antiquated equipment. However, one cannot ethically randomize patients to receive nonstandard versus standard treatment when the only real purpose of the exercise is to measure the adverse consequences of the nonstandard approach. We can therefore only learn about this type of issue by investigating the impact of inadvertent or unavoidable deviations from standard practice in retrospective, observational studies of the type discussed previously.[25,26]

It is important to be cautious in the interpretation of "negative findings" in studies that attempt to explore the consequences of deviations from standard practice. Studies that fail to show a statistically significant difference in outcome between nonstandard and standard treatments often lack the statistical power that would be necessary to rule out small but clinically important adverse effects. When patient safety is on the table, the absence of evidence of adverse effects should never be misconstrued as evidence of their absence.

When a Randomized Trial Is Not Feasible. Some issues should ideally be addressed in a randomized trial, but either cannot, or will not, be addressed in this way. Rare clinical problems are often impossible to study in randomized trials because it is difficult to sustain enthusiasm for any trial or maintain the infrastructure necessary to support it over

a protracted period of slow accrual. Large well-organized, multicenter clinical trial groups have a greater chance of success in this situation than any individual institution, but there are limits to what any group can do. Nearly all of what we know about the relationship between treatment and outcome in rare situations has to come from observational studies. In other situations, a clinical trial may be theoretically feasible but is rendered impossible by entrenched opposing views about treatment that effectively preclude recruitment to any trial. One such example was the controversy regarding the primary management of more advanced cancers of the larynx. The issue was hotly debated for decades and opinions were highly polarized. The depth of the controversy is clearly illustrated in the results of an international mail survey of patterns of care in laryngeal cancer done in the early 1990s.[81] This showed, for example, that most otolaryngologists in Canada, the United Kingdom, and Scandinavia regarded primary RT, reserving surgery for salvage, as the standard approach for T3 glottic cancer, whereas most of their counterparts in the United States and Australia favored primary laryngectomy.

Under these circumstances, it may be possible to learn about the relative effectiveness of the competing approaches by comparing the outcome they achieve at the population level. The rationale for this approach is that variations in practice driven by differences in physicians' beliefs, or any other factors unrelated to the characteristics of the patients, can be treated as a natural experiment. For example, Groome et al performed a study comparing the outcomes of treatment for locally advanced laryngeal cancer between Ontario, Canada, and the United States. They found that primary laryngectomy was used much more frequently in the United States than in Ontario,[97] consistent with the results of the previous mail survey.[81] Survival at 5 years proved to be identical in the two populations, whereas laryngectomy-free survival was significantly higher in Ontario than in the United States. These observations lend support to the position that primary RT, reserving surgery for salvage, permits retention of natural voice without compromising survival.

Evaluating the Adoption and Generalizability of the Results of Clinical Trials. Randomized clinical trials are unquestionably the best way of comparing the efficacy of a new treatment with the previous standard treatment. However, clinical trials rarely involved more than a small fraction of potentially eligible cases. Therefore, it cannot be taken for granted that the benefits observed in the context of the trial will be reproduced when the treatment is adopted in the general population. It has therefore been argued that population-based "phase IV" studies should be carried out as new treatments are introduced into routine practice to evaluate their effectiveness in the real world.[98,99] Box 12-3 describes some of the unique advantages of phase IV studies.

Many phase IV studies have used temporal changes in practice to evaluate the effectiveness of RT. For example, Pearcey et al studied the impact of the rapid adoption of concurrent cisplatin-based chemoradiotherapy (C-CRT) in 1999 on population-based outcomes of cervical cancer in Ontario.[99] Use of C-CRT increased from <10% of RT cases diagnosed from 1992 to 1998 to >60% in those from 1999 to 2001. There was no observable change in survival for the subgroup of patients treated with surgery alone. Among those treated with primary RT with or without chemotherapy, survival significantly increased from 58.6% in 1995 to 1998 to 69.8% in 1999 to 2001 ($p < 0.01$). The magnitude of change in survival was in keeping with randomized trials. These findings supported the population-based effectiveness of C-CRT for cervical cancer.

An important assumption of a phase IV study is the comparability of treatment groups. This may often be assured through ecological comparisons such as in Pearcey et al's study of C-CRT for cervical cancer.[99] Over modest time periods, the spectrum of cases in the population usually does not change sufficiently to threaten study validity. This stability is not always the case, however, as demonstrated by Gupta et al's study of the impact of C-CRT on head and neck cancer population outcomes in Ontario,[100] which showed an increase in survival from 43.6% in the preadoption cohort to 51.8% in the postadoption cohort. However, the survival increase for oropharynx cancer was greater than predicted based on randomized trials of C-CRT (38.8% preadoption and 57% postadoption). The observed findings were in keeping with known increases in incidence of the prognostically favorable oropharyngeal cancer associated with human papillomavirus (HPV) over the study period. Notably, the survival increase for all other head and neck sites combined was in keeping with randomized trials (45.6% preadoption and 48.3% postadoption).

Phase IV studies provide information on treatment adoption and its consequences that is not available through any other means. For example, in the study of adoption of C-CRT for head and neck cancers, it was possible to study the impact of C-CRT on hospitalization rates in the general population. There was a significant increase in hospitalizations after C-CRT adoption for head and neck cancers (23.4% versus 43.3%), but no increase in treatment-related deaths. Additionally, the adoption of C-CRT was far more gradual for head and neck cancers than for cervical cancer. In both cases, however, when superiority of one treatment over another was demonstrated in randomized trials, practice changed.

In the case of equally effective options, this may not always be the case. Ashworth et al studied fractionation of post-lumpectomy radiation for invasive breast cancer in Ontario before and after the publication of the Ontario Clinical Oncology Group (OCOG) trial that demonstrated equivalence of 16- and 25-fraction schedules.[75] They found that after completion of the OCOG trial, shorter fractionation schedules increased from 48% to 71% of cases, though large intercenter variation existed, including two of nine centers treating the majority of patients with longer schedules.

BOX 12-3 Proposed Roles of Phase IV, Population-Based Outcomes Studies

1. To describe uptake of new therapy.
   - What is the prevalence or incidence of eligible cases?
   - What proportion of eligible patients has received therapy?
   - Are quasi-eligible patients receiving therapy?
   - To what extent is therapy appropriately delivered (i.e., complete versus partial adoption)?
2. To evaluate the association among a change in practice or policy and outcomes.
   - Is there benefit at the population level?
   - Is the magnitude of benefit commensurate with that observed in clinical trials?
   - Are there previously unrecognized (or underrecognized) adverse events?
3. To explore the real-world economic ramifications of a new medical therapy.
4. To provide an empirical process to determine which aspects of the randomized controlled trial design are associated with a minimal efficacy-effectiveness gap.
5. To provide a measure of the societal benefit of medical research.

From Booth CW, Mackillop WJ: Translating New Medical therapies into Society Benefit: The role of population-based outcome studies. [commentary] JAMA *300:2177–2168, 2008.*

There are a number of statistical techniques available to minimize treatment selection bias and confounding in observational studies of effectiveness. These include multivariable model risk adjustment, propensity score methods, stratification, time series analysis, matching, restriction, and instrumental variable analysis. A full discussion of the relative merits of these techniques is beyond the scope of this chapter. As a general rule, validity is strengthened when multiple techniques produce comparable results.

STUDYING THE EFFICIENCY OF RADIOTHERAPY

Health economics is the area of specialization within the field of economics that concerns itself with all economic aspects of health and health care. Much of health economics deals with health-related issues on a higher plane than HSR. Macroeconomic analysis of the societal impact of health and health care at the national and international levels lies well beyond the scope of HSR. On the other hand, microeconomic analysis of the costs and benefits of specific healthcare programs lies squarely within the domain of HSR. We briefly describe how health economic analysis fits into HSR, introduce the methods that are commonly used, and illustrate their relevance to radiation oncology.

The resources available for health care in any society are finite. What is achievable for patients with cancer depends on the size of the total healthcare budget, on how much of that total budget is directed to cancer care, and on how efficiently the available resources are used in providing cancer care. Health economics aims to provide the information necessary to make rational choices about how to deploy funding for health care and how to make the best possible use of the funds available. Economic analyses are useful at many levels in the health system. High-level decisions about allocation of resources to different healthcare programs are increasingly based on a comparison of their impact on health in relation to their cost. These decisions are most clearly visible in publicly funded systems, but in the private sector decisions made by insurers about which services will be reimbursed are based on similar considerations and have a similar effect. Information about the benefits of RT in relation to its costs is, therefore, required to ensure that an appropriate slice of the cancer budget is allocated to radiation oncology. Economic analyses are also needed to optimize the internal efficiency of RT programs. To ensure that we get the maximum value per dollar invested in RT, it is important that we should be aware of the relative costs of alternative approaches for providing RT.

Health economics involves much more than the measurement of healthcare costs, which most economists would regard as no more than accounting. However, economic analysis does require the measurement of costs, and a number of useful studies have been done in comparing alternative approaches for measuring the cost of RT,[101] and in defining units of workload to which costs can be assigned.[102] In assessing the overall costs of RT, it is important to consider not only the direct costs of providing treatment but also the indirect costs of supportive care for complications of RT. It is important to specify the perspective from which an economic analysis is carried out. If the analysis is being conducted from the perspective of the RT provider, it may be appropriate to focus primarily on direct costs, whereas if the perspective is that of the health system as a whole, indirect costs incurred in other sectors must also be considered. If the analysis is being conducted from the societal perspective, loss of productivity as a consequence of the treatment needs to be included and balanced against loss of productivity as a result of the untreated disease.

Economic analyses typically consider the benefits of health care as well its costs. Four different types of study are usually distinguished: cost minimization studies, cost-benefit studies, cost-effectiveness studies, and cost-utility studies.

Cost minimization studies, often simply called cost studies, compare the costs of alternative treatments or processes, on the explicit or implicit assumption that each produces similar health outcomes. In RT, this type of study has provided information pertinent to decisions about the acquisition of new equipment,[103] about the decision to purchase or lease equipment,[104] about service contracts,[105] and so on. In some instances, simple cost comparisons have been done between slightly different approaches to treatment, such as high-dose rate versus low-dose rate brachytherapy.[106]

In cost-benefit analysis, the health benefits of treatment are described only in terms of their dollar value; health outcomes are considered only insofar as they have an impact on costs or affect the productivity of those affected. This type of analysis may be useful in some circumstances in demonstrating to policy makers that apparently expensive programs of treatment or prevention may in fact be cost neutral or even save money when the overall financial consequences of providing the program are compared to those of not providing it. However, the idea that the benefits of health care can be adequately described in terms of the money they save is counterintuitive to most clinicians, and this type of analysis has not been widely used in the field of radiation oncology.

Cost-effectiveness studies compare alternative treatments or processes with respect to their effectiveness, as well as their cost. Effectiveness is usually described in terms of a single objective outcome measure, such as survival. This is useful in that it enables us to put a dollar value on the outcomes achieved by RT, and it has often revealed that RT is relatively inexpensive in relation to the benefits it delivers.[107,108]

Because cost-effectiveness analysis describes the benefits of treatment in terms of a single measure of outcome, it does not provide a satisfactory way of describing and comparing the value of treatments that are associated with different types of health benefit, such as radical RT for cervical cancer and palliative RT for bone metastases. Survival alone is an inadequate measure of palliative RT, and quality of life is an inadequate measure of the effectiveness of curative treatment. The concept of utility, a measure of the relative value of different life states, is useful in reducing the benefits of treatment to a common currency. If utility can be measured, and there is still some question as to whether this is really possible, years of survival can be adjusted for relative value and outcomes expressed as quality-adjusted years of life (QALYs). This measure is sensitive to both duration of survival and quality of life. Cost per QALY can be used to compare the value of treatment in curative and palliative contexts. The value of other forms of medical care has been measured in cost per QALY, and this permits comparison of the value of RT with the value of other treatments both in oncology and in other spheres of medicine.[109,110]

Information about the relative benefits of RT in different clinical contexts could be used as a basis for assigning priorities to one type of case over another in circumstances in which resources are insufficient to provide RT for everyone who needs it. This type of explicit rationing has not, to our knowledge, been used to control access to RT in any of the countries where access to RT is constrained by inadequate supply. Although this approach would serve to mitigate the adverse effects of inadequate access to RT and maximize the societal benefits of the available resources, it seems to have little appeal to policy makers. It has, however, been proposed that cost-effectiveness or cost-utility analysis be used as the basis for selecting the most effective components of care for inclusion

in healthcare programs. In the future, as both the demand for health services and the cost of care continue to increase across the developed world, we anticipate that decisions about which services will be provided within publicly funded systems or managed care programs will increasingly be based on these types of economic analysis. Research in the economics of radiation oncology is likely to be of increasing practical importance in optimizing the effectiveness of RT programs in the future.

SUMMARY

In the past, radiation oncologists and their traditional partners in physics and radiobiology have devoted most research efforts to creating the knowledge necessary to optimize the outcomes of RT in the individual patient. There is a lot of evidence to suggest that we currently fall far short of making the benefits of that research available to all the patients who might benefit from it. It has been demonstrated that in many parts of the world, access to RT is both inadequate and inequitable and that the quality of RT is variable and often suboptimal. These deviations from optimal practice cause us to fall far short of achieving what is theoretically achievable for patients with cancer today within the limits of existing scientific knowledge and technology. Deviations from optimal practice represent real opportunities for enhancing the results of RT, without placing reliance on the uncertain outcome of the slow process of basic research, which frequently promises much but delivers little. Although fundamental and clinical research must continue, a greater proportion of our efforts should be devoted to enhancing our understanding of the factors that influence access to RT and determine the effectiveness and efficiency of RT programs. RT provides major health benefits for a large proportion of patients with cancer, and even a small incremental gain in health system performance would be expected to translate itself into large societal benefits.

HSR in radiation oncology is still a relatively new field, and it offers new investigators a great opportunity to make a real difference. There are a number of good opportunities for training in health services and policy research, and the funding for HSR has greatly increased in recent years. There is real need for radiation oncologists to become involved in leadership roles in HSR because the clinician's insights are vital in choosing the right research questions. Getting the right answers, however, may require a high level of methodologic expertise in areas that are unfamiliar to most radiation oncologists. Success in HSR often depends on building effective collaborations with scientists in other fields such as epidemiology, health economics, and the social sciences. Those who enter the field should also be aware that getting the most out of HSR requires a degree of diplomacy and academic ability. Clinicians involved in HSR need to remember that in the pursuit of the goal of evidence-based management of healthcare programs, they need to influence health system managers as well as their peers. Investigators need to learn the skill of working collaboratively with the health system managers and policy makers who hold the power to implement some of the changes necessary to optimize outcomes, while keeping some control of the research agenda.

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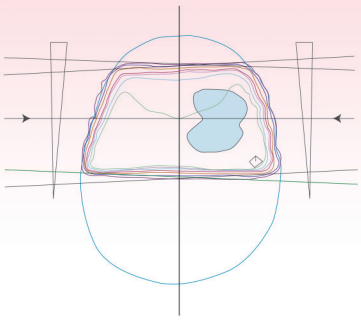
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CHAPTER

13 Statistics and Clinical Trials



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In this chapter we address some of the statistical issues associated with clinical trials. We begin with a short description of the basic role of statistics and statisticians and illustrate some sample communications between investigators and statisticians. We provide an overview of the statistical issues relevant to each phase of clinical trials (phases I, II, and III) and discuss some of the unique aspects of phase II and III trials. We introduce standard and newly developed phase II experimental designs. We are particularly interested in the essential roles of randomization and stratification in comparing new and standard therapies. We discuss the important *intent-to-treat principle*, which is fundamental to analyzing phase III trials. We emphasize the importance of appropriate monitoring in ongoing trials. In addition, we consider some of the special problems that arise in the analysis of survival data that are caused by the phenomenon of *censoring*, which occurs when a patient's time to death cannot be completely determined either because he or she becomes lost to follow-up before death or is still alive when the data are to be analyzed. Finally, we briefly discuss several relevant topics in modern clinical trials: surrogate endpoints, biomarkers, and adaptive design.

Our intent in this chapter is to provide the reader with insight regarding the use of statistics (and statisticians) in the design and analysis of clinical trials rather than to provide all of the details required for an investigator to perform his or her own analyses. Several excellent texts provide the details required for performing analyses, and we cite several such references.

We define a clinical trial as a designed study involving the treatment of prospectively accrued humans that is specified by a document (protocol) with specific goals and analysis plans. Meinert[1] describes some of the unique aspects of clinical trials that distinguish them from other medical research studies, including, among others, observational studies and case-control studies, and enumerates the requirements of a good protocol document.

WHY ARE STATISTICS AND STATISTICIANS USEFUL?

It has been a long-standing paradigm that clinical research is best conducted through collaborations requiring multidisciplinary expertise. Among these scientists, statisticians are often viewed as technicians who provide statistical services, rather than collaborators who make critical scientific contributions to the research. For example, an improper opinion that occasionally exists is that the involvement of statisticians only starts with analyzing data after the completion of the study. Actually, optional collaboration between statisticians and clinical investigators is involved in every step of a clinical trial and can be extremely fruitful. These collaborations cover the whole cycle of a study—from design, conduct, continuous monitoring, data analysis, and interpretation to decision making and publishing results, as well as generating new hypotheses for subsequent studies. Furthermore, the methodology research centered on clinical trials is a driving force of innovative designs in clinical research.

The ultimate goal of conducting clinical trials is to make beneficial influences in future clinical practice, which requires that the conclusions made at the end of the trial have a high degree of credibility, reproducibility, and external validity.[2] Just like all experiments, realities of environment, conditions, and resources introduce both controllable and uncontrollable errors. This is especially true in oncology studies. Genetic, behavioral, environmental, and sociological heterogeneities introduce great complexities in disease progresses and the impact of the studied treatment. Generally speaking, there are two types of errors. One is random, which is purely the result of chance. Another is systematic, known as bias, which describes errors that are not a consequence of chance alone. A fundamental difference between random errors and bias is that pure random errors have no preferred direction, whereas biases present effects of distortion.

Random errors are commonly caused by sampling variability, subject heterogeneity, measurement error, and other source of noises. In reality, the random errors in any experiment can never be completed eliminated. For instance, two patients who have cancer may have nearly identical clinical (and pathologic) characteristics and receive the same treatment. But one may fail (experience relapse or die) within months whereas the other may be cured. A practical definition of *variance* could be the unexplained differences in outcomes that exist among seemingly similar patients. If one looks at two sets of 15 patients who differ in one characteristic (possibly treatment) and notices that one group has a median survival time that is 2 months longer than the other group, one cannot immediately conclude that the characteristic is truly associated with survival difference or just by chance. Statistical techniques will be required to evaluate the likelihood that a median survival difference of 2 months was quite likely to occur even if these two sets of patients who actually did not differ in the characteristic had been compared (a so-called type I error). Quantifying the magnitude and likelihood of the errors resulting from chance requires knowledge of probability and statistical theory. Reducing the relative impact of random errors can be achieved by averaging over a large number of observations. This is commonly known as the *sample size calculation* in clinical trial design.

Bias, on the other hand, cannot be reduced by averaging after repletion or taking additional observations. In clinical settings, although biases can arise in numerous ways, there are often a set of factors that have been studied and well known to contribute to the possibility of bias. In many cases, these sources of bias can be understood well enough to be controlled. For example, bias can occur in medical research studies if treatments are compared between groups of patients who are not equivalent in terms of characteristics that are associated with prognosis. The fundamental strategy used in clinical trials to avoid biased treatment comparisons is randomization of treatment assignments (with stratification), which guarantees the comparability of patients assigned to different treatments under the comparison(s) in terms of his or her prognosis under the condition of no treatments. In observational studies, such an assurance is simply not possible. Although it may be feasible to adjust for potential sources

of bias at the data analysis stage, based on our present knowledge of factors influencing disease outcomes within individual patients, there is no way to ensure that patients receiving two different treatments are comparable in the absence of randomization. There are other critical considerations to reduce bias and include concurrent controls, objective assessments, consistent active follow-up and endpoint ascertainment, no post-hoc exclusions, and so on.

Reducing and controlling random errors and systematic biases are essential elements of clinical trials to provide valid and generalizable trial inferences. These cannot be achieved without sound statistical design. Sophisticated analyses can almost never salvage design faults and poor implementation of the design.[2,3] Since the recognitions of statisticians' involvements in clinical trials in 1970s, a subgroup of statisticians have been actively contributing their knowledge and creativity in cancer therapeutic research by providing core techniques to transfer the conceptional clinical ideas into sound, efficient, and practical clinical trials throughout the entire lifetime of the study.

INTERACTION BETWEEN AN INVESTIGATOR AND A STATISTICIAN

Inadequate communication between an investigator and a statistician might be the most frequent cause of inappropriate designs or analyses in clinical research. This may occur because the investigator does not explicitly state what he or she is trying to learn from a particular study or because the statistician lacks the insight of what methods that satisfactorily address the study question. Planning and conducting a clinical trial is an interactive and iterative collaboration process between investigators and statisticians. For example, in the designing phase, many critical communications are centered on the following components:

1. What is the targeted disease population? This provides the set of critical disease characteristics and known (potential) confounders that the statistician needs to consider in the design or analyses for controlling biases or identifying effect modifier (e.g., predictive markers).
2. How is study "success" defined? This indicates the choice of study type including decision-making studies with superiority, noninferiority, or equivalence designs, exploratory studies aimed to quickly screen promising agents, or trials conducted to provide estimation of the key parameters of the new agents.
3. What is the existing knowledge of the tested agent? This describes the stage of the study design, for example, phase I trials for dose finding, phase II trials for preliminary evidence of efficacy, or phase III trials for confirming efficacy and regulatory approval for marketing. Commonly, the level of uncertainty tolerance (i.e., significance level and power) varies according to the phase of the design.
4. What is the clinical meaningful treatment effect? This requires an appropriate choice of endpoint, which is a measurement that reflects how patients feel and function and can be reliably and precisely measured. Historical data of this endpoint in the targeted population serves the benchmark of the design. Discussions of the expected clinical meaningful effect size give reasonable derivation of sample size and study operating characteristics.

Other details include whether a control group should be included; should a biomarker be used in the design, and if so how should it be incorporated; and what are the logistical and practical challenges in trial conduct? These components of communications between investigators and statisticians are never isolated from each other. Transparent, informative, comprehensive, and persistent communications are essential for a good trial design.

CLINICAL TRIALS

Clinical trials performed to develop and test new agents or modalities in oncology are often categorized as phase I, phase II, or phase III trials according to their primary aims.

Phase I Trials

Phase I trials are generally the first trials involving human subjects in which a new treatment is tested. The goal of a phase I trial is to test a new regimen's tolerability and toxicity. These trials usually enroll a limited number of patients who have exhausted other treatment options. Phase I trials may enroll patients with a specific tumor type only or be open to patients with different tumors. Different primary endpoints and study designs should be considered for regimens with different cancer therapeutic mechanisms.

Traditional Cohorts-of-3 Phase I Design

Historically, cancer therapies have been designed to act as cytotoxic, or cell-killing, agents. The fundamental assumption regarding the dose-related activity of such agents is that there exists a monotone nondecreasing dose-response curve, meaning that as the level of the dose increases, tumor shrinkage will also increase, and this phenomenon should translate into increasing clinical benefit. Under this assumption, both the toxicity and the clinical benefit of the agent under study will increase as the dose increases; therefore, an appropriate goal of a phase I trial is to find the highest dose with acceptable toxicity. Because the monotone nondecreasing dose-response curve has been observed for most cytotoxic therapies, toxicity has historically been used as the primary endpoint for identifying the dose that has the greatest likelihood of being effective, yet tolerable, in subsequent testing.

In this context, the typical goal for phase I clinical trials has been to determine the maximum tolerated dose (MTD), which is the highest dose level at which the rate of dose-limiting, toxicity (DLT) does not exceed the targeted toxicity level (TTL). Which adverse events will be considered as DLT vary depending on the type of cancer and the specific agent under study. The traditional design is the cohort-of-3 design, which is easy to use and requires no complicated statistical computations. Specifically, three patients are enrolled at the starting dose level. If no DLT is observed, three patients will be enrolled at the next higher dose level. If one DLT is observed, another three patients will be enrolled at the same dose level. Out of the six patients at a given dose level, if one DLT is observed, three patients will be enrolled at the next higher dose level. If two or more DLTs are observed (out of three or six patients at a given dose level), then the MTD will be considered to have been exceeded, and the next lower dose level will be defined as the MTD as long as six patients have been evaluated at that level.

Although the cohort-of-3 phase I design has considerable appeal (it is straightforward to conduct, easy to explain, and has considerable historical precedent), there are several limitations with this design. Particularly with newer agents that will be discussed, use of the cohort-of-3 design poses increasing challenges in modern clinical trials. For instance, the TTL is arbitrarily set to 33%, which may not suitable for every disease-agent setting. High uncertainty is unavoidable because of the inherited small sample size. For example, the exact 95% confidence interval for the observed rate of DLT at MTD is 0.00 to 0.64 when 1 of 6 patients experienced DLT. Also, it is a common misunderstanding that the true DLT rate at MTD

identified by this design is 0.33. It is actually closer to 0.22.[4] For the assumption of monotone nondecreasing dose-response curve for cytotoxic agents, this fact increases the risk of failure in phase II studies because the lower toxicity also indicates lower efficacy. When the true DLT rate presents small variations across dose levels, it may require a long time and many patients treated at suboptimal dose levels, such as in a cohort-of-3 phase I study[5] in which 56 patients were accrued during a period of 38 months to determining the MTD of CPT-11 in the regimen of CPT-11/5-FU/LV for patients with metastatic or locally advanced cancer.

Newer Phase I Designs

Over the last several decades, statistically based improvements have been proposed for phase I study design. One of the statistical theories (i.e., Markov Chain) demonstrates that when assigning patients to the next dose level, up or down, based on observed number of DLTs (0 or ≥1) and prespecified TTL, the dose assignment will converge to MTD when the number of assignments is sufficiently large.[6] A class of up-and-down designs was developed based on this theory. One example is biased-coin design (BCD) with dose assignment based on a single patient's DLT occurrence.[7] Later this method was extended to enroll patients in cohorts to each dose level.[8]

In parallel to up-and-down design, another class of nonfixed dose assessment design, using a model-based approach, was started with the first proposal of continual reassessment method (CRM),[9] with further improvements for practical use.[10,11] One of the key features of the CRM is that the DLT rates at different dose levels are reestimated based on data from treated patients across all dose levels examined to date, whenever there are new data observed. Each newly enrolled patient is assigned to the dose level whose current DLT rate estimate is closest to TTL. At the end of study, the MTD is determined by final DLT rate estimates using all treated patients' data. Garrett-Mayer gave an excellent tutorial on the CRM design.[12]

As the therapeutic development in oncology moves from cytotoxic to cytostatic or targeted agent, additional challenges are present in dose-finding studies. For example, the dose-response relationship for novel agents may take forms other than monotone nondecreasing curve, such as quadratic, or increasing with a plateau. In this case, evaluating toxicity and efficacy simultaneously is necessary to find the biologically optimal dose (BOD), which balances the needs of minimizing toxicity (to an acceptable rate) and maximizing the efficacy. Weighted-outcome[13] or utility-based[14] approaches were proposed to handle the tradeoffs between two endpoints. Another example is dose finding in combination treatment; CRM methods have been extended to generalized CRM[15] or partial order CRM[16] methods aimed to address this situation.

Despite the development of more effective designs, the standard chort-of-3 still remains the most popular phase I study design in practice. Rogatko et al examined more than 1,200 published phase I studies and found only 1.6% adapted more sophisticated design than chort-of-3 design.[17] The major reasons may be statistical complexity and lack of user-friendly software.[18] However, increased awareness and greater communication between investigators and statisticians increases the possibility of applying these newer methods.

Phase II Trials

In phase II trials, the goal is to establish clinical activity and further evaluate the treatment's toxicity. Unlike phase I trials, which commonly accrue patients with a variety of cancers, a phase II trial should restrict accrual to a reasonably well-defined patient population. Historically, the response rate has been the most common endpoint for phase II trials. However, in the last decade, progression-free survival/disease-free survival (PFS/DFS) and overall survival (OS) rates have been used increasingly as the primary endpoint in the phase II setting.

Traditional Single-Arm Phase II Designs: One-Stage Design

The starting point for a discussion of phase II trials is the single-arm, one-stage design. In these trials, patients are accrued to a single arm and are treated at a single dose level that has been suggested by previous phase I trials. If the treatment appears sufficiently active in comparison with historical success rates (typically, tumor response) in patients with disease and prognosis similar to those accrued to the phase II trial, the treatment may be considered a viable candidate for the phase III setting. Toxicities, expense, and other considerations will often influence the decision as to whether the drug or radiation versus chemoradiation regimen has enough promise compared with standard regimens to warrant further interest.

We explain this type of design by means of an example. Suppose that in recent treatment trials for a given disease, the response rate ranged between 15% and 20%. A new trial might then be designed to show that the new treatment will not be worth continuing if the true response rate is 10% or less and that the new treatment should be continued if the true response rate is 25% or greater. Such a design implies, by default, that if the response rate is in the range of 15% to 20%, the probability of either decision being made (i.e., to abandon the new therapy or to bring it to phase III testing) may be nearly equal. One critical consideration is to make sure that patients in the new study are comparable to those enrolled in the previous studies, a factor that in many cases is impossible to verify.

As described, the typical phase II trial is structured to provide the basis for a recommendation either to abandon the therapy or to consider it for further testing. Working together, the investigator and the statistician choose an "unacceptable" response rate, p_0 (10% in our example) and a "promising" response rate, p_1 (25% in our example). The study is designed so that if the response rate is as low as p_0 there will be little chance that the treatment will be recommended, whereas if the response rate is as high as p_1 there is a high probability that the treatment will be recommended. These benchmark response rates should in no case be chosen arbitrarily; considerable thought must be given to their selection, and they should be fully justified by comparison with historical data in patients with comparable disease and prognosis.

The considerations just given might lead to the following study design criteria:

1. If the true response rate is $p_0 = 10\%$, there should be no more than a probability of 0.10 (significance level) of erroneously concluding that the treatment should be carried forward.
2. If the true response rate is 15% to 20%, it will not be harmful to have a fairly high probability of reaching either conclusion.
3. If the true response rate is $p_1 = 25\%$, there should be a probability of at least 0.90 (power = 0.90) of concluding the treatment is effective enough to be carried forward.

Using well-known methods, the statistician could determine that each of these criteria would be satisfied if 40 patients were accrued, and the treatment would be recommended for further consideration if, and only if, at least 7 of the 40 patients responded. Table 13-1 gives the probabilities that the treatment will be carried forward for various hypothetical response rates.

It is worth noting that the formal decision rule is to conclude the treatment is worth carrying forward if the estimated

TABLE 13-1 Operating Characteristics of a One-Stage Phase II Study Design

	True Response Rate					
	5%	10%	15%	20%	25%	30%
Probability of recommending treatment for further consideration	0.003	0.10	0.39	0.71	0.90	0.98

TABLE 13-2 Operating Characteristics of a Two-Stage Phase II Study Design Allowing Early Stopping for Zero Responses in the First 15 Patients

	True Response Rate					
	5%	10%	15%	20%	25%	30%
Probability of recommending treatment for further consideration	0.003	0.10	0.39	0.71	0.90	0.97
Probability of stopping after first stage of accrual	0.46	0.21	0.09	0.04	0.01	0.005

TABLE 13-3 Operating Characteristics of a Two-Stage Phase II Study Design Allowing Early Stopping for Zero Responses or One Response in the First 15 Patients

	True Response Rate					
	5%	10%	15%	20%	25%	30%
Probability of recommending treatment for further consideration	0.003	0.09	0.35	0.66	0.86	0.95
Probability of stopping after first stage of accrual	0.83	0.55	0.32	0.17	0.08	0.04

response rate is at least $7/40 = 17.5\%$ but not if the response rate is less than or equal to $6/40 = 15\%$. As Table 13-1 indicates, the probability of observing a response rate of at least 17.5% in our trial if the true response rate is 10% is only 0.10. In contrast, the probability of observing a response rate of at least 17.5% is 0.90 if the true response rate is 25%, and a positive recommendation is extremely likely (probability = 0.98) if the true response rate is as high as 30%. Other factors may enter into the final decision, particularly if the observed response rate is close to 15% or 20%.

Traditional Single-Arm Phase II Designs: Two-Stage Design

Because many experimental treatments ultimately do not demonstrate efficacy, ethical considerations lead to the usual recommendation of an early stopping rule for lack of efficacy in phase II trials. For example, suppose that the first 15 patients who are accrued do not respond to the therapy. At that point, an investigator might begin to believe that the treatment is no better than standard therapy and might even be worse. This raises the question of whether the trial should be terminated. On the one hand, there is some probability that 7 of the next 25 patients will respond, resulting in a recommendation for continued consideration of the treatment. Statisticians have developed clinical trial designs that allow a prospectively specified examination of the data from the ongoing trial to address this issue.

Generally, the issue of *early stopping rules* is as follows: When designing a trial, it may be appropriate to introduce the possibility of stopping early if there is strong evidence that the treatment is no more and possibly less effective than the standard treatment, as long as doing so would not substantially reduce the probability of detecting a true beneficial effect (power). Of course, one might also want to stop early if the treatment appears to be extremely effective, although there is no ethical constraint against assigning patients to an apparently effective treatment, unless doing so would unduly prolong the further development of a promising therapy.

Consider the following modification of the phase II study design just described. Accrual will proceed in two stages. In the first stage, 15 patients will be accrued, treated, and observed for clinical response. If no patients respond, the trial will be terminated, and the candidate treatment will not be recommended for further consideration; otherwise, an additional 25 patients will be accrued. If in total at least eight responses are observed, the treatment will be recommended for further consideration; otherwise, it will not be so recommended.

This new design has some nice properties. The maximum number of patients required is the same as before, and, as shown in Table 13-2, the new design still satisfies each of the desired criteria 1 to 3 listed previously. However, if the new treatment has a true response rate of 5% or less, the study has a 0.46 chance of stopping after 15 patients have been accrued, therefore sparing 25 patients from treatment with an inactive regimen.

Now consider a design that requires early stopping if only 0 or 1 of the first 15 patients responds; otherwise, 25 more patients are accrued, and the treatment is recommended for further consideration if at least 7 patients respond. This design provides much better protection against the possibility of accruing an excessive number of patients to an ineffective regimen. However, if this design is used, it would be slightly less likely that a truly effective regimen would be recommended for further consideration. Table 13-3 shows the properties of this design.

Notice that with this design, there is a 0.83 probability that the study will terminate after 15 patients are entered if the regimen has only a 5% response rate. However, the probability of recommending the treatment is now only 0.86 if there is a 25% response rate. Numerous authors have discussed optimal strategies for choosing phase II designs, including Gehan,[19] Herson,[20] Lee, Staquet, and Simon,[21] Fleming,[22] Chang et al,[23] Simon,[24] Therneau, Wieand, and Chang,[25] Bryant and Day,[26] and Thall, Simon, and Estey.[27]

Newer Phase II Designs: Randomized Phase II Design

Single-arm phase II designs can demonstrate biologic activity of an agent with relatively small sample size and short study duration. However, the potential for patient selection bias, the evolving methodologies for the assessment of "success" (i.e., changes in computed tomography [CT] scanners, changes in

response criteria), and a general lack of robustness of historical rates of this type of design result in a high possibility that a positive single-arm phase II trial will be followed by a negative phase III study.[28] A potential solution to this fundamental limitation of single-arm phase II designs is the use of a randomized design. Two types of randomized phase II designs, the randomized selection designs and the randomized screening designs, have been proposed and used widely.

In a selection design, all arms are considered experimental arms. These could be different new regimens or different doses or schedules of the same regimen. The sample size is calculated to guarantee that with a small probability, perhaps 10%, an inferior arm (for instance, one in which the response rate is 15% lower) will be selected for the future phase III study. In a standard selection design, the arm with the highest estimated success rate for the primary endpoint will be recommended for a follow-up phase III study, no matter how small the difference of estimates might be among arms.[29] On the other hand, a flexible selection design, or "pick-the-winner" design, will recommend the arm with the best estimated primary endpoint if the difference is larger than a prespecified criterion.[30] Otherwise, toxicities, expense, and other factors will be taken into consideration when making the decision.

If a standard of care is included in the comparison, a screening design should be applied.[31] A screening phase II design is similar to a randomized phase III trial but has larger type I and type II errors. For instance, a range of 10% to 20% for both error rates is acceptable. A screening phase II design provides a head-to-head comparison between the experimental regimen and the standard of care using a relatively smaller sample size and clear guidance as to the likelihood of success if the agent is moved forward into phase III testing.

Overall, randomized phase II designs balance prognostic factors among all arms, avoid patient selection bias, and provide robust arm comparison results. The major concerns for randomized phase II designs are (1) the larger required sample size, (2) the relatively high risk of false-negative and false-positive rates resulting from the small sample size, and (3) the possible desire (or ethical mandate) to skip a confirmatory phase III study given a positive phase II result.

Another type of newly developed randomized phase II design is the phase II/III design. A phase II/III design starts with a phase II component. Patients are randomized among several experimental arms or a standard-of-care arm versus one or more experimental arms. Experimental arms could be compared with the historical control or the standard-of-care control to select arms for entering the phase III component. The main advantage of this type of design is (1) the speed of transition from phase II to phase III and (2) the fact that data obtained from the phase II component could be applied toward the phase III comparison as long as the protocol treatment is not altered between phases.

Phase III Trials

It is generally recognized that judging the value of a new therapy by comparing it with historical data may give an erroneous impression of the therapy's efficacy. Pocock[32] related a number of illuminating examples of this phenomenon. Therefore the phase III trial, in which a new agent, modality, or combined treatment modality is tested against an accepted standard treatment in a randomized comparison, is considered the most satisfactory method of establishing the value of the proposed treatment.

Under most circumstances, the goal of a phase III trial is to determine whether the proposed treatment is superior to the standard treatment (superiority trial). Alternatively, if the alternative treatment is easier to administrate, costs less, or is less toxic than standard of care, showing superiority is not necessary; a definitive demonstration of noninferiority (noninferiority trial[33]) is all that would be required. Because the goal of a phase III trial is to make a definitive conclusion regarding a new treatment's efficacy, enough patients need to be accrued to guarantee a small probability of false-positive results (i.e., declaring that a regimen is effective when in fact it is not) and a large probability of true-positive results (i.e., declaring that a regimen is effective when in fact it is). The probability of false-positive results is also called the size of the study, which usually is limited to 5% or less. The probability of true-positive results is also called the power of the study, which usually is set at 80% to 95%. The primary endpoints for comparison are usually OS and PFS/DFS, and a common secondary endpoint is quality of life (QOL). In this section, we discuss the rationale for requiring randomized treatment assignment and stratification in a phase III trial. We introduce the intent-to-treat principle, and we emphasize the importance of monitoring in ongoing trials.

Rationale for Randomization

A random assignment is defined as any assignment resulting from a mechanism ensuring an equal probability to all possible assignments. The most obvious reason for randomized assignment is to eliminate the possibility of bias, that is, the intentional or inadvertent assignment of treatments by means of procedures that allow patient characteristics to influence the assignments in a way that may promote an imbalance in patient characteristics between the two treatment arms. The basic idea is simple. If chance alone determines treatment assignments and enough patients are accrued, the law of averages will ensure that the characteristics of patients in different treatment arms will be nearly identical.

Treatments must be assigned in such a way that the accruing physician or coordinator will have no reasonable basis for predicting the arm to which a patient will be assigned. For example, if an accruing physician suspects that at some point their next patient may be assigned to a new treatment study, he or she may recruit patients who might have more favorable outcomes, thereby allowing subtle differences in patient characteristics to influence treatment comparisons. For this reason, it is common for the randomization of patients to be permitted only through contact with a centralized randomization coordinator.

Other potential sources of bias exist that cannot be eliminated by randomized treatment assignment. In some diseases, application of a treatment may convey psychological effects or promote expectations that affect some endpoints of interest. In cancer research, the most obvious example is that treatment with chemotherapy or other agents gives rise to expectations of toxicity. Therefore, whenever it is feasible without causing undue hardship to patients, treatment assignments should be masked by use of placebos. Perhaps even more important is the need to keep medical personnel unaware of actual treatment assignments whenever possible to eliminate bias in assessing response, relapse, or attribution of causality to adverse events.

Stratification of Treatment Assignments

For trials with large sample sizes, randomization of treatment assignments—together with the law of averages—will result in nearly balanced patient characteristics across treatment arms. However, if certain patient characteristics are known to be strongly prognostic of outcome, a better balance can be achieved by allowing separate randomization of treatments to patients within subpopulations defined by the various levels of prognostic variables. Such a restricted randomization scheme is referred to as *stratified random assignment*, and the

prognostic variables are referred to as *stratification variables*. For example, in clinical trials of adjuvant therapy for breast cancer, it is known that rates of relapse are strongly related to the number of axillary nodes found to be positive for tumor on histologic examination and are less strongly related to the age of the patient. Therefore, the assignment of treatments to patients might be stratified within eight subpopulations, defined by combinations of nodal status (node negative, 1 to 3 positive nodes, 4 to 9 positive nodes, 10+ positive nodes) and age at randomization (≤49 years, ≥50 years). In this way, stratification (to balance the effects of strongly prognostic characteristics) and randomization (to prohibit bias resulting from less obvious or even unforeseen factors) may be used together to promote an unbiased comparison of treatments.

In some cases, it is difficult or even impossible to achieve completely balanced treatment assignments within every combination of the levels of all potential stratification variables. For example, in multicenter cancer clinical trials, it is generally thought to be good practice to balance treatment assignments within each accruing institution because patient selection may differ from institution to institution. However, it is not unusual for cooperative groups in oncology to conduct phase III clinical trials using several hundred accrual sites. Clearly, it would be difficult to stratify completely in the accruing institutions together with other potentially prognostic variables, because the number of resulting combinations of levels of all the stratification variables would be excessive. To circumvent this problem, cooperative groups commonly use algorithms that dynamically maintain nearly balanced assignment of treatments across the levels of all stratification variables marginally but that do not guarantee balance within all combinations of the levels of all of the stratification variables. This approach also results in nearly balanced treatment assignments at all times, which will be beneficial if, as often happens, the characteristics of patients for whom the trial is considered most appropriate in the judgment of accruing physicians tend to change as the trial matures. Details of several such dynamic balancing algorithms may be found in articles by Taves,[34] Pocock and Simon,[35] Freedman and White,[36] and Begg and Iglewicz.[37]

Intent to Treat

If treatment assignments are randomized as described previously, one can be reasonably confident that important prognostic factors will be balanced across treatment arms. However, if any patients are excluded at the time the data are analyzed, the possibility of bias arises once again. An analysis that includes all randomized patients, regarded as though each had received precisely the treatment to which he or she had been randomized, irrespective of compliance or administrative errors (e.g., errors in eligibility or other protocol deviations), is an intent-to-treat (ITT) analysis. Another type of analysis is called per-protocol (PP) analysis, in which only eligible patients who adhered to the treatment according to the protocol are included. In this section, we show how treatment comparisons may be seriously biased by excluding patients from an analysis, even for apparently valid reasons. We then show how an intent-to-treat analysis may effectively reduce biases that can creep into analyses when not all patients actually receive the treatments to which they have been randomized. We discuss these issues in the context of the following example:

Example 1. A clinical trial was designed to compare the effect of radiation therapy relative to observation in patients with rectal cancer. Three hundred patients were randomized between radiation therapy (arm A) and observation (arm B), 150 to each arm. Suppose that all patients actually received all of their intended therapy and that after 7 years of follow-up,

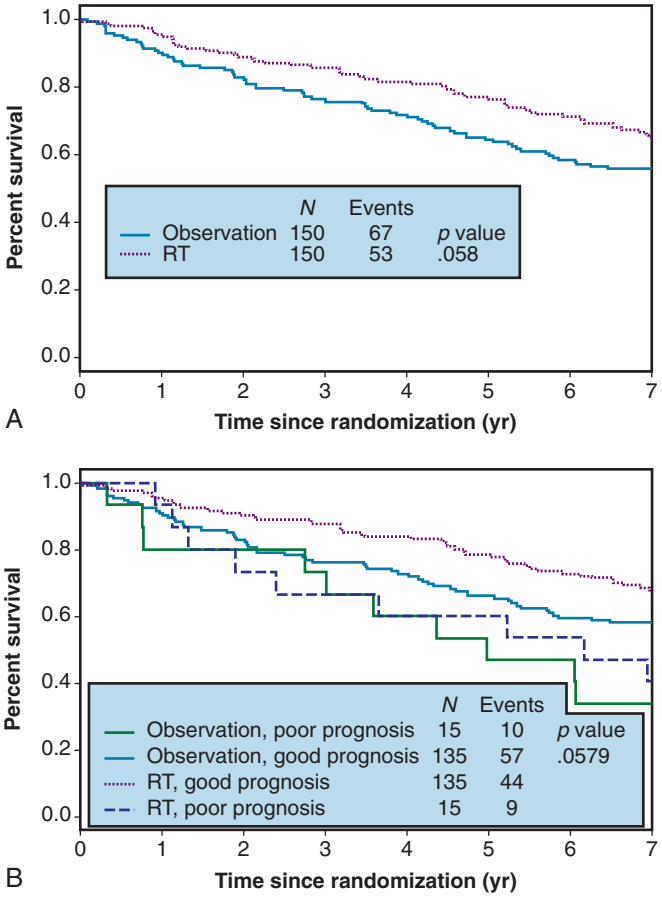


Figure 13-1 **A,** Survival curves that would be observed if all patients receive the prescribed therapy (percent survival versus years from randomization). **B,** Survival curves that would be observed if all patients receive the prescribed therapy, stratified by risk group (percent survival versus years from randomization). *RT*, Radiation therapy.

survival curves were as shown in Figure 13-1, *A*. Although the survival curve for patients receiving radiation therapy lies above that for patients in the observation-only arm, suggestive of a benefit from radiation therapy, the difference is not quite statistically significant ($p = 0.058$).

In any clinical trial, the patients who are accrued exhibit considerable variation in their prognoses. Suppose that we could make use of certain prognostic patient characteristics that were unavailable in the analysis summarized previously. Suppose further that by using this new information, we could identify the 10% of patients with the worst prognoses. Then we might redraw the survival curves after stratifying according to risk, resulting in the plots shown in Figure 13-1, *B*. An analysis of these data that takes this stratification into account again yields a p value of 0.058, which agrees with the p value from the unstratified analysis to three decimal places. This insensitivity of analysis to stratification is a direct consequence of the randomization used in the design of the trial, which tends to balance the poor-prognosis patients equally across the two arms of the trial.

Returning to the original analysis of these data, suppose that not all patients in arm A had actually received the radiation therapy to which they had been randomized. The statistician must decide what to do with these noncompliant cases. There are at least three ways to proceed: (1) it may seem logical to discard data corresponding to the noncompliant patients because they did not receive the radiation therapy that was assigned to them; (2) it might even seem reasonable to analyze

the noncompliant patients as though they had been randomized to arm B rather than arm A because, in fact, they received no adjuvant therapy, similar to those patients who were randomized to observation; (3) the ITT principle states that the noncompliers should be analyzed just as though they had received radiation therapy, even though in actuality they did not.

We now consider the possible consequences associated with these three possibilities. Under the assumption that patients' reasons for refusal of treatment are completely unassociated with prognosis, methods 1 and 2 just presented should lead to estimated treatment differences that are essentially identical to the analysis of Figure 13-1, *A*. If there is a treatment difference, the ITT analysis will tend to underestimate this difference because some of the patients who were not irradiated are counted as having received that therapy. The differences in the three analyses should be rather small under this assumption of no association between refusal of treatment and prognosis.

Alternatively, it is rather likely that reasons for refusal of treatment will be associated with patient prognosis. For example, patients with poorer performance status, or their physicians, may be less liable to accept assignment to a treatment that is known to be associated with significant toxicity. Deteriorating health may lead to difficulties in traveling to receive treatment; advancing disease may correlate with a patient's level of depression or anxiety, which, in turn, may correlate with compliance. Suppose that it is the 10% of patients with the worst prognosis who refuse to accept their radiotherapy. Under these conditions, analysis of the data after deleting the noncompliant patients overstates the effect of radiotherapy, as shown in Figure 13-2, *A*. This is because the patients with the worst prognosis are deleted from consideration in arm A, but no similar deletion of patients with poor prognosis is made in arm B. The result is a spuriously significant p value of 0.021. Treating the noncompliers as though they had been randomized to observation (see Figure 13-2, *B*) results in an even more serious overstatement of the radiotherapy effect, associated with a p value of less than 0.009. In contrast, the ITT analysis yields a slightly attenuated treatment effect ($p = 0.065$) (Figure 13-2, *C*) but no serious misrepresentation of the true effect.

Why did the ITT analysis correspond to the "truth" more closely than the analysis that omitted the subset of patients who did not receive their assigned radiation? This is because the effect of the prognostic factor (risk group) was larger than the treatment effect and the likelihood of patient refusal was associated with both the treatment received and the prognostic group of the patient. Although patient prognoses were balanced as randomized, they are not balanced as treated. In this case, the baseline prognosis of patients who actually received radiation was better than the baseline prognosis of those who were under observation. It is precisely this type of imbalance that the ITT analysis is designed to prevent.

There is no one correct answer as to the best approach to analysis when not all patients receive their assigned therapy. However, there is general agreement among statisticians that it is always appropriate to perform an ITT analysis in which each patient is analyzed according to the treatment assigned at randomization, regardless of what treatment was actually received. Results of any other analysis should be compared with the results of the ITT analysis, and if the results differ substantively, the interpretability of the data must be questioned.

The prior examples illustrated only one type of problem that may be addressed by an ITT analysis. Biases similar to those just described can occur if patients elect to cross over study arms, accept a nonstudy therapy, or receive only a portion of the assigned therapy or if they are determined to be ineligible. Therefore, we advocate attempting to obtain complete follow-up for all patients registered to every phase III trial and performing an ITT analysis. Sometimes this may not be possible because patients who refuse protocol therapy may also refuse to be followed. If only 1% or 2% of patients

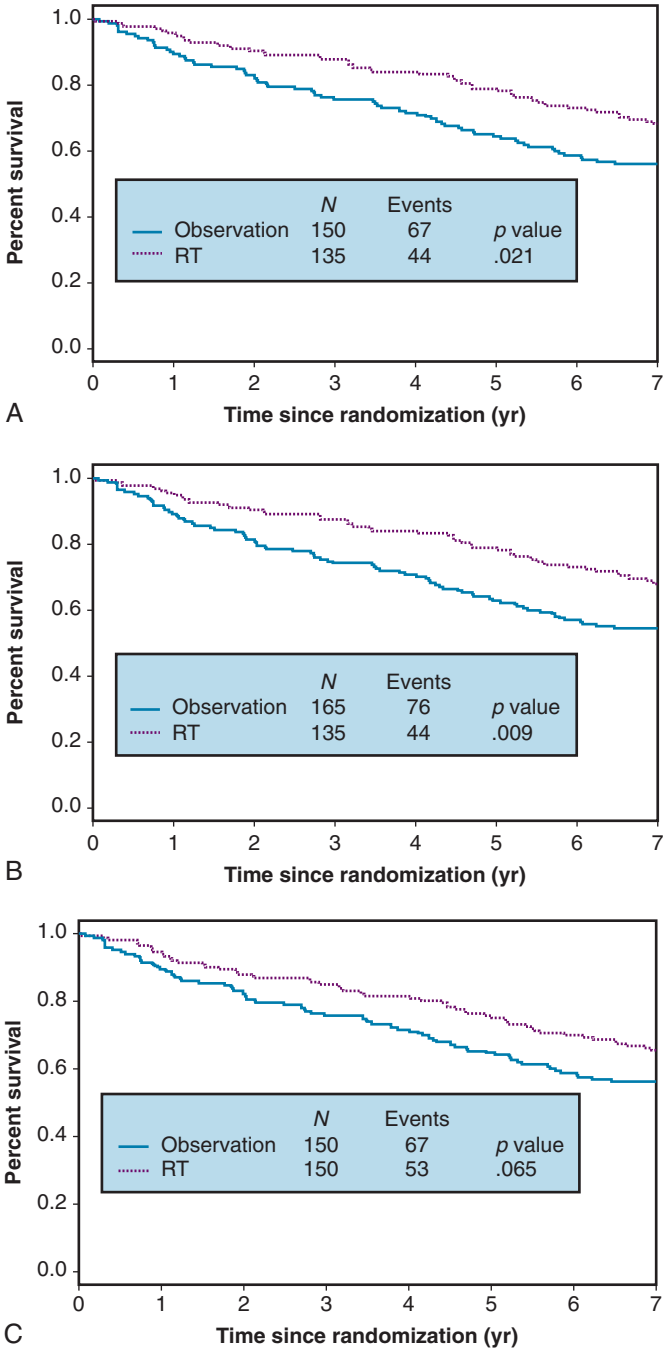


Figure 13-2 **A,** Survival curves that would be observed if the patients of poor risk who refuse radiation therapy *(RT)* are excluded from the analyses (percent survival versus years from randomization). **B,** Survival curves that would be observed if the patients of poor risk who refuse radiation therapy are included as untreated patients (percent survival versus years from randomization). **C,** Survival curves that would be observed if the patients of poor risk who refuse radiation therapy are included as radiation therapy patients (i.e., the results that would be obtained using an intent-to-treat analysis [percent survival versus years from randomization]).

fall into this category, there is little danger of important bias, but if this number is larger, say 5% to 10%, there is a real danger that the study results may be biased. One might then want to perform what are called sensitivity analyses to examine the possible effect of having so many patients without follow-up. In its simplest form, one might perform one analysis assuming that all of the patients without outcome data on arm A failed early on, whereas those on arm B survived; and then perform an analysis assuming that all of the patients without outcome data on arm A survived, whereas those on arm B failed. If one reaches the same conclusion about treatment effect in either analysis, then the exclusions do not represent a serious problem.

There is often disagreement concerning the inclusion of ineligible patients in analyses, particularly in analyses dependent on patient covariates because ineligible patients may not fit any reasonable classification. The decision as to whether it is appropriate to exclude ineligible patients depends on the methods used for determining ineligibility. For example, in some studies, each patient is reviewed for eligibility in a uniform way by a reviewer (or review committee) who is unaware of the assigned treatment and uses only information that was obtained before randomization. If that is the only mechanism for classifying patients as ineligible, one could reasonably exclude such patients from analyses. However, any less stringent approach that allows patients to be classified as ineligible after randomization could introduce subtle biases. For example, in a trial of radiation versus observation, one might routinely perform a pretreatment examination immediately after a patient is assigned to radiation therapy. If, during that examination, it is determined that the patient had not met an eligibility requirement, exclusion would cause a bias because a similar patient not assigned to radiation would not have had the pretreatment examination and would, therefore, not have been determined to be ineligible.

To summarize, we recommend always performing an ITT analysis using all patients as randomized and reporting the results of that analysis in any publication. Further analyses may be performed, especially for noninferiority trials, but one should be aware of potential biases similar to those described previously. Further discussion of these issues can be found in articles by Pocock[32] and Gail.[38]

The data used in Example 1 were generated using the following assumptions. The expected 5-year survival rate for an untreated good-risk patient was 0.73, and for an untreated bad-risk patient, 0.54. The reduction in the death rate associated with radiation treatment was assumed to be 20% in each group. For Figure 13-2, we assumed that all the patients with poor risk had an expected 5-year survival rate of 0.54 because none received treatment.

Monitoring Ongoing Trials

In clinical trials, patients enter a study sequentially over time; therefore, information about the treatment accumulates as the trial progresses. An interim analysis is a planned analysis conducted before the final planned analysis, which allows the study sponsor to evaluate the trial's success probability while controlling the overall statistical error rates. As the trial progresses, interim analyses are usually conducted at prespecified time points, which are quantified by the number of total events. Interim analyses could be used to monitor superiority, futility, or both: If a new regimen is convincingly demonstrated to be superior to the active control, there is an ethical obligation to stop the randomization and provide the new regimen to every patient. If an interim analysis shows that there is little chance for the new regimen to outperform the control, it would be prudent to terminate the trial and save patients for other promising regimens.

There are different approaches in setting interim monitoring boundaries for superiority. For instance, Pocock[39] proposed to spend the type I error (false-positive rate) equally throughout all interim and final analyses. O'Brien and Fleming[40] proposed to reserve most of the type I error for the final analysis. The general approach is to set the interim boundaries conservatively so that the trial will not stop early for efficacy unless convincing evidence is present.

Typically, setting the interim boundaries for futility is not done as conservatively as is setting them for superiority. A nice rule of thumb proposed by Wieand et al[41] is as follows: Assuming that a study has a time-to-event primary endpoint, an interim futility check will be conducted when 50% of events targeted for final analysis have been observed. If the hazard ratio of the experimental treatment versus the control is larger than 1 (i.e., the outcomes on the experimental arm are poorer than those on the control arm at that time), the trial should be stopped for reasons of futility. The rule is simple to follow, and the probability of falsely determining that an experimental regimen is no better than the control situation when, in fact, the experimental regimen actually works is 2% or less.

Interim monitoring mainly focuses on treatment efficacy. To monitor additional aspects of a trial—for instance, to protect the safety of enrolled patients, to ensure the validity of study results, or to identify unacceptably slow accrual rates, unusually high dropout rates, or unacceptable ineligibility rates—a Data Safety Monitoring Board (DSMB) is usually recommended, if not required. The DSMB is composed of an independent panel of experts. Usually, a physician and a statistician are required. Other representatives could include epidemiologists, laboratory scientists, a patient representative, or representatives of different groups. DSMB members have access to all data and report directly to the study sponsor. In current clinical trial practice, the U.S. Food and Drug Administration (FDA) strongly recommends using a DSMB for all phase III trials and many institutional internal review boards now require use of a DSMB.

SURVIVAL ANALYSIS

Survival analysis differs from other types of statistical analysis in that the analysis of time to an event often is complicated by the lack of complete follow-up for every patient (i.e., there is censored data). An example illustrates why this is important. The example uses hypothetical data chosen to illustrate clearly the problem that censoring can cause.

Example 2. Suppose a radiation oncologist decides to review the outcomes of patients with rectal cancer treated with radiation therapy. Of primary interest is the determination of the proportion of patients who remain relapse free for 5 years. Suppose patients have been accrued over the past 7.5 years, and by chance the patients have started treatment in pairs at intervals of 1 year. Suppose, furthermore, that if no more patients were accrued and the oncologist could wait 5 more years to obtain 5-year follow-up for every patient, he or she would find that half of them were relapse free for more than 5 years. This (unobserved) relapse pattern is shown in Figure 13-3.

Twelve years after the first patient was entered, the 5-year relapse-free pattern would be as shown in Figure 13-4 (time 0 is the date of entry for each patient). If the investigator had waited 12 years (i.e., until 5-year data for all 16 patients were complete), he or she would have observed that half of the patients were relapse free 5 years after entry (i.e., the 5-year relapse-free rate is 0.50). Suppose, in fact, that the investigator decided to look at the patients' experience 7.5 years after the first patient had entered. Then the investigator would have observed everything to the left of the vertical line in

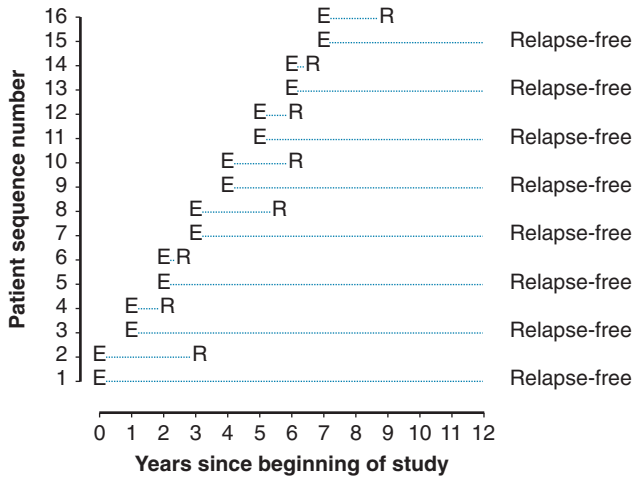


Figure 13-3 Date of entry *(E)* and relapse *(R)* of 16 patients monitored over a 12-year period; 8 did not experience relapse.

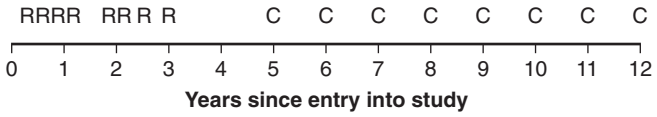


Figure 13-4 Relapse history of 16 patients seen 12 years after the beginning of the study: time from entry into the study until relapse or last follow-up. *C*, Censored; *R*, relapsed.

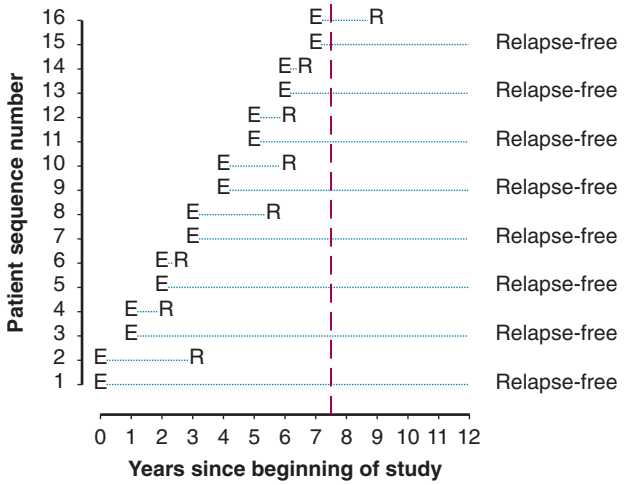


Figure 13-5 Status of follow-up 7.5 years after the first patient was entered in the trial. *E*, Entry; *R*, relapse.

Figure 13-5. Translated into time from entry, this would be represented as shown in Figure 13-6. In that case, the investigator would have complete 5-year data for 7 of the 8 patients who relapsed and for 3 patients who were relapse free at 5 years (those who were entered at year 0, 1, or 2). For the other 6 patients, his or her knowledge would be that they were relapse free for some length of time less than 5 years. The investigator's first instinct might be to exclude these 6 patients from analysis because he or she does not know what their relapse status will be after 5 years of follow-up. Of the remaining 10 patients, 7 are known to have relapsed and 3 are known to be disease free for more than 5 years, so that the estimated relapse-free rate at 5 years is 0.30. This estimate does not seem to reflect the data accurately.

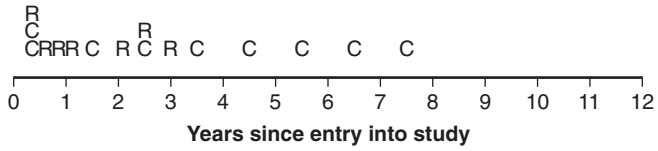


Figure 13-6 Relapse history of 16 patients seen 7.5 years after the beginning of the study: time from entry into the study until relapse or last follow-up. *C*, Censored; *R*, relapsed.

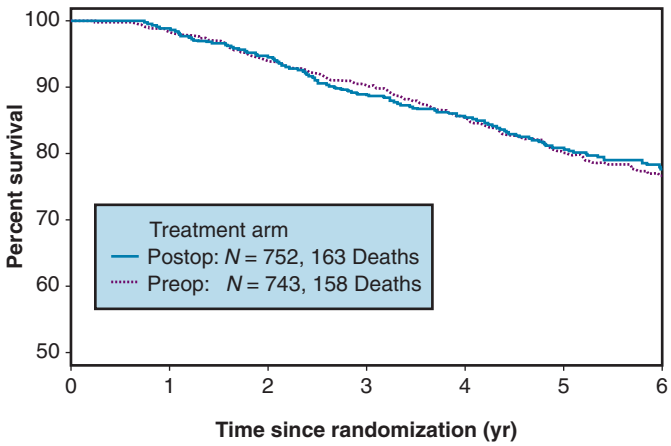


Figure 13-7 Survival of patients with operable breast cancer treated with doxorubicin and cyclophosphamide.

The estimate is so different from 0.50 because the method of calculation is biased. The cause of the bias can be seen by studying the seventh and eighth patients in the series of patients (i.e., the patients entered 3 years after the first patient entered). Notice that the seventh patient entered was still relapse free when the radiation oncologist performed his or her analysis but had only been followed for 4.5 years (i.e., did not have a known status at 5 years) and, hence, was excluded. However, the eighth patient (who was entered on the same day) had relapsed by the time of analysis and, therefore, was included. The bias is that patients who relapse have a better chance of being included in the analysis than those who do not relapse. One way to avoid a biased estimate would be to exclude all patients who did not have the potential to be monitored for 5 years. Therefore the oncologist would only be able to use the information from the first six patients entered. In this artificial example, this would have led to a correct estimate of the 5-year relapse-free rate because three of the first six patients relapsed within 5 years.

This method is unsatisfying because not all of the available information is used. In statistical terms, the disadvantage of our proposed solution is that there is considerably more variance associated with an estimate that uses the data from only six patients than one that uses all of the available data. For example, if patients 6 and 7 had entered the study in the opposite order, the relapse-free estimate would jump from 50% to 67%. A better method is described in the next section.

Kaplan-Meier Method

A common way to summarize survival data is to estimate the "survival curve," using a method proposed by Kaplan and Meier.[42] The Kaplan and Meier curve shows—for each value of time—the proportion of subjects who survive at least that length of time. Figure 13-7 shows survival curves for patients with operable breast cancer who have been treated with either preoperative or postoperative chemotherapy (doxorubicin

and cyclophosphamide) in a large clinical trial. Here, we offer two examples that provide some insight regarding the Kaplan-Meier method. The first example concerns a data set having no censored observations; the second example extends these ideas to accommodate censored observations.

Example 3. Suppose four patients are entered into a study, possibly at different times, and all four die, with death times of 10 months, 20 months, 25 months, and 40 months, respectively, from time of entry. We want to estimate the 3-year survival rate. Three of the four patients died within 3 years from entry, and one patient remained alive more than 3 years from entry (i.e., one fourth of the patients entered lived at least 3 years). Therefore, a reasonable estimate of the 3-year survival rate is $S(3) = 0.25$. This estimate (the proportion of patients who remained alive at 3 years) is referred to as the empirical survival estimate, and the graph of estimates obtained this way at all time points is called the *empirical survival curve.*

Example 4. Suppose that in the previous example three of the patients have died at 10 months, 25 months, and 40 months, respectively. The fourth patient is still alive but has been monitored for only 20 months. We want to estimate the 3-year survival rate. Notice that if we could wait another 16 months to obtain the estimate (so that we would have 3-year data for all patients), we would obtain an estimate of either one fourth (if the fourth patient dies soon) or one half (if the patient remains alive for another 16 months). The rather intuitive approach we used in Example 3 to estimate the 3-year survival rate does not work here because we do not know whether there will be two or three survivors when all the patients have died or have been monitored for 3 years (i.e., we do not know how to handle the patient whose follow-up was censored at 20 months). Kaplan and Meier proposed an approach that updates the survival estimate at the time of each death using only those patients who are at risk of failing at each update.

Because none of the patients died during the first 10 months, the Kaplan-Meier estimate of the probability of surviving to any time point less than 10 months is equal to 1. Because four patients are alive at 10 months but only three quarters of them survive beyond 10 months, the Kaplan-Meier estimate changes to three quarters for time points beyond 10 months but before the next death. Although one patient is censored at 20 months, this gives no information regarding the likelihood of a death, so the Kaplan-Meier estimate remains at three quarters for all time points between 10 months and 25 months. One of the two patients who are still at risk just before 25 months dies at that time. Therefore, the estimate of the probability of a patient surviving beyond 25 months, given that the patient survived at least 25 months, is one half. The Kaplan-Meier estimate of surviving more than 25 months is the product of three quarters (the estimated probability a patient will survive until 25 months) times one half (the estimated probability that a patient will survive more than 25 months given that the patient was alive at 25 months), which is three eighths. There are no other deaths before 3 years, so the Kaplan-Meier estimate of the 3-year survival rate is three eighths. The Kaplan-Meier method uses all the relevant available data from each patient but excludes the patient who was censored at 20 months from all computations beyond that time.

If the Kaplan-Meier approach is applied to the data in Example 3, the estimate $S(3)$ is equal to the (probability of surviving 10 months) × (probability of surviving more than 10 months given survival of 10 months) × (probability of surviving more than 20 months given survival of 20 months) × (probability of surviving more than 25 months given survival of 25 months), or $1 \times \frac{3}{4} \times \frac{2}{3} \times \frac{1}{2} = \frac{1}{4}$, which matches the empirical survival estimate. In fact, the Kaplan-Meier estimate and the empirical estimate always match when they are applied to uncensored data.

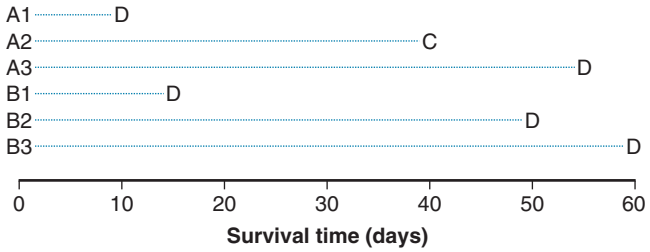


Figure 13-8 Survival times of six patients treated with one of two regimens. *C*, Censored; *D*, death.

TABLE 13-4 Observed Deaths (t=10)

Treatment	Dead	Alive	Total
A	1	2	3
B	0	3	3
Total	1	5	6

The reader may verify that application of the Kaplan-Meier approach to the data in Figure 13-6 will result in an estimate of 0.45 for the probability of remaining relapse free through 5 years.

Log-Rank Statistic

Perhaps the most common application of survival analysis techniques is the comparison of survival times (or other times to event, such as time to disease relapse) between two or more groups of patients that differ in some aspect (e.g., male versus female, or treated versus untreated). The log-rank statistic, the stratified log-rank statistic, and the Cox proportional hazard model are commonly used to compare survival times between groups.

The log-rank statistic deals with the problem of censoring by comparing the groups only when a patient within any of the groups experiences an "event" (if survival times are to be compared across groups, an event would be a death; if times to relapse are to be compared, an event would be a relapse, and so on). This idea is most easily explained in the context of a simple example. Suppose we monitored three patients receiving a standard treatment regimen (this might even be no treatment), which we refer to as treatment A, and three other patients receiving an experimental regimen, which we refer to as treatment B. Suppose, furthermore, that the survival times for the patients receiving treatment A are 10, 40+, and 55 days, respectively, and for the patients receiving treatment B, 15, 50, and 60 days, respectively (a plus sign after a value refers to a censored time; i.e., a patient with a time of 40+ days was last known to be alive at 40 days and no further follow-up is available). These data are represented graphically in Figure 13-8; the three patients receiving treatment A are labeled A1, A2, and A3, and those receiving treatment B are labeled B1, B2, and B3. Deaths are denoted by the letter D, and censored survival times are labeled with the letter C.

When evaluating the log-rank statistic, the first computation occurs at time $t = 10$, the time at which the first death is observed. Just before this point in time, all six patients are known to be alive (and, hence, are "at risk" to die at time $t = 10$). Three of these patients received treatment A and three received treatment B. Exactly one of these six patients is known to have died at time $t = 10$, and he or she received treatment A. Table 13-4 summarizes the status of patients at this time point. Notice that at the time of this computation

TABLE 13-5 Observed Deaths (t=15)

Treatment	Dead	Alive	Total
A	0	2	2
B	1	2	3
Total	1	4	5

TABLE 13-6 Observed Deaths (t=50)

Treatment	Dead	Alive	Total
A	0	1	1
B	1	1	2
Total	1	2	3

TABLE 13-7 Observed Deaths (t=55)

Treatment	Dead	Alive	Total
A	1	0	1
B	0	1	1
Total	1	1	2

there are three patients on each arm. Therefore, if treatment B was equivalent to treatment A and only one death occurred on one arm or the other, there would be a one half chance that the death is on arm A. In fact, the death is on arm A; hence, we observe one death when the probability of observing a death on arm A is one half (i.e., there is one half more death on arm A than is expected).

Observations at time $t = 15$ are listed in Table 13-5. At this point there would be a two fifths probability that the death would occur on treatment A (if the treatments were equivalent), but the death did not occur on treatment A, so there were two fifths fewer deaths on arm A than expected (i.e., the observed deaths minus the expected number is $0 - \frac{2}{5} = -0.4$).

The next computation occurs at time $t = 50$; observations are listed in Table 13-6. Notice that patient A2 is not included in this table, even though she is not known to have died at any time before $t = 50$. Because she was lost to follow-up (censored) at time 40, she is no longer "at risk" at time 50. At this time, there would be a one third probability that the death would occur on treatment A (if the treatments were equivalent), but the death does not occur on treatment A, so there are one third fewer deaths on arm A than expected (i.e., the observed deaths minus the expected number is $0 - \frac{1}{3} = -0.33$).

One may go through the same computations at time $t = 55$ (Table 13-7) and will determine that the number of deaths minus expected deaths on treatment A is $1 - \frac{1}{2} = 0.5$. At time $t = 60$, all remaining patients are on the same arm, so the observed minus the expected number of deaths must be 0. Adding up the observed minus the expected number of deaths at times 10, 15, 50, and 55, one obtains 2 observed deaths minus 1.733 expected deaths, so that there were 0.27 deaths more than expected on arm A, indicating that this treatment might be harmful. However, one's intuition is that this is not a significant difference (i.e., such a small difference could easily be attributed to the play of chance), and in fact this is true. Therefore, there is no strong evidence in this example that treatments A and B differ.

More formally, the log-rank statistic is defined to be the difference in observed and expected numbers of deaths on one of the two treatment arms. The statistic may be standardized by dividing by the square root of its variance, yielding a score that, under the hypothesis of equivalent treatments, is approximately standard normal. In the present example, the variance of the log-rank statistic can be shown to equal 0.9622, so the standardized test statistic is $(2 - 1.733)/0.9622 = 0.27$, corresponding to a two-sided p value of about 0.79.

Cox Proportional Hazard Model

When controlling for the association of a single variable with patient survival, the stratified log-rank test can be used. However, in terms of adjusting for additional explanatory variables, the most popular method is the Cox proportional hazards model.[43] The Cox model explores the relationship between survival experience and prognostic variables or explanatory variables. It estimates and tests the hazard ratio between different groups. In the Cox regression model, explanatory variables could be continuous (for instance, age or weight or systolic blood pressure), categorical (for instance, gender or race or Eastern Cooperative Oncology Group [ECOG] performance score), or an interaction between different categorical variables. The Cox regression model does not make any parametric assumption about the survival probability distribution of each group; however, it does assume a proportional hazard between two groups. If we use $h_i(t)$ and $h_0(t)$ to denote the hazards of death at time t for the ith patient and the baseline patient, that is, the patient with all explanatory variables taking values 0, respectively, the proportional hazard model can be expressed as

$$h_i(t) = \exp(\beta_1 x_{1i} + \beta_2 x_{2i} + \beta_3 x_{3i} + \ldots + \beta_p x_{pi}) h_0(t),\ t \geq 0$$

where $x_1, x_2, \ldots x_p$ are p different explanatory variables, $h_0(t)$ is called the baseline hazard function, and $h_i(t)/h_0(t)$ is a constant, called the hazard ratio. The βs are the regression coefficients. For a continuous explanatory variable x_p, β_p stands for the log of the hazard ratio between the ith patient and the baseline patient. For a categorical explanatory variable x_1, for instance, assume that $x_1 = 0$ if the patient is randomized to the control group, or $x_1 = 1$ if the patient is randomized to the experimental group. Then β_1 stands for the log of the hazard ratio between patients in the experimental group versus the control group, whereas all other explanatory variables are the same.

Because the Cox regression model assumes the proportional hazard between different groups, it is necessary to check this assumption before concluding the estimations. Most of the model check procedures are based on graphs or plots of model-fitting residuals. If the proportional hazard assumption does not fit the data even after the data transformation, other models should be considered.

CURRENT TOPICS IN PHASE III CLINICAL TRIALS

Surrogate Endpoints

The primary endpoint is one of the most critical elements in formulating the study design, data collection, and statistical analysis plan of a clinical trial. It is a quantitative measurement implied or required by the primary objective of a study. The best endpoint is a clinical measurement reflecting the most relevant potential treatment effect of the new regimen that can be defined with rigorous mathematical and statistical properties. The OS rate has historically been the primary outcome for most phase III oncology trials because of its clear virtues: it is simple to measure, unambiguous, the least susceptible to investigator bias, and of unquestionable clinical relevance. Despite these many advantages, the role of OS as a primary endpoint is challenged in modern phase III clinical trials. Two primary challenges to the OS endpoint

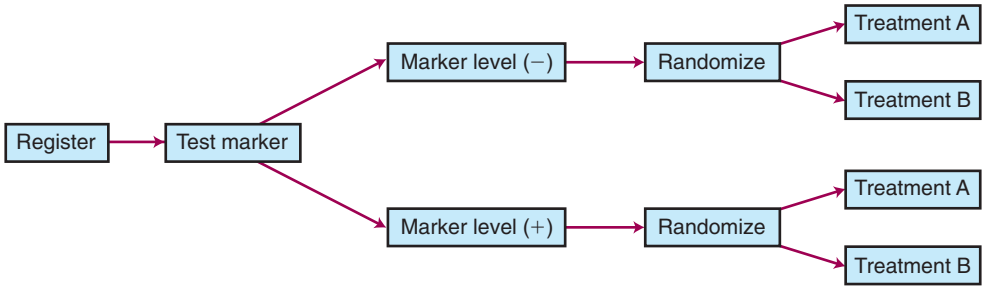


Figure 13-9 Marker by treatment interaction to test a predictive factor question; same treatments in both prognostic groups.

are that in many cases an extensive follow-up period is needed to obtain survival status and that in many diseases, multiple effective therapies are now available. In this case, OS is affected by all therapies given to a patient and, as such, this endpoint is insensitive to the impact of changing a single line of therapy.

One of the alternatives is to use a surrogate endpoint instead of a clinical endpoint in a phase III trial. A surrogate endpoint is an endpoint obtained sooner, at lesser cost, or less invasively than the long-term clinical efficacy endpoint. The Biomarkers Definitions Working Group (BDWG) defines a surrogate endpoint as "a biomarker that is intended to substitute for a clinical endpoint. A surrogate endpoint is expected to predict clinical benefit (or harm, or lack of benefit or harm)."[44] When using a surrogate endpoint, one would like to make the same inference as if one had observed a true endpoint. Therefore, a critical requirement of a valid surrogate endpoint is that the treatment effect observed on a surrogate endpoint should reliably predict the treatment effect on the clinical endpoint. This implies a stronger requirement for a surrogate endpoint than simply a significant correlation between it and the clinical endpoint. In circumstances where the speed of the study is a major concern, where second-line therapies that affect the OS potentially obscure the assessment of first-line treatment benefit, or where crossover becomes unavoidable, a surrogate endpoint might be considered in place of the long-term clinical endpoint.

From statistical perspectives, there are two branches of surrogate evaluation methodologies: a single-trial or meta-analytic evaluation. In the single-trial approach, the "proportion of treatment effect" (PTE)[45,46] explained by the surrogate, has been the predominant approach. However, a single study is unable to provide reliable information regarding the prediction of the treatment effect on the clinical endpoint based on the observed treatment effect on potential surrogate endpoint. Therefore, to validate an endpoint as a legitimate surrogate endpoint, a meta-analysis is usually required. In addition, heterogeneity between the trials included in the meta-analysis strengthens the robustness of results from individual trials. In conducting a meta-analysis, using individual patient data instead of summary data is highly recommended, and, ideally, both positive and negative trials should be included. Examples of meta-analyses conducted to examine potential surrogate endpoints can be found in articles by Sargent and colleagues[47] and Burzykowski and associates.[48]

Biomarkers

A marker is a single trait, or a group of traits, that differentiates patients with respect to an outcome of interest. If a marker can be used to identify patients with differing risks of a clinical outcome (such as progression or death) in the absence of therapy or when receiving nontargeted standard treatment, the marker is usually called a *prognostic marker.* If a marker predicts differential efficacy of a specific therapy, the marker is called a *predictive marker.*

Validation of a prognostic marker is usually conducted retrospectively in patients treated with placebo or a standard treatment. Validation of a predictive marker could also be conducted retrospectively based on data from a randomized controlled trial.[49] However, a prospective randomized controlled trial would be ideal. Two types of clinical designs can be used to validate a predictive marker: a targeted/selection design or an unselected design. A targeted trial enrolls only patients who are most likely to respond to the experimental therapy based on their molecular expression levels. On the one hand, a targeted trial could result in a large savings of patients for other trials. On the other hand, it could miss efficacy in other patients and miss the opportunity to test the association of the biologic endpoints with clinical outcomes.

Different types of unselected designs have been proposed and discussed. For instance, the marker-by-treatment interaction design (Figure 13-9) stratifies patients according to their marker status and randomly assigns patients in each marker group to two different treatments. Hypothesis setting and sample size estimation could be different in each marker-defined subgroup. Either a formal test for marker-by-treatment interaction or a separate superiority test within each marker group could be conducted. Another popular unselected design is the marker-based strategy design (Figure 13-10), in which the random treatment assignment could be based on the patient's marker status or could be independent of it. Examples for each type of design can be found in the article by Sargent and colleagues.[50]

Adaptive Design

An adaptive design could be defined as a design "that allows adaptations to trial procedures (for instance, eligibility criteria, study dose, or treatment procedure, etc.) and/or statistical procedures (for instance, randomization, study design, study hypothesis, sample size, or analysis methods, etc.) of the trial after its initiation without undermining the validity and integrity of the trial."[51] Many types of adaptation could be applied to an ongoing trial. For instance, a study could be resized based on an interim review of the outcomes in the control group. Assume, for example, that in the design of a study, the progression-free survival (PFS) under the standard of care was assumed to be 12 months. However, on an interim review of accrued data from the control arm, the estimated PFS was 15 months. In this case, more patients need to be accrued for the study or patients need to be followed longer for the same hazard ratio to be detected. No statistical penalty is required for this review, because only data from the control arm have been analyzed.

For another example of an adaptive design, assume that a study started with n experimental arms and one control arm. Within this study, based on a prespecified plan, all

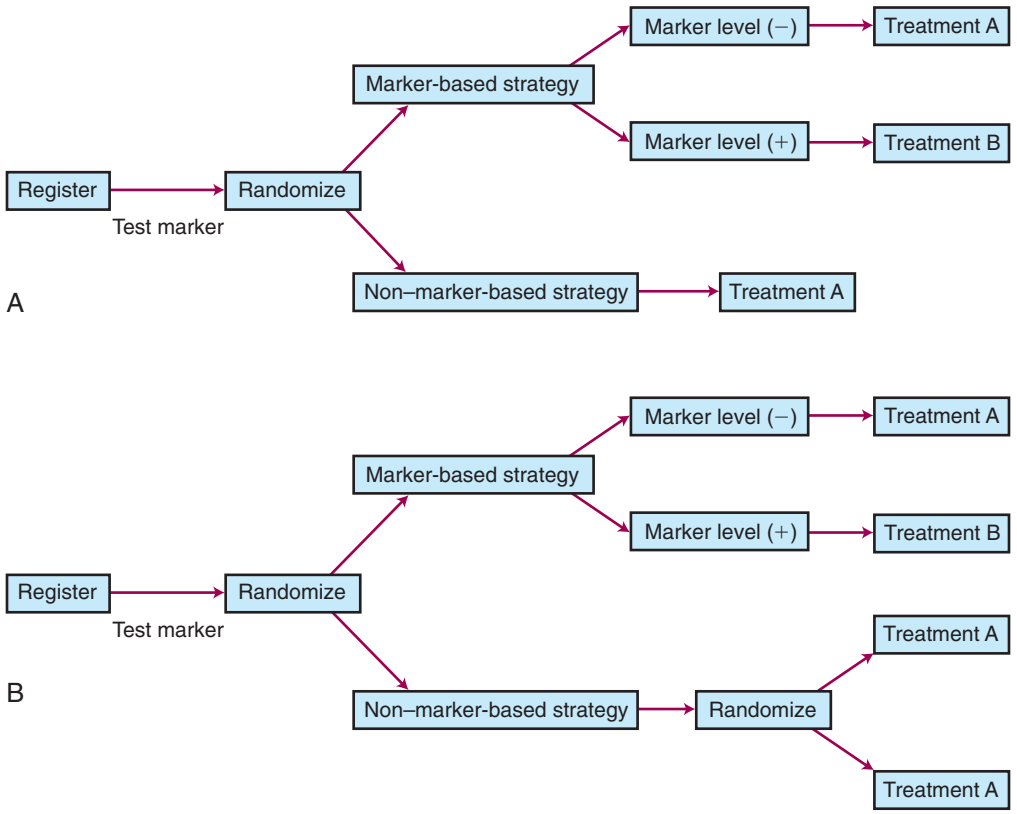


Figure 13-10 **A,** Marker-based strategy design to test predictive factor question; no randomization in non–marker-based arm. **B,** Marker-based strategy design to test predictive factor question; randomization in both arms.

experimental arms are to be compared with the control arm, at the interim analysis, and only the most promising experimental arm and the control arm will continue to accrue when patient accrual is resumed. In other words, the study will have started with $n+1$ arms and ended with 2 arms, and $n-1$ arms will have been dropped after the interim analysis. Because no conclusions regarding superiority were allowed to be made at the interim analysis, no statistical penalty for the interim review is needed. Under other circumstances, if an adaptation relates to (1) altering the randomization ratio between the arms, (2) resizing the trial based on interim comparison between the experimental and control arms, or (3) changing the primary endpoint, then a penalty for looking at the data before the end of the study is definitely needed. In planning an adaptive design, possible adaptations must be specified in the protocol before accrual takes place. In applying an adaptive design, an efficient mechanism for processing and analyzing data is critical.

As drug development moves toward targeted agents with particular treatment mechanisms through a targeted pathway, the disease population for testing the treatment effects may need to be refined and subseted based on a relevant biomarker signature. By subgrouping the disease population, the traditional design becomes challenging. Under this circumstance, Bayesian adaptive designs guided by biomarkers have been explored and applied. For example, the Biomarker-integrated Approaches of Targeted Therapy for Lung Cancer Elimination (BATTLE) trial and Investigation of Serial Studies to Predict Your Therapeutic Response with Imaging and Molecular Analysis 2 (ISPY-2) trials are two recent biomarker-based adaptively randomized studies. In the BATTLE trial, four treatments (Erlotinib, Vandetanib, Eroltinib + bexarotene, Sorafenib) and four biomarker profiles (EGFR mutation, KRAS/Braf mutation, VEGF/VEGFR-2 expression, RXRs/Cyclin D1 expression and CCND1 copy number) were considered. The trial started with equal allocation randomization to four treatments, then was switched to adaptive randomization that would increasingly assign patients into treatments with greatest potential for efficacy based on their individual biomarker profile.[52] Similarly, ISPY-2 was aimed to identify regimens which can improve outcomes for patients with particular biomarker signatures in the neoadjuvant chemotherapy setting for patients with breast cancer. A concurrent randomization between experimental and standard care regiments was conducted within the patient populations defined by biomarkers. The adaptation was based on the Bayesian predictive probability of the experimental agent being more effective than standard therapy to allow "graduation" or "dropping out" of the pair of regimen and biomarker.[53] Both studies highlight the feasibilities of applying advanced trial designs in practice and also illustrate powerful collaboration between statisticians and clinical, laboratory, and bioinformatics investigators.

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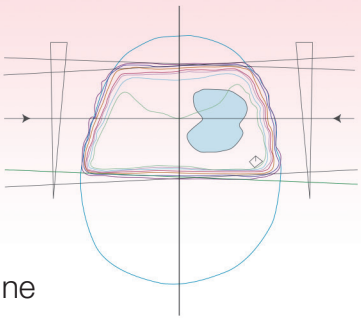
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CHAPTER

14 Late Effects after Radiation



Michael T. Milano, Lawrence B. Marks, and Louis S. Constine

INTRODUCTION AND GENERAL CONSIDERATIONS

Statement of the Problem

Incidental irradiation of normal tissues is unavoidable during radiation therapy. Predicting the risk of radiation-induced injury is challenging. The primary determinants of injury are the radiation dose (total dose and dose per fraction) and the volume of normal tissue irradiated. Additional treatment factors that influence risk include dose rate, overall treatment time, treatment energy, the use of concurrent chemotherapy, radiation protectors, or other biological modifiers, and the interval between radiation courses in patients undergoing a second course of radiation. Host-related factors include comorbid conditions (e.g., diabetes, collagen vascular disease), inherent radiation sensitivity (e.g., underlying genetics), and patient age. Organ related variables include preradiation organ compromise or loss, development of severe acute toxicity (resulting in consequential late effects), regional variation of radiosensitivity within an organ, and hierarchal organization of the organ (i.e., whether damage to a portion of the organ affects only that portion or has more widespread effect). Furthermore, an organ may have more than one type of late toxicity that may or may not have different tolerance doses. Tumors can infiltrate into normal tissues, either at presentation or after treatment (i.e., local failure), compromising organ function and leading to late sequelae.

What Are the Target Cells/Tissues for Radiation-Associated Normal Tissue Injury?

Different organs have different dose/volume thresholds for the development of radiation-associated injury. The critical question arising from this observation is: what are the dose-sensitive targets in normal tissues resulting in late toxicity. Damage to either the functional (parenchymal) or stromal cells of the organ, or the fine vasculature, have been implicated. Differences in radiation susceptibility of different organs may therefore be as a result of different sensitivities of these functional cells, regional variation in the susceptibilities of small vessels because of the stroma or microenvironment, different capacities for neo-vascularization, or differences in the redundancy of the blood flow (i.e., those tissues relying on fewer vessels may be more susceptible to radiation damage), or functional reserve.

Utility and Limitations of Dose-Volume Histograms

The focus of this chapter will be on the review of credible data associating radiation dose/volume parameters with the risk of normal tissue injury. Three-dimensional (3D) planning has become standard practice, allowing the radiation oncologist to quantitate doses to normal tissues in the region of interest. 3D dose/volume data can be difficult for clinicians to easily comprehend because the distributions are two dimensional (2D). Visualizing isodose distributions is challenging and comparing competing distributions is largely subjective. Therefore, dose-volume histograms (DVHs; essentially 2D representations of the 3D data) were embraced as a rapid way to summarize the dose distribution. A DVH is generated by tallying the doses delivered to each (or a representative sample of) voxel of tissue and represents that information as a cumulative histogram of dose (x-axis) and volume (y-axis). Each point along the histogram represents the volume of that organ receiving more than or equal to that dose (e.g., V20 is the volume of an organ receiving at least 20 Gy). A DVH can be readily visualized and provides a quick and easy way to describe the dose/volume characteristics of the 3D dose distribution. However, a DVH achieves this by discarding all spatial information and the DVH does not account for variations in fraction size. Functional and structural complexities, and spatial variations in function or sensitivity, are thus not considered in DVHs. Possible interactions between organs are also not considered with this construct.

Despite the marked data reduction in going from a 3D plan to a DVH, DVHs also remain challenging for clinicians to consider and compare because of the previously mentioned issues relating to functional heterogeneity but also incomplete knowledge about radiation sensitivity of tissues. Therefore, it has become attractive to further data reduce and extract "figures of merit" from the DVH. The critical metrics that will considered in this review are the mean organ dose and discrete points on the DVH. These include (Figure 14-1):

1. *Vx* reflects the volume of tissue (generally a percentage) receiving ≥*X* Gy. This is probably the most commonly used metric for parallel-type organs such as the lung and kidney. For these, as discussed, the portions of the organ exposed to a "regionally injuring" dose of radiation will become dysfunctional. Thus, the percentage of the organ exposed to that dose is a useful parameter.
2. *Dx* reflects the minimum dose to the hottest *x*% (generally percentage of total volume) of tissue. This parameter is not widely used clinically. It might be most useful for parallel-type organs where the percentage of an organ's function that can be lost is known (e.g., let's say 30%). Then, if the D30 is less than the locally injuring dose, global organ function should remain. Similarly, for organs where an injury might be clinically manifest if there is a hot spot of a particular size, the *Dx*, where *x* is equal to that critical size, might be a useful parameter to predict outcomes.
3. *Dmax* is the maximum dose delivered to an organ and is most useful for series organs. *Dmax* is analogous to *Dx* as the volume *x* decreases toward zero.
4. Mean dose is the simple arithmetic average of the dose to an organ. For parallel organs where there is a gradual dose-response function for radiation-induced regional injury, the mean dose might reasonably correlate with outcomes.

More complex modeling has also been widely used to extract figures of merit that better reflect the entire DVH, rather than a single point (e.g., *Dmax, Dx, Vx*). These models will "sum up" the risk associated with each component of a DVH and apply different methods of summing, depending on the type (or architecture/structure) of the organ. For example, for a series-structured organ, the high-dose region of the DVH

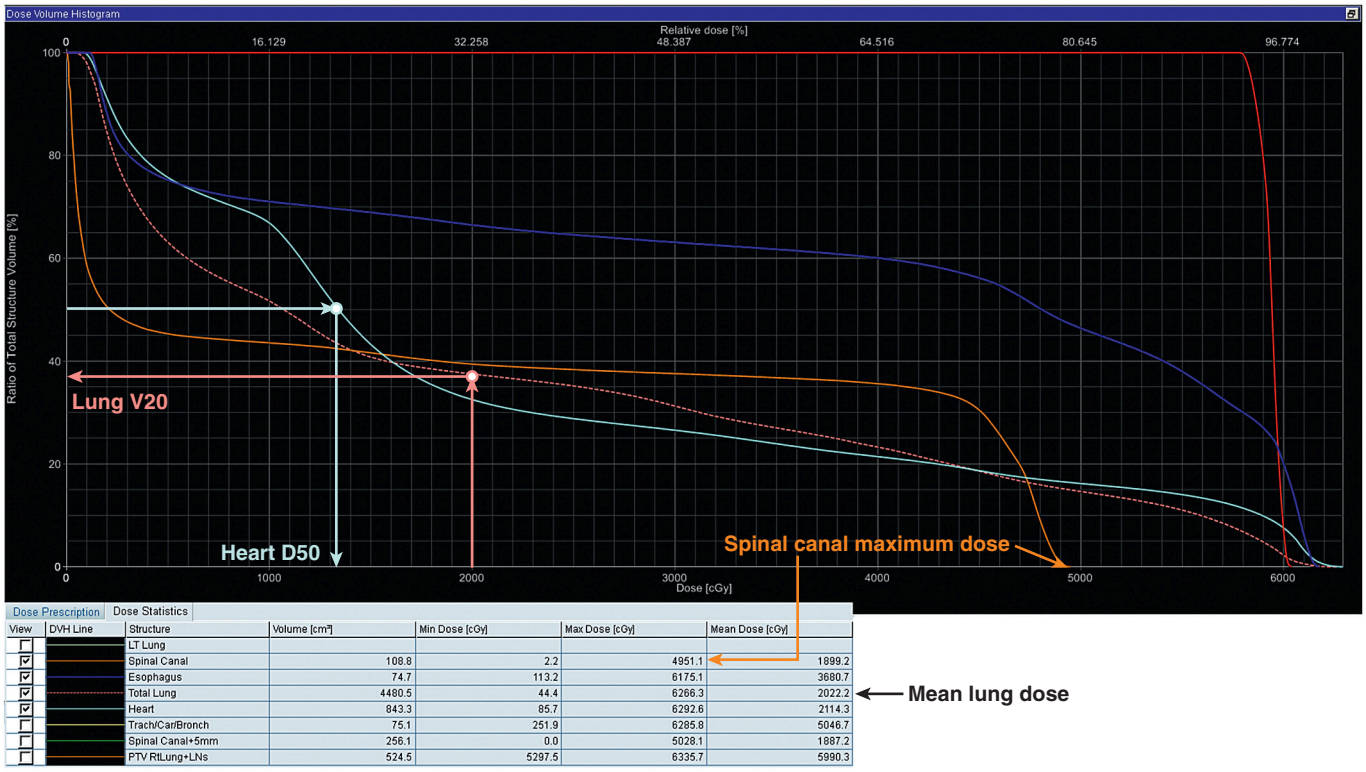


Figure 14-1 Illustration of *Vx*, *Dx*, and *Dmax*. Mean organ dose is calculated by averaging the dose to each voxel of a tissue and is generally calculated by the treatment planning software. The volume of lung receiving greater than 20 Gy (V20) and mean lung dose are shown (37% and 20.2 Gy, respectively). The dose to 50% of the heart (D50) is shown (13.3 Gy), which is not a commonly used dose-volume metric but presented for illustrative purposes. The maximal dose to the spinal canal is depicted as well (49.5 Gy).

might be most weighted more heavily in the "summing," although this is less strongly considered in a parallel-structured organ. Early work in this area led to the Lyman, Kutcher Burman (LKB) model, and more recently the equivalent uniform dose (EUD) model, that both reduce a DVH to a single normal tissue complication probability (NTCP). These models and their relationships are summarized elsewhere.[1]

The Opportunities and Challenges of Modern Radiation Technologies

Several new radiation planning and delivery tools, such as intensity modulated radiation therapy (IMRT), image-guided radiotherapy (IGRT), stereotactic body radiotherapy (SBRT), and charged particle irradiation give the physician increased flexibility in determining how to deliver the desired target dose while minimizing or redistributing the dose exposure to normal tissue. The clinical application of these new technologies requires that the physician and dosimetrists/physicists have an in depth knowledge of the dose/volume/outcome relationships for critical normal tissues, hence the need for this chapter in this book. However, these new technologies have altered the relationship between the target doses and the doses to surrounding normal tissues that might impact the applicability of historic data for our modern era. With conventional beams (often opposed beam pairs treated sequentially), the normal tissues were exposed to fraction sizes similar to that of the tumor. With these newer approaches, the fractional radiation doses delivered to the normal tissues adjacent to the target are typically lower than that received by the target. Further, there is a movement toward the use of shorter hypofractionated regiments. Ironically, the use of increasing fractions sizes, along with an increasing number of beams, leaves (at least some of) the surrounding normal tissue receiving a daily fraction size close to what is typically seen with conventional approaches. However, with the more modern techniques, the heterogeneity of dose within the normal tissues is increased. Despite these caveats, much of the published data regarding radiation-associated normal tissue injury remains applicable in the modern era. Continued study of this important topic is clearly needed.

Broadly Defining Organ Structure

Normal tissues can be functionally defined as "serial," "parallel," or a combination of both, analogous to the terminology used for electrical circuits (Figure 14-2). In parallel functioning organs, the functional subunits function independently (i.e., functional redundancy exists). Thus, when some functional subunits of a parallel organ are damaged, the surrounding functional subunits continue to function. Examples of parallel functioning organs include lung, liver, and kidney. Small to moderate, and perhaps even large, volumes of parallel organs can be damaged without causing global dysfunction because there is enough reserve in the undamaged portion of the organ or there is a capacity to regenerate (e.g., liver). In "serial" organs, the functional subunits are arranged in a linear or branching fashion, and hence there is interdependence. Damage to the subunits of a serial organ can result in compromise or incapacity of the entire organ. Examples of series organs include spinal cord, portions of the central nervous system, peripheral and cranial nerves, gastrointestinal tract, and tracheal-bronchial tree. Although the concept of serial and parallel functioning organs is useful in assessing risk to tissues,

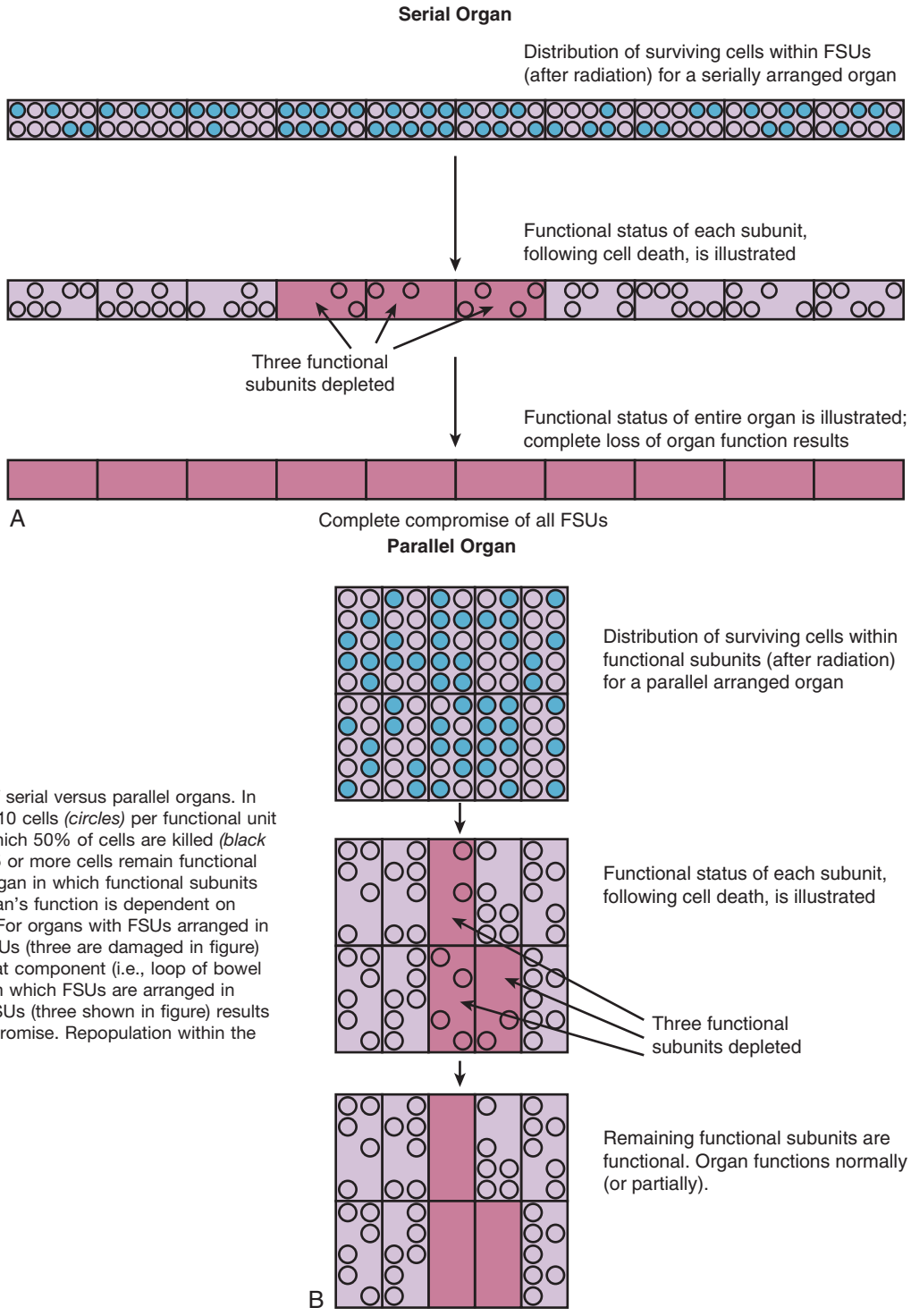


Figure 14-2 Illustrative comparison of serial versus parallel organs. In this figure, a hypothetical example of 10 cells *(circles)* per functional unit *(square)* is shown, after radiation in which 50% of cells are killed *(black circles)*, and functional subunits with 5 or more cells remain functional after radiation. Figure 1A shows an organ in which functional subunits (FSUs) are arranged in series; the organ's function is dependent on connectivity to its neighboring FSUs. For organs with FSUs arranged in series **(A),** damage to one or more FSUs (three are damaged in figure) results in complete compromise of that component (i.e., loop of bowel or region of spinal cord). For organs in which FSUs are arranged in parallel **(B),** damage to a portion of FSUs (three shown in figure) results in partial, or no apparent, organ compromise. Repopulation within the FSUs is not shown.

it should be appreciated that this is only a model. The function of many organs requires the integrity of both serial and parallel components (e.g., the lung requires the "parallel" alveoli, as well as the "series" conducting airways).

Further complicating this issue is the fact that, in both serial and parallel organs, there are often regional heterogeneities in function (e.g., gray matter and white matter tracts of the "parallel" spinal cord). These anatomic subregions may have different functions and different susceptibilities to treatment-related damage.

QUANTEC

This chapter will summarize and expand on several reviews published as a special issue in *International Journal of Radiation Oncology Biology Physics* (volume 76, issue 3, Supplement), all of which were written as part of the Quantitative Analysis of Normal Tissue Effects in the Clinic (QUANTEC) initiative. Because the QUANTEC reviews were published in 2010, this chapter also summarizes some studies published after QUANTEC.

QUANTEC arose from a proposal from the Science Council of the American Association of Physicists in Medicine (AAPM) to revise and update guidelines published by Emani in 1991.[2] QUANTEC's goals are (1) to provide a critical review of the current literature on quantitative dose-response and dose-volume relationships for clinically relevant normal-tissue endpoints; (2) to produce practical guidelines to allow reasonable toxicity risks based on dose-volume parameters; (3) to identify future research initiatives. Using the QUANTEC reviews as a backbone, this chapter will focus on recently published data relevant to late toxicity from radiation, with an emphasis on relevant dose-volume metrics. Key summary points of the QUANTEC reviews are briefly summarized at the end of each section, and the QUANTEC reviews are referenced after each subheading. Table 14-1 summarizes the dose-volume metrics that are supported by the literature; this table has been modified from the one published in the QUANTEC issue.[1]

Although the QUANTEC initiative and associated reviews addressed a broad range of issues relating to normal tissue damage, this chapter will focus on late toxicity after an initial course (i.e., excluding reirradiation) of conventional radiation (i.e., excluding hypofractionated regimens). Many of the individual QUANTEC reviews discussed brachytherapy, reirradiation, or hypofractionated radiation, particularly in the context of hypofractionated stereotactic body radiation and stereotactic radiosurgery. Future AAPM initiatives will focus on hypofractionated stereotactic radiation, a topic that is also reviewed elsewhere.[3,4] A separate initiative is under way addressing quantitative dose-volume relationships for pediatric survivors of cancer. This chapter will primarily focus on studies relating three dimensional dose-volume metrics to clinical outcomes.

NERVOUS SYSTEM: BRAIN

Organ Function and Clinical Significance

The structural and functional complexity of the brain puts this organ at risk for a spectrum of radiation-associated toxicities. Some specific functions of the brain can be correlated with

TABLE 14-1 Dose-Volume Metrics Supported by Published Data

Organ	Volume Segmented: Irradiation Type	Endpoint	Dose-Volume Parameters	Rate	Comments
Brain	Whole organ: 3DRT	Symptomatic necrosis	Dmax <60 Gy	<3%	Data at 72 and 90 Gy, extrapolated from BED models
	Whole organ: 3DRT	Symptomatic necrosis	Dmax <72 Gy	5%	
	Whole organ: 3DRT	Symptomatic necrosis	Dmax <90 Gy	10%	
Brainstem	Whole organ: whole brainstem	Permanent cranial neuropathy or necrosis	Dmax <54 Gy	<5%	
	Whole organ: 3DRT	Permanent cranial neuropathy or necrosis	D1-10 mL ≤59 Gy	<5%	
	Whole organ: 3DRT	Permanent cranial neuropathy or necrosis	Dmax <64 Gy	<5%	Point dose <1 mL
Optic nerve/ chiasm	Whole organ: 3DRT	Optic neuropathy	Dmax <55 Gy	<3%	Given the small size, 3DRT is often whole organ
	Whole organ: 3DRT	Optic neuropathy	Dmax 55-60 Gy	3%-7%	
	Whole organ: 3DRT	Optic neuropathy	Dmax >60 Gy	7%-20%	
Spinal cord	Partial organ: 3DRT	Myelopathy	Dmax 50 Gy	0.2%	Including full cord cross-section
	Partial organ: 3DRT	Myelopathy	Dmax 60 Gy	6%	
	Partial organ: 3DRT	Myelopathy	Dmax 69 Gy	50%	
Cochlea	Whole organ: 3DRT	Sensory neural hearing loss	Mean dose ≤45 Gy	<30%	Mean dose to cochlea, hearing at 4 kHz
Parotid	Bilateral whole parotids: 3DRT	Long-term parotid salivary function reduced to <25% of pre-RT level	Mean dose <25 Gy	<20%	For combined parotid glands
	Unilateral whole parotid: 3DRT	Long-term parotid salivary function reduced to <25% of preradiation level	Mean dose <20 Gy	<20%	At least one parotid gland spared to <20 Gy
	Bilateral whole parotids: 3DRT	Long term parotid salivary function reduced to <25% of preradiation level	Mean dose <39 Gy	<50%	For combined parotid glands
Pharynx	Pharyngeal constrictors: 3DRT	Symptomatic dysphagia and aspiration	Mean dose <50 Gy	<20%	
Larynx	Whole organ: 3DRT	Vocal dysfunction	Dmax <66 Gy	<20%	With chemotherapy
	Whole organ: 3DRT	Aspiration	Mean dose <50 Gy	<30%	With chemotherapy
	Whole organ: 3DRT	Edema	Mean dose <44 Gy V50 <27%	<20%	Without chemotherapy
Lung	Whole organ: 3DRT	Symptomatic pneumonitis	Mean dose 7 Gy	5%	Excludes purposeful whole lung irradiation
	Whole organ: 3DRT	Symptomatic pneumonitis	Mean dose 13 Gy	10%	
	Whole organ: 3DRT	Symptomatic pneumonitis	Mean dose 20 Gy	20%	
	Whole organ: 3DRT	Symptomatic pneumonitis	Mean dose 24 Gy	30%	
	Whole organ: 3DRT	Symptomatic pneumonitis	Mean dose 27 Gy	40%	

TABLE 14-1 Dose-Volume Metrics Supported by Published Data—cont'd

Organ	Volume Segmented: Irradiation Type	Endpoint	Dose-Volume Parameters	Rate	Comments
Esophagus	Whole organ: 3DRT	Grade ≥3 acute esophagitis	Mean dose <34 Gy		A variety of alternate threshold doses have been implicated
	Whole organ: 3DRT	Grade ≥2 acute esophagitis	V35 <50%		
	Whole organ: 3DRT	Grade ≥2 acute esophagitis	V50 <40%		Appears to be a dose/volume response
	Whole organ: 3DRT	Grade ≥2 acute esophagitis	V70 <20%		Similar constraints are applicable to late toxicity
Heart	Pericardium: 3DRT	Pericarditis	Mean dose <26 Gy		
	Pericardium: 3DRT	Pericarditis	V30 <46%		
	Whole organ: 3DRT	Long-term cardiac mortality	V35 <10%		Overly safe risk estimate based on model predictions
Liver	Whole liver—GTV: Whole liver or 3DRT	Classic RILD	Mean dose <30-32 Gy	<5%	Excluding patients with preexisting liver disease or hepatocellular carcinoma
	Whole liver—GTV: 3DRT	Classic RILD	Mean dose <42 Gy	<50%	
	Whole liver—GTV: Whole liver or 3DRT	Classic RILD	Mean dose <28 Gy	<5%	In patients with Child-Pugh a preexisting liver disease or hepatocellular carcinoma, excluding hepatitis B reactivation
	Whole liver—GTV: 3DRT	Classic RILD	Mean dose <36 Gy	<50%	
Kidney	Bilateral kidneys (not TBI) Bilateral kidneys or 3DRT	Clinically relevant renal dysfunction	Mean dose <15-18 Gy	<5%	
	Bilateral kidneys (not TBI) Bilateral kidneys	Clinically relevant renal dysfunction	Mean dose <15-18 Gy	<50%	
	Bilateral kidneys (not TBI) 3DRT (combined kidney)	Clinically relevant renal dysfunction	V12 <55% V20 <32% V23 <30% V28 <20%	<5%	
Stomach	Whole organ: Whole stomach	Ulceration	D100 <45 Gy	<7%	
Small bowel	Individual small bowel loops: 3DRT	Grade ≥3 toxicity (acute)	V15 <120 mL	<10%	Dose-volume data on late toxicity is lacking; data for acute toxicity data may be a reasonably good surrogate
	Peritoneal cavity: 3DRT	Grade ≥3 toxicity (acute)	V45 <195 mL	<10%	
Rectum	Whole organ: 3DRT	Grade ≥2 toxicity Grade ≥3 toxicity	V50 <50%	<15% <10%	Data derived mostly from prostate cancer treatment
	Whole organ: 3DRT	Grade ≥2 toxicity Grade ≥3 toxicity	V60 <35%	<15% <10%	
	Whole organ: 3DRT	Grade ≥2 toxicity Grade ≥3 toxicity	V65 <25%	<15% <10%	
	Whole organ: 3DRT	Grade ≥2 toxicity Grade ≥3 toxicity	V70 <20%	<15% <10%	
	Whole organ: 3DRT	Grade ≥2 toxicity Grade ≥3 toxicity	V75 <15%	<15% <10%	
Bladder	Whole organ: 3DRT	RTOG grade ≥3 late toxicity	Dmax <65 Gy	<6%	Based on bladder cancer treatment
	Whole organ: 3DRT	RTOG grade ≥3 late toxicity	V65 <50% V70 <35% V75 <25% V80 <15%	<6%	Variations in bladder size, shape, location during radiation hamper ability to generate accurate data
Penile bulb	Whole organ: 3DRT	Severe erectile dysfunction	Mean dose to 95% of gland <50 Gy	<35%	
	Whole organ: 3DRT	Severe erectile dysfunction	D90 <50 Gy	<35%	
	Whole organ: 3DRT	Severe erectile dysfunction	D60-D70 <70 Gy	<35%	

3DRT, *3-dimensional conformal radiotherapy;* BED, *biologically effective dose;* Dmax, *maximum radiation dose;* Dx, *minimum dose received by the "hottest" x% (or x cc) of the organ;* RILD, *radiation-induced liver disease;* TBI, *total body irradiation;* Vx, *volume of the organ receiving ≥ x Gy.*

All at standard fractionation (i.e., 1.8 Gy to 2.0 Gy per daily fraction). All data are estimated from the literature summarized in the QUANTEC reviews and in the chapter. Clinically, these data should be applied with caution. Clinicians are strongly advised to use the individual QUANTEC articles to check the applicability of these limits to the clinical situation at hand. They largely do not reflect modern IMRT.

discrete location(s) within the brain, whereas others are spread throughout the brain. Primary toxicity endpoints include frank brain necrosis with associated symptoms or signs and neurocognitive decline.

Dose-Volume Data

Prospective studies in adults have shown that partial (and limited) brain irradiation in the dose range of 50 Gy to 60 Gy, causes minimal to no discernible effect on memory and cognition.[5-10] However, another study has suggested that patients undergoing partial brain radiation for low-grade glioma, versus patients who do not undergo radiation, are at greater risk for neurocognitive deficits, particularly attention, executive functioning, and information processing.[11] More detailed studies, correlating neurocognition with susceptible regions within the brain, are needed. Certainly, ample data suggest that the volume of brain that is irradiated affects the degree of radiation-associated neurocognitive decline (with whole brain radiation faring worse).[12] In adult patients who have received whole brain radiation, neurocognitive decline is well described. However, the degree to which the brain radiation (versus other factors such as surgery, a history of hydrocephalus, other chronic diseases and comorbid illnesses, chemotherapy exposure, and tumor progression) impacts neurocognitive function is not clear.[10,13,14]

There has been growing interest in the hypothesis that minimizing radiation dose to the hippocampal or subventricular zone stem cell niches can reduce the risk of neurocognitive deficits.[15] However, it is not known if there are particular critical individual avoidance structures (or regions) or combination of avoidance structures, nor whether there are well-defined dose-volume thresholds and what these dose-volume limits might be. In a prospective study of 18 patients with low-grade glioma treated at the University of Wisconsin, a dose of >7.3 Gy (in 2 Gy equivalents) to the bilateral hippocampi was significantly associated with impairment in delayed recall, whereas any dose (i.e., dose in excess of 0 Gy) trended toward significance.[16] In the RTOG 0933 Phase II study of hippocampal sparing (100% dose and maximum dose to not exceed 10 Gy and 17 Gy, respectively) in 113 patients with brain metastases, memory preservation at 4 and 6 months (measured by the Hopkins Verbal Learning Test Delayed Recall) was significantly better than historical controls.[17] In a study of 75 patients with pituitary adenoma, 30 of whom had undergone 3-5 field pituitary irradiation to a dose of 45 Gy, neither hippocampal dose nor prefrontal cortex dose correlated with cognitive outcomes.[18]

A prospective study of pediatric patients correlated hippocampal, temporal, and cerebral doses with objective neurocognitive measures.[19] For children, younger age at radiation and larger irradiated volumes (with higher doses having a greater impact) are associated with objectively worse neurocognitive function.[20-23] For example, central nervous system prophylaxis for acute lymphoblastic leukemia with 24 Gy whole brain radiation in addition to intrathecal methotrexate (versus methotrexate alone) resulted in a median 13 point IQ reduction at 5 years postradiation and poorer academic achievement, self-image, and greater psychological distress at 15 years.[24] Lower risks are associated with lower doses of 14 Gy to 18 Gy.[25-27] For medulloblastoma, increasing brain dose in the 18- to 36-Gy range has been correlated with greater neurocognitive decline.[20-22,28,29] Girls were observed to be more vulnerable to injury than boys.[30] Reported toxicities were lower (or not detected) when 14 Gy to 18 Gy was used.[25-27] A recent study has shown that increased dose (from 0 Gy to 24 Gy) and younger age at diagnosis are correlated with worse neurocognitive outcomes that increased with time from diagnosis; furthermore, chemotherapy in the absence of radiotherapy (particularly methotrexate-based chemotherapy), resulted in severe impairment of complex neurocognitive processes, similar to impairment after cranial radiation dose in excess of 18 Gy.[31]

Radiation necrosis can occur in any part of the brain. Although there may be regional variations of susceptibility within the brain related to differences in vascularity, glial cell population, and so on, this data is sparse, and it is generally believed that location does not generally affect susceptibility to necrosis. However, certain regions, such as the brainstem, are more likely to cause symptoms. There is a paucity of data correlating dose-volume parameters with the risk of radiation necrosis with conventional fraction, though many studies have documented an association of fraction size with the risk of necrosis.

In a study from Queen Elizabeth Hospital in China, 1008 patients with nasopharyngeal cancer, treated prior to 1985, received 45.6 Gy to 53.2 Gy in 3.8 Gy fractions, 50.4 Gy in 4.2 Gy fractions or 60 Gy in 2.5 Gy fractions.[32] The 10-year risk of temporal lobe necrosis was 18.6% in those treated with 4.2 Gy fractions versus <5% for the other dose schemes ($p < 0.001$). A multiinstitutional Chinese study examined 1032 patients with nasopharyngeal cancer treated after 1990 with one of several fractionation schemes (mostly 2 Gy to 3.5 Gy fractions, though one scheme used a 1.6 Gy twice-daily component).[33] The 5-year actuarial incidence of necrosis ranged from 0% (after 66 Gy in 2 Gy fractions) to 14% (after 2.5 Gy × 8 followed by 1.6 Gy twice daily to 71.2 Gy). In both of the aforementioned studies, the product of total dose and dose per fraction significantly impacted risk; shorter overall treatment time and twice-daily fractionation also increased risk. A Chinese study comparing 71.2 Gy in 1.6 Gy twice-daily fractions versus 60 Gy in 2.5 Gy fractions was terminated early because of excessive neurologic toxicity, including temporal lobe toxicity, in both arms. The risk of toxicity was greater, and the interval to developing toxicity was shorter, with the twice-daily regimen.[34] In another Chinese study, 27% of patients receiving an accelerated hyperfractionated regimen (64 Gy in 1.6 twice-daily fractions) versus 0% receiving hyperfractionated radiation (70.8 Gy in 1.2 Gy twice-daily fractions) developed symptomatic radiation necrosis.[35]

Radiation necrosis has also been studied in patients with primary brain tumors. The risk is dose dependent, with doses of <50 Gy rarely causing necrosis.[36-38] In patients treated for brain metastases, there was a low (<2%) risk of necrosis developing after 1.6 Gy twice daily to the whole brain (32 Gy) followed by a boost to 54.4 to 74.4 Gy, and no necrosis was seen after a boost to 48 Gy.[39,40]

Summary and Other Key Points from QUANTEC Review[41]

A high level of evidence to quantify the risks of radiation-induced brain injury is lacking. For brain necrosis, the brain appears to be especially sensitive to fraction size in excess of 2 Gy, and to twice-daily fractionated treatment. Symptomatic necrosis is uncommon with doses <60 Gy with conventional (1.8 Gy to 2 Gy) fractionation, though the risk increases with increasing dose (see Table 14-1). More detailed studies correlating neurocognition with susceptible regions within the brain are needed. Long-term (>5 years) follow-up is necessary to best assess neurological and cognitive decline. For children, younger age and higher whole brain dose strongly correlate with cognitive decline. Future studies should provide a clear definition of toxicity and report actuarial (as opposed to crude) rates that can be correlated with detailed normal brain dose-volume metrics.

NERVOUS SYSTEM: BRAINSTEM

Organ Function and Clinical Significance

The brainstem serves as a conduit from the brain to the cranial nerves and spinal cord. As a result, the brainstem is involved with motor, sensory, and special sensory function, as well as regulation of temperature, cardiac function, respiratory function, and consciousness. It is well accepted that the entire brainstem may be treated to 54 Gy using conventional fractionation with minimal risk of late brainstem toxicity. Small volumes of brainstem may tolerate higher doses. Similar to the brain, the brainstem is heterogeneous, and it is not well known which regions are most susceptible to radiation-induced damage.

Dose-Volume Data

Several institutions have published their dose-volume constraints for brainstem, most of which have not reported any brainstem toxicity. These constraints for patients undergoing external beam radiation therapy for head and neck cancers include V60 <5 mL, V65 3 mL,[42] V55 <0.1 mL,[43] D1 <54 Gy,[44] and maximum <50 Gy[45]; for patients undergoing proton or combined proton/photon therapy for base of skull lesions the constraints include: <63 Gy to 64 Gy CGE to the brainstem surface and 53 to 54 CGE to the brainstem center.[46-49]

Some patients in these studies received a maximum brainstem dose of 66 CGE to 68 CGE (greater than the recommended constraints) to adequately treat the tumor.[46,48,49] In one study, the dose constraint of 63 CGE to the brainstem surface and 54 CGE to the brainstem center was "relaxed" in 38% and 17% of patients, respectively, with no reported neurologic toxicity. In these patients, the volume receiving more than the threshold dose was 0.2 mL and 1.2 mL for the brainstem surface and center, respectively.[48] In another study, two of four patients developing neurologic toxicity received brainstem maximal doses in excess of 64 Gy CGE to the surface and 53 CGE to the center.[49]

In an analysis of 367 patients from Massachusetts General Hospital, an increased risk of late toxicity was associated with the maximal delivered dose (>64 CGE), V50 (>5.9 mL), V55 (>2.7 mL), V60 (>0.9 mL), history of diabetes, hypertension, and more than two surgical procedures of the base of skull, on univariate analysis.[50,51] On multivariate analysis, only V60, history of diabetes and more than two surgical procedures remained significant. A V60 <0.9 mL compared to >0.9 mL resulted in toxicity-free survival of 96% compared to 79% (p = 0.0001), and on multivariate analysis resulted in an 11.4 risk ratio (p = 0.001). In a study from St. Jude Children's Research Hospital on 68 patients with infratentorial ependymoma, several interrelated variables were associated with brainstem injury, including tumor volume (and thus radiation volume), surgical morbidity, male gender, younger patient age, and cerebral spinal fluid shunting. The radiation dose was homogeneous between 54 Gy and 59.4 Gy.[52]

In a study of 40 patients undergoing IMRT for meningioma, one patient developed fatal brainstem necrosis after receiving a maximum dose to the brainstem of 55.6 Gy, with 4.74 mL exceeding 54 Gy.[53] This demonstrates that other poorly understood factors likely increase the risk of brainstem toxicity because this dose constraint would be considered acceptable in most of the studies referenced previously.

Summary and Other Key Points from QUANTEC Review[54]

Investigating radiation-induced brainstem injury is challenging because of the low incidence of toxicity with conventional doses, the short survival of patients, and the challenges of distinguishing between tumor progression and toxicity. Whole brainstem doses <54 Gy appear to be safe. Small volumes of brainstem appear to tolerate doses in excess of 55 Gy to 60 Gy. The risk of brainstem necrosis is low if the volume receiving >60 Gy is <0.9 mL.

NERVOUS SYSTEM: SPINAL CORD

Organ Function and Clinical Significance

The spinal cord consists of the motor and sensory tracts, communicating information between the peripheral nerves and the brain. Radiation-induced spinal cord injury can result in pain, paresthesias, sensory deficits, paralysis, Brown-Séquard syndrome, and bowel/bladder incontinence.

Dose-Volume Data

It is well accepted that the spinal cord can tolerate 45 Gy to 50 Gy with conventional fractionation, though the dose resulting in 5% toxicity risks (TD5) is most likely much higher. The spinal cord is generally limited to 45 Gy to 50 Gy because the anticipated risk of cord injury must be low to be clinically acceptable. In an analysis of several studies, Schultheiss calculated the probability of cervical cord myelopathy, after full cross-sectional irradiation, as 0.03% after 45 Gy, 0.2% after 50 Gy, and 5% after 59.3 Gy.[55] The thoracic spinal cord was calculated to be less sensitive than the cervical spinal cord (though because of the dispersion of data, a good fit could not be obtained). This model does not incorporate spinal cord volume, which might be acceptable given the "series" nature of the cord. Nevertheless, Schultheiss cautions that long lengths of cord, concomitant chemotherapy, and other factors may increase risk.

Little data exists exploring the dose-volume tolerance of the spinal cord. No spinal cord toxicity was reported in a study in which the V50 was <0.1 mL,[43] or in another study in which the D1 <45 Gy.[44] Massachusetts General Hospital studied 85 patients treated to the cervical spinal cord in the range of 45 Gy to 59.4 Gy (1.5 Gy equivalent fractions) equivalent uniform dose (EUD), 42 Gy to 57.5 Gy maximal dose to cord center, and 57 Gy to 74 Gy maximal dose to cord surface.[56] Fifteen percent of these patients experienced L'hermitte syndrome (self-limited symptoms of electric shocklike sensation most notable with neck flexion, attributable to focal demyelination) and 5% developed objective neurologic findings at or below cord level treated. Toxicity was not significantly correlated with cord length, cord volume, maximal dose to cord center, maximal dose to cord surface or effective uniform dose. The authors conclude that an EUD to the cervical cord of 60 Gy in 1.5 Gy fractions or 52.5 Gy in 2 Gy fractions is safe. In a recent study of 437 patients with laryngeal or oropharyngeal carcinoma (with maximum spinal cord dose of 22 Gy to 69 Gy) none developed myelopathy (at a median follow-up 27 months) whereas 17 developed L'hermitte's sign; the average spinal cord V45 of these 17 patients was 14 mL compared to 8 mL for those without L'hermitte's sign.[57] It has been postulated that the dose to the spinothalamic tract is most clinically significant for the occurrence of L'hermitte's sign.[58]

Summary and Other Key Points from QUANTEC Review[59]

There is not yet a consensus on the best approach to delineating the spinal cord, with options including delineating the entire thecal sac, the spinal canal, the spinal cord (as seen on magnetic resonance imaging [MRI]) or the spinal cord plus a

several millimeter margin. Though rare, radiation-induced spinal cord injury can be clinically devastating. With conventional fractionation of 1.8 Gy to 2.0 Gy per fraction to the full thickness of the spinal cord, the estimated risk of spinal cord myelopathy is <1%, <10%, and 50% at 54 Gy, 61 Gy, and 69 Gy, respectively. Although there is limited data on high dose per fraction using conventional radiation techniques, the estimated α/β ratio of 0.87 suggests a strong dependence of spinal cord toxicity on dose/fraction. Small volumes of spinal cord can likely receive doses in excess of 55 Gy to 60 Gy (with the high doses limited to the surface) with low risk of toxicity, though long-term data are lacking to derive a dose/volume relationship for myelopathy risk. Thus, recommendations for safe dose-volume metrics above 55 Gy to 60 Gy are lacking.

NERVOUS SYSTEM: OPTIC NERVES AND CHIASM

Organ Function and Clinical Significance

The optic nerve and chiasm serve as the neural conduit connecting the retinal fibers to the optic tracts, which, via the lateral geniculate body, terminate in the visual cortex. It is generally accepted that the entire optic nerves and chiasm may be treated to 54 Gy using conventional fractionation with minimal risk of late visual toxicity, though lower doses can result in other ophthalmologic toxicity.[60] A classic study showed that among patients treated to the same dose for pituitary adenomas or craniopharyngiomas, those who developed optic neuropathy (5 to 34 months after radiation) had received ≥2.5 Gy per fraction.[61] In a study from M. D. Anderson Cancer Center (MDACC), in which 219 patients were treated in the pre-3D radiation era, 10-year actuarial rates of optic neuropathy were 0%, 3%, and 34% for 43 Gy to 49 Gy at ~1.9 Gy/fraction, 50 Gy to 60 Gy at ~2.1 Gy/fraction, and 61 Gy to 76 Gy at ~2.2 Gy/fraction, respectively. Chiasm damage was similar with rates of 0%, 8%, and 24% for 15 Gy to 49 Gy at ~1.5 Gy/fraction, 50 Gy to 60 Gy at ~2.0 Gy/fraction, and 61 Gy to 76 Gy at ~2.1 Gy/fraction, respectively.[62] Greater total dose as well as larger fraction size impact risk.[63-66] With 3D planning, small volumes of optic nerve and chiasm may tolerate higher doses.

Dose-Volume Data

Several institutions have published their dose-volume constraints for the optic nerves and chiasm, most of which have not reported any neurologic visual toxicity. These constraints for patients undergoing external beam radiation therapy for head and neck cancers include V55 <0.1 mL of optic nerves/chiasm,[43] D1 <54 Gy for optic nerves, and D1 <45 Gy for optic chiasm[44] and maximum <54 Gy to the optic nerves and 52 Gy for the chiasm. These dose constraints are more conservative compared to what has been reported with proton therapy for base-of-skull tumors; base-of-skull tumors may be in close proximity to the optic apparatus, and tumors such as chordomas and chondrosarcomas are prescribed relatively high doses. For patients undergoing proton or combined proton/photon therapy for base-of-skull lesions, published dose constraints include <55 CGE to 56 GGE[47-49] or <60 Gy CGE[46] to optic nerves and optic chiasm.

Several studied have reported ophthalmologic toxicity after radiation. In a study from the University of Florida, the optic nerve dose (defined as the minimum dose delivered to one third of the optic nerve) in patients who developed optic neuropathy was 50.4 Gy to 79 Gy (median 68 Gy).[66] In a University of Michigan study, seven patients developed ophthalmologic toxicity: one patient received a chiasm maximum of 59.5 Gy; six patients received an optic nerve maximum of 47.5 Gy to 75.5 Gy (average 63 Gy).[67] Moderate to severe optic nerve complications (four patients) were associated with doses >64 Gy. In one study, four patients developed ophthalmologic toxicity, of whom three received a maximal dose of 56 CGE to 62 CGE to the optic chiasm/nerves and one received a maximum dose of >62 CGE. In two studies, bilateral visual loss occurred, with no evidence of tumor progression, ~8 months after conventional radiation; in one, the prescribed target dose was 49.3 Gy (maximum dose 56.1 Gy; chiasm maximum not reported, but <1 mL received >45 Gy)[68]; and in the other the chiasm maximum was <58 CGE.[47]

Some patients appear to tolerate a maximum optic nerve or chiasm dose of >60 Gy or >63 CGE to 69 CGE.[45,46,48,49,67] This demonstrates that other poorly understood factors likely increase the risk of optic nerve and chiasm toxicity. Optic nerve maxima >80 Gy and chiasm maxima >70 Gy were tolerated in some patients in the University of Michigan study discussed previously.[67] In another study, the dose constraint of 56 CGE to the optic nerve and chiasm was "relaxed" in 28% and 48% of patients, respectively, with no reported visual toxicity. In these patients, the volume receiving above the threshold dose was 0.11 mL and 0.12 mL for the optic nerves and chiasm, respectively; the volume receiving >105% of the threshold dose was 0.05 mL and 0.01 mL.[48]

Summary and Other Key Points from QUANTEC Review[69]

Data clearly show that the total dose and fraction size are the most important treatment-related risk factors for optic nerve/chiasm injury. There are scarce data to suggest a dose-volume effect on the optic nerve and chiasm. The risk of visual problems is <3% with <55 Gy, 3% to 7% for 55 Gy to 60 Gy, and >7% for >60 Gy. In the 55 Gy to 60 Gy experience, almost all of the reported cases of optic nerve injury received doses in the 59- to 60-Gy range (i.e., the high edge of that dose range).

NERVOUS SYSTEM: HEARING

Organ Function and Clinical Significance

The cochlea and acoustic nerve are the essential auditory structures that are susceptible to radiation injury and consequential sensory neural hearing loss. These are small structures, and therefore dose-volume measures are less determinable and clinically relevant. Other dose-dependent susceptible parts of the auditory system include the external ear and ear canal, tympanic membrane, ossicles, and eustachian tube.[70] Platinum based chemotherapy also is a well-established cause of sensory-neural hearing loss. Other factors such as baseline function and patient age are also relevant.

Dose-Volume Data

Several studies suggest that the dose to the cochlea correlates with the rate of sensory-neural hearing loss. A study from University of Florida showed that incidence of sensory-neural hearing loss increased consistently with dose to the cochlea; the 10-year actuarial risk of sensory neural hearing loss was 3% at doses <60.5 Gy compared to 37% at doses >60.5 Gy.[70]

Several other studies have shown hearing loss to be directly related to the inner-ear dose,[71-76] with sensory neural hearing loss becoming more apparent at doses >45 Gy to 50 Gy.[72,74,75,77] A German study examined hearing loss during and after radiotherapy for patients with head and neck cancers; for bone and air conduction after radiation, a 15-dB reduction in 50% of

patients over a range of frequencies was in the 20-Gy to 30-Gy range of doses to the inner ear (which ranged from 1.7 Gy to 64.3 Gy).[76] Cisplatin dose is also relevant to the threshold for auditory impairment. Cisplatin doses as low as 270 mg/m^2 can result in hearing loss when combined with cranial radiotherapy dosages of 40 Gy to 50 Gy.[78] In one study of patients with head and neck cancers, in those treated with radiation alone, hearing loss developed with cochlear doses >40 Gy; however, among those who received cisplatin (100 or 40 mg/m^2) and radiation, hearing loss developed with cochlear doses >10 Gy,[79] although the risk is likely low below doses of 30 Gy. The sequence of chemoradiotherapy also appears to influence risk. Risk and severity of ototoxicity are greater when cisplatin is administered after cranial radiation.

In a recent study of patients with base-of-skull tumors treated with radiation (median 50.4 Gy) radiographic opacification of the middle ear or mastoid, which correlates with subacute/chronic otitis media with effusion, occurred in 40 of 61 patients (with median follow-up of 21 months); this resolved in 17 of 40 patients 2 to 45 months (mean 17) after radiation.[80] Dose-volume analyses were performed for the eustachian canal, middle ear, mastoid air cells, vestibular apparatus, cochlea, internal auditory canal, lateral and posterior nasopharynx, and temporal lobes. Multivariate analysis showed that mastoid dose >30 Gy (odds ratio = 28.0, $p < 0.001$) and posterior nasopharynx dose >30 Gy (odds ratio = 4.9, $p = 0.009$) were associated with Grades 2 to 3 middle ear effusions.

Summary and Other Key Points from QUANTEC Review[81]

Because of the small volume of the cochlea, quantifying mean dose to the cochlea is more feasible than a dose/volume measure. Based on available data, the cochlear mean dose should be limited to ≤45 Gy (or more conservatively ≤30 Gy) and should be more strictly limited when delivered with cisplatin chemotherapy.

SALIVARY GLANDS

Organ Function and Clinical Significance

The salivary glands produce saliva, which aids in the swallowing, lubricating the oral cavity, taste, and food digestion. The parotid glands generate ~60% of saliva, and the majority of serous saliva, with the remainder of saliva secreted by submandibular, sublingual, and minor salivary glands. Radiation-induced salivary gland dysfunction—xerostomia—can result in difficulty swallowing, altered taste, and an increased risk of dental caries and oral infections. Because of the proximity of the parotid glands to the Level II lymphatics, IMRT is often used in the treatment of patients with head and neck cancers to reduce the parotid dose, in an attempt to prevent xerostomia.

Dose-Volume Data

The University of Michigan has published several studies investigating radiation dose-volume effects on serially measured stimulated and unstimulated salivary flow (directly from a given parotid gland). With salivary flow measured up to 12 months after radiation, significant parotid sparing was observed after a mean parotid dose below 24 Gy (for unstimulated flow) to 26 Gy (for stimulated flow).[82-84] Mean doses correlated with V15 of ≤67%, V30 of ≤45%, and V45 of ≤24%. The TD50 was 28.4 Gy.

Investigators at Washington University also examined whole salivary flow. Their technique differed from that from the University of Michigan in that they measured flow from all glands, though they included only patients whose submandibular glands received >50 Gy in an attempt to minimize this confounding variable.[85,86] Salivary flow was noted to be exponentially reduced by ~0.054/Gy of mean parotid dose (i.e., $e^{(-0.054^* \text{ mean dose})}$), equating to a reduction to 25% of the pr-treatment salivary flow with a mean dose of 25.8 Gy, essentially equivalent to the University of Michigan number.[87] The mean dose model was more predictive of the risk of late effects than threshold dose levels of V5 to V70 as well as other models studied.

Other groups have corroborated the mean dose as significant variable impacting salivary function,[88-93] with a Belgian study suggesting a lower threshold mean dose of 22.5 Gy.[94] A Dutch group demonstrated the TD50 for stimulated salivary function (risk of <25% of pretreatment rates) to improve with time, with TD50s of 34 Gy at 6 weeks to 40 Gy at 6 months, 42 Gy at 12 months, and 46 Gy at 5 years.[95,96] In a University of Michigan study, with flow rates measured in 142 patients up to 24 months after radiation, salivary flow rate was modeled as a function of time.[97] With mean parotid doses <25 Gy, the model predicted salivary function recovery to pretreatment functioning at 12 months. For mean parotid doses >30 Gy, stimulated saliva did not return to pretreatment functioning after 2 years.

In the parotid-sparing intensity modulated versus conventional radiotherapy in head and neck cancer (PARSPORT) trial, 94 patients with T1-4N0-3M0 pharyngeal squamous cell carcinoma were randomized (of whom 73 were evaluable for xerostomia).[98] IMRT compared to conventional radiotherapy allowed significant lowering of the ipsilateral (mean 25.4 Gy versus 61.0 Gy) and contralateral (mean, 47.6 Gy versus 61.0 Gy) parotid dose and resulted in a significantly lower incidence of xerostomia and greater recovery of salivary function 1 and 2 years after therapy. Randomized studies of IMRT in patients with nasopharyngeal cancer have shown similar findings.[99,100] In a recent study of 126 patients from Germany, restraining the mean dose to both parotids <26 Gy (versus only one) significantly reduced xerostomia and dysphagia.[101]

Radiation dose to the submandibular glands also impacts salivary function.[102] In a study from Helsinki University, the mean unstimulated salivary flow was 60% of the pretreatment function among patients who had one submandibular gland spared (mean dose of 26 Gy and range from 21 to 34 Gy) and 25% among those who did not ($p = 0.006$).[103] However, sparing of a submandibular gland did not affect the *stimulated* saliva flow rates. Another study showed that intentional sparing of submandibular glands (average mean dose of 20.4 Gy and V30 of 14.7%) versus no submandibular gland sparing (average mean dose 57.4 Gy and V30 99.8%), resulted in a nonsignificant trend toward better recovery of salivary flow.[104] Investigators at Vrije University in Amsterdam have demonstrated that mean submandibular dose is a significant variable impacting the sensation of sticky saliva.[105] In addition to submandibular dose and parotid gland dose, the University of Michigan group showed that oral cavity dose (containing the minor salivary glands) is also predictive; although no well-defined thresholds were observed, an oral cavity mean dose of <40 Gy was associated with low xerostomia rates.[106] The Radiation Therapy Oncology Group (RTOG) has demonstrated the feasibility and efficacy of surgically transferring the submandibular salivary gland to the submental space and shielding (>70%) of this gland during radiation to mitigate xerostomia.[107]

NTCP modeling of 178 patients treated with IMRT showed that baseline salivary function and mean contralateral parotid gland dose were predictors for xerostomia, and that mean contralateral submandibular gland dose, mean sublingual dose, and mean dose to minor salivary glands in the soft palate were predictive for sticky saliva.[108,109]

Summary and Other Key Points from QUANTEC Review[110]

Several studies have nicely demonstrated a dose response relationship between the salivary flow and mean parotid dose. From the available data, it appears that severe long-term salivary dysfunction (generally defined as reduction of salivary flow to less than 25% of baseline) can be avoided if one parotid gland is spared to a dose of less than 20 Gy or if both parotid glands have a mean dose of less than 25 Gy. A recent clinical study confirmed that adherence to these guidelines effectively avoids xerostomia.[111] Much of the data on submandibular gland and minor salivary gland dose-volume effects discussed previously were published in recent years, after QUANTEC was published.

LARYNX AND PHARYNX

Organ Function and Clinical Significance

The larynx and pharynx are involved with phonation and swallowing, respectively. Late complications include laryngeal edema and fibrosis, laryngeal dysfunction, dysphagia, and necrosis. A study from University of Michigan showed that damage to the pharyngeal constrictors and the glottic and supraglottic larynx may cause dysphagia and aspiration after chemoradiation.[112]

Dose-Volume Data: Larynx

For laryngeal edema, in a study from University of Texas, Galveston (with most patients receiving radiation alone), the mean laryngeal dose and laryngeal V30 to V70 were significantly associated with grade ≥2 edema with a univariate analysis, whereas mean laryngeal dose and N stage were significant with multivariate analysis.[113] V50, which was highly correlated with mean laryngeal dose, was significant in a multivariate analysis in which mean laryngeal dose was replaced by V50. The 1-year rate of grade ≥2 edema was 20% after a mean laryngeal dose of 43.5 Gy (or V50 <27%) versus 45% after a mean dose of 44 Gy to 57 Gy (or 94%< V50 >27%) versus >80% after a mean dose >57 Gy (or V50 >94%).

There is a paucity of data correlating dose-volume metrics with vocal dysfunction. Generally, after therapeutic doses of 60 Gy to 66 Gy for early stage glottic cancer, the risks of vocal dysfunction are low. In a study from University of Iowa, point doses in excess of 66 Gy to the aryepiglottic folds, preepiglottic space, false vocal cords, and lateral pharyngeal walls resulted in a sharp increase in risk of vocal function.[114]

Summary and Other Key Points from QUANTEC Review[115]

Radiation-induced laryngeal edema is a common and expected side effect. Progressive edema and associated fibrosis[116] can lead to long-term problems with phonation as well as swallowing. Tumor infiltration, particularly with locally advanced cancers can cause voice and swallowing symptoms, and may exacerbate radiation toxicities. To minimize risks of laryngeal edema, a larynx V50 ≥27% and the mean laryngeal dose of ≤44 Gy are recommended.

Dose-Volume Data: Swallowing

Several studies have investigated dose-volume metrics predictive of swallowing dysfunction, with many studies published after the QUANTEC report. In a study from University of Michigan, mean dose to the pharyngeal constrictors was correlated to risk of aspiration.[117] The risk of aspiration increased with a mean dose of >60 Gy to the pharyngeal constrictors, and with a V40 >90%, V50 >80%, V60 >70%, and V65 >50%, and with a V50 >50% for the larynx. Three patients who developed strictures had a pharyngeal constrictor V70 >50%.

In a study from Aarhus University, several significant correlations were found between both subjective and objective swallowing problems and DVH parameters of the base of tongue, pharyngeal constrictors, supraglottic larynx, esophageal sphincter, and glottic larynx.[118] Doses less than 60 Gy to the supraglottic region, the larynx, and upper esophageal sphincter resulted in a low risk of swallowing difficulties and aspiration.

In a study from University of Iowa, point doses to the false vocal cords, lateral pharyngeal walls, and the upper esophageal sphincter were correlated with dietary difficulties.[114] As an example, the dose to the left lower pharyngeal wall for patients who had no oral intake 1 year after treatment was 79.7 Gy versus 65.1 Gy for those with an unrestricted diet. A greater radiation dose to the aryepiglottic folds was associated with greater weight loss and a great radiation dose to the false vocal cords was associated with gastrostomy tube use.

In a study from Rotterdam, doses >50 Gy to the middle and superior pharyngeal constrictors resulted in a 20% probability of dysphagia, with an incremental 19% risk for each additional 10 Gy.[119] Another study (of 39 patients) suggested that the dose (V60 to V65 and mean) to the inferior pharyngeal constrictors is most predictive of gastrostomy tube dependence,[120] whereas in two other studies (of 50 and 53 patients),[121,122] the V50 (one study) and mean dose (both studies) of the middle pharyngeal constrictors were most predictive of dysphagia, along with mean supraglottic larynx dose (one study).[122] In an analysis of 96 patients from the Dana-Farber Cancer Institute, the inferior pharyngeal constrictor V50 and larynx V50 were significantly associated with aspiration and stricture risk.[123] MDACC investigators recommended a V30 <65% and V35 <35% for anterior oral cavity and V55 <80% and V65 <30% for superior pharyngeal constrictors, which was predictive for swallowing dysfunction in 31 patients.[124] University of Alabama at Birmingham investigators recommended V60 <24% to the larynx and <12% to the inferior pharyngeal constrictors to reduce risk of aspiration and gastrostomy tube dependence, and V65 <75% to the middle pharyngeal constrictors, and <33% to the superior pharyngeal constrictor to reduce risk of stricture requiring dilation.[125] In a Nordic study of 354 patients,[126] mean dose to the superior pharyngeal constrictor and supraglottic larynx were most predictive of radiation-induced swallowing dysfunction; different models (resulting in different significant dosimetric variables) were developed specifically for dysphagia to liquids, soft foods, or solids.

A recent analysis, based upon 53 of 189 patients who developed grade ≥3 dysphagia, designed a predictive model by analyzing clinicopathologic, treatment, and dosimetric parameters (dose to pharyngeal constrictor and esophageal structures) as well as genetic polymorphisms; the best model incorporated concurrent chemotherapy, dose to 2% of the pharyngeal constrictors and an XRCC1 polymorphism.[127]

Summary and Other Key Points from QUANTEC Review[115]

Because swallowing is complex, involving voluntary and involuntary stages coordinated through several cranial nerves and muscles, defining the most important anatomic structures whose dose-volume parameters have a major impact on dysphagia has been challenging. Emerging data has demonstrated

significant correlations between pharyngeal constrictor doses and dysphagia. With limited available data, it is recommended to limit the volume (to the extent possible without compromising target coverage) of the pharyngeal constrictors and larynx receiving ≥60 Gy, and reducing when possible the volume receiving ≥50 Gy. From data published after the QUANTEC review, it is readily apparent that mean dose and dose in excess of 50 Gy to 60 Gy to the larynx and pharyngeal constrictor muscles are predictive of swallowing difficulties, though it is unclear which of the pharyngeal constrictor muscles and which component(s) of the larynx are most critical.

LUNG

Organ Function and Clinical Significance

The lung's main function is gas exchange of oxygen and carbon dioxide. Radiation damage to the lung can result in symptomatic pneumonitis and fibrosis. Symptomatic radiation pneumonitis is characterized by dyspnea, cough, and sometimes a low-grade fever, typically occurring several weeks to months after radiation. More long-term lung fibrosis can lead to respiratory insufficiency. It is often challenging to distinguish radiation-related pulmonary symptoms from comorbid illnesses (e.g., exacerbation of chronic obstructive pulmonary disease, infection, cardiac events).[128] Objective reductions in the lung's ability to move and exchange gas can be measured by formal pulmonary function tests (PFTs).

Recent meta-analyses have shown that patient-related adverse risk factors for radiation pneumonitis among patients with non–small-cell lung cancer include older age,[129,130] history of chronic lung disease or diabetes,[131] and low preradiotherapy lung function.[131] Smoking was an adverse risk factor in one meta-analysis,[131] whereas not being an active or prior smoker[129] was an adverse risk factor in another, a discrepancy that is attributed to the complexity of the relationship between smoking, chronic lung disease, and pneumonitis.[131] Chemotherapy concurrent with radiation therapy,[131] particularly carboplatin/paclitaxel chemotherapy,[130] has been reported to increase the pneumonitis risk.

Cytokines appear to play a role (at least perhaps as a marker and maybe as a mediator) in the development of clinical radiation pneumonitis. Seminal work implicates transforming growth factor beta (TGF-β).[132,133] A powerful association between native circulating IL-1 and IL-6 levels and radiation pneumonitis have been reported from the University of Rochester.[134] A French study has also shown a correlation between circulating levels of IL-10 and IL-6 and the development of radiation pneumonitis.[135] Nevertheless, the literature reports in this area are not totally consistent. Cytokines may not be important for pulmonary fibrosis.[136] More recent data have also demonstrated pneumonitis risks correlated with polymorphisms of DNA repair[137-139] and TGF-β[140] genes correlating with pneumonitis risks. Positron emission tomography (PET) avidity of lung tissue after radiation has also been correlated with pneumonitis risk.[141]

Dose-Volume Data: Pneumonitis and Fibrosis

Several dosimetric parameters have been shown to be associated with the risk of radiation pneumonitis, including V5 to V70, mean lung dose (MLD), and model-based parameters.[142-146] These variables are correlated with each other, accounting for the fact that in most studies examining a range of *Vx* variables, many/most are significant.[147-161] The dosimetric parameters predictive of pneumonitis can also be used to predict fibrosis risks.[136] How normal lung is defined (i.e., lung minus gross target volume [GTV] or PTV) will affect the magnitude of the calculated dose-volume metrics.[162]

Table 14-2 summarizes many of the studies discussed here. Most of the published dose-volume data describes pneumonitis risks in patients with lung cancer, though data also exist for patients with breast cancer[150,163,164] and Hodgkin lymphoma.[165,166] In patients with Hodgkin lymphoma, pneumonitis risks appear to be lower for given dose-volume metrics that may relate to the younger age of this patient population.

An NTCP analysis from the Netherlands, in collaboration with the University of Michigan, suggests that using the MLD (linear function) is more predictive than using VX (step function).[150] However, V13 tended to be more predictive in situations where the MLD exceeded 20 Gy or V13 exceeded 50%. The TD50 values in this study were MLD of 30.8 Gy, V13 of >77%, and V20 of >65%, similar to the MLD of 31.8 Gy reported in a previous multiinstitutional study.[167] From an NTCP analysis from the Memorial Sloan Kettering Cancer Center (MSKCC),[148] a mean lung dose of ~26 Gy, V13 of >80% to ipsilateral lung, or V40 of >32% to lower lung results in a 50% risk of developing late complications. A mean lung dose of ~12 Gy or a V13 of >40% to ipsilateral lung results in a 5% late complication risk. A V13 of 36% of the lower lung, 42% of the total lung, or 62% of the ipsilateral lung results in a 20% risk of developing late grade ≥3 complications.

In a 1997 study from MSKCC, of patients treated with radiation alone, there was a significantly increased risk of grade ≥3 pulmonary toxicity, 38% with a V25 of >30% compared to 4% with a V25 of <30% ($p = 0.04$).[168] In subsequent studies from this same group, significant variables for predicting grade ≥3 pulmonary toxicity included mean lung dose, the range of V5 to V40 of total lung, V5 to V40 of ipsilateral lung, and V5 to V50 of lower lung.[148,153] The range of V5 to V20 ipsilateral lung was most predictive.

Investigators at Washington University also showed that the risk of pneumonitis significantly correlated with the V20; the 2-year incidence of grade ≥2 radiation was 36% versus 13% versus 7% versus 0% with a V20 of >40%, 32% to 40%, 22% to 31%, and <22% ($p = 0.0013$), respectively.[142] In another study from Washington University, radiation pneumonitis was significantly correlated with V5 to V80, with peak significance in the V5 to V15 and V70 to 75 ranges; radiation pneumonitis was also significantly correlated with the dose delivered to 5% to 100% of the lung (D5-100), with peak significance in the D30 to D40 and V90 to V95 ranges.[156]

In a 2001 study from Duke (in which 18% of patients received concurrent chemoradiotherapy) a V30 of >18% versus <18% was associated with a risk of grade ≥1 radiation pneumonitis of 24% versus 6% ($p = 0.0003$).[147] MLDs of <10 Gy, 10 Gy to 20 Gy, 21 Gy to 30 Gy, and >30 Gy were associated with risks of 10%, 16%, 27%, and 44%, respectively. A Japanese study of patients treated with platinum-based chemoradiotherapy found a 6-month risk of grade ≥2 radiation pneumonitis to be 85%, 51%, 18.3%, and 8.7% ($p < 0.0001$) with a V20 of ≥31%, 26% to 30%, 21% to 25%, and ≤20%, respectively.[169] In a University of Michigan study, a 10% risk for grade ≥2 pneumonitis and fibrosis was associated with a V20 >30% and an MLD >20 Gy. These thresholds provided a positive predictive value of 50% to 71% and a negative predictive value of 85% to 89%.[170] In a study from MDACC, the mean lung dose and V5 V65 were highly correlated with risk of pneumonitis, and V5 was the most significant factor in a multivariate analysis.[155] For a V5 ≤42% versus >42%, the risk of grade ≥3 pneumonitis at 1-year was 3% versus 38% ($p = 0.001$). In a Mayo Clinic study, V10 to V13 were most predictive of radiation pneumonitis; a V10 of 32% to 43%, V13 = 29% to 39%, V15 = 27% to 34%, and V20 of 21% to 31% resulted in a 10% to 20% risk of pneumonitis.[160] From a recent meta-analysis of 836

TABLE 14-2 Summary of Selected Studies Analyzing Dose-Volume Parameters Predictive of Lung Toxicity

Author, Year (*Center*)	Patient Population	Endpoint	Subgroup	Toxicity Rate
Seppenwoolde, 2003 (*van Leeuwenhoek Hosp.*)	Breast cancer, lymphoma, non–small cell lung cancer	Radiation pneumonitis	MLD = 31.8 Gy V13 = 77% V20 = 65%	50% (NTCP) 50% (NTCP) 50% (NTCP)
Yorke, 2002 *(MSKCC)*	Non–small cell lung cancer	Acute grade ≥3 pulmonary toxicity	MLD = 25 Gy MLD = 12 Gy V13 = 42% V13 (ipsilateral lung) = 80% V13 (ipsilateral lung) = 62% V13 (ipsilateral lung) = 40% V40 (lower lung) = 32% V13 (lower lung) = 36%	50% (NTCP) 5% (NTCP) 20% (NTCP) 50% (NTCP) 20% (NTCP) 5% (NTCP) 50% (NTCP) 20% (NTCP)
Armstrong, 1997 *(MSKCC)*	Non–small cell lung cancer	Acute grade ≥3 pulmonary toxicity	V25 > 30% V25 < –30%	38% 4%
Graham, 1999 (*Washington Univ.)*	Non–small cell lung cancer	Grade ≥3 radiation pneumonitis	V20 > –40% V20 = 32%-40% V20 = 22%-31% V20 < –22%	36% 13% 7% 0
Hernando, 2001 (*Duke Univ.*)	Non–small cell lung cancer, small-cell lung cancer	Grade ≥1 radiation pneumonitis	V30 > –18% V30 < –18% MLD <10 Gy MLD 10-20 Gy MLD 21-30 Gy MLD >30 Gy	24% 6% 10% 16% 27% 44%
Tsujino, 2003 (*Hyogo Medical Center*)	Non–small cell lung cancer	Grade ≥2 radiation pneumonitis	V20 ≤20% V20 = 21%-25% V20 = 26%-30% V20 ≥31%	9% 18% 51% 85%
Kong, 2006 (*U. Michigan)*	Non–small cell lung cancer	Grade 2 radiation pneumonitis	V20 > –30% MLD > –20 Gy	10% 10%
Wang, 2006 (*MDACC)*	Non–small cell lung cancer	Grade ≥3 radiation pneumonitis	V5 ≤42% V5 >42%	3% 38%
Koh, 2006 (*Princess Margaret H)*	Hodgkin lymphoma	Grade ≥2 radiation pneumonitis	V20 >40% V20 ≤40%	25% 0%
Schallenkamp, 2007 (*Mayo Clinic)*	Non–small cell lung cancer, small cell lung cancer	Grade ≥2 radiation pneumonitis	V10 = 32%-43% V13 = 29%-39% V15 = 27%-34% V20 = 21%-31%	10%-20% 10%-20% 10%-20% 10%-20%
Mazeron, 2010* (*U Lyon)*	Non–small cell lung cancer	Radiation fibrosis	V10 <33% V20 <18% V30 <13% V40 <10% V50 <5% V10 >33% V20 > 8% V30 >13% V40 >10% V50 >5%	11% 13% 14% 14% 13% 26% 24% 23% 23% 24%
Ramella, 2010* (*Rome, Italy)*	Non–small cell lung cancer	Grade ≥2 radiation pneumonitis	ipsilateral V20 ≤52% ipsilateral V30 ≤39% ipsilateral MLD ≤22 Gy ipsilateral V20 >52% ipsilateral V30 >39% ipsilateral MLD >22 Gy	9% 8% 7% 46% 38% 23%
Fox, 2012* (*Brigham and Women's H)*	Hodgkin lymphoma	Grade ≥2 radiation pneumonitis	V20 ≥33.5% V20 <33.5% MLD >13.5 Gy MLD <13.5 Gy	21% 2% 19% 4%

TABLE 14-2 Summary of Selected Studies Analyzing Dose-Volume Parameters Predictive of Lung Toxicity—cont'd

Author, Year (*Center*)	Patient Population	Endpoint	Subgroup	Toxicity Rate
Meta-analysis, 2013*	Non–small cell lung cancer	Grade ≥ radiation pneumonitis	V20 <20%	18.4%
			V20 = 20%<30%	30.3%
			V20 = 30%<40%	32.6%
			V20 >40	35.9%
	Non–small cell lung cancer	Fatal (grade 5) radiation pneumonitis	V20 <20%	0%
			V20 = 20%<30%	1.0%
			V20 = 30%<40%	2.9%
			V20 >40	3.5%

NTCP, *Normal tissue complication probability modeling.*
**Published after QUANTEC review.*

patients, lung V20 of <20%, 20 to <30%, 30 to <40%, and >40% were associated with symptomatic pneumonitis risks of 18.4%, 30.3%, 32.6%, and 35.9%, respectively, and fatal pneumonitis risks of 0%, 1.0%, 2.9%, and 3.5%, respectively.[130]

Several dose escalation studies have used V20, V_{eff} or NTCP to allocate patients into given dose levels.[171-174] In the RTOG 93-11 dose escalation study, patients with a V20 of <25% experienced a 7% to 16% 18-month actuarial rate of grade ≥3 late lung toxicity with prescribed doses of 70.9 Gy to 90.3 Gy; the absolute risk of grade ≥2 late lung toxicity was 30% to 45%, with one fatal lung complication at the 90.3-Gy dose level. Patients with a V20 of 25% to 36% treated to doses of 70.9 Gy to 77.4, Gy experienced 15% grade ≥3 late toxicity at 18 months, and an absolute risk of grade ≥2 late lung toxicity of 40% to 60%.[171] D15 was the most predictive variable for radiation pneumonitis.[159]

In Dutch study, the effect of regional dose on the lung was investigated, with the lung divided into: central and peripheral; ipsilateral and contralateral; caudal and cranial; and anterior and posterior subvolumes.[175] The mean regional dose to the posterior, caudal, ipsilateral, central, and peripheral lung subvolumes significantly correlated with the incidence of steroid-requiring radiation pneumonitis; caudal location was correlated with greater pneumonitis risks, whereas no statistical difference in risks were observed between anterior and posterior locations or central and peripheral locations. In a similar study from MSKCC, the risk of radiation pneumonitis was better correlated with the radiation dose to the inferior aspect of the lung, rather than the superior aspect.[148]

Tumor location in the lower lung also appears to be an adverse factor affecting risk of pneumonitis in patients with lung cancer.[129-131] In the aforementioned study from Washington University,[156] inferior tumor location was the most significant predictor of radiation pneumonitis. Tumor location was not a strong correlate to radiation pneumonitis in a study from patients treated on RTOG 93-11, perhaps attributable, in part, to differences in treatment (with RTOG 93-11 designed to treat smaller volumes to higher doses) and differences in tumor size and location (the RTOG 93-11 tumors tended to be smaller and more superiorly located).[159] Using a combined data set of patients from RTOG 93-11 and Washington University, tumor location, in addition to MLD were significant. In a recent Washington University study of 209 patients, cardiac dose, specifically V65 and D10, was more predictive of radiation pneumonitis than lung dose-volume metrics; the reason is unknown and the authors demonstrate that that heart variables are not simply surrogates for lung variables.[176]

For some patients with advanced stage non–small-cell lung cancer, IMRT yields unique dose distributions, with improved target conformality and increased (albeit modest) target heterogeneity.[177] The IMRT-based dose distributions appear to reduce the risk of normal tissue injury in patients with non–small-cell lung cancer. Investigators at MDACC compared their rates of lung toxicity in patients with treated IMRT versus 3D planning and noted a reduction in toxicity with the IMRT approach.[178] Investigators at MSKCC noted a similarly low rate of clinical lung injury in patients with non–small-cell cancer treated with IMRT.[179] In the MDACC study, a V5 >70% was associated with a 21% risk of grade ≥3 pneumonitis versus a 2% risk with a V5 ≤70% (p = 0.017). Proton therapy also allows for reduction of lung volume receiving a given dose, and data are emerging on its utility.

IMRT has also been used to treat patients with mesothelioma. In a study from Dana Farber, in which patients received thoracic IMRT after pneumonectomy for mesothelioma, 6 of 13 patients developed fatal pneumonitis.[180] The median V20, V5, and MLD for patients who developed pneumonitis was 17.6%, 98.6%, and 15.2 Gy, respectively, versus 10.9%, 90%, and 12.9 Gy for those who did not develop pneumonitis. Although these differences were not significant, the severity of the toxicities merits caution in treating patients to large volumes after a pneumonectomy. In a study from Duke, 1 of 13 patients treated with IMRT for mesothelioma died from pneumonitis, and 2 others developed symptomatic pneumonitis.[181] The median V20, V5, and MLD for patients developed pneumonitis was 2.3%, 92%, and 7.9 Gy, respectively, versus 0.2%, 66%, and 7.5 Gy for those who did not develop pneumonitis, versus 6.9%, 92%, and 11.4 Gy for the patient who developed fatal pneumonitis. In a study of mesothelioma patients from MDACC, 6 of 63 patients died from pulmonary-related causes (including 2 patients with fatal pneumonitis).[182] The V20 was significant on univariate and multivariate analyses (p = 0.017), with a V20 >7% corresponding to a 42-fold increase in the risk of pulmonary death.

Summary and Other Key Points from QUANTEC Review[183]

A variety of studies note a dose-response relationship for a variety of metrics predictive of radiation pneumonitis. The QUANTEC review pooled the data from many centers. This shows that there is no specific threshold for pneumonitis, with risks increasing gradually with increased dose. Because many dose/volume parameters of the lung (i.e., V5 through V30, MLD) are correlated with each other, there likely is not an "optimal" parameter. For patients with non–small-cell lung cancer, it is prudent to limit the V20 to <30% to 35%, and the mean lung dose to <20 Gy to 23 Gy, to limit the risk of pneumonitis to less than 20%. In patients irradiated postpneumonectomy for mesothelioma, it is prudent to limit the V5 <60%, the V20 <4% to 10%, and the mean lung dose to <8 Gy. Radiation-induced pneumonitis appears more commonly in

patients with lower- versus upper-lobe tumors and may be better correlated with radiation doses to the lower versus upper lung. The cause of this correlation is unknown and requires further investigation. Perhaps it is related to differences in ventilation and perfusion of different lung regions.

Dose-Volume Data: Pulmonary Function

The majority of studies have considered shortness of breath as the relevant endpoint. This is what is typically recorded in patient records, and, from the patient's perspective, perhaps the most meaningful endpoint. However, symptoms can be non specific and difficult to quantify. Therefore, investigators have also considered more specific and objective endpoints such changes in PFTs and imaging.

Changes in PFTs following thoracic radiation reflect a combination of improvements because of tumor shrinkage (typically acutely), and declines because radiation-induced injury (both acute and chronic).[184] Several studies have noted long-term declines in PFTs following thoracic radiation,[185-187] although changes can be transient.[188] The association between shortness of breath following radiation and declines in PFTs is complex.[189] Duke University studies have shown a correlation between V30 and NTCP with changes in forced expiratory volume in 1 second (FEV1) and diffusion capacity (DLCO).[190] The University of Michigan investigators, however, did not find any correlation of V20, MLD, or V_{eff} with changes in FEV1 or DLCO.[191] Attempts have been made to model the risk of changes in PFTs,[192,193] though certainly this is a complicated area of study. Recent data from MDACC suggest that severity of pneumonitis is correlated with reduction in DLCO.[194]

Similarly, imaging tests provide clear objective metrics. Several studies have noted an association between regional radiation doses and changes in regional imaging tests (CT-defined density or single-photon emission computed tomography [SPECT]-defined perfusion/ventilation).[195-198] The extent or severity of these imaging changes is related to changes in global lung function (assessed as either symptoms or changes in PFTs), but the correlations are relatively weak.[184,192,193,198]

Summary and Other Key Points from QUANTEC Review[183]

For pulmonary function, it appears that minimizing the V30 minimizes risk of decline in pulmonary function test parameters, though, as is the case with pneumonitis, other dose-volume measures may be predictive as well. The study of radiation-induced lung injury is confounded by the use of ambiguous endpoints, as well as toxic exposures (e.g., smoking) and treatment with chemotherapy (e.g., bleomycin and cisplatinum). Many toxicity scoring systems combine radiologic, functional, and symptomatic criteria in their grading system. However, each pulmonary toxicity endpoint may have different dose/volume dependence, and future studies should be explicit in defining endpoints.

HEART

Organ Function and Clinical Significance

The heart is the muscular organ, located in the left hemithorax (with the rare exception of dextrocardia) which, via continuous rhythmic contraction, pumps blood throughout the blood vessels. The functional and structural complexity of the heart places it at risk for a spectrum of radiation and chemotherapy injuries that can manifest months to years following therapy. All components of the heart and the surrounding pericardium are susceptible to radiation damage. Radiation-induced cardiac injury includes pericarditis, congestive heart failure, restrictive cardiomyopathy, valvular insufficiency and stenosis, coronary artery disease, ischemia, and infraction. A history of anthracycline chemotherapy can exacerbate radiation-elated cardiac toxicity.

Dose-Volume Data

Abundant studies have demonstrated an increased risk of cardiac morbidity following left-sided thoracic radiation versus right-sided thoracic radiation in patients irradiated for breast cancer. It is well accepted that reducing the dose prescribed to the mediastinum and reducing the volume of heart in the radiation field reduces the risk of late toxicity.[199-201] Studies from Duke demonstrated that an increased percentage of the left ventricle irradiated correlates with a greater risk of cardiac perfusion defects.[202-204] Even over the range of low dose exposure (~8 Gy to 20 Gy) to small volumes of the cardiac apex, an increased risk of heart disease has been reported.[205]

A study from Stockholm used normal tissue complication probability modeling to predict the risk of late heart toxicity in women treated for breast cancer.[206] In their models, the TD50 was optimized to a value of 52 Gy to the myocardium. A 5% risk of excess cardiac mortality at 15 years was associated with a myocardial dose of ~30 Gy, a V33 of >60%, V38 of >33%, or a V42 of >20%. Calculations using the whole heart volume (as opposed to myocardium) yielded similar values.

The same group from Stockholm used a similar analysis to assess cardiac risk in patients with Hodgkin disease.[207] Patients were stratified into two risk groups: those with a V38 of >35% and those with a V38 of <35%. The excess mortality risk at 15 years was 7.9% and 4.7%, respectively. The TD50 was calculated to be 70 Gy. A heart dose of 42 Gy resulted in a 5% normal tissue complication probability, whereas a heart dose of 53 Gy resulted in a 10% NTCP. The corresponding values in the patients with breast cancer were 37 Gy and 44 Gy respectively (lower threshold doses and steeper gradient). The differences in complication probabilities and TD50 between the breast and Hodgkin disease cohorts suggest that radiation exposure to different portions of heart results in differences in cardiac risk,[207] though there may be other confounding variables not easily identified (e.g., patient age at treatment, similar risk factors between breast cancer and cardiac disease, etc.)

Mean heart dose to the left ventricle, both ventricles, or whole heart were not predictive for cardiac toxicity in a study of 328 survivors of non–small-cell lung cancer.[208] A Wayne State University study of 102 survivors of esophageal cancer, demonstrated thresholds for symptomatic cardiac toxicity to be heart V20, V30, and V40 above 70%, 65%, and 60%, respectively.[209]

A recent landmark Swedish/Danish study analyzed 960 survivors of breast cancer who experienced major coronary events and 1,205 controls, treated from 1958 to 2001.[210] The authors showed a linear relationship with mean heart dose and coronary events, with the risk being increased by 7.4% per Gy with no apparent threshold and persisting decades after treatment. The concept of no-threshold dose conflicts with our historical understanding (that "low doses" were likely inconsequential) as well as a recent University of Michigan study looking at myocardial perfusion scans after low-dose exposure (average heart mean dose <5 Gy) in patients with breast cancer; the authors found no correlations between cardiac doses and assessed cardiac function.[211] A potential criticism of the Swedish/Danish study is that radiation fields were reconstructed using a CT scan of a "typical woman" to generate DVH information. This undoubtedly introduced uncertainties

in their analysis that are acknowledged by the authors. Nevertheless, this was really the best that could humanly be done because the patients were treated in the pre-3D planning era. The investigators performed in-depth dosimetric reconstructions based on the available information.

The lack of a dose threshold might be related in part to the techniques used and potential differences between the delivered and planned doses. Radiation is delivered in daily fractions over many weeks. Inter- and intrafraction variations (e.g., because of daily set-up and motion from breathing) result in differences between the planned and delivered dose. The planned dose is *not* necessarily a good representation of the "average" of the delivered fractions, particularly for patients with a low planned mean heart dose. Such a patient likely has a beam edge close to, or encroaching to a small degree on, the heart. Because the dose gradient is steep near the beam edge, setting-up the beams too deep will markedly increase the cardiac dose. Setting them up too shallow does *not* yield a corresponding decrease in dose, because if the planned dose is already low, one cannot reduce dose appreciably lower. Thus, although set-up irregularities *might* be geometrically equally distributed relative to the planning scan, the dosimetric effects are not symmetrical, and such set-up variations often tend to *increase* the cardiac exposure. This might, to some degree, explain the low-dose effects seen by Darby.[212]

The findings from Darby et al may not be necessarily applicable to women treated with modern radiation planning and deliver methods because the doses are far lower, and the set-up techniques are likely more robust. In fact, the lead author previously showed no increase in cardiac mortality among women treated with radiotherapy after 1992 in the United States.[213] Nevertheless, the recent Darby study is a reminder that radiation-induced cardiac injury is a serious consideration.

In the Darby study, the mean heart dose was as good (or better) a predictor of risk than doses to the coronary arteries. This is surprising because the coronary arteries are often implicated as the main target for radiation-associated heart injury. Darby's observation may be the result of uncertainties in their estimation of coronary artery doses. Nevertheless, several studies note reduced perfusion in irradiated cardiac regions that do *not* correspond to a coronary artery's territory,[202] thus implicating microvascular injury as a potential mechanism for radiation-associated heart injury and an endpoint more plausibly associated with mean dose. The mean heart dose is likely largely a surrogate for dose to critical substructures such as the left-ventricular muscle and arteries.[212]

In another Swedish study, which correlated angiography findings with coronary artery dose-exposure extrapolated from the radiation treatment fields, an approximate twofold increase risk in high-grade coronary artery stenosis was found in women who received high-risk radiotherapy (i.e., specific coronary arteries were exposed to the highest radiation doses during breast cancer radiotherapy).[214] Furthermore, stenosis in these high-risk patients was more likely to occur in irradiated regions, specifically the right coronary artery (not accounted for[215] in the Swedish/Danish study) and distal left anterior descending artery.

There is little data on correlating heart dose-volume metrics with subsequent ejection fraction. In a study of patients with esophageal cancer treated with chemoradiation at Roswell Park Cancer Institute, the radiation dose to heart, left ventricle, and left anterior descending artery (quantified as V20 to V40) were not clinically or statistically associated with changes in the ejection fraction (albeit in a small study, with limited follow-up).[216] The aforementioned University of Michigan study likewise did not show a dose correlation with ejection fraction.[208]

A study from MDACC described the risk of pericardial effusions in patients treated for esophageal cancer.[217] A mean dose >26 Gy and relative volumes of the pericardium treated to doses greater than 3 Gy to 50 Gy (rV3 to rV50) was associated with effusions, with the strongest association being rV30. At 18 months postradiation, for a rV30 of >46% versus <46%, the rate of pericardial effusion was 73% versus 13% (p = 0.001); for a mean pericardium dose >26 Gy versus <26 Gy, the rate of pericardial effusion was 73% versus 13% (p = 0.001). A study from the University of Michigan also demonstrated that a mean dose >27 Gy and maximum dose 47 Gy correlated with risk of pericardial effusion; however, only patients treated with 3.5 Gy fractions developed pericardial effusions.[218]

Radiotherapy has been associated with valvular heart disease.[219] The incidence has been related to mediastinal radiation doses >30 Gy and younger age at irradiation. Subclinical valvular disease has been detected at 2->20 years postradiation,[219] but it appears to take much longer for clinical symptoms to become apparent (median interval 22 years from radiation to symptoms). For patients receiving radiation for Hodgkin lymphoma, at a median of >10 years after radiation aortic valvular disease usually consists of mixed stenosis and regurgitation and is more common than mitral and right-sided valvular disease.[219,220] From NTCP modeling of radiation-induced asymptomatic heart valvular defects, among 20 of 56 survivors of Hodgkin lymphoma, the cardiac chamber (left ventricle and left atrium) V30, cardiac chamber volume, and lung volume were predictive.[221]

Antracyclines and Other Risk Factors

In patients with Hodgkin disease, radiation exposure, in conjunction with anthracyclines, may impair ejection fraction and increase risk of myocardial infarction, congestive heart failure, and valvular disorders. Data on the combined effects of anthracycline and radiation remain sparse. A report of 1474 survivors of Hodgkin lymphoma younger than 41 years at treatment and followed for a median of 18.7 years has shed some light.[222] Risks of myocardial infarction and congestive heart failure were significantly increased, with standard incidence ratios of 3.6 and 4.9, respectively for survivors of Hodgkin lymphoma versus the general Dutch population. Mediastinal radiation alone increases the risks of myocardial infarction, angina pectoris, congestive heart failure, and valvular disorders (two- to sevenfold). The addition of anthracyclines further elevated the risks of congestive heart failure and valvular disorders from mediastinal radiation, with hazard ratios of 2.81 and 2.10, respectively. The 25-year cumulative incidence of congestive heart failure following combined radiation and anthracycline chemotherapy was 7.9%.

Other risk factors for cardiac disease, particularly coronary artery disease, must be considered. For example, data from the University of Rochester assessed the risk of coronary artery disease in survivors of Hodgkin lymphoma and also the prevalence of cardiac risk factors. The relative risk of cardiac death was 3.1 for males versus 1.8 for females. Other risk factors were more common than in the general population; among patients with Hodgkin lymphoma experiencing morbid cardiac events, 72% smoked, 72% were male, 78% had hypercholesterolemia, 61% were obese, 28% had a positive family history, 33% had hypertension, and 6% had diabetes.[223]

Summary and Other Key Points from QUANTEC Review[224]

The substructures of the heart, as well as the intersection of the heart and great vessels can be challenging to differentiate with

axial CT imaging, and the heart border is often difficult to differentiate from the adjacent liver and diaphragm. The heart moves with the respiratory and cardiac cycles, with different regions moving to different degrees. Several clinical factors, such as increasing age, comorbidities, and anthracycline exposure, appear to increase the risk of radiation-induced injury. Whereas based on limited data, there appears to be a dose or volume dependence for pericardial disease, cardiac mortality, and perfusion abnormalities. A heart V30 of >45% and a mean cardiac dose of >26 Gy are associated with a higher risk of pericarditis. A heart V30 to V40 of ~30% to 35% is associated with a ~5% excess risk of cardiac death at ~15 years. These dose-volume metrics likely oversimplify risk estimates related coronary artery disease, which are probably best correlated with high dose (>50 Gy) to small volumes of coronary artery.[215] In patients with breast and lung cancer, it is recommended that the irradiated heart volume be minimized as much as possible degree without compromising target coverage. In patients with lymphoma the whole heart should be limited to <30 Gy if the patient is treated with radiation alone, and 15 Gy for those also receiving anthracycline chemotherapy.

GASTROINTESTINAL SYSTEM: ESOPHAGUS

Organ Function and Clinical Significance

The esophagus is the muscle lined organ that allows and facilitates the transit of solids and liquids from the mouth to the stomach. The esophagus is a moveable (slightly), hollow, distensible organ. On CT images, the cross-sectional esophageal area/volume is highly variable. This may not accurately reflect the true anatomy of the organ. In gross esophageal specimens, the cross-sectional area of the esophagus is fairly uniform at all axial levels.[225]

Acute esophagitis is common, and is often severe, in patients receiving radiation for thoracic malignancies (e.g., esophageal cancer, primary lung cancer). Some patients may require a feeding tube or treatment interruptions due to acute esophagitis. Because most patients with thoracic cancers have a poor prognosis, acute toxicity may be considered more clinically relevant than late injury. Late esophageal complications include dysphagia, stricture, dysmotility, odynophagia, and rarely necrosis or fistula.

Dose-Volume Data

In a series from Washington University, grades 3 to 5 esophageal toxicity (acute and late) was associated with a maximal dose (*Dmax*) of >58 Gy, a mean dose of >34 Gy and the administration of concurrent chemotherapy.[226] The V55 was not significant. A Chinese study reported that maximal dose >60 Gy, as well as the use of concurrent chemotherapy were significant factors for esophageal toxicity (acute and late).[227] In a series from Duke University, the V50, the surface dose receiving ≥50 Gy (S50), the length of esophagus receiving >50 Gy to 60 Gy, and a circumferential *Dmax* >80 Gy were significant predictors of late esophageal toxicity.[228] A V50 of >32% or an S50 of >32% resulted in crude rates of ~30% late esophageal toxicity versus 7% below these thresholds ($p = 0.02$ and 0.04, respectively). With >3.2 cm of the esophagus receiving >50 Gy, late toxicity occurred in ~30% versus 4% in those with <3.2 cm receiving >50 Gy ($p = 0.008$). In another series from Duke, late grade ≥1 toxicity was correlated with several dose parameters: the entire circumference receiving ≥50 Gy and ≥55 Gy; 75% of the circumference receiving ≥70 Gy; and maximal percentage of circumference receiving ≥60 Gy to 80 Gy.[229] The rate of grade ≥1 late toxicity was ~5% in patients with a V50 to V70 of 0% to 30% versus ~25% in those with a V70 of 31% to 64% and ~10% in those with a V50 >60% (nonsignificant). Acute esophageal toxicity was the greatest predictor of late toxicity. In two studies, most of the patients who developed late grade ≥3 toxicity had developed acute grade ≥3, though roughly 25% to 40% of patients who developed grade ≥3 late toxicity had only grades 0 to 2 acute esophageal toxicity.[226,227]

From the data analyzed for QUANTEC, several studies noted an increased risk with increasing dose/volume parameters. However, because different studies considered different variables, optimal dose/volume predictors were considered elusive. Further, because different dose/volume parameters are correlated to each other, it may be that there are no true "optimal" parameters and that alternative predictive models will be equally useful. From a 2013 meta-analysis of 1082 patients treated with chemoradiation for non–small-cell lung cancer, esophageal V5 to V70 parameters (in 5-Gy increments) were all significant predictors of grade ≥2 esophagitis; on multivariate analyses V60 proved to be the most significant predictor of grades ≥2-3 esophagitis.[230] Recursive partitioning identified three risk groups: low (29% and 4% risk of grades ≥2 and ≥3 esophagitis with V60 <0.07%), intermediate (41% and 10% risk of grade ≥2 and ≥3 esophagitis with V60 ≥0.07% to 17%), and high (59% and 22% risk of grades ≥2 and ≥3 esophagitis with V60 ≥17%). These authors did not consider dose-surface metrics or esophageal length or circumference.

Summary and Other Key Points from QUANTEC Review[231]

The esophagus can be difficult to differentiate from surrounding soft tissues. Acute esophageal injury is much more common, and thus most studies have explicitly analyzed acute toxicity (which is not explicitly reviewed here). For acute and late injury, there is a dose response for a variety of threshold volumes (V20 to V70). A *Dmax* >55Gy to 60 Gy as well as esophageal surface, volume, length, and circumference receiving >50 Gy to 60 Gy appear to correlate with toxicity. Acute esophageal toxicity can result in late toxicity. It was not possible to identify a single-best threshold volumetric parameter for esophageal irradiation because a wide range of dose-volume parameters correlate with toxicity. Based on the RTOG 0617 dose escalation study for non–small cell lung cancer, it was suggested that the mean dose to the esophagus be kept <34 Gy; in that study, the esophageal V60 will also be reported. A recent meta-analysis suggests that V60 is most predictive for esophagitis.

GASTROINTESTINAL SYSTEM: STOMACH AND SMALL BOWEL

Organ Function and Clinical Significance

The stomach and small bowel aid in the digestion and absorption of food and nutrients. Symptoms from radiation-related late toxicities include dyspepsia, gastric ulceration, diarrhea, bowl obstruction, and bowel ulceration, fistula, or perforation. The primary long-term endpoints considered for the small bowel are stricture and diarrhea. For the stomach, perforation and ulceration are commonly considered. Several patient-related variables, such as history of diabetes, age, race, body habitus, and prior surgery, likely impact the risk of late toxicity.[232] Because stomach and small bowel are mobile and distensible, determining accurate dose-volume (or dose-surface) constraints are challenging. Factors affecting risk of late toxicity include total dose (with doses in excess of 40 Gy to 50 Gy increasing the risk of late complications), fractional dose, prior abdominal surgery (which increases the risk of bowel obstruction), and concurrent chemotherapy use.

Dose-Volume Data

Dose

Late radiation induced stomach injury has been reported to occur with increasing frequency with increasing doses. In a study from Walter Reed, the rates of gastric ulceration were 4% and 16% after treatment of <50 Gy versus >50 Gy. Similarly, the rates of perforation were 2% and 14% in the same dose cohorts. Overall, the dose of approximately 50 Gy to the stomach was associated with about a 2% to 6% incidence of severe late injury. The volume affect for late stomach injury is not well defined. For late small bowel toxicity, a dose of approximately 50 Gy is associated with obstruction or perforation rates that are approximately 2% to 9%. Prior abdominal surgery appears to increase the risk of late small bowel injury following radiation. In the European Organization for Research and Treatment of Cancer (EORTC) study, the rate of complications was 3% without prior abdominal surgery versus 12% with prior abdominal surgery.[233]

Dose Volume

There is a paucity of good quantitative data on dose-volume metrics that predict for gastric or bowel late toxicity. Nevertheless, there are data that demonstrate a volume effect. The risk of bowel obstruction among patients with rectal cancer whose fields extended to L1 or L2 was 30% versus 9% in those treated with pelvis only fields.[234] The University of Michigan investigated gastric and duodenal bleeding after radiation of patients with liver tumors.[235] Normal tissue complication modeling was consistent with a dose threshold (~60 Gy) for bleeding without a large volume effect.

A few studies published after QUANTEC correlated small bowel toxicity risks with dose-volume metrics. In a study of 46 patients with locally advanced pancreatic cancer, treated with concurrent gemcitabine and radiotherapy, duodenal V35 >20% was associated with a 41% risk of grade ≥3 small bowel toxicity (acute or late), versus 0% for a V35 <20%.[236] In another study of patients with locally advanced pancreatic cancer (n = 106), in which V40 to V60 was analyzed, a V55 ≥1 mL versus < 1 mL was significantly correlated with grade ≥2 toxicity (47% versus 9%, p = 0.0003).[237] In a study of 46 women treated with extended field radiation for gynecologic malignancies up to 65 Gy, only three patients experienced acute grade ≥3 gastrointestinal toxicity and thee patients experienced late grade ≥3 gastrointestinal toxicity (none of which was duodenal toxicity); V5 to V65 did not correlate with toxicity risks.[238] From a recent systematic review of women undergoing extended field radiation, a point maximum of 55 Gy to small bowel was estimated to yield a 10% toxicity risk within 5 years.[239]

Summary and Other Key Points from QUANTEC Review[240]

The stomach and the intestines are mobile structures with definite inter- and intrafraction motion. This makes some of the doses/volumes/outcomes data less certain. Two different approaches have been considered when defining small bowel volumes. Either the entire potential space of small bowel-containing volume (i.e., incorporating all regions where bowel can be situated),[241] or the actual visualized loops of bowel on the planning CT[242] can be considered as an organ at risk. Using the entire potential small bowel space, it is suggested that the small bowel exposed to V45 to V50 should be less than 195 cc to reduce acute toxicity (not discussed previously)[241]; while using the visualized loops of bowel, it is recommended that the V15 should be less than 120 cc.[242] A study (with neoadjuvant radiation for rectal cancer) published after QUANTEC predicts a 10% risk of grade ≥3 small bowel toxicity with a V15 <275 cc for contoured bowel loops and <830 cc for the peritoneal space.[243] Although these dose constraints were derived from acute toxicity data, they do provide guidelines that should help minimize risk of late toxicity as well. For the stomach, it is recommended to maintain the dose to the whole stomach to <45 Gy; a maximum point dose might be an important predictor of toxicity, but more data are needed to confirm this hypothesis.

GASTROINTESTINAL SYSTEM: RECTUM

Organ Function and Clinical Significance

The rectum is the terminal portion of the large intestines that functions as a temporary storage for feces, as well as providing the urge to defecate. The most common late radiation related rectal complication is bleeding. Rectal ulceration and fistula are much less common. Other late injuries include stricture and decreased rectal compliance, which can result in frequent small stools. The anus is also at risk of late complication including stricture and laxity, leading to fecal incontinence. Patients are at a higher risk of late rectal sequelae, including gastrointestinal bleeding, proctitis, diarrhea, and tenesmus, with higher maximal and mean rectal doses. Several patient-related variables, such as history of diabetes or vascular disease, inflammatory disease, and age may impact the risk of late toxicity.[232,244-246] Acute bowel toxicity appears to be correlated with late proctitis and increased stool frequency.[246] Prior abdominal surgery is also relevant.[247] An XRCC1 polymorphism has also been implicated as a risk factor for late rectal toxicity.[248]

Dose-Volume Data

Abundant dosimetric data has shown a correlation of risk with rectal volume and surface/rectal wall doses.[249-264] Table 14-3 summarizes many of these studies, also discussed here.

MSKCC has shown a significant difference in the DVHs between patients who developed rectal bleeding versus those who did not after conformal radiation for prostate cancer.[249] The percentage of rectum exposed to 62% and 102% of the prescription dose (70.2 Gy or 75.6 Gy) was significant; the rectal wall being encompassed by the 50% isodose line, higher maximal dose to the rectum, and smaller rectal volume were also significantly adverse risk factors.[249,250] In a study of 1571 patients treated at MSKCC, the use of IMRT and the lack of acute rectal toxicity predicted for lower risk of late rectal toxicity.[251]

An Austrian study found that a V59 of ≥57% resulted in increased grade 2 rectal toxicity (31% versus 11%, p = 0.003).[252] Two Italian multicenter studies found a significant dose volume effect from V50 to V70, with suggested cutoff values of V50 ≤60% to 65%, V60 ≤45% to 50%, and V70 ≤25% to 30%; the risk of grade ≥2 rectal complications was ~4% to 8% versus ~20% to 30% risk above and below the cutoff values.[253,254] A rectal volume <55 mL was also a significant risk factor for late bleeding. In the postprostatectomy setting, this Italian group demonstrated that a mean rectal dose ≥54 Gy, V50 ≥63%, V55 ≥57%, V60 ≥50%, and rectal volume <60 mL were predictive of late bleeding.[255]

In a randomized trial of 70 Gy versus 78 Gy from MDACC in the treatment of early- to intermediate-risk early stage prostate cancer, the risk of late grade ≥2 rectal complications was significantly greater with a rectal V70 ≥25% versus V70 <25% (46 versus 16%, p = 0.001).[256] A retrospective analysis from MDACC showed that the risk is a continuous function of dose and volume, with suggested cut-off points for lowering the

TABLE 14-3 Summary of Selected Studies Analyzing Dose-Volume Parameters Predictive of Rectal Toxicity

Author, Year (*Center*)	Patient population	Endpoint	Subgroup	Toxicity Rate
Wachter, 2001 (*Univ. Hosp. Vienna*)	Prostate cancer	Grade 2 Rectal toxicity	V59 ≥57% V59 <57%	31% 11%
Fiorino, 2002, 2003 (*Hosp. San Raffaele*)	Prostate cancer	Grade 2 Rectal toxicity	V50 ≤60%65% V60 ≤45%-50% V70 ≤25%-30% V50 >65% V60 >50% V70 >30%	4%-8% 4%-8% 4%-8% 20%-30% 20%-30% 20%-30%
Cozzarini, 2003 (*Hosp. San Raffaele*)	Prostate cancer s/p prostatectomy	Late rectal bleeding	Mean rectal dose ≤54 gy V50 ≤63% V55 ≤57% V60 ≥50% Mean rectal dose <54 gy V50 <63% V55 <57% V60 <50%	7% 7% 7% 7% 22% 21% 21% 19%
Huang, 2002 (*MDACC*)	Prostate cancer	Grade ≥2 Rectal toxicity	V70 ≥ 26% V70 <26%	54% 13%
Peeters, 2006 (*van Leeuwenhoek Hosp.*)	Prostate cancer	Rectal bleeding Requiring laser treatment or packed red blood cells Use of incontinence pads	V65 = 7%-23% V65 = 23%-29% V65 = 29%-36% V65 >36% Anal mean <28 gy Anal mean 28 gy-38 gy Anal mean 38 gy-46 gy Anal mean >46 gy	<1% 4% 11% 10% <5% 7% 9% >20%
Boermsa, 1998 (*NKI*)	Prostate cancer	Rectal bleeding	Rectal wall v65 <40% Rectal wall v70 <30% Rectal wall v75 <5% Rectal wall v65 >40% Rectal wall v70 >30% Rectal wall v75 >5%	0% 0% 0% 10% 9% 9%
Kupelian, 2002 (*Cleveland Clinic*)	Prostate cancer	Rectal bleeding	Rectal wall v70-v78 <15 mL Rectal wall v70-v78 >15 mL	5% 22%
Vargas, 2005 (*William Beaumont*)	Prostate cancer	Grade ≥2 Rectal toxicity	V70 <25% V70 = 25%-40% V70 >40% Rectal wall v70 <5 mL Rectal wall v70 5 mL-15 mL Rectal wall v70 >15 mL Rectal wall v70 <25% Rectal wall v70 = 25%-40% Rectal wall v70 >40%	9% 19% 24% 8% 13% 32% 9% 18% 25%
Pederson, 2012* (*Univ. Chicago*)	Prostate cancer	4-Year Grade ≥2 Gastrointestinal toxicity	V70 ≤10% V65 ≤20% V40 ≤40% V70 ≤20% V65 ≤40% V40 ≤80% V70 >20% V65 >40% V40 >80%	0% 0% 0% 8% 8% 8% 15% 15% 15%

**Published after QUANTEC review.*

complication risk: V60 ≤41%, V70 ≤26%, V76 ≤16% or 3.8 mL and V78 ≤5% or 1.4 mL.[257] At 6 years, the risk of late grade ≥2 rectal complications was 54% for patients with a rectal V70 ≥26% versus 13% for a V70 <26%.

Among patients treated on the Dutch randomized trial of 68 versus 78 Gy,[245] the mean anal dose (as well as V5 to V60) significantly predicted the rate of grade ≥2 gastrointestinal toxicity (at 4 years, 16% versus 31% for a mean dose <19 Gy versus >52 Gy).[258] The mean dose (as well as V5 to V70) also predicted the risk for use of incontinence pads (at 5 years, <5% versus >20% for a mean dose <28 Gy versus >46 Gy). The anorectal V65 (as well as V55 to V60) was significantly predictive of rectal bleeding (4-year risk <1% and >10% for a V65 <23% versus >29%).[258]

The percentage of rectum or rectal wall receiving a given dose can be subjective (i.e., based on how much of the rectum

is segmented); using the absolute volume of rectum[262] or rectal wall is less subjective, though defining the rectal wall is not standardized. The rectum extends from the rectosigmoid junction to the anus, with the inferior extent generally defined as the level of the anal verge, above the anus, the ischial tuberosities or 2 cm below the ischial tuberosities. Dosimetric parameters of the rectal wall or rectal surface may be more predictive of some late toxicities.[265] William Beaumont Hospital demonstrated that the rectal volume as well as rectal wall V50 to V70 values predict late toxicity, with rectal wall being more predictive of grades 2 to 3 late effects; acute toxicity is also predictive of late toxicity.[259] MDACC has also shown rectal wall to be better predictive of late rectal bleeding.[260] From a 1998 Dutch study, recommendations for the volume of rectal wall exceeding 65 Gy, 70 Gy, and 75 Gy are <40%, <30%, and <5%, respectively.[261] Data from the Cleveland Clinic[262] and William Beaumont[259] showed a significantly increased risk of grade ≥2 rectal toxicity with rectal or rectal wall V70 to V78 of ≥15 mL versus <15 mL (~20% >30% versus ~5% to 10%).

More than a dozen NTCP modeling studies have been published. In one study, many individual models did not fit clinical data accurately, so the authors suggested that consolidating risk estimates from multiple models could yield more accurate predictions of toxicity risks.[266]

Summary and Other Key Points from QUANTEC Review[267]

The rectum is mobile and distensible, and therefore its position and volume can vary between and during radiation fractions. The superior and inferior borders of the rectum are not always easy to define on CT imaging. Most of the published studies of rectal toxicity address late rate rectal bleeding. However, most toxicity scoring systems are nonspecific, in that a patient can be considered as having a grade 2 or 3 event on the basis of diarrhea, stool frequency, rectal mucus, or bleeding. For patients undergoing radiation therapy for prostate cancer, it is recommended to limit the V50, V60, V65, V70, and V75 to less than 50%, 35%, 25%, 20%, and 15%, respectively. From a Phase I/II RTOG study published after the QUANTEC review,[268] in which 1009 men received 68.4 to 79.2 Gy, in 1.8 to 2.0 Gy fractions, rectal doses <60 Gy had no detectable impact on the fit of the NTCP model, and multivariate modeling showed only V75 to be significantly associated with late rectal toxicity.[269]

GASTROINTESTINAL SYSTEM: LIVER

Organ Function and Clinical Significance

The liver is a vital organ, with a breadth of metabolic functions including metabolism of ingested nutrients, detoxification, protein synthesis, bile production, glycogen storage, and red blood cell decomposition. Sequelae of radiation-induced liver damage include elevation of liver enzymes, ascites, jaundice, asterixis (tremor), encephalopathy, or coma. One of the most important patient-related predictors of susceptibility to liver damage is the baseline liver function, which is characterized by the Child-Pugh scoring system and accounts for serum bilirubin, albumin, coagulation times, the presence of ascites, and encephalopathy. The risk of radiation toxicity appears to be greater in the patient population with primary liver malignancies as opposed to liver metastases.

Dose-Volume Data

The RTOG 84-05 Phase I study, in which patients with liver metastases received whole liver radiation with 1.5 Gy twice daily fractions, none of the 122 patients who received 27 Gy to 30 Gy developed biochemical evidence of liver toxicity, compared to 5 of 51 who received 33 Gy.[270] In a study of 79 patients treated with liver radiotherapy at the University of Michigan, only those patients who received whole liver radiotherapy (1.5 to 1.65 Gy BID, with or without a boost) developed late radiation toxicity (crude risk of 9/33 versus 0/46 treated with partial liver radiation). Those who received a mean dose of >37 Gy (delivered twice daily with infusional fluorodeoxyuridine) and less sparing of normal liver had greater risk of late radiation toxicity (crude risk of 9/34 versus 0/45).[271]

Several studies have explored partial liver radiation in more detail, many of which used mean liver dose as a dose-volume metric. In a later study from University of Michigan, no late liver toxicity was observed with a mean liver dose <31 Gy, with NTCP models being optimized with a TD50 of 43 Gy and TD5 of 31 Gy for whole liver radiation; the risk of complications was strongly dependent on volume of liver irradiated.[272] Other risk factors for late toxicity included primary hepatobiliary carcinoma (as opposed to metastatic disease), use of bromodeoxyuridine chemotherapy (as opposed to fluorodeoxyuridine), and male gender. The NTCP models predict a TD5 in excess of 80 Gy if less than one third of the liver is irradiated. With irradiation of two thirds of the liver, the TD5 is on the order of 50 Gy and TD50 on the order of 60 Gy.

In a series from Taipei, patients with irradiated hepatocellular carcinoma who developed late liver toxicity had received a mean hepatic dose of 25 Gy (versus 20 Gy in patients without toxicity, $p = 0.02$).[273] The TD50 for whole liver, two thirds liver, and one third liver radiation were modeled to be approximately 43 Gy, 50 Gy, and 67 Gy, respectively. The TD5 for whole liver, two thirds liver, and one third liver radiation were modeled to be approximately 25 Gy, 28 Gy, and 38 Gy, respectively. The volume effect of liver radiation was less in this series. In another study from the same group, the mean liver dose and hepatitis B virus positivity were significant predictors or radiation toxicity; with NTCP modeling, the TD50 was ~50 Gy.[274]

In a Korean study of 105 patients with hepatocellular carcinoma, the mean dose and V20 to V40 parameters to total liver and normal liver (total liver minus GTV) were investigated.[275] The total liver V30 was the only significant parameter ($p < 0.001$). Grade ≥2 liver toxicity was observed in only 2.4% of patients with a total liver V30 ≤60% and 55% of patients with a total liver V30 >60% ($p < 0.001$). Another Korean study demonstrated a correlation of V15 with reduction in Child-Pugh score and recommends a V15 cutoff of <43.2%.[276]

The data from Asia differ from Western data, perhaps reflecting differences in the treated malignancy (mostly metastases in the West versus primary liver cancer in Asia, which often occurs in the setting of liver cirrhosis), radiation fractionation, and or concurrent therapies delivered with radiation.

Summary and Other Key Points from QUANTEC Review[277]

An understanding of radiation-induced liver toxicity necessitates an appreciation of liver motion. Extensive work has described liver motion as a result of breathing, which can displace the liver in excess of 2 cm. Preexisting liver dysfunction secondary to comorbid conditions such as hepatitis B or C infection and cirrhosis appears to increase the susceptibility to radiation-induced liver injury. For patients with liver metastases undergoing partial volume liver radiation, the risk of radiation induced liver toxicity appears to be more dependent upon the volume of liver irradiated. Partial volumes of liver can tolerate relatively high doses. Tolerances however

are lower for patients with primary liver cancer (who are more apt to have underlying liver disease). For whole liver radiation, doses ≤28 Gy to 30 Gy in 2 Gy fractions (28 Gy for liver metastases and 30 Gy for primary liver cancer) and ≤21 Gy in 3 Gy fractions are recommended. For partial liver radiation, treated with standard fractionation, the mean dose to normal liver (liver minus GTV) is suggested to be <30 Gy for liver metastases and <28 Gy for primary liver cancer.

GENITOURINARY SYSTEM: KIDNEY

Organ Function and Clinical Significance

The kidney functions to remove wastes, regulate electrolytes, produce erythropoietin, which stimulates red blood cell production, and modulate blood pressure through the renin-angiotensin pathway as well as through fluid/electrolyte balance. Perhaps late-kidney toxicity is underreported because of its long latency as well as toxicity being attributed to more common causes. Late renal complications include decreased kidney function, azotemia, hypertension, and kidney atrophy. Chronic radiation nephropathy in its mildest forms may not be diagnosed until years after therapy. Clinically silent abnormalities may include only proteinuria and azotemia with urinary casts and mild or no hypertension. Certainly, patients with only one functioning kidney or poor baseline renal function, are more vulnerable to damage (with or without symptoms) for any given volume of renal irradiation. Platinum and ifosfamide based chemotherapeutics can also impact renal function. Cisplatin at dosages greater than 200 mg/m^2 can result in glomerular or tubular injury and renal insufficiency.[278] Ifosfamide can cause glomerular and tubular toxicity, with renal tubular acidosis, or Fanconi syndrome. A study examining grades 3 to 4 ifosfamide-induced nephrotoxicity among adult and pediatric patients found a prevalence of 17% in both; neither age nor cumulative ifosfamide dose were risk factors.[279]

Dose-Volume Data

Several studies have investigated whole kidney dose tolerance, either after whole abdominal radiation or total body irradiation (generally delivered with lower fractional doses). Renal toxicity can occur after bilateral kidney doses ≥10 Gy, and the risk is quite high (50% to 80%) after 20 Gy. Thus, the kidneys have a relatively low threshold for damage. The dose volume-effect on the kidneys has been long recognized, even before the planning CT because kidneys are well visualized on plain simulation films. From these studies, when greater than half of the kidney receives doses >20 Gy to 30 Gy, or greater than one third receives >30 Gy to 40 Gy, patients are at increased risk of developing renal atrophy, decreased kidney function, and hypertension.[2,280-282]

There is little published on dose-volume parameters to predict late renal toxicity, in part because clinicians make an effort to minimize the volume of kidney exceeding the accepted tolerance dose. Low doses, 10 Gy to 15 Gy, to large volumes of kidney increase the risk of nephrotoxicity,[283-285] whereas smaller volumes of kidney exceeding ~20 Gy to 25 Gy can result in late renal toxicity.[283,285-287] In a series from Heidelberg, normal tissue complication modeling was used estimate the risk of late complications.[286] A median dose of ~17.5 Gy to 21.5 Gy and 22 Gy to 26 Gy corresponded to a 5% and 50% late complication risk (anemia, azotemia, hypertension, and edema), respectively. In another German study, reduced kidney function, as measured by scintigraphy changes, was analyzed as a function of dose and volume.[283] After irradiation of 10% to 30%, 30% to 60%, and 60% to 100% of the kidney volume to 20 Gy, the incidence of reduced activity was <10%, ~40%, and >70%, respectively. After irradiation of 10% to 30%, 30% to 60%, and 60% to 100% of the kidney volume to 30 Gy, the incidence of reduced activity was ~35%, >90%, and >98%, respectively. In a Dutch study of patients with gastric cancer (treated with concurrent radiation and cisplatin or capecitabine), the left kidney V20 ≥64% and mean left kidney dose of ≥30 Gy were associated with a significant decrease in left kidney function as compared to the right.[287] In a recent study of 125 patients with upper gastrointestinal malignancies, kidney V5 to V20 and mean kidney dose were significantly correlated with reduction in creatinine clearance.[288] A 15% to 20% decrease in creatinine clearance was associated with a V5 >50%, V10 >30%, V20 >30% (or >100 mL), and mean kidney dose >10 Gy.

Summary and Other Key Points from QUANTEC Review[289]

Radiation-associated kidney injury has a poorly understood pathophysiology and is likely underreported because of its long latency. For whole (bilateral) kidney radiation (not discussed), recommendations are for doses <10 Gy delivered over 5 to 6 fractions (at <6 cGy/min dose rate) and <15 to 18 Gy for radiation delivered over ≥5 weeks. For partial kidney radiation, the volume of kidneys receiving >20 Gy predicts risk of renal toxicity. The recommendation for partial kidney radiation is to maximally spare the kidneys and maintain a mean dose of <18 Gy to both kidneys or maintain a V6 <30% if one kidney cannot be adequately spared.

GENITOURINARY SYSTEM: BLADDER

Organ Function and Clinical Significance

The bladder is a highly distensible organ that collects urine. Symptoms from late radiation related toxicities include increased urinary frequency, hematuria, and dysuria. Necrosis, contracted bladder, and hemorrhage are less common, severe effects. Perhaps late-bladder toxicity is underreported because of its long latency as well as toxicity being attributed to more common causes. Because the bladder is mobile and distensible, determining accurate dose-volume (or dose-surface) constraints are challenging. Endpoints for bladder injury can reflect focal damage (e.g., bleeding) or more global injury (reduced bladder capacity with secondary urinary frequency). Recent data suggests that acute toxicity is predictive of late toxicity (particularly urinary frequency and hematuria) risks and pretreatment bladder dysfunction is predictive of late urinary symptoms (particularly urinary frequency, incontinence, and slow stream).[246]

Dose-Volume Data

Detailed dose-volume (or dose-surface) constraints have not been published, in part because of the complexities of assigning dose-volume metrics to a mobile, distensible structure. For whole bladder irradiation, doses in excess of 60 Gy, particularly with fraction sizes >2 Gy or accelerated radiation regimens, result in a significant risk of late grade ≥3 toxicity. Risks are lower when the whole bladder receives 45 Gy to 55 Gy, followed by a boost to >60 Gy to a portion of the bladder, though toxicity risk has not been correlated to dose-volume metrics. A recent Fox Chase Cancer Center study of 503 patients with prostate cancer examined urinary bladder V60 to V70 and area under the DVH, with bladder defined as just the bladder wall ("hollow" structure) or entire bladder and contents ("solid" structure); with multivariate analyses, the

mean bladder dose and area under the DVH were significant predictors of grade ≥2 genitourinary toxicity.[290] In a recent University of Chicago study of 296 patients with prostate cancer (in which the bladder was contoured as whole organ, after drainage and infusion of 120 mL of saline), no bladder dose-volume relationships were associated with the risk of grade ≥2 genitourinary toxicity.[263] With prostate cancer treated to high doses (≥72 Gy), the inferior portion of the bladder (e.g., trigone area) also receives ≥70 Gy. This tends to be well tolerated with respect to bladder toxicity. Arguably, the urinary toxicity that does develop after radiation results in part from the prostatic urethra receiving suprathreshold doses.

Summary and Other Key Points from QUANTEC Review[291]

The primary limitations of deriving strict dose-volume guidelines for the urinary bladder include the lack of robust 3D dose/volume data as well as the complicating factor that the bladder is a mobile structure of variable volumes/position. For whole bladder radiation, the reported risks of grade ≥3 toxicity in doses of 50 Gy to 60 Gy range from ≤5% to 40%. This variation is likely attributable to the challenges of correlating toxicity with dose delivered to a mobile structure, which is even more problematic when correlating partial volume exposures to toxicity. With the caveat of these issues, bladder constraints of ≤15%, ≤25%, ≤35%, and ≤50% receiving ≥80 Gy, ≥75 Gy, ≥70 Gy, and ≥65 Gy, respectively, as recommended in the RTOG 0415 study of prostate cancer, are suggested. The protocol advises an empty bladder at the time of simulation and treatment; the bladder is segmented from the base to the dome.

GENITOURINARY SYSTEM: PENILE BULB

Organ Function and Clinical Significance

The penile bulb is located at the base of the penis, caudal to the prostate.[292,293] Radiation dose to the penile bulb can affect erectile function, either as a direct result of damage to this structure (less likely) or damage to surrounding structures, whose radiation-induced damage is correlated with the dose exposure of the penile bulb. The most common scenario in which the penile bulb is irradiated is in the treatment of prostate cancer. IMRT is often used to minimize the dose to the penile bulb.[294,295] Interpretation of erectile dysfunction and the effect of penile bulb dose is complicated by preexisting function, comorbid conditions, and other therapies that may hinder (e.g., hormonal therapy) or help (e.g., drugs used to treat erectile dysfunction) erectile function. Also, determining which patients experience erectile dysfunction—a toxicity with varying severity—also complicates data interpretation.

Dose-Volume Data

Several studies have investigated dose-volume parameters to predict risk of erectile dysfunction. In several studies, no correlation was discerned for penile bulb dose and erectile function.[295-297] In one study, attempts were made to reduce the dose to the penile bulb (mean dose of 25 Gy), and thus few patients received high dose to the penile bulb.[295] In another study of 70 patients, no correlation was found for mean dose or maximal dose to the penile bulb, penile crura, or superiormost 1 cm of the penile crura; DVHs were also compared and found to be similar.[296]

In a small (21 patients), early study from University of California–San Francisco, patients receiving a D70 of <40%, 40% to 70%, and >70% to the penile bulb had a 0%, 80%, and 100% risk, respectively, of experiencing radiation-induced impotence.[298] In a study (29 patients) from Thomas Jefferson University, several dose-volume metrics were analyzed; a D30 >67 Gy, D45 >63 Gy, D60 >42 Gy, and D75 >20 Gy to the proximal penis were correlated with increased erectile dysfunction as well as ejaculatory function.[299] In a study from Royal Marsden Hospital, a D90 >50 Gy to the penile bulb was associated with significantly worse erectile function, whereas D15, D30, and D50 showed similar (albeit not significant) trend toward increased doses in impotent vs. intermediate potency versus potent patients.[300] Another recent small (19 patients) study found that mean dose <50 Gy was predictive of erectile potency.[301]

The largest study (158 patients) to date to investigate penile bulb dose is an analysis of the RTOG 9406 dose-escalation study.[302] A median dose of ≥52.5 Gy was associated with a greater risk of impotence (50% versus 25% at 5 years).

Summary and Other Key Points from QUANTEC Review[303]

There is some uncertainty regarding the critical anatomic structures for radiation-induced erectile dysfunction. Several studies from different academic centers have correlated the dose-volume exposure to the penile bulb with erectile dysfunction and have impressively similar results. Based on published data, it is recommended to keep the mean dose to 95% of the penile bulb <50 Gy and to limit the D70 and D90 to 70 Gy and 50 Gy, respectively.

CONCLUSIONS

The study of radiation-associated normal tissue injury has interested investigators for decades. Much progress has been made over the last 20 years. Additional technologies (e.g., gating, image-guided therapy) will provide some refinements in these physical advances. The emergence of novel technologies such as stereotactic body radiotherapy/stereotactic ablative body radiotherapy (SBRT/SABR), image-guided radiotherapy (IGRT), intensity-modulated radiotherapy (IMRT), charged particle therapy and four-dimensional planning have resulted in the increasing use of hypofractionated radiation, more conformal radiation delivery, and heterogeneous dose distributions (i.e., dose painting). Thus, future studies should account for fraction size and small-volume high-dose exposures. Eventually, models predicting dose/volume injury will likely more consistently consider the underlying physiology and substructures of organs, potential interactions between organs and differences in regional physiologic importance (e.g., different regions of the kidney being more important such as the cortex versus the medulla, different regions of the heart being more important, such as the coronary arteries or the left ventricle). There is a need to gain further understanding of the biological underpinnings of radiation-associated normal tissue damage. This will hopefully improve our abilities to predict, prevent, and treat radiation-associated normal tissue injury. As we employ more advanced technologies to further limit normal tissue exposure to lessen the risk of radiation-associated injury, we need to be careful not to compromise target coverage. Missing the tumor to avoid a grade 2 (or even grade 3 injury) might not be a reasonable trade-off, as a local tumor recurrence can be morbid. There are several published data sets that demonstrate that this is not a theoretical concern. In patients with orbital tumors and prostate cancer, more conformal techniques (applied to reduce normal tissue risks) have been associated with poorer clinical tumor control outcomes.[304,305] Radiation oncology is a dynamic field with constantly emerging technologic advances. In tandem with these advances is the critical

need for radiation oncologists to build their understanding of the normal tissue consequences of radiation administration. Not only do we need to explore associations of normal tissue damage with volume, dose, fraction size, and particle type, but we need to integrate this with the equally rapid evolution of novel systemic therapies and our pursuit of the pathophysiologic (including molecular genetics) basis of normal tissue injury.

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CHAPTER

15 Brachytherapy

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GENERAL PRINCIPLES

Brachytherapy is arguably the most conformal of all the modes of radiotherapy. Accurate placement of sources directly in the target area allows for precise dose delivery to the target with unparalleled sparing of normal adjacent tissue. Although a conformal therapy, it is by nature nonhomogenous in dose delivery, with the advantage that much of the central regions of target get a greater dose than the minimum prescribed dose covering the target volume.

The physics and radiobiology of brachytherapy are areas of great breadth and scholarship and are described elsewhere. In this chapter our aim is to provide the reader with a set of up-to-date references and more importantly an experience-based guide to the initiation and development of a brachytherapy program.

Brachytherapy takes advantage of the physical process of radioactive decay; an exponential phenomenon represented in general terms by the equation: $A = A_0\, e^{-\lambda t}$

Where A_0 is the initial activity, t is the elapsed time, and λ the decay constant (ln2/half-life).

This decay releases energy, which is deposited as dose to the target structure.

The primary clinical isotopes in use currently are shown in Table 15-1. Generally photon-emitting beta, gamma, and x-ray emitters are employed. High linear energy transfer (LET) emitters such as neutron and alpha sources are seldom encountered clinically in brachytherapy. The dose rates of treatment delivery vary and are detailed in Table 15-2. Isotope selection is based on the emission type, the energy of the emission and half-life of the isotope. Cost and availability of the isotope are also a practical consideration.

Developing a brachytherapy physics treatment program can at first seem daunting. However the fundamentals of any program can be reduced to:

- What source do we wish to use in terms of energy, half-life, and emission?
- Can we confirm its position?
- Can we control its duration?
- Can we accurately anticipate, calculate, and verify dose distributions?
- Can we minimize risk to the patient and staff?

Practitioners are referred to American Association of Physicists in Medicine (AAPM) TG 43[1] and supplements for standardization of dose calculation.

Time, Distance, and Shielding

Good practice allows the practitioner to use the aforementioned physical entities to maximize efficiency and safety. Of the three parameters, distance, because of the inverse square relationship with dose, can be most useful in reducing dose to staff. The use of long-handled implements for source handling is recommended. Preplanned choreography of source loading and unloading and thoughtful layout of sources and equipment can reduce the time of exposure and hence dose to staff or patients. Finally the use of appropriate afterloading techniques and appropriate barriers can maximize the shielding of personnel from the radioactive sources. In the United States, the Nuclear Regulatory Commission has a guidance and compliance document 10CFR35,[2] which specifies regulations pertaining to authorized users of radioactive by-products, license requirements, equipment specifications, and the reportage of medical events. Some states—agreement states—have local regulation that meet or exceed these federal requirements.

Essential to a brachytherapy program is the ability to independently verify the stated activity of any received radioisotope before administration. The physics unit should have a variety of appropriately calibrated and traceable well-chambers and electrometers with seed specific seed holders.

Planning

Central to good brachytherapy planning practice is the importance of good geometry. The spacing of sources or catheters in regular arrays and patterns mitigates the later need to overmodulate the source dwell times or position. The historical planning techniques of Paterson-Parker,[3] Quimby,[4] and Paris[5] systems serve as safe starting points from which minor planning modifications can be made.[6]

Brachytherapy practitioners may use three principal planning approaches. A single site example, Iodine-125 (^{125}I) seed placement for prostate cancer, is used for illustration.

Preplanning

The prostate volume is assessed using three-dimensional (3D) imaging: ultrasound, magnetic resonance imaging (MRI), or computed tomography (CT). An initial plan is run to evaluate pubic arch interference, volume of target and the number, and activity of sources required. With practice each institution can make an accurate determination of the number and activity of seeds to be ordered based on the target volume. The configuration of needles, seeds, and spacers is determined and prepared before the procedure and brought into the operating room (Figure 15-1, *A, B*).

Real-Time/Dynamic Planning

In this scenario, the plan is developed during the operative procedure. Some prepreparation is needed to assure adequate supplies are available for any eventualities. Advantages include the ability to dynamically compensate for any needle or seed misdirection that may occur during insertion with adjustments to subsequent needle or seed insertion. Secondly, during the brachytherapy procedure edema secondary to needle insertion can be compensated for.

Postplanning

This is used as a passive assessment following the implant. This technique is best practiced by experienced users who will position seeds or catheters a priori with a good idea of the likely dosimetric outcome. Manual or automated seed finding is employed, usually using CT imaging. Postsurgical edema

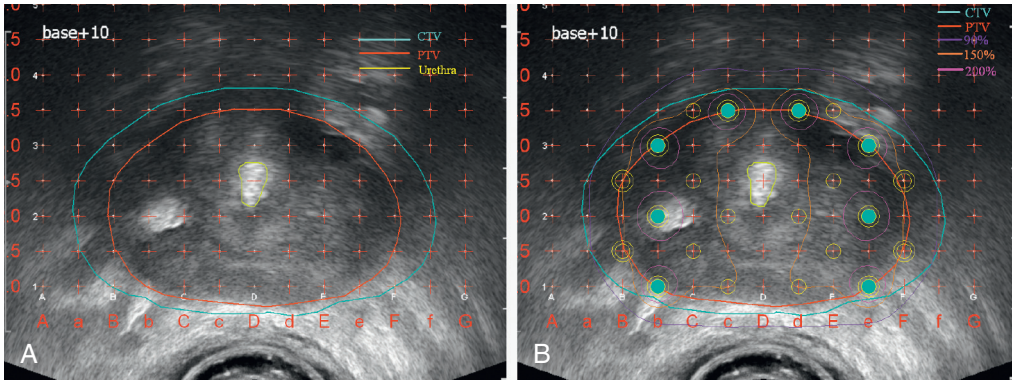


Figure 15-1 **A,** Volumes drawn on prostate transrectal ultrasound for preplanning. **B,** Preplanned dose distribution and seed location for treatment of prostate cancer with vLDR permanent seeds.

TABLE 15-1 Radio-Isotopes in Common Clinical Use with Their Relevant Physical Properties

Isotope	Half-Life	Emission Type	Mean Therapeutic Energy	Half Value Layer mm of Lead
Iodine-125	59.6 d	Gamma	28 keV	0.025
Palladium-103	17 d	Gamma	21 keV	minimal
Cesium-131	9.6 d	Gamma	29 keV	minimal
Cesium-137	30 yr	Gamma	662 keV	5.6
Iridium-192	74.2 d	Gamma	380 keV	2.5
Gold-198	2.7 d	Gamma/Beta	412 keV	2.7
Strontium-90/Yttrium-90	28.8 yr/2.7 d	Beta	2.27 MeV	>1
Ruthenium-106	373 d	Beta	3.54 MeV	>1
Californium-252	2.6 yr	Neutron	2.3 MeV	*

TABLE 15-2 Brachytherapy Dose Rates and Common Clinical Sites of Use

Definition	Rate of Dose Delivery	Common Clinical Sites
High dose rate (HDR)	>12 Gy/hr	Cervix, endometrium, vaginal
Low dose rate (LDR)	0.4-2 Gy/hr	Gynecologic, sarcoma
Very low dose rate (vLDR)	<0.4 Gy/hr	Prostate, lung
Pulsed dose rate (PDR)	>12 Gy/hr delivered over multiple pulses per day	Gynecologic, head and neck

and resolution of the same may be tracked at intervals; day 0, day 1, and day 30 may be used as proxies for initial, near maximum edema, and steady-state seed configurations, respectively.

Planning Systems

Brachytherapy planning systems are commonly license add-ons to external beam systems and require modules for DICOM import/export, contouring, 3D display dose volume analytics. The AAPM TG 53[7] offers a quality assurance (QA) strategy to assure contour quality, positional fidelity, and accurate dose calculation in the system. Commercial isotopes have been evaluated using the TG 43[1] protocols and competent systems will have standard seed configurations preloaded and accommodate manual entry of new seed data.

CLINICAL SCENARIOS

Gynecologic Cancers

Cervical Cancer

Cervical cancer was one of the first tumors to be treated with brachytherapy with initial reports of cervix low dose rate (LDR) brachytherapy using radium published in 1903. The original principles of treatment with a central tandem and ovoids placed against the cervix have remained, although fortunately we have moved away from the use of wine corks as applicators. For many years, a fixed dosimetry technique based on the Manchester principles was used to deliver a defined dose to point A 2-cm superior and lateral to the external os. This was then enhanced by the use of the International Commission on Radiation Units (ICRU) rectal and bladder points to predict toxicity to organs at risk. However, the advent of 3D imaging moved cervix cancer brachytherapy away from point dosing and estimation of dose to organs at risk to volumetric dosing and precise determination of maximal dose received. This has resulted in fewer toxicities and the ability to deliver higher doses, which results in higher cure rates.[8,9] It has also moved treatment in general away from LDR and toward high dose rate (HDR) and pulsed dose rate (PDR) brachytherapy with the ability to optimize dose and sculpt it around the organs at risk. Randomized studies have shown the equivalence of LDR to HDR with the possibility of lower toxicity with HDR.[10] There are no randomized studies of PDR versus LDR or HDR but retrospective data indicate they are likely to be comparable.

The brachytherapy applicator is generally placed operatively. A preoperative MRI close to the time of brachytherapy improves applicator selection and target definition.[11] The

patient may receive general anesthesia or regional anesthesia. Analgesia can be maintained throughout the length of a PDR implant or a single-insertion fractionated HDR implant using a spinal catheter.[12] Spinal anesthesia does not cause tumor hypoxia during an HDR implant.[13] Examination under anesthesia confirms the preoperative imaging findings. The cervix is dilated and a uterine tandem is placed, preferably using ultrasound guidance; see Figure 15-2, *A, B*.[14] A variety of applicators are available for intracavitary brachytherapy. For tumors more than 5 cm, the addition of interstitial needles into specialized applicators[15] is becoming more common because it has brought the ability to deliver interstitial brachytherapy to a wider group; see Figure 15-3. Interstitial template applicators such as the MUPIT[16] or the Syed-Neblett[17] applicator should be used to treat disease with marked lateral or vaginal extension, although it is important to maintain a degree of central dose heterogeneity (in contrast to the heterogeneity preferred in interstitial implants in other areas of the body) to maintain the central cervix doses needed for cure.[18] Studies of intensity modulated radiation therapy (IMRT) versus brachytherapy show that external beam radiation therapy (EBRT) techniques cannot deliver the high-dose regions that are required for cure, so brachytherapy remains a necessary component of treatment.[19]

Because of anatomy of the pelvis, the bladder and rectum always receive a proportion of the radiation dose. This dose varies according to physiological variations (e.g., the bladder dose may vary according to the extent of bladder filling, which may also affect the amount of small bowel in the field).[20] The traditional ICRU reference points[21] have been widely used in gynecologic brachytherapy since their inception. However, in the era of CT- and MRI-based gynecologic brachytherapy treatment planning, it has been shown in cervix cancer brachytherapy that the ICRU reference points do not provide a good surrogate for normal tissue dose evaluation in the pelvis.[22] The GEC/ESTRO and ABS recommendations for normal tissue

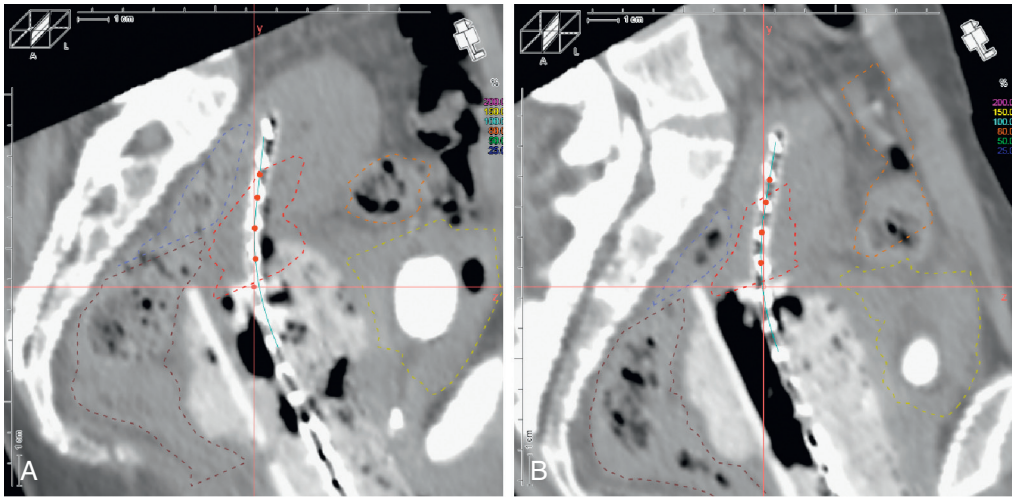


Figure 15-2 Sagittal planning CT image demonstrating placement of uterine tandem without ultrasound guidance, causing a posterior myometrial perforation (not penetrating serosa), and with ultrasound guidance, showing the tandem within the uterine cavity.

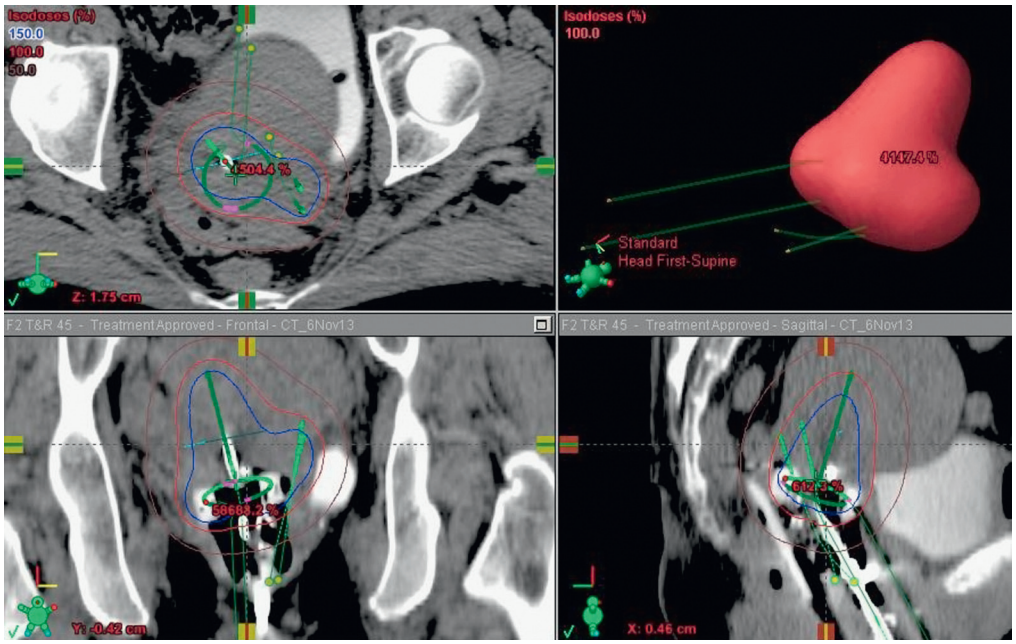


Figure 15-3 Illustration of tandem and ring with interstitial needles allowing additional dose coverage to tumor.

dose evaluation in cervical cancer based on CT- or MRI-based treatment planning allow a much more accurate determination of the doses received by the bladder and the rectum during cervical tandem and ring brachytherapy.[23] This allows not only better prediction of late effects but also dose sculpting using HDR optimization to ensure clinical target volume (CTV) coverage while minimizing normal tissue irradiation. Although devised for cervical brachytherapy dosimetry, these recommendations are generally used for evaluation of treatment plans in all areas of gynecologic brachytherapy.

Endometrial Cancer

Brachytherapy for the management of endometrial carcinoma was first described by Heyman in 1935, before the routine use of hysterectomy for uterine cancer.[24] Endometrial cancer is the most common gynecologic malignancy in the United States and the incidence is predicted to rise as obesity rates increase. Fortunately, the majority of patients with endometrial cancer are caught at an early stage because of vaginal discharge and bleeding. The use of radiation alone has now evolved and the primary treatment for endometrial cancer is surgery, total abdominal hysterectomy (TAH), and bilateral salpingo-oophorectomy (BSO).

Vaginal cylinder brachytherapy can be used in the treatment of selected gynecologic malignancies.[25-27] It may be indicated as adjuvant treatment following hysterectomy or for vaginal recurrence of gynecologic cancer in selected patients. The majority of patients receiving adjuvant radiotherapy will have EBRT to the whole pelvis followed by a fractionated course of brachytherapy. The use of pelvic radiotherapy in selected stage I patients has been examined in randomized trials[28-30] and a Cochrane meta-analysis.[31] The three main trials (including PORTEC[29,30] and GOG 99[32]) showed that the addition of pelvic radiotherapy to surgery resulted in significantly lower rates of local relapse but no difference in overall survival (OS). The lack of a difference in OS may be because of these patients already have a low risk of relapse and the sample sizes of the trials may be too low to accurately assess OS, especially in view of high rates of intercurrent illness in this patient population. Also, salvage radiotherapy to the vagina in the event of relapse is generally successful. The Cochrane meta-analysis found that the number of patients needed to treat to prevent one local recurrence was 16.7.[31] In patients with multiple high-risk factors there was a trend toward improved OS with pelvic radiotherapy.

The most common site of relapse in early stage endometrial cancer following surgery alone is the vaginal vault.[33] Adjuvant primary vaginal vault irradiation has been shown to decrease the incidence of vaginal apex recurrence in endometrial cancer from 12% to 15% to as low as 0% in selected patients, although it has no impact on OS.[25,34] Selected patients may have vaginal cylinder brachytherapy alone as adjuvant radiotherapy (e.g., patients with a well-differentiated adenocarcinoma of the endometrium with myometrial invasion >50%, which gives similar regional control rates to pelvic EBRT with significantly less toxicity).[25,34] The use of HDR vaginal cylinder brachytherapy is well established.[35-37] The role of pelvic lymphadenectomy and postoperative radiotherapy in that setting is a controversial and less well-defined area.[38,39]

Vaginal vault brachytherapy can be administered using a variety of different applicators. The most commonly used applicator is a single-channel cylinder that comes in a variety of widths, chosen according to patient anatomy and comfort (Figure 15-4). HDR afterloading has become increasingly common for vaginal cylinder brachytherapy, with no increase in morbidity or local control rates seen in retrospective analysis.[37] The target for vaginal vault brachytherapy is the vaginal mucosa and the operative scar. Ninety percent of recurrences occur at the vaginal vault and 10% in the distal vagina; therefore, in the majority of cases the upper third to half of the vagina is treated. This decreases the morbidity associated with treating the whole vagina, such as vaginal dryness or shortening.[40] Brachytherapy can be prescribed at the cylinder surface or at 5 mm into tissue, a depth which approximates the vaginal lymphatics.

The conversion of LDR dose to HDR dose is the area of the greatest variation between investigators, with fractionation schemes chosen as much because of the availability of local resources as radiobiological parameters. For HDR to be radiobiologically equivalent to LDR, the dose per fraction should be kept as low as is practically possible, usually requiring the total dose to be split into several fractions. The most common endometrial cancer HDR postoperative vaginal vault brachytherapy fractionation schedule in the United States in 2002 was 15 Gy in three fractions when given with EBRT and 21 Gy in three fractions when brachytherapy alone was used, both prescribed at 0.5 cm from the cylinder surface.[36] The dose and fractionation of HDR administered is closely correlated with local control and late complications in gynecologic brachytherapy.[41,42] Sorbe et al showed equivalent locoregional

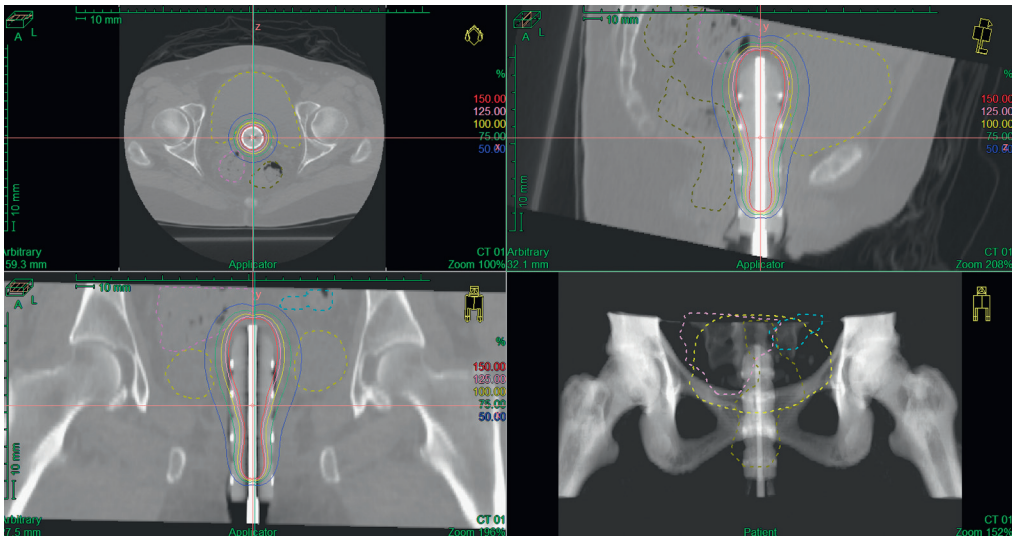


Figure 15-4 Single-channel cylinder to deliver vaginal brachytherapy. Axial and sagittal images show relation to the rectum and bladder.

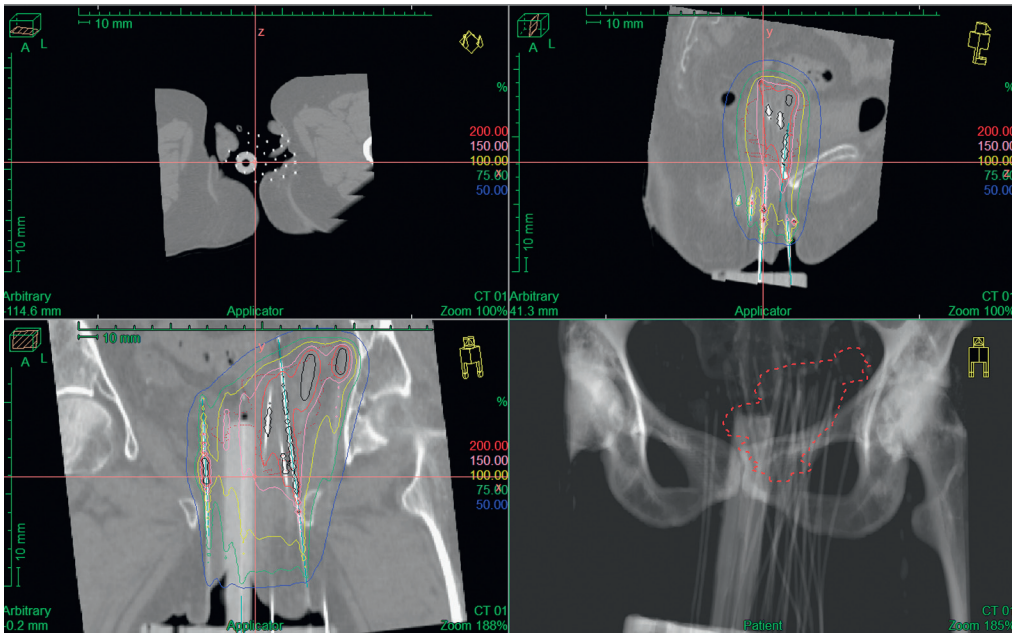


Figure 15-5 Interstitial brachytherapy treatment for endometrial cancer recurrence at the vaginal vault. A central obturator is placed into the vagina with sources allowing for central vaginal dose. A template is placed over the obturator to allow placement of interstitial needles allowing coverage of disease.

recurrence rates when treating the vaginal vault with HDR brachytherapy alone, randomizing to a schedule of 15 Gy in six fractions or 30 Gy in six fractions at 0.5 cm from the cylinder surface over 8 days.[43] However, there were much lower rates of late vaginal morbidity in the lower dose per fraction group. The biological effects increase faster with an increasing dose per fraction in late reacting than early reacting normal tissue.[43,44] Therefore, a small dose per fraction in HDR may be associated with a lower risk of late complications and a better therapeutic ratio providing that overall treatment time is not overprotracted. Vaginal vault brachytherapy can also be used to treat other gynecologic malignancies such as postoperative early stage cervix cancer[27] or early stage vaginal cancer.

For patients with >1-cm residual disease at the vaginal vault at the time of brachytherapy, an interstitial applicator should be used for the boost treatment. There are commercially available vaginal cylinders with interstitial needles integrated within them or alternatively a full interstitial template should be used. The central dose heterogeneity as described with interstitial cervix implants is not as easily achieved in this situation because of the lack of a uterus (Figure 15-5).

As endometrial carcinoma is linked to obesity and hypertension, some patients have medical comorbidities that preclude surgery; for those, radiation therapy may be the definitive treatment of choice. In this group, treatment is delivered via intracavitary uterine brachytherapy applicators, with or without EBRT. A variety of brachytherapy techniques have been described including Heyman capsules, and double-lumen intrauterine catheters, with acceptable rates of OS in this group of patients with high levels of intercurrent illness. Initial experiences described techniques using LDR brachytherapy[45,46] with applicator insertion under anesthesia and the patient immobilized throughout the treatment often for several days. Immobilization prevents complications such as applicator movement or uterine perforation, but the risk of morbidity such as deep vein thrombosis and decubitus ulcers increases. Retrospective analysis has shown similar disease control comparing LDR and HDR remote afterloading brachytherapy in inoperable disease.[27] HDR carries the advantage over LDR in this subset of patients with significant comorbidities that treatment times are greatly reduced, from several days to multiple fractions of several minutes. Various series have reported the use of different applicators, showing that multiple channels are generally preferable to a single channel and 3D planning achieves better target coverage while still constraining the surrounding normal structures, particularly the rectum, to below recommended doses[47,48]

Genitourinary Cancers

Prostate

Brachytherapy for prostate cancer is evolving. In the past, brachytherapy was most commonly used for men with low-risk prostate cancer. The use of prostate brachytherapy has widened over recent years and now incorporates both permanent implant of very low dose rate (vLDR) sources and temporary implants of HDR sources. Both techniques are now used as monotherapy for patients of low- or intermediate-risk disease or as a boost for patients with high-risk disease. Prostate brachytherapy is also being evaluated as a salvage treatment option after previous EBRT.

Image guidance is the principle factor that guides both vLDR and HDR prostate brachytherapy. The most common technique for vLDR brachytherapy is with transrectal ultrasound (TRUS) guidance using preoperative or intraoperative planning techniques (Figure 15-1, *A, B*). HDR brachytherapy for prostate cancer also involves image guidance, using ultrasound or CT, with placement of catheters into the prostate (Figure 15-6, *A, B*).

Relative contraindications for vLDR brachytherapy include high International Prostate Symptom Score (IPSS), prior pelvic radiotherapy, transurethral resection defects, large median lobe, gland size >60 cc, and inflammatory bowel disease.[49] Different loading techniques can be used to achieve dose coverage to the CTV as well as protect organs at risk.[50] Pre- and postprocedure dose evaluation should include dose to 90% of

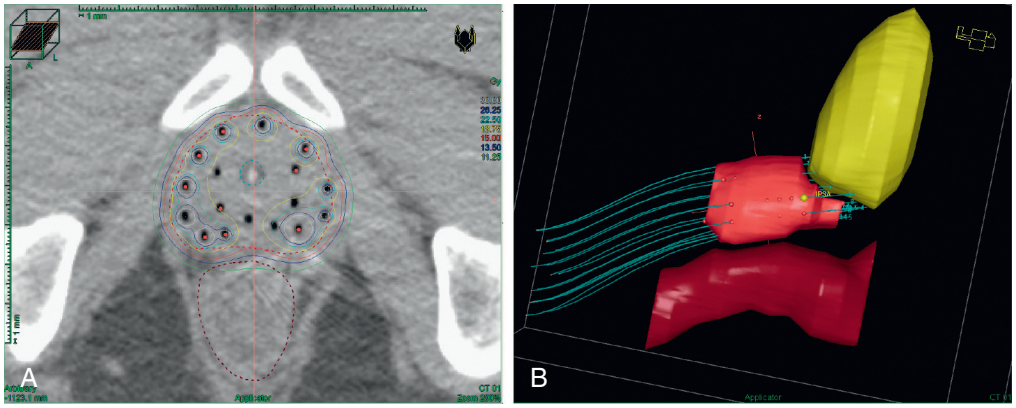


Figure 15-6 **A,** HDR prostate axial image showing placement of HDR catheters and dose distribution around the prostate. **B,** 3D rendering of the prostate with catheters and relation to the bladder and rectum.

the CTV (D_{90}), volume receiving 100% of the dose (V_{100}), volume receiving 150% of prescription dose (V_{150}), rectal D2cc, urethral volume receiving 150% of dose (UV_{150}).[51]

There are three radioactive isotopes used in vLDR prostate brachytherapy: Iodine (^{125}I), Palladium-103 (^{103}Pd), and Cesium-131 (^{131}Cs). There is no published difference in clinical outcomes between ^{125}I or ^{103}Pd seeds.[52,53] Radiation proctitis has been reported to be more intense in the first month with ^{103}Pd as would be expected because of its shorter half-life.[54] Quality of life at 1 year is similar between the two isotopes. ^{131}Cs is being evaluated as an alternative isotope.[55] The dose characteristics and half-life are listed in Table 15-1.

HDR brachytherapy, on the other hand, uses high-activity Iridium-192 (^{192}Ir). The advantage of HDR includes remote afterloading of the source and dosimetry that can be optimized to the implant. Also the high fraction sizes associated with HDR brachytherapy theoretically take advantage of the potentially low alpha-to-beta ratio of prostate cancer cells.[56] The advantages of HDR brachytherapy include the ability to implant patients with large prostates (>60 cc), patients with extra-capsular extension, and in those patients who have had previous transurethral resection of the prostate (TURP).[57,58] There are no specified dose tissue constraints for HDR prostate brachytherapy secondary to the variety of dose options available. The urethral dose range has been reported at <110% of prescription dose to <125% of prescription dose depending on the dose and fractionation. The rectal doses range from D2cc <70% of prescription dose or volumes receiving 80% of the prescription dose <0.5 cc.[59]

Indications for Monotherapy

Patients with low-risk prostate cancer are appropriate for vLDR monotherapy and have shown good outcomes in the literature.[60,61] The use of vLDR monotherapy has also been evaluated in patients with intermediate-risk prostate cancer with or without the use of androgen deprivation with good results.[62] The results of the RTOG 0232 trial will be valuable in determining whether EBRT is required in the intermediate-risk group. The literature for HDR monotherapy is not as robust. The disadvantage of HDR monotherapy is the potential need for multiple implants to attain an effective dose. Dose fractionations of between one and nine fractions have been described. The clinical outcomes for HDR monotherapy show good 5-year local control (LC) and biochemical relapse-free rate in the order of 95% LC and 83% to 95% biological freedom from recurrence despite a heterologous group of patients.[63-67] A recent American College of Radiology (ACR) appropriateness paper did not support more hypofractionated monotherapy regimens and felt that the more fractionated regimens had longer follow-up and support for use.[56]

TABLE 15-3 Dose Ranges Reported for HDR and vLDR Prostate Brachytherapy

Dose Range	Monotherapy	Boost
HDR*	12-13.5 Gy × 2 10.5 Gy × 3 9.5 Gy × 4 6.5 Gy × 6 7.25 Gy × 6	15 Gy × 1 10.5 Gy × 2 7 Gy × 3 6 Gy × 4
vLDR		
Iodine-125	140-160 Gy	108-110 Gy
Palladium-103	110-125 Gy	90-100 Gy

Adapted from ABS consensus guidelines.
**No particular dose fractionation can be recommended because of heterogeneity of reported doses in the literature.*

Indications for Boost

There is increasing evidence that increased radiation dose in patients at high risk results in improved LC and prostate cancer metastasis-free survival.[59,68-72] Dose escalation can be with EBRT alone or using brachytherapy as a boost. Hoskin et al randomized 220 patients to EBRT alone 55 Gy in 20 fractions or EBRT 35.75 Gy in 13 fractions followed by an HDR boost of 17 Gy in 2 fractions. The HDR boost group showed improved biochemical relapse-free survival (bRFS) and had a lower incidence of acute rectal symptoms.[71]

The dose for both LDR and HDR must be adjusted to account for the addition of EBRT (Table 15-3). Sequencing of the brachytherapy component can be before or after the EBRT or in the case of HDR sandwiched between. RTOG 0321 was a prospective Phase II trial of HDR brachytherapy in combination with EBRT (2 HDR fractions of 19 Gy were used in combination with 45 Gy in 25 fractions of EBRT). The grades 3 to 4 gastrointestinal (GI) or genitourinary (GU) toxicity rate was 2.6% at 18 months.[73] A Canadian trial showed that further hypofractionation of the dose was achievable with acceptable toxicity (15 Gy in a single brachytherapy fraction following 37.5 Gy in 15 fractions EBRT).[74] Trimodality therapy with androgen deprivation therapy, EBRT, and brachytherapy boost is becoming a standard for patients at high risk.

Acute urinary retention is <5% in the HDR literature and ranges from 5% to 10% in vLDR literature.[75] For HDR, late

grade 3 GU toxicity is reported in approximately 3% of patients, but late grade 3 rectal toxicity is rare.[66,76] In the vLDR literature, late rectal toxicity ≥RTOG grade 2 is 9%.[77-79] Erectile dysfunction rates appear to be similar between vLDR and HDR literature with preservation of potency in 40% of patients.[68,80]

Brachytherapy is also being evaluated as salvage treatments in patients with recurrence after previous radiation. Salvage brachytherapy has been reported in the LDR, HDR, and PDR literature[81-83] and is currently under investigation in a Phase II trial (RTOG 0526). In a Phase II study by Yamada et al HDR brachytherapy salvage was used in 42 patients (32 Gy in four fractions over 30 hours with a single insertion). The 5-year bRFS was 68.5% and cause specific survival (CSS) 90%. There was only 7% grade 2 late urinary toxicity and one patient with grade 3 urinary incontinence. Rectal toxicity was minimal. These findings are in keeping with the long-term follow-up results of salvage treatment of 37 men who underwent brachytherapy for salvage treatment by Burri et al in which the 10-year bRFS was 54% and CSS 96%.[81]

Penile Cancer

Squamous cell carcinoma of the penis is a rare cancer accounting for only 1% of male cancers. Brachytherapy is an alternative to penectomy in T1 and T2 tumors confined to the glans that are less than 4 cm in size.[84] The most common technique is an interstitial technique, either template or freehand. LDR, PDR, and HDR treatments have been described.[85,86] The treatment volume includes the gross disease and a wide margin (1 cm). A multiplanar implant is recommended for most procedures to ensure dose coverage at depth. The implantation technique has been described in detail in the literature.[87] The spacing between needles for LDR and PDR is recommended to be between 1.4 cm and 1.6 cm but closer spacing (1 cm to 1.2 cm) is described for HDR techniques. The typical dose for LDR and PDR is 60 Gy at 0.5 to 0.6 Gy/hour over 5 days (assuming hourly fractions for PDR). There is less literature to support an HDR dose but recent ABS guidelines recommend 38.4 Gy in 3.2 Gy fractions twice daily over 6 days.[86]

The 5 year LC is 70% to 87% with penile preservation in 70% to 88% of the cases.[86,88-92] The rate of soft-tissue necrosis ranges between 0% and 26% and increases with doses over 60 Gy and large-volume disease. The rate of urethral stenosis ranges between 9% and 45% and relates to the proximity of the needles to the urethra.[86]

Urethral Cancer

Brachytherapy solely or with EBRT can be part of the treatment in urethral cancers in women or men. For any tumor more than 5 mm, an interstitial technique (Figure 15-7) is required and for higher stage disease multimodality treatment is recommended.[93] The doses are similar to that described for penile brachytherapy. In the treatment of female urethral cancers the entire length of the urethra can be implanted. The dose for LDR monotherapy is 60 to 65 Gy in 3 to 5 days or 20 to 25 Gy if prescribed as a boost.[94] In a review by Milosevic et al,[95] the outcomes of 34 women treated with either EBRT alone (14 patients), EBRT with brachytherapy (15 patients) or brachytherapy alone (5 patients) were evaluated. Brachytherapy led to improved LC 77% versus 32% in the no brachytherapy cohort. OS was 41%, at 7 years which is similar to other reports in the literature. Fistula formation was reported in 15% of patients.

Breast Cancer

Breast-conserving surgery followed by whole-breast irradiation (WBI) is a standard of care for many early breast cancers. The rationale for partial breast irradiation comes from reports



Figure 15-7 Interstitial brachytherapy implant of a urethral cancer in a female patient.

of in-breast failure patterns following partial mastectomy versus partial mastectomy and WBI where the location of failure was most often in the region of the primary lesion or the surgical bed.[96,97] Partial breast irradiation therefore allows for decreased volume of normal tissue receiving radiation and the potential to decrease the overall treatment time (accelerated partial breast irradiation [APBI]). Radiobiologically there may also be benefit to APBI because the alpha-to-beta ratio for the tumor is relatively low and reported as between 3.4 and 4.1.[98,99]

The publication of large randomized trials is awaited for the APBI technique.[100-102] Patient selection remains uncertain with consensus statements from organizations differing.[103-105] Factors that are considered when contemplating APBI as a treatment modality include: patient age, size of tumor, margin status, histology, lymphovascular space invasion, and nodal status (Table 15-4). Husain et al[106] published a SEER patterns-of-care analysis of APBI using brachytherapy to compare with the ASTRO consensus statement groupings.[105] Of the 4172 patients who received APBI through brachytherapy between 2002 and 2007, 60% would have been grouped in the ASTRO cautionary/unsuitable categories.

There are many techniques for APBI. Interstitial multicatheter techniques using LDR were the first reported (Figure 15-8, *A, B*), this technique has now evolved for HDR and PDR treatment. HDR is the more typical treatment because of dose optimization and outpatient treatments. Multiple catheters are placed percutaneously through the lumpectomy cavity, commonly in the postoperative setting under image guidance using a template. Typically the CTV is the lumpectomy cavity plus an additional 1- to 2-cm margin. Multiplanar implants are required to cover the CTV with catheter spacing between 1 and 1.5 cm.[107] Polgar et al have recently published the 10-year results of their single-institution randomized trial of APBI with multicatheter interstitial HDR brachytherapy (5.2 Gy × 7 fractions) or electrons (50 Gy/25 fractions) versus WBI. The 10-year local recurrence (LR) results between APBI and WBI were similar (5.9% versus 5.1%), with superior cosmesis in the APBI cohort.[102] Similarly Shaw et al reported 12-year follow-up of a matched pair analysis of 199 WBI and 199 APBI patients.

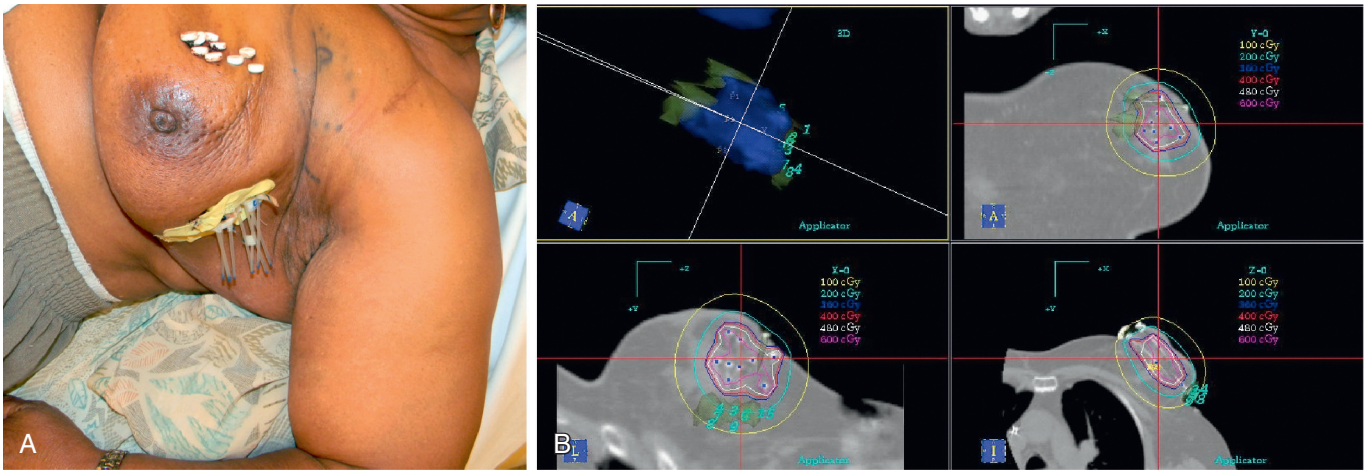


Figure 15-8 **A,** Clinical photo of a patient with interstitial HDR catheters placed to give coverage to the tumor bed and margin. **B,** Dosimetry images of an interstitial breast treatment plan.

TABLE 15-4 Recommendations on Patient Selection for Accelerated Partial Breast Irradiation

	GEC/ESTRO[104]			ASTRO[105]			ABS[103]
	Good Candidate (Low Risk)	**Possible Candidate (Intermediate Risk)**	**Contraindication for APBI (High Risk)**	**Suitable Candidate**	**Cautionary Candidate**	**Unsuitable Candidate**	**Acceptable Candidate**
Age (yr)	>50	>40-50	≤40	≥60	50-59	<50	≥50
Histology	IDC*	IDC*	—	IDC*	IDC*	—	IDC*
ILC	Absent	Allowed	—	Absent	Allowed	—	Allowed
LCIS	Allowed	—	—	Allowed	—	—	—
DCIS	Absent	Allowed	—	Absent	≤3 cm	>3 cm	Allowed
Grade	Any	—	—	Any	—	—	Any
Tumor size	pT1-2 (≤3 cm)	pT1-2 (≤3 cm)	pT2 (≥3 cm), pT3-4	pT1 ≤2 cm	pT0-2 (2.1-3 cm)	>3 cm	≤3 cm
Margins	≥0.2 cm	<0.2 cm	Positive	≥0.2 cm	<0.2 cm	Positive	Negative
Multicentric	Unicentric	Unicentric	Present	Unicentric	Unicentric	Present	—
Multifocal	Unifocal	Multifocal within 2 cm of index lesion	Multifocal >2 cm of index lesion	Clinically unifocal (≤2 cm)	Clinically unifocal (2.1-3 cm)	Clinically multifocal or microscopically >3 cm of index lesion	—
EIC	Absent	Absent	Present	Absent	≤3 cm	>3 cm	—
LVI	Absent	Absent	Present	Absent	Limited/focal	Extensive	Not allowed
ER/PR	Any	—	—	Positive	Any	—	Any
Lymph node status	pN0	pN1mi, pN1a	pNx; ≥pN2a	pN0(I,i+)	pN0(I,i+)	pN1,pN2,pN3 or pNx	Negative
BRCA1/2 mutation	—	—	—	Absent	Absent	Present	—

DCIS, *Ductal carcinoma in situ;* EIC, *extensive intraductal component;* ER/PR, *estrogen receptor/progesterone receptor;* IDC, *invasive ductal carcinoma;* ILC, *invasive lobular carcinoma;* LCIS, *lobular carcinoma in situ;* LVI, *lymph-vascular invasion.*
**Subtypes include mucinous, tubular, and colloid.*

There was no difference seen in rates of LR or regional recurrence or disease-free survival.[108]

RTOG 95-17 was a Phase II trial of multicatheter brachytherapy for APBI. One hundred patients with either stage I or II breast cancer <3 cm in size, ≤3 lymph nodes involved (no extracapsular extension) were eligible. Brachytherapy treatments consisted of either LDR 45 Gy in 3.5 to 5 days (33 patients) or HDR 34 Gy in 10 fractions twice daily over 5 days (66 patients). The trial was not designed to compare the two brachytherapy arms, but similar rates of in-breast failure (3% to 6%) were seen at 6 years using the two brachytherapy techniques.[109] Cosmesis was rated excellent/good in 66% of patients. However fibrosis was reported in 45%, skin catheter marks in 54%, and symptomatic fat necrosis in 15%.[110] Wazer et al published pooled analysis of outcomes predicting for suboptimal cosmetic outcome and toxicity. The factors associated with increased toxicity were number of source dwell positions, volume receiving 150% of the dose (V150), volume

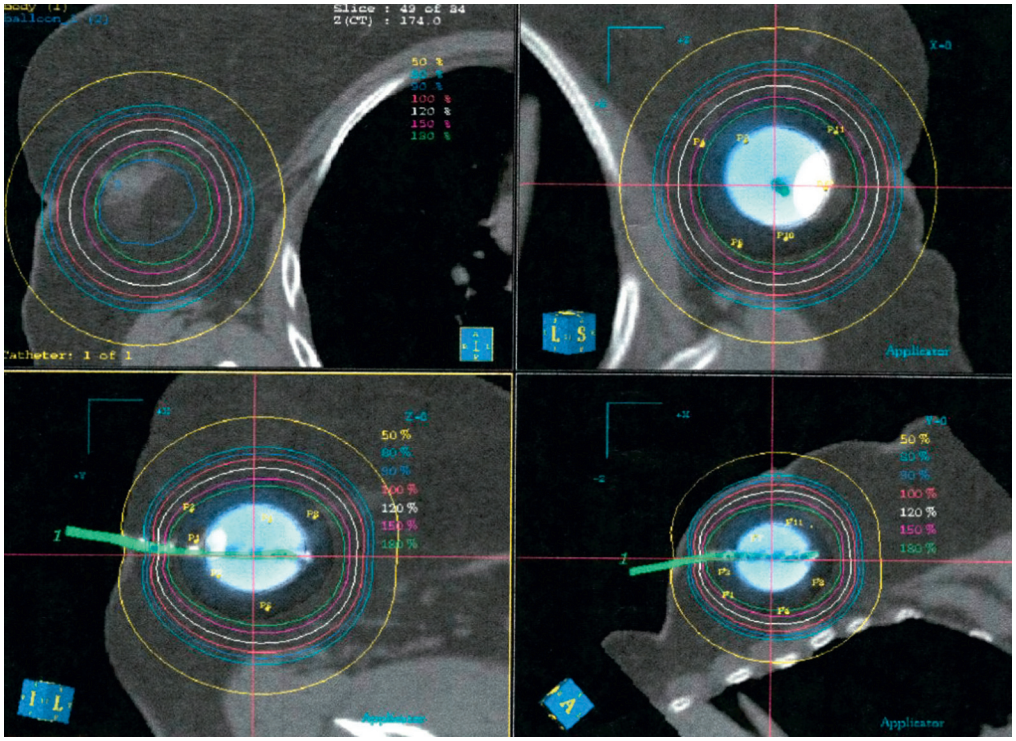


Figure 15-9 Single-lumen catheter within the breast seroma. The treatment planning images illustrate uniform radiation dose delivery.

receiving 200% of the dose (V200) as well as the dose homogeneity index (DHI). Large V150 hotspots were associated with symptomatic fat necrosis.[111]

Balloon-Based Intracavitary Technique

Mammosite (Hologic Inc, Bedford, MA) was developed and marketed as an accessible way to perform APBI. This single-lumen catheter can either be placed into the surgical cavity at the time of surgery or postoperatively under ultrasound guidance. Once the catheter is placed into the surgical bed, a balloon around the catheter is inflated to fill the cavity and compress the adjacent breast tissue. The limitation of this technique is that it had only a single dwell position and hence the dose distribution was uniform around the catheter and could not be optimized to irregular volumes or to avoid chest wall or skin (Figure 15-9). The spacing of the catheter to the chest wall and skin was found to relate to toxicity leading to recommendations of skin spacing ≥7 mm.[112,113] The final analysis of the American Society of Breast Surgeons MammoSite Breast brachytherapy registry trial has been published. In this trial 1449 women were treated with 34 Gy in 3.4 Gy fractions, the majority (87%) of whom had invasive breast cancer. The median follow-up was 63.1 months. The 5-year actuarial recurrence rate for in-breast recurrences was 3.8% (3.7% invasive breast cancer, 4.1% ductal carcinoma in situ). Only the tumor size and estrogen receptor (ER) negative status were associated with in-breast recurrence. There was a trend toward increased in-breast recurrence in the case of positive margins and ASTRO "unsuitable" status ($p = 0.06$ and $p = 0.07$) but these were not significant.[114] The rate of seroma at any time in this trial was 13.4%, symptomatic fat necrosis 2.5%, infection 9.6%, and telangiectasia 13%. At 84 months 90.6% of patients were rated with excellent/good cosmesis.

Further enhancements of the intracavitary techniques led to multichannel balloon–based catheters and a multichannel strut-adjusted volume implant (SAVI) applicator. The multichannel catheters allow for multiple dwell positions and were found to be dosimetrically superior to the single lumen/single dwell MammoSite with improved target coverage and decreased dose to the chest wall and skin even in cases where the skin and chest wall were ≤7 mm.[115-118] The Contura catheter is a multichannel balloon catheter with one central catheter and four peripheral catheters offset from the center by 5 mm. The MammoSite Multi-Lumen has one central catheter surrounded by three peripheral catheters. The SAVI applicator has a central catheter surrounded by 6, 8, or 10 peripheral catheters. The peripheral catheters once placed into the surgical cavity are expanded to fill the cavity. The dosimetry of the SAVI applicator is more similar to the multichannel interstitial implants in terms of dose inhomogeneity of multiple dwell positions. The SAVI applicator has been found to be useful in cases of close skin spacing or small breast size.[119]

Electronic balloon brachytherapy (Xoft Axxent) differs from other balloon-based treatments because the radiation source is an electronic x-ray tube that produces a 50-kVp photon range as opposed to the average of 380 keV for Iridium-192. The advantage of this technique includes increased access as a radiation vault is not required and rapid dose fall off results in decreased dose to normal tissues. In dosimetric comparisons between electronic brachytherapy and HDR the doses to the planning target volumes (PTV) were comparable, but the electronic brachytherapy had higher dose at the surface of the balloon and decreased dose to the heart and ipsilateral lung.[120,121] Further follow-up of this technique is required to evaluate outcomes and toxicity, especially given that the radiobiological effective dose using low energy photons differs from standard HDR treatments.

Interstitial permanent seeds are also being evaluated for partial breast irradiation (PBI) in the low-risk population with the potential advantage of a further reduction in the time a patient would be required to be undergo treatment as well as decreased dose to critical normal structures because of the relatively low-dose penetration of the ^{103}Pd isotope.[122,123] Patient selection for this technique is limited by general

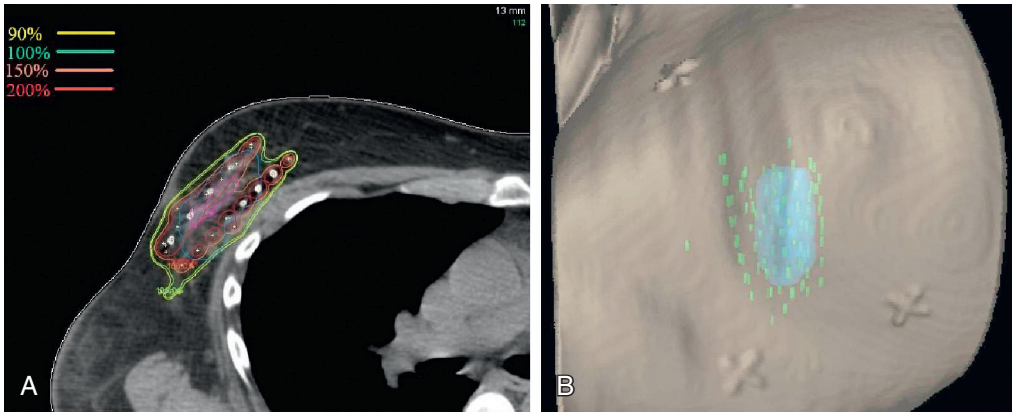


Figure 15-10 **A,** Axial image of an interstitial breast implant with permanent seeds showing dose distribution and **B,** 3D rendering of the breast with the CTV and seed strands.

criteria for PBI as well the size of the postoperative cavity (≤2.5 cm) and planned implant volume (≤120 cc). Imaging of the tumor bed using ultrasound or CT is performed and similar to permanent prostate brachytherapy a preplan with the desired placement of needles and seeds is made (Figure 15-10, *A, B*). A vLDR dose of 90 Gy to the tumor bed plus margin is planned keeping the dose to the skin ≤90% of the prescription.[124] The implant is performed under image guidance using local anesthetic and conscious sedation. This technique continues to be evaluated through a multiinstitutional registry trial. A dosimetry study of ^{131}Cs versus ^{103}Pd has shown a potential theoretical advantage to using ^{131}Cs with decreased V200 but this may not be clinically significant.[125]

Breast brachytherapy is also being evaluated as a boost technique either through conventional HDR techniques described or using a noninvasive breast brachytherapy (NIBB) technique with Accuboost (Billerica, MA). NIBB uses image guidance and immobilization to target the tumor cavity. The mammography-based visualization system that allows the applicators to be centered on the target[119] while the breast is immobilized. This allows for directed photons at the cavity without the usual PTV margin required for standard EBRT boost resulting in comparatively smaller treatment volumes with the potential for decreased toxicity. A 2:1 matched control study of NIBB versus EBRT boost showed that there is less combined skin and subcutaneous toxicity in patients treated with NIBB (2% NIBB versus 9.5% EBRT boost, $p = 0.046$).[126]

APBI has also been described as salvage treatment for in-breast tumor recurrence (IBTR). The GEC-ESTRO breast cancer working group reported that interstitial multicatheter brachytherapy was feasible and effective in preventing a second local recurrence and with OS equivalent to salvage mastectomy.[127] Likewise Kauer-Dorner et al reported on a prospective trial of interstitial PDR brachytherapy in 29 patients where local control of the tumor was comparable to mastectomy and ≥grade 3 late side effects were reported in 16%.[128]

Intraoperative radiation (IORT) for breast cancers has also been described as a technique to deliver partial breast radiation in one fraction with either electrons or 50 kv x-rays. However this technique differs significantly in terms of dosing and radiobiology from brachytherapy techniques. Recent updates of two large randomized trials of IORT APBI versus WBI have reported increased IBTR in the APBI arms.[129,130] The increased IBTR may be related to patient selection[131] highlighting that APBI remains investigational and if offered should be under the guidance of a trial.

Lung–Endobronchial Brachytherapy

In 1922 Yankauer described the use of radium placed endobronchially to treat lung cancer,[132] and brachytherapy continues to be used to deliver radical or palliative endoluminal therapy to the bronchus. Local treatment can be important to improve the quality of life for lung cancer patients. A narrow bore brachytherapy tube is placed under bronchoscopic guidance, which extends at least 2 cm past the tumor, and is firmly secured at the nostril. The dose is delivered, usually using HDR, as a single or multiple fractions. The 2001 ABS guidelines recommend dose prescription at 1 cm[133]; however, in the era of CT planning the orientation of the catheter within the bronchus has been identified as an area of concern (Figure 15-11). High localized doses to surrounding blood vessels are demonstrated when the catheter position is offset against the luminal wall.[134] This may be overcome by using placement methods which stabilize the catheter centrally[135,136] or by individualized dose prescription.[134] This is important since fatal hemoptysis rates ranged from 7% to 22% in randomized trials.[137-139]

ABS guidelines recommended the use of endobronchial brachytherapy for palliation, particularly for endobronchial lesions not amenable to laser or stenting. A range of doses were recommended using 10 to 24 Gy in two to four fractions as sole treatment or 15 to 16 Gy in two to four fractions following EBRT[133]; these guidelines are currently being updated. Subsequently, a 2012 Cochrane meta-analysis[140] examined 14 randomized trials that used endobronchial brachytherapy, either alone or in combination with other therapies such as EBRT, chemotherapy, or laser. This showed that a variety of dose and fractionation schedules were used and they appear to be similar in OS with 14.8 Gy in two fractions showing superiority for improved LC and less hemoptysis over 15.2 Gy in four fractions. There appears to be no advantage to adding endobronchial brachytherapy to an EBRT treatment course, either palliative or radical. When used for palliation as sole therapy, 50% of brachytherapy-only cases proceeded to receive EBRT with a median time to treatment of 4 months, compared to under a third requiring brachytherapy following EBRT with a median time to treatment of 10 months.[137] Secondary analysis subsequently showed a survival advantage to EBRT with a relative risk reduction of 61%. The Cochrane review concluded that endobronchial brachytherapy can be considered for palliation in patients previously treated with EBRT with symptoms resulting from central obstruction. Recent ACR guidelines recommend that it can be used for palliation of patients with symptomatic endobronchial tumors.[141]

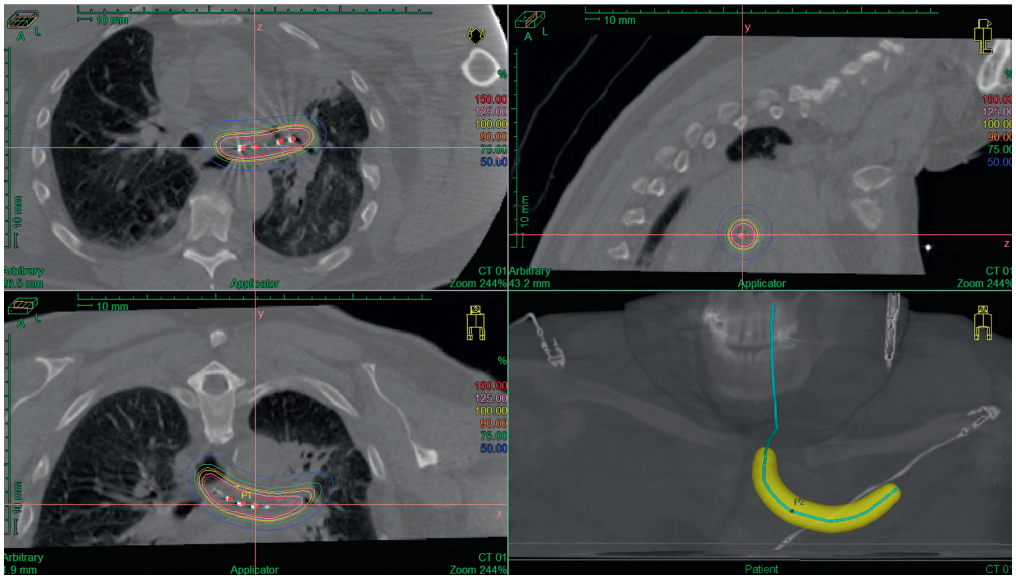


Figure 15-11 Endobronchial catheter with CT planning allowing for evaluation of the placement of the catheter and relation to clinical target volume and organs at risk, including a pulmonary vein, which is in close proximity to the implant.



Figure 15-12 Permanent interstitial seeds placed in a single plane mesh.

Thoracic Wall Brachytherapy

Interstitial seeds formed into a single plane mesh implant can be placed intraoperatively in areas at high risk of relapse (Figure 15-12). These are commonly used within the thorax but are also described in other anatomic sites, particularly in sarcoma resections. Most institutions describe the use of ^{125}I but the use of ^{103}Pd and ^{131}Cs is also described.[142-144] The use of a planar ^{125}I implant placed along the suture line following sublobar resection was described as decreasing recurrence rates over those that would be expected with sublobar resection alone.[145] However, the early results from the ACOSOG z4032 randomized trial have not shown a difference in recurrence; full results are awaited. Placement of mesh implants following close or positive surgical margins has shown lower rates of recurrence than would otherwise be expected in thoracic and para-spinal tumor resections.[145,146]

Institutions with the ability to use intraoperative brachytherapy have described the use of brachytherapy applicator placement at the time of surgery to deliver highly localized radiation to areas at operative risk. This has the benefits of target localization under direct vision and the ability to shield or displace organs at risk, resulting in reduced risk of long-term toxicity.[133]

Gastrointestinal

Esophageal Cancer

Esophageal brachytherapy can be administered in the radical and palliative settings. A brachytherapy catheter is placed over a guide wire under endoscopic guidance traversing the tumor and firmly secured at the nose. The treatment volume should extend 2 cm superior and inferior to all macroscopic disease to encompass any microscopic tumor foci. Treatment is generally prescribed at 1 cm from the source axis, though 3D planning can be used for complex cases and the dose received by organs at risk determined. If a stent is present, the dose may be attenuated by the stent with higher localized doses around the stent, 5% higher at 0.5 mm and up to 245% in the immediate vicinity of the stent.[147]

As part of the radical treatment of esophageal cancer brachytherapy can be used to deliver a highly localized boost following radical EBRT. The ABS recommends 10 Gy prescribed at 1 cm in two fractions 1 week apart following chemoradiation 45 to 50 Gy or radiotherapy alone up to 60 Gy[148] (Figure 15-13). This dose/fractionation follows the RTOG 92-07 trial, which showed complete remission rates of 74% following EBRT and brachytherapy with a 1 year OS of 49% but used a dose of 10 Gy in two fractions following unacceptable rates of toxicity using 15 Gy in three fractions.[149] A thicker applicator may minimize the hotspots that were thought to be the cause of fistulas.

For palliation, brachytherapy delivers improvement of swallowing in the majority of cases, with maintenance of swallowing in most of the remainder. A range of doses for HDR esophageal brachytherapy is considered acceptable. The ABS recommends palliative doses of 14 Gy in 1 to 2 fractions following EBRT of 30 Gy in 10 fractions and for sole treatment, 15 to 20 Gy in 1 to 2 fractions.[148] A dose comparison study of 18 Gy in 3 fractions versus 16 Gy in 2 fractions by the International Atomic Energy Agency (IAEA)[150] showed no difference in

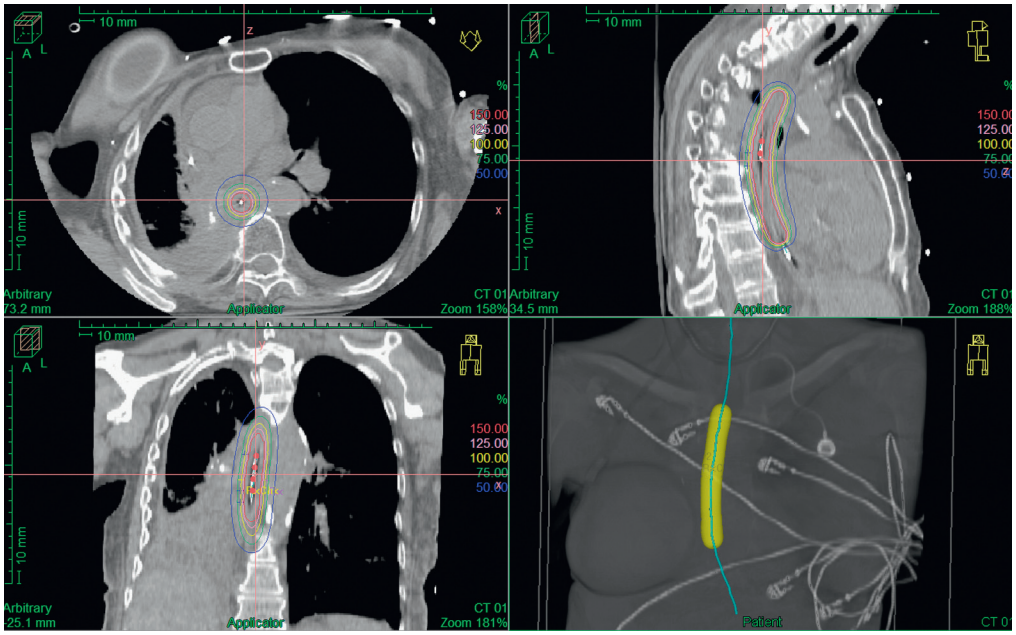


Figure 15-13 Esophageal brachytherapy prescribed 1 cm from the source axis demonstrating simple line source dose distribution.

efficacy or toxicity with an overall 11% stricture rate and 10% fistula rate. It is not known how much brachytherapy may have contributed to fistula formation but it was noted that all fistulae occurred in the presence of disease progression.

A European randomized trial showed improved efficacy of brachytherapy 12 Gy in 1 fraction over stenting[151] with improved quality of life, longer duration of symptom palliation, and equivalent overall healthcare costs.[152] Because there is a slight delay in onset of symptom palliation with brachytherapy it was recommended that brachytherapy should be used instead of stenting in patients with a predicted survival over 2 months. If the predicted survival is under 2 months stenting should be used. A trial of fractionated treatment using 21 Gy in 3 fractions versus stenting did not show any evidence of benefit though the number of patients in the trial may have been too small to draw definitive conclusions.[153] A Cochrane meta-analysis in 2009 showed that brachytherapy has a longer duration of palliation than stenting with significantly better quality of life and lower complications (33% versus 47%)[154] and may even provide a survival advantage. Brachytherapy was seen to be comparable to laser for palliation and may improve the dysphagia-free interval when EBRT is added to the combination of laser and brachytherapy. An IAEA randomized study showed that the addition of EBRT 30 Gy in 10 fractions to 16 Gy in 2 fractions brachytherapy resulted in significantly better symptom relief than brachytherapy alone.[155] There was no difference in OS between the two groups. Thus, patients with a greater predicted survival (e.g., over 6 months) may benefit from the addition of EBRT to brachytherapy. The use of a stent implanted with iodine seeds has been described, with a small randomized trial showing a significant improvement in OS over conventional stenting at 7 months versus 4 months.[156] This technique is not currently practiced in North America.

Rectal

Brachytherapy can be considered in two situations for rectal cancer: attempting to avoid colostomy formation as organ preservation in early rectal cancer or for palliation in surgically unfit patients, either as a boost following EBRT or as sole palliation. Two methods of treatment exist, contact radiotherapy or HDR brachytherapy. A recent consensus statement on rectal cancer treatment described rectal brachytherapy as an elegant option to downstage tumors and facilitates resection but that it requires further assessment.[157]

Contact radiotherapy, often called Papillon radiotherapy, uses a 50-kVp source to deliver highly localized doses directly to the tumor with rapid dose fall off, and with the advent of dedicated modern machines, contact brachytherapy for rectal cancer is enjoying a renaissance. Following sigmoidoscopic assessment a fixed diameter applicator is placed into the rectum and the radiation delivered under direct vision to the tumor. Generally a dose of 110 Gy in 4 fractions delivered at two weekly intervals is used for sole treatment of T1 tumors and for T2 and above 85 to 90 Gy in 3 fractions is used in addition to EBRT 45 Gy in 25 fractions. In a randomized trial of patients unfit or unwilling to have surgical excision those assigned to 39 Gy in 13 fractions EBRT alone had a 63% rate of colostomy at 10 years compared to 29% in the group receiving 85 Gy in 3 fractions contact brachytherapy in addition to the EBRT.[158] Because contact brachytherapy has a higher recurrence rate than surgery, patients who are surgically eligible must be counseled accordingly and accept the requirement for increased sigmoidoscopic and MRI screening for the first 2 years. However, the majority of patients will remain colostomy free and OS is unchanged.[159]

HDR brachytherapy uses a flexible silicone applicator with multiple channels to provide a conformal dose that can treat larger fields with slightly deeper penetration than contact radiotherapy, see Figure 15-14, *A, B*. Before applicator placement, the superior and inferior extent of the tumor are marked with clips. The applicator is then inserted and the treatment field defined, preferably using CT or MRI planning. A dose of 26 Gy in 4 daily fractions is used for radical treatment or up to 30 Gy in 3 fractions for palliation, usually following pelvic EBRT. A Phase II study of neoadjuvant HDR brachytherapy has shown recurrence rates of 5% with low rates of toxicity. Matched pair analysis has shown lower rates of reoperation within 30 days with HDR brachytherapy used neoadjuvantly (in Canada) compared to short course radiotherapy or no neoadjuvant treatment (in Sweden), although different surgical techniques in the two countries may have contributed to this difference.[160]

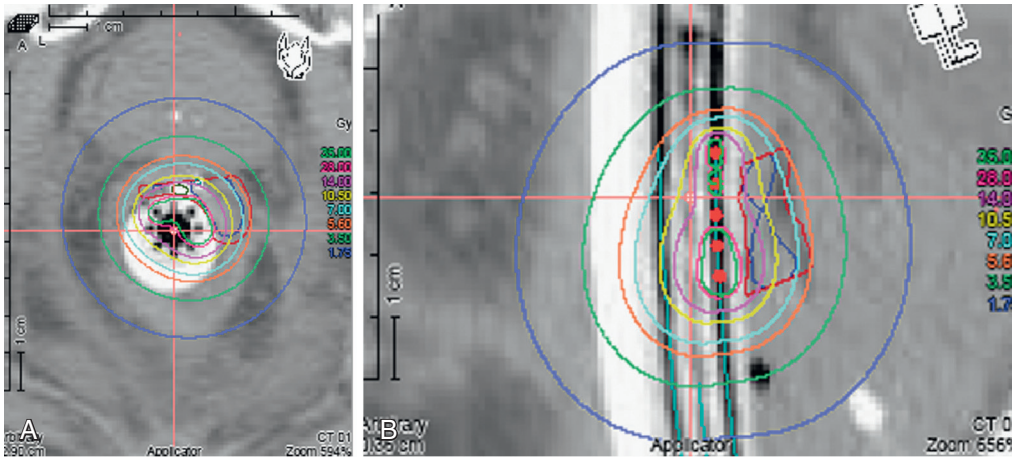


Figure 15-14 Axial **(A)** and saggital **(B)** images of a flexible silicone rectal applicator in place. A high dose rate plan has been created to cover the gross tumor volume *(blue)* with a 2-mm expansion to the planning target volume *(red)*. Note low doses received by contralateral bowel wall.

Older, medically unfit patients may be suitable for pelvic radiotherapy even if they are not fit for surgery. For those with smaller tumors contact brachytherapy may be a useful option. For institutions without access to contact brachytherapy or for patients with larger more bulky tumors HDR endorectal brachytherapy is an option. This is usually given after EBRT—either a long course with or without chemotherapy or a short course of 25 Gy in 5 fractions or 39 Gy in 13 fractions. A variety of dose/fractionation schemes have been described with up to 36 Gy in 6 fractions following EBRT[161,162] showing good tumor control with acceptable late toxicity.

Anal Cancer

Squamous cell carcinoma of the anus is a rare cancer that is usually treated with concurrent chemoradiation with good rates of sphincter preservation, disease-free survival, and OS. Relapse most commonly occurs locally with radical surgery required to achieve cure. Therefore, methods of local dose escalation for primary treatment have been explored. EBRT plus concurrent chemotherapy is used to treat the tumor and wider nodal area and the tumor boost can be delivered using EBRT, electrons, or brachytherapy.[163] Interstitial implants typically target the volume of interest using a horseshoe-shaped perineal template curved around the anus. Improved catheter placement may be achieved by the use of advanced imaging techniques such as 3D endoluminal ultrasound.[164,165] Papillon described an LDR boost using ^{192}Ir to deliver 20 to 30 Gy in 221 patients 2 months after completing EBRT. LC rates were comparable to surgical techniques.[166] Although a split course technique for anal cancer is no longer recommended, if treatment delays because of toxicity or illness occur between the Phase 1 EBRT and the boost, a brachytherapy boost may provide better local control than EBRT.[167] PDR techniques have been described with similar rates of disease control and toxicity to LDR.[168-170] HDR brachytherapy has been described but is rarely used because it may take longer to deliver as a result of the fractionation that is required in an area of normal tissue already greatly affected by EBRT. In retrospective review, an HDR dose of 14 Gy in 7 fractions over 3 days gave equivalent control to an EBRT boost with lower skin toxicity for HDR.[171]

Head and Neck Cancers

Head and neck brachytherapy was one of the first radiation therapies. The early methods were simply the placement of radium sources in or on tumors for various amounts of time to look for resolution of the tumor. The development of afterloading techniques both in Europe and the United States led to several parallel methods that have inspired modern practice. The enhancement of modern brachytherapy with PDR and HDR afterloading and computer optimization of dose has only made the conformality and utility of this surgical type of brachytherapy more attractive. A myriad of techniques have been described including the gutter guide Pierquin technique, the plastic tube technique of Henschke, the through and through technique, the loop technique, the sealed end technique, the hypodermic technique, the thread techniques, as well as direct implantation. However, the combined innovations of IMRT and chemosensitization of radiation therapy have diminished the deployment of all of these once robust forms of practice.

Brachytherapy has been described in the setting of primary localized tumors as either monotherapy or as a boost to EBRT for lip, buccal mucosa, oral tongue, floor of mouth, base of tongue and pharyngeal wall, parotid, and nasopharynx. Additionally IORT, given as HDR surface applicator brachytherapy, has been described for recurrent nodal disease in the neck.[172]

Perhaps the most adventurous of all head and neck brachytherapy, the base-of-tongue implant may serve as an illustrative example. The oropharyngeal tumors often present in the younger human papillomavirus (HPV)–associated form of cancer and require a definitive approach to potentially curable disease. The greatest challenge in this setting is to get sufficiently high dose delivered to a target between the angles of the mandible and in close proximity to the pharyngeal constrictors and the muscles of mastication. An implant will provide a highly conformal boost that will optimize the chance for cure and minimize the late effects of radiation therapy. This technique is also of significant importance in the setting of recurrent disease after previous radiation therapy. Harrison et al reported the Memorial Sloan Kettering Cancer Center (MSKCC) series in which for largely node-positive disease there were high rates of LC and distant control of disease.[173] Karakoyun-Celik et al reported the Massachusetts General Hospital series deploying the gold button technique with excellent LC and distant control.[174] Cano et al also reported reduced dose after concomitant chemotherapy and EBRT again showing excellent results in a largely locally advanced and node positive cohort.[175] The ongoing role of base of tongue implants in the IMRT era is also worth considering as to the effect on swallowing function. Teguh et al[176] and Al-Mamgani et al[177] reported significantly

more dysphagia, trismus, and dry mouth after an IMRT boost when compared to an interstitial boost.

Although there is not space for a full review of each technique, a comprehensive review of head and neck brachytherapy applications and techniques is available giving an international approach and perspective.[178]

Skin/Superficial

Brachytherapy has been described for superficial treatments of both benign and malignant skin neoplasms. The most common malignant process is nonmelanoma skin cancers (squamous cell carcinoma and basal cell carcinoma). There are a variety of treatment options with radiation for these lesions including EBRT, electrons, orthovoltage, and brachytherapy. Brachytherapy techniques can include LDR, PDR, HDR, and more recently electronic brachytherapy.[179] Brachytherapy has advantages over the other radiation treatments in areas of the body with complex superficial targets (see Figure 15-15) and allows for shorter treatment courses. Both interstitial and surface techniques have been described. Interstitial implants can often be placed under local anesthetic and are usually single plane; however, for deeper lesions multiple planes may be required to get coverage at depth. Ducassou et al reported their experience in 132 patients treated with LDR interstitial treatments for squamous cell and basal cell carcinomas. The 5-year local relapse-free survival (LRFS) was 87.3%. Patients who were treated with primary brachytherapy had better LRFS compared to patients treated at time of recurrence (HR 2.91), also the LRFS was superior in patients treated for basal cell compared with squamous cell carcinoma (90.4% versus 70.8%, $p = 0.03$).[180]

Superficial techniques can be with either custom molds or surface applicators or with commercial contact applicators such as the Leipzig applicator (Nucletron, an Elekta company, Veenendaal, The Netherlands). Superficial applicators are limited to superficial tumors. Electronic brachytherapy and the Leipzig type applicators have a surface dose of 100% and rapid dose fall off after 3 mm.[181] Other HDR surface techniques using molds or flaps have the ability to treat larger volumes and slightly deeper, but the skin dose has to be evaluated. Gauden et al treated 236 lesions with Leipzig applicators to a dose of 36 Gy prescribed at 3 to 4 mm daily in 3 Gy fractions (36 Gy/12 fractions). They reported 98% LC and 88% excellent/good cosmesis.[182] Similarly Guix et al reported LC of 98% using customized surface molds and HDR brachytherapy with ^{192}Ir with doses between 60 and 65 Gy/30 to 33 fractions. Tumors larger than 4 cm were boosted after a treatment break to 75 to 80 Gy.[183] Bhatnagar et al reported their experience using electronic brachytherapy in 122 patients treated to 40 Gy in 8 fractions given twice weekly. LC at 1 year is 100%; no grade 3 or above adverse events were noted.

Success has also been reported for palliative treatments of Kaposi's sarcoma, cutaneous metastatic melanoma, angiosarcoma, Merkel cell metastases as well as T-cell and B-cell lymphomas.[184-187] Doses and fractionation for these treatments differ significantly. Superficial treatments using brachytherapy in the postoperative setting are also described for keloid scarring using dose ranges between 15 and 20 Gy in 3to 10 fractions.[188-190]

Sarcoma

Sarcomas are a rare tumor group that can occur throughout the body. The majority of the literature for sarcoma brachytherapy comes from the trunk and extremities. Brachytherapy for sarcomas can be used as a monotherapy postoperatively to improve LC or in combination with EBRT. Although much of the initial literature for brachytherapy in soft-tissue sarcomas (STS) used LDR brachytherapy, there is now sufficient evidence to support the use of both HDR and PDR brachytherapy in the treatment of STS.

The seminal MSKCC study evaluating LDR brachytherapy in STS randomized 164 patients with superficial truncal or extremity STS following R0/R1 (no residual/microscopic residual) resection to surgery alone versus surgery and brachytherapy. LC at 5 years was observed in 82% of brachytherapy patients versus 69% with surgery alone ($p = 0.04$). The LC difference was seen in patients with high-grade lesions (5-year LC 89% versus 66%, $p = 0.0025$), but brachytherapy had no impact on LC in patients with low-grade lesions.[191] There was no improvement in OS. In this study tumor size, margin of resection, and depth had no impact on LC.

Whether brachytherapy monotherapy is sufficient for tumors with positive margins is uncertain. In early MSKCC analyses, patients with high-grade STS and positive resection margins had trends for improved LC when treated with EBRT plus brachytherapy compared to brachytherapy alone (LC in 90% [9/10] versus 59% [10/17], $p = 0.08$).[192] However, in

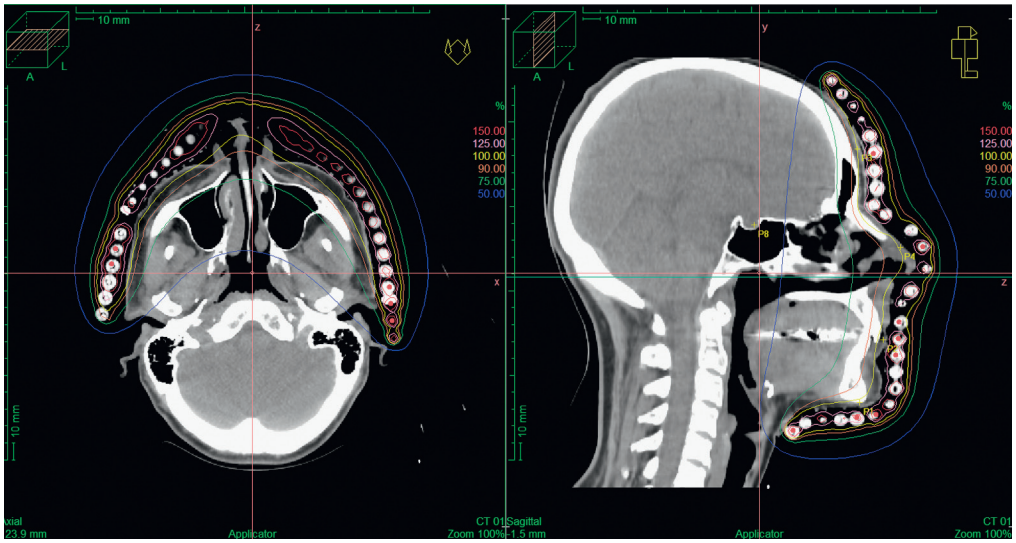


Figure 15-15 Custom surface mold with HDR applicator with an optimized treatment plan to a complex superficial target showing equivalent dose penetration despite multiple contours of the face.

subsequent publications that difference was not seen (LC 75% for brachytherapy versus 74% for EBRT with brachytherapy, $p = 0.9$).[193] Factors that may influence consideration of EBRT with brachytherapy include positive margins, low-grade tumor, size of tumor, and prior surgeries.[194] The dose for brachytherapy monotherapy and boost can be seen in Table 15-5.

The implant technique for LDR, PDR, and HDR interstitial STS brachytherapy is the same. At the time of the surgical resection the radiation oncologist and surgeon define the CTV and arrange a series of brachytherapy catheters to cover the CTV plus a margin of 1 cm to 2 cm. The catheters can be placed perpendicular to the scar or parallel with equal distance between the catheters. Typically the scar and drain sites are not included in the CTV. Single-plane implants are the most common, but multiplanar implants have also been described. The catheters are secured within the tumor bed and to the skin. CT planning allows for 3D evaluation of the CTV and normal tissues including the skin (Figure 15-16). Source loading of the implant typically occurs at least 5 days postoperatively because this has been found to decrease acute toxicity.[195] LC for brachytherapy monotherapy ranges from 55% to 100% and EBRT with brachytherapy from 71% to 100%.[196]

In a prospective cohort comparison the treatment outcomes of patients treated with brachytherapy monotherapy were compared with IMRT. The IMRT cohort had more adverse features including positive margins and tumor size, but the LC was better compared with brachytherapy monotherapy (91% versus 81%). The LC of the IMRT group was, however, comparable to other studies of brachytherapy monotherapy or brachytherapy boost as mentioned previously.

The most common acute toxicity is delayed wound healing with reoperation reported between 2.3% and 13.8% in the literature.[197] Bone fractures and neuropathy are reported, but the incidence does not appear to be increased by brachytherapy.[196] There are no trials to evaluate toxicity outcomes based on dose rate.

Brachytherapy has also been described as a boost for retroperitoneal sarcomas with mixed results. In a Princess Margaret Hospital (PMH) study, investigators initially reported EBRT plus brachytherapy to be well tolerated acutely except in the upper abdomen. In a subsequent PMH analysis with longer follow-up, EBRT plus brachytherapy was associated with increased toxicity with no difference in disease control compared to EBRT alone.[198]

TABLE 15-5 Recommended Brachytherapy Prescription Doses for Soft-Tissue Sarcoma

Modality	Dose		Dose Per Fraction or Dose Rate
	Monotherapy	Boost	
LDR	45-50 Gy	15-25 Gy	0.45-0.5 Gy/hr
PDR	45-50 Gy	15-25 Gy	0.45-0.5 Gy/hr
HDR	30-54 Gy	12-20 Gy	2-4 Gy/fraction

Modified from Holloway CL, Delaney TF, Alektiar KM, et al: American brachytherapy society (ABS) consensus statement for sarcoma brachytherapy. Brachytherapy 12:179–190, 2013.
Brachytherapy boost dose based on delivery of 45-50 Gy with EB.

Central Nervous System

Primary central nervous system (CNS) tumors continue to be one of the most aggressive and resistant of all human tumors. Despite the potential for higher tumor control through dose escalation the results have continued to disappoint. Whereas CNS brachytherapy at initial surgery is not practiced, it is reasonable to consider brachytherapy in treating recurrences in younger and high performance status patients when all EBRT options have been exhausted.

The most common form of CNS brachytherapy is the intraoperative placement of ^{125}I seeds along the walls of the resection cavity, held in place by various methods. Individual case series show reasonable level of LC with a tolerable level of radionecrosis. Another method uses an intracavitary balloon connected to a subcutaneous reservoir/port that is then filled with ^{125}I colloid for up to a week to deliver a therapeutic dose. The Brain Metastasis Study Group reported a Phase II study in which this device was used as a perioperative boost of 60 Gy with survival and recurrence similar to other published series of resection followed by EBRT.[199]

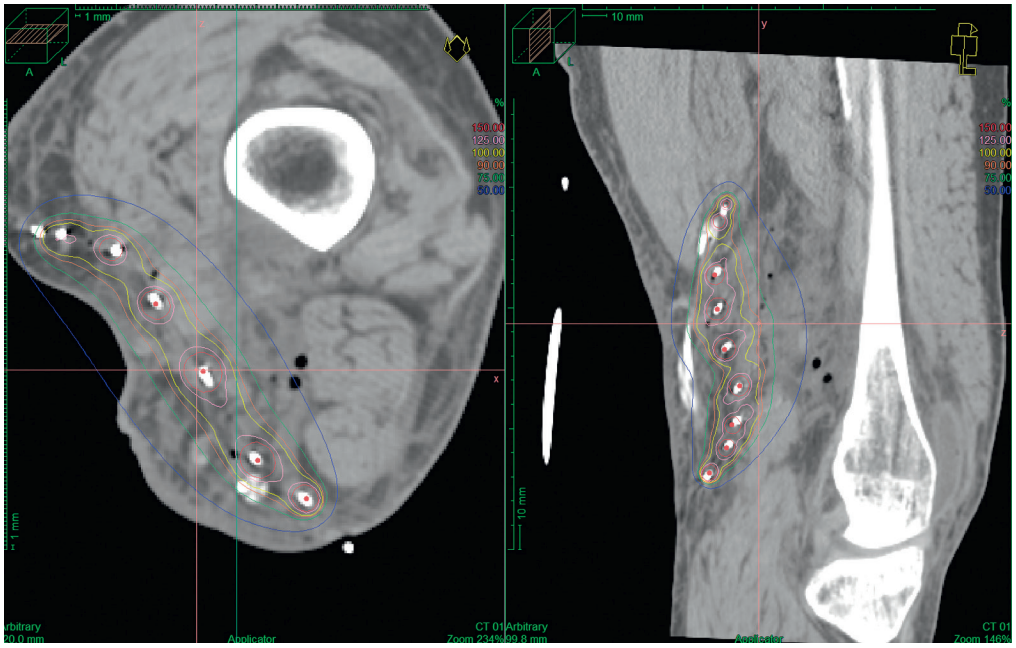


Figure 15-16 Single-plane implant for sarcoma brachytherapy delivery. The catheters are placed at the time of surgery.

Two prospective trials showed no statistically significant OS advantage for CNS brachytherapy. Brain Tumor Cooperative Group 87-01 trial randomized patients with newly diagnosed glioblastoma multiforme (GBM) to temporary ^{125}I brachytherapy as an addition to the regimen of EBRT and Carmustine (BCNU) chemotherapy; 270 patients were evaluated, 137 with EBRT alone and 133 EBRT with brachytherapy. The survival advantage of 10 weeks favored the addition of brachytherapy but did not reach statistical significance.[200] The University of Toronto randomization of an interstitial temporary ^{125}I boost after EBRT also showed no survival advantage.[201] Age, performance status, and the use of chemotherapy were associated with relative improved survival.

Recent attention has been turned to other CNS histologies, especially atypical meningioma in which small case series demonstrate the potential for brachytherapy in the recurrent setting when all external beam approaches have been exhausted and for which best resection can be attempted.[202]

Spinal CNS brachytherapy has been reported both as the use of permanent radioactive ^{125}I seeds placed in the region of the tumor and close margin at the dura at the time of partial of total vertebrectomy and reconstruction for various diseases.[199] An innovative approach deploys the temporary intraoperative use of a dural plaque coated with a beta-emitting foil such as Yittrium-90 (^{90}Y).[203]

Pediatrics

Brachytherapy is seldom considered a part of first-line therapy for children with cancer. However, the excellent use of this modality in the adult population combined with its inherent tissue-sparing abilities continues to stimulate pediatric radiation oncologists to develop innovative uses of brachytherapy as a part of modern multimodality care.

Case series for many solid tumor sites including Wilms tumor, neuroblastoma, hepatoblastoma, Ewing sarcoma, osteosarcoma, STS, rhabdomyosarcoma, retinoblastoma, and craniopharyngioma demonstrate the reasonableness of such considerations. Such series involve rare tumors, spread over many centers in different parts of the world with heterogeneous equipment and training. These case series demonstrate the reasonable use of ^{192}Ir HDR afterloading brachytherapy with computer graphics optimization, IORT with HDR brachytherapy, temporary ^{125}I-based extremity therapy, and sophisticated uses of ^{125}I eye plaques and even colloid. For consideration of the use of brachytherapy the patients would be referred to a pediatric cancer program that had the equipment and expertise. A comprehensive review of the applications and techniques in modern pediatric brachytherapy can be found in the Brachytherapy Applications and Techniques, ed 2.[204]

Ophthalmic

Ophthalmic plaques can used to deliver brachytherapy to the conjunctiva or the sclera. The choice of isotope used determines the type of applicator. Curved solid isotope applicators use Strontium-90 (^{90}Sr) with a fixed diameter applicator (typically 12 mm; see Figure 15-17) or Ruthenium-106 (^{106}Ru) in a range of diameters. These can be held in place for short applications or sutured directly to the sclera for longer applications. Alternatively customizable silicone or gold applicators can be loaded with seeds, usually ^{125}I, although the use of ^{103}Pd and ^{131}Cs seeds has also been investigated with promising dosimetric results.[205,206] Brachytherapy can be used for benign disorders such as pterygium and macular degeneration or for the treatment of primary malignant conjunctival tumors such as melanoma, squamous cell carcinoma, and lymphoma or for palliation of metastatic disease.[207]



Figure 15-17 Strontium applicator being held in position to deliver radiation to the sclera.

Before implant of anterior lesions, the eye is anesthetized using local anesthetic eye drops. The applicator is applied directly to the area of bare sclera, adjacent limbus, and affected cornea and either held in place by the operator for short applications or sutured to the sclera for longer applications. Following brachytherapy, the patient must wear an eye patch to prevent inadvertent damage to the eye. The use of natural spacers such as amniotic membrane has been described and may help to decrease pain during the procedure and reduce late toxicity.[208]

Following treatment, mild conjunctivitis is common, long-term sequelae are unusual, but the risks increase as fraction size and total dose increase. Scleral ulceration is the most common complication. Maculopathy may occur and is significantly associated with larger tumor size.[209] Retinal detachment is a rare late complication, with a reported rate of 1.48% up to 10 years after ^{106}Ru treatment of ocular melanoma[210] responding well to surgical management. Radiation-induced cataracts are rare, occurring following higher doses and responding well to surgery. Irradiation dose to the surgeon's fingers during implantation is low.[211]

Pterygium is a benign proliferation of the conjunctiva over the cornea. Locally applied ^{90}Sr decreases the rate of recurrence following surgery to as low as 0.5%,[212] using doses varying from 20 to 60 Gy in 1 to 6 fractions. Late scleral complications are decreased with fractionated treatment (4.5%

versus 1%). However, alternative treatments such as topical chemotherapy and conjunctival autografting are replacing ophthalmic plaque brachytherapy,[213,214] possibly because of ease of surgical administration.

^{90}Sr has also been used in the treatment of wet macular degeneration caused by neovascularization beneath the pigment of the retina. However, studies including brachytherapy for wet macular degeneration have not shown conclusive results with the potential toxicity of radiation retinopathy, thus this technique has been largely supplanted by the use of vascular endothelial growth factor inhibitors.[215] Brachytherapy may be of use in selected cases, particularly large areas.[216]

The Collaborative Ocular Melanoma Study (COMS) group conducted two randomized trials in North America, examining the use of ^{125}I for choroidal melanoma. When the use of ^{125}I brachytherapy was compared to enucleation for tumors of 3- to 8-mm depth there was no difference in survival and similar rates of toxicity.[217,218] Van Ginderdeuren et al demonstrated a 90% 15-year tumor control for sclera melanoma using a ^{90}Sr applicator using doses of 450 Gy to 800 Gy at the sclera.[219] There were a proportion of recurrences at the edge of the target volume, possibly because of the small applicator size. There was a 45% preservation of vision, which was generally dependent on tumor position rather than dose delivered.

Vascular

Endovascular brachytherapy in the treatment of peripheral vascular stenosis following angioplasty has fallen out of favor. A Cochrane meta-analysis of randomized control trials of percutaneous transluminal angioplasty (PTA) alone compared with PTA and brachytherapy in the femoropopliteal artery did not find sufficient evidence to support widespread use of endovascular brachytherapy.[220] Several trials comparing drug eluting stents versus brachytherapy for bare metal stent in-stent restenosis (ISR) of coronary vessels have shown brachytherapy to be associated with an increased incidence of target vessel failure.[221-223] In the TAXUS V-ISR trial, 396 patients with bare metal stent ISR were randomized to a stent eluting paclitaxel or beta source brachytherapy. At 24 months the freedom from clinical restenosis was worse for the brachytherapy cohort, but there were similar rates of death and myocardial infarction and target vessel thrombosis.[223] The randomized BetAce trial evaluating intracoronary brachytherapy for de novo lesions also failed to show benefit beyond 6 months with delayed and progressive restenosis.[224] Nonetheless, in the setting of multiple drug-eluting stent ISR failures for whom there is not a surgical bypass option then coronary vessel brachytherapy can be attempted to achieve suppression of refractory intimal hyperplasia. The BRAVO-II trial evaluated beta radiation for arterial-venous graft outflow stenosis in patients who undergo dialysis following angioplasty of a thrombosed graft. This trial closed early but did not show benefit to endovascular brachytherapy.[225]

SUMMARY AND FUTURE POSSIBILITIES

Brachytherapy is a fundamental part of any radiation oncology program. There are now more techniques and sources than ever before to use the unique physics and radiobiology of brachytherapy. Clinical research must continue to evaluate brachytherapy techniques allowing for more precise targeting of the volume of interest while minimizing dose to normal tissues. These further studies will also help guide dose and fractionation and define dose constraints and parameters.

Brachytherapy in the future will strive to deliver more personalized treatment through the use of image guidance and the ability to choose the best applicators and dose rate to fit the clinical scenario. Brachytherapy is particularly suited to subvolume dose escalation because of the ability to deliver a highly localized dose with rapid dose fall-off in the surrounding tissue. New biological and functional imaging modalities such as magnetic resonance spectroscopy (MRS) or positron emission tomography (PET) scanning could identify zones of aggressive cell repopulation that may allow dose escalation using brachytherapy.

The delivery systems for brachytherapy are also likely to evolve and improve in the future. The move from multiple catheter interstitial partial breast irradiation to the single-channel catheters is an example of this type of innovation. Delivery systems could be made more versatile with the capability to deliver different treatment modalities through the same applicator (e.g., brachytherapy and hyperthermia or chemotherapy). Brachytherapy delivery systems are not restricted to applicators. The use of injectable radioisotopes bound to delivery agents such as tagged antibodies or annealed spheres is likely to increase with future developments in antibody technology.

Future indications for brachytherapy are ever increasing, but it must be remembered that recommendations for the use of resource intense treatment and planning modalities, such as CT-guided implant placement, or MRI brachytherapy planning, may create treatment paradigms that are unsustainable in many healthcare systems around the world. When international guidelines are devised, emphasis should be placed on the use of available and accessible technology.

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CHAPTER

16 Intensity-Modulated and Image-Guided Radiation Therapy



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DEFINITIONS FOR CONFORMAL AND IMAGE-GUIDED THERAPY

Conformal therapy describes radiotherapy treatment that creates high-dose volume(s) that are shaped to closely "conform" to the desired target volumes and prescription doses while minimizing (as much as possible) the dose to critical normal tissues. As capabilities have improved, the definition of conformal therapy has expanded to incorporate the fact that high-quality conformal therapy is designed to conform to all the target dose requirements (both target volume shape(s) and the potentially complex dose distributions desired inside each target) while minimizing the normal tissue doses. Although these features are the general aim of any radiotherapy treatment, normally the term *conformal* is applied to treatment plans in which (1) the target volumes are defined in three dimensions using contours drawn on many slices from a computed tomography (CT) (or other) imaging study; (2) multiple beam directions are used to cross fire on the targets; (3) the individual beams are shaped or intensity modulated to create a dose distribution that conforms (in shape and dose) to the target volume shape(s) and desired dose levels; and (4) appropriate use is made of image guidance, accurate patient setup and immobilization, and management of motion and other changes to ensure accurate delivery of the planned dose distributions to the patient, so that deviations from the planned treatment of the patient are minimized. Figure 16-1 illustrates the conceptual difference between standard and conformal therapy: Figure 16-1, *A* shows a standard four-field box treatment for a given target volume that everyone would agree is a nonconformal approach, whereas Figure 16-1, *B* shows a conformal approach achieved with conformally shaped fields.

A number of different treatment planning techniques and various treatment delivery techniques are routinely used to perform clinical conformal therapy. Three-dimensional conformal radiotherapy (3DCRT) was the first conformal therapy technique developed, based on use of three-dimensional (3D) treatment planning and multiple cross-firing, carefully shaped fixed fields. A more recent planning method—inverse planning—involves creation of the radiotherapy plan using mathematical optimization techniques; often, this inverse planning technique is used to define intensity-modulated beams, which are radiation beams with a complex intensity distribution rather than the "flat," uniform intensity fields typically used for 3DCRT. The combination of inverse planning and intensity-modulated beams is called *intensity modulated radiation therapy* (IMRT). In recent years, the combination of IMRT delivery and optimization methods with arc therapy, volumetric modulated arc therapy (VMAT), has become an important method for the delivery of conformal therapy. All of these conformal therapy delivery methods are greatly improved by (and usually require) the use of image-guided radiation therapy (IGRT) techniques to accurately position and set up the patient, using integrated megavoltage or kilovoltage diagnostic imaging, cone beam CT, radiofrequency beacons or radiographic fiducials, and other image-guidance methods. Active consideration of the patient's respiratory (or other) motion in planning is described by four-dimensional (4D) imaging and 4D planning, and active motion management strategies are used during treatment to address the motion issues.

In general, there can be many different combinations of technologies used to develop and implement sophisticated conformal therapy. Conformal therapy is defined by the kinds of dose distributions that are planned and delivered to the patient, not by the specific technique(s) that are used. For example, one often performs conformal therapy by using IMRT, but the fact that IMRT is used does not necessarily imply that the treatment is conformal.

A SHORT HISTORY OF CONFORMAL AND IMAGE-GUIDED THERAPY

For many decades it has been known that delivering a high dose to the tumor is critical for control of the tumor and that the probability of complications increases with radiation dose and volume of organ irradiated. The basic concept of conformal therapy was elucidated quite early: "Treat the tumor to a high dose while minimizing the dose to normal tissues." However, it was not until the 1950s and 1960s that techniques recognizable as modern conformal therapy began to be developed.

One of the most important pioneers in "conformation therapy" was Shinji Takahashi, who described many of the important concepts of conformal therapy delivery and 3D treatment planning in a 1965 monograph.[1] Takahashi's innovations included early multileaf collimators, automated (mechanical) conformal beam shaping, dynamic conformal treatments, orthogonal light beams to identify the machine isocenter, and 3D tumor models based on early tomography.[1] Other notable work in this area was performed by Harold Perry and colleagues[2] in Detroit and by Proimos, Wright, and Trump at the Massachusetts Institute of Technology (MIT)–Lahey Clinic.[3-7] Another early approach to conformal therapy, known as the Tracking Cobalt Project,[8,9] was led by Green, Jennings, and others at the Royal Northern and Royal Free Hospitals in England. First reported in the late 1950s,[10] and summarized by Jennings, a series of mechanical, electrical, and finally, computer-controlled treatment machines were developed to track disease spread, particularly along lymph node chains. By 1980, the computer-controlled version of the tracking system was in clinical use,[11] although Brace summarized the major limitation to the delivery technique: "The major obstacle to the routine use of conformation therapy is treatment planning."[11] Finally, workers at the Joint Center for Radiation Therapy (JCRT) in Boston added computer control to a modern linear accelerator, so that the treatment table,

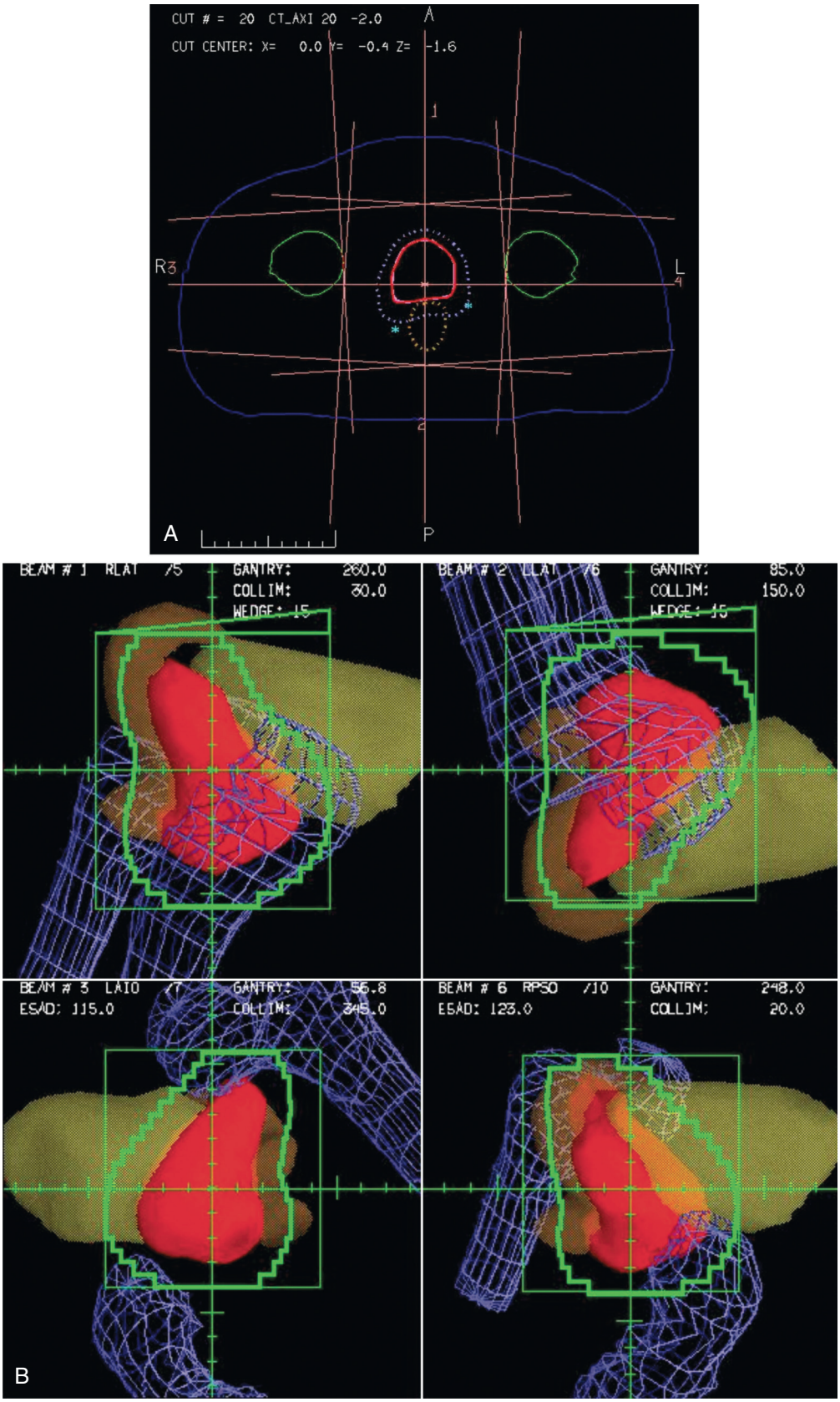


Figure 16-1 **A,** Four-field box treatment of the prostate. Contours shown include *blue* external contour, *red* prostate, *dotted* PTV, *yellow (dotted)* rectum, and *green* femoral heads. **B,** Beam's-eye view of a nonaxial four-field conformal plan for prostate treatment, where the *green* outlines show the conformally shaped MLC patterns for each field. *Red* is prostate, *blue* is femoral heads, *yellow* is bladder, and *brown* is rectum.

gantry, collimator, collimator jaws, dose rate, and other parameters could be controlled dynamically while the beam was in use. The JCRT achieved the delivery of what is now called "dynamic conformal therapy,"[12-15] which was a modern basis for computer-controlled conformal therapy.

As already described in the quote by Brace, treatment planning was one of the main limitations for the conformal delivery techniques that were developed during this time period. The introduction of CT in the early 1970s was a key to the development of the modern 3D planning that is crucial to conformal therapy because it made available a complete 3D description of the anatomy of each patient that could be the basis for planning. Early evaluation of the use of CT in treatment[16-18] quickly led to widespread use of CT-based planning (see Ling[19]) as well as new interest in the use of inhomogeneity-corrected dose calculations, which became possible because CT provided the necessary electron-density maps of the patient.[20] Other imaging data, including magnetic resonance imaging (MRI) and positron emission tomography (PET), also became available and began to be used for planning in the mid-1980s.[21]

With the widespread implementation of CT-based planning, it became possible to make use of continuing improvements in computer technology and new software developments to create fully 3D treatment planning systems that incorporated 3D graphics and the "beam's-eye view" (BEV), a 3D graphic reconstruction of the patient anatomy projected into the divergent geometry used by the x-rays in the radiation beam[22-26] (Figure 16-2). Using BEV displays to design field shaping[27] and evaluate coverage of tumor and sparing of normal tissues is perhaps one of the most effective concepts in the entire 3D planning paradigm. Routine clinical use of 3D radiation treatment planning (RTP) began in 1986,[28] and many academic centers began development and then use of 3D planning systems in their clinics.[29-32]

The development of 3D treatment planning systems helped drive the need for and design of more sophisticated treatment delivery systems because the 3D planning systems

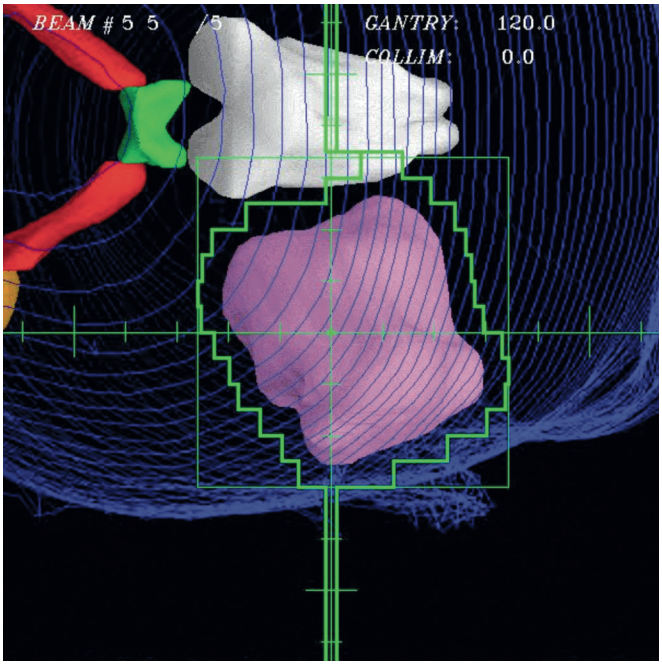


Figure 16-2 Beam's-eye view of a brain tumor showing a multileaf collimator shaped to the *violet* target volume. Normal tissues include brainstem *(white)*, chiasm *(green)*, and optic nerves *(red).*

demonstrated treatment improvements that would be possible to use clinically if more sophisticated machinery were available to make efficient delivery possible. The first treatment machine designed specifically to perform computer-controlled conformal radiotherapy (CCRT), the Scanditronix MM50 Racetrack Microtron, was developed during this same time period.[33-35] Among other unique features, this machine included a fully computerized control system and a computer-controlled multileaf collimator (MLC),[36] consisting of two sets of thin tungsten leaves that are used to shape the radiation field. Virtually all other radiation therapy machines have since also implemented computer control systems and MLC systems.[37-39]

The capabilities of computer control and MLC systems have made possible the delivery of complicated plans, including those that make use of modulated intensities (a beam with different intensities in different parts of the field). Intensity modulation created using multiple segments[40-45] or dynamic MLC motions[33,46,47] and computer plan optimization (inverse planning)[48-52] have been integrated and called *intensity modulated radiation therapy* (IMRT).[53] The basic concepts of IMRT were described in 1987 by Brahme[33,48,54] and a practical implementation was described by Bortfeld soon after.[55] The combination of the flexibility of computer-controlled IMRT delivery with sophisticated plan optimization techniques has made IMRT an extremely powerful tool that can be used to perform conformal therapy.

The initial commercial IMRT implementation by NOMOS in 1992[56] was a form of IMRT now called *serial tomotherapy*, in which patients were treated slice by slice (as with early CT scanners) by the machine rotating around the patient using a special multileaf collimator (MIMIC) that performed the intensity modulation. Within a few years, all major vendors had implemented MLC systems, with leaf widths varying from 1 cm to a few millimeters, that could perform IMRT using either dynamic motions of the MLC leaves ("DMLC") or a number of static segments (called "SMLC").[53] A more sophisticated implementation of tomotherapy based on helical delivery of IMRT, helical tomotherapy,[57] also became widely disseminated. In the last several years, a rotational MLC-based IMRT technique, originally described by Yu,[58] has been implemented and widely disseminated (VMAT).[59,60] Inverse planning has also developed substantially during this time. Though much of this optimization makes use of quadratic weighted sum cost functions and simple gradient-based search algorithms, there have also been developments of sophisticated cost functions[61] and the use of more biologically related costs that make use of normal tissue control probability (NTCP) models and equivalent uniform dose (EUD). Most inverse planning systems use the weighted sum cost functions, but there has been development of sophisticated multicriteria methods[62,63] that more directly take into account the numerous optimization goals involved in a typical clinical radiotherapy treatment plan and prioritize clinical tradeoffs.

One of the developments that made the conformal therapy revolution possible was the development of amorphous silicon flat panel imagers,[64] which allowed effective electronic portal imaging verification of the accuracy of these newly conformal fields. This technology then was further developed, first for kilovoltage (diagnostic quality) imaging and then to provide cone beam CT (CBCT) capability using kilovoltage imaging systems mounted directly on the treatment machine.[65] The availability of these high-quality CBCT or kilovoltage imaging modalities directly on the treatment machine led to the development of IGRT, in which diagnostic imaging is used to correct patient setup and positioning for treatment every day. IGRT processes have greatly increased the delivery accuracy that can be routinely achieved and have led to the possibility of much smaller margins for setup errors. This improved

confidence in targeting accuracy has made possible the development of stereotactic body radiation therapy (SBRT), which is now used routinely to give very high doses to well-localized targets in the liver, lung, and other sites using highly conformal treatment delivery performed with IGRT. The use of IMRT and the proper handling of patient motion, respiration, and other 4D issues have been pursued for many years and are still major threads of much current research and development.

ISSUES FOR CLINICAL USE

A number of important clinical features are crucial for planning and delivery of high-quality conformal therapy, and these issues should be carefully considered throughout the conformal therapy planning and delivery process.

- Conformal therapy attempts to carefully conform the dose to the target(s), so delineation of the target(s) and careful specification of the desired dose distribution(s) are crucial.
- Patient immobilization, localization, and motion are crucial, and setup accuracy and motion management must be considered throughout the process to minimize normal tissue that will be irradiated because needing to increase target margins will significantly decrease the advantages provided by conformal treatment.
- Improvement of the clinical results achieved by conformal therapy, compared with standard techniques, depends on choosing the correct tradeoffs between target coverage and normal tissue sparing, so these choices must be made carefully and appropriately.
- It is the quality and precision of the dose distribution that is achieved which is important. The techniques used for planning and delivery (e.g., DMLC IMRT, VMAT, 3D) are simply the means to achieve the desired dose distribution.
- The quality of the delivered dose distribution can be destroyed by motion, respiration, setup error, or involuntary motions during treatment, so use of motion management techniques to control motion (e.g., active breathing control, respiratory gating, tumor tracking) is essential for some clinical sites. The use of 4D CT for planning and IGRT for setup and motion analysis are all big contributors to the quality of the treatment.

PLANNING FOR CONFORMAL THERAPY

Treatment planning is one of the most critical parts of the conformal therapy process. In this description, we include all preparatory aspects of the planning process, including many activities that occur outside the therapy planning system (TPS). Many treatment delivery issues (e.g., setup accuracy, patient motion, portal and localization imaging) are briefly mentioned here and are more completely described later. Figure 16-3 shows a schematic of the basic components of the planning process for both forward (interactive) and inverse (i.e., IMRT optimization) planning.

Positioning and Immobilization

One of the basic ideas of conformal therapy is to minimize the dose to normal tissues while conforming the dose to the target, so it is of course crucial to accurately position and immobilize the patient for each procedure in the planning and delivery process. One of the first clinical decisions to be made for each patient includes what position to use for the patient's treatment and whether any positioning and immobilization devices or aids will be used.

Basic patient positioning, including location of the arms and legs and positioning of the patient (supine, prone, or in some other more unusual position), depends mainly on two issues: (1) patient comfort and stability and (2) the beam directions that will be used. In most cases, conformal therapy plans make use of three or more beams that cross fire on the target from a number of different angles arranged around the patient, so the patient is typically positioned with both arms up (if the target is somewhere in the torso) or arms down (head and neck and brain targets). For superficial targets, the target is typically positioned facing up to allow easy visualization of the target, but for most deep tumors, the cross-firing beam directions can be achieved with the patient in standard supine or prone positions, whichever is most stable and accurately set

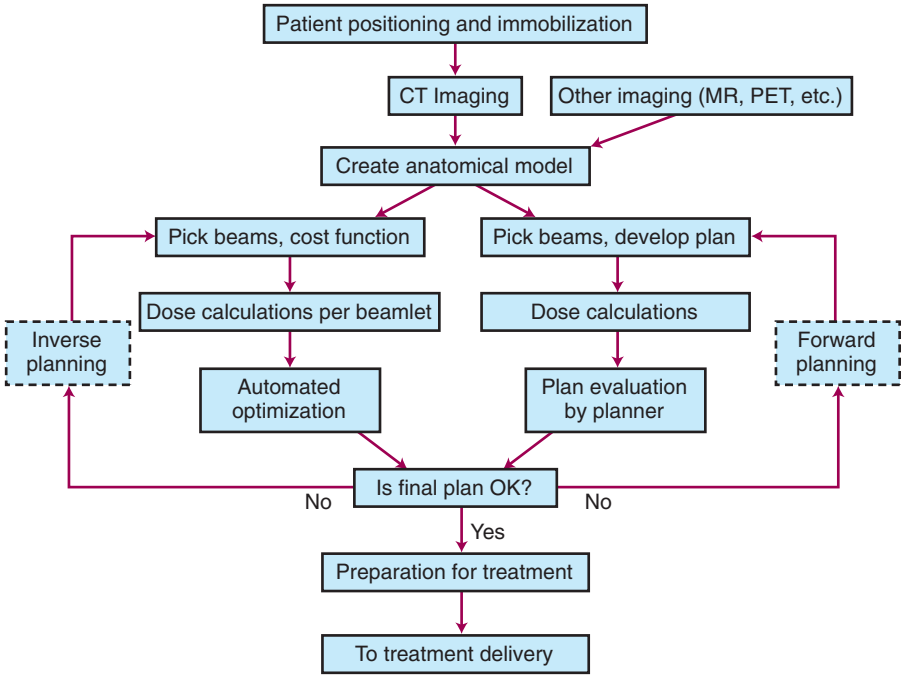


Figure 16-3 Schematic chart of the basic components of the planning process, shown for both forward and inverse planning.

up. There have been studies of the benefits of various positioning decisions (e.g., prone versus supine) for patients with prostate tumors[66]; there is some debate about the relative merits of the possible anatomic changes that occur for the prone versus the supine position, relative to other advantages and disadvantages for planning, daily setup, and respiratory motion-related stability.

The use of various types of so-called immobilization devices to help with patient positioning and immobilization for conformal therapy has run the entire gamut of possibilities, from the use of stereotactic head frames and other such devices that are physically attached to the patient's skull to other techniques that do not use any immobilization device. Early conformal therapy (1980s to 1990s) often incorporated a foam cradle device to help position the patient[67] though currently it is thought that more precision can be achieved without use of the cradle devices in many situations. In the end, each clinic should document the setup accuracy that is achieved with their chosen methods, for each clinical site, so that the planning and delivery process can take proper account of the expected systematic and random setup uncertainties. The use of in-room imaging systems (e.g., diagnostic and megavoltage CBCT) has provided more detailed information about setup accuracy and makes it possible to improve setup accuracy and minimize margins using IGRT setup.

Imaging for Planning: CT, CT Simulation, MRI, and Other Cross-Sectional Imaging

The development of x-ray CT in the 1970s and its application to radiotherapy planning[18] were absolutely crucial milestones in the development of conformal therapy techniques. Without the cross-sectional anatomic imaging provided by CT (or MRI), there was not enough anatomic knowledge about the tumor or normal anatomy to consider the use of highly conformal dose distributions. Once the detailed anatomic information provided by CT became available, it was clear that radiotherapy planning and treatment should make use of this new and detailed description of the patient to better spare normal tissues and more accurately deliver dose to the tumor. Conformal therapy is a logical response to the detailed information provided by CT.

Modern conformal therapy is always based on a 3D anatomic model of the patient, which is typically based on a CT scan of the involved region. Usually, a specific type of CT scan, the treatment planning scan or CT simulation, is obtained for use as the basis for treatment planning. Features of a basic treatment planning CT scan are listed in Box 16-1. One specific treatment planning CT scan procedure often used is called CT simulation. The CT simulation usually consists of a treatment planning CT scan plus the addition of the delineation of a reference point within the CT dataset (to be used for later planning or setup procedures), followed by marking this reference mark on the patient's skin. Sometimes CT simulation software on the CT scanner workstation is used to define the beams for the treatment plan, though this activity is really just simple treatment planning performed on the CT workstation.

Developments in CT and treatment delivery technology have made the consideration of motion during CT scanning (and radiotherapy treatment) an important topic. 4D CT describes various techniques for obtaining CT data correlated with patient respiratory phase information so that the changes associated with respiration (or other motion) are displayed. For certain clinical sites (e.g., lung, breast, upper abdomen), it is clear that consideration of respiratory motion is an important aspect of the initial imaging of the patient, so 4D CT is used to create an appropriate motion model of the patient for further planning and analysis. 4D CT,[68] respiratory gating,[69] active breathing control (ABC),[70,71] or other methods for motion management are often used for many treatment sites, though which combinations of techniques and methods are most efficient and appropriate is not yet clear.

BOX 16-1 Treatment Planning CT Scan Features

- Use a flat tabletop to mimic the treatment machine couch. Make use of couch coordinates or other documentation of exact positioning if possible.
- Use patient immobilization devices to position the patient in the same way as for treatment, including registration of the device with the couch top (if available).
- Scan extent should include completely any organs to be considered as organs at risk because planning typically requires delineation of entire organs to make use of biologic effect data. For example, treatment anywhere in the thorax would typically require scanning from the apex of the lung to below the diaphragm, so that the entire lung could be delineated.
- Modern CT scanners are efficient enough that 1- to 3-mm-thick slices can be obtained throughout the entire region of the scan, though use of thicker slices outside the target region is possible. This can amount to several hundred CT slices per study.
- Careful consideration must be given to the advantages and disadvantages of using contrast during the scans. Contrast can help identify organs but can also make accurate dose calculations difficult (because it distorts the apparent electron density of the tissue, affecting dose calculations).
- The treatment planning CT scan study is used for (1) target definition and delineation, (2) normal tissue delineation, (3) the overall anatomic model of the patient, (4) planning, (5) dose calculations based on electron density obtained from CT numbers, and (6) creation of digital reconstructed radiographs (DRRs) used to set up and verify patient position. Each of these uses may require some individualization of the CT scan protocol or use.
- The CT scan protocol should be defined for each clinical site, including slice thicknesses, scan extent (top and bottom), reconstruction window size, use of contrast, patient positioning and immobilization, patient breathing control or instructions, and so on.

CT provides anatomic and electron density information that is critical for most treatment planning, and it also provides a geometrically accurate base for planning. However, it provides only anatomic information, not the physiologic and functional information that would be helpful for planning, and it has only a limited amount of soft tissue contrast. MRI can provide complementary data, including excellent soft-tissue contrast and different kinds of physiologic information. In addition, functional magnetic resonance imaging (fMRI) studies can provide some of the functional information that to this point has been unavailable. Other kinds of imaging also contain complementary or new information. Positron emission tomography (PET) and single-photon emission computed tomography (SPECT) provide functional and physiologic information that can be quite important in helping define target volumes and regions that should be included or excluded from the radiation fields. Which modalities, scans, tracers, and analysis methods should be used for specific features is well beyond the scope of this work. However, to quantitatively make use of any additional imaging modality for treatment planning, one should incorporate a number of important procedures into the imaging process, as listed in Box 16-2.

BOX 16-2 Imaging for Treatment Planning (Not Including CT Imaging)

- Use a flat tabletop to mimic the radiotherapy Linac couch.
- Use patient immobilization devices to position the patient as you would for treatment.
- Ensure that the imaging protocol provides enough anatomic information to allow geometric registration of the new scan study with the base CT information.
- Imaging protocol parameters should be optimized to provide the anatomic, physiologic, or function data that are desired.
- The scan protocol should be defined for each clinical site and protocol, including slice thicknesses, scan extent (top and bottom), scan orientation (nonaxial slices are possible in most non-CT methods), reconstruction window size, use of contrast, patient positioning and immobilization, patient breathing control or instructions, and so on. For MRI, many additional scan technique parameters must be defined.
- CT scans should be performed in a manner that will allow accurate registration of other scan information (e.g., MRI, PET) with the CT scans.
- Motion management (consideration of how motion will be managed for CT scanning and for treatment) is an important part of the preparation for planning. It is appropriate to (1) control respiratory motion or (2) perform a 4D CT scan[68] for patients who demonstrate any significant motion in the target region. It may be necessary to perform a quick scan to evaluate motion before deciding on the final planning scan protocol and methodology.

To use more than one imaging dataset for planning, the additional datasets will have to be registered geometrically to the original (base) CT dataset (as described later). It is important during the imaging process (1) to position and align the patient similarly for each of the imaging studies because this makes the registration process more straightforward, and (2) to obtain all the information necessary so that the dataset registration and fusion process can be performed quickly and accurately. If the patient geometry is different between scans, deformable registration may be useful to "align" datasets, but the accuracy of that alignment is still being worked out for each registration method and situation.

Anatomy for Treatment Planning

Treatment planning is a computer simulation of the process of radiotherapy treatment, and it is based on creating a model of the patient inside the planning software, simulating radiation beams and the dose that those beams deliver to the patient. The definition of the virtual model of the patient, based on CT, MRI, and other types of imaging data, and how that anatomic model is used are crucial parts of the radiotherapy treatment planning process.

Three-Dimensional Anatomic Model

For conformal therapy planning, the representation of the patient used for treatment planning must be realistic and three dimensional. In general, the basic data used to define the anatomy come from a CT study, typically consisting of 50 to 200 CT scan slices. The anatomic model of the patient is based on this CT data and consists of a number of objects (structures) that delineate organs or other objects (e.g., target volumes) in 3D (or 4D; see Motion, Setup, and Four-Dimensional Anatomy). These structures can be defined by (1) a series of contours, (2) a 3D surface description, (3) a voxel-based description, or (4) a set of points distributed either randomly or on a grid. Methods used to delineate these structures are described in the section on Structure Delineation and Contouring.

The 3D anatomic structures are crucial to the planning process. The various target and normal tissue structures describe the areas to be irradiated or to be spared (respectively) so beams can be oriented and shaped. Graphic display of the 3D structures can also be used for geometric registration of the treatment planning anatomy to localize images obtained during simulation or treatment procedures. The external surface and any inhomogeneities are used for the dose calculation process. Most plan evaluation tools (e.g., dose-volume histograms [DVHs]) make use of these 3D structures for plan evaluation of the planned dose distribution.

Structure Delineation and Contouring

The delineation of the 3D anatomic objects (structures) used for planning and plan evaluation is one of the most important and time-consuming aspects of the entire conformal therapy process. It would be nice if all the anatomic structures could be automatically delineated once the CT data (and other imaging data) were obtained, but in general, this technology is still under investigation and development. Most anatomic structures are delineated by drawing contours on top of each of the CT (or other) images that are available. Because several hundred CT slices are often used, and there are many organs of interest that appear on each CT slice, there are many contours to be defined. Clever computer graphics drawing tools and techniques can make this easier, but defining the contours still requires much effort and care.

Accurately defining the structure contours is a critically important aspect of the conformal therapy process, and because it defines the target and normal structure extents for the entire process, any error or inaccuracy becomes a systematic error throughout the entire conformal therapy process. Errors in the process may come from sloppiness, from not knowing what is being visualized on the image on which contours are drawn, from limitations in the accuracy of the scan information (e.g., motion during the scan acquisition), interpolation of contours, and from many other problems. It is important that the 3D character of the objects being outlined is handled correctly: for example, sharp corners or spikes in a contour on just one slice are usually incorrect because such a structure will usually show related features on a number of images. To avoid this type of drawing problem, it is important to review all the contours serially or to visualize the 3D shape of the object, using coronal and sagittal planes, so that any unrealistic "spikes" can be identified and edited.

Target Volume Definition and Margins

To plan and deliver conformal therapy, it is essential to accurately define the volumes that must receive high radiation doses, the "target volumes." As described in detail in the International Commission on Radiological Units (ICRU) report ICRU-50,[72] three kinds of target volumes are typically defined, as summarized in Table 16-1.

The gross target volume (GTV) is typically delineated by drawing the imaged tumor on each of the imaging studies that are available. CT is used often, but for many sites, MR and PET can be useful. When multiple imaging studies are available, the GTV can be drawn on each study, and then, using dataset registration to geometrically align the different datasets (see "Multiple Imaging Modalities: Dataset Registration and Fusion" section), one can combine or transfer the different GTV contours onto a single dataset. How to combine the various GTVs defined is the subject of ongoing research;

TABLE 16-1 ICRU-50 Target Volume Definitions

Abbreviation	Name	Description
GTV	Gross tumor volume	Volume of macroscopic tumor that is visualized on imaging studies
CTV	Clinical target volume	Volume that should be treated to a high dose, typically incorporating both the GTV and volumes that are assumed to be at risk as a result of microscopic spread of the disease
PTV	Planning target volume	Volume that should be treated to ensure that the CTV is always treated, including considerations of systematic and random daily setup errors and inter- and intratreatment motion

however, typically, one will combine or take the union of all the defined GTVs to make sure that no gross tumor is missed within the defined GTV. Depending on the quality of the registration, additional margin is sometimes warranted for registration error.

The definition of the clinical target volume (CTV) is probably the most important thing that the physician does in the conformal therapy process, because the CTV defines the region that is supposed to be treated with the prescribed dose. The CTV typically combines the GTVs plus any volumes that may contain microscopic disease that could not be imaged. The CTV depends on knowledge of the patterns of disease spread and incorporates any other clinical knowledge of the disease or the specific risks for spread that apply to the individual patient. The CTV is usually created by combining two kinds of information: (1) often, an expansion of the GTV by some margin (0.5 to 1 cm, typically) is used to account for microscopic invasion, and (2) additional anatomic areas may be included in the CTV based on standard directions of spread for the particular tumor type. In the end, the goal is to outline all the areas that should receive the intended dose.

Whereas GTV and CTV definition are the job of the physician, definition of the planning target volume (PTV) is mainly the responsibility of the physicist and treatment planner because the goal of the PTV is to make sure that the CTV is adequately treated in the face of setup error, inter- and intrafraction motion, delineation errors, and other errors in the planning and delivery process. The definition of the PTV should be done with as much information as possible because the region between the CTV and PTV contours is all "normal tissue" and increasing the PTV margin will just cause more normal tissue to be irradiated. In a way, the physician is also involved in PTV definition by thoughtfully ordering appropriate patient or tumor immobilization for simulation and treatment. If a large PTV will not produce significant toxicity, and the prescribed dose will be low, then immobilization can be basic. If, however, each additional millimeter of PTV margin will clinically make a difference, then strict immobilization must be ordered.

Often, the PTV is designed by simply defining an isotropic margin (e.g., 1 cm), and the CTV is expanded by this margin to create the PTV (Figure 16-4). This expansion should be performed in three dimensions because expansion of contours only in the axial plane will lead to PTVs that are not correct in the third dimension. If the uncertainties are not isotropic but are larger in one direction than in the others (e.g., as a result of respiration), then the margin to be applied should be anisotropic.

There has been a great deal of work studying patient positioning, motion, and target volume delineation errors, and analysis of these issues has led to specific recommendations for the size of the margin (between the CTV and the PTV) that should be used for the PTV. As described in the "Consideration of Setup Error and Patient Motion" section, one reasonable method for deciding the PTV-CTV margin has been determined to be $(2.5 \times \Sigma) + (0.7 \times \sigma)$, where Σ is the standard deviation of the systematic error and σ is the standard deviation of the random errors for the population of patients treated in that particular site.[73] To apply this formula, it is important to have measured, for your institution and each clinical site, the two different standard deviations. As can be seen from the formula, the systematic errors in the process, such as incorrect contouring or use of a nonrepresentative CT scan for target delineation, are much more important issues than random day-to-day setup errors.

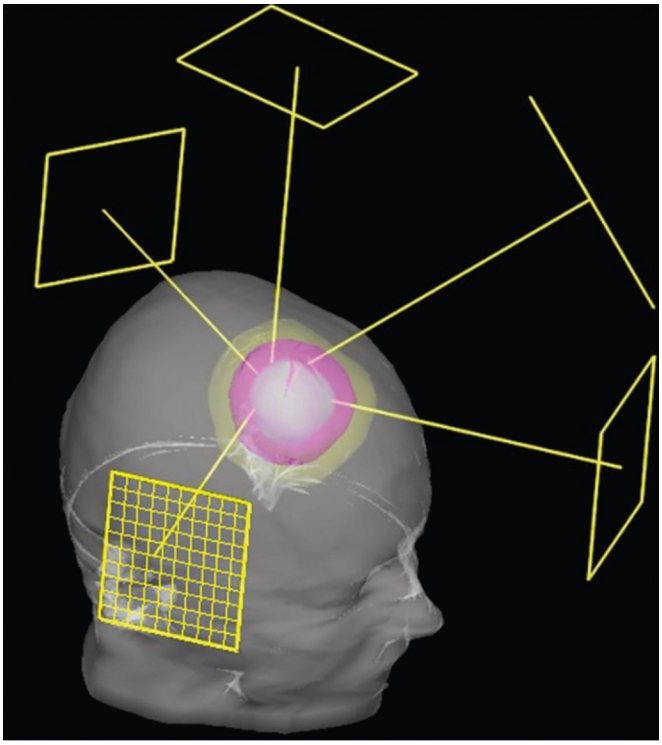


Figure 16-4 Noncoplanar IMRT plan for treating a brain tumor, with the ICRU-50 target volumes shown: gross tumor volume *(white)*, clinical target volume *(pink)*, and planning target volume *(yellow)*.

Further discussion of other types of target volumes, including the internal target volume (ITV), is included later in the section on motion.

For an individual patient, there can be multiple sets of GTVs, CTVs, and PTVs because there are often a CTV and PTV that correspond to each individual GTV. In the head and neck, where often a number of different nodal CTVs need to be treated, it can be important to develop an organized and clear naming convention for the various CTVs and PTVs.

Normal Tissues

Definition of *normal tissues* is also a critical task for conformal therapy because identifying the critical tissues will allow the treatment planner to avoid or at least minimize delivery of dose to those normal tissues. The planning tools used to avoid these structures can be simple graphic tools such as the BEV

display, which allows the planner to shape the radiation fields to avoid important structures, or it may involve detailed dosimetric and DVH analysis, as is often the case for IMRT planning.

To perform DVH or other dosimetric analysis, it is important that each organ to be analyzed be contoured completely because most current DVH data are characterized with respect to the whole organ's volume (either absolute volume or as a percentage of the whole organ). This has several implications:

1. The CT scans or other studies for a given site must image all the relevant normal tissues completely as well as the tumor. For example, a lung tumor CT scan should always include images from the neck down to below the bottom of the diaphragm, so that the complete volume of the relevant normal tissues can be identified (e.g., lung, heart, esophagus, spinal cord, rectum).
2. Contouring of normal structures must be done consistently if the DVH information is to be useful. Whole organs should always be contoured. For tubelike structures (e.g., spinal cord, rectum, esophagus) that can often extend out of the region of the tumor, it is important to have a defined protocol for how the structure will be defined, so that the superior and inferior extents of the contours for the structure are specified (e.g., the rectum during prostate planning). This is particularly important if relative volumes (e.g., <50% receiving >50 Gy) or mean doses of these normal structures will be used for plan construction and evaluation.

Multiple Imaging Modalities: Dataset Registration and Fusion

Although CT scans are the primary imaging modality used for radiotherapy planning, information from other types of imaging, particularly MRI and PET, can be useful for identifying disease or better identifying functional or anatomic areas that should be spared. Target volumes and normal structures can be identified on these additional imaging datasets, and that information can be incorporated into the treatment plan along with the contours and data from the CT scans. As described before, a CT scan set is typically taken to be the geometric basis for the treatment planning because the CT data are of high resolution, are geometrically accurate, describe the electron density information needed for inhomogeneity corrections, and are quickly obtained.

Several issues need to be solved to make quantitative use of the additional imaging information.

- For each imaging procedure, the patient should be positioned within the imaging device using the same position and immobilization and localization devices as for treatment. However, there are often positioning differences that must be taken into account.
- Even if the patient positioning is perfect, the coordinate system used in the new imaging device is usually different than the coordinate system used by the original CT scan. Therefore, a geometric registration of the new imaging information must be performed, to align the new images with the base imaging information. Otherwise, with different coordinates, one does not know how to map pixels in the new image dataset to the coordinates of the original image set.
- For many imaging modalities, for example, MRI, various kinds of distortion are possible. If the new image dataset has geometric distortions, then these must be corrected (or at least accounted for) before the imaging information can be transferred into the base coordinate system for use in planning.
- The resolution, slice thickness, and slice orientations of different imaging modalities can often be different than those of the original CT dataset, so any quantitative use of the new imaging data must also handle these kinds of differences.

To address these issues, the process of dataset (or image) registration is used to align the coordinates for the various imaging datasets so that information can be passed from one image set into a coordinate system to be used for treatment planning. The registration process finds the geometric transform between the new dataset's coordinate system and the base coordinate system (typically, the CT scan). If one considers only rigid body registration, the transform can consist of x, y, and z translations, or both translations and rotations, and it can include scaling as well (although typically, the scale of each dataset is known accurately and should not be modified).

Handling of deformable image registration is an important current research topic. These efforts work to develop methods for mapping deformations from one system to another, so the deformations resulting from imaging or patient motion (e.g., respiration) can be taken into account. Many different mathematical methods have been employed, including thin plate splines, B-splines, demons, and others.[74] However, the main current issue is that deformation is handled well for things that are imaged well, but there is no way to determine how to do the deformation mapping for tissues that are not well imaged. Most current algorithms do not take into account anatomic constraints and sliding organs (e.g., the diaphragm and lungs during respiration). Much work remains here.

To determine the best registration transform, an optimization algorithm is applied to the problem. The optimization process consists of choosing the metric to be optimized (some metric that describes the quality of the registration) and choosing an optimization search algorithm that will perform the search over possible transforms so that the optimal one can be found. The metric can be something as simple as the sum of the squares of the distances between predicted and actual point locations, if it is possible to define point-based landmarks on both imaging studies, or it can be image-based metrics such as the correlation between gray scale values of two CT scans, or mutual information that can be used to register different image studies (e.g., CT and MRI or PET). This is a rapidly developing area of research.

No matter what kind of registration algorithm is used, it is necessary to verify the registration and then to use the data from the various imaging studies. Verification typically consists of image-based or structure-based comparisons between the two datasets, with the goal of confirming that known structures from the two imaging studies accurately line up (Figure 16-5). The quality of the registration depends on what parts of the images are most important clinically and must be reviewed by the planner or physician because at this point, no quantitative measure accurately takes into account all the clinical knowledge of the case. Once the registration is verified, then contours or 3D structure definitions from one dataset can be transferred into the base coordinate system for planning. This combination of data from multiple imaging sources is sometimes called image fusion.

Motion, Setup, and Four-Dimensional Anatomy

So far, there has been little consideration of the fact that real patients breathe, move, are different from day to day, and change over time. Until recently, it was difficult to take such motions and localization differences into account within treatment planning, with the exception of defining appropriate PTV margins for the tumor. Fast helical CT scans, fast MRI, 4D-CT, and 4D-CBCT imaging using the treatment machine

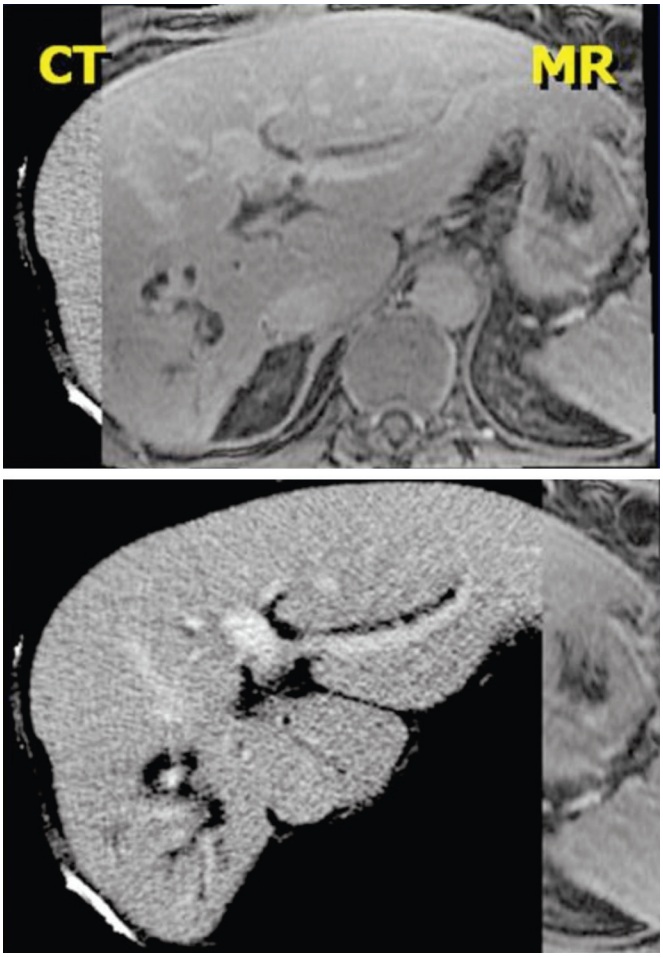


Figure 16-5 Split-screen comparisons of CT *(top)* and MR *(bottom)* image data to confirm the accuracy of the geometric registration of CT and MR scans of the liver.

have begun to provide detailed anatomic data as a function of time. These data have clearly demonstrated that a static anatomic description of the patient is not always appropriate and that treatment delivery schemes must also consider setup and motion effects if we are to achieve the optimal delivery of dose to the patient.

Several methods to handle motion and setup effects are in use or being investigated:

- As described in the section on Target Volume Definition and Margins, the standard way to handle motion and setup error is to determine the appropriate margin and then to expand the CTV by that margin to make a PTV that is the target for planning. If done correctly, the PTV ensures that the high-dose region always encompasses the CTV, even as the CTV moves around because of motion or setup error. The price, however, is that the larger the margin is, the more normal tissue is irradiated. Therefore, if the motion and setup error are taken more directly into account, this margin may be decreased, reducing the amount of normal tissue irradiated.
- One popular intermediate strategy for handling motion issues is to define the target volume extent at both ends of the respiration cycle. By combining those volumes, an *internal target volume (ITV)* is created that shows all the locations the target volume will move to during respiration, so it shows the envelope of volumes to be treated if the main goal is target coverage. As with the PTV margin, this ITV ensures coverage of the target, but increases the amount of normal tissue which is irradiated. Technically the ITV also includes the CTV, but in the era of 4D CT, "ITV" often is used interchangeably with the concept of the motion envelope of the GTV, and additional CTV margins are sometimes then added to the ITV after its creation.
- Stereotactic treatments and treatments using daily setup correction (IGRT) try to significantly reduce the daily setup variations by carefully reproducing the position of the patient each day.
- Using imaging with 4D CT, respiratory-correlated CBCT, and other such 4D methods, it is now possible to visualize the motions of the tumor (and normal tissue) with the CT data, and to create structure outlines that better approximate the clinical targets and structures to be avoided. This technology is currently undergoing rapid developments.
- With use of active breathing control (ABC) or patient-controlled respiratory methods,[75] it is possible to control the breathing of the patient with the goal of turning on the treatment beam only when the patient is in the correct breathing state. This method can help minimize respiration motion and allow smaller PTV margins.
- It is also possible to gate the radiation beam, turning it on only when the target structure is in the correct location, based either on external or internal markers or fiducials.
- Various radiographic and radiofrequency transponder markers are also used to help identify the position of the target. Transponders that identify their position 10 times per second allow real-time tracking of the target[76] and can help to dramatically reduce the PTV margin needed for treatment. This system is currently approved for use in the prostate, but is also being investigated in the lung and other sites.

This is a rapidly changing area with continuing technical progress expected.

Use of Functional Imaging Modalities

Standard CT and MRI techniques provide basically anatomic information, although some simple physiologic information is obtained from MR. However, PET, SPECT, and various fMRI imaging sequences can all lead to much more detailed knowledge of the physiologic and functional state of various tissues or organs. The details of these many different types of studies are well beyond the scope of this chapter. However, several features of any such use are similar: the patient must be positioned as close to the treatment position as possible, the imaging study must be carefully registered geometrically with the rest of the treatment planning imaging information, and the actual meaning of the imaging information should be known. Although many different imaging scans show some response in the image, it takes detailed clinical knowledge and trials to clearly define the clinical meaning of any imaging result, a crucial step before the imaging information is used clinically. The development and study of these functional and physiological imaging markers (imaging biomarkers) is a critical and fast-developing field.

Plan and Beam Definition

After the anatomic model of the patient has been established, the next major step in the planning process is to use the planning system to create a set of beams to be used for planning. This collection of beams, usually known as a "plan," can be created using standard protocols ("treat all prostates with a six field conformal plan") or designed based on the specific anatomy of the case. Basic decisions on beam technique are often made early in the planning process, using experience or

site-specific protocols. Typically, these decisions include picking the energy and number of beams, the basic orientations for the beams, and the type of beam shaping or intensity modulation to be used.

Beam Technique (Energy, Direction, and Type)

The first things to be decided as a treatment plan is generated are the number of beams to be used, their energy (and modality), and their direction. These choices are all interrelated, so typically this decision is based on standard experience or protocols. Although it is hard to summarize all of the useful ways to make this decision, there are a few standard rules that apply to most conformal planning.

- Avoid opposed beams. Simple nonconformal planning often used opposed beams (AP-PA and opposed laterals or obliques) to create a relatively uniform region of high dosage extending through the patient. For conformal planning, one typically wants to avoid pairs of opposed beams because one wants to conform the dose to the target. For IMRT plans, this is even more important because opposed beams can cause degenerate solutions for the optimization search, leading to the optimization bouncing between two fairly equivalent solutions for opposing beamlets.
- Typically, lower energies are used for relatively superficial targets or for beams that traverse less normal tissue on the way to the target, whereas beams that must penetrate a greater volume of tissue are typically of higher energy. Changing energies for individual beams often makes a relatively small difference in the dose distribution achieved, and this possible improvement should be balanced against the additional complexity of the plan if multiple photon energies are used.
- For sites in which one is attempting to make sure the dose in the buildup region is relatively high, lower energies are usually used because there is less skin sparing for these beams.
- The most conformal plans can be achieved by ensuring that there are beams arranged around the target in all three dimensions, so that the plan includes some nonaxial beams.
- There is a great deal of debate (still) over the best energy beams to use for plans that involve large inhomogeneities such as the lung.
- As one creates more complex IMRT plans that have many degrees of freedom available to be optimized, it is possible to achieve highly conformal plans. Typically, these plans include an odd number of fields, although the goal is just to make sure there are no opposing fields. There has been much discussion saying that IMRT plans can all be accomplished with 6 MV photons and that higher energies are not necessary, but there is little hard evidence to demonstrate that such a conclusion is correct. In addition, it is often said that IMRT plans can be achieved with only axial beams, but the use of noncoplanar beam arrangements will still result in at least slightly better plans (typically reducing somewhat the normal tissue dose for the same target conformality).
- Even when using IMRT or conformal arc therapy, beam selection is important because it could limit the degree of normal tissue sparing or target coverage. For example, if beams are placed so they shoot through the kidneys, no matter what cost function is used, kidney dose will be higher than if the beams are aimed outside of the kidneys. For arc therapy, if the arc is limited away from a particularly crucial organ, sparing will be improved.

Shaping with Blocks and Multileaf Collimator

Although beam directions are important, shaping the radiation field to conform to the shape of the target volume is one of the crucial and defining concepts for conformal therapy. The shaping can be accomplished equally well by focused blocks or with an MLC, as illustrated in Figure 16-6. The conformal shaping of focused blocks is in fact "more conformal" than the jagged shape created by an MLC, although the MLC has a number of other advantages that have led to its popularity.

The routine use of conformally shaped fields designed during treatment planning depends in large part on the availability of the BEV display in the planning system because this view of the target shows the projection of the shape of the targets from the point of view of the radiation beam, which is what is needed to design field shaping. The simplest method used to conformally shape the fields (with either blocks or MLC) is to create a uniform geometric margin around the projection of the targets in the BEV and to set the shape to that margin, as shown in Figure 16-7. This method, the basis of the simplest type of conformal therapy, is sometimes called *geometric conformation*, or BEV targeting. Shaping a block to a given contour is easy, but with an MLC it is more complicated. The most commonly used method for an MLC is the so-called equal area method (Figure 16-7).

Using a uniform geometric margin for the field shaping does not lead to the most conformal dose distribution. To truly conform the dose distribution to the target, one must optimize the shaping of each of the beams so that the dose distribution

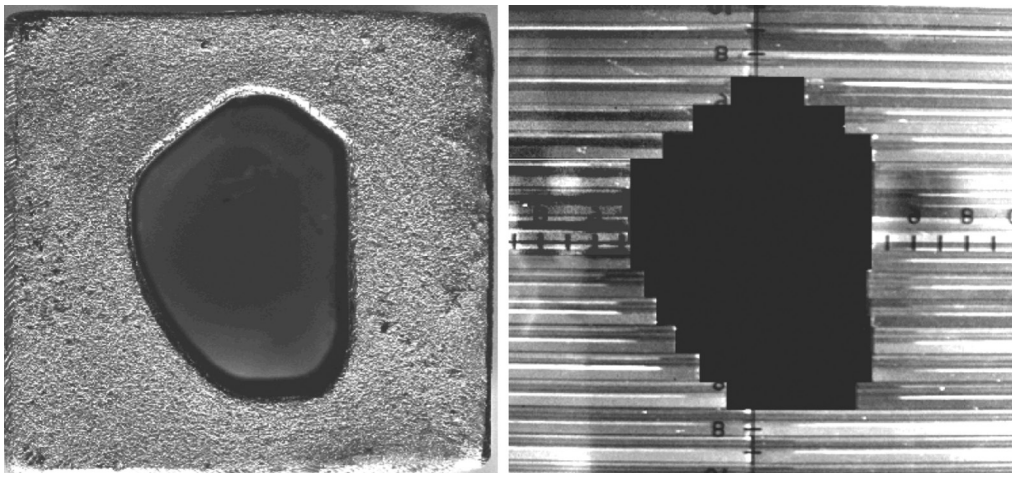


Figure 16-6 Shaped blocks and multileaf collimators can be used to shape the beam conformally.

is conformal. Figure 16-8 demonstrates the types of differences that occur when beam shapes are designed with a uniform margin and when the shapes are optimized to conform the dose to the target. Beam directions, the penumbra, and how the beams cross-fire on the target affect the margins required for individual beam shapes.

Collimator angle is one more thing that can directly affect the conformality of a plan, mainly when an MLC is used. The leaves from an MLC move in only one direction, so to minimize the "stair-step" or jagged edges caused by MLC leaves when shaped to an angled contour, one may use collimator rotation to cause the MLC leaves to best fit the shape of the target or normal tissue. By minimizing the jaggedness of the MLC edges, one can decrease the amount of penumbra in that particular region of the beam, thereby allowing the beam to do a better job making a sharp penumbra between a target and normal tissue. For example, for beams trying to make a sharp dose gradient between the prostate and the rectum, rotating the collimator to parallel the edge of the rectum can help make the edge sharper.

It is possible to create intensity-modulated beams using a limited number of MLC-shaped "segments" all from the same gantry angle. This "segmental" IMRT can be created using the normal interactive planning paradigm ("forward planning")[77] or the limited number of segments can be created by an inverse planning paradigm (see, e.g., "direct aperture optimization").[78] The use of a few segments to improve target homogeneity (e.g., in the treatment of breast cancer with tangential fields) is a logical extension of the concept of wedged tangents when 3D planning is available.

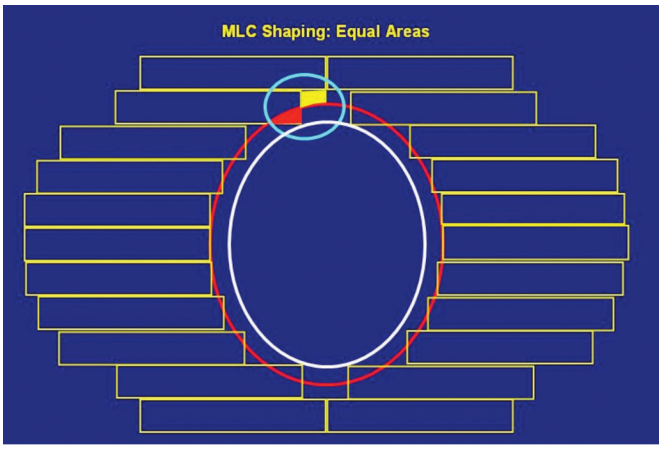


Figure 16-7 When using geometric conformal shaping for an MLC, the most common method is to create a contour at the desired margin *(red contour)* and then push the MLC leaves up to that contour so the areas overlapped and underlapped by each leaf are equal.

Other Beam Technique Decisions

There are numerous other decisions to be made when creating the plan.

- One must choose the intensity of each beam, typically called the *beam weight*. How this decision is made depends on the specific beam normalization methods used within the planning system. Because the beam weight or intensity is directly related to the number of monitor units (MUs) that will be delivered from each beam, it is essential that translation of beam weights into MUs be understood and carefully handled because errors in this step deliver the wrong dose to the entire field.
- For certain beam combinations, use of wedges in the field can help achieve a more uniform dose in the target volume. Standard two-dimensional (2D) planning makes routine use of pairs of fields known as "wedged pairs," where the wedges help compensate for the fields entering the patient at 90 degrees (or some other angle) to each other. For conformal planning in three dimensions, there is a broader range of combinations of fields for which wedges are useful. For example, a 3D cone has some number of fields placed around a cone, and each of the fields usually requires

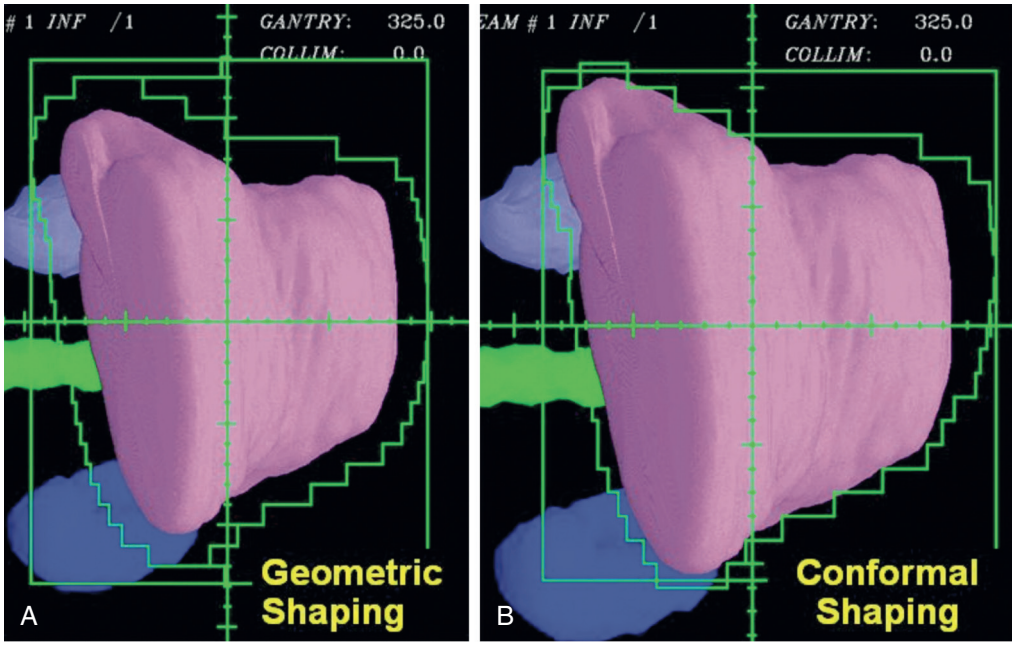


Figure 16-8 Beam's-eye view of conformal fields: uniform geometric margin *(left)* and conformal dose distribution *(right).* Using a uniform geometric margin typically does not achieve a dose distribution that is as conformal as possible. For this three-field pancreas treatment plan, the beam on the right had its shape optimized to make the dose distribution more conformal to the target.

a wedge to keep the target dose uniformity. This beam distribution is the 3D analog of the wedged pair.

- When the target is near the surface of the patient, it is often difficult to achieve the desired dose coverage of the target because of low doses in the entrance region of megavoltage photon beams. In this case, some amount of bolus can be added to the skin of the patient, for one or more beams, so that the photon beams can transit more material, therefore decreasing the skin sparing. This bolus description can be designed using the planning system, as long as care is taken in creating the physical bolus so that it actually matches the description that was put into the planning system.
- Most conformal treatment plans are isocentric, with the isocenter of the machine placed within the center of the target, and the beams rotating around the isocenter in the target. Other arrangements are possible, depending on the geometry of the normal anatomy and targets. For some situations, it is also possible to create pseudo-isocentric beams, which use 3D table motions to move the patient away from the head of the machine along the beam central axis, so that the plan is apparently isocentric but with a larger source-to-isocenter distance than the machine has. This technique can be used to create a larger range of table and gantry angles that can be used for treatment without the machine's head getting too close to the patient.[79]

Intensity Modulated Radiation Therapy

Soon after conformal therapy began to be used clinically in the late 1980s, Brahme,[54] Bortfeld,[55] and others introduced the idea of modulating the intensity across each radiation beam, assisted by computer-based optimization algorithms to help determine the intensities required of the different parts of the beam. This combination of beams with modulated intensities and the use of optimization (inverse planning) is commonly called IMRT, and is now a commonly used method for the creation of highly conformal treatment.

Intensity modulated fields can be achieved in a number of different ways. There is a continuum of situations ranging from a flat field to multiple shaped segments to a beamlet-type description (beamlets refer to dividing the beam cross-section into numerous "beamlets," which each have an independent intensity or fluence). The intensity modulation is created by either a series of SMLC segments or a dynamic DMLC sequence. For plan optimization strategies, there is a similar range from simple (forward) iterative planning to optimized (inverse) planning that is driven completely by a mathematical cost function. Typically, the most complex intensity distribution (IMRT) is generated with inverse planning, but it is also possible to perform optimization for flat field conformal therapy.[80,81]

Beam design for IMRT depends on the type of planning to be used (forward or inverse) and the photon energies and beam arrangement expected. It should consider the tradeoff between the planning goals chosen and the complexity of the plan that will be allowed. If simple multiple segments are planned, then the individual segments may be created by the planner, whereas for more complex IMRT planned with "beamlets," the beamlet size (1×1 cm, 0.5×0.5 cm, etc.) to be used for planning will be chosen by the planner (or by the planning system).

Dose Calculations

Once the initial treatment plan is designed, the next step is typically to perform a dose calculation, so that the planner and physician can evaluate the dose distribution expected from the plan. Currently, because biologic effects are not well documented and understood in general, the physical dose distribution is the main characteristic that is used (1) to choose between plans, (2) to choose what dose to deliver to the patient, and (3) to evaluate the quality of various plans proposed by the planner.

Three-Dimensional Dose Calculations

Treatment planning dose calculations have been performed on one (or more) 2D slices (or contours) of the patient since the 1940s. Often, these calculations were performed by hand, from table or chart look-ups, using a single traced contour of the external shape of the patient on a single axial slice of the patient at the center of the treatment fields. Even if performed on a number of slices, these dose distributions were in principle 2D and did not give a complete description of the dose to be delivered to the patient.

Continuing increases in computer capabilities and improved treatment planning and dose calculation algorithm developments resulted in availability of 3D dose calculations in the 3D planning systems that became available in the late 1980s. Since that time, most planning systems have implemented 3D calculation algorithms that (1) calculate the dose throughout a 3D volume of points, (2) calculate the dose with algorithms that take 3D scatter into account, (3) have algorithms that take the 3D effects of inhomogeneities into account, (4) use a 3D description of the anatomy, (5) fully take into account 3D beam divergence, and so on. Because the calculation of dose with high resolution using an accurate and realistic dose calculation algorithm still takes a significant amount of time, every dose calculation algorithm and implementation makes tradeoff choices between accuracy, speed, computer resources needed, resolution, features, and effects that are correctly modeled, and other factors. Determination of the appropriate mix of approximation, compromise, and robustness needed for particular kinds of clinical planning dose calculations is an important responsibility of the radiation oncology physicist.

To accurately perform planning for conformal therapy, accurate and 3D dose calculations must be performed. An accurate 3D anatomic model is required; the dose must be determined throughout the volume encompassing the targets and the critical normal tissues; and the calculations should be done at high resolution if one wants to know how conformal the plan actually is. This is particularly critical for small organs in which toxicity is driven by max dose, such as the chiasm and optic nerves. It is critical that all limitations in the calculations be understood and the effects of those limitations should be considered in any clinical decisions that are based on the results of the calculations.

Algorithms

Many different types of calculation algorithms have been developed for photon and electron beams, and new improvements or implementations are continually becoming available. It is beyond the scope of this text to describe any algorithms in detail. Algorithms ranging from simple table look-ups based on measured data to Monte Carlo simulations that require many hours of calculation time on fast calculation servers all have their place, and different algorithms can be the appropriate choice for different specific situations. Table 16-2 summarizes some of the advantages and disadvantages of each class of photon algorithm. If there is a choice between different algorithms for use with conformal planning, the choice should be made with careful consideration of the potential limitations of the chosen algorithm. The radiation oncology physicist should carefully commission the algorithm

TABLE 16-2 Advantages and Disadvantages of Each Class of Dose Calculation Algorithms for Photon Therapy

Algorithm Class	Description	Limitations	References
Matrix, data based	Based on measured data; often used for situations with specific field size capabilities (e.g., stereotactic applicator systems, very small field techniques). Very fast.	Only usable for specific measured situations—mainly radiosurgery applicators	82
Analytic beam models	Algebraic formulas model different aspects of the dose distribution. Very useful for fast 2D calculation models; limited in ability to model all the features in 3D dose distributions. Very fast.	Does not accurately model shaped beam scatter, patient contour changes, inhomogeneities	83-85
Scatter integration	The most used class of models from the 1970s until the last few years. Includes the well-known TAR-SAR (tissue-air ratio–scatter-air ratio) integration method developed by Cunningham.[70] 2D integration of scatter around the field handles most field-dependent scatter well but does not handle 3D inhomogeneities. Pencil beam models, often used for IMRT calculations, fall into this class. Fast.	OK for field shaping, 3D CRT, except for inhomogeneities	86,87
3D integration	Convolution/superposition algorithms are the most popular of the 3D integration models. These algorithms calculate, for every point inside the 3D calculation grid, the scatter contribution from each voxel. To be done completely, this involves a seven-dimensional integration over all voxels, all primary dose deposition points, and energies, although many implementations compromise to speed up the calculations. Based on a dose-spread kernel typically calculated once by Monte Carlo and then used for all calculations.	In principle, should get most photon-related effects correct, though inhomogeneities can still be a problem if energy spectrum and other issues are compromised	88,89
Monte Carlo	This method tracks dose deposition for millions of particle histories, using the basic physics interactions to determine what happens in each history. This algorithm has the best potential for accurate results but is costly in terms of calculation time and needs accurate simulation of the behavior and scattering, which occurs in the head of the machine. Slower, but easily parallelizable.	Most reliable if it includes good simulations of particle behavior in head of machine	90,91

for clinical use by comparison with appropriately measured data for the local machines to demonstrate the adequacy and limitations of the algorithm for clinical use.[92]

Other Dose Calculation Issues: Grids, Resolution, Inhomogeneities, and Other Issues

Aside from the inherent capabilities and limitations of the dose calculation algorithm that is used, many other user-controlled factors, as well as implementation decisions by the algorithm developer, affect the final accuracy of the doses predicted by the calculations that are performed for a plan. Unfortunately, it is not possible to address all these issues with a few simple guidelines.

Every step of the treatment planning, dose calculation, and plan evaluation process involves decisions about how much time, effort, and precision to spend defining or reviewing each aspect of the planning, and the accuracy of the final product depends on all those individual decisions. If one chooses to calculate the dose on a dose calculation grid with spacing $0.5 \times 0.5 \times 0.5$ cm, it will clearly be difficult to evaluate the dose 2 mm from the target with a significant degree of confidence, given that dose gradients at the edge of a beam can be approximately 10% per millimeter. Highly conformal therapy will require that dose calculations be performed with high-resolution grids (perhaps 2 to 3 mm), leading to large numbers of points that need to be calculated, thus leading to longer calculation times and computer resource requirements. Similarly, if truly conformal therapy is going to be performed in lung tumors, where inhomogeneities are significant, an advanced calculation algorithm that can accurately predict the dose in inhomogeneities should be used if one wants to understand the real dosimetric situation in the patient. For IMRT plans, there are further dose calculation-related issues (discussed later).

Plan Evaluation Tools

After the dose distribution from the plan has been calculated, the next step in the process is to evaluate the plan and the predicted dose distribution. Typically, the dose distribution is evaluated by looking at isodose curves on individual CT (or MR) slices through the plan, looking at isodose surfaces (3D displays of the isodose information), as well as using DVH analysis of the dose delivered to individual organs. If the capability and appropriate data are available, it is also possible to use biologic modeling results such as NTCP, tumor control probability (TCP), and EUD to help with the plan evaluation. If simultaneous integrated boosts are being used, or treatment is hypofractionated, it is important to keep in mind that biologic corrections must be performed to ensure safe doses to critical structures. For example, 50 Gy in 2 Gy fractions may be acceptable for the spinal cord, but 50 Gy in 2.5 Gy fractions may not be.

Dose Display

The most commonly used type of display of the dose distribution for a plan consists of displaying contour lines of constant dose, or "isodose lines," on top of the anatomic information that was used for the plan. These kinds of displays have been used for many years—first with only the contours of the patient (obtained by hand measurement using solder wire or other techniques) and then later displaying the isodose lines on top of the CT scan. For conformal planning, not only axial

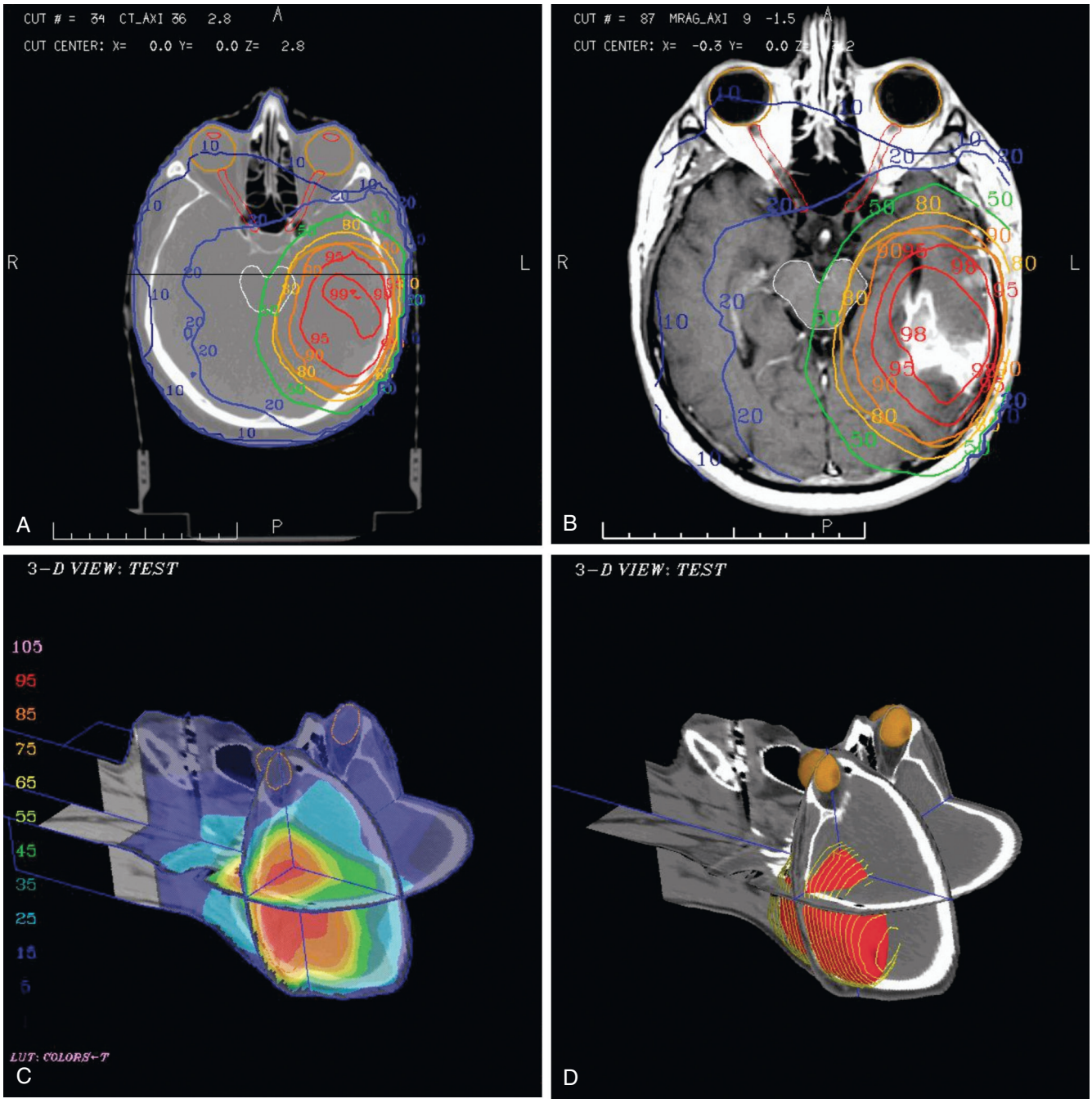


Figure 16-9 Dose display for a conformal brain plan. **A,** Axial CT with isodose lines. **B,** Axial MRI with isodose lines. **C,** Three-dimensional axonometric view with dose colorwash. **D,** Target volume *(red contour)* and isodose surface *(yellow contour)*.

cuts should be used for the isodose lines but also coronal and sagittal CT images because display of isodose lines on multiple orthogonal cuts can give the planner a more 3D sense of the coverage of the target volume. 3D graphics techniques can be used to put the images and dose lines in 3D perspective, as shown in Figure 16-9. A variation of the isodose line display is the colorwash display, in which the dose level calculated for each pixel of the image is used to assign a color value (see Figure 16-9, C).

Any image that is part of the anatomic model of the patient should, in principle, be usable for dose calculation and dose display (though this is not always permitted by some TPS systems). If MRI, PET, or other image datasets have been registered with the basic anatomy, then the PET or MR images can also be the backdrops for the dose display. By comparing the location of the isodose lines with the contours of the targets and critical normal tissues, the planner and physician can evaluate the quality of the dose distribution that is obtained for this particular beam arrangement and decide whether the plan is adequate or whether further modification of the plan is necessary.

The goal of conformal therapy is typically to conform the shape of the high-dose region to the target in three dimensions, so display of the 3D dose distribution shape may be a help when evaluating the conformality of the plan. The 3D analog of an isodose line, called an *isodose surface* or sometimes

a "dose cloud," is typically displayed in a 3D perspective graphic image (see Figure 16-9, *D*).

The dose displayed in isodose curves or surfaces, or any other dose display, can be shown in a number of ways. The most common mode used for conformal therapy is the relative dose distribution, where all the dose display is normalized to the dose value at the isocenter or center of the target. With this kind of relative dose normalization, typical conformal therapy plans would have the 95% isodose surface surrounding the target, with the shape of the 95% surface (or isodose lines) conforming to the target. One could, however, equally well display the dose in absolute terms so that the high-dose region demonstrated the desired total dose for the plan (e.g., 60 Gy) or the desired dose per fraction (e.g., 2 Gy/fraction). It is of course essential that the output of the plan that is used for treatment preparation should be carefully understood and documented, so that there is no confusion between the different ways the dose can be displayed.

Dose-Volume Histograms

Review and evaluation of the dose throughout the patient in three dimensions can be a complex and time-consuming process, and it is also difficult to give specific guidelines for normal tissue or tumor responses with respect to that complex data. It has become standard to evaluate the dose received by the target volumes and normal tissues using DVHs. To form a DVH for any 3D object, one looks at the dose value for each voxel in the object and forms a histogram, counting the number of voxels that receive each different dose level. Because the volume of each voxel is known, the volume of the organ receiving each dose level is known. See the review by Kessler[93] for more detail.

Both the volume (vertical) and dose (horizontal) axes can be displayed in absolute terms (as cubic centimeters [cc] or Gray [Gy]) or in relative terms (% volume or % dose), depending on how the planner wants to analyze the results. DVHs are displayed in three different forms: direct, cumulative, and differential.

- The direct histogram is the generic form of any histogram, displaying the volume of the organ that receives dose within each dose bin (1% or 0.5 to 1 Gy is a typical dose bin width). The direct DVH is most useful for display of the dose-to-target volumes, because one can easily visualize the minimum dose, the maximum dose, and the dose most representative of the dose to the entire target volume (Figure 16-10, *B*).
- The DVH display most commonly used in radiotherapy is the cumulative DVH, a plot that shows the volume receiving at least a given dose value. The cumulative DVH is an integration of the direct histogram, so it always begins at 100% (100% of the organ receives at least 0 dose), and ends at the maximum dose (see Figure 16-10, *A*). Figure 16-10, *A* illustrates a desirable cumulative DVH for a target (PTV, which has a uniform target dose with no underdosing or overdosing of the target). Figure 16-10, *A* also shows two normal tissue DVHs: normal brain, which has some volume of the organ receiving a high dose, and chiasm, with a smaller volume of organ receiving high dose, even though the mean dose of the two DVHs is about the same. Whether a normal tissue DVH shaped like the example normal brain DVH is better than one shaped like the example chiasm DVH is only known once reliable clinical data are obtained for the two situations.
- The third type of DVH used for radiotherapy analysis is the differential DVH. This type is necessary to appropriately compare DVHs formed with different dose bin sizes because the volume contained in any dose bin changes as the dose bin size changes. The differential DVH plots $(1/D_{bin}) * DV/DD$, so different differential DVHs can be compared even if their dose bin sizes are different.

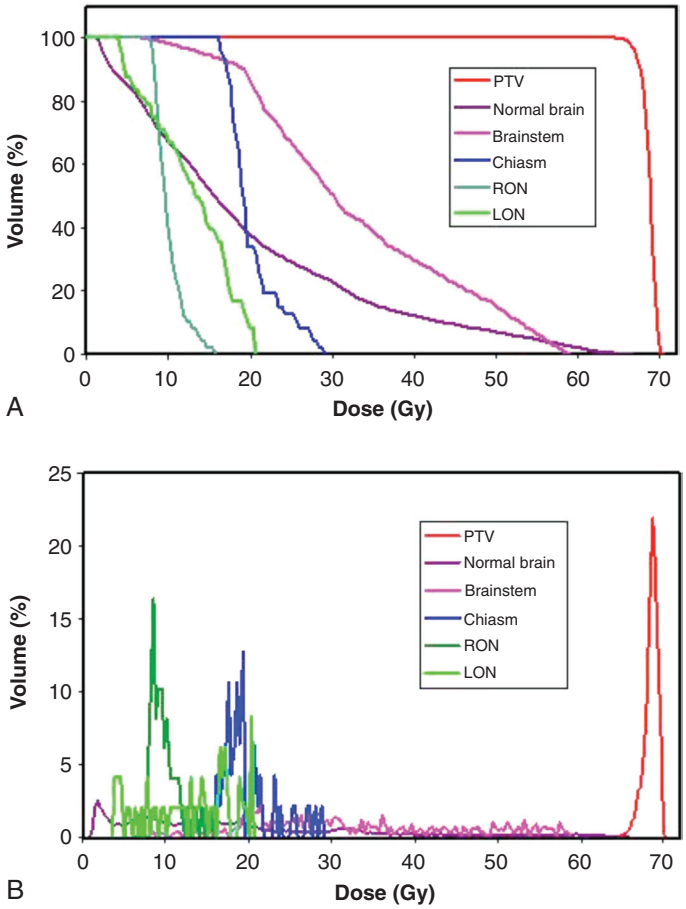


Figure 16-10 DVH displays for a brain treatment plan. **A,** Cumulative DVHs. **B,** Direct DVHs. *LON,* Left optic nerve; *RON,* Right optic nerve.

DVH analysis is an important part of conformal therapy planning, but DVHs of target and normal structures do not tell the entire story. The DVH of an organ summarizes the dose to that organ, but it does not give any information about the geometric distribution of the different doses within the organ. If the DVH for a PTV shows cold and hot spots, it is not possible to tell if either the hot spots or the cold spots are in the center of the PTV or along the edges. Whenever the location of some dosimetric feature may make a difference, it is important to review the dose distribution using dose display tools.

Minimum, Maximum, and Other Quantitative Metrics

DVHs are only one kind of dosimetric analysis that can be used for conformal planning, and many other kinds of analysis are possible. For example, simple dosimetric metrics are often used to help make planning decisions. The maximum dose allowed within a target volume, or inside critical organs, is often specified in conformal therapy protocols. Particularly for IMRT conformal plans, the maximum dose may be a fairly difficult metric to use clinically because it may depend strongly on the dose calculation grid spacing used and on details of the dose calculation algorithm implementation. A volume-based maximum dose criterion (e.g., the maximum dose to 1 cc of

the object) is typically less sensitive to algorithmic details. Similarly, the minimum dose to the PTV is subject to the same algorithm-related limitations and may be of limited value, particularly for IMRT planning. Another common dose metric is the mean dose to a structure, often used to describe target doses and for certain volume-effect organs such as the lung and liver, where the NTCP generally scales with the mean dose to the normal tissue.[94]

Use of Equivalent Uniform Dose and "Biologic Models"

To this point, all the treatment plan analysis has been based directly on the dose distribution. In reality, of course, it is the biologic effects that are important, especially the probability of controlling the tumor and of causing acute or late complications in normal tissues. Analyzing the dose distribution is in many ways a surrogate for the analysis that is really needed, the biologic effect analysis. It is expected that there will be major and continuing improvements in biologic effect knowledge and modeling over the coming years, and as these improvements happen, they should be integrated into use for treatment planning. At the moment, however, the only biologically related parameters that are commonly used in treatment planning are the NTCP, the TCP, and the EUD. This section discusses each briefly.

The most commonly used "biologically related" parameter used in treatment planning is the NTCP. The term *NTCP* actually has several meanings: (1) The NTCP is a probability that can be determined clinically for an organ; (2) there are NTCP models that attempt to model how the probability of a particular complication changes as a function of dose, volume of the organ irradiated, and potentially other factors; and (3) the NTCP is used as the value of the complication probability that has been determined by an NTCP model for a particular situation. It is important to make sure that it is clear how to differentiate between the real clinical NTCP, an NTCP model, or the particular expected value of the NTCP for a situation.

There are many kinds of models that have been developed for the NTCP, and these models have been applied to specific complications for many different organs. Discussion of these different models is beyond the scope of this work, so here we briefly describe only the most well-known model, the Lyman NTCP model. John Lyman developed the three-parameter "Lyman" model early in the 1980s.[95,96] This power law model is a phenomenological model that characterizes complications using three parameters: the TD_{50} for uniform irradiation, the slope of the dose sensitivity (n), and the volume parameter (m):

$$NTCP = (1/(2\pi)^{1/2}) \times \int_{-\infty}^{t} \exp(t^2/2)dt \qquad \text{(Eq. 1)}$$

where

$$t = [D - TD_{50}(\upsilon)]/[m \times TD_{50}(\upsilon)] \qquad \text{(Eq. 2)}$$

$$\upsilon = V/V_{ref} \qquad \text{(Eq. 3)}$$

$$TD_{50}(\upsilon) = TD_{50}(1) \times \upsilon^{-n} \qquad \text{(Eq. 4)}$$

To use this model for a real clinical DVH, one typically uses the Kutcher-Burman DVH reduction method[97] to convert the clinical DVH curve into a DVH with a single dose and volume, which are then used inside Equation 1. Together, these techniques are called the LKB (Lyman-Kutcher-Burman) model.

When developing this model, Lyman made no claim that it was a real biologic model; he simply developed the simplest model that agreed with some of the most basic behavior of NTCPs, at least as characterized at that time. The model has been used extensively, either as a way to characterize complication data or for plan evaluation and comparison. An important starting point for study of NTCPs of various organs was published by Emami,[98] who summarized a tabulation of then-current knowledge of clinical complication expectations (based on a physician working group) using Lyman NTCP model parameters. Recently, the Quantec Project evaluated complication data and parameterizations for many clinical sites, performing a review of the published data using site-specific groups of experts with the goal of providing updated complication modeling information.[99] The Lyman model has proven to be a useful way to parameterize clinical NTCP data and has been used as part of dose escalation studies based on treating patients with a specific isocomplication level (for liver[100] and lung[101]).

One of the most important things that can be done to improve conformal therapy planning is to perform clinical studies that (1) document, for each normal organ, the distribution of doses and volumes of various organs that are irradiated, (2) include careful patient follow-up, and (3) are analyzed to find the dose-volume-complication relationship for each organ. The dose-volume-complication relationship for each organ (and each complication) is unique and must be determined clinically. Once these results are known for all normal tissues, we will know better how to optimize treatment plans.

Just as the dose-volume-effect relationship is important to know for normal tissues, it is also important to know for the tumor. The tumor control probability (TCP) is the subject of clinical studies and modeling and is a way of comparing expected tumor responses with planned dose distributions. A number of different models exist, including the Niemierko-Goitein[102] and Nahum[103] TCP models. Most of these models use various basic assumptions about tumor cell density and distribution, the statistical interactions between dose and tumor cell survival, the incorporation of population-based statistics for tumor heterogeneity, and may also consider effects that depend on tumor stage, hypoxia, and other issues. Tumor cell biology and predicting local tumor control are complicated subjects that are well beyond the abilities of current models. TCP modeling is used in a reasonably limited way because it is known that the predictions are of limited accuracy.

The EUD is often regarded (at least partially) as a biologically related parameter that is often used for treatment plan evaluation and optimization. The EUD was originally described by Niemierko[104] by using a biologically and statistically influenced method to derive a dose parameter that was related to the effects one would expect on the tumor. The EUD has been generalized further[105,106] to be useful for normal tissues and targets. Because the EUD is in principle a generalized mean of the dose distribution according to a specific weighting method, one may use the parameters to represent the sensitivity of the tumor to underdosing in a small region or the effect of hot spots in the tumor. Because the concept of the EUD is relatively new, numerous publications and analyses continue to explore and expand the characterization of tumor and normal tissue responses using various EUD representations.

FORWARD PLANNING

Since computerized treatment planning began (in the late 1950s) until the last decade, nearly all planning has made use of the basic paradigm that is currently called "forward" planning, using the following process:

1. Define the anatomy. Use contours on multiple axial cuts through the patient (e.g., CT scans or manual contours) to define the external surface, targets, and important normal structures. Also include PTV margins.

2. Create the plan. Create a beam arrangement, choosing beam energies, locations, directions and shapes, weights, and addition modifiers if necessary (e.g., wedges, compensators).
3. Calculate the dose. Calculate the dose distribution that results from that beam arrangement, on 2D slices or through the full 3D volume.
4. Evaluate. Evaluate the dose distribution, usually by looking at isodose line displays relative to the anatomy and (in recent years) by calculating DVHs for the normal tissues and targets.
5. Optimize the plan iteratively. If the plan is not adequate, or if the planner wishes to try to improve the plan, then the planner will iteratively modify the plan technique in an attempt to improve the plan result. Each iteration involves modifying the plan, performing a new dose calculation, and reevaluating the plan. Consultation with the treating physician is helpful for input on which clinical tradeoffs to accept.
6. Complete the plan. Once the plan is judged acceptable (or complete) by the planner and physician, the iterative optimization stops, and the plan is prepared for use. This involves calculation of MU for treatment, calculation of digital reconstructed radiographs (DRRs) to be used for patient localization, and transfer of the plan to the treatment delivery system.

Iterative forward planning is driven by the treatment planner and usually relies a great deal on the visual dosimetric evaluation performed by the planner or physician.

Setting Planning Goals

Creation of a high-quality conformal plan using forward planning depends crucially on the planning goals set by the physician. A typical set of conformal therapy planning goals may include the following:

- Usually, the plan is normalized to the dose at the isocenter of the plan.
- The plan will typically make the 95% isodose line (for example) conform to the PTV (target volume) shape, so the minimum dose to the PTV will be 95% of the plan normalization point dose. For IMRT plans, sometimes the coverage goals can be more restrictive (e.g., 99% of the PTV receiving 99% of the plan normalization point dose, but this should be done carefully because it also can escalate hot spots as minimum coverage is escalated).
- The dose uniformity inside the PTV should be specified (e.g., ±5%), which will determine the maximum dose allowed in the PTV (in this example, 105%).
- Keep the maximum dose to the spinal cord less than some limit (typically, 45 to 50 Gy).
- Minimize the dose to all normal tissues.
- Prescribe the target dose—either prescribe the dose to the plan normalization point and accept ±5% uniformity throughout the target, or prescribe the minimum dose to the target volume, and accept that the dose in the target may be as much as 10% (for example) higher.
- If normal tissue responses are known, specify reasonable normal tissue limits for the planner. For example, one can specify that the mean dose to the normal lung stay below some given value because it is known that mean dose can be used to predict the chances that pneumonitis will develop.

The physician should also specify any other constraints or evaluation expectations that will be used for final plan evaluation. One of the primary causes of additional planning iterations and frustrated planners is a physician who chooses to use some plan evaluation criterion or rule that was not described to the planner as a goal or expectation.

Beam Arrangements

Beam arrangements useful for conformal therapy planning are site specific and depend on the geometry of the target volumes and normal tissues. Virtually all conformal plans have at least three beam directions, and seven, nine, or many more beam directions are sometimes used (e.g., conformal stereotactic radiosurgery). Plans with more than seven beam directions are relatively uncommon when forward conformal planning is used, simply the result of the complexity involved in designing and determining the correct beam orientations, shapes, and weights interactively when there are so many different beams to consider. Nonopposing beam directions are useful, as are beams that separate the target from the most critical normal tissues (increasing the distance between the target and normal tissues when viewed in BEV display). It is useful to have beams not in the axial plane because they can help improve the conformality of the plan in all three dimensions.

Iterative Planning

Shaping beams is an important part of the iterative planning process. Typically, a BEV margin of 6 to 7 mm is a good starting point for conformal beam shaping, but the shape of each field will then need to be modified to improve the conformality of the calculated dose distribution, as discussed previously. This is the part of the iterative forward planning process that is most time-consuming, potentially, because in principle one needs to optimize the location of each leaf of the MLC for each beam, and there 50 to 100 involved MLC leaves in each field. The changes in shape that are needed are somewhat predictable, though, because larger MLC margins are needed in regions where there are no other beams (e.g., the superior and inferior aspects of the PTV for a plan with axial-only fields), whereas the margins can be much smaller if there are other beams that are transiting from an orthogonal direction. In the end, however, many iterations of the shapes may be necessary to get reasonably close to the optimal shaping. This is the part of forward planning that is often time-limited by clinical needs, and it could potentially be significantly improved by the application of computerized optimization methods to perform this shaping automatically.[81] Beam weights, use of wedges, and collimator angle rotation followed by revised beam shaping can also be part of the iterative planning process.

Plan Evaluation for Forward Planning

Evaluations of plans resulting from forward planning are typically based on isodose line display and DVH plots for target (PTV) and normal tissues. The physician evaluates the plan using these tools and decides if the plan is adequate for clinical use, as well as whether the plan has the potential to be improved through plan technique changes, or by the physician modifying the dosimetric planning goals that were specified initially for the planning. In forward planning, most clinical tradeoff decisions are made in a qualitative way by inspection of the displayed dose distribution and the DVHs.

INVERSE PLANNING

Rather than trying plans and seeing what kind of dose distribution can be achieved, as in forward planning, the basic concept of inverse planning is to decide up front what the dose distribution should look like and to then "invert" the problem to solve for the beams (and beam intensities) that will give the desired doses. This inverse problem, which is the inverse of the CT back-projection process, would be wonderful except

for two small problems: (1) Because there are no negative radiation intensities, it is not possible to invert the problem, and (2) planners probably do not know what the best "achievable" dose distribution would be to use as a goal. Planners do know that the goal of full dose to the target and zero dose to the normal tissues is not possible.

To get around these problems, inverse planning makes use of computerized optimization techniques to search for the best plan among all possible candidate plans, using an objective or cost function to drive the optimization toward the plan that is "optimal." This kind of inverse planning or plan optimization process could in principle be performed for any kind of radiotherapy plan. In practice, however, the plan needs to have many adjustable (optimizable) parameters so there is enough flexibility in the plan to allow the optimization search to find a good solution to the planning problem. This is the reason that up to this point, most inverse planning and optimization efforts have been applied to IMRT plans created with many separate beamlets or intensity "bixels" per beam because there are a large number of degrees of freedom in the plan that make it possible for the optimization process to work effectively.

A typical inverse planning process can be summarized as follows:

1. Define the anatomy. The planner and physician must define (contour) all the target and normal tissue structures of interest. Whereas in forward planning one is not "forced" to delineate all important structures, in inverse planning one must define all anatomic objects that are to be considered by the optimization to prevent unplanned dose from being deposited in unintended regions. One must also define how calculation points are to be distributed throughout the involved objects.
2. Create the plan. Define the beam energies and directions, determine the largest extent of the beam shape, and divide the beams into beamlets.
3. Calculate the dose per beamlet. For each relevant dose point, calculate the dose per unit fluence from each beamlet. This "D_{ij}," or "influence," matrix tells how much dose each point receives as the intensity in an individual beamlet is changed by the optimization search algorithm.
4. Prepare the optimization algorithm parameters. One must define the cost function (and possibly the optimization search algorithm if more than one is available) to be used for the inverse plan. The cost (or objective) function definition is crucial because it will be used to direct the optimization search and to drive the solution toward the desired dose distribution. The cost function is defined individually, at least for each planning protocol, and perhaps for each patient, and is likely to be the most crucial decision involved in determining what kind of plan will result from the optimization process.
5. Iterative plan optimization. Inverse planning uses the optimization search algorithm, driven by the evaluation of the chosen cost function, to perform iterative plan optimization, with the search algorithm determining how the plans are modified, and the cost function serving as the judge of plan quality. In most current inverse planning, only the beamlet intensities are varied, so to recalculate the change in the plan dose distribution and cost function, one only needs to resum the dose contributions from the changed beamlets, a calculation that can be performed quickly. The optimization search will continue until predefined stopping criteria are achieved.
6. Plan evaluation and reoptimization. Once the optimization process is complete, the physician and planner must evaluate the plan, dose distribution, cost function results and metrics, and any other relevant information, to decide if the plan is acceptable. If it is not, then the plan optimization process must be rerun; however, it is necessary to make changes in the cost function to drive the plan toward a different result, because running the optimization again using the same cost function should result in approximately the same plan result as the first time.
7. Plan completion. Once the plan is judged acceptable (or complete) by the planner and physician, the plan is prepared for use. For a beamlet-optimized IMRT plan, this completion step includes leaf sequencing, which is the preparation of the MLC leaf trajectories (DMLC delivery) or MLC segment shapes (SMLC delivery) that will create the desired beamlet distribution. Leaf sequencing issues are described in more detail later. Other preparation steps include calculation of MU for treatment (usually included in leaf sequencing for IMRT), calculation of DRRs to be used for patient localization, and transfer of the plan to the treatment delivery system.

Comparison of this process for inverse planning with the previously described forward planning process (see Forward Planning) shows that only a couple of steps are really different; most of the planning process is approximately the same. However, for inverse planning, most interactions aimed at improving the plan must be made by modifying the cost function used for the optimization, a much more indirect type of control on the plan parameters than one has when modifying a beam shape while doing forward planning.

Goals for Inverse Planning

As with forward planning, it is critical for the physician and planner to decide the overall goals for the inverse plan and to prioritize the various clinical issues. Goals for inverse planned IMRT may include the following:

- The dose to the target volumes should be specified: typically, this is the minimum dose, the mean dose, or the dose to a specific point inside the targets.
- Often, the dose distribution is defined in absolute terms (i.e., a plan will specify either the total dose [for the course of treatment, e.g., 60 Gy] or the dose/fraction [e.g., 2 Gy/fraction]). Relative dose can also be used, but given the use of IMRT, the dose to any defined reference point can be variable, so the relative dose mode of treatment planning is somewhat less useful than it is for flat field conformal therapy. In addition, if one wants to use a biological model or other such evaluation or analysis tools, then the absolute dose mode of planning is much more useful than the relative dose mode.
- The dose uniformity inside the PTVs should be specified (e.g., ±5%). Many current inverse planning systems may have a hard time achieving the ±5% uniformity in the target volume that is commonly used for conformal treatments, but this is not caused by using IMRT per se but rather by the kinds of cost functions used within those planning systems.[107]
- Keep the absolute maximum dose to the spinal cord to less than 50 Gy. Note that for many (but not all; see previous discussion) cost functions, there are tails on the DVH of many structures that may allow higher doses to a small volume of the organ.
- Minimize the dose to all normal tissues.
- If normal tissue responses are known, specify reasonable normal tissue limits for the planner. For example, one can specify that the mean dose to the normal lung stay below some specified value because it is known that mean dose can be used to predict pneumonitis.

The physician should also define and specify any other constraints or evaluation expectations that will be used for the

cost function because there is no other way to specify to the optimization method what it should do or should not do.

Beam Arrangements for Inverse Planned Intensity-Modulated Radiation Therapy

The rules usually applied to beam arrangements for forward planned conformal therapy also apply to inverse planned IMRT beams in general. The beam arrangements that are most useful still depend on the site to be treated and on the geometry of the target volumes and normal tissues. Virtually all IMRT plans have at least three different beams, and many beam directions are sometimes used. Another type of IMRT called volumetric modulated arc therapy (VMAT, discussed later) uses rotational beams. In much of the early IMRT literature, it was common to find plans with seven or nine axial beams, with beam directions evenly distributed about the patient. This number of beams allowed enough flexibility for the optimization to achieve an adequate plan, even if the beam directions were not tuned with respect to the anatomy. However, as IMRT planning has progressed, the use of nonaxial and geometrically optimized beam directions has become more popular. Even with a strict cost function, the best way to minimize dose in a normal tissue is not to place beams that enter through this structure. Contrary to some early IMRT literature, it is still useful to use beams from outside the axial plane because they help to improve conformality. However, with IMRT, it is often only obvious that the nonaxial beams are useful when considering low-priority normal tissues because the IMRT optimization can typically achieve all of the higher-priority goals without use of nonaxial beams. One feature of most IMRT plans still remains the same: typically, one avoids the use of opposed beams because opposing beams tend to lead to degenerate solutions that can cause difficulties for some optimization search algorithms, preventing them from reaching the optimal solution.

Optimization Method

The most important issue affecting the quality of the final IMRT plan is typically the type of cost function used and, in particular, how the different parts of the cost function are defined for each relevant organ or other anatomic object. In some systems, there is limited flexibility in the type of cost function available because the cost function is limited to a simple method (often, a quadratic function of dose) to allow the gradient descent-based optimization search method to easily calculate the derivative of the cost function for each variable. However, other cost function methods can be quite general, allowing the use of dose, dose-volume, biologic model, or other types of costlets that can be combined into an overall cost function.[61] In any event, it is the relationship of the different costlets (individual pieces of the cost function) that determines how important the various parts of the plan evaluation are, so by changing one or more parameters in a costlet or costlets, one can drive the solution of the plan toward a different type of solution. Learning how to modify the cost function to modify the kind of solution achieved for the plan is one of the most important aspects of inverse planning and may take a significant amount of effort to master.

Regardless of the type of inverse planning system or cost function used for inverse planning, one of the easiest ways to choose the appropriate cost function parameters for the plan is to first make sure that the clinical goals for the plan have been prioritized. Then, one constructs the cost function using the highest weights (or power or importance) for the high-priority issues and decreasing weights for the lower-priority issues. How this works in detail is specific for each type of inverse planning system, search method, and clinical site, but the general concept holds true for most inverse planning methods.

A number of different types of search algorithms are used for IMRT optimization, and these different methods can have specific characteristics that are useful to know. Many current inverse planning systems, however, make use of only one search method, so many planners will not be able to choose different methods for specific patients or plans. Many inverse planning systems use gradient descent-based search methods because they are fast, but this forces their cost functions to be limited to easily differentiable functions, typically quadratic dose penalties that take the form $w_i(D - D_i)$,[2] where w_i is the weight of the penalty and D_i is the dosimetric goal for the i^{th} object. This type of cost function tends to lead to tails on the DVHs because a small volume of the object can go higher than the desired dose without causing too much of a penalty. Another common concern about gradient-descent algorithms is the possibility of local minima in the cost function. For simple cost functions this is not a problem, but use of many costlets or complex functions can potentially lead to local minima that may trap the optimization search at a solution that is not the "global" minimum (the optimal solution). To avoid the possibility of being trapped in such local minima, stochastic search algorithms such as simulated annealing[52] and others can be used. These algorithms can perform a global search that is more certain to achieve the global minimum of the cost function, but they often are quite slow and can also be sensitive to the search parameters used (as in fact are all of the search algorithms).

Plan Evaluation for Inverse Planning

If we knew exactly how to define the cost function so that it correctly summarized all of the physician's goals and desires for the treatment plan, then if the optimization method worked correctly and achieved the global minimum, we would know that the best plan had been found, and that would complete the plan evaluation. However, this is not the case at the current time. Most clinical inverse planning is still limited by many things; therefore, many IMRT plans still involve some "forward" iterative plan optimization. Often when an inverse plan is performed and the plan is evaluated by the physician or planner, the cost function is modified, and then the plan is reoptimized as the planner or physician attempts to push the plan toward some goal that he or she believes is a better clinical result than what the inverse plan gave on the first attempt. As cost functions and search methods become more sophisticated, we can expect that this iterative forward planning use of inverse planning technology will become less necessary.

This problem demonstrates that there are some important issues for plan evaluation. The biggest problem to resolve is that the cost function determines what the search method will choose as the optimal plan, but the physician evaluation of the plan may not be consistent with what the cost function is telling the optimization to do. Whenever this happens, the physician will find the "optimized" plan to be less beneficial than desired and will often attempt to make modifications in the cost function and then reoptimize the plan, perhaps many times, to achieve what was desired. A second complication is the fact that the metrics that physicians use to evaluate plans are often not the same kinds of metrics used by the cost functions, causing another mismatch between physician and cost function. Methods that use clinically relevant metrics as part of the cost function may help decrease this problem somewhat. A third problem with IMRT plan evaluation is that most planners and physicians still have a difficult time knowing what is actually achievable with a given plan, beam

arrangement, and anatomic situation, so even when an acceptable plan is achieved they are not sure whether they might be able to achieve a "better" plan by changing something. New methods are needed to help give the planner and physician tools that can show them the kinds of changes that may be possible, so they can better know when the optimal plan is achieved. Defining several levels of priorities can help minimize the number of iterations of a plan, particularly if multiple tradeoffs are being made between targets and normal tissues. For example, one can set a nonnegotiable limit and a negotiable one which can be exceeded if beneficial for a competing structure.

One final plan evaluation issue involves the many compromises and approximations that are involved in current inverse planning and IMRT processes. Because of the huge number of calculations involved in a single iteration of the optimization method, and the large number of iterations that are necessary to optimize a given plan for some search methods, it is essential to make compromises in the dose calculation method, the evaluation of the cost function, and other parts of the process, and to limit the resolution of dose calculation points used within the calculation. In addition, as described in more detail in the next section, various compromises in the plan must be made when converting the ideal intensities of the beamlets into a deliverable set of MLC segments (SMLC) or trajectories (DMLC), and these compromises will generally degrade the quality of the plan that is delivered to the patient. As any plan is evaluated, one must also keep in mind the further degradation that will occur. The limited resolution used for dose calculations can often lead to changes in apparent conformality or target coverage if a new dose calculation (with different resolution or calculation grid placement) is used. More discussion about plan degradation caused by MLC sequencing is included in the section on conformal therapy delivery.

Plan Preparation

After a plan has been approved by the physician for clinical use, it must be prepared for treatment delivery and transfer to the delivery system. These preparations include the following:

- Documentation of plan approval. Documentation of the physician's approval of the plan for treatment should be clearly performed (e.g., signature on the treatment plan output, or electronic signature in the electronic chart). Other approvals (e.g., quality assurance approval for IMRT treatments) may also be required.
- Preparation of treatment instructions. Creating a treatment plan for the patient usually involves determining the treatment beams to be used, but often does not consider other parts of the treatment delivery process, including patient setup and localization imaging, the treatment delivery methods to be used (e.g., automated delivery of all the beams, or manual delivery). For complex or automated treatments, creation of a complete treatment delivery script may be required. A graphic treatment delivery simulator can be quite useful.[108]
- Calculation of MUs may be required for non-IMRT fields, although some treatment planning systems also provide the MUs for the plan. In any event, an independent check of the MUs required for treatment should always be part of the process.
- Quality assurance (QA) checks for IMRT and other complex plans. Before delivery of a complex plan to the patient, it is often appropriate to perform various QA checks on the treatment plan delivery, to assure that the treatment will work correctly and accurately. These kinds of QA checks are routine for IMRT treatments to confirm the correct dosimetric delivery of the complex beam intensity patterns that IMRT uses, and for stereotactic radiosurgery treatments to verify that the geometric accuracy of the treatment delivery is adequate because large single doses are often delivered for these treatments.
- Hard copy plan output. Once a plan is finalized, it is important to create a hard copy (or electronic) output describing the treatment plan, to be used in the patient's chart.
- Calculation of DRRs. The creation of DRRs is an important part of the plan preparation process because these DRRs will be used for localization checks of the patient position while one is performing the setup of the patient.
- Plan transfer. Transfer of the plan information into the paper or electronic treatment chart and the treatment delivery system is an important part of the process. For manual transfer methods, one of the biggest potential problems is the large probability of transcription errors as the various parameters for each field are transferred from the planning system to the delivery system or chart. For electronic transfers of the plan information to a computer-based delivery system, the errors that happen are typically not random transcription errors, but systematic errors are more likely. The difference between the manual and electronic methods and their most likely errors means that the QA procedures for the two methods should be carefully defined to be appropriate for the method in use.
- If IMRT beams are used, then rather than calculation of MUs, "leaf sequencing" is performed for each beam to convert the planned IMRT intensity pattern into either multiple fixed MLC segments (SMLC) or dynamic trajectories of each leaf pair if the DMLC method is used.

MLC Leaf Sequencing

To convert an IMRT intensity pattern into a delivery prescription that will create the desired pattern of intensities, a leaf sequencing algorithm is used. Many different leaf sequencing algorithms exist, and all have advantages and disadvantages. Any leaf sequencing algorithm is really an optimization procedure that attempts to find the best way to create the desired intensity pattern while still adhering to all the constraints or limitations of the MLC and machine that are to deliver the IMRT intensity pattern. There are always compromises in the final result achieved by any of these algorithms, so one always knows that the plan has been changed (usually degraded) by those compromises. It is thus important to verify that the final "deliverable" plan is still acceptable. Many IMRT systems use a second-dose calculation, based on the actual delivery sequence, to check that the plan is still within acceptable limits even after the compromises.

Several different methods of IMRT delivery make use of MLC systems (Figure 16-11). Segmental MLC (SMLC) uses a set of fixed MLC segment shapes to deliver the intensity pattern with the beam off as the MLC moves from one shape to the next. Many algorithms have been developed for this kind of MLC sequencing.[45,109] Dynamic MLC (DMLV) uses MLC leaves that move on a trajectory that is defined so that the desired intensity pattern is created. Typically, a "sliding window" algorithm is used to derive the trajectories required.[47]

Volumetric Modulated Arc

VMAT is a relatively new IMRT method that combines rotational (or arc) delivery and MLC-based IMRT.[59,60] VMAT makes use of the same fundamental methods (intensity modulation, inverse planning) as IMRT, but is different in the constraints that the rotational IMRT delivery places onto the plan optimization strategies that are used. Typically, completely

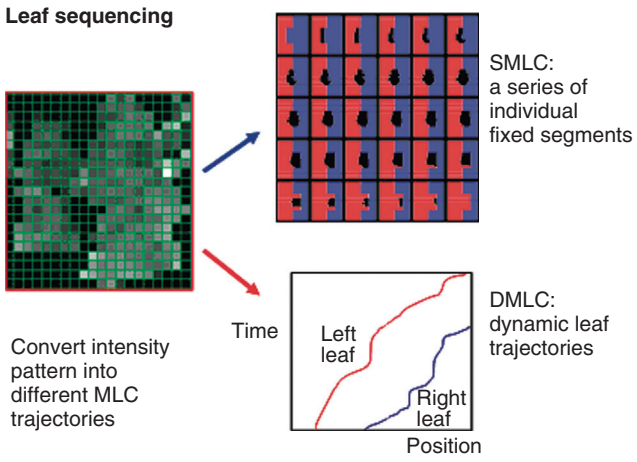


Figure 16-11 Segmental multileaf collimator (SMLC) and dynamic multileaf collimator (DMLC) leaf sequencing.

different optimization strategies are used for VMAT planning because the strategy must be tuned differently to make it possible for the optimization to reach a high quality plan, given the constraints on MLC motion during the arc rotation of the gantry. Given the type of rotational delivery used, the dose distributions achieved with VMAT are different than fixed field IMRT, often spreading more low dose regions over the volume of the patient. The tradeoffs and differences between IMRT and VMAT plans have been the subject of many studies and are still the subject of ongoing work. One important advantage of current VMAT delivery techniques is that often the VMAT delivery for a single arc, or even for a multiple arc plan, can be much faster than that for fixed field IMRT delivery. This decrease in delivery time can sometimes be a significant advantage that may overshadow some of the dosimetric constraints of the VMAT plan optimization and can be particularly useful when particularly uncomfortable immobilization is being used (e.g., head and neck cancer) or targets are spread out in large multiple-split fields (e.g., anal cancer).

CONFORMAL THERAPY DELIVERY

Careful, efficient, and accurate treatment delivery is just as important as sophisticated treatment planning if the patient is to receive the benefits typically ascribed to conformal therapy.

Patient Setup and Localization: Transitioning to Image-Guided Radiation Therapy

One of the most crucial aspects of patient treatment involves the setup and localization of the patient for each treatment fraction. For many years, this process has typically involved lining the patient up to laser lines using skin marks defining lateral and anteroposterior (AP) projections of the plan isocenter. To verify correct patient positioning, lateral and AP localization films were obtained (typically, once per week) to confirm the correct placement of the isocenter inside the patient. The "orthogonal pair" films were compared by eye with the expected location (shown by simulator film, DRR, or BEV display from treatment planning) to document the accuracy of the setup. Use of a calibrated gradicule in the accelerator head when making the megavoltage images[110] was helpful in making the comparison somewhat quantitative.

In the last decade, many new developments have dramatically changed the setup and localization process for many patients, a set of much more quantitative and automated setup procedures that are known as IGRT. The development and implementation of electronic portal imaging devices (EPIDs)[111] for megavoltage imaging, diagnostic x-ray imagers,[108] and megavoltage or diagnostic cone beam CT (CBCT) scanning[65] using accelerator-based systems have revolutionized the setup and localization process. If the new digital imaging capabilities are integrated with the computer-control system of the treatment accelerator, it is possible to perform relatively automated patient setup with accuracy much improved over the old manual method.[112] As this technology is disseminated, it is clear that use of IGRT methods for patient setup, on a daily basis, will lead to significantly improved accuracy for routine patient setup.

Tools for Image Guidance

A number of new tools are now available for patient positioning and localization and are mentioned here as tools for image guidance.

MV Imaging

Megavoltage imaging was the initial development that made IGRT possible because it made routine use of imaging (on a daily basis) practical. After early development of an ion-chamber based portal imager (or electronic portal imaging device, EPID),[113] amorphous silicon (a-Si) EPIDs were developed[114] and quickly became the standard EPID device for most accelerator systems.

KV Imaging

The a-Si technology developed for the megavoltage EPID has also been optimized for kV imaging[115] and is now widely available on many newer treatment machines. The large and high resolution a-Si flat panel imagers have allowed high-quality diagnostic imaging systems to be installed on many accelerators, thus making both kV imaging and cone beam CT imaging possible. The availability of high quality kV imaging has also made many x-ray fiducial markers[116] much easier to use.

CBCT

Cone beam CT has revolutionized the amount of pretreatment localization information available for use in image guidance.[117] Most CBCT is created with a kV x-ray tube and a-Si flat panel imager that are mounted on the accelerator system orthogonal to the megavoltage radiation beam, and typically create a volumetric CT image in about 1 minute of accelerator time. The usual process involves acquiring a CBCT image set, registering those images with the treatment planning CT performed during CT simulation at the beginning of the treatment course, and then determining the shift required to place the patient in exactly the same position (and configuration) as originally planned.

RF Beacons

In place of x-ray fiducials, small RF transponders ("beacons")[76] can be implanted in the patient (just like fiducials), and the position of those beacons can be electronically determined by the system in real time (typically happens about 10 times a second). This kind of system allows real-time monitoring of the position of the target during therapy, with the opportunity to stop the irradiation if the target beacons move outside a predetermined tolerance.

MR Devices

A number of new devices using MRI have also been developed for IGRT treatment. A number of centers have installed

either an MR or CT system on rails, in the treatment room, so that a patient may be scanned in the treatment position and then directly moved underneath the accelerator for their treatment.[118,119] A startup company has developed a novel device (ViewRay), that incorporates a rotational gantry system mounted with 3 Cobalt-60 sources (evenly distributed around the ring), each with its own MLC system, all installed with a 0.3 T permanent magnet system for MRI imaging.[120] This system allows treatment with concurrent MR imaging. Several types of MR-Linac systems are currently also being developed, each with the goal of delivering sophisticated photon treatment using 6 MV photons while at the same time performing 1.5 T MR imaging.[121-123]

Video Surface Imaging

Another type of imaging currently being used for IGRT patient setup and monitoring uses video cameras and various methods for projecting information onto the patient's skin so that the 3D shape of the patient surface can be determined in real time, so that it can be compared to the expected model of the patient surface as a way of identifying positional or motion differences between the current patient surface and the model. Though this technology has been studied for many years, current technological improvements have helped bring these devices into the commercial and clinical mainstream.[124]

The IGRT Process

Although IGRT can be used to describe any use of any image guidance technique to help set up or position the patient for treatment, or to monitor the position, motion, or field localization during treatment delivery, the true IGRT process is integrated into many parts of the overall radiation planning and delivery process. The main parts of this integrated process are briefly summarized here:

CT-simulation imaging: obtain the imaging data that will be used for planning and as the model used when matching the treatment imaging

Delineation of the target and normal structures. Used for planning, but also for comparison to the treatment day imaging results.

Determination of the appropriate margins to use for the planning target volume (PTV) or other normal structure limits (PRV, planning organ at risk volume). Each institute must document the setup accuracy achieved, so these margins can be designed appropriately.

Setup and image guidance instructions must be transmitted to the treatment machine for use daily along with the treatment plan information.

Daily, the patient is set up and then imaged. The imaging information is then compared to the model (planned) image set, and the two sets of images are registered (or "matched"). If the patient's position (or pose) do not match precisely, then the shifts (or rotations) needed to move the patient so their position agrees with the planned position are determined from the registration process, and the patient can then be moved to the correct position. The region of interest for matching can be an actual visible tumor, surrogate soft tissue or bony anatomy for the tumor, or an avoidance structure if there is a steep dose fall off between acceptable and unacceptable dose to a particular structure (e.g., spinal cord, bowel, etc.). Documentation that the shifts of the patient are made correctly should be performed, though sometimes this is not done. The patient is then treated.

IGRT information can also be used during treatment to monitor the patient's position, pose, breathing state, and any other factor that might indicate the treatment should be stopped and positioning corrected. Some real-time imaging systems are equipped with triggers that can automatically stop the irradiation if necessary.

Review and analysis of the daily IGRT results are critical to the accuracy of the guidance procedure. This review includes both peer review of the imaging registration procedures as well as more technical review of the daily results so that trends (e.g., drift, or systematic deviations) can be separated from the more typical random variations. It is this kind of analysis that will determine the specific margins that are appropriate for target volumes for a given type of patient in each particular clinic.

Manual and Computer-Controlled Treatment

The treatment delivery process used for modern conformal therapy has also changed. For many years, the standard treatment process involved two or more therapists carrying the paper treatment chart into the treatment room, setting up the patient (as described using lasers and skin marks), and then positioning the accelerator manually for each treatment field using the accelerator hand pendant controls. The therapists would exit the room to allow the treatment of each field, which was controlled by the treatment machine console in the control room. Although some machines were equipped with computer-based "record and verify" systems[125,126] that would confirm the parameters to be used for each field, many of these systems were of limited sophistication. Most parameters used for patient treatment were set by hand and susceptible to various random errors.

Since the 1990s, integrated computer-controlled systems have entered widespread use for control of the treatment process, usually tied to a treatment plan or information system database that contains all the treatment plan information. To varying degrees, the progression through the setup process and treatment delivery is often automated, controlled via the machine's system. However, much remains to be done to optimize the efficiency, safety, and accuracy of the computer-controlled treatment delivery process. There has been some published work on the treatment delivery process,[108,127-129] but too often a treatment process taken directly from the old manual techniques is implemented with the computer-controlled system, without implementing modifications that would improve the accuracy, safety, or efficiency of the computer-controlled treatments. The more recent introduction of the wide variety of image-guided delivery methods also leads to the need for further improvements in the workflow of the process, and additional effort to optimize the process is required. Much work is needed in this area.

The use of IMRT treatment delivery has also caused a dramatic change in various aspects of the delivery process. With simple nonconformal fields, it was common to outline the shape of each treatment field on the patient's skin and to confirm at treatment that the shape and placement of each radiation field agreed with the shape drawn on the skin. This limited large errors but certainly was not a highly accurate positioning check. With modern IMRT treatment fields, understanding the fluence pattern that will be delivered requires computer-generated images, and there is no intuitive way to check the field shape, position, or intensity pattern directly on the patient, so more sophisticated QA checks or procedures are necessary. With modern EPID systems, so-called portal dose measurements (intensity or "dose" measured with the EPID) can be compared with that which is expected and used as a QA check that can potentially identify both geometric and dosimetric differences between the desired and delivered dose distributions.[130,131] It is also possible to reconstruct the

delivered intensity distribution by analysis of MLC trajectory information.[132] The further development of quantitative online delivery QA checks along with their integration into the treatment delivery process is an area of significant ongoing experience that is expected to lead to much more sophisticated delivery systems.

Electronic Medical Records, the Patient Treatment Chart, and Treatment Management Systems

As computer systems have increased the sophistication of planning, treatment delivery, and treatment verification and QA, the need for more sophisticated treatment documentation has also grown. Computer-controlled treatment plans and IMRT require the use of electronic patient treatment charts because there is just too much technical information to allow sole use of a paper treatment chart. The trend toward the use of electronic medical records (EMRs) to replace paper patient charts is certainly mirrored throughout the healthcare system as all major medical systems convert their paper-based record systems to electronic EMRs.

It is incumbent on all users of EMR systems to carefully implement and use the new technology. It is not appropriate to just convert all the old paper-based documentation practices into electronic forms because some standard paper-based methods just do not work well in the electronic world. For example, writing notes in a chart in pencil to show what should happen in some number of future treatments cannot be easily mimicked in an electronic system.

Some analysis of the needs for electronic treatment charts has been published,[129] but the ongoing transition from paper to electronic charts should be evaluated and performed with care. Complex IMRT-based prescriptions and plans probably require new methods that were not supportable in a paper-based chart, and users of highly sophisticated conformal therapy will have to develop their own migration from paper to electronic prescriptions and treatment charts.

In radiation oncology, the transition to EMR use has involved more of a migration than just replacement of the paper chart with an electronic one. The early computer-based record and verify systems that were originally developed in the 70s[125,126] have morphed into complete treatment management systems (TMS) that can support all of the electronic medical record needs of stand-alone radiation therapy centers, while also needing to work along with the larger hospital EMR systems in hospital settings. The TMS is a major component of the hardware/software that is needed to run a radiation oncology department, and it is quite complex, extending from general patient care all the way into the treatment delivery arena. Although early efforts to develop such integrated systems have been published,[39,108,127-129] there is relatively little current literature to help users of the systems (this means most radiation therapy professionals) to understand commissioning, optimization of use, and ways to improve workflow through the planning/delivery process through more effective use of the TMS. More work in this area is needed.

Consideration of Setup Error and Patient Motion Management

As the field of radiation therapy has made the transition from four-field boxes and AP-PA fields to sophisticated conformal therapy based on 3D treatment planning and IMRT, it has become more obvious that considerations of daily setup uncertainties and errors and patient and organ motion during treatment are important considerations that should affect both treatment planning and treatment delivery methods. During multiple fraction treatment, all of the following effects should be considered:

- Daily setup variations
- Changes in patient anatomy and target shape over time
- Patient movement and organ motion during treatment

For many years, the ICRU-50 concept of the PTV[72] has been the response to these issues. However, the desire to perform precise conformal therapy has led many institutions to study these issues in more detail and to measure the associated uncertainties.

The importance of correcting the systematic setup uncertainty, if possible, has also led many institutions to convert their positioning verification procedure from the use of weekly port films, with position correction if a large-enough error is seen, to a more sophisticated offline or online repositioning scheme.

It is now quite routine to use the sophisticated setup, localization, and imaging strategies of IGRT (described previously). Use of daily IGRT setup correction based on imaging (megavoltage imaging, kilovoltage imaging using an integrated kilovoltage tube and imager, or kilovoltage or megavoltage CBCT) is a significantly more accurate method for daily patient positioning than the methods used previously, although these IGRT techniques require more effort. Even relatively straightforward daily imaging techniques using EPID imaging and automated repositioning of the treatment table demonstrate large improvements in setup accuracy (e.g., improvement in Σ [the systematic setup uncertainty] from >8 mm to 2.3 mm for liver patients).[133] It is also possible to apply "decision rule" protocols[134,135] in an offline manner: verification imaging is performed several days in a row, and only after the systematic error in the setup is determined is a correction made.

Daily IGRT also provides detailed information about the stability of patients and their positioning, and can make possible adaptive treatment changes that can allow individualization of the margins and setup techniques used for individual patients. This is a rapidly developing area, and promises improvements in patient treatment precision, as well as in improving our ability to image[136] and respond to changes in the patient, tumor, or normal tissue behavior through the course of therapy.

In the last decade, major progress has been made in taking account of motion and patient respiration throughout the patient imaging, planning, and delivery process. 4D CT[137,138] is now regularly available in many clinics, giving the physician and planner the ability to visualize, at least to a limited degree, the motion which occurs as a result of respiration or other such internal motions. Planning strategies that take into account respiratory motion have been described,[139] including the definition of an ITV, which describes the extra margin required to keep the CTV in the high-dose region of the dose distribution. Respiration management systems[71,140] are routinely used to minimize respiratory motion, leading to a significant decrease in the additional margins, which need to be left to keep the target in the high-dose volume in the face of motion as a result of respiration. Using deep inspiration breath hold (DIBH) methods for patients with left-sided breast cancers has helped significantly decrease cardiac dose from the usual tangent-like fields used for those patients.[141,142] Finally, real-time monitoring of motion in the target can be accomplished with radiofrequency beacons, video surface imaging, and other real-time methods that can give direct information about motion during treatment.

CLINICAL CONSIDERATIONS

To this point, the technical process of conformal therapy planning and delivery has been described. This final section

describes some of the clinical considerations involved in the application of conformal therapy techniques and provides a brief summary of some clinical results of IMRT treatments.

Immobilization and Setup Uncertainties

Patient positioning and immobilization should be reproducible and comfortable enough to be maintained for the duration of the treatment, whether it is 5 or 50 minutes. Because position reproducibility and PTV (or planning organ at risk, PRV) margin are necessarily linked, careful consideration must be given to both. For example, if a target intended for high doses is near a critical structure like the spinal cord, a small PTV margin is desired; thus, careful immobilization is required, even if less comfortable. Without nearby critical structures, immobilization can be less restrictive.

PTV margins also vary per site, depending on specific immobilization devices or techniques. The clinically measured range of motion and setup uncertainties for each clinical site should be known, as those uncertainties will determine the margins required for the PTVs and PRVs (if used) during treatment planning. Additional margin information can be obtained from the literature, as margins for a sample of patient populations using commercial, widely available immobilization systems have been determined and published; for example, the setup error standard deviation when using a commercial thermoplastic mask for head and neck immobilization has been determined to be 3 to 4 mm if patient-specific information is obtained and daily patient repositioning protocols using portal imaging are enacted.[143] Although weekly verification is considered the standard method for conventional radiation therapy and 3D radiation therapy, daily imaging of the skeletal anatomy or implanted fiducial markers using an EPID has reduced systematic and random variations.

Systematic setup error can be established from imaging during the first three to five treatments[72] and can then be corrected, leaving only the random deviation to be accounted for by adequate PTV margins. Daily patient imaging and correction of setup deviations can reduce it even further, making it possible to minimize the PTV margin, thereby increasing the sparing of adjacent noninvolved tissue.

Considerations of patient setup and immobilization approaches are complex. For example, in prostate cancer, the prone patient position can improve the separation between the prostate and the rectum compared with the supine position, thus potentially improving sparing of the rectum. However, prone positioning also can increase breathing-related motion of the prostate,[143,144] which may increase the required margin in the superior-inferior dimension, actually increasing the length of rectum within or close to the PTV. In breast cancer, prone positioning is gaining popularity for patients with large or pendulous breasts. However, with prone positioning, the heart can fall closer to the chest wall and potentially into the tangential fields for a left-sided breast cancer.[145] Thus, careful evaluation of how immobilization position impacts not only target, but also normal tissue geometry, is crucial.

Patient and Organ Motion

Individual measurements of motion and setup uncertainties, and their corrections, are especially important in sites where breathing or internal motion is significant, such as the thorax and abdomen. Techniques for dealing with this motion can be separated into two basic categories: eliminating motion or including motion in planning and delivery. Methods to eliminate motion include forced or voluntary breath hold. With these methods, assessment of tumor position can be performed using cone-beam CT or orthogonal imaging of implanted fiducials or the chest wall, and setup variation can be reduced to just a few mm.[133,146] Methods to confirm position of external surrogates[147] are popular and user friendly, but rely on the assumption that there is a consistent relationship between external surrogates and specific internal anatomy, which is not always the case.[148] Not all patients can tolerate breath-hold treatments, and they also increase time on the treatment machine and patient discomfort. Thus, methods to include motion in planning and delivery are important to avoid treating a PTV that is too small and risking a marginal tumor failure, or treating one too large and risking increased toxicity. Most free-breathing motion management strategies start with a 4D CT, to understand the trajectory of tumor motion, which can be quite complex and variable.[143] The apparent tumor (if identifiable without optimal intravenous contrast-enhancement) is contoured on all phases to include the GTV with motion envelope. Then, a clinical target volume margin is added to include regions of microscopic spread, and finally, a margin must still be added for setup uncertainty before arriving at the final PTV. This workflow is most commonly used for lung tumors. If the tumor is only apparent on breath-hold contrast-enhanced CT or MRI, the GTV is still contoured, and a motion envelope for asymmetrical expansions can be created by studying the motion of an internal surrogate in close proximity to the tumor, ideally implanted fiducials. Adding margins for microscopic spread (if appropriate) and setup uncertainty would also follow. This is most useful for liver tumors.

Although most of the focus is on motion of targets, it is important to keep in mind that normal tissues also move, often differently. This can happen during as well as between treatments. During respiration, even different abdominal organs have varying amplitudes of motion.[149] Additionally, the shape of and relationship between organs can change, most notably for the stomach, but for other organs such as the colon, duodenum, gall bladder, and bladder as well.[150] Thus, a PRV margin and patient instructions on empty versus full stomach and bladder can be helpful to avoid inadvertently high doses to nearby organs.

Both breath-hold and free-breathing techniques can be used with treatment gating or tracking. With gating, the beam is only on through a prespecified range of positions, within the ITV and PTV margin employed.[151] With tracking, the radiation beam follows the motion of the tumor.[152] Selection of gating versus tracking is a complex choice, with considerations including practical (which technology is available in a particular center) and theoretical (considerations of duty cycle, margins, etc.).[153]

Determining the Targets

The dosimetric advantages of IMRT must be balanced with potential pitfalls related to the production of tight dose distributions around targets contoured on the CT scan. The most important issues are the reliability and reproducibility of outlining the targets that typically rely on a single planning scan performed before the start of treatment, and the error of image registration if supplemental imaging, like an MRI, is used. The GTV is contoured on the treatment planning CT scan using clinical and radiologic information. In many cases, contrast-enhanced CT combined with clinical information derived from physical examination is the main modality used for the delineation of the targets. For some sites, CT is not the best imaging modality for the definition of the extent of the macroscopic tumor, and ancillary studies such as MRI or fluorodeoxyglucose (FDG)-PET may add important information. MRI can be limited by its sensitivity to artifacts, long examination time, and cost. FDG-PET is often limited by a lack of

specificity regarding tumor versus inflammation, and by uncertainties in interpretation, which may be subjective and differ depending on the observer's experience. PET-defined target volumes can also depend substantially on the standardized uptake value (SUV) chosen to contour the PET scan. The best added information from these studies is derived following their registration either with diagnostic CT or with the planning CT scans. Rigid body geometric registration of multiple scan types can now be performed in many cases using commercially available software, whereas registration of nonrigid structures is the subject of ongoing research, with less than satisfactory commercial products available today.[154-157] Careful review of the registration is necessary to evaluate its quality and any potential need to add additional margin for registration errors.

Future improvements in the anatomic and metabolic imaging of tumors are expected to decrease the uncertainties in contouring the GTV while determining the volume to receive high radiation dose. However, the definition and contouring of the tissue volumes at risk of harboring subclinical disease (CTVs) depend on clinical judgment alone. It is not surprising that large interobserver differences have been noted in outlining these volumes.[158-162] The uncertainties in outlining the target volumes raise concerns about the potential of highly conformal radiotherapy to miss disease while striving to spare organs adjacent to the targets. Efforts to define the volumes at risk for subclinical disease for each tumor site have been made for head and neck cancer,[163,164] breast cancer,[165,166] and cancer at other sites.[167-170] They constitute the initial steps in this direction. Clinical validation, based on data regarding the sites of locoregional tumor recurrence and their relationships to the targets, is necessary. To date, relevant data are scant. They suggest that when target outlining is performed by experienced investigators, the large majority of the locoregional tumor recurrences are in-field, and only few marginal failures are observed.[171,172] Until more data are available, target outlining should be done in a conservative manner. Target volume definition requires thorough knowledge and understanding by the radiation oncologist of the anatomy and the locoregional tumor spread pattern. Recently, atlas-based automatic segmentation has become a reality within several planning systems. Validation studies are encouraging, but even these contours require careful examination and cannot completely replace dedicated physician time and expertise.[173-175]

An outline of imaging studies required for each tumor site and other considerations for determining the targets, normal tissues, and image guidance requirements are described next.

Head and Neck Cancer

Most head and neck target volumes are defined using CT information. However, MRI is a necessary adjunct to CT for tumors close to the base of skull (i.e., nasopharyngeal and paranasal sinus cancer), where it provides better details of tumor extension and the parapharyngeal and retropharyngeal spaces, compared with CT.[176] FDG-PET, in most cases, defines smaller primary targets compared with CT, and the volumes depicted by each modality do not completely overlap.[177] Relying on FDG-PET may result in changes in the outlining of the GTVs compared with outlining based on CT, at least in some patients. Whether FDG-PET is more accurate than CT in delineating the primary tumor GTV has not yet been established, because of the paucity of data correlating the imaged extent of the gross tumor and its size in pathologic specimens following resection. Current data from series involving imaging followed with surgical validation suggest slightly more accurate definition of the gross tumor by FDG-PET compared with CT. Until more data are available, the most prudent practice seems to be outlining the GTV as the composite of the lesions observed on CT and PET, as FDG-PET has poor sensitivity for microscopic disease. In cases of recurrent cancer, where extensive scars from previous surgeries confound the CT-based delineation of the tumor, FDG-PET has a clear advantage[178] and should be used as the primary modality for the delineation of the GTV.

The CTVs for head and neck cancer include subclinical disease in the vicinity of the primary tumor and lymph node groups at risk of subclinical disease. Outlining the CTVs requires knowledge of the natural history and pattern of failure of each tumor site. Suggestions for the selection and delineation of the targets have been published, and atlases detail the recommended delineation of various lymph nodal groups.[163,164] Although PET has been useful for definition of the GTV, it cannot be used to justify omitting radiotherapy to established, standard CTV volumes based on patterns of nodal spread. Perhaps more so than in any other disease site, the radiation oncologist and dosimetrist or physicist treatment planner must make the most clinically rational tradeoffs between target coverage and normal tissue sparing. Because these tradeoffs are complicated and depend on balancing the likelihood of cure and likelihood of toxicity, they require individual consideration for each patient.

The PTVs for head and neck treatments, as with all other sites, depend on IGRT strategies, as discussed previously. For tumors near the base of skull, where accuracy is particularly important to avoid overdosing the optic chiasm and optic nerves, CBCT is particularly useful to assure alignment, particularly when minor rotations can cause clinically significant dosimetric differences that could translate to major toxicities. In this case, alignment should be biased toward the most critical structure.

Lung Cancer

In lung cancer, the primary lesion should be contoured on the CT scan using window/level settings for pulmonary visualization (i.e., a pulmonary window), with mediastinal settings to aid in defining borders near the mediastinum or chest wall. FDG-PET can be helpful when a PET avid but anatomically indistinct tumor is present. In particular, PET can differentiate atelectasis from tumor, preventing unnecessary inclusion of noninvolved lung tissue in the GTV.[179] On the other hand, PET is certainly not perfect, and there is still controversy regarding proper thresholding of imaging to most closely approximate the actual tumor size.[180,181] Unfortunately, appropriate radiographic-pathologic correlation studies are still lacking. Additionally, because 4D-PET is still not widely available, most PET images depict an "average" intensity of a moving target and may overestimate the true tumor size.

The CTV for non–small cell lung cancer is typically an approximate 5 mm uniform expansion of the GTV allowing for direct microscopic spread, although some advocate for customized margins based on exact tumor histology.[182,183] Elective nodal radiation has fallen out of favor because recurrences in nodal basins are quite rare compared with recurrences in the primary tumor and the elective irradiation significantly increases dose to normal tissues.

Because respiratory motion can significantly affect the dose distribution, lung target volumes often require use of an internal target volume-like margin (from ICRU-62[184]) for respiratory motion of the target, depending on whether measures to reduce the motion are used (e.g., ABC or gating). In the absence of such measures, large variability in tumor motion is observed among patients, on average 1 cm in different directions, with high variability. Methods to minimize respiratory motion,

such as abdominal compression and coached breathing, may minimize but not eliminate motion. In the end, the PTV for a lung tumor is typically comprised of radiographically apparent tumor, motion envelope, CTV margin for microscopic spread, and PTV margin for setup variation. The PTV margin is preferably small because of the extreme sensitivity of the lungs. Thus, reproducibility of setup is crucial. Advanced image-guided systems, including CBCT and tomotherapy, can visualize the tumor and organs at risk in three dimensions before treatment and allow for online correction. Imaging of internal fiducials placed within the tumor may also be used when CBCT is not available.[185]

Brain Cancer

For brain tumors, multiple sequences of MRI, with and without contrast, are typically crucial for both GTV and CTV delineation. Registration of these images to a planning CT is usually quite straightforward, compared with areas of the body that may deform. Still, careful review of the registration is necessary, with particular attention focused on the optic chiasm or other sensitive normal structures, especially for tumors in close proximity to those structures. If a preoperative MRI is fused with a postoperative planning CT, clinical judgment must be used to determine how much of the normal brain parenchyma to include because it often falls into the tumor bed.

Immobilization typically consists of a thermoplastic mask, and with a typical accuracy of as little as 3 mm, helpful for tumors near the chiasm or brainstem. Still, for those cases, daily imaging with not only orthogonal images but with CBCT is advised to minimize both systematic and random error of setup in that critical region.

Gastrointestinal Cancer

Contrast-enhanced CT is crucial for many sites including pancreas and liver cancers. MRI is usually necessary for identification of hepatocellular carcinoma, although liver metastases are usually well-seen on a high-quality CT with delayed imaging. Radiographic data must be supplemented with physical examination and endoscopy reports for rectal cancer, and PET scan and endoscopy reports for esophageal cancer. Many site-specific atlases have been developed to aid in consistency in delineation of target volumes.

Target definition must take into account significant respiratory-related organ motion for upper abdominal tumors, which can be up to 25 mm.[148,149] Without methods to reduce respiratory movement, the large margins required to accommodate this motion can markedly increase the volumes of small bowel and duodenum receiving target doses and limit the ability to escalate tumor dose. With tightly defined target volumes, the volume of small bowel and duodenum irradiated are reduced, producing improved toxicity and potentially allowing higher radiation doses in certain sites.[186,187]

Image guidance has traditionally consisted of orthogonal imaging, but for mobile tumors, the relationship with bony surrogates is changing and unpredictable. Thus, confirmation of soft-tissue location with CBCT may be necessary, either by aligning the tumor itself, or if not visible, implanted fiducials or a nearby surrogate landmark. Historically, tumor control for pancreatic cancer has been poor and toxicity rates high. Likely contributors to the problem included poor tumor definition because of inadequate imaging, poor accounting for tumor and organ-at-risk (OAR) motion, lack of highly-conformal treatment techniques, and poor image-guidance. Thus, with advances in these, there is hope that tumor control and toxicity will both improve.

Prostate Cancer

Gross disease within the prostate gland cannot be defined accurately using conventional imaging, so routine practice is to treat the entire prostate as the CTV. Research in magnetic resonance spectroscopy (MRS) suggests that it may be used to identify aggressive tumor foci within the prostate using the choline-to-citrate ratio, which is higher in tumor cells compared with prostatic cells.[188-190] Other sequences may also be useful to identify nodules of high Gleason grade for additional boosting, although lower grade tumors are not consistently detected, confirming the need to treat the entire gland with radiation. Still, if confirmed, MRS imaging may be used to define the high grade GTV, or the boost volume, within the prostate, with the hypothesis that high radiation doses may prevent failures in these nodules.[191,192] In any case, MRI is extremely helpful for prostate contouring. The prostate's superior margins at the base of the bladder and its inferior margin (apex) are better defined on MRI compared with CT. MRI is also better at defining the rectal and bladder boundaries and the penile bulb. Target delineation for the post-prostatectomy setting is aided by a contouring atlas.[168]

The size of the PTV depends on image-guidance strategy. Implanted gold fiducials, which can be visualized with standard orthogonal imaging, or electromagnetic transponders, can help allow for a reduction in PTV margin to 5 mm, although this must be closely monitored for both translations and rotations.[193] Daily imaging with tomotherapy or CBCT can also reduce required margins.[194] Recently transponders have been integrated into a gating system and linked to MLC tracking for the first time.[195]

Gynecologic Cancer

Accurate target delineation is vital in the conformal radiation treatment of cervical cancer. MRI defines gross abdominal disease better than CT and is strongly recommended in defining the tumor volume, which may be further aided by FDG-PET.[196] Fusion of the T2-weighted MRI images to the simulation planning CT scan is advised when possible. To assist in delineating targets, the RTOG consensus panel has proposed guidelines.[170] Because of substantial organ motion, tumor regression, and deformation associated in patients with cervical cancer, margins of 1.5 to 2 cm around the CTV are recommended for the primary PTV with a PTV margin of 7 mm around the nodal CTV. Whether IMRT can be useful in the treatment of an intact cervix, replacing brachytherapy or, more likely, serving to augment GTV doses after brachytherapy, is not yet known. Brachytherapy remains the standard of care. If IMRT is considered for the intact cervix, daily soft-tissue image-guided verification is required to avoid the risk of geographic miss.

Breast Cancer

Typically, the whole breast is considered the clinical target volume, with an additional lumpectomy cavity volume designated for a boost in most cases after breast-conserving surgery. The lumpectomy cavity is outlined on CT, with the assistance of surgical clips, as the CTV, and a margin is often assigned as the PTV, for breathing motion and setup uncertainties. When regional lymph nodes require irradiation, treatment complexity is higher, and heart doses in left-sided breast cancer therapy may be substantial. For the outlining of the lymphatic CTVs, particularly the supraclavicular lymphatics, in addition to other relevant structures, including the heart, anatomic guidelines, and atlases have been published.[165,197,198]

Accelerated partial breast irradiation (APBI) is increasingly being used to treat early-stage breast cancer patients, as

elsewhere (outside of the lumpectomy cavity) breast failures are rare. The optimal margin of tissue requiring radiation after lumpectomy in patients treated with APBI remains somewhat controversial. However, contemporary radiographic and pathologic data suggest that a margin of 10 mm around the tumor bed appears adequate to cover any disease remaining in the breast after lumpectomy in most (>90%) of patients, provided the final margins are negative.[199]

Noninvolved Normal Tissue

Forward planned 3DCRT allows intuitive decisions by the planner regarding beam apertures and directions, but such decisions cannot be made in inverse planned IMRT. This requires that all targets and organs at risk be determined and outlined in the planning CT for use in the inverse planning. Many normal tissue atlases have recently been published to standardize delineation, and thus aid in consistent dose reduction to critical organs.[165,197,200-202] In addition, inverse planning typically requires the definition of "non-specified tissue." This information is usually obtained by subtracting all targets and specified organs at risk from the external contour of the patient in the CT dataset. It allows limits on the maximum doses delivered outside the targets and the organs at risk, which is necessary to reduce unexpected damage to soft tissue, nerves, blood vessels, and so on. This is particularly important when a new technique is being implemented. For example, in the early days of IMRT, alopecia and dermatitis of the posterior low scalp were an unanticipated result of using multiple beams without dose limits on the nonspecified normal tissue of the scalp. With the resurgence of arc therapy and development of new techniques, it is particularly important to carefully set dose limits on normal tissues, often requiring contouring of structures which had traditionally been spared by avoiding beams entering through these regions.

Treatment Goals and Rationale for Highly Conformal Radiotherapy

Data from many disease sites suggests that target dose escalation improves local control. At the same time, we are learning more about the dose-response curves for toxicity after irradiation of organs at risk. Additionally, as the number of normal tissues with avoidable toxicity increases, often treatment planning becomes similar to avoiding mines in a battlefield. In many situations, this absolutely could not be accomplished without IMRT, newer modes of arc therapy, and potentially proton therapy.[72] However, this must be balanced against the increased time and cost required, for each situation. The clinical considerations for several sites are described here.

Head and Neck Cancer

Delivery of the prescribed dose to the targets in advanced head and neck cancer is often limited by the dose to the spinal cord and brainstem, especially in advanced nasopharyngeal cancer, posterior pharyngeal wall cancer, and thyroid cancer. Also, irradiation of gross disease in the posterior neck may be suboptimal because of dosimetric deficiencies due to the off-cord photon and posterior neck electron beams if 2D or simple 3D treatment planning is used. By making possible concave dose distributions, IMRT can overcome these deficiencies and potentially improve tumor control rates. Dose escalation to the GTVs[203] or to hypoxic subvolumes within the GTV[204] using IMRT has been proposed.

Sparing of the parotid glands, in an effort to reduce xerostomia, has been a major goal of earlier 3DCRT[205] and subsequent IMRT studies.[206,207] Randomized studies of IMRT versus 2D radiation therapy in nasopharyngeal cancers demonstrated improvement in salivary production and in observer- and patient-reported xerostomia.[208-210] Sparing the contralateral submandibular gland in cases where contralateral level IB is not a target has been proposed, suggesting a mean dose of less than 39 Gy as a goal.[211] However, IMRT cannot substantially preserve the function of the submandibular glands in some cases because these glands lie anterior to the subdigastric nodes that are important targets in both sides of the neck, and this poses a limitation on reducing xerostomia even by IMRT. Similarly, reducing the doses to the noninvolved oral cavity, striving to spare the minor salivary glands and to reduce mucositis, is an important planning goal. Additional objectives, depending on the clinical scenario and balance between adequately treating targets and sparing normal tissues, include reducing doses to the optic pathways, inner ears, swallowing structures, skin, and carotid arteries.[212-215]

Brain Cancer

Dose escalation trials attempting to increase the currently poor local control of high-grade gliomas have been conducted at the University of Michigan.[171,216,217] These trials used 3DCRT or IMRT, more recently with concurrent temozolomide, delivering a high dose to the GTV while keeping a constant dose to the CTV and limiting the doses to the optic pathways and noninvolved brain to minimize the risk of brain necrosis and visual decline. IMRT may be superior to 3DCRT for tumors that are close to the optic nerves or chiasm, or for irregularly shaped tumors, particularly if dose is escalated.

Lung Cancer

Facing low local tumor control, the goals of conformal irradiation are to improve target irradiation while reducing lung volumes receiving a high dose. Using 3DCRT, trials of dose escalation have been conducted using various constraints on uninvolved lung doses, such as the mean dose, the lung volume receiving more than 20 Gy (V_{20}), and a fixed low normal tissue complication probability. Using similar dose constraints, IMRT has been used to treat lung cancer. However, substantial geometric uncertainties about beamlet doses in lung tissue may influence the accuracy of imaging, treatment planning, and delivery. To improve the optimization of IMRT beam direction, the role of ventilation perfusion scans is being explored so that well-ventilated lung may be more appropriately spared.[218] Additionally, because of a completely different pattern of dose distribution with IMRT as compared with 3D and 2D, some are concerned that traditional models to predict pneumonitis may not completely apply, and that restrictions on even low doses such as 5 and 10 Gy (V5 and V10) are necessary, as treatment of high volumes of lung tissue to even low doses has been associated with fatal toxicity, and concurrent chemotherapy may increase this risk.[219-221] Other potential reasons to use IMRT for lung cancer would depend on geometry, specifically proximity of the tumor to organs at risk including spinal cord, heart, and brachial plexus.

Breast Cancer

IMRT can potentially produce more homogeneous doses to the intact breast compared with lateral tangential beams. In randomized trials, this has translated into reduced rates of moist desquamation, improved quality of life, and improved cosmesis compared with 2D radiotherapy.[222,223] An active area of research is how much IMRT would add to excellent 3D

conformal planning for these endpoints, and which patients would be most likely to benefit. IMRT potentially also could aid in reduction of dose to the heart, particularly for left-sided breast cancers, although because of anatomical variation, even treatment plans for right-sided breast cancers can deliver considerable dose to the heart.

The use of hypofractionated partial breast irradiation is a recent strategy for the treatment of early-stage breast cancer. The main advantages of this technique include shortened overall treatment time, and better access and compliance. This accelerated hypofractionated irradiation regimen to the lumpectomy site takes into account the pattern of breast relapse that predominates in the original tumor quadrant and assumes that good cosmetic outcome may be achieved if high fraction doses are delivered to limited breast volumes using highly conformal therapy. Recent reports call this into question, with poor cosmesis observed.[224-227] Therefore, this approach should not be taken outside the context of a clinical trial.

Prostate Cancer

Dose escalation to the prostate and limiting the doses to the rectum and bladder to reduce the gastrointestinal and genitourinary toxicities of therapy have been the major goals of 3DCRT and IMRT, particularly given the benefit for dose escalation seen in four randomized trials.[228-231] IMRT potentially can help create sharper dose-gradients and allow for safer dose escalation. Indeed, a subgroup analysis of the high-dose arm of RTOG 0126 suggested that patients treated with IMRT had lower rates of acute (15% versus 10%, $p = 0.04$) and late (22% versus 15%, $p = 0.04$) grade 2 or higher genitourinary or gastrointestinal toxicity, likely related to improved dosimetry.[232] Efforts have also been made to reduce the doses to the penile bulb and the pudendal arteries to possibly minimize the rates of treatment-related erectile dysfunction, although conclusive dose-volume-toxicity relationships have not been validated.[233,234] In patients with high-risk of prostate cancer, when IMRT is used to treat the pelvic nodes along with the prostate and seminal vesicles, IMRT is helpful to reduce dose to the small bowel and bladder, in addition to the rectum.

Gastrointestinal Cancer

Pancreatic cancer has high rates of local and distant failure despite aggressive surgical resection. Traditionally, large volumes, including the primary tumor and potentially involved nodal basins, have been treated with radiotherapy, with concurrent moderately active chemotherapy. IMRT is helpful to minimize dose to large volumes of bowel and kidneys. Recently, many groups have advocated delivering escalated doses of radiotherapy to smaller volumes (only the gross tumor with PTV margin) with more potent chemotherapy (full dose gemcitabine), relying on the chemotherapy to sterilize microscopic disease. With dose-escalated radiotherapy, the sharp dose gradients achievable with IMRT are crucial to protect the adjacent duodenum. In both cases, IMRT improves sparing of the gastrointestinal structures including the duodenum, stomach, small bowel, colon, and liver, in addition to the kidneys.

IMRT is also crucial for treatment of anal cancer. Traditionally, patients have required treatment breaks because of severe perineal and inguinal desquamation. RTOG 0529 demonstrated that IMRT for anal cancer is feasible across institutions and resulted in lower dermatologic, gastrointestinal, and hematological toxicities compared with historic controls.[187] Additionally, with less than optimal local control of advanced tumors, dose escalation may also have a role in this disease.

Gynecologic Cancer

Most current studies of IMRT for gynecologic cancer aim at reducing the volume of small bowel irradiated during postoperative treatment. Escalating the dose to the GTV using IMRT as a replacement for brachytherapy has been proposed, but it is unlikely that escalated external beam doses can match the extremely high doses delivered safely by brachytherapy.[170] In recent years, there has been growing interest in the potential for IMRT to reduce dose to marrow-producing regions of bone to reduce hematologic toxicity. Recently, an analysis of RTOG 0418, a study of postoperative IMRT for gynecologic cancer, suggested that the volume of marrow receiving 40+ Gy and the median bone marrow dose correlated with higher rates of grade 2+ toxicity in patients receiving concurrent weekly cisplatin chemotherapy, thus justifying the use of IMRT for this purpose. Efforts to incorporate functional bone marrow sparing into treatment planning are under way.[235,236]

Pediatric Tumors

The rationale for highly conformal radiotherapy in pediatric tumors is to limit the high-dose volumes in growing and critical organs, especially the cochlea, brain parenchyma, brainstem, bowel, and bones. Although IMRT may achieve this goal better than 3D radiation therapy in some cases, it increases the volumes receiving low-dose radiation and the potential for future radiation-related cancers. This should be an important consideration, particularly since follow up of patients who received this type of dose-distribution is limited, and second malignancies can appear 10 to 20 years or more later. Only when an obvious benefit is expected should IMRT rather than simpler techniques be used in children. For example, in medulloblastoma, IMRT can reduce the dose delivered to the cochlea when a posterior fossa boost is planned with IMRT compared with parallel-opposed beams, but similar benefit may often be gained by the use of 3DCRT.[237] This requires thoughtful decision making from the physician and dosimetry-physics team.

Target and Organ Prescription: Dose Considerations

Standard 2D radiotherapy has typically been delivered in two or three phases. For a typical head and neck example, in the first phase radiation is delivered to all targets, including nodal and high-risk volumes. After a dose that is likely to eradicate subclinical disease is delivered (typically, 46 to 50 Gy), additional irradiation is delivered only to the high-risk targets, to a total of approximately 70 Gy. In this scheme, all of the targets receive the same daily dose of 1.8 to 2 Gy. In contrast, with IMRT, the most commonly used strategy is a single treatment plan with a simultaneous integrated boost (SIB) technique. High-risk targets receive both a higher total dose and a higher daily dose compared with the lower-risk targets, and compared with critical normal structures whose total maximal dose is limited to total doses that are lower than the prescribed target doses. Smaller daily doses reduce the biologic effect of the doses delivered to the critical organs (described by the normalized total dose [NTD]), so the SIB technique creates the situation in which the maximum critical organ doses usually allowed in standard radiotherapy become much more conservative when used with the SIB IMRT technique, if they are treated with lower doses per fraction. Conversely, doses above 2 Gy per fraction should be used with caution because this would deliver a higher biologic dose to normal tissues (e.g., mandible) adjacent to these targets. In addition, the maximum doses specified in IMRT or 3DCRT are delivered to smaller (or

much smaller) organ volumes compared with conventional radiotherapy. IMRT or highly conformal 3DCRT treatments may be safer than corresponding standard radiotherapy treatments even if nominal maximum critical organ doses are similar. On the other hand, higher-than-standard total target doses, delivered inadvertently as a result of nonuniform dose distributions typical of many IMRT plans, or resulting from intentional GTV dose escalation in an effort to increase tumor control rates, are associated with increased daily doses, causing a further increase of the NTD to the tumor. This has the potential to increase toxicity related to tissue embedded within the target. Such toxicity may only be apparent long after therapy and its prevalence is not yet known. Dose escalation relying on the ability of IMRT to restrict the high-dose volume to the GTVs should be conducted only within careful clinical trials. For clinical situations in which the range between the dose intended for microscopic and gross disease is large, two IMRT plans are generated to avoid both low (<1.5 Gy per fraction) or high (>2.5 Gy per fraction) daily doses, which would risk increased tumor recurrence and late toxicity rates, respectively. Consecutive IMRT plans are commonly used for prostate and sarcoma treatments.

When Should the Use of Highly Conformal Radiotherapy/Intensity-Modulated Radiation Therapy Be Considered?

Planning, delivery, and QA of 3DCRT/IMRT are more complex, costly, and work-intensive compared with these factors for previous technologies. The use of 3DCRT/IMRT is justified if it offers apparent clinical advantages. The advantage in the dose distributions achieved by IMRT compared with 3D radiation therapy is mainly in the ability to form concave, horseshoe-like dose distributions. Such distributions are desirable in cases in which the target partly encircles a critical involved structure whose tolerance is less than the desired target dose. This includes cases of head and neck cancers in which the targets are arranged anterior and lateral to the spinal cord and are bounded laterally by the major salivary glands; in prostate cancer, in which the prostate abuts the anterior rectal wall and sometimes extends slightly laterally as well, particularly in the postoperative setting; in lung cancer, in which the target (usually, the mediastinal lymph nodes) may lay close to the esophagus, or the primary tumor may be in close proximity to the spinal cord, brachial plexus, or heart; in gynecologic cancer, in which the lymph node targets are arranged lateral to and posterior to the small bowel; in left-sided breast cancer, in which the target is concave and anterior to part of the lung and heart; in brain tumors near the optic pathways; in medulloblastoma, in which the posterior fossa partly surrounds the inner ear; and in others. IMRT may also be indicated in cases in which minimizing the extent of the tissues receiving a high dose (at the expense of higher volumes receiving low doses) is likely to be beneficial, such as retreatment of recurrent cancer. On the other hand, it is less likely that a dosimetric benefit will be gained from IMRT in cases in which tumors are remote from sensitive tissues or are adjacent to a sensitive tissue but do not (partly) surround it, compared with simpler conformal techniques. Even when dosimetric differences between 3DCRT and IMRT are small, like in prostate cancer, where the anterior wall of the rectum can protrude somewhat into the posterior prostatic target, these differences still may be translated into a clinically meaningful benefit in reducing rectal complications by IMRT compared with 3DCRT.

Patient-related issues include the ability to tolerate treatment times that are longer than those required for less complex treatments, although more rapid methods, such as VMAT, are reducing this problem. Poor immobilization and breathing-related motion increase uncertainties regarding the accurate positions of the targets and adjacent normal tissue in the chest and abdomen and, to a lesser degree, in the pelvis. Daily changes in the shapes of organs such as the rectum and bladder may affect their spatial relationships with the prostate target. Because of the tight dose distributions produced by 3DCRT and IMRT, these uncertainties require the use of techniques that minimize, or take into account, target and OAR internal motion in most sites apart from the brain and head and neck. An additional concern is tumor shrinkage during therapy, which may also change the shape and relative position of adjacent organs. Whether these changes over the course of treatment require modifications of the treatment plans in most patients is the subject of current investigations.[238-240]

The high flexibility in creating desired dose distributions by IMRT or other highly conformal techniques provides the ability to deliver high doses to part of tumors judged to be at higher risk than other parts, as identified by functional imaging. Clinical accomplishment of this concept, termed "dose sculpting," or "dose painting" depends on the verification of the reproducibility and reliability of innovative imaging of tumor physiology and early tumor response prediction.

IMRT treatment plans are often characterized by nonhomogeneous dose distributions in the targets that produce "hot spots," receiving substantially more than the prescribed dose. It is imperative that these hot spots are confined to the GTVs, but as with SBRT, these high dose regions may be associated with higher tumor control. Still, the potential for increased local toxicity as a result of "hot spots" is not yet clear and may depend on the site irradiated; high doses delivered to the nasopharynx may be well tolerated, as attested by the common use of an intracavitary boost with radioactive sources for nasopharyngeal cancer, but may not be well tolerated by the mucosa in other sites in the head and neck. In any case, heterogeneous dose distributions by IMRT are not a necessity. By strictly limiting maximum doses, homogeneous dose distributions can be created, as for use in breast cancer. The decision of whether to deliver homogeneous dose belongs to the physician and planner, who can force more homogeneity by limiting maximum doses allowed by the optimization cost function.

Potentially Negative Aspects of Intensity-Modulated Radiation Therapy

Several potential negative aspects of IMRT exist, for which there is as yet no clinical validation. Although IMRT reduces the tissue volumes receiving high doses, larger tissue volumes receive low doses compared with standard radiation therapy or 3DCRT. This is primarily a result of the use of many beams, many MUs, and leakage through the MLC leaves. This characteristic may increase the risk of radiation therapy–related second malignancies because the risk of radiation therapy–related mutations and carcinogenesis increases at intermediate rather than at high doses and is also related to volume of irradiated tissues. This risk is especially relevant for young patients. As the risk of radiation therapy–related cancers increases over time, usually beyond 5 to 10 years after therapy, clinical data are not available at this time.

Another theoretical concern is the loss of biologic effect of radiation therapy when treatment delivery time is prolonged. Prolonged treatment delivery time is characteristic of some IMRT delivery techniques. There are differences in IMRT delivery modes that make a difference in this respect. For example, tomotherapy delivers sequential treatment throughout the target volumes, so that the exposure time of each tumor cell to daily radiation is short. In contrast, other systems irradiate all the targets simultaneously over a relatively prolonged daily

treatment time. Whether the prolonged fraction delivery time translates into a clinical difference is not known.

A last caution for clinics starting to implement IMRT and other highly conformal techniques is definition of all normal tissues of interest because with inverse planning, beam selection alone cannot limit dose to organs at risk, as often done in 3D planning. For example, if small bowel is not specifically contoured for abdominal or pelvic cases, with dose limits specified in optimization, dose may be the same if not higher with IMRT as compared with 3D, wasting the potential to reduce dose.

Future Efforts

To further improve the technical clinical contribution of IMRT to cancer therapy, additional steps need to be taken. They include better understanding of tumor and organ motion and changes during each treatment fraction and during the total course of therapy, and an improved ability to image the anatomic extent and metabolic activity of tumors. Detailed knowledge of the clinical dose-volume-response relationships for all tissues involved in irradiation, to be gained from careful clinical studies and analyses, will help lead to improved treatments using the tools provided by conformal therapy and IMRT planning and delivery.

CONCLUSION

Conformal therapy describes a general strategy for conforming the dose distribution to the desired target volume(s) while minimizing the dose to all normal tissues. Many different techniques can be used to accomplish this, ranging from multiple flat conformally shaped fields (3D conformal) to complex intensity modulated (IMRT) or VMAT plans. The key to high-quality conformal therapy is the accuracy and precision with which targets and normal tissues are defined, the treatment plan(s) are optimized, and the treatments are delivered using image-guidance methods (IGRT), so any technical improvement that enhances any of those capabilities will potentially improve the outcome of the therapy. Though conformal therapy has now been studied and used for as long as 20 years, the most important remaining task continues to be the clinical study of normal tissue complications and tumor control as a function of dose, volume, fractionation, and other factors, so radiation oncologists have the basic clinical data necessary to further improve the optimization of conformal therapy treatment.

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CHAPTER

17 Intraoperative Irradiation

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Intraoperative radiation therapy (IORT) is the delivery of radiation at the time of surgery. The rationale is straightforward: increasing doses of radiation therapy enhance local tumor control. In many clinical situations, the dose delivered by external-beam radiation techniques is limited by tolerance of surrounding normal tissues. To overcome this, intraoperative irradiation has been employed as a technique facilitating tumor dose escalation. Recent Phase III trials have explored IORT, testing noninferiority or equivalence in patients with early breast cancer.[1,2]

This chapter reviews the rationale and treatment strategies of intraoperative electron irradiation (IOERT), intraoperative high-dose-rate brachytherapy (HDR-IORT), as well as orthovoltage techniques with surgery. These strategies frequently integrate external beam irradiation (EBRT) and chemotherapy.

HISTORY

The use of IORT was first employed almost 100 years ago.[3] The contemporary approach to IORT was initiated in the 1960s by Abe et al in Japan. These investigators advocated resection (where possible) with large, single dose radiation therapy (25 to 40 Gy using Cobalt-60).[4] In the mid- to late 1970s, many institutions in the United States had adopted IORT as a treatment approach, primarily as a radiation boost component, using linear accelerator-based electron treatment in the operating room, including Howard University, Massachusetts General Hospital (MGH), Mayo Clinic, and the National Cancer Institute (NCI). Presently, there are about 90 centers in at least 16 countries worldwide with active IORT programs.[5]

RATIONALE

IORT has the potential to improve local control and the therapeutic ratio in many tumor sites by reducing the volume of the irradiation "boost" field by direct tumor/tumor bed visualization and conformal treatment, exclusion of part or all of dose-limiting normal structures by operative mobilization, direct shielding, or varying electron beam energy, and allowing the delivery of high dose irradiation by the preceding methods.

Although early investigators studied this modality separately in the treatment of resected and unresectable malignancies, current approaches frequently employ this technique in combination with fractionated EBRT (with or without concomitant chemotherapy) and resection. The rationale is that EBRT fields encompass the primary tumor and surrounding tissues harboring potential microscopic disease. In contrast to a large single fraction of irradiation, fractionated radiation (EBRT) is radiobiologically advantageous in promoting tumor control while minimizing late normal tissue injury.

Shrinking field techniques permit dose escalation. This approach is used in many malignancies, including head and neck cancers, breast cancer, and cervical cancer with excellent local control and acceptable morbidity to dose limiting normal tissues. These "boost" fields can be delivered in a multitude of ways, including interstitial and intracavitary techniques as well as superficial electrons. For selected intraabdominal, pelvic, thoracic, and other malignancies, IORT is a technique for localized dose escalation while optimizing normal tissue protection.

BIOLOGY OF IORT

When EBRT is fractionated there is a preferential therapeutic advantage for normal tissues relative to tumor as defined by the 4R's of classical radiobiology (normal tissue repair, tumor reoxygenation, cell-cycle redistribution, and normal tissue repopulation). With a single large fraction of radiation therapy, these advantages are lost. In addition, large doses per fraction may result in increased risk of late effects. There is evidence that small vessel injury caused by large doses per fraction may contribute to late effects, and ischemic complications are dose dependent.[6] Furthermore, tumor response to single and fractionated radiation therapy depends on the percentage of hypoxic cells within a tumor. This differential sensitivity between hypoxic and well-oxygenated cells increases with increasing dose.

Using alpha/beta calculations (α/β), biologically equivalent doses to a fractionated EBRT course using 2 Gy per fraction for varying IORT doses have been estimated (Table 17-1). As shown, there are disadvantages from a late effects standpoint with IORT; however, many of these disadvantages are mitigated by exclusion of nontarget tissues from the radiation field by direct inspection, mobilization, and shielding.[7] When combined with EBRT and resection, IORT doses of 10 to 20 Gy provide local control for most solid tumors, especially in the setting of microscopic residual disease. When combined with EBRT and surgery, there is little reason to exceed IORT doses of 10 to 20 Gy. Late normal tissue complications are often the limiting sequelae of IORT administration, and careful planning and administration with techniques designed to reduce dose to nontarget tissues is of paramount importance. Experimental animal data and clinical studies have documented the tolerance of normal tissues to IOERT, EBRT, or both modalities combined, with detailed description of incidence and characteristics of reported observations and toxic events expected in the clinical practice scenario.[8]

LOCAL CONTROL: AN IMPORTANT ENDPOINT

For any treatment, a patient is incurable if local control of the tumor is not achieved. If conventional treatment methods of EBRT, chemotherapy, and surgery provided high local control rates, IORT as a component of treatment would be unnecessary. Single-dose irradiation with precise radiotherapy techniques has also emerged as a valid alternative in patients with metastatic disease[9] or as a potentially cost-effective technique for patients with tumors in early stages and with a favorable prognosis[10] tumors. Although local control rates are satisfactory in many tumor sites using conventional techniques, local failure is problematic in other sites, including abdominal and

TABLE 17-1 Estimated Biologically Equivalent EBRT Doses (2 Gy per Day) of Varying IORT Doses

IORT Dose	10 Gy	15 Gy	20 Gy
Normal tissue (acute) ($\alpha/\beta = 7$)	20 Gy	37 Gy	60 Gy
Tumor ($\alpha/\beta = 10$)	17 Gy	31 Gy	50 Gy
Normal tissue (late) ($\alpha/\beta = 2$)	30 Gy	65 Gy	120 Gy

pelvic malignancies. Treatment of these areas employing standard EBRT techniques is limited by normal tissue tolerance. Examples of such sites are discussed herein.

Pancreatic Cancer

EBRT with 5-fluorouracil (5-FU) based chemotherapy employed in the treatment of unresectable pancreatic cancer results in a doubling of median survival compared to surgical bypass/stenting alone (3 to 6 months versus 9 to 13 months) and an increase in 2-year survival from between 0% to 5% and 10% to 20%.[11] Unfortunately, these techniques result in poor local control rates (20% to 30%). The use of IORT has been evaluated in patients with both resectable and unresectable pancreatic cancer patients.

Retroperitoneal Sarcoma

When surgery is used as the primary treatment modality for retroperitoneal sarcomas, local failure has been reported to range from 40% to 90%. Despite the addition of EBRT to surgery, local failure rates are 40% to 80%. This is in contrast to extremity sarcomas where local control rates approach 90%. Because of the limited tolerance of surrounding normal tissue (small intestine, stomach, liver, kidney, spinal cord), EBRT doses are limited. A randomized NCI trial evaluating IORT in retroperitoneal sarcomas demonstrated that patients receiving IORT with EBRT experienced significantly improved local control and less small bowel toxicity versus patients treated with EBRT alone (80% in-field relapse; discussed later).[12]

Colon and Rectal Cancer

In patients with locally advanced (T4) or locally recurrent colon and rectal cancers, local control is difficult to achieve, despite multimodality therapy. Studies from Princess Margaret Hospital and Mayo Clinic report local failure rates of 90% or greater in evaluable patients treated with EBRT with or without systemic therapy.[13,14] In patients who are radiation naive, the optimal approach in locally advanced patients is preoperative EBRT combined with 5-FU-based chemotherapy followed by resection. Despite this, local recurrence occurs in 30% to 70% of patients.[15]

Cervical Cancer

For patients with cervical cancer, paraaortic nodal metastases are common. Despite the presence of these "distant" metastases, approximately 15% to 20% of patients are cured by radical radiotherapy techniques employing EBRT doses of 55 to 60 Gy. However, high complication rates have been reported with these doses and techniques.[16,17] As in rectal cancer, patients with recurrent cervical cancer in the pelvis or paraaortic region have a poor long-term prognosis with five-year overall survival (OS) rates ranging from 5% to 30%. These patients have often been previously irradiated and retreatment with meaningful doses of EBRT is usually not feasible given normal tissue tolerance. When patients have paraaortic or locally recurrent disease, administration of IORT is a feasible method to escalate dose and enhance local control.

Oligorecurrences: Miscellaneous Intraabdominal Sites

Active follow-up of patients with cancer initially treated for cure has identified new entities including oligometastatic or oligorecurrent disease still amenable to salvage treatment by combining surgical and radiotherapy components. Recent analyses of patient cohorts including varying cancer primaries and histological subtypes have reported local control rates of greater than 80% and 5-year survivals of 35% in patients with extrapelvic, oligotopic disease.[18] In the case of intrapelvic gynecological oligorecurrences, salvage therapy with extended surgery and IOERT has demonstrated a 10-year locoregional control of 58%, with improved results if EBRT treatment was integrated into this approach.[19]

LOCAL CONTROL: RADIATION DOSE, COMPLICATIONS, SHRINKING FIELD TECHNIQUES, AND DISTANT METASTASES

Influence of Dose

In both animal and human models, the probability of local control of a tumor by radiation is generally proportional to the total dose administered. The dose of radiation to control a tumor locally depends on several factors, including tumor type, clonogen number, and tumor microenvironment. Thus, a given radiation dose may be able to control a small tumor with high probability and acceptable morbidity; however, that same dose may be insufficient against disease of larger volume. Clinical experience has generated a body of data correlating local control by tumor type and radiation dose. Figure 17-1 summarizes in vivo data for a variety of irradiated human tumors of varying sizes and types.[20]

The studies of Fletcher examined local control probability as a function of radiation dose for patients undergoing treatment for breast carcinoma and squamous cell carcinoma of the upper aerodigestive tract (eTable 17-1). For patients with breast cancer, control of subclinical disease was approximately 60% to 70% with 30 to 35 Gy, 85% with 40 Gy, and 95% with 45 to 50 Gy. For larger/palpable tumors, EBRT doses of 46 Gy, 59 Gy, and 76 to 90 Gy result in a local control probability of 20%, 35% to 50%, and 70% to 80%, respectively.[21-24] Dose response data is summarized for patients with squamous cell carcinomas of the upper aerodigestive tract in eTable 17-2. These data suggest that marked improvements in local control can be achieved by escalating radiation doses.

Dose versus Complications

The chief limitation of EBRT to control macroscopic disease in the abdomen and pelvis is normal tissue tolerance. Normal organs such as stomach, small bowel, and kidney have tolerance levels well below the radiation doses required to eradicate most abdominal and pelvic malignancies. Exceeding these, EBRT doses results in prohibitive risk of late normal tissue damage (see eTable 17-2). Because of this, "conventional" tolerable doses of EBRT from 45 to 55 Gy using 1.8 to 2 Gy per fraction are not curative in most abdominal and pelvic malignancies, with resultant local persistence/local recurrence of disease common in patients treated with

eTABLE 17-1 Tumor Control Probability Correlated with Irradiation Dose and Volume of Cancer

Dose (Gy)	Tumor Control Probability
SQUAMOUS CELL CARCINOMA: UPPER AERODIGESTIVE TRACT	
50*	>90% subclinical ~60% T1 lesions of nasopharynx ~50% 1-cm to 3-cm neck nodes
60*	~90% T1 lesions of pharynx and larynx ~50% T3 and T4 lesions of tonsillar fossa ~90% 1-cm to 3-cm neck nodes ~70% 3-cm to 5-cm neck nodes
70*	~90% T2 lesions of tonsillar fossa and supraglottic larynx ~80% T3 and T4 lesions of tonsillar fossa
ADENOCARCINOMA OF THE BREAST	
50*	>90% subclinical
60*	90% clinically positive axillary nodes, 2.5-3 cm
70*	65% 2-3 cm primary
70-80 (8-9 wk)	30% >5 cm primary
80-90 (8-10 wk)	56% >5 cm primary
80-100 (10-12 wk)	75% 5-15 cm primary

Modified from Fletcher GH, Shukovsky LJ: The interplay of radiocurability and tolerance in the irradiation of human cancers. J Radiol Electrol 56:383–400, 1975.
**10 Gy in five fractions each week.*

eTABLE 17-2 Gastrointestinal Radiation Tolerance

		Doses (in Gy)*		
Organ	**Injury at 5 Yr**	**$TD_{5/5}$**	**$TD_{50/5}$**	**Volume or Length**
Esophagus	Ulcer, stricture	60-65	75	75 cm^3
Stomach	Ulcer, perforation	45-50	55	100 cm^3
Intestine (small)	Ulcer, stricture	45-50	55	100 cm^3
Colon	Ulcer, stricture	55-60	75	100 cm^3
Rectum	Ulcer, stricture	55-60	75	100 cm^3
Anus	Ulcer, stricture	60-65	≥75	—
Pancreas	Secretory functions	—	—	—
Liver	Liver failure, ascites	35	45	Whole
Biliary ducts	Stricture, obstruction	50	70†	—

Modified from Gunderson LL, Martenson JA: Gastrointestinal tract radiation tolerance. Front Radiat Ther Oncol 23:277–298, 1989.
$TD_{5/5}$, *5% chance of severe intolerance within 5 years;* $TD_{50/5}$, *50% chance of severe intolerance within 5 years.*
**Data based on supervoltage (6/18 MV), 9 Gy/wk (5 × 1.8).*
†External beam radiation to 50.4 Gy (28 × 1.8/5½ weeks) plus 20 Gy at 1-cm radius with iridium 192.

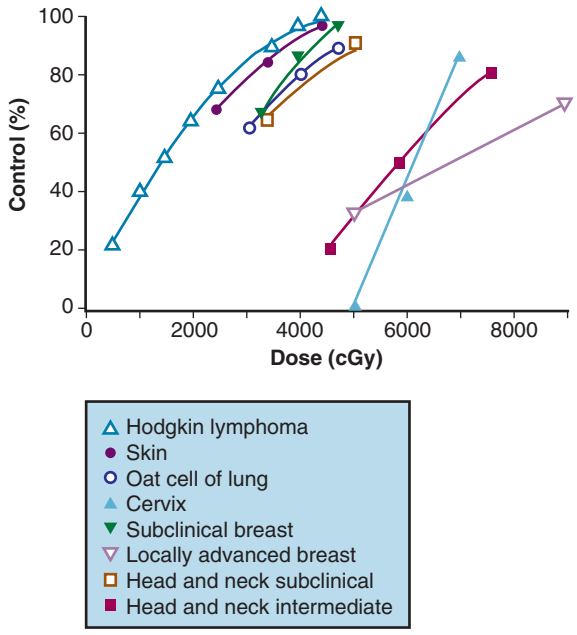


Figure 17-1 Local control versus dose of irradiation.
Modified from Gunderson LL, Tepper JE, Biggs PJ, et al: Intraoperative ± external beam irradiation. Curr Probl Cancer 7(11):1–69, 1983.

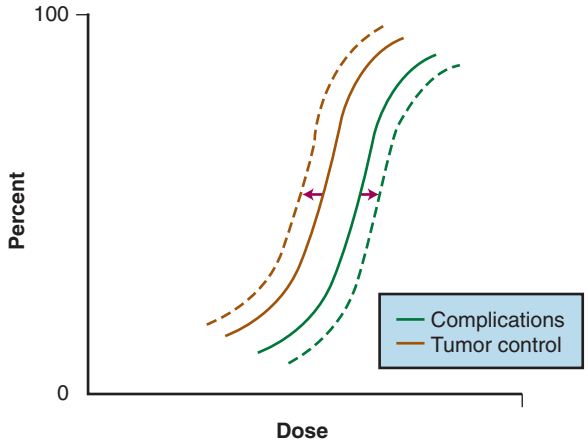


Figure 17-2 Radiation dose versus incidence of tumor control or complications.
Modified from Gunderson LL, Tepper JE, Biggs PJ, et al: Intraoperative ± external beam irradiation. Curr Probl Cancer 7(11):1–69, 1983.

radiation therapy alone. This often results in tumor-related morbidity and mortality such as bowel obstruction and perforation, ureteral obstruction, and neuropathy.

Although local control is enhanced with increasing doses of radiation, tumor dose response curves with EBRT closely resemble normal tissue complication curves. Therefore, efforts to improve local control through escalating EBRT doses may also result in treatment-related complications (Figure 17-2). In an R1 (microscopic residual) resection, EBRT doses of 60 Gy or higher using conventional fractionation schemes are necessary to achieve a high probability of local control. In an R2 (gross residual) resection, even higher doses are usually required. Such doses exceed normal tissue tolerance (see eTable 17-2).

Because of the risks associated with dose escalation beyond normal tissue tolerance, an attractive alternative in patients with locally advanced malignancies is to deliver moderate doses of EBRT (i.e., at or below accepted tolerance of surrounding normal tissue). A typical course would range from 45 to 50 Gy at 1.8 to 2 Gy per fraction, followed by surgical exploration. After resection, IORT would be performed, avoiding or minimizing irradiation of surrounding organs by shielding or mobilization. With this approach, an increase in local control with decreased risk of normal tissue complications (relative to an EBRT-only approach) can be achieved (see Figure 17-2—local control curve shifts to left with IORT; complication curve shifts to right with increasing EBRT doses).

Shrinking-Field (Boost) Techniques

The concept of shrinking-field irradiation, otherwise known as administering "boost" treatments, has been used for decades by radiation oncologists. This strategy entails treating larger fields encompassing the primary/recurrent tumor along with local-regional lymph node basins and other tissues at risk for subclinical disease. These larger fields receive a dose sufficient to control microscopic disease yet respect normal organ tolerance (often 45 to 50 Gy using 1.8 to 2 Gy per fraction). Fields are then reduced to encompass gross disease with smaller margins, excluding dose-limiting normal tissues. An additional 20 to 35 Gy may then be administered to these fields using either EBRT or brachytherapy techniques, bringing the cumulative dose to 65 to 80 Gy. These approaches are employed in many tumor sites including gynecologic and head and neck cancers with excellent long-term outcomes and local control with relatively low and acceptable morbidity levels. The concept of administering IORT in conjunction with EBRT is a logical application of this approach.

Local Control and Development of Distant Metastases

Preclinical data suggests that the incidence of distant metastases is related to both tumor size as well as the development of locally recurrent disease in multiple spontaneous tumor systems.[25-27] In fibrosarcoma and squamous cell carcinoma cell lines in rodent models, Ramsay et al reported increased rates of distant metastases in tumors measuring 6 mm versus 12 mm in size, as well as primary versus recurrent tumors.[25] Additionally, Suit et al showed that in mouse mammary tumors treated with single-dose irradiation, increasing rates of local failure were associated with increasing rates of distant metastases.[27] Specifically, the incidence of metastatic disease was 31% (16 of 52) of mice with local control, 50% (9 of 18) in those with local relapse salvaged by resection, and 80% (12 of 15) in mice with local relapse in whom salvage was not attempted. Similar high rates of metastases associated with local failure have been observed in human malignancies including cervix,[28] prostate,[29] head and neck,[30] and breast[31] cancers. These and other data suggest that metastases may arise from locally recurrent disease.

PATIENT SELECTION AND EVALUATION

Patient Selection Criteria

Candidates for IORT should be evaluated by the treating surgeon and radiation oncologist in the multidisciplinary setting. This allows for joint decisions regarding the appropriateness of IORT and whether further studies that may influence IORT and EBRT planning are appropriate. Additionally, joint decisions can be made defining the optimal sequencing

of surgery/IORT and EBRT. Informed consent should be obtained from both specialties, specifically with regard to potential risks, benefits, and side effects of proposed treatments. Criteria for the appropriate selection of patients for IORT generally include:

1. Surgery alone will result in a high probability of incomplete resection (microscopic or gross residual disease) and resultant high probability of failure within the tumor bed. Potential candidates must be appropriate for surgical attempts at gross total resection. IORT administration should be performed at the time of a planned operation.
2. There is no evidence of distant metastases. Rare exceptions include resectable single-organ metastasis, slow progression of systemic disease, excellent chemotherapy options, and patients with oligometastatic disease with slow systemic progression and high probability of symptomatic local failure.
3. EBRT doses required for high probability of local control following subtotal or no resection exceed normal tissue tolerance (Total doses required for eradication in this setting: 60 to 70 Gy for microscopic disease and 70 to 90 Gy for gross disease at 1.8 to 2 Gy per fraction)
4. Surgical displacement or shielding of dose-limiting structures or organs can be accomplished during IORT administration, allowing for acceptable risks of immediate and late effects. Theoretically, EBRT in conjunction with IORT should result in an improved therapeutic ratio between disease eradication and normal tissue complications.

Patient Evaluation

Pretreatment patient evaluation in patients eligible for IORT should include a thorough history and physical examination, with attention to palpable disease and its relationship to anatomically immobile normal structures. Examples include pelvic disease and its relationship to the pelvic sidewall, presacral space, prostate, or vagina. Computed tomography (CT), magnetic resonance imaging (MRI), and endoscopic ultrasound may aid in identifying adherence to structures (e.g., bony pelvis, large vessels) that may be surgically unresectable for cure. Examination under anesthesia may be helpful in some situations including locally advanced gynecologic and rectal cancers. Routine blood counts including complete blood count (CBC), liver function tests, renal function tests, and tumor-specific serum test (e.g., carcinoembryonic antigen, CA19-9) should be obtained where appropriate. Patients should be evaluated clinically and radiographically for evidence of distant spread. Positron emission tomography (PET), preferably in conjunction with CT, may facilitate defining local disease extent as well as unsuspected distant metastases. Evaluation of distant metastases is particularly important in the recurrent setting where concurrent distant failure is common. Biopsy confirmation of disease should usually be obtained before proceeding with resection.

SEQUENCING AND DOSE OF EBRT AND IORT

Sequencing of EBRT, IORT, and Surgery

For patients with localized malignancy, the goal of curative oncologic surgery is an R0 (margin-negative) resection. Because of the locally advanced and infiltrative nature of many primary tumors (including colorectal, gynecologic, and upper gastrointestinal [GI] malignancies, sarcomas, etc.) and locally recurrent malignancies, surgery may be compromised with close margins or microscopic/gross residual. For patients with locally advanced tumors, preoperative EBRT to doses of 45 to 50 Gy using 1.8 to 2 Gy fractions (with or without chemotherapy) followed by laparotomy, resection, and IORT offers theoretical and clinical advantages over resection and IORT followed by EBRT. These are listed as follows:

1. By postponing surgical resection until after preoperative therapy is completed, patients with disease that is rapidly progressive may avoid an unnecessary surgical procedure with associated morbidity.
2. Preoperative therapy may allow for tumor downstaging and facilitate resection with curative intent.
3. Preoperative therapy may reduce the risk of tumor seeding/dissemination at resection.
4. Preoperative therapy allows delivery of treatment to disease with an intact vasculature, potentially improving the delivery of chemotherapy and improving oxygen delivery for EBRT.
5. The morbidity and delayed recovery time associated with extensive surgical procedures may prevent the timely delivery of postoperative therapy in a high percentage of patients.[32,33]

The role of preoperative versus postoperative therapy has been evaluated in rectal cancer. A large German randomized trial demonstrated that patients undergoing neoadjuvant irradiation and chemotherapy experienced significantly improved local control and less toxicity than patients receiving postoperative irradiation and chemotherapy.[34]

Radiation Dose and Technique

Techniques combining EBRT and IORT have been fairly uniform in the United States and Europe. In previously untreated patients, EBRT doses of 45 to 54 Gy have been employed delivering 1.8 to 2 Gy per fraction, 5 days per week, over a period of 5 to 6 weeks. Because of the anatomical location of pelvic and abdominal malignancies, high-energy (>10 MV) photons delivered via linear accelerators using multifield, shaped techniques are required. CT-, PET-, or MRI-based treatment planning permit accurate definition of the target volume. For extrapelvic, unresected or residual disease following resection, radiation doses of 40 to 45 Gy delivered at 1.8 to 2 Gy per fraction with a 3- to 5-cm margin accounting for microscopic extension and target mobility are sometimes used. Treatments are generally delivered through multifield techniques aided by three-dimensional (3D) or IMRT-based treatment planning. Reduced-field or "boost" techniques are often used to bring the total dose to 45 to 54 Gy as dictated by tolerance of surrounding normal tissue (see previous discussion). Concurrent chemotherapy administration during EBRT varies by tumor site; for patients with gastrointestinal malignancies, concurrent 5-FU–based regimens (plus cisplatin or mitomycin C) are frequently implemented, and for patients with gynecologic cancers, concurrent cisplatin is frequently given. In carefully selected patients who have received prior irradiation, low-dose preoperative EBRT doses of 20 to 30 Gy at 1.5 to 1.8 Gy per fraction (often with concurrent chemotherapy) may be employed.

Dose of IORT

IORT dose should be based on extent of residual disease at resection, the amount of EBRT delivered previously, and the type and volume of normal tissue irradiated. For patients who have received preoperative doses of 45 to 54 Gy (1.8 to 2 Gy per fraction, 5 days per week), IORT doses usually range from 10 to 20 Gy. For patients with microscopic residual or close margins, doses of 10 to 12.5 Gy are often administered. Patients with gross residual disease require higher doses and 15 to 20 Gy is usually administered. In previously irradiated

patients, in whom additional EBRT is feasible (20 to 30 Gy), the dose of IORT generally ranges between 15 Gy and 20 Gy. In patients in whom no or very limited EBRT is planned, IORT doses from 25 to 30 Gy have been administered; however, doses in this range should be judiciously employed given the risk of normal tissue damage, specifically peripheral nerve injury.

The biological effectiveness of single-dose IORT in early responding tissues (tumor) relative to an equivalent total dose of fractionated EBRT has been estimated to be 1.5 to 2.5 times the IORT dose delivered (Table 17-1).[7,35,36] Therefore, the effective tumor dose (when "normalized" to fractionated EBRT doses) of IORT treatment added to 45 to 50 Gy given by EBRT are as follows: 10 Gy IORT dose, 60 to 80 Gy; 15 Gy IORT dose, 75 to 87.5 Gy; 20 Gy IORT dose, 85 to 100 Gy. These figures are not intended to be exact but represent educated estimates.

Technical Aspects

The technical aspects of IORT administration are beyond the scope of this chapter and have been discussed in other publications (see reference list). In brief, the implementation of IORT-based treatment is a multidisciplinary effort including one or multiple surgeons, radiation oncologist, anesthesiologist, operating room nurse, radiation physicist/dosimetrist, and therapist. In its broadest sense, IORT may be administered with either electrons (IOERT) or HDR photon afterloading techniques (HDR-IORT). Each method has potential advantages and disadvantages, which are summarized later.

IORT DOSE-LIMITING STRUCTURES AND TOLERANCE

The development of normal tissue late effects increases with increasing radiation dose as well as dose delivered per fraction. Therefore, the incidence of late normal tissue effects in patients receiving IORT plus EBRT would be higher than those receiving EBRT alone.[37] However, in this context the severe morbidity and mortality associated with locally recurrent tumor is often overlooked. As an example, when EBRT alone is used as the primary treatment modality for locally advanced rectal cancer, more than 90% of patients experience local persistence or local recurrence of disease with associated symptomatology. These symptoms include severe pelvic pain and neuropathy, which are difficult to manage clinically and the vast majority of patients experience disease-related death within two to three years. An argument can be made that the tumor-related morbidity/mortality approaches 100% in these patients.[38]

IORT tolerance for intact or surgically manipulated organs or structures in animals (primarily canines) is seen in Table 17-2. Much of this information has been derived from studies from the NCI[39-44] and Colorado State University (CSU).[45-47]

Several dose-sensitive structures have been studied in humans receiving IORT, including the ureter and peripheral nerve. These are discussed next.

Ureter

Clinical studies of the effect of IOERT on the ureters of patients with cancer have been undertaken at the Mayo Clinic. Doses

TABLE 17-2 Normal Tissue Tolerance to Intraoperative Electron Irradiation in Animals (Usually Dogs)

Tissue	Maximum Tolerated Dose (Gy)	Tissue Effect	Dose (Gy)
INTACT STRUCTURE			
Aorta, vena cava	50	Fibrosis of wall (patency up to 50 Gy)	≥30
Peripheral nerve	15	Neuropathy, sensory-motor	≥20
Bladder	30	Contraction and ureterovesical narrowing	≥25
Ureter	30	Fibrosis and stenosis	≥30
Kidney	<15	Atrophy and fibrosis	≥20
Bile duct	20	Fibrosis and stenosis	≥30
Small intestine	<20	Ulceration, fibrosis, stenosis	≥20
Large bowel	15	Ulceration, fibrosis, stenosis Perforation	≥17.5 50
Esophagus Full thickness Partial thickness	 ≤20 40	 Ulceration, stricture No sequelae at this dose	 ≥30 ≥40
Muscle (psoas)	23	50% decrement muscle fibers	38
Heart (right atrium)	20	Fibrosis	≥30
Lung	20	Fibrosis	≥20
Trachea	30	Submucosal fibrosis	≥30
SURGICALLY MANIPULATED			
Aorta anastomosis (end to end)	20	Fibrosis and stenosis No anastomosis disruption	≥20 ≤45
Aortic prosthetic graft	25	Graft occlusion	25
Portal vein anastomosis	40	Stenosis	>40
Biliary-enteric anastomosis	<20	Anastomotic breakdown	≥20
Small intestine (defunctionalized)	45	Fibrosis and stenosis No suture line breakdown	≤20 ≤45
Bladder	30	Healing but contraction	≥30
Bronchial stump	>40	Absence of air leak	>40

of 10 Gy administered intraoperatively resulted in a 50% incidence of ureteral obstruction, increasing to 70% with doses from 15 to 25 Gy. This high complication rate relative to canine models may be as a result of age-related factors, surgical manipulation, EBRT, or tumor bed effects.[48]

In an update of this experience, investigators from the Mayo Clinic reported on 146 patients with locally advanced malignancies receiving IORT to one or both ureters of doses between 7.5 Gy and 30 Gy. They reported the risk of obstruction following IOERT is significant and increases with time and IORT dose. The rates of clinically apparent type 1 obstruction (obstruction from any cause) after IOERT at 2, 5, and 10 years were 47%, 63%, and 79%, respectively. The rates of clinically apparent type 2 obstruction (obstruction occurring at least 1 month after IOERT, excluding obstruction caused by tumor or abscess and patients with stents) at 2, 5, and 10 years were 27%, 47%, and 70%, respectively. Multivariate analysis revealed that the presence of obstruction before IOERT was associated with an increased risk of clinically apparent type 1 obstruction ($p < 0.001$). Increasing IOERT dose was associated with an increased risk of clinically apparent type 2 obstruction ($p < 0.04$). Obstruction rates in ureters not receiving IOERT at 2, 5, and 10 years were 19%, 19%, and 51%, respectively, suggesting an underlying risk. However, obstruction risk for ureters not receiving IOERT was also high, which suggests an underlying risk of ureteral injury from other causes (EBRT, surgical manipulation of ureters).[49]

Peripheral Nerve

Peripheral nerve is the principal dose-limiting normal tissue for IORT in the pelvis and retroperitoneum. Data regarding peripheral nerve tolerance and neuropathy comes from canine models as well as clinical analyses from patients treated intraoperatively.[40,43,45,48,50-60] Peripheral nerve is often situated adjacent to or directly involved by tumor in the abdomen and pelvis. Because of this, the relative surgical "immobility" of peripheral nerves and inability to shield the nerve from the IORT field, nerve tissue will often receive full dose EBRT and IORT.

The mechanism of neuropathy following IORT is poorly understood. Peripheral nerve tolerance depends on the volume of nerve irradiated and total dose delivered. In animal models, histomorphologic findings following IORT have demonstrated decreased central nerve fiber density, particularly in large nerve fibers receiving >20 Gy. Electron microscopy analysis has demonstrated increased microtubule density and neurofilament accumulation within axons without associated myelin changes, suggesting possible hypoxic injury related to vascular changes.[60]

A Spanish study evaluated 45 patients with primary or locally recurrent extremity soft-tissue sarcoma undergoing resection with IOERT (10 to 20 Gy). Nine patients received IOERT alone secondary to prior EBRT or patient refusal. Five patients developed neurotoxicity at a median of 13 months; 4 of 5 showed objective weakness or sensory loss. Most patients developing neuropathy received IOERT doses greater than 15 Gy.[61]

An analysis from the Mayo Clinic evaluated peripheral nerve tolerance in 51 patients undergoing IOERT for primary or recurrent pelvic malignancies. Patients received EBRT (median dose 50.4 Gy), maximal resection where possible, and IOERT boost from 10 to 25 Gy using 9 MeV to 18 MeV electrons. Sixteen patients (32%) experienced grades 1 to 3 peripheral neuropathy as manifested by pelvic/extremity pain, leg weakness, numbness, or tingling. Pain was severe (grade 3) in 3/51 patients (6%)[48] (eTable 17-3).

A follow-up study from the Mayo Clinic evaluated 178 patients with locally advanced colorectal cancer receiving IOERT. This study suggested a relationship between increasing doses of IOERT and the incidence of clinically significant neuropathy (Table 17-3). In patients with primary and locally recurrent colorectal cancer, the incidence of severe (grade 3) neuropathy was approximately 5%, and the incidence of any neuropathy was approximately one third. This is consistent with canine studies suggesting increasing IOERT doses are related to the incidence of clinical and electrophysiologic neuropathy.[51,52]

TABLE 17-3 Colorectal IOERT, Mayo Clinic IOERT Dose versus Neuropathy

Disease Presentation	IOERT Dose versus Grade 2 or 3 Neuropathy ≤12.5 Gy	≥15 Gy	*p*
Primary[52*]	1/29 (3%)	6/28 (21%)	0.03
Recurrent, no prior EBRT[51†]	2/29 (7%)	19/101 (19%)	0.12
Primary + recurrent	3/58 (5%)	25/129 (19%)	0.01

EBRT, *External beam irradiation;* IOERT, *intraoperative electron irradiation.*
**57 IOERT fields in 55 evaluable patients. Incidence of grade 3 neuropathy by dose: ≤12.5 Gy, 0 of 9; 15 Gy or 17.5 Gy, 1 of 19, or 5%; ≥20 Gy, 2 of 9, or 22%.*
†130 IOERT fields in 123 patients.

A more recent Mayo Clinic analysis of 607 patients with locally recurrent colorectal cancer receiving IORT reported an incidence of grades 1 to 3 neuropathy of 15% (grade 1, 5%; grade 2, 7%; grade 3, 3%). A dose-related increase in grades 2 and 3 neuropathy was seen in patients receiving ≥15 Gy compared to ≤12.5 Gy.[53]

Conclusions

All patients considered for IORT should undergo thorough pretreatment informed consent, including a discussion regarding neuropathy-related side effects. It should also be remembered that uncontrolled tumor frequently causes symptoms related to neural impingement, and in fact many potential IORT candidates present with neuropathic symptoms related caused by primary or recurrent disease. Based on human and animal data evaluating IORT induced neuropathy, IORT doses are generally limited to 10 to 20 Gy when a full course of EBRT is administered (45 to 54 Gy using 1.8 to 2 Gy per fraction). Doses exceeding 20 Gy in the intraoperative setting should be used with caution, and our general policy regarding such is to administer higher doses only in the setting of limited EBRT options (i.e., prior EBRT treatment).

IORT RESULTS FOR SELECTED DISEASE SITES

A summary of IORT results and future possibilities in selected disease site (pancreas, breast, colorectal, gynecologic cancers, and retroperitoneal/pelvic sarcomas) are now presented. For a more detailed discussion, the reader is referred to dedicated chapters on each site in an IORT text.[64]

Pancreas Cancer: EBRT and IORT

Given local failure rates of 50% to 80%, the use of IORT in the setting of pancreatic cancer is rational. Available data in patients receiving IORT after pancreaticoduodenectomy

eTABLE 17-3 Clinical Peripheral Neuropathy Characteristics with Pelvic IOERT, Mayo Clinic

Characteristic	Incidence*	Severity		Time Course (mo from IORT)	
		Mild/Moderate	Severe	Onsets†	Resolution, Range
Pain	16/50 (32%)	13 (26%)	3 (6%)	1/2-18 (15)	6/14 (42%),‡ 5-32§
Motor	8/50 (16%)	6 (12%)	2 (4%)	3-22 (7)	1/8 (13%), 20
Sensory	11/50 (22%)	11 (22%)	0 (0%)	3-22 (7)	4/11 (36%), 1, 7, 19, 20

Modified from Shaw E, Gunderson IL, Martin JK, et al: Peripheral nerve and ureteral tolerance of intraoperative radiation therapy: Clinical and dose-response analysis. Radiother Oncol 18:247–255, 1990.

IOERT, *Intraoperative electron irradiation;* IORT, *intraoperative irradiation.*

**One patient excluded who died postoperatively.*

†Values in parentheses represent median.

‡Two patients excluded who were lost to follow-up.

§Median, 15 months.

demonstrates an improvement in local control; however, a clear survival benefit has not been demonstrated. Series of patients with locally advanced pancreatic cancer suggest local control and pain relief, with select studies demonstrating an OS benefit.

IORT in Resected Disease

In the United States, initial feasibility of IORT in conjunction with surgery was demonstrated at the NCI. Thereafter, the NCI reported a series evaluating 24 further patients randomized to receive IORT (20 Gy) versus EBRT. After excluding 7 perioperative deaths, an improvement in local control (67% versus 0%) and median survival (median OS 18 versus 12 months, $p = 0.01$) was seen in the patients who received IORT.[65]

Further data on IORT at the time of surgery are limited to single and multiinstitutional retrospective series (Table 17-4A). The largest of the single institution series evaluated 127 patients treated with surgery and IORT compared to a cohort of 26 patients who underwent surgery alone. No additional operative morbidity or mortality was seen with the addition of IORT; however, for patients with Stage I/II disease IORT resulted in lower rates of local failure and significantly longer time to local failure, time to failure, and OS compared to surgery alone. These data suggest possible local control benefit with the use of IORT after resection in select patients.[63]

These data are corroborated by two multiinstitutional series. A Japanese series evaluated 210 patients undergoing surgery and IORT with and without EBRT. Median IORT and EBRT doses were 25 Gy and 45 Gy, respectively. Seventy-one percent of patients experienced disease relapse with local failure occurring in 15% of patients. Median and 2-year OS were 19.1 months and 42%, respectively. The combination of IORT and chemotherapy resulted in improved survival compared to IORT alone. The authors concluded that IORT yields excellent local control rates for pancreatic cancer with a low incidence of toxicity, and IORT combined with chemotherapy confers a survival benefit compared to IORT alone.[62]

A European multiinstitutional series evaluated 270 patients treated at five institutions between 1985 and 2006.[69] Neoadjuvant EBRT or concurrent chemoradiation (CRT) was delivered in 24% of cases and median IORT dose was 15 Gy (range 7.5 to 25 Gy). Significantly better local control was seen in patients undergoing preoperative radiation therapy (RT) with a median time to local relapse not reached and median OS of 30 months compared to 22 months with postoperative EBRT or CRT and 13 months with IORT alone. The authors concluded preoperative EBRT increases the effect of IORT in terms of local control and survival, with favorable long-term local control rates.[69] Compared to historical controls, these low rates of local failure and reasonable median survival reflect the possible benefit of IORT in patients with resected pancreatic cancer.

IORT in Locally Unresectable Disease

The role of IORT has been more clearly defined in the treatment of patients with locally unresectable pancreatic cancer. Many studies have documented both safety and pain control with IORT, resulting in complete pain resolution in 75% to 90% of cases.[72] Table 17-4B shows outcomes of select series using IORT in locally unresectable pancreatic cancer patients.

A study from Mayo Clinic evaluated 159 patients with locally unresectable pancreatic cancer who underwent exploratory laparotomy; 122 had postoperative EBRT alone or plus concurrent 5-FU and 37 received an IOERT boost followed by EBRT alone or plus 5-FU. One-year local control (LC) with the combination of EBRT and IORT was 82% compared to 48% with EBRT alone (2-year LC was 66 versus 20%, $p = 0.0005$).

TABLE 17-4A Results of Selected Studies of IORT in Patients with Resected Pancreatic Cancer

Series/ Treatment	Year/ Pt No.	IORT Dose (Gy)	EBRT (%)	Operative Mortality	Postop Complication	Local Recurrence	Survival	
							Median	2-yr
Sindelar et al[62,135]	(1999)	—	100%	27%	71%	—	—	
Surgery/EBRT	12	—		Overall	Overall	100%	12 mo	
Surgery/IORT/EBRT	12	20 Gy				33%	18 mo (p = .01)	
Zerbi et al[136]	(1994)	—	36%	—	—	—	—	
Surgery alone	47	—	—	2.1%	23.4%	56.3%	12 mo	16%
Surgery & IORT	43	12.5-20	—	2.3%	23.2%	27%*	19 mo	24%
Alfieri et al[137]	(2001)	—	67%	—	—	(5 year)	—	
Surgery ± EBRT	20	—		8%	43%	71.2%	10.8 mo	
Surgery/IORT ± EBRT	26	10		9%	57%	41.6%	14.3 mo	
Reni et al[63]	(2001)	—	28%	—	—	(median to LR)	—	
Surgery ± EBRT	76	—		4%	45%	11 months	12 mo	
Surgery/IORT ± EBRT	127	10-25		3%	39%	14 months	15.5 mo	
Ogawa et al[64]	(2010)	—	—	—	—	—	—	
Surgery/IORT ± EBRT	210	20-30	30%	—	—	16.3%	19 mo	42%
Valentini et al[65]	(2009)	—	—	—	—	—	—	
Surgery/IORT ± EBRT	270	7.5-25	64%	2%	24%	(median to LR)	—	
Preop EBRT/CRT	63					Not reached	30 mo	
Postop EBRT/CRT	106					28 mo.	22 mo	
IORT/no EBRT	95					8 mo.	13 mo	
Bachireddy et al[138]	(2010)	(Ortho)	—	—	—	—	—	
Surgery/IORT ± EBRT	23	6-15	78%	—	6%	39%	—	27%
Calvo et al[139]	(2013)	—	100%	—	—	(5 year)	20% (5year)	
Surgery + EBRT/CRT	41	—		0%	39%	72%		
Surgery/IORT + EBRT	29	10-15		7%	48%	8%		

CRT, *Chemoradiation;* EBRT, *external beam irradiation;* IORT, *intraoperative irradiation;* LR, *local recurrence;* mo., *months;* Ortho, *orthovoltage;* Postop, *postoperative;* Preop, *preoperative;* Pt No., *patient numbers;* yr, *year.*

*$p < 0.01$.

TABLE 17-4B Results of Selected Studies of IORT in Patients with Locally Unresectable Pancreatic Cancer

Author/ Reference Institution or Group	Year	Pt. No./Type of Treatment	IORT Dose, Gy	Local Recurrence	Survival	
					Median	2-yr
Roldan et al[67]; Mayo Clinic	1988	159	—	(2-yr)	—	—
		122 EBRT ± 5FU	—	80%	12.6 mo	16.5%
		37 IORT/EBRT ± 5FU	20	34%	13.4 mo	12.0%
Shibamoto et al[68]	1996	115	30-33	—	No difference	
		44 EBRT, 16 IORT				
		55 EBRT & IORT				
Tepper et al[140]; RTOG	1991	51 analyzable	20	Not assessable	9 mo	—
		EBRT & IORT				
Willett et al[70,71]; MGH	2013	194	15-25	(2-yr)	12 mo	16%
		EBRT & IORT		59%		
Mohiuddin et al[72]; TJUH	1995	49	—	—	—	—
		EBRT & IORT	10-20	29%	16 mo	22%
Schuricht et al[73]; TJUH	1998	105	15-20	(2-yr)	—	—
		33 EBRT & IOERT		30%	18 mo	17%
		43 EBRT & ^{125}I			15 mo	19%
		29 EBRT alone			9 mo	NS

CRT, *Concurrent chemoradiation;* EBRT, *external beam irradiation;* IORT, *intraoperative irradiation;* MGH, *Massachusetts General Hospital;* mo., *months;* Pt. No., *patient numbers;* RTOG, *Radiation Therapy Oncology Group;* TJUH, *Thomas Jefferson University Hospital;* yr, *year.*

Despite a benefit in LC, there was no difference in median or long-term survival between the groups because of the high incidence of liver or peritoneal relapse in both groups (>50%).[73]

A Japanese study evaluated the use of IORT in the treatment of 115 patients with locally unresectable pancreatic cancer. Patients received either a combination of EBRT and IORT, EBRT alone, or IORT alone. In the subgroup of patients with a CA19-9 <1000, the combination of EBRT and IORT produced superior survival compared to EBRT alone.[74]

Investigators at MGH initially published early results of the use of IORT (15 to 20 Gy) in patients with locally unresectable pancreatic cancer.[80] Updated publication of 194 consecutive MGH patients with locally unresectable cancer demonstrated a median survival of 12 months and long-term survival in 6 patients. Patients treated with a smaller diameter applicator, a surrogate for smaller tumor size, had superior survival rates and the only long-term survivors were within the smaller applicator diameter cohort. On multivariate analysis small applicator size, low comorbidity index, and receipt of chemotherapy predicted improved OS.[76,77]

Two retrospective studies from the Thomas Jefferson University Hospital (TJUH) evaluated the use of IORT in patients with locally unresectable primary disease. In the initial TJUH series, 49 patients were treated with IORT and perioperative chemotherapy followed by concurrent CRT. Median survival was 16 months with a 4 year OS of 7%.[78] In a follow up series from TJUH, 105 patients received multimodality therapy including surgery, chemotherapy, and radiation therapy. Patients were subdivided into three groups: IORT via electrons (IOERT), IORT with Iodine 125 implant, and no IORT. Median OS in the group receiving IOERT was 18 months with 2-year LC of 70%.[79] The median and long-term survival results from these IORT series are significantly longer than outcomes seen in other studies evaluating patients with locally advanced pancreatic cancer treated with conventional combined modality approaches.

Future Possibilities

Although slight gains in survival may be achieved by improving LC in patients with pancreatic cancer, the high rate of distant metastases limits significant improvements in long-term survival by IORT approaches. Given the high incidence of failure in the peritoneal cavity and liver, pilot studies are evaluating novel combinations of systemic agents in the treatment of this disease, including "targeted" agents as well as novel combinations of more traditional chemotherapeutics.

Breast Cancer

IORT Alone

Randomized trials have demonstrated equivalent disease-free survival (DFS) and OS in selected patients with breast cancer undergoing either mastectomy or breast-conserving surgery followed by EBRT.[81] Local recurrences frequently occur at or adjacent to the original tumor bed following breast-conserving surgery. There is increasing interest in the use of IORT as a supplement to or alternative to EBRT in selected cases in both Europe and the United States.[82-92]

Phase III Trials

The Italian ELIOT trial of 1305 patients was a randomized Phase III trial comparing 21 Gy IOERT versus standard EBRT whole-breast/boost therapy.[83] IOERT was delivered with a mobile linear accelerator (the NOVAC 7) while shielding the thoracic wall with a lead plate. Women aged 48 to 75 years with early breast cancer, a maximum tumor diameter of up to 2.5 cm, and suitable for breast-conserving surgery were randomly assigned to the two treatment arms. This was an equivalence trial with a primary endpoint of ipsilateral breast tumor recurrence (IBTR). After a median follow-up of 5.8 years, 35 patients in the IOERT group and 4 patients in the EBRT group had experienced an IBTR ($p < 0.0001$). The 5-year outcomes for the IOERT compared to EBRT arms included an IBTR rate of 4.4% compared to 0.4% (hazard ratio 9·3 [95% confidence interval, 3.3 to 26.3]) and 5-year OS of 96.8% compared with 96.9%. Significantly fewer skin side effects occurred in women in the IOERT than in the EBRT arms ($p = 0.0002$). The authors concluded the rate of IBTR was significantly greater with IOERT than with EBRT, and OS did not differ between groups, while improved selection of patients could reduce the rate of IBTR with IOERT.[93]

An approach of targeted IORT using the INTRABEAM system (TARGIT) implements a 50 kV x-ray generator mounted on a flexible floor stand with a set of spherical applicators ranging from 1.5 cm to 5 cm in diameter (eFigure 17-1) Radiotherapy is delivered to the tumor bed by placing the applicator within the tumor cavity and conforming the adjacent breast tissues around the applicator before treatment. A potential disadvantage of this approach is that low-energy x-rays could potentially lead to underdosing of residual tumor cells removed from the tumor cavity.

In an international phase III TARGIT-A trial, patients were randomized to IORT alone (n = 1721) or a typical course of EBRT (n = 1730). If resected patients were at high risk of local recurrence in other quadrants (extensive intraductal component, extensive lymphovascular invasion, nodal metastases, etc.) then EBRT could be delivered postoperatively. Supplemental EBRT after TARGIT was necessary in 15.2% of patients who received TARGIT. Median follow-up for 3451 patients was nearly 2.5 years and 1222 had median follow-up of 5 years. The 5-year risk for local recurrence in the conserved breast was 3.3% for TARGIT versus 1.3% for EBRT (p = 0.042). Overall, breast cancer mortality was similar between groups (2.6% for TARGIT versus 1.9% for EBRT; p = 0.56), but there were significantly fewer deaths related to breast cancer with TARGIT (1.4% versus 3.5%; p = 0.0086), attributable to fewer deaths from cardiovascular causes and other cancers. Overall mortality was 3.9% for TARGIT versus 5.3% for EBRT (p = 0.099). Wound-related complications were similar but grade 3 or 4 skin complications were significantly reduced with TARGIT (4 of 1720 versus 13 of 1731, p = 0.029). The authors concluded TARGIT concurrent with lumpectomy within a risk-adapted approach should be considered as an option for carefully selected, eligible patients with breast cancer as an alternative to postoperative EBRT.[94] Late toxicity data was available in 305 patients with significantly fewer telangiectasias in the IORT arm.[95]

In summary, randomized trials to date show that IORT alone may result in slightly higher rates of ipsilateral breast cancer recurrence when compared to adjuvant EBRT techniques and that careful patient selection when using this approach is warranted.

Phase II Trials

Extensive Phase II data from single or multiinstitutional IORT alone series is also available. Series design and outcomes can be found on the Expert Consult website.[85,88,96,97]

IORT Plus EBRT

In the Medical College of Ohio and Centre Regional de Lutte Contre le Cancer (France) combined series, 72 patients with early stage breast cancer underwent lumpectomy with axillary lymph node dissection followed by 10 to 15 Gy IOERT using 6 MeV to 20 MeV electrons. Patients later received EBRT doses of 45 to 50 Gy at 1.8 to 2 Gy per fraction. No significant complications were observed and cosmetic results were described as excellent. Eight of 72 patients developed minor palpable fibrosis at the lumpectomy site. At a minimum two-year follow-up in all patients, no patients had experienced local relapse.[90]

The University of Salzburg investigators used IOERT combined with EBRT in 351 consecutive patients from October 1998 to April 2002 and reported their results in the initial 170 patients treated through December 2000.[91] LC results were compared to patients treated with EBRT alone. At the time of publication, 3-year LC with an IOERT compared to EBRT boost was 100% to ~97%.

The University of Heidelberg reported a preliminary experience in 155 patients with breast cancer using a 20 Gy orthovoltage IORT boost followed by EBRT in women with T1-T2 breast cancers. The 5-year local relapse-free survival was 98.5% at a median follow up of 34 months. Grade 3 fibrosis of the tumor bed was found in 5% of patients at 3 years.[92]

A European pooled analysis by Sedlmayer et al evaluated 1200 patients with limited breast cancer resection plus IOERT (median dose 9.7 Gy, range 5 to 17 Gy) followed by whole-breast EBRT using standard fractionation. Patients undergoing immediate secondary mastectomy as a result of extensive margin involvement were excluded. At median follow up of 59.6 months, local tumor control was 99.3%. The authors concluded IOERT boost during breast-conservation therapy results in optimal dose delivery and outstanding LC rates.[98,99] The most recent update of this experience with long-term follow-up (72.4 months median follow-up) reported a 99.2% local tumor control with an annual in-breast recurrence rate of 0.64%, 0.34%, 0.21%, and 0.16% in patients younger than 40 years, 40 to 49 years, 50 to 59 years, and older than 60 years, respectively.[100]

Early results of the TARGIT trial using IORT as boost therapy reported 183 patients treated with the INTRABEAM system of 5 Gy or 7.5 Gy followed by EBRT. At a median follow up of 16 months, actuarial 2-year LC was 99% with serious complications (including fistula, wound dehiscence, and ulceration) occurring in 11% of patients.[87] In summary, the available data suggest that IORT used as a boost technique with EBRT results in low rates of ipsilateral breast tumor recurrence.

Future Possibilities

Multiple Phase II or III trials evaluating adjuvant IORT continue to actively accrue patients in the United States, Europe, United Kingdom, and Australia. These trials use varying IORT techniques including 50 kV photons as well as low-energy electrons. Identification of patients appropriate for breast IORT remains an area of investigation. Long-term results from these and other trials will be necessary to demonstrate ultimate local recurrence, late effect, and survival data with these approaches.

Retroperitoneal and Pelvic Soft-Tissue Sarcomas

NCI Randomized Phase III Trial

The NCI conducted a randomized Phase III trial in patients undergoing surgical resection of primary retroperitoneal sarcoma. All patients underwent gross total resection, although most had microscopically involved margins. Patients were randomized to receive 20 Gy IOERT followed by 35 to 40 Gy of EBRT postoperatively versus postoperative EBRT alone to a dose of 50 to 55 Gy. Patients receiving IOERT were treated with concurrent misonidazole given 15 to 30 minutes pretreatment. EBRT treatments were delivered over 4 to 5 weeks at 1.5 to 1.8 Gy per fraction in both arms; however, patients receiving EBRT only received an additional 15 Gy using similar fractionation by reduced fields. The incidence of in-field local-regional recurrence was significantly lower among patients receiving IOERT compared to patients receiving EBRT only (3/15 versus 16/20, $p < 0.001$). Patients receiving IOERT experienced fewer episodes of radiation enteritis than EBRT alone patients (2/15 versus 10/20, $p < 0.05$); however, radiation-related peripheral neuropathy was more frequent in patients receiving IOERT (9/15 versus 1/20, $p < 0.01$).[12]

Mayo Clinic Experience

Investigators at Mayo Clinic Rochester reported on 87 patients with primary or recurrent retroperitoneal or intrapelvic sarcomas receiving IOERT as a component of treatment.[101]



eFigure 17-1 The INTRABEAM system for IORT of breast cancer. This consists of a 50-kV x-ray generator mounted on a flexible floor stand and a set of applicators ranging from 1.5 to 5 cm in diameter.
Figure used with permission-PENDING.

A preliminary report from the Italian Collaborative Breast IOERT Group described a multicenter trial comparing IOERT alone following lumpectomy to conventional fraction EBRT in tumors less than 3 cm with negative margins. IORT patients received a single 21-Gy fraction using 6 MeV to 9 MeV electrons. Of 314 evaluable patients, no local recurrence was detected in either treatment group at a median follow-up of 31 months, although a significant difference in the incidence of grades 1 to 2 late toxicity was seen in favor of the IORT group (3% versus 63%).[84]

A systematic review of seven published IORT alone series in early breast cancer suggested that short-term LC, DFS, and OS were similar to reported EBRT series. Local recurrence rates ranged from 0% to 29% with IORT. However, many of these small, single institution studies had short follow-up (median, 2 years).[85]

Veronesi et al reported on 237 patients with primary tumors ≤2 cm undergoing wide excision with either sentinel lymph node biopsy or axillary lymph node dissection. Patients received IOERT using 3 MeV to 9 MeV electrons with doses of 17 to 21 Gy (>90% received 21 Gy as the prescribed dose). At a median follow-up of 19 months, the rate of posttreatment complications was low, with 1.7% developing breast fibrosis. A follow-up report from this group of 574 patients revealed 3 patients with local recurrence and 3 additional patients with ipsilateral recurrence in other quadrants at median follow-up of 20 months.[88] A similar report by Veronesi et al of 1822 patients treated with the ELIOT strategy, but outside of a randomized trial, showed that after a mean follow-up of 36 months, the incidence of local recurrence was 2.3% and new primary ipsilateral carcinomas was 1.3%.[96]

Another report of long-term side effects and cosmetic results has been analyzed in 119 patients selected randomly selected from 1200 cases. After a median follow-up of 71 months, grade 2 fibrosis was observed in 31.9% of patients and grade 3 in 5.9% of patients. Physicians and patients scored cosmesis as excellent or good in 84% and 77% of cases, respectively.[97]

The addition of boost treatment following lumpectomy and conventional EBRT has been shown to reduce local recurrence rates by 50% in all age groups versus EBRT alone.[89] Potential advantages of an IORT boost compared to EBRT boost are as follows: more precise delivery of irradiation to the tumor bed, skin sparing with avoidance of associated late cosmetic sequelae, and a smaller boost area with a more homogeneous dose distribution.

TABLE 17-5 Mayo Clinic IOERT Analysis: Factors Influencing 5-Year Local Control and Survival in Resected Primary Retroperitoneal Sarcomas

	n	OS (%)	*p*	LC (%)	*p*
RESIDUAL AT IOERT					
None	11	62		100	
Microscopic	25	54		92	
Gross	7	29	0.15	60	<0.01
BRODERS GRADE					
1-2	9	42		100	
3-4	34	54	0.70	84	0.32
TUMOR SIZE* **(cm)**					
≤10	23	66		83	
>10	19	33	0.15	92	0.80

LC, *Local control;* IOERT, *intraoperative electron irradiation;* OS, *overall survival.*
**From references 101-108.*

Seventy-seven patients received EBRT (53 preoperatively, 12 postoperatively, and 12 both) to a median dose of 48 Gy, usually through a shrinking field technique. Fifteen patients (17%) had gross residual disease following resection, 56 (64%) microscopic residual, and 16 (18%) either negative margins or no residual disease. Median IOERT dose was 15 Gy (range 9 to 30 Gy). Five-year OS was 47%. Patients with tumors >10 cm experienced a significantly worse survival compared to smaller lesions (5-year OS 28% versus 60%, $p = 0.01$) and patients with gross residual disease following resection experienced worse 5-year survival versus gross totally resected patients (37 versus 52%, $p = 0.08$). Five-year LC rates in patients with gross, microscopic and no residual tumor were 37%, 57%, and 100%, respectively. Factors influencing 5-year LC and survival for patients with primary disease are shown in Table 17-5 and eTable 17-4. Patients with R0 or R1 resection experienced significantly improved LC and those with tumors greater than 10 cm were less likely to be long-term survivors.[101]

A further update of the Mayo Clinic reported on 226 IORT patients (52% primary) treated from 1981 to 2008.[102] Most (63%) had high-grade tumors and 36 (16%) had received prior EBRT. In previously unirradiated patients, EBRT was delivered preoperatively in 70% of patients, postoperatively in 10%, and both in 10%. R0 and R1 resection was achieved in 39% and 50% of patients, respectively. Median IORT dose was 12.5 Gy. Five-year OS was 50% (R0 resection, 52%; R1, 55%; R2, 28%). For the entire population, 5-year local failure was 29% (R0, 18%; R1, 31%; R2, 61%), with distant metastases developing in 42% of patients. Central failure in the IORT field occurred in only 10% of patients. The authors concluded that: (1) patients with retroperitoneal sarcoma undergoing gross total resection experience improved LC relative to subtotal resection when treated with combined modality treatment including IORT; (2) improved outcomes were seen in patients with primary versus recurrent disease; and (3) the high rates of distant relapse suggest more effective systemic therapy is needed for patients with high-grade disease.

Massachusetts General Hospital Experience

Investigators from MGH described 37 patients with primary or recurrent retroperitoneal sarcoma who underwent EBRT (median dose, 45 Gy) and resection. Twenty patients received IOERT (10 to 20 Gy). In twenty-nine (78%) patients receiving gross total resection and IOERT, 5-year survival and LC rates were 74% and 83%, respectively. In comparison, 13 patients undergoing gross total resection without IOERT had 5-year survival and LC rates of 30% and 61%, respectively. Four patients receiving IOERT experienced significant complications including neuropathy, hydronephrosis, and fistula formation.[103]

A subsequent report from MGH described 103 patients with primary retroperitoneal sarcoma, 62 of who underwent gross total resection. In this group, patients with high-grade disease or involved margins received EBRT with or without IOERT, particularly when a localized area of close margin of residual tumor was identified. This study again demonstrated a trend for IORT to further improve survival versus EBRT alone with significant increased time to both local and distant relapse. In patients who were completely resected, a trend toward improved survival with IOERT was seen compared to EBRT alone (5-year OS of 77% versus 45%, $p = 0.13$).[104]

Pooled European Analysis

A pooled European analysis described 122 curatively approached patients (81 recurrent) with retroperitoneal sarcoma undergoing maximum resection plus IOERT (median dose 15 Gy). Most received adjuvant EBRT. Five-year OS, DFS, LC, and freedom from metastatic disease rates were 64%, 28%, 40%, and 50%, respectively. Five-year LC within the IOERT field was 72%. In patients receiving IOERT, EBRT, and R0 resection, 5- and 10-year OS were 80% and 5- and 10-year LC were 100%. Only 5% of patients experienced an in IOERT-field relapse after R0 resection, 23% after R1 resection, and 75% after R2 resection. Late complications ≥grade 2 were seen in 21% of patients. The authors concluded that in selected patients, IOERT resulted in excellent LC and survival with accepted morbidity.[105]

Conclusions and Future Possibilities

IORT combined with EBRT and resection offers an effective means of improving LC in patients with primary and recurrent retroperitoneal sarcomas, as demonstrated in a randomized trial from the NCI as well as multiple U.S. and European single-institution studies.[101-108] A randomized NCI trial showed an 80% tumor bed relapse rate with adjuvant EBRT alone, likely as a result of an inability to deliver effective EBRT doses given normal tissue constraints. Because these results are similar to reports of resection alone, the use of adjuvant EBRT without IORT following marginal resection could be questioned. A more practical approach would be to administer preoperative EBRT following confirmation of diagnosis by thin-needle biopsy. This would be followed by resection at an institution with IORT capabilities.

Even with improved LC rates, locoregional and distant failure remains common modes of failure, emphasizing the need for improved therapies. Pilot studies are evaluating dose escalated EBRT using IMRT techniques in combination with IORT, as well as the role of concomitant radiochemotherapy with preoperative EBRT, IORT, and maintenance chemotherapy for resectable moderate- and high-grade retroperitoneal and pelvic sarcomas.[109] An Italian Sarcoma Group Phase II study is evaluating preoperative EBRT with high-dose continuous infusion ifosfamide, using IOERT or postoperative EBRT for radiation dose escalation following maximal resection.

Gynecologic Cancers

Patients with locally advanced or locally recurrent gynecologic cancers often have involvement of the pelvic sidewall, pelvic lymph nodes, or paraaortic nodes. The use of radical resection and IORT with or without EBRT or chemotherapy may benefit patients when compared with EBRT alone.

A Mayo Clinic analysis described 148 patients with primary (23 patients) or recurrent (125 patients) gynecologic

eTABLE 17-4A Mayo Clinic IOERT Analysis: Factors Influencing 5-Year Local Control in Resected Retroperitoneal Sarcomas

	Primary Tumors			Recurrent Tumors			All		
Factor	***n***	**LC (%)**	***p***	***n***	**LC (%)**	***p***	***n***	**LC (%)**	***p***
RESIDUAL AT IOERT									
None	11	100		5	100		16	100	
Microscopic	25	92		31	36		56	57	
Gross	7	60	<0.01	8	67	0.12	15	37	0.04
BRODERS GRADE									
1-2	9	100		24	28		33	47	
3-4	34	84	0.32	20	58	0.52	54	75	0.16
TUMOR SIZE (cm)									
≤10	23	83		30	50		17	64	
>10	19	92	0.80	14	34	0.69	69	62	0.96

IOERT, *Intraoperative electron beam radiotherapy;* LC, *local control.*

eTABLE 17-4B Mayo Clinic Analysis: Factors Influencing Survival in Resected Retroperitoneal Sarcomas with IOERT

	Factors Influencing Overall Survival at 5 Years								
	Primary Tumors			Recurrent Tumors			All		
	I	**OS (%)**	***p***	***n***	**OS (%)**	***p***	***n***	**OS (%)**	***p***
RESIDUAL AT IOERT									
None	11	62		5	80		16	68	
Microscopic	25	54		31	44		56	48	
Gross	7	29	0.15	8	45	0.60	15	37	0.12
BRODERS GRADE									
1-2	9	42		24	53		33	50	
3-4	34	54	0.70	20	35	0.36	54	48	0.32
TUMOR SIZE* (cm)									
≤10	23	66		30	54		53	60	
>10	19	33	0.15	14	19	0.04	33	28	0.01

IOERT, *Intraoperative electron beam radiotherapy;* OS, *overall survival.*
**One value missing.*

TABLE 17-6 Mayo Clinic Analysis: Factors Influencing Local Control and Survival in Resected Gynecologic Malignancies with IOERT

		Survival %			Relapse: 5 year		
Treatment Group	**#Pts**	**Med (mo.)**	**2 yr**	**5 yr**	**Local**	**Distant**	**Central**
All patients	148	19	41	27	40	51	28
Amount residual							
≤Microscopic	115	21	44	31*	42	49*	29
Gross	33	15	31	13	26	58	19
Site of primary							
uterine, ovary	58	30	53	41†	30	na	17‡
cervix, vagina	86	17	34	18	47	na	34
Prior EBRT							
None	63	22	47	35*	37	46	26
Yes	85	15	33	15	45	58	32

EBRT, *External beam irradiation;* Med, *median;* mo., *months;* Pts, *patients;* na, *not available;* yr, *year.*
*$p = 0.01$.
†$p = 0.002$.
‡$p = 0.007$.

malignancies treated with IOERT-containing regimens.[110-112] Preoperative or postoperative EBRT was delivered in 113 patients; 85 (57%) had received prior EBRT. The 5-year OS for all patients was 27%, and the 5-year local failure rate was 40% (Table 17-6).[111,112] On subset analysis, patients with R0 or R1 resection ($N = 115$) had improved 5-year OS compared to patients with R2 resection (31% versus 13%, $p = 0.01$); patients with uterine or ovarian primary origin had better survival than those with cervical or vaginal primaries (5-year OS 41% versus 18%, $p = 0.002$); patients with no prior EBRT had better 5-year OS than those with prior EBRT (35 versus 15%, $p = 0.01$). The rate of distant metastases at 5 years was 49% (R0 resection, 63%; R1/R2, 41%; $p = 0.04$). Fewer metastases were seen in patients treated with MVAC (methotrexate, vinblastine, doxorubicin, cisplatin) chemotherapy in a prior analysis.[110]

Cervical Cancer: Primary Locally Advanced Disease

IOERT containing regimens for locally advanced primary cervical cancers have been reported by several investigators. A Mayo Clinic analysis[113] of 13 patients with locally advanced cervical cancer treated with preoperative EBRT followed by resection and IOERT (median 12.5 Gy) and adjuvant chemotherapy in 77% reported a 29% 3-year survival and pelvic control in 69%. Spanish investigators treated 31 patients with primary locally advanced cervical cancer with 45 Gy EBRT in 1.8 Gy fractions followed by resection and 12 Gy IOERT. Survival at 10 years was 58% and LC was observed in 93%.[114]

A study from Xian Jiaotong University in China reported on 78 patients with stage IIb squamous cell carcinoma of the cervix who received IOERT during hysterectomy and selected lymphadenectomy. A comparison group of 89 patients was treated contemporaneously with standard therapy without surgery. IOERT-treated patients received 20 Gy EBRT at 2 Gy per fraction followed by 1 to 2 intracavitary brachytherapy HDR treatments with Ir-192, receiving 7 Gy per fraction to point A, followed by surgery and IOERT using 12 MeV electrons with doses of 18 to 20 Gy. Patients treated with standard therapy received 30 Gy EBRT whole pelvis and 20 Gy split pelvis, all in 2 Gy fractions, followed by 5 to 6 HDR insertions with Ir-192 delivering a dose of 35 to 40 Gy to point A. The 5-year OS, DFS, and LC in the IOERT patients were 89%, 87%, and 96%, respectively, versus 73%, 67%, and 73% in the standard therapy group ($p < 0.05$). Ten-year OS and LC were 85% and 94%, respectively, in the patients who underwent IOERT compared to 55% and 65%, respectively, in patients who underwent standard therapy. The patients who underwent IOERT had fewer rectal and bladder complications.[115]

Italian investigators reported the results of a Phase II trial containing IOERT as part of the multimodality regimen in patients with stage IIA bulky-IVA cervical cancer.[116] Forty-two patients were treated with 50.4 Gy EBRT in 1.8 Gy fractions with concomitant cisplatin and 5-FU followed by radical hysterectomy and IOERT (11 Gy median; range, 10 to 15 Gy). Seven patients were not resected because of refusal (1), progression (3), unresectability (2), and hemorrhage (1). For the 35 patients with radical hysterectomy and IOERT, the 5-year OS and DFS were 49% and 46%, respectively. Crude pelvic control was observed in 63% and control within the IOERT fields was 89%.[116]

Cervical Cancer: Recurrent Disease

Treatment of patients with recurrent cervical cancer is challenging, especially in those treated with high-dose radiotherapy for primary disease. There are several reports in the literature of curative attempt regimens including surgery and IOERT with or without EBRT. Stanford investigators evaluated 17 patients with recurrent cervical cancer treated with orthovoltage IORT (median 11.5 Gy). LC, distant metastasis-free survival, and disease-specific survival (DSS) rates at 5 years were 45%, 60%, and 46%, respectively.[117] A University of Washington series included 22 patients with recurrent cervical cancer. IOERT doses ranged from 14 to 27.8 Gy and 12 patients had R2 resections, with R1 or close R0 in 10 patients. LC at 5 years was 48% and DSS was 48%. Peripheral neuropathy was observed in 32%.[118]

Spanish investigators reported on 36 patients with recurrent cervical cancer treated with IOERT (median, 15 Gy).[114] Previously unirradiated patients were generally treated with preoperative EBRT to 45 Gy at 1.8 Gy per fraction with concurrent cisplatin and 5-FU. Previously irradiated patients underwent immediate resection or neoadjuvant chemotherapy if unresectable. Ten-year LC rate (within the IOERT field) was 47%, control in pelvic and paraaortic region was 42%, and 10-year survival was observed in 14%. Factors adversely influencing LC included involved parametrial margins, gross residual disease, and pelvic lymph node involvement. Patients with two or more risk factors had a 10-year LC rate of 0%, and there were no 10-year survivors with R2 resection. Six of 36 (17%) patients experienced nerve pain that resolved after a few months. All failures within the IOERT field occurred concomitant with relapse in the pelvis or distant metastases.[114]

Contrary to the relatively favorable results reported in most series, a French multiinstitutional analysis found relatively poor survival and LC with IORT. Seventy patients were treated in seven institutions with IORT alone (40 patients) or IORT with EBRT (30 patients) in addition to surgery. The pelvic sidewall was involved in 80% of cases and resection was macroscopically complete in only 47% of patients. IORT doses ranged from 10 to 30 Gy with a median of 18 Gy in patients with R0-R1 resections and 19 Gy in patients with R2 resections. LC was observed in only 21% and 5-year survival was 8%.[119]

A Mayo Clinic series included 73 patients with recurrent cervical cancer treated with IOERT to a median dose of 17.5 Gy. EBRT (median, 45 Gy) was included as part of the treatment in 66% of patients and 48% received perioperative chemotherapy. The median OS was 17 months with 25% survival observed at 3 years. The 3-year cumulative incidences of central relapse, locoregional relapse, and distant relapse were 23%, 39%, and 44%, respectively. On multivariate analysis, central control and locoregional control were associated with pelvic exenteration and use of EBRT. R2 resection was associated with a higher risk of distant metastases and poorer cause-specific survival (CSS). High-tumor grade and relapse within 6 months of primary diagnosis were associated with poor cause-specific survival and no patients treated within 6 months of primary diagnosis survived 3 years. Some degree of peripheral neuropathy was observed in 19% of patients.[113]

Endometrial Cancer: Recurrent Disease

Mayo Clinic investigators reported on 25 patients treated with IOERT for recurrence of endometrioid endometrial cancer.[120] Most patients (21/25, 84%) had involvement of the pelvic sidewall and the remaining 4 patients had paraaortic with and without upper abdominal involvement. EBRT was delivered to 21 patients (84%) to a median dose of 45 Gy (range, 9 to 50.7 Gy). EBRT was given preoperatively in 81% of cases. The median IOERT dose was 15 Gy (range, 10 to 25 Gy). The surgical resection was R0 with close margins in 7 (28%) patients, R1 in 11 (44%) patients, and R2 in 7 (28%) patients. The 5-year OS was 47% and median survival was 57 months. Survival was associated with resection margins with 5-year OS of 71%, 40%, and 0% in R0, R1, and R2 patients, respectively. Central relapse within the IOERT field was observed in 4 patients (16%), local relapse with control in IOERT field in 2 patients (8%), and distant relapse in 6 patients (24%). Peripheral neuropathy was observed in 8 patients (32%).[120]

Uterine Sarcoma

Mayo Clinic investigators reported on the use of IOERT as component of therapy in 16 patients with primary (3) or recurrent uterine sarcoma, including 9 patients with leiomyosarcoma, 4 with stromal sarcoma, and 3 with carcinosarcoma. All were treated with perioperative EBRT (median, 50.4 Gy; range, 20 to 62.5 Gy) and 6 (38%) received perioperative chemotherapy. Surgical resection was classified as R0 in 8 (50%) patients, R1 in 2 (12.5%) patients, and R2 in 6 (37.5%) patients. The median IOERT dose was 12.5 Gy with a range of 10 to 20 Gy. The 5-year OS was 43% and CSS was 47%. There were no central relapses within the IOERT field and only 1 local relapse (6%). Nine patients (56%) relapsed in distant sites. Peripheral neuropathy was observed in 3 patients (19%).[121]

Ovarian Cancer

Although the primary pattern of relapse of ovarian cancer is peritoneal, a subset of ovarian cancer patients experience isolated locoregional relapse. There are several reports on the use of IOERT in selected patients with ovarian cancer. A Chinese series included 25 patients with primary ovarian cancer and 20 with isolated local relapse. Intraperitoneal chemotherapy was delivered to 33 patients (73%) and intravenous chemotherapy to 7 (16%) patients. No EBRT was used. The IOERT dose was 18 to 20 Gy in 43 patients and 10 Gy in the remaining 2 patients. Five-year survival was observed in 64% in the primary group and 60% in the recurrent group. In the primary group 8 patients (32%) relapsed locally and 3 (12%) distantly. In the recurrent group there were 6 local relapses (30%) and 2 distant relapses (10%). The rate of central relapse within the IOERT field was 9% for the entire group. Five patients (11%) experienced peripheral neuropathy.[122]

Stanford investigators reported on 22 patients with recurrent ovarian cancer who received orthovoltage IORT as a component therapy.[123] The median IORT dose was 12 Gy (range, 9 to 14 Gy) and treated sites included pelvis, paraaortic nodes, inguinal nodes, and the porta hepatis. Nine patients received whole abdominal EBRT, 5 locoregional EBRT, and 6 chemotherapy. The median survival was 26 months, 5-year OS was 22%, and DFS 18%. Locoregional control was 68% at 22 months and 55% of patients experienced distant relapse. There were no long-term peripheral neuropathies.[123]

A Mayo Clinic analysis described 20 patients with recurrent ovarian cancer treated with IOERT as a component of therapy.[124] Thirteen patients (70%) had epithelial ovarian carcinomas and the remaining histologies were granulosa cell tumor, malignant teratoma, adenosarcoma, stromal tumor, and squamous cell carcinoma. The site of recurrence was pelvis in 14 patients, paraaortic nodes in 6, and inguinal nodes in 1. Sixteen patients received a median EBRT dose of 50 Gy (range, 20 to 54.3 Gy). Surgical resection was classified as R0 in 9 patients, R1 in 11, and R2 in 1. The median IOERT dose was 12.5 Gy (range, 10 to 22.5 Gy). Median survival was 30 months with 49% 5-year OS. Central control within the IOERT field was observed in 76% with all central relapses occurring in patients with R1 resections. Distant relapse was observed in 9 patients (45%). Three patients experience grades 1 to 2 peripheral neuropathy.[124]

Future Possibilities

Because of the high incidence of distant metastases observed in patients with gynecologic cancer with microscopic and gross residual disease following resection, evaluation of newer systemic and maintenance regimens is indicated. Investigation of newer chemotherapeutic and targeted biologic agents may hold promise in improving distant metastases rates and ultimate survival in these malignancies.

Colorectal Cancer: Primary and Recurrent Disease

Primary Locally Advanced Cancers

Locally advanced colorectal cancers are tumors that cannot be resected without microscopic or gross residual secondary to tumor adherence to adjacent structures. In selected patients, the optimal approach is to administer preoperative chemoradiation in efforts to "downstage" disease and facilitate surgical resection. At the time of resection, if clinical suspicion for involved margins is high, the use of IORT may be appropriate.

In an MGH series, 64 patients with locally advanced primary rectal cancer underwent preoperative irradiation (with or without 5-FU) followed by resection and IOERT. Patients undergoing R0 resection had a 5-year LC and DSS of 91% and 63%, respectively. Patients with R1 resection experienced 5-year LC and DSS of 65% and 47%, respectively, and patients with R2 resection, 57% and 14%, respectively (Table 17-7).[125]

A Mayo Clinic Rochester report described 56 patients with primary locally advanced colorectal cancer undergoing EBRT

TABLE 17-7 Primary Rectal (MGH) or Colorectal (Mayo Clinic) IOERT Series: Disease Control and Survival by Degree of Resection and Amount of Residual Disease

	MGH Results 5-Yr Act (%)*†			Mayo Clinic Results 5-Yr Act (%)			
Degree of Resection	***N***	***LF***	***DSS***	***N***	***LF***	***DF***	**OS**
No tumor	—	—	—	2	0	0	100
Complete resection	40	9	63	18	7	54†	69
Partial (subtotal) resection	24	37	35	—	—	—	—
Microscopic residual	17	35	47	19	14	50†	55
Gross residual	7	43	14	16	27	83†	21
No resection	—	—	—	—	—	—	0
Total series	64			56	16	59	46

Act, *Actuarial;* DF, *distant failure;* DSS, *disease-specific survival;* LF, *local failure;* MGH, *Massachusetts General Hospital;* OS, *overall survival.*

**Data from Gunderson LL, Nelson H, Martenson JA, et al: Locally advanced primary colorectal cancer: Intraoperative electron and external beam irradiation ± 5-FU. Int J Radiat Oncol Biol Phys 37(3):601–614, 1997 and Willett CG, Shellito PC, Tepper JE, et al: Intraoperative electron beam radiation therapy for primary locally advanced rectal and rectosigmoid carcinoma. J Clin Oncol 9(5):843–849, 1991.*

†Three-year actuarial DF of 43%, 38%, and 66%, respectively, for complete resection, microresidual, and gross residual.

(45 to 55 Gy, usually with concurrent 5-FU administration) followed by resection and IOERT (10 to 20 Gy). Five-year OS for all patients was 46%. Patients with R0 or R1 resection had an improved OS relative to patients with R2 resection (5-year OS of 59% versus 21%, $p = 0.0005$). Failure within the IOERT field occurred in 4 of 16 patients (25%) with R2 resection versus 2 of 39 (5%) with R0 or R1 resection ($p = 0.01$)[52] (see Table 17-7).

An update from Mayo Clinic Rochester analyzed 146 patients with locally unresectable primary colorectal cancers who received IOERT in addition to preoperative or postoperative combined modality therapy. Median survival was 44 months with 5-year OS of 52%. Three-year local and distant relapse rates were 10% and 43%, respectively. Patients receiving preoperative combined modality therapy appeared to have a survival advantage versus those receiving postoperative therapy (median survival 76 months versus 26 months, 5-year OS of 55% versus 38%, $p = 0.02$).[53]

Madrid investigators from the General University Hospital Gregorio Marañon described 558 patients with T3-T4 rectal cancer, 281 of which received preoperative combined modality therapy plus IOERT and 277 who received postoperative chemoradiotherapy without IOERT. Patients receiving preoperative therapy plus IOERT (despite higher stage disease at presentation) had a significant improvement in pelvic control (92% versus 84%, $p = 0.03$), DFS (65% versus 56%, $p = 0.05$), and OS (68% versus 58%, $p = 0.016$).[55] In a recent and selected update of the postchemoradiation plus IORT presacral boost experience, 335 patients treated from 1995 to 2011 (median follow-up 52.2 months) showed 5-year LC, in-field and out-field control rates of 94.4%, 97.0%, and 93.4%, respectively. In multivariate analysis, nonsphincter-preserving surgery and grade 3 histology were associated with increased risk of presacral relapse.[56]

A pooled European analysis of 651 patients treated with IOERT from four major centers showed that 5-year OS was 67% with 5-year LC of 88% in patients with locally advanced rectal cancer.[57] Positive circumferential margins were a strong predictor for both OS and local relapse, and the addition of preoperative CRT appeared to improve 5-year OS (70% versus 64%, $p < 0.05$). An update of the pooled European analysis in 605 patients demonstrated that chemoradiotherapy led to more downstaging and complete remissions compared to radiotherapy alone.[58] Local recurrence, distant metastasis, and OS rates were 12%, 29%, and 67%, respectively. Risk factors for local recurrence included lack of downstaging with preoperative therapy, lymph node involvement, margin involvement, and lack of postoperative chemotherapy. The authors concluded that oncological results following multimodality therapy including IORT showed promising outcomes and the addition of adjuvant chemotherapy could potentially improve local recurrence rates.

The feasibility of IOERT at the time of laparoscopic resection of locally advanced rectal cancer, after preoperative chemoradiation, has been reported by the Gregorio Marañon Hospital team. In a group of 125 patients, laparoscopic resection plus IOERT had significantly less blood loss and shorter hospital stay. Oncological and toxicity results were similar.[59]

Locally Recurrent Colorectal Cancer

Patients developing local recurrence following curative resection of primary colon or rectal cancer are treated with palliative intent at most institutions. Local recurrence from rectosigmoid cancer often causes pelvic pain due to nerve involvement in the presacral space or pelvic sidewall. The likelihood of margin negative resection is low. Patients undergoing surgery alone for pelvic recurrence from rectal cancer have reported 5-year survival rates of 0%.[126]

When IOERT is combined with EBRT with or without chemotherapy and surgical salvage, 5-year OS in the range of 20% to 30% has been achieved.[51,126-130] In an MGH analysis of 41 patients with locally recurrent rectosigmoid cancer undergoing IOERT, patients with gross residual disease experienced 5-year LC and DFS of 21% and 7%, respectively, versus 47% and 21% with clear or microscopically positive margins.[127] Eindhoven investigators described a series of 147 patients with locally recurrent colorectal cancer receiving IOERT. Median OS was 28 months with 5-year OS, DFS, metastases-free survival, and LC rates of 32%, 34%, 50%, and 54%, respectively. R0 resection was associated with improved disease outcomes. Patients treated with IOERT alone had worse outcomes vs those who were reirradiated or treated with full dose preoperative EBRT.[128]

The potential of extended resection in combination with IOERT and EBRT has been analyzed at the University Hospital Gregorio Marañon. In a 16-year experience an adaptive surgical approach based on extent of recurrence extension was systematically combined with IOERT: 60 patients underwent extended surgery (43% multiorgan, 28% bone, 38% soft-tissue resection) and 22 had nonextended resection. With a median follow-up time of 36 months, locoregional control was 44% at 5-years and OS was 43%. On multivariate analysis, positive margins, EBRT at the time of rescue, lack of tumor fragmentation, and lack of lymph node metastasis were significant factors associated with locoregional relapse.[131]

A Mayo Clinic Rochester report described the outcome of 106 patients undergoing palliative resection of locally recurrent, nonmetastatic rectal cancer. Forty-two patients received IOERT as a component of treatment (most 15 to 20 Gy) and 41 EBRT (most ≥45 Gy). Patients with R2 resection had a significantly worse outcome versus R1 resection (5-year OS of 9% versus 33%, $p = 0.03$). Patients who underwent IOERT compared to those that did not had 5-year OS of 19% versus 7% ($p = 0.0006$).[126]

An updated Mayo Clinic analysis described 175 patients with locally recurrent colorectal cancer (123 no prior EBRT, 52 prior EBRT) undergoing IOERT. Five-year OS in previously unirradiated patients was 20% versus 12% in previously irradiated patients. Three-year LC rate in previously unirradiated patients was 75% versus 51% in those previously irradiated. Three-year distant metastases rates were 64% and 71%, respectively.[132]

An even more recent Mayo Clinic analysis described 607 patients with recurrent colorectal cancer who received IOERT as a component of treatment. Five-year OS was 30%. In patients undergoing R0 resection, 5-year OS was 46%. Prior in-field radiation was associated with an increased risk of local relapse (3-year local relapse of 39% versus 20%, $p < 0.0001$) but not with survival. On multivariate analysis, complete resection, no prior chemotherapy, and treatment after 1996 were associated with improved survival. Three-year local and distant relapse rates were 27% and 55%, respectively.[54]

Systematic reviews and meta-analysis are available to evaluate results of IORT in colorectal cancer. From 1965 to 2011, 14 prospective and 15 retrospective studies were identified meeting methodological quality and design (3003 patients involved: 1792 primary locally advanced category). When comparative studies were evaluated, a significant effect favoring improved LC ($p = 0.003$), DFS ($p = 0.009$), and OS ($p = 0.001$) was noted with no increase in total urologic or anastomotic complications, although increased wound complications were observed after IORT ($p = 0.049$). Heterogeneity in methodology and reporting practice warrant caution in the interpretation of these results.[133]

Future Possibilities

Based on the preceding and other data, it appears improved LC and survival may be achieved when IORT is combined with preoperative chemoradiation for locally advanced or locally recurrent colorectal cancer. Many patients will develop distant metastases; relapse within the IORT and EBRT fields is common if gross total resection is not obtained. Based on the proven survival benefit of concurrent 5-FU–based regimens with EBRT in colorectal and other gastrointestinal malignancies, 5-FU–based chemotherapy should be administered concurrent with EBRT. Although adjuvant 5-FU with leucovorin has previously been shown to improve survival in patients with advanced stage colorectal cancer, the addition of newer therapies (oxaliplatin, capecitabine, irinotecan, bevacizumab, cetuximab, panitumumab) has demonstrated further survival benefit in patients with stage IV cancer. These agents have been evaluated as adjuvant therapy in patients with stages II and III cancer (see Colon and Rectal Cancer, Chapters 50 and 51). Given the high rate of subsequent distant metastases in patients with locally advanced and recurrent colorectal cancer, significant improvement in long-term survival will likely be achieved through further improvements in systemic agents.

CONCLUSIONS AND FUTURE POSSIBILITIES

Conclusions

IORT is the delivery of radiation at the time of operation. This can be accomplished using different techniques including IOERT, HDR-IORT, and orthovoltage. IORT is usually given in combination with EBRT with or without chemotherapy and surgical resection. IORT allows exclusion of part or all dose-limiting sensitive structures, thereby increasing the effective dose to the tumor bed (and therefore LC) without significantly increasing normal tissue morbidity.

Despite optimal therapy with non-IORT approaches, high rates of local relapse occur in patients with retroperitoneal sarcoma, pancreatic cancer, colorectal cancer, gynecologic cancer, and other malignancies. The addition of IORT to conventional treatment methods has improved LC as well as survival in many disease sites in both the primary and recurrent disease settings. In view of newer, lower cost treatment devices, the use of IORT in clinical practice will likely continue to grow, with increasing integration into the treatment of "nonconventional" malignancies. Cancer sites in which IORT has been explored and found to be feasible include renal cancer,[134] prostate cancer,[135] extremity sarcomas,[136] and pediatric cancers.[137]

IORT: Technical Considerations

Many limitations and perceived drawbacks of IORT in past decades were the result of inefficiencies associated with nondedicated facilities. Patients were often transported from the operating suite to the radiation oncology department where they were treated with nondedicated linear accelerators. These inconveniences have been overcome with dedicated IOERT, HDR-IORT, or orthovoltage facilities. Presently, dedicated IORT suites within or adjacent to the operating room exist at many institutions in the United States, Europe, and Far East. These facilities simplify treatment by avoiding transportation and sterility problems. A major limiting factor is the expense associated with outfitting a dedicated room (e.g., retrofitting an operating room with proper shielding, purchase of a linear accelerator dedicated for use in the operating room, construction of a separate IORT suite adjacent to the operating room, etc.). However, newer technologies have lowered these costs. Contemporary options include mobile IOERT units (Mobetron, Liac) as well as mobile HDR-IORT.[138] The Mobetron is a mobile, self-shielded compact linear accelerator with C-arm design that generates electron energies of 4 MeV to 12 MeV (Intraop Medical, Inc., Santa Clara, CA, Figure 17-3). This can be transported in and out of the operating theater. HDR-IORT units are remote afterloading devices that use an Ir-192 source (Figures 17-4, 17-5). In contrast to the Mobetron, HDR-IORT requires room shielding, which may be achieved by retrofitting an existing room or construction of a smaller shielded room adjacent to the operating suite. In either situation, patients are monitored by camera during radiation administration. After completion, the HDR-IORT unit can be transported to the radiation oncology department for outpatient HDR appropriate malignancies, including gynecologic and prostate malignancies. Mobile IOERT devices used in Europe include the Liac machine. The INTRABEAM system for breast cancer IORT consists of a 50-kV x-ray generator mounted on a flexible floor stand and a set of spherical applicators ranging from 1.5 cm to 5 cm in diameter (see eFigure 17-1).

Treatment planning systems specifically designed for IOERT are now commercially available (Radiance). Initial clinical testing demonstrated feasibility and multispecialist agreement for simulation of different cancer sites and anatomic locations, including breast cancer, locally advanced rectal cancer, retroperitoneal sarcoma, and isolated recurrence of rectal and ovarian cancer.[139] Research opportunities in IORT are a multidisciplinary endeaver that spans knowledge ranging from radiation beam adaptive development to advanced molecular biology for biopredictability of outcomes. Technical innovation requires further improvements in quality assurance and



Figure 17-3 The mobile electron-beam radiation device (MOBETRON) (seen here in the operating room) allows use in an existing operating room with little or no additional shielding required.
Courtesy IntraOp Medical, Inc., Sunnyvale, California.



Figure 17-4 Source housing for Ir-192 source. This device allows computer-assisted treatment delivery during IORT.
Courtesy Varian Medical Systems.

clinical practice. The incorporation of treatment planning systems for IORT use will help decision-making processes and its registration will facilitate normalization of medical and surgical practice in IORT programs. Opportunities in radiation beam modulation, delivery, dosimetry and planning, infrastructure, and treatment factors are recognized and expected to be developed over the next decade.[140]

A detailed description of the relative advantages and disadvantages of IOERT and HDR-IORT has been discussed elsewhere and is beyond the scope of this chapter[36] (eTables 17-5 and 17-6). In summary, treatment or procedure times

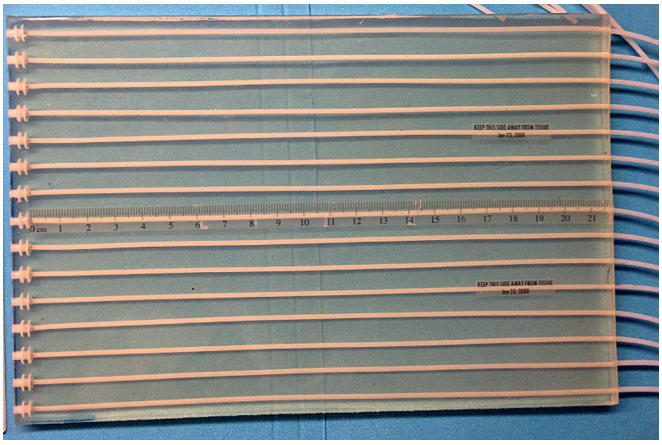


Figure 17-5 Harrison-Anderson-Mick (HAM) applicator used to guide Ir-192 source during HDR-IORT.

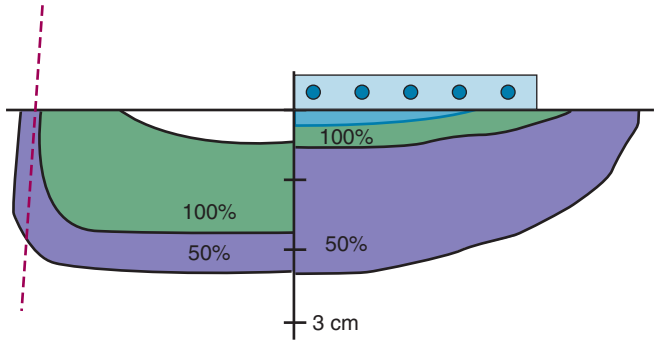


Figure 17-6 Dose distribution characteristics of IOERT *(left)* and in HDR-IORT *(right).* Note IOERT is utilizing 6 MeV electrons; HDR-IORT is utilizing 1 cm surface applicator with dose prescribed to 0.5-cm depth.

are generally shorter with IOERT compared to HDR-IORT. Additionally, IOERT allows variation of electron energies and therefore treatment of both superficial and deeper-seated targets, whereas HDR-IORT is appropriate only for targets ≤0.5 cm in thickness (Figure 17-6). The flexible Harrison-Anderson-Mick (HAM) applicator used in HDR-IORT may allow more conformal treatment along curved body surfaces (e.g., large pelvic sidewall fields, lateral abdominal wall, and thoracic cage) that may prove difficult with rigid IOERT applicators (Figure 17-5). Separate, matching fields may be required to treat larger target areas with IOERT-based applicators. A comprehensive IORT program would ideally have IOERT, HDR-IORT, as well as perioperative brachytherapy available to treat all disease sites and situations. These modalities should be viewed as complementary and not competitive.

Future Possibilities

Although there is a large body of data supporting the use of IORT in various malignancies, there is a relative paucity of Phase III randomized trials. This is at least in part because of the limited number of IORT facilities in any given country as well as relative rarity of diseases commonly treated with IORT. Completion of Phase II/III trials will likely require cooperation among multiple institutions and countries. Future treatment approaches should include "standard" courses of EBRT with or without concurrent chemotherapy and surgical resection with the integration of novel radiation sensitizers, protectors, and targeted biologic agents with IORT.[141]

eTABLE 17-5 Relative Advantages and Disadvantages of IOERT versus HDR-IORT Brachytherapy after Gross Total or Near-Total Resection (Maximum Tumor Thickness ≤0.5 cm)

IOERT Potential Advantage If Technically Feasible	Potential Disadvantages of IOERT	Potential Solution to Disadvantage
Better dose homogeneity	Surface dose <90% with 6 ± 9 MeV	Add bolus over tumor bed to improve surface dose; use HDR-IORT
Faster treatment time		
Less shielding required in OR	Unable to include area at risk in single field within either abdomen or pelvis	Use abutting IOERT fields (difficult in pelvis): use HDR-IORT
Can treat full thickness of organ or structure at risk with relative homogeneity (e.g., aorta or vena cava, bladder sidewall)	Area at risk is technically inaccessible because of location	Use HDR-IORT; surgically displace small bowel or stomach with vascularized flap (omentum, muscle) and give postoperative EBRT boost or perioperative brachytherapy

eTABLE 17-6 Potential Differences between IOERT and HDR-IORT

	IOERT	HDR-IORT
Actual treatment time	2-4 min	5-30 min
Total procedure lime	30-45 min	45-120 min
Treatment sites	Accessible locations	All areas where depth at risk is ≤5 cm from surface of applicator
Surface dose	Lower (75%-93%)	Higher (150%-200%)
Dose at depth (2 cm)	Higher (70%-100%)	Lower (30%)
Dosimetric homogeneity (surface to depth)	<10% variation	>100% variation

From Nag S et al: Intraoperative irradiation with electron-beam or high-dose-rate brachytherapy. Ch 7 in intraoperative irradiation. In Gunderson L, Willett C, Harrison L, Calvo F, editors: Humana Press, Inc., 1999, Totowa, NJ, pp 111–130.

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CHAPTER

18 Total Body Irradiation

Christopher Andrew Barker and Joachim Yahalom

Total body irradiation (TBI) is a radiotherapy technique that has been applied to treat various benign and malignant diseases over the past century. The technique has evolved in parallel with an increase in the knowledge of the biologic response to ionizing radiation and improvements in radiation dosimetry and treatment delivery. TBI remains an important component of hematopoietic stem cell transplant (HSCT), with the goal of eradicating residual malignant cells or modulating the immune system of the transplant recipient. In the context of HSCT, TBI is advantageous because biologic effects can be exerted uniformly, without the sparing of "sanctuary" sites such as the nervous system or tests or interference from metabolic or resistance processes.

HISTORY OF TOTAL BODY IRRADIATION

Only a decade after Roentgen described the "x ray," German biophysical engineer Friedrich J. Dessauer[1,2] first described a "new technique of radiotherapy" that involved homogenous irradiation of the entire body. In his initial report describing the technique in 1905, he proposed irradiating a supine patient using three simultaneously active, low-voltage roentgen-ray sources (Figure 18-1). In 1907, Aladár Elfer,[3] a medical professor in Hungary, reported his experience using a TBI technique that spared the head in three patients with leukemia. Although there is a paucity of data regarding the early use of the technique, some have speculated that untoward hematologic toxicity probably limited its application.[4]

Early success using TBI to treat hematopoietic and lymphoid malignant tumors in Europe (there named the Teschendorf method) prompted development of the technique in the United States.[5-7] Arthur C. Heublein, in collaboration with Gioacchino Failla, is credited with the development of the first TBI unit in North America, located at Memorial Hospital in New York City. In the United States, the technique became known as Heublein therapy.[8] A specially constructed treatment ward was designed to treat four patients at extended distance (5 to 7 m) simultaneously at an exposure rate of 0.7 roentgen (R)/hour, for about 20 hours/day, typically over 1 to 2 weeks, using a 185-kV x-ray tube at 3 mA, with a 2-mm copper filter. The goal was to deliver 25% of the erythema dose (750 R).

Remarkably, in Heublein's initial report, no hematopoietic toxicity was noted with this treatment schedule. Seven of 12 patients (58%) with advanced lymphomas and leukemias and 2 of 8 patients (25%) with metastatic breast, melanoma, and kidney cancers were noted to demonstrate some form of improvement after treatment.[9,10] A later report of the experience with 270 patients with cancer from Memorial Hospital treated with TBI between 1931 and 1940 confirmed that the technique was more successful in patients with hematopoietic and lymphoid cancers compared with those with carcinomas or sarcomas, for whom it was ineffective. The authors emphasized that the technique was safe if doses were prescribed cautiously. They did not recommend exposures greater than 300 R and noted hematopoietic and gastrointestinal toxicity with exposures as low as 50 to 100 R.[8]

In the early 1940s, World War II prompted an initiative to develop nuclear weapons, known as the Manhattan Project. Part of this endeavor sponsored research into the human biologic response to ionizing radiation, including TBI. The military's interest in TBI was primarily to help understand human tolerance for radiation exposure during occupational duties and warfare and to develop radiation biodosimetric assays. Several research studies coordinated through the Manhattan Project were initiated in patients with advanced cancers,[11-13] as well as patients with benign diseases.[13] For example, studies of dose escalation, radiation biologic dosimetry, and cognitive and psychomotor function were carried out at the M. D. Anderson Hospital for Cancer Research.[14] A detailed report of 30 patients treated at the maximum exposure level (200 R) in the initial study concluded that side effects primarily consisted of nausea, vomiting, and myelosuppression, and that intervention was necessary in 10% of patients treated with this dose of TBI.[15] At Baylor University College of Medicine, studies using 25 R to 250 R of TBI with 250 kV to 2 MV photons were performed to find a biologic dosimeter, as well as to study acute effects of radiotherapy.[16] The Sloan-Kettering Institute for Cancer Research also participated in similar studies of at least 20 patients, although the results were never published. The military conducted similar studies at the Naval Hospital in Bethesda, Maryland, and reported palliation of patients with radiosensitive diseases treated with fractionated TBI.[17] The most recent research study of TBI sponsored by the U.S. Department of Defense was conducted at the University of Cincinnati. It focused on identifying biochemical markers in the urine that predicted response to TBI. Later, studies of the neuropsychiatric effects of TBI were initiated. Ultimately, only results regarding the palliation of advanced cancers were reported.[18] Patients with advanced metastatic radioresistant malignant tumors, for whom chemotherapy was unavailable, were often treated with TBI in the absence of any clear anticipated benefit. Patients treated with TBI in this manner were included in research studies, often without consenting to participate. The ethics of this practice was called into question by a report written in 1995 by the U.S. Department of Energy's Advisory Committee on Human Radiation Experiments,[19] which may have contributed to the public's general uneasiness regarding radiation.[20]

TBI was not only used in malignant diseases, but it was also considered the critical immunomodulator in the first successful solid organ transplant. In 1959, a kidney was successfully transplanted between dizygotic twins after TBI at exposures of up to 450 R (given to the recipient).[21] Around the same time in France, successful kidney transplants after TBI were being reported.[22,23] Of the first seven patients who underwent kidney transplant following TBI or pharmacologic immunomodulation worldwide between 1959 and 1962, the two who did not experience kidney failure were treated with TBI alone (without chemical immunosuppression) before transplant, and each survived for more than 20 years after transplant.[21-23] However, successful preclinical studies with pharmacologic therapy prompted the use of chemical immunosuppressants (corticosteroids, 6-mercaptopurine, and azathioprine) for solid organ transplantation after 1963.[24]

With an increased understanding of the human response to TBI and a rapidly growing body of preclinical in vivo studies

of TBI, therapeutic protocols were developed to maximize benefit in patients with malignant diseases. In 1957, Nobel laureate E. Donnall Thomas[25,26] first reported the use of bone marrow infusion in humans following whole body irradiation or chemotherapy, and less than 1 year later he published his experience in using TBI with exposures up to 600 R followed by bone marrow transplantation. In the series of the first five patients with leukemia treated with TBI, who then received intravenous infusion of normal donor marrow, Thomas et al[26] noted the difficulty of acute myelosuppression and resultant hemorrhage and infection during the period leading up to engraftment. The report also commented that low dose rates (delivery over 2 to 3 days) appeared preferable to higher dose rates, for metabolic and immunologic reasons. In addition, patients receiving 200 R to 300 R fared better than those receiving 400 R to 600 R. The problem of delivering an adequately homogenous dose was raised, and suggestions about using higher-energy photons were proposed. Thomas et al[27] later reported on syngeneic bone marrow transplantation in two children after 850 R to 1140 R was delivered in a single fraction over 22 to 25 hours, using cobalt-60 (^{60}Co) sources. The authors concluded that 1000 R of TBI did not produce "troublesome" acute radiation sickness, did produce remission of leukemia, but did not cure the disease. The first report of successful cure of a patient with leukemia with allogeneic transplantation after TBI was reported in 1969. The technique involved opposed ^{60}Co sources, which operated at 5.8 R/minute, to a total exposure of 1620 R, calculated to be 954 rad at midline. With appropriate supportive care, no major acute radiation sickness was noted, but the patient died of overwhelming cytomegalovirus infection, without evidence of leukemia.[28]

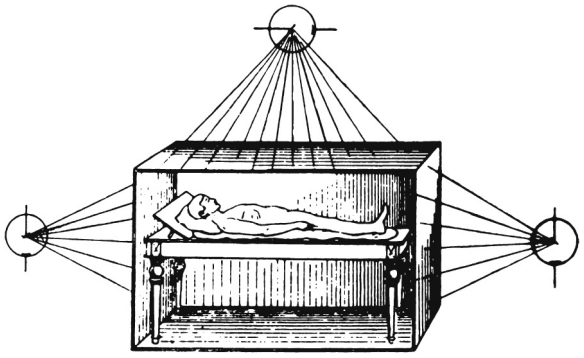


Figure 18-1 Diagram demonstrating the total body irradiation technique proposed by Dessauer in 1905.
Reprinted from Wetterer J editor: Handbuch der Röntgentherapie nebst Anhang. In Die radium therapie, Leipzig, 1908, Otto Nemnich.

Over the next several years, techniques of combining chemotherapy and TBI were developed and refined, with promising results.[29,30] Success in the treatment of advanced leukemias and severe aplastic anemia was achieved. Departure from the use of TBI alone was primarily fostered by the development of more effective cytotoxic chemotherapeutics and immunologic therapies, which when combined with TBI, yielded fewer leukemic recurrences.[29] Although the use of TBI without HSCT has largely been abandoned, primarily for fear of inducing secondary malignant tumors and limiting later therapeutic options, some question the validity of this fear and still contend that low dose TBI (1.5Gy to 2 Gy in 10 to 20 fractions over several weeks) is a viable option for initial therapy in advanced indolent lymphomas.[31] Figure 18-2 demonstrates how the use of TBI during HSCT has changed over a recent 15-year period.[32]

HEMATOPOIETIC STEM CELL TRANSPLANT

HSCT has evolved into a highly complex clinical discipline, firmly rooted in immune system and cancer biology, the details of which are beyond the scope of this chapter. When HSCT was initially performed (see History of Total Body Irradiation section), bone marrow was extracted from the donor and infused intravenously into the recipient. Later, peripheral blood stem cells, instead of bone marrow, were collected from the donor as an alternative to bone marrow grafting. For this reason, bone marrow transplants are now more appropriately termed *hematopoietic stem cell transplants* because the critical component of the graft is the hematopoietic stem cell (HSC), independent of the source. The peripheral blood stem cells

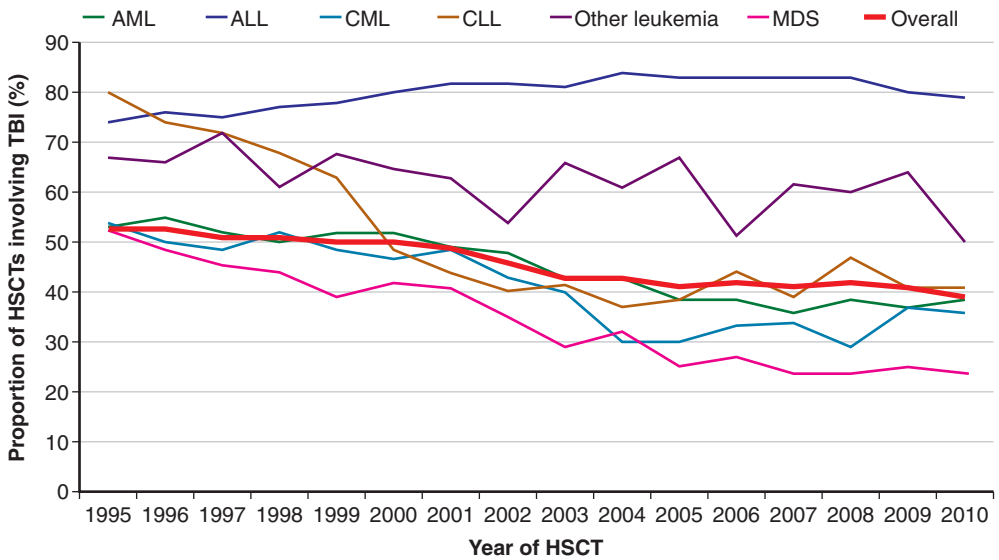


Figure 18-2 Temporal trends in the five diseases most frequently involving TBI as part of allogeneic HSCT, and overall. *ALL*, Acute lymphoblastic leukemia; *AML*, acute myelogenous leukemia; *CLL*, chronic lymphocytic leukemia; *CML*, chronic myelogenous leukemia; *HSCT*, hematopoetic stem cell transplant; *MDS*, myelodysplastic syndrome.
Data from Hong S, Barker CA, Klein JP, et al: Trends in utilization of total body irradiation (TBI) prior to hematopoietic cell transplantation (HCT), worldwide. Biol Blood Marrow Transplant 18(2 Supplement 2):S336–S337, 2012.

are often "mobilized" from the donor using hematopoietic growth-stimulating factors and are removed from the donor by apheresis. In addition, recent success using HSCs derived from human umbilical cord blood has been described. Depending on the source of HSCs, various postcollection processing measures (e.g., cell selection and depletion) may be undertaken to optimize the outcome of the transplant.

When transplant occurs between different individuals, the hematopoietic graft is said to be an *allogeneic graft.* This is in contradistinction to reinfusion of native HSCs back into the donor in an *autologous transplant,* more appropriately termed an *autoplant,* because nothing is being transferred between different individuals.[33] A rare but alternative situation is when an organ from a genetically identical twin of a patient is transplanted *(syngeneic transplant).* Of these three methods of HSCT, autologous and syngeneic transplantations are generally associated with less risk because issues related to immunocompatibility are minimized. Allogeneic transplantations require the "matching" of donor and recipient and are typically carried out through identification of human leukocyte antigen (HLA) compatibility. The donor may be related to the recipient or may be identified through registries of volunteers, such as the National Marrow Donor Program.

Before undergoing HSCT, most patients will require intensive antineoplastic or immunomodulatory therapy, often referred to as *conditioning,* in preparation for HSCT. Conditioning can involve cytotoxic chemotherapy, immunomodulators, antibody therapy, or radiation therapy. The nature of the conditioning regimen can be referred to as of high or reduced intensity or as myeloablative, submyeloablative, or nonmyeloablative, to carry out conventional or mini-(ature) transplants.[33] Although agreed-on formal definitions of these regimens do not exist,[34] the goal of high-intensity/myeloablative/conventional transplant is to completely eliminate the recipient's native HSC compartment, which necessitates HSCT (autologous or allogeneic) for survival. High-intensity, myeloablative, and conventional transplants may or may not involve TBI to high doses (>5 Gy in a single fraction, >8 Gy in multiple fractions). Reduced-intensity, nonmyeloablative, minitransplant conditioning regimens are often used for older patients or those with medical problems, for whom a high-intensity, myeloablative, and conventional transplant would cause excessive morbidity or mortality and may or may not involve TBI to lower doses. During and immediately after conditioning, the transplant recipient is at significant risk for infections and other hematologic complications. For this reason, the supportive care of HSCT recipients is complex and should only be undertaken in specialized facilities. Nonetheless, some groups have developed reduced-intensity and myeloablative HSCT regimens, including TBI, which have been safely undertaken on an outpatient basis.[35,36]

After undergoing conditioning and HSCT, the major challenges are related to engraftment, the permanent reconstitution of the recipient's hematopoietic system, and prevention of graft rejection and associated postengraftment complications. The former process can be facilitated through the use of hematopoietic growth-stimulating factors, and the latter can be mitigated with chemical and biologic immunomodulators. Once the graft has successfully taken, the recipient is at risk of developing graft-versus-host disease (GVHD), in which engrafted HSCs recognize the host's native, non-HSC tissues as foreign and attack them. Specific organs at risk are the skin, gastrointestinal tract, and liver. The risk of GVHD is only present in patients undergoing allogeneic HSCT. Moreover, it has been recognized that part of the beneficial effect of transplant is the graft-versus-tumor (GVT) effect, a fundamental component of the therapeutic effect of HSCT, which can occur in autologous or allogeneic transplants.

According to data summarized by the Worldwide Network for Blood and Marrow Transplantation in 2006, the diseases most commonly treated with HSCT are lymphoproliferative disorders (54.5%, most often multiple myeloma [MM], non-Hodgkin lymphoma [NHL], and Hodgkin lymphoma [HL]), leukemias (33.8%, most often acute myelogenous leukemia [AML], acute lymphocytic leukemia [ALL], myelodysplastic syndrome [MDS], chronic myeloid leukemia [CML], and chronic lymphocytic leukemia [CLL]), solid tumors (5.8%), and nonmalignant disorders (5.1%).[37] The 2014 National Comprehensive Cancer Network (NCCN) guidelines for therapy indicate that allogeneic or autologous HSCT may be a treatment option for testicular cancer, AML, MM, MDS, CML, HL, and NHL, depending on the clinical situation. HSCT with or without TBI-based conditioning has also been described in the treatment of solid tumors, including breast cancer, germ cell tumors, renal cell carcinoma, melanoma, neuroblastoma, and other pediatric cancers. Detailed discussion of these diseases and their management is beyond the scope of this chapter, and the reader is referred to other chapters in this text and other reviews.[38-41] The role of TBI in nonmalignant diseases will be discussed in subsequent sections of this chapter.

RADIOBIOLOGY

Experimental radiobiologists have described much of what is known regarding the fundamental biologic effects of TBI, and clinicians have applied these principles to optimize the therapeutic benefit for patients. The essential rationale for TBI in the context of HSCT is to eradicate malignant or dysfunctional cells or modulate immune system function. Therefore, the critical radiobiologic in vitro data related to efficacy of treatment deal with normal and malignant hematopoietic cells.

Preclinical studies have helped define some of the fundamental radiobiologic properties of the normal lymphocytes. The D_0 (see Chapter 5) of normal lymphocytes has been reported to be 0.5 Gy to 1.4 Gy,[42-45] depending on the in vitro or in vivo model used to calculate this parameter. This D_0 suggests that normal lymphocyte cells are sensitive to ionizing radiation. A small shoulder on the radiation cell survival curve has been noted,[46,47] suggesting little repair between fractions of radiation. Clinical data have revealed similar findings in patients undergoing hyperfractionated TBI, with lymphocyte survival demonstrating an effective D_0 of 3.8 Gy, according to one study.[48] Other radiobiologic phenomena have been ill defined in other normal hematopoietic cells. Radiobiologically relevant levels of hypoxia are unlikely in the hematopoietic compartment. Repopulation is not likely to influence hematopoietic cell survival, given the short duration of most TBI regimens (1 to 5 days), although given the variable life span of leukocytes (days to years), it may be of some relevance. Redistribution would appear to be of significance, given the time scale for TBI; however, this has been difficult to assess.[49]

The radiobiology of malignant hematopoietic cells has been described. The D_0 of leukemic cells generally ranges from 0.8 Gy to 1.5 Gy; however, compared with normal hematopoietic cells, a wider range of radiosensitivities have been described.[50,51] Many have cited the technical nuances and variations in assay technique for this great range.[49,52] Similar to normal hematopoietic cells, their malignant counterparts are thought to demonstrate little sublethal damage repair,[53-57] although split-dose-rate and low-dose-rate experiments have demonstrated the capacity of leukemic cells to repair radiation-induced damage.[58-64] Generally, leukemic cells are thought to have a cell survival curve with a minimal shoulder or no shoulder, although this varies across cell types and cell lines.[47,61-63,65] For example, Cosset et al[52,66] summarized preclinical and clinical findings, concluding that AML demonstrates

little repair, whereas CML does demonstrate repair; ALL, myeloma, and lymphomas have not been well studied but appear to demonstrate a wide range of repair capacity.

Similar to normal hematopoietic cells, reoxygenation is unlikely to be radiobiologically relevant to malignant hematopoietic cells during TBI. Redistribution and repopulation, however, may be relevant but have not been systematically studied. Recent molecular studies suggest a significant effect of TBI on peripheral blood mononuclear cell immune-related gene expression in patients.[67]

In vivo preclinical research laid the foundation for the first successful HSCT in humans. Studies in rats,[68] dogs,[69] and nonhuman primates[70] demonstrated that reconstitution of the hematopoietic system was possible after TBI with supralethal doses of radiation. Later work in animals revealed that delivering TBI in several fractions required a higher total dose relative to the biologically isoeffective dose given in a single fraction.[71,72] Another model demonstrated no significant difference in the effect of a low-dose-rate (0.04 Gy/minute), single-fraction of TBI compared with a hyperfractionated course of TBI given three times a day to the same total dose.[73]

Although the hematopoietic system is the target of TBI, normal tissues effectively limit the dose that can be safely delivered. The sparing of normal tissues with fractionated TBI was proposed by Peters et al[53,54] and was subsequently supported by preclinical data in mice[74,75] and dogs[76] that showed that less lung injury occurred with fractionated TBI regimens.

IMMEDIATE TOXICITY AND MANAGEMENT IN TOTAL BODY IRRADIATION

Although a good deal of what has been learned about the acute in vivo biologic effects of TBI has been derived from laboratory-based animal studies, whole-body irradiation also has been studied in people exposed during accidental or wartime nuclear events.[77,78] These large-scale studies are valuable because they deal with apparently normal subjects; however, the retrospective nature limits the quality of the data. The reader is referred to several excellent reviews of acute and fatal radiation syndromes (gastrointestinal, hematopoietic, and cerebrovascular syndromes) that can be caused by TBI in an uncontrolled setting.[79-81]

Acute side effects of therapeutic TBI can be difficult to distinguish from other HSCT-related morbidities. However, Chaillet et al[82] conducted an informative prospective clinical study of the symptoms and signs that occur in patients after TBI, before the initiation of any other HSCT-related therapy. Thirty-one patients, 4.5 to 55 years of age, were treated using parallel-opposed anteroposterior 18-MV photons from a linear accelerator. Shielding was used to limit the lung dose to 8 Gy. A total dose of 10 Gy was given as a "single dose" as six discrete fractions of 1.6 Gy each given over 15 minutes, with a 30-minute break between fractions, for a mean dose rate of 0.04 Gy/minute and an instantaneous dose rate of 0.11 Gy/minute to 0.12 Gy/minute. Symptoms and signs were assessed regularly during the 4-hour TBI and for 20 hours after the completion of TBI. Antiemetics, but no chemotherapy or steroids, were given before the start of TBI. Table 18-1 displays the symptoms and signs experienced by patients during the 4 hours of TBI and within 24 hours of starting TBI. Fever was a common finding, and a maximum of 40.8° C (105.4° F) was noted in one patient. Tachycardia frequently paralleled febrile episodes; a maximum rate of 130 beats/minute was noted. Drowsiness was noted only in patients who received sedating antiemetics. Parotid gland pain was common, and bilateral parotid swelling was noted in 29% of patients. Marked lacrimation was noted in 6% of patients, whereas 16% of patients experienced ocular dryness. Two patients experienced mild conjunctival edema. Hypertension was noted only during TBI. The results of a similar study conducted by Buchali et al[83] of patients who were treated with a fractionated course of TBI delivered mostly to a total dose of 12 Gy using 2 Gy per

TABLE 18-1 Signs and Symptoms in Patients after Single-Dose or Fractionated TBI

	Single-Fraction TBI		Fractionated TBI
Symptom/Sign	Percentage of Patients Experiencing during TBI	Percentage of Patients Experiencing after TBI	Percentage of Patients Experiencing during 3 Days of TBI
Nausea	90	45	43
Vomiting	80	23	23
Parotid gland pain	26	74	6
Xerostomia	61	58	30
Headache	42	33	15
Fatigue	N/R	N/R	36
Ocular dryness	None	16	N/R
Esophagitis	N/R	N/R	4
Loss of appetite	N/R	N/R	16
Indisposition	N/R	N/R	25
Erythema	None	None	41
Pruritus	None	None	4
Diarrhea	None	None	4
No symptoms	N/R	N/R	17
Fever (>38° C)	42	97	N/R
Hypertension	42	None	N/R

Data from Chaillet MP, Cosset JM, Socie G, et al: Prospective study of the clinical symptoms of therapeutic whole-body irradiation. Health Phys 64(4):370–374. 1993; Buchali A, Feyer P, Groll J, et al: Immediate toxicity during fractionated total body irradiation as conditioning for bone marrow transplantation. Radiother Oncol 54(2):157–162, 2000.

N/R, *Data not reported;* TBI, *total body irradiation.*

fraction, twice daily, 8 hours apart, with lung doses limited to 10 Gy, are also summarized in Table 18-1.

A prospective clinical study showed that fractionation of TBI can reduce acute nausea, vomiting, mucositis, diarrhea, and parotitis, although the differences were not statistically significant. Late cutaneous eruptions were more common in patients undergoing fractionated TBI, although the numbers were not statistically significant. The same study, which randomized patients to either high- or low-dose rate TBI, revealed no differences in the acute toxicities mentioned when comparing dose rate.[84] Another randomized controlled trial (RCT) reported that fractionating TBI revealed "no apparent difference in acute toxicity" compared with single-fraction TBI, with both regimens being "well-tolerated."[85]

Older studies cite nausea and vomiting as frequent side effects of TBI. These symptoms have been substantially lessened with the advent of more effective antiemetics, such as the 5-hydroxytryptamine (serotonin) receptor-3 (5-HT3) antagonists. Several small but high-quality controlled clinical studies support the prophylactic use of 5-HT3 antagonists to reduce nausea and vomiting during TBI[86-90]; they are summarized in eTable 18-1. The use of corticosteroids in conjunction with 5-HT3 antagonists is supported by a trial listed in eTable 18-1. However, given the toxicity associated with this approach, consensus regarding routine administration in conjunction with TBI is lacking.[91-93] Of note, less nausea and vomiting have been noted in myeloablative conditioning regimens involving TBI compared with those that use chemotherapy alone, even with modern antiemetics.[94]

Oral mucositis is a side effect of TBI in up to 75% of patients undergoing myeloablative TBI, causing mouth pain and odynophagia and necessitating intensive supportive care such as total parenteral nutrition and opioid analgesics.[95] In one study, intensive dental hygiene conferred a reduction in the rate of moderate and severe mucositis, although the authors thought the rate to be clinically insignificant.[96] Topical oral agents, such as chlorhexidine digluconate and neutral calcium phosphate in conjunction with topical fluoride treatments can decrease pain duration and severity of oral mucositis, as well as pain and need for opioid analgesics.[97-99] Similarly, prophylactic oral sucralfate and clarithromycin have reduced moderate and severe oral mucositis rates.[100,101] One study showed that when given prophylactically, amifostine limited the duration of mucositis, with an associated decrease in the rate of moderate and severe infections, with no effect on HSCT outcome.[102] Low-level laser (650 nm) therapy has been reported to reduce the incidence of oral mucositis in a RCT.[103]

In one study, researchers noted that short-term intravenous recombinant granulocyte-macrophage colony–stimulating factor decreased rates of moderate to severe mucositis,[104] but in another study, no effect was found when this agent was delivered topically.[105] Recently, Spielberger et al[106] reported the results of a trial of the recombinant human keratinocyte growth factor palifermin, given before and after conditioning with 12 Gy of fractionated TBI. Palifermin reduced the rate and duration of moderate and severe mucositis by 35% and 3 days, respectively, and decreased mouth and throat pain, as reflected in reduced morphine usage and decreased need for total parenteral nutrition (by 24%). This study dealt only with patients undergoing autologous HSCT; however, in the setting of TBI for allogeneic HSCT, palifermin may also confer a protective effect on the mucosa, although studies suggesting this have been small and inadequately designed.[107]

Skin erythema may also be noted toward the end of a course of TBI; desquamation is rare. Hyperpigmentation may be noted in the long term. Alopecia typically occurs 7 to 14 days after TBI, and hair typically returns 3 to 6 months after treatment.[108] Changes in the color or texture of regrown hair have been noted. Of note, myeloablative conditioning regimens using chemotherapy alone have produced a significantly higher incidence of permanent alopecia.[109]

LATER TOXICITY AND ITS MANAGEMENT IN TOTAL BODY IRRADIATION

Hematopoietic Toxicity

As previously mentioned (see Radiobiology section), the hematopoietic system is particularly sensitive to TBI, and lymphopenia is often seen with doses of 0.5 Gy and can be seen with doses of 0.3 Gy. Lymphopenia is typically followed by neutropenia, thrombocytopenia, and finally anemia. Soon after a TBI dose of 4 Gy to 6 Gy has been given, lymphocytosis can be seen, but it typically is followed by neutropenia within 1 week. Three to 4 weeks after TBI, neutrophils fall to their minimum[110] (Figure 18-3). Regeneration of the HSC compartment depends on the total dose used because higher doses cause more rapid myelosuppression of greater duration. Administration of hematopoietic growth factors after TBI have the theoretical potential to alter hematopoietic system reconstitution, although reports in the setting of allogeneic HSCT have demonstrated an increased risk of GVHD and compromised survival,[111] and therefore, routine use is controversial.[112,113] Of note, hematopoietic growth factors have only been used in the period following TBI, given the concerns raised by a trial in lung cancer, where growth factors increased pulmonary toxicity and thrombocytopenia when given concurrently with chemoradiation therapy.[114]

Oral Toxicity

As noted before, the salivary glands frequently are affected by TBI. Although acute parotitis is typically self-limited and can be managed with antiinflammatory medicines, long-term salivary gland dysfunction can result in xerostomia, which may lead to dental caries. In a study of children who underwent allogeneic HSCT, the risk of developing impaired salivary function was 22% in those who received TBI as part of conditioning versus 1% in those who did not.[115] Salivary flow can improve up to 1 year after the completion of TBI.[116] Fractionated TBI was shown to reduce salivary dysfunction by 54% in one study.[117]

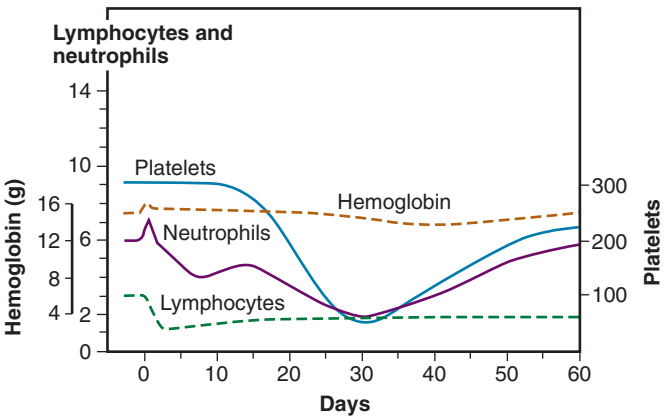


Figure 18-3 Representative hematologic response to total body irradiation, given as a single fraction of 200 cGy on day 0.
Data from Andrews GA: Radiation accidents and their management. Radiat Res Suppl 7:390–397, 1967; Figure 1, with permission from Radiation Research Society.

eTABLE 18-1 Randomized Controlled Trials of Prophylactic Antiemetics in Patients Undergoing TBI

Author	No. Patients	Total TBI Dose/ No. Fractions	Experimental Antiemetic	Control of Antiemetic	Outcome
Tiley et al.[86]	20	10.5 Gy/1	8 mg oral ondansetron at start of TBI + standard (metoclopramide, dexamethasone, lorazepam)	Placebo + standard (metoclopramide, dexamethasone, lorazepam)	Significantly fewer emetic events with ondansetron (60% vs. 10%, $p < 0.03$) during TBI
Spitzer et al.[87]	20	13.2 Gy/11 (in 4 days)	8 mg oral ondansetron 1.5 hr before TBI tid	Placebo	Significantly more patients had two or fewer episodes of emesis with ondansetron (60% vs. 10%, $p < 0.03$): significantly longer time to first emetic episode ($p < 0.005$) and significantly fewer episodes of emesis during the first 24 hours and over the entire study period ($p < 0.05$) with ondansetron
Prentice et al.[88]	30	7.5 Gy/1	3 mg IV granisetron 1 hr before TBI	Metoclopramide, dexamethasone, and lorazepam 1 hr before TBI	Significantly higher rates of complete control of emesis within first 24 hr with granisetron (53% vs. 13%, $p = 0.02$) and significantly longer duration of emesis control ($p < 0.005$) with granisetron
Okamoto et al.[89]	58	74% of patients received TBI: 6-12 Gy/1-6	40 μg/kg IV granisetron twice daily 30 min before TBI	Various	Significantly higher rates of complete control of emesis within the first 24 hr with granisetron (92% vs. 44%, $p < 0.01$) and throughout the duration of HSCT (68% vs. 0%, $p < 0.001$) with granisetron in patients receiving TBI
Matsuoka et al.[90]	50	64% of patients received TBI: 12 Gy/4-6	4 mg IV dexamethasone + 40 μg/kg granisetron bid 30 min before treatment	40 μg/kg IV granisetron twice daily 30 min before treatment	Significantly higher (100% vs. 63%. $p = 0.02$) rates of complete emesis control within the first 24 hr with dexamethasone in patients receiving TBI; insomnia, headache, flushing, and hyperglycemia were more common in patients with corticosteroid

TBI, *Total body irradiation.*

Myeloablative conditioning regimens with and without TBI have been associated with abnormalities in tooth development in children.[117-119] In one series, myeloablative conditioning regimens using chemotherapy alone were associated with significantly higher rates of tooth developmental abnormalities than those involving TBI, although rates of salivary gland dysfunction were highest among the patients treated with single-fraction TBI.[120] Because of the increased risk of oral pathology associated with TBI, careful pretransplant evaluation by a dental specialist is recommended to minimize the risk of serious morbidity.[121] Pilocarpine has been noted to help relieve symptoms of xerostomia in patients treated with TBI.[122]

Pulmonary Toxicity

The major dose-limiting toxicity of TBI is pneumonopathy (restrictive or obstructive lung disease), which can manifest early as pneumonitis or later as pulmonary fibrosis. In the setting of HSCT, radiation pneumonopathy can be difficult to distinguish from other causes of lung pathology; moreover, lung damage is likely multifactorial, with the risk of acute lung complications estimated to be 30% to 60%, depending on factors such as infection, conditioning regimen, GVHD, age, and diagnosis.[123] Likewise, late pneumonopathy occurs in 10% to 26% of patients and is associated with underlying lung dysfunction, type of conditioning regimen, acute and chronic GVHD and prophylaxis, donor and recipient age and immunocompatibility, stage of disease, and genetic predisposition.[124] TBI is a risk factor for idiopathic pneumonia syndrome,[125] as well as for diffuse alveolar hemorrhage.[126] Although rates of pneumonopathy in patients receiving TBI vary widely (10% to 84%),[127] some series have reported pneumonitis in up to 20% of patients undergoing HSCT who never received TBI.[128] In the modern era, with appropriate TBI techniques, the risk of pneumonopathy in patients treated with TBI may not be increased at all.[129] Nevertheless, the significance of the problem is clear, given that mortality related to interstitial pneumonitis in patients treated with TBI can be 60% to 80%.[128,130,131]

Several TBI-specific factors (e.g., total dose, fractionation, dose rate, and use of lung shielding) have been shown to have a significant bearing on the development of pulmonary complications. The total dose used during TBI has frequently been cited as a major factor influencing lung complications.[127,132,133] In two prospective RCTs using 12 Gy versus 15.75 Gy, higher rates of mortality were noted within the first 6 months in patients treated with 15.75 Gy, although pulmonary complications were not specifically cited as the cause of excess deaths.[134-137] In a retrospective dosimetric study, a mean lung dose of more than 9.4 Gy was found to be an independent predictor for lethal pulmonary complications in patients receiving TBI to a total dose of 10 Gy in three daily fractions, at 0.055 Gy/minute using parallel opposed lateral fields.[138] Two RCTs have demonstrated that fractionated TBI can reduce pneumonitis compared with single-fraction TBI, although only one study showed differences that were statistically significant.[85,139,140] A retrospective study found no difference in pneumonitis rates when comparing a single fraction of 6 Gy and three daily fractions of 3.33 Gy, suggesting that total doses of less than 10 Gy may not require fractionation to prevent toxicity, although no randomized data support this.[141] The necessity of hyperfractionation to prevent lung toxicity is unclear: A comparison of two prospective single-arm trials at the same institution revealed that conventional fractionation given with anteroposterior fields and lung blocks to a total dose of 12 Gy in daily three-Gy fractions may not be any different than hyperfractionated TBI given twice daily with 1.7 Gy per fraction to a total dose of 10.2 Gy over 3 days, using parallel opposed lateral fields and no blocks.[142] An RCT suggested that the angiotensin-converting enzyme inhibitor, captopril, may mitigate pulmonary toxicity associated with TBI.[143]

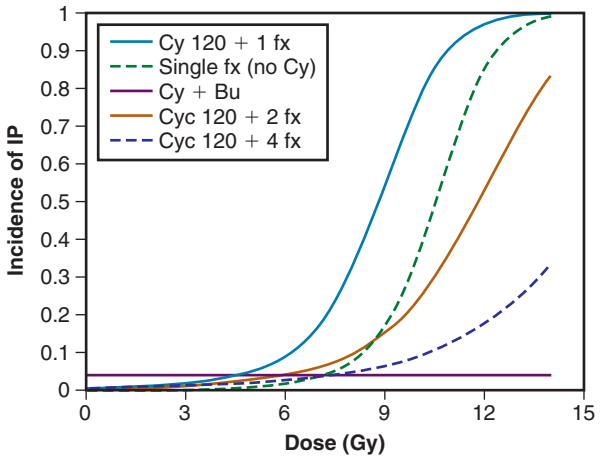


Figure 18-4 Incidence of pneumonitis based on dose-response model accounting for TBI fractionation, as well as chemotherapy effects. *Bu*, Busulfan; *Cy and Cyc*, cyclophosphamide; *fx*, fraction(s). *Data from Sampath S, Schultheiss TE, Wong J: Dose response and factors related to interstitial pneumonitis after bone marrow transplant. Int J Radiat Oncol Biol Phys 63(3):876–884, 2005; Figure 2, © 2005, Elsevier, with permission from Elsevier.*

Sampath et al[144] reviewed 26 studies involving 1096 patients to create a dose-response model for predicting the risk of pneumonitis from TBI while taking other factors into consideration. Although unable to estimate the risk of pneumonitis for hyperfractionated regimens, they were able to determine the effect of fractionation, cyclophosphamide, and busulfan on the risk of developing pneumonitis, in a dose-response model, as seen in Figure 18-4.

Pneumonitis rates were not significantly different in a trial that randomized patients to high- or low-dose-rate TBI.[84] However, there is an abundance of retrospective clinical data suggesting that lowering the dose rate (<0.025 to 0.09 Gy/minute) does decrease the likelihood of pulmonary complications,[127,133,137,145,146] especially if TBI is delivered as a single fraction.[147] If TBI is fractionated, some report that a low dose rate (<0.069 Gy/minute) is not necessary,[131] whereas others found a beneficial effect.[148,149] Studies of patients receiving fractionated TBI with lung shielding have demonstrated a reduction in pneumonopathy[150,151]; however, one RCT found no difference in pneumonopathy rates if the shielding allowed a lung dose of either 6 Gy or 8 Gy in a single fraction.[152]

Pulmonary function tests (PFTs), such as spirometry and diffusion capacity, are often helpful in the assessment of patients with pulmonary symptoms or radiographic abnormalities. Studies of PFTs in patients treated with HSCT have demonstrated a deleterious effect on spirometry and diffusion capacity, which often resolves in the absence of other complicating factors[153-155] and is related to the TBI dose.[156] A retrospective study found that lung shielding had a small but significantly beneficial effect on PFTs 1 year after HSCT, especially in patients with abnormal function before HSCT.[157] In one study, busulfan and not TBI, was associated with a negative effect on PFTs.[158] There is no evidence that obtaining PFTs improve pulmonary outcome after HSCT in adulthood, and for this reason they are not recommended.[159] However, some groups recommend baseline PFTs as part of long-term follow-up care for children treated with TBI.[160] Counseling regarding smoking cessation is of critical importance for all patients, especially those who are at increased risk of developing lung injury. In the event of acute pneumonitis, high-dose

steroids (30 mg to 60 mg of prednisone/day) typically alleviate symptoms within 24 to 48 hours.

Cardiovascular Toxicity

Cardiovascular toxicity in adults as a result of HSCT is relatively rare, given the stringent selection criteria for patients treated with this aggressive therapeutic modality. Nevertheless, in adult patients who survived autologous or allogeneic HSCT, cardiac events were responsible for 2.4% and 3% of deaths, respectively; this represents a greater than expected occurrence.[161,162] Most of the recent literature has identified no association between TBI and the development of cardiovascular disease in adults.[163,164] In several detailed prospective analyses using plasma cardiac troponin and brain natriuretic peptide levels, electrocardiography and echocardiography revealed no evidence of cardiac dysfunction in previously healthy individuals treated with TBI.[165,166] However, a prospective study of children who underwent allogeneic HSCT found a 12% and 26% cumulative incidence of abnormalities in ejection fraction (<30%) on echocardiography before HSCT and 5 years after HSCT, respectively. This study revealed that TBI was associated with abnormalities in cardiac function on univariate analysis but not multivariate analysis; the 5-year cumulative incidence of cardiac abnormality was 26% or 2% in children treated with TBI, with or without prior anthracycline therapy, respectively.[167] Recent data from large studies of survivors of childhood cancer suggest that the risk of cardiac mortality is significantly elevated for children who receive heart doses of 5 Gy, although it should be noted that anthracycline doses of more than 360 mg/m^2 similarly increased the risk.[168] Importantly, the rate of death from recurrence or progression of cancer exceeds the rate of death from cardiac disease by approximately a factor of 7.[169] The reason for excess late cardiovascular toxicity in TBI in children is probably because of the association of TBI with the premature development of cardiovascular disease risk factors (e.g., hypertension, dyslipidemia, diabetes) that result in deleterious consequences rather than direct radiation cardiotoxicity.[170-172] Therefore it is prudent to screen patients who have undergone HSCT for cardiovascular disease risk factors, whether treatment involved TBI, to minimize late morbidity and mortality.

Hepatic Toxicity

Hepatotoxicity from TBI manifests primarily as venoocclusive disease (VOD), also known as sinusoidal obstructive syndrome (SOS), of the liver. This clinicopathologic phenomenon was first described in 1977 by Shulman et al,[173] who noted the onset of weight gain from ascites, painful hepatomegaly, and jaundice from centrilobular liver acinus necrosis 1 to 4 weeks after HSCT. Up to 70% of patients who undergo HSCT can be affected by VOD. TBI, along with many other risk factors, has been implicated in the development of VOD.[174] An RCT and a meta-analysis found that patients treated with busulfan instead of TBI were significantly more likely to develop VOD.[175,176] Two RCTs have concluded that fractionated TBI reduces the incidence of VOD compared with single-dose TBI.[139,140] Another RCT found no difference in the rate of VOD when the dose rate was either 0.06 Gy/minute or 0.15 Gy/minute,[84] although a retrospective study of single-dose TBI found that dose rates of 0.07 Gy/minute were associated with less VOD than dose rates of 0.18 Gy/minute to 1.2 Gy/minute.[177] A TBI dose greater than 13.2 Gy has been reported to be associated with higher rates of VOD on univariate analysis,[178] although a dose greater than 12 Gy was not associated with VOD in another retrospective study.[179] Lawton et al[180] reported a nonstatistically significant 10% decrease in the rate of fatal VOD in patients treated with TBI as part of HSCT when a 10% attenuation liver block was employed. Ursodeoxycholic acid was effective in preventing VOD in an RCT of patients undergoing TBI followed by HSCT,[181] although another RCT did not support this finding.[182] Reduced-intensity conditioning regimens may also prevent VOD. Treatment of VOD can include the fibrinolytic antithrombotic agent defibrotide; decompressing the sinusoids by a transjugular intrahepatic portosystemic shunt and liver transplantation is another, more invasive, option for the management of severe disease.[183]

Visual Toxicity

Cataracts are one of the most common complications of TBI. Patients may present with painless vision loss and may be noted to have opacification of the lens on examination. In one series of patients treated with TBI in one or two fractions, severe visual impairment was noted in about half of patients.[184] This problem has been noted to arise in a large proportion of patients treated with TBI, depending on the total dose, use of fractionation, and the dose rate. When considering risk factors associated with HSCT, steroid use,[185-187] prior cranial irradiation,[188,189] and the development of GVHD[187] have been shown to predispose to cataractogenesis, whereas heparin use appears to be protective.[190]

Delivering TBI in a single fraction is the single biggest risk factor for developing a cataract after HSCT.[190-195] High-dose-rate (>0.035 Gy/minute to 0.048 Gy/minute) TBI also appears to increase the risk of cataract formation.[188,190,193,196] A prospective study that randomized patients to high- or low-dose rate TBI found that the incidence of cataract 5 years after treatment was 12% and 34% in the low- and high-dose rate arms, respectively, with 13% and 39% of the cataracts, respectively, occurring in patients who received fractionated or single-dose TBI.[197] Kal[198] and van Kempen-Harteveld[199] recently reviewed the subject of TBI-induced cataracts and concluded that a biologically equivalent dose of 40 Gy yields a 10% chance of developing cataracts, using linear-quadratic modeling that included corrections for dose rate, with an α/β of 0.65 for late effects on the lens. On the basis of this, they suggest considering lens shielding for single-fraction TBI regimens,[198] although this is controversial in the setting of malignant disease.[199] Given the frequency of cataracts occurring after TBI, patients should be monitored for the development of this complication.[200] Management of cataracts that impair vision or degrade quality of life may involve phacoemulsification and extraction; recent data suggest that these procedures are safe, with an adverse event rate of 0.1% for experienced surgeons,[201] and effective, with a 90% chance of 20/40 vision postoperatively.[202]

Renal Toxicity

Kidney dysfunction occurs in approximately 17% of survivors of HSCT[203] and can manifest in a number of ways, with the most to least frequent syndromes being idiopathic chronic kidney disease, nephrotic syndrome, thrombotic microangiopathy (thrombotic thrombocytopenic purpura and hemolytic uremic syndrome), and acute renal failure.[204] The syndrome most associated with TBI is thrombotic microangiopathy, which can manifest as nephritis, hypertension, proteinuria, or anemia 6 to 12 months after HSCT. HSCT-related risk factors for nephropathy can include GVHD, infections with cytomegalovirus or BK virus, nephrotoxic medications such as cytotoxic chemotherapeutic agents (cytarabine, cyclophosphamide, ifosfamide, cisplatin, retinoic acid, carmustine, actinomycin D, melphalan), antibiotics (acyclovir, ganciclovir, foscarnet, vancomycin, amphotericin, aminoglycosides), and

immunosuppressants (cyclosporine, tacrolimus, methotrexate). The larger and more contemporary studies of chronic kidney disease after HSCT have not demonstrated an association with TBI.[205-209]

Total dose has been implicated as the most important factor in predicting renal morbidity from TBI; a retrospective study found that GVHD and high-dose TBI (13.5 Gy) were associated with elevated serum creatinine levels.[210] A prospective evaluation of renal function using radioisotopes found that early nephropathy was associated with age of younger than 40 years, use of kidney blocks (possibly related to nephrotoxic contrast media given during simulation), and nephrotoxic drug use, whereas late nephropathy was associated with nephrotoxic drug use but not TBI dose.[211] The benefit of kidney shielding has been assessed in two retrospective studies, both of which demonstrated significant improvement in long-term kidney function, with no evidence of dysfunction when the hyperfractionated dose was limited to 9.8 Gy to 10 Gy.[212,213] Two recent dose-effect modeling studies have demonstrated that nephropathy is unlikely after a biologically equivalent total dose of 16 Gy (calculated using a linear quadratic model, with corrections for dose rate and an α/β of 2.5 Gy) and that fractionating TBI and delivery of a low dose rate (<0.10 Gy/minute) prevent kidney dysfunction.[198,214] Monitoring blood chemistry and counts, as well as blood pressure and urine studies, is advised given the prevalence of kidney disease after HSCT.

Although no therapies have been proven to treat HSCT-related nephropathy, medication therapies (antihypertensives, corticosteroids), plasma exchange, hemodialysis, and renal transplant are possible options for management.[204] The angiotensin-converting enzyme inhibitor captopril prevents chronic nephropathy in patients with diabetes[215] and may reduce the risk of radiation nephropathy from TBI in preclinical studies.[216,217] A small RCT in which captopril was given to mitigate chronic renal failure in patients undergoing 12 Gy of fractionated TBI (with a kidney dose of 9.8 Gy) before HSCT revealed less nephropathy; however, the results were not statistically significant.[218]

Endocrine Toxicity

Hypothyroidism is the most common endocrinopathy after HSCT.[219] Most cases are overt and primary in nature, but subclinical and autoimmune thyroid dysfunction have also been noted. Hypothyroidism has been reported in up to 90% of patients after TBI delivered with a single dose of 10 Gy[220] and in up to 15% of patients treated with hyperfractionated TBI to 15 Gy.[221] These findings demonstrate the benefit of fractionation in avoiding this complication. One of the largest studies with a lengthy follow-up of children treated with or without TBI before HSCT revealed that TBI was not a risk factor for developing hypothyroidism when compared with equivalent conditioning with busulfan. In this study, the risk of hypothyroidism was higher in children undergoing HSCT before 10 years of age, and the risk continued to increase until 28 years after HSCT.[222] A recent study demonstrated that reduced-intensity conditioning with lower doses of radiation during TBI was not associated with lower rates of hypothyroidism,[223] suggesting that there is no dose threshold effect. Nevertheless, this complication should be monitored with assessment of thyroid hormones and can be easily managed with thyroid hormone replacement and monitoring.

Gonadal and reproductive endocrine functions can be altered by HSCT and TBI, as reviewed by Chemaitilly and Sklar.[219] In males, Leydig cell function is typically preserved, given the dose of radiation delivered during full-dose TBI.[224] However, in patients who have received prior testicular radiation or who will have a testicular boost during conditioning, Leydig cell function may be threatened. Germ cells are typically thought to be exquisitely sensitive to radiation. A recent study demonstrated that fertility is significantly reduced among boys treated with a radiation dose of more than 7.5 Gy to the gonads, although it should be kept in mind that other antineoplastics, such as alkylating agents, also profoundly reduce fertility.[225] Although there have been case reports of men being treated with TBI and later having children, most men are rendered sterile by HSCT with full-dose TBI; most will experience azoospermia with reduced-dose TBI, but some may also be rendered sterile. With this in mind, male patients should be counseled regarding gamete cryopreservation before initiation of therapy. Likewise, postpubertal women are likely to experience ovarian failure as a result of intensive conditioning, including TBI, and should be counseled about this before treatment. However, about half of prepubertal girls who are treated with fractionated TBI will experience normal reproductive development.[226] As reviewed by Schmidt et al,[227] several fertility-preserving options may be available to women who wish to bear children after HSCT. In a longitudinal prospective study, TBI was reported to be associated with worse sexual functioning among men (but not women) who underwent HSCT.[228]

Hypothalamic-pituitary function appears to be unaffected by TBI of adults to doses of 12 Gy.[229] However, if additional brain radiotherapy is delivered, this complication could be encountered. Growth dysfunction may be caused by TBI through a variety of mechanisms, including growth hormone deficiency and skeletal dysplasia; other factors, including GVHD, liver dysfunction, and busulfan-based conditioning, may also contribute. Younger patients are more likely to be affected by growth impairment. In addition, children treated with single-fraction TBI (as opposed to fractionated TBI) are more likely to experience growth impairment.[230] Growth hormone replacement therapy has been recommended to correct this deficiency,[231] although RCTs have not shown proven benefit[232] and treatment is associated with significant toxicities.

Bone Toxicity

Bone health is another concern after HSCT. Although TBI has been shown to be a risk factor for avascular necrosis of bone,[233] a prospective study found no association between bone metabolism and conditioning with TBI; corticosteroid use is probably the major factor in HSCT causing bone health problems.[234] Monitoring bone health with growth assessments, biochemical hormone assessments, and dual-energy x-ray absorptiometry (DEXA) scans is appropriate, and consideration of counseling, weight-bearing exercise, and use of calcium and vitamin D supplementation or antiresorptive agents (bisphosphonates) should be given in patients with evidence of abnormalities.

Nervous System Toxicity

Mild to moderate neurocognitive impairment has been noted in up to 60% of adults undergoing HSCT with TBI.[235] However, these findings have not been consistent, and several studies have documented no impairment at all.[236,237] As recently confirmed in a prospective multicenter study,[238] TBI-based conditioning (compared with non–TBI-based conditioning) has not been associated with neurocognitive impairment in adults who received full-dose[239] or reduced-intensity conditioning.[240] Children treated with TBI may experience mild neuropsychologic effects.[241] The effects are more prominent in young children,[242] especially those younger than 3 years of age.[243] Similar to adults, no difference in neurocognitive function has been

associated with TBI and non–TBI-based conditioning regimens in older children.[244] However, in young children, TBI-based regimens appear to exert more of a negative effect than non–TBI-based regimens.[245] The magnitude of the deficit has been described as statistically, but not clinically, significant (i.e., a deficit of 3 points in IQ) in recent investigations.[246]

Beyond generally mild cognitive effects of TBI on the nervous system, other types of toxicity are rare. Myelopathy is uncommon, but it has been reported to occur with TBI in conjunction with involved radiation therapy fields, even at cumulative doses considered to be "tolerable" (e.g., 45 Gy).[247] Similarly, severe and fatal neurologic toxicity was reported in a series of children treated with TBI and was generally associated with prior whole-brain radiotherapy to 18 Gy; therefore the cumulative radiation dose in this approach must be considered carefully.[248] Other neurologic toxicity has not been associated with TBI in adults[249] or children.[250]

Risk of Secondary Malignant Tumors

Beyond organ-specific toxicities, the risk of developing secondary malignant neoplasms is increased in patients who have undergone HSCT. Typically, three groups of secondary malignant neoplasms after HSCT are described, and they follow a distinct pattern of development[251] (Figure 18-5): myelodysplastic disease (MDS) and acute myelogenous leukemia (AML), posttransplant lymphoproliferative disorder (PTLD), and solid tumors.[252] There are multiple risk factors that may predispose a patient to the development of a secondary malignant tumor after HSCT, including, but not limited to, genetic aberrations, therapy given before HSCT, conditioning regimen, graft source and processing, posttransplantation immunosuppression, and GVHD[38]; only the association of TBI with secondary malignant neoplasms will be discussed here.

Secondary MDS or AML after HSCT has been reported to occur at rates between 1.1% at 20 months and 24.3% at 43 months. The World Health Organization classifies secondary MDS and AML as alkylating-agent or radiation-related disease, typically occurring 4 to 7 years after treatment, or topoisomerase-II inhibitor–related disease, typically occurring 6 months to 5 years after treatment.[253] Several studies have attempted to quantify the risk of developing secondary MDS or AML after undergoing TBI, with conflicting results. Studies from research groups from Minnesota,[254] Newcastle,[255] the City of Hope,[256] and France[257] have demonstrated no increase in rates of MDS or AML after myeloablative HSCT using TBI. Other studies from Nebraska,[258] the European Group for Bone Marrow Transplantation (EBMT),[259] Paris,[260] Barcelona,[261] and France[262] have found weak associations of borderline or no statistical significance. One study found an association of secondary MDS or AML with TBI on multivariate analysis when TBI was used with etoposide and cyclophosphamide.[263] A recent, detailed study of this subject found that among 4000 patients treated with autologous HSCT for lymphoma, 57 developed MDS or AML, with a cumulative incidence rate of 3.7%, 7 years after HSCT. A case-control analysis revealed a weak association of TBI and the subsequent development of MDS or AML that was not statistically significant. In a small subgroup analysis, a TBI dose of 13.2 Gy was associated with MDS or AML, but the authors cautioned that this group of patients may have shared other non–TBI-related factors that could have contributed to leukemogenesis. Older age also appeared to increase the risk.[264] The dose threshold effect was not supported by a more recent study that found no differences in the rate of MDS or AML after TBI, whether 12 Gy or 14 Gy of TBI was given.[265]

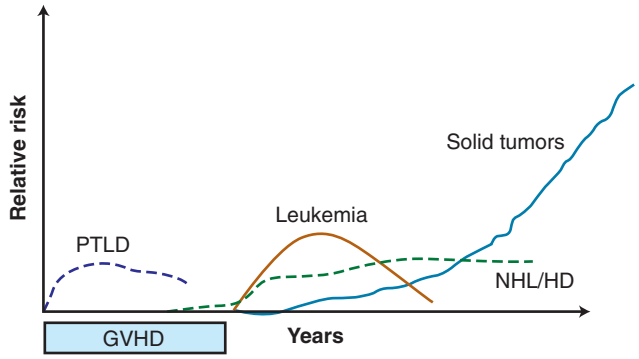


Figure 18-5 Relative risk and chronology of second malignant tumors after allogeneic hematopoietic stem cell transplant (HSCT). *GVHD*, Graft-versus-host disease; *HD*, Hodgkin disease; *NHL*, non-Hodgkin lymphoma.
Data from Ades L, Guardiola P, Socie G: Second malignancies after allogeneic hematopoietic stem cell transplantation. New insight and current problems. Blood Rev 16(2):135–146, 2002; Figure 1, © 2005, Elsevier, with permission from Elsevier.

The association of TBI with the subsequent development of a PTLD has been described in several studies. Because it is thought to result from immune system dysfunction, PTLD occurs primarily in patients following allogeneic, not autologous, HSCT. The cumulative incidence of PTLD at 12 years varied by the number of risk factors the patient had and ranged from 0.2% to 8.1%.[266] Small early studies from Seattle[252] and the Center for International Blood and Marrow Transplant Research (CIBMTR)[267] suggested an association between TBI use during HSCT and subsequent development of a PTLD. However, later research from Minnesota,[254] Vancouver,[268] and Nebraska[269] suggested no association between TBI and PTLD. A follow-up study from the CIBMTR, the largest and most comprehensive study available, involving 26,000 patients who underwent allogeneic HSCT over a 30-year period, clearly demonstrated no association between PTLD and TBI, in contrast to their previous findings.[266]

The risk of solid tumors after HSCT involving TBI has been studied extensively.[270-280] The largest and most recently updated analysis from the CIMBTR suggests that among patients who undergo allogeneic HSCT, the cumulative incidence of developing a solid malignant tumor (including carcinomas in situ that are not of the skin) is 1%, 2.2%, and 3.3% at 10, 15, and 20 years after transplant, respectively, based on the competing risk analysis method.[281] The number of secondary solid tumors was double what would have been expected in this population; significantly higher rates of oral cavity and pharyngeal, liver, central nervous system, thyroid, bone, and soft-tissue cancers and melanomas were observed. TBI was found to be a risk factor for developing a secondary solid tumor, with the risk increased in those who survived more than 5 years from the HSCT and in those younger than 30 years old at the time of HSCT. Although a previous study found that TBI doses of less than 10 Gy were associated with fewer secondary solid tumors,[270] this dose association was not maintained in the subsequent analysis.[281] There was no difference in the rate of secondary solid tumors in patients treated with fractionated or single-dose TBI. There was no increased risk of squamous cell carcinomas in patients treated with TBI and no increased risk of secondary solid tumors in patients treated with TBI after age 30. Chronic GVHD and male sex were associated with the development of secondary solid tumors and squamous cell carcinoma, respectively.[281]

Given the increased risk of secondary malignant neoplasms after TBI, careful surveillance of long-term survivors is a desirable (but not yet proven effective) strategy for minimizing secondary morbidity and mortality. Guidelines published by

the American Cancer Society,[282] the National Comprehensive Cancer Network (NCCN; www.nccn.org), and the Children's Oncology Group[160] provide important references regarding assessing patients at higher risk of developing a secondary solid tumor.

PHYSICAL PRINCIPLES OF TOTAL BODY IRRADIATION

Although irradiating the entire body may seem like a simple exercise, TBI is a highly specialized technique fraught with unique challenges. Nevertheless, the physical aspects of TBI have not changed significantly over the last three decades. The American Association of Physicists in Medicine (AAPM) Report 17, Task Group 29, "The Physical Aspects of Total and Half Body Photon Irradiation," is still considered the authoritative reference for methodology and recommendations regarding the physical aspects of TBI.[283] More recently, the American College of Radiology created a practice guideline for TBI treatment delivery.[284] The reader is referred to these resources and others[285] for detailed information on this subject.

As with all radiotherapeutic techniques, TBI requires meticulous attention to the details of patient measurement, set-up, dosimetry, and quality assurance. Among institutions that perform TBI, most have a dedicated and specially trained team of physicians, dosimetrists, physicists, and therapists who participate in successful implementation because the technique is quite different than typical external beam radiation therapy. Backup systems are essential given the critical time- and situation-dependent nature of HSCT. Readers intending to develop a TBI program are encouraged to contact and learn from centers that have experience with the technique.

Comparison of Techniques of Total Body Irradiation

A report from 1980 highlighted several approaches that have been explored in TBI.[286] The common factor in the different ways of delivering TBI is the goal, which is to deliver the prescribed dose of ionizing radiation to the entire body in a uniform manner (±10% of the prescription dose). An opposed-parallel anterior-posterior (AP/PA) horizontal field setup was developed at Memorial Sloan-Kettering Cancer Center (MSKCC) many years ago.[287] In this technique, the patient is positioned upright several meters from the source with the support of a custom-designed stand. In this technique, high-energy photons are used to increase dose homogeneity although high-energy photons will reduce the dose in superficial structures (skin and subcutaneous tissues), and therefore a beam spoiler is used to increase the surface dose. The beam spoilers are affixed to the stand, which can also accommodate blocks for shielding, imaging equipment for field and patient position verification, and placement of dosimeters (Figure 18-6). When using shielding, compensatory electron boosts can be delivered to superficial tissues such as those of the chest wall (Figure 18-7).

An alternative to the AP/PA field arrangement is a lateral field arrangement, pioneered by Khan.[288] In this approach, the patient is able to recline in a comfortable position during treatment, typically with the knees drawn toward the chest and the arms by the side. As with the AP/PA technique, the patient is typically positioned several meters from the radiation source and the arms can provide shielding to the lungs from the lateral beams. However, as the lateral body thickness is quite disparate over the head-to-toe length of a patient, compensators (usually fixed to the gantry head) will often be required to reduce the dose to the head, neck, and legs. Positioning with this technique is critical; therefore performing and confirming several measurements as well as determining symmetry using in-room light fields and lasers are essential.

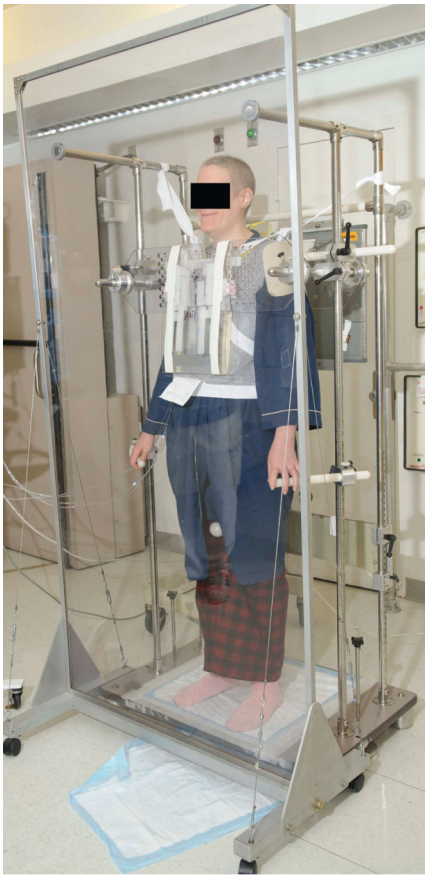


Figure 18-6 Patient in position for total body irradiation using anteroposterior beam arrangement, with lung blocks in place.

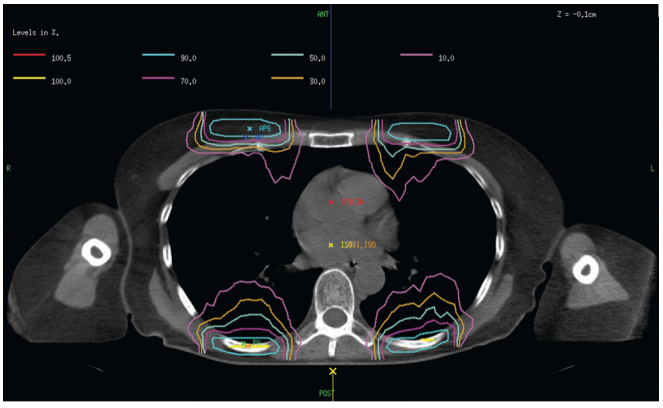


Figure 18-7 CT axial section demonstrating electron-boost dose distribution.

Although the AP/PA and lateral field arrangements are the most commonly employed TBI techniques, other methods exist. Children undergoing TBI may require conscious sedation during radiation therapy, making the previously described techniques impossible. In this situation, TBI can be delivered with the child lying on or near the floor with the gantry pointed down. The child's smaller body size often will facilitate this arrangement; however, in larger children it may be necessary to match two fields. An alternative would be

translating the patient or radiation source during treatment.[287] Logistic considerations largely prohibit this type of approach.

In recent years, several novel approaches to delivering radiation therapy to the entire body have been described. One of these approaches involves rotational intensity-modulated radiation therapy (delivered by a TomoTherapy unit). This approach appears dosimetrically advantageous because it could allow targeting and radiation dose escalation in the bone marrow, and for this reason, it is often referred to as total marrow irradiation (TMI).[289] Early phase clinical trials suggest the technique is tolerable.[290,291] However, sparing the circulating hematopoietic cells from radiation therapy might defeat the purpose of delivering radiation to the entire body. Another approach of delivering systemic radiation therapy is using radionuclides conjugated to monoclonal antibodies, commonly referred to as radioimmunotherapy, instead of external beam radiotherapy. The feasibility of this concept has been demonstrated by several groups, with encouraging results in allogeneic[292,293] and autologous HSCT.[286,287] The uncertainty in biodistribution and clearance of this form of radiotherapy is the major drawback.

Because there are no clinical data to suggest that one technique is advantageous over others, dosimetric benefits have largely dominated the choice of which TBI method to use. Because the AP/PA TBI technique is employed most frequently and is preferred under most conditions, the remaining discussion will focus on its application.

Simulation and Planning for AP/PA Total Body Irradiation

Patients undergoing TBI should be simulated in the treatment position, which is often most easily reproduced in the treatment room. For AP/PA TBI, height must be measured to ensure that the field will adequately encompass the entire patient; exceptionally tall patients might need to sit on the seat of the treatment stand. Other measurements of the AP thickness at the suprasternal notch, chest, abdomen, and pelvis are performed for dosimetric calculations.

While the patient is in the treatment position, radiographs of the thoracic cavity can be obtained to create lung shielding or other blocks. Careful attention should be paid to the size of the blocks so that they are produced in a manner proportional to the treatment field size and distance from the source; this often requires a magnification correction factor. For example, lung shielding is typically designed so that block edges are 1 cm to 2 cm from the bony thoracic periphery, diaphragm, and vertebral bodies. When shielding is used, some institutions choose to perform compensatory electron boosts matched to the blocks. In these situations, computed tomography (CT) can be helpful for planning purposes (Figure 18-7), although the obvious limitation is that CT cannot be performed when the patient is in the treatment position. Alternative imaging modalities (e.g., ultrasound) performed in the treatment position may be helpful in specific situations (e.g., chest wall boosts in patients with large, pendulous breasts).

Beam Energy, Angling, and Production

A wide variety of beam energies have been used for TBI. Most radiation oncology departments now use linear accelerators to generate ionizing radiation, although it should be noted that ^{60}Co generators, which typically produce lower-energy photons than linear accelerators, were the source for many of the early clinical studies. As noted previously, higher beam energies will achieve a more uniform dose distribution but may provide doses lower than desired to superficial structures, so beam spoilers may be needed. The thickness of the patient along the beam axis is the dominant factor dictating the choice of beam energy; typically, lateral field arrangements require higher beam energies than AP/PA field arrangements; however, this ultimately depends on patient size, beam spoilers, and source-axis distance. The source-axis distance can be up to 5 meters; it will often depend on the size of the treatment room relative to the size of the radiation field (dictated primarily by the size of the patient) and may restrict the application of some specific geometric approaches.

The central axis of the beam should be incident at the umbilicus; this usually requires around 5 degrees of gantry angling. The collimator is usually opened to its maximum size (40 × 40 cm) and is rotated to 45 degrees, maximizing the height of the field. The total dose can be prescribed to any anatomic point, but it is often prescribed in the midplane of the pelvis or at the umbilicus.

Compensation

As higher beam energies will reduce the dose delivered to the superficial structures, beam spoilers are often used. Typically an acrylic screen 1 cm to 2 cm thick is used to produce electrons that should increase the surface dose to at least 90% of the prescribed dose. If required, shielding is affixed to the plastic holder on the beam spoiler and placed using reference marks on the patient. For example, at MSKCC, a half-value layer block is employed for lung shielding. Electronic portal imaging can be used to confirm accurate placement of shields. Electron boost fields matched to the lung shields can also be set up using reference marks on the patient.

Calibration and Quality Assurance

Several groups recommend calibrating the treatment delivery unit for TBI using a dosimeter in a large water tank at the distance that will be used for treatment, in the treatment stand, if possible. Given the extended distance, large field size, and compensators used in this technique, a significant amount of scatter radiation will be produced and must be accounted for during calibration. For this reason, the typical percent depth dose (PDD) or tissue maximum ratio (TMR) measurements used for external beam radiation therapy should not be used for TBI; these measurements must be made specifically for the TBI setup. Moreover, variations in dose based on patient size and dose heterogeneity throughout the body should be anticipated and verified during the calibration process. In vivo dosimetry should be performed at several locations (i.e., along the central beam axis, under shielding blocks, and at distal extremities) to verify accurate dose delivery. Regular quality assurance checks should be undertaken according to AAPM guidelines.

ROLE OF TOTAL BODY IRRADIATION IN CONTEMPORARY HSCT

The role of TBI in HSCT has been refined over the last several decades. High-level evidence guides some of the rationale for using TBI, and in some situations, institutional and practitioner preference dictates the use of the technique. Major questions that have been answered deal with the necessity of using TBI during HSCT, as well as questions regarding dose, fractionation, shielding, and boosting.

Necessity of Using Total Body Irradiation in HSCT Conditioning

Although the earliest studies of HSCT for malignant hematopoietic diseases involved both chemotherapy and

radiotherapy (see History of Total Body Irradiation), in the 1970s several regimens using only chemotherapy (without TBI) were developed, largely for logistic reasons, because facilities adequate for performing TBI were not widely available.[294] Soon thereafter, the availability of conditioning regimens for HSCT *without* TBI (primarily involving busulfan and cyclophosphamide)[295] gave rise to several important clinical studies that investigated the necessity of TBI in HSCT in various hematopoietic diseases.

Acute Myelogenous Leukemia

There have been two RCTs comparing TBI-based conditioning regimens with non–TBI-based conditioning regimens for AML. In 1987, the Groupe d'Etude des Greffes de Moelle Osseuse (GEGMO) initiated a prospective multicenter RCT to evaluate whether TBI could be replaced by busulfan, in an effort to limit toxicity in allogeneic HSCT.[296] A similar single-institution study was initiated at the University of Minnesota, for patients receiving autologous HSCT, but accrual was poor and the study was terminated early.[297] As noted in eTable 18-2, superior rates of overall survival, disease-free survival, and fewer relapses were noted with the TBI conditioning regimen in both trials, with only the French trial demonstrating a statistically significant difference.[296,298] An updated analysis of three trials of allogeneic HSCT for AML that randomized patients to conditioning with or without TBI found marginally significant improvements in overall survival and disease-free survival rates. In patients treated with TBI, the estimated 10-year survival rate was 63%, and in those not treated with TBI, the rate was 51% ($p = 0.068$); patients treated with TBI had a 10-year disease-free survival rate of 57%, and untreated patients had a rate of 47% ($p = 0.051$). On multivariate analysis, TBI was associated with significantly less hair loss and no difference in the rates of GVHD, cataracts, avascular necrosis, or pulmonary complications.[299] A retrospective analysis by the CIBMTR revealed that TBI-based conditioning yielded fewer relapses (especially in extramedullary and central nervous system sites) and less hepatic VOD than busulfan-based conditioning.[300] This topic continues to generate controversy, with recent retrospective analyses of registry data demonstrating no difference in TBI and non-TBI, intravenous busulfan-based conditioning,[301] and other similarly designed observational studies suggesting improved outcomes with non–TBI based regimens.[302,303]

Chronic Myelogenous Leukemia

Two RCTs have compared the efficacy and toxicity of allogeneic HSCT in patients with CML, preceded by conditioning with either TBI with cyclophosphamide or busulfan with cyclophosphamide[305-307] (see eTable 18-2). Both studies showed no significant difference in rates of overall survival, event-free survival, or transplant-related mortality. The French study found more relapses in patients treated with TBI (especially fractionated TBI), but this was not seen in the study from Seattle, which used fractionated TBI exclusively. The Seattle trial did show significantly longer episodes of fever, more blood cultures revealing bacteria or fungi, more hospitalizations in the 100 days after transplantation, and a higher incidence of grades 2 to 4 GVHD in patients treated with TBI. An updated, combined analysis of three studies that randomized patients with CML to different conditioning regimens before allogeneic HSCT confirmed no significant difference in rates of survival (65% and 63%) and disease-free survival (52% and 42%) for patients treated with busulfan and cyclophosphamide or cyclophosphamide and TBI, respectively. There were no differences in the 5-year cumulative incidence of chronic GVHD (37% and 39%). However, cataracts were more common among patients treated with TBI.[299] Retrospective data also suggest that busulfan-cyclophosphamide–conditioning regimens before allogeneic HSCT for CML may be favored because of lower relapse rates,[308] although higher rates of GVHD, hepatotoxicity, and hemorrhagic cystitis have been reported with chemotherapy alone.[309]

Acute Lymphoid Leukemia

The Pediatric Blood and Marrow Transplant Consortium conducted the only RCT comparing the effect of preallogeneic HSCT conditioning using busulfan or TBI, in children with ALL. A central nervous system boost of 6 Gy was given to patients with a history of prior central nervous system disease but no prior central nervous system irradiation if randomized to TBI; if randomized to busulfan, patients with a history of central nervous system disease received 18 Gy of central nervous system radiation therapy before receiving busulfan. The study showed no difference in overall survival rates; however, longer event-free survival times were noted for patients treated with TBI. Patients 6 years old or younger, as well as those in their first complete remission, appeared to experience the most benefit from the TBI regimen.[310] A retrospective study by Davies[311] using the CIBMTR data of 627 children with ALL who underwent HSCT after conditioning with cyclophosphamide and TBI (CY/TBI) or busulfan and cyclophosphamide (Bu/CY) found that the risk of relapse was not significantly different in the two cohorts. However, the risk of treatment-related mortality was significantly greater in the Bu/CY group. The use of CY/TBI was associated with superior rates of overall survival and leukemia-free survival. Based on these data, the authors concluded that less treatment-related mortality in the CY/TBI group led to greater rates of overall survival and leukemia-free survival. A multivariate analysis of adults with ALL who underwent HSCT preceded by conditioning with fractionated TBI to 12 Gy (lung dose of 9 Gy) or busulfan found that shorter times of event-free survival and disease relapse were more likely among patients who did not receive TBI on multivariate analysis. There were no differences in the rates of transplant-related mortality, hepatic VOD, or GVHD.[312]

Multiple Myeloma

The Intergroup Francophone du Myelome conducted a trial (9502) that randomized 399 patients with newly diagnosed multiple myeloma to high-dose therapy in preparation for autologous HSCT, after three cycles of vincristine-Adriamycin-dexamethasone chemotherapy. High-dose therapy consisted of melphalan 200 mg/m^2 (HDM200) or melphalan 140 mg/m^2 and 8 Gy of TBI delivered in four daily fractions without lung shielding (HDM140). Overall survival rates were longer in the HDM200 group ($p = 0.05$); however, event-free survival rates were not different in the two groups. The authors speculated that the improved overall survival rate was attributed to the better salvage regimens available after initial therapy with HDM200 and suggested that the standard conditioning regimen for autologous HSCT for MM should be without TBI.[313]

Mixed Diseases

Two prospective trials of conditioning have been carried out in groups of patients with leukemias and lymphomas. Because these trials included a heterogeneous group of diseases, results should be interpreted with caution. Nevertheless, in 1988, the Nordic Bone Marrow Transplantation Group initiated a

eTABLE 18-2 Randomized Controlled Trials Comparing HSCT Conditioning Regimens with and without TBI

Disease	Author (Group)	No. Patients	Type of Transplant	TBI-Based Conditioning	Non-TBI–Based Conditioning	Total TBI Dose Number and Frequency of Fractions Dose Rate	Technique
ALL	Bunin (PBMTC)[298]	43	Allogeneic marrow, cord, or peripheral blood	TBI, etoposide 40 mg/kg in 1 day, then Cy 120 mg/kg in 2 days	Bu 16 mg/kg in 4 days, then Cy 120 mg/kg in 2 days	12 Gy 6 bid (dose rate not described)	Not described
ALL AML CML Lymphoma	Ringden (NBMTG)[107,171]	167	Allogeneic marrow	Cy 120 mg/kg in 2 days, then TBI	Bu 16 mg/kg in 4 days, then Cy 120 mg/kg in 2 days	10-12.7 Gy 1-7 given once or more daily 4 cGy/min-12.7 cGy/min	Varied; all had lung blocks limiting dose to 9 Gy-10 Gy
ALL AML CML	Blume (SWOG)[302]	122	Allogeneic marrow	TBI, then etoposide 60 mg/kg in 1 day	Bu 16 mg/kg in 4 days, then Cy 120 mg/kg in 2 days	13.2 Gy 11 tid (dose rate not described)	Not described
AML	Dusenbery (Minnesota)[291]	35	Autologous marrow	Cy 120 mg/kg in 2 days, then TBI	Bu 16 mg/kg in 4 days, then Cy 200 mg/kg	13.2 Gy 8 bid (4.5 hr apart) 10 cGy/min	6 MV-24 MV photons Bilateral parallel-opposed Head and neck, lung, lower extremity compensators
AML	Blaise (GEGMO)[290,292]	101	Allogeneic marrow	Cy 120 mg/kg in 2 days, then TBI	Bu 16 mg/kg in 4 days, then Cy 120 mg/kg in 2 days	10-13.5 Gy 1-6 given once or twice daily (6 bid†) 3 cGy/min-25 cGy/min (5 cGy/min†)	Varied; all had lung blocks (8.8 Gy^2)
CML	Clift (Seattle)[294,304]	142	Allogeneic marrow	Cy 120 mg/kg in 2 days, then TBI	Bu 16 mg/kg in 4 days, then Cy 120 mg/kg in 2 days	12 Gy 6 qd 6-7 cGy/min	Dual opposed ^{60}Co sources Geometry not described Blocks not described
CML	Devergie (SFGM)[295]	120	Allogeneic marrow	TBI, then Cy 120 mg/kg in 2 days	Bu 16 mg/kg in 4 days, then Cy 120 mg/kg in 2 days	10 Gy-12 Gy 1-24 given 1-8 times daily (bid†) 3-25 cGy/min (8 cGy/min†)	Varied; all had lung blocks (8.8 Gy^2)
MM	Moreau (IFM)[301]	282	Autologous peripheral blood	TBI, then Mel 140 in 1 day	Mel 200 in 1 day	8 Gy 4 qd (dose rate not described)	Not described No lung blocks

bid, *Twice daily;* Bu, *busulfan;* Cy, *cyclophosphamide;* EFS, *event-free survival;* HSCT, *hematopoietic stem cell transplant;* Mel, *melphalan;* mo, *month;* OS, *overall survival;* qd, *once daily;* RFS, *relapse-free survival;* TBI, *total body irradiation;* tid, *thrice daily;* TRM, *transplant-related mortality.*

All drug doses are given as mg/m^2 unless otherwise stated.

**Statistically significant difference.*

†*Observed incidence.*

‡*Median.*

Conditioning Regimen	OS	EFS	Relapse	Non-relapse Mortality	TRM	Other Findings
TBI Non-TBI	3 yr: 67% 3 yr: 47%	3 yr: 58% 3 yr: 29%*	43%[1] 36%[1]	24%[1] 9%[1]	— —	No significant difference in GVHD, or pulmonary, cardiac, or neurologic toxicity after HSCT The TBI group had significantly better EFS among patients who received unrelated donor stem cells, and who were under 6 years
TBI Non-TBI	7 yr: 63% 7 yr: 54%	7 yr: 62% 7 yr: 51%	7 yr: 29% 7 yr: 29%	— —	7 yr: 14%* 7 yr: 34%	No significant difference in immunosuppressant use, interstitial pneumonitis, or Karnofsky score, growth, renal, pulmonary or thyroid function at follow-up The TBI group had less hepatic VOD, hemorrhagic cystitis, chronic GVHD, death from GVHD, obstructive bronchiolitis, with more cataracts
TBI Non-TBI	3 yr: ~24% (7 mo[2]) 3 yr: ~28% (7 mo[2])	— —	— —	— —	— —	No significant difference in GVHD, hemorrhage, sepsis, lung complications, infections VOD, drug toxicity, relapse, disease-free survival
TBI Non-TBI	2 yr: 46% 2 yr: 35%	2 yr: 50% 2 yr: 24%	2 yr: 43% 2 yr: 70%	Reported as "not different" Reported as "not different"		No significant difference in time to engraftment, GVHD, time in the hospital, infection, hepatic VOD, hemorrhagic cystitis, pneumonitis
TBI Non-TBI	12 yr: 59%* 12 yr: 43%*	12 yr: 55% 12 yr: 35%	12 yr: 25% 12 yr: 37%	— —	12 yr: 16% 12 yr: 27%	No significant difference in time to engraftment, GVHD The TBI group had less chronic GVHD related mortality
TBI Non-TBI	9 yr: 65% 9 yr: 73%	9 yr: 48% 9 yr: 55%	9 yr: 22% 9 yr: 19%	9 yr: 25% 9 yr: 20%	— —	No significant difference in the rate of engraftment, GVHD, hepatic VOD, number of fevers, deaths from infection, mean duration of first hospitalization The TBI group did have significantly longer fevers, more blood culture revealing bacteria or fungi, more than 1 hospitalization in the 100 days after transplant, and higher incidence of grades 2-4 GVHD
TBI Non-TBI	5 yr: 66% 5 yr: 61%	5 yr: 51% 5 yr: 59%	5 yr STBI: 11%* 5 yr FTBI: 31% 5 yr: 4%*	Not reported Not reported	29%[1] 38%[1]	No significant difference in the rate of engraftment, GVHD, hepatic VOD, interstitial pneumonitis, hemorrhagic cystitis, GVHD
TBI Non-TBI	3.75 yr: 45.5%* 3.75 yr: 65.8%*	21 mo‡ 20.5 mo‡	— —	— —	3.6%[1] 0%[1]	No significant difference in growth factor use, cardiac, pulmonary, renal, liver toxicity, or response rates The TBI group had significantly higher rates of mucositis hospitalizations —

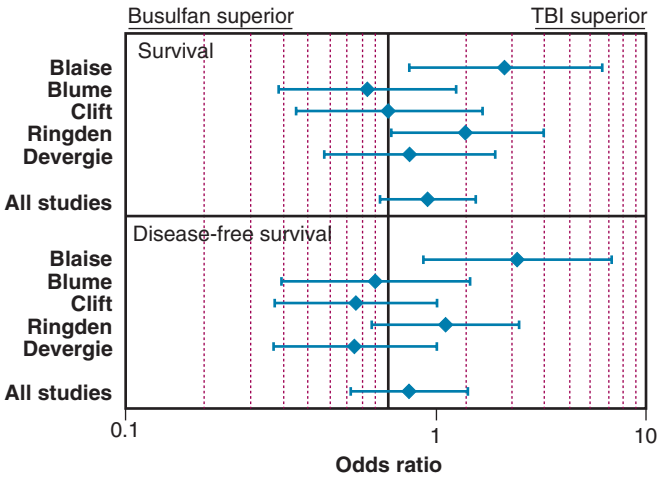


Figure 18-8 Odds ratio and 95% confidence intervals of survival and disease-free survival in a meta-analysis of TBI–based conditioning versus non-TBI–based conditioning in five randomized controlled trials (RCTs).
From Hartman AR, Williams S, Dillon JJ: Survival, disease-free survival and adverse effects of conditioning for allogeneic bone marrow transplantation with busulfan/cyclophosphamide vs total body irradiation. A meta-analysis. Bone Marrow Transplant 22(5):439–443, 1998; Figure 1, © 1998 Nature Publishing Group, with permission from Nature Publishing Group.

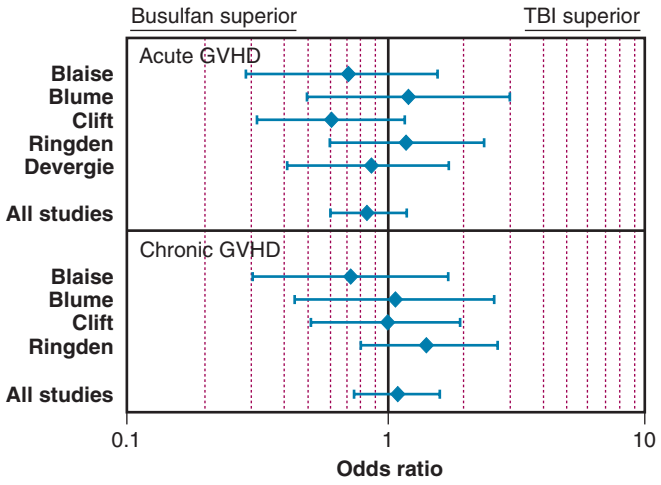


Figure 18-9 Odds ratio and 95% confidence intervals of acute and chronic graft-versus-host disease (GVHD) in a meta-analysis of TBI–based conditioning versus non-TBI–based conditioning in five and four randomized controlled trials (RCTs), respectively.
From Hartman AR, Williams S, Dillon JJ: Survival, disease-free survival and adverse effects of conditioning for allogeneic bone marrow transplantation with busulfan/cyclophosphamide vs total body irradiation. A meta-analysis. Bone Marrow Transplant 22(5):439–443, 1998; Figure 2, © 1998 Nature Publishing Group, with permission from Nature Publishing Group.

multicenter RCT of 167 patients (27 children and 140 adults); 68 patients had AML, 38 had ALL, 57 had CML, and 4 had lymphoma before allogeneic HSCT.[175] With 7 years of follow-up, the authors found a survival benefit in the TBI group among patients with "advanced" disease, with less toxicity compared with busulfan regimens; no differences were identified in the subset analysis of the different diseases that were treated.[109] The Southwest Oncology Group's RCT (SWOG 8612) also investigated the role of TBI before allogeneic HSCT for ALL ($n = 48$), AML ($n = 40$), and CML ($n = 34$) patients who were not in their first remission. This regimen substituted etoposide for cyclophosphamide in the TBI group only, making a meaningful comparison difficult. Although rates of overall survival and disease-free survival appeared to be superior for "good-risk" patients in the TBI group, the differences were not statistically significant.[314]

In the setting of allogeneic HSCT, a meta-analysis of the RCTs by Hartman and colleagues[176] summarized how TBI influences the outcome of conditioning regimens before allogeneic HSCT. As illustrated in Figure 18-8, overall survival and disease-free survival rates are slightly better with TBI-based regimens, although the results were not statistically significant. As shown in Figures 18-9 and 18-10, rates of GVHD were roughly equivalent, whereas hepatic VOD was clearly more common with busulfan-based regimens. The occurrence of interstitial pneumonitis also appeared similar in both groups. Another recent meta-analysis of 18 prospective and retrospective studies comparing TBI-based conditioning regimens with those not involving TBI (busulfan-based regimens) found that TBI improved disease-free survival rates in AML and ALL but not in CML. Growth and development problems, interstitial pneumonitis, and cataracts were more common with TBI-based regimens, but transplant-related mortality, VOD, and hemorrhagic cystitis were more common with busulfan-based regimens.[315]

There is much less data regarding the role of TBI before autologous HSCT. A non–TBI-based conditioning regimen is preferred for MM; however, no other trials have randomized

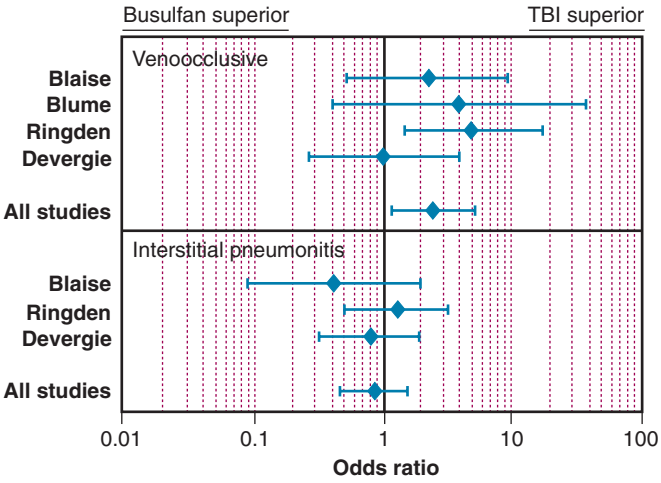


Figure 18-10 Odds ratio and 95% confidence intervals of hepatic venoocclusive disease and interstitial pneumonitis in a meta-analysis of TBI–based conditioning versus non-TBI–based conditioning in four and three randomized controlled trials (RCTs), respectively.
From Hartman AR, Williams S, Dillon JJ: Survival, disease-free survival and adverse effects of conditioning for allogeneic bone marrow transplantation with busulfan/cyclophosphamide vs total body irradiation. A meta-analysis. Bone Marrow Transplant 22(5):439–443, 1998; Figure 3, © 1998 Nature Publishing Group, with permission from Nature Publishing Group.

patients to a TBI or non-TBI conditioning regimen before autologous HSCT, and therefore, institutional preference primarily dictates choice of the technique in these situations.

Dose of Total Body Irradiation

The appropriate radiation dose to use during conditioning with TBI has been investigated by several groups. In 1985, researchers in Seattle conducted an RCT of two TBI regimens

as part of the HSCT for AML. Seventy-one patients were randomized to receive 12 Gy in six daily fractions (2 Gy/fraction/day) or 15.75 Gy in seven daily fractions (2.25 Gy/fraction/day). TBI was delivered using opposed ^{60}Co sources, at 0.06 Gy/min to 0.07 Gy/minute. The use of shielding was not described. Higher-dose TBI (15.75 Gy) was associated with higher rates of mortality in patients who did not relapse, although the authors note that this was limited to the first 6 months after transplant and to higher rates of grades 2 to 4 acute GVHD ($p = 0.02$). Patients receiving higher-dose TBI were less likely to receive adequate immunosuppression. Nonetheless, patients treated with lower-dose TBI (12 Gy) appeared to be more likely to relapse, although this finding was only marginally significant ($p < 0.06$).[134] A report of the long-term results (minimum follow-up of 7.5 years) of the trial revealed no difference in overall survival rates between the two TBI groups.[136]

In a similar trial, also from Seattle, 116 patients with CML were randomized to receive either 12 Gy or 15.75 Gy, as described previously. Higher-dose TBI (15.75 Gy) was associated with a superior relapse-free survival rate and with more grades 2 to 4 acute GVHD, although this was not statistically significant ($p = 0.15$). Initially, survival rates appeared to be superior in patients receiving lower-dose TBI (12 Gy). However, further follow-up revealed no significant difference in survival rates. Similar to the experience with AML, the authors concluded that higher-dose TBI was associated with greater relapse-free survival but at the cost of more acute GVHD, which likely led to transplant-related mortality that offset the survival benefit.[135]

Retrospective data suggest a benefit to higher-dose (>12 Gy) TBI in certain clinical scenarios. The highest doses of TBI reported in the literature are 20 Gy before autologous HSCT,[316] but at least one study has reported lower relapse rates and less transplant-related mortality in a subset of patients with ALL who received a TBI dose of more than 13 Gy.[317] Although modeling studies suggest that higher biologically effective doses are associated with lower relapse rates and longer overall survival times,[318] the finding of excess toxicity with higher doses in clinical dose-escalation studies does warrant caution.[319-322] For these reasons, fractionated TBI doses used before myeloablative HSCT typically range between 12 Gy and 15 Gy.

Reduced-intensity conditioning regimens have been used more often over the last decade for patients who might not be able to tolerate a myeloablative HSCT (because of advanced age or comorbidities) but could benefit from the graft-versus-tumor effects of allogeneic HSCT. A recent RCT suggested that reduced-intensity conditioning regimens (with TBI to 8 Gy in four fractions and fludarabine) offer fewer side effects than standard conditioning (with TBI to 12 Gy in six6 fractions and cyclophosphamide), but no difference in disease control or survival.[323] The role of TBI as part of reduced-intensity regimens is ill defined; however, a recent RCT compared reduced-intensity condition with busulfan or TBI (2 Gy in one fraction) and found inferior disease control, but lower nonrelapse mortality with TBI, and no difference in overall or progression-free survival.[324] Likewise, the optimal dose of TBI as part of reduced-intensity autologous HSCT has not been defined in an RCT. Several notable studies of allogeneic HSCT have employed TBI doses of 2 Gy to 8 Gy, often in conjunction with chemotherapy.[325-340] eTable 18-3, lists some representative allogeneic HSCT regimens using low-dose TBI.

Fractionation and the Total Body Irradiation Dose Rate

Laboratory-based radiobiologic data (see Radiobiology section) and clinical observations prompted trials investigating fractionation and dose-rate delivery in TBI. Thomas and et al were the first to conduct an RCT of single-dose or fractionated TBI in patients with AML. In this study, 53 patients with AML were randomized to receive TBI in a single 10 Gy dose or in a dose of 12 Gy in six daily fractions after receiving cyclophosphamide. TBI was delivered using opposed ^{60}Co sources, at a rate of 80 R/minute in air at midpoint (~0.06 Gy/minute). Disease-free survival times were significantly longer in the patients who were treated with fractionated TBI. There was no apparent difference in acute toxicity in the two treatment groups.[85] A follow-up report from the same institution described similar results using a slightly lower dose of single-fraction TBI (9.2 Gy using opposed ^{60}Co sources at 0.04 Gy/minute). Among the patients randomized, those who received fractionated TBI survived significantly longer than those receiving single-fraction TBI. Patients receiving single-fraction TBI experienced twice as many leukemic recurrences compared with those receiving fractionated TBI, although this was not statistically significant ($p = 0.09$). VOD of the liver was significantly more common in patients receiving single-fraction TBI ($p = 002$).[139]

Ozsahin et al[84] conducted a study investigating the effect of dose rate in patients undergoing single-dose or fractionated TBI as part of autologous or allogeneic HSCT for a variety of hematologic and lymphoid cancers. One-hundred fifty-seven patients receiving single-dose or multiple-fraction TBI were randomized to a low dose rate (0.06 Gy/minute or 0.03 Gy/minute, respectively) or a high dose rate (0.15 Gy/minute or 0.06 Gy/minute, respectively). Radiotherapy was delivered with ^{60}Co or 6-MV photons. Single-dose TBI was delivered to a total dose of 10 Gy with the lung dose limited to 8 Gy. Fractionated TBI was delivered to a total dose of 12 Gy in six fractions over 3 days, with the lung dose limited to 9 Gy. A variety of chemotherapies were used. The authors found no significant differences in rates of overall survival or relapse-free survival, pneumonitis, VOD, or GVHD. Cataracts were significantly more common among patients receiving single-fraction, high-dose-rate TBI. In a follow-up report, with a median follow-up time of 50 months, TBI in a single fraction or at a high dose rate was associated with the development of cataracts.[197]

Girinsky et al[140] conducted an RCT of 160 patients older than 15 years who were undergoing autologous or allogeneic HSCT for a variety of hematologic and lymphoid cancers. Patients were treated with a single fraction of TBI (STBI) with 10 Gy over 4 hours (average dose rate of 0.045 Gy/minute; instantaneous dose rate of 0.125 Gy/minute) or with hyperfractionated TBI (HTBI) with 14.85 Gy in 11 fractions over 5 days at a dose rate of 0.25 Gy/minute. A linear accelerator was used to deliver 18-MV photons with lung shielding; patients receiving STBI received a lung dose of 8 Gy, and patients undergoing HTBI received a lung dose of 9 Gy. After TBI, cyclophosphamide or melphalan was given, followed by HSCT. With a median follow-up of 8 years in 147 assessable patients, rates of overall survival and cause-specific survival were higher in the HTBI group; however, the differences were not statistically significant. A multivariate analysis that controlled for prognostic variables revealed greater cause-specific survival rates but not greater overall survival rates in patients treated with HTBI ($p = 0.04$). There was no significant difference in the rates of lethal pneumonitis, hepatic VOD, GVHD, graft failure, infection, or organ failure. However, the rate of hepatic VOD was significantly higher in the STBI group.

The necessity of hyperfractionation versus conventional daily fractionation has never been tested in a prospective trial. Investigators from the M. D. Anderson Cancer Center compared the outcome of patients in different prospective HSCT protocols and found that fewer patients in the conventionally fractionated group had recurrences of disease. These results

eTABLE 18-3 Representative TBI-Based Reduced-Intensity Conditioning Regimens for Allogeneic HSCT

Disease	Author (Group)	No. Patients	Total TBI Dose Number and Frequency of Fractions Dose Rate	Additional Conditioning Therapy	Technique	Type of Transplant
AML	Hegenbart (multicenter)[312]	122	2 Gy 1 0.07 to 0.20 Gy/min	84% received Flu 90 in 3 days, then TBI	Dual opposed ^{60}Co sources or linear accelerator Geometry not described Blocks not described	Allogeneic marrow (5%) and peripheral blood (95%)
AML	Stelljes (CGTSG)[313]	71	8 Gy 4 given bid 8.9-30 cGy/min	TBI, then Flu 120 in 4 days ±ATG	Not described	Allogeneic marrow (4%) and peripheral blood (96%)
AML	Hallemeier (Washington University)[199]	32	5.5 Gy 1 27.6-36.4 cGy/min	Cy 120 in 2 days, then TBI	6-MV photons from linear accelerator Parallel opposed lateral fields Arms at side for lung shielding	Allogeneic peripheral blood
CLL	Sorror (Seattle)[315]	64	2 Gy 1 7 cGy/min	83% received Flu 90 in 3 days, then TBI	Dual opposed ^{60}Co sources or linear accelerator Geometry not described Blocks not described	Allogeneic peripheral blood
CML	Kerbauy (Seattle)[316]	24	2 Gy 1 7 cGy/min	67% received Flu 90 in 3 days, then TBI	Dual opposed ^{60}Co sources or linear accelerator Geometry not described Blocks not described	Allogeneic peripheral blood
CML	Khoury (Washington University)[317]	30	5.5 Gy 1 26.4-36 cGy/min	Cy 120 in 2 days, then TBI	6 MV photons from linear accelerator Parallel opposed lateral fields Arms at side for lung shielding	Allogeneic peripheral blood
Hematologic malignancy	McSweeney (Seattle)[318]	45	2 Gy 1 7 cGy/min	None	Dual opposed ^{60}Co sources or linear accelerator Geometry not described Blocks not described	Allogeneic peripheral blood
Hematologic malignancy	Baron (Seattle)[319]	221	2 Gy 1 7 cGy/min	77% received Flu 90 in 3 days, then TBI	Not described	97% allogeneic peripheral blood
Lymphoma	Tomblyn (Minnesota)[320]	76	2 Gy 1 dose not reported	Flu + Cy, then TBI or Flu + Bu, then TBI or Bu + Clad, then TBI	Not described	Allogeneic marrow (10%), peripheral blood (46%), and cord blood (43%)
Mantle cell lymphoma	Maris (Seattle)[321]	33	2 Gy 1 7 cGy/min	Flu 90 in 3 days, then TBI	Linear accelerator Geometry not described Blocks not described	Allogeneic marrow (4%) and peripheral blood (96%)
MDS/AML	Schmid (Wiesbaden)[322]	75	4 Gy 1 dose rate not reported	TBI, then Cy 80-120 in 2 days, ATG	Not described	Allogeneic marrow (19%) and peripheral blood (81%)
MDS/MPD	Laport (multicenter)[323]	148	2 Gy 1 7 cGy/min	97% received Flu 90 in 3 days, then TBI	Linear accelerator Geometry not described Blocks not described	Allogeneic marrow (2%) and peripheral blood (98%)

Continued

eTABLE 18-3 Representative TBI-Based Reduced-Intensity Conditioning Regimens for Allogeneic HSCT—cont'd

Disease	Author (Group)	No. Patients	Total TBI Dose Number and Frequency of Fractions Dose Rate	Additional Conditioning Therapy	Technique	Type of Transplant
MPD/ secondary AML	Hallemeier (Washington University)[324]	51	5.5 Gy 1 25.3-37.2 cGy/min	Cy 120 in 2 days, then TBI	6-MV photons from linear accelerator Parallel opposed lateral fields Arms at side for lung shielding	Allogeneic peripheral blood
MM	Maloney (Seattle)[325]	54	2 Gy 1 7 cGy/min	17% received Flu 90 in 3 days, then TBI	Linear accelerator Geometry not described Blocks not described	Allogeneic peripheral blood
MM	Badros (Arkansas)[326]	31	2.5 Gy 2 given bid; dose rate not reported	TBI and Mel 100, then Flu 60 in 2 days	Not described	Allogeneic peripheral blood

AML, *Acute myelogenous leukemia;* ATG, *antithymocyte globulin;* Bu, *busulfan;* Clad, *cladribine;* CLL, *chronic lymphoid leukemia;* CML, *chronic myelogenous leukemia;* Cy, *cyclophosphamide;* Flu, *fludarabine;* MDS, *myelodysplastic syndrome;* Mel, *melphalan;* MM, *multiple myeloma;* MPD, *myeloproliferative disorder;* TBI, *total body irradiation.*

All drug doses are given in mg/kg unless otherwise stated.

should be interpreted with caution because this study was not randomized and other factors not related to TBI may have influenced the results.[142] Investigators in Seattle have conducted phase I/II studies of twice- and thrice-daily hyperfractionation protocols that did not suggest a significant benefit with hyperfractionation versus conventional fractionation when they were compared with historical results.[315,321]

Organ Shielding During Total Body Irradiation

The necessity of shielding to prevent normal tissue toxicity has been investigated in several studies; because pneumonopathy has been considered the dose-limiting toxicity of TBI, the studies have primarily been concerned with lung shielding. Labar et al[150] conducted a trial in 64 patients with AML, ALL, and CML who were undergoing TBI and cyclophosphamide conditioning. Patients were treated with 12 Gy of TBI in three fractions given once daily and were randomized to TBI with or without lung shielding after stratifying by age group (<20, 21 to 30, 31 to 40, >40 years), sex, underlying disease, GVHD prophylaxis, and donor-recipient sex combination. TBI was delivered using a ^{60}Co source, and blocks were used to limit the estimated lung dose to 9 Gy in the group of patients treated with lung shields. There was no difference in rates of leukemia-free survival or relapse. Although interstitial pneumonitis was more common in the group of patients treated without lung blocks (12%) compared with those treated with lung blocks (4%), this difference was not statistically significant.

Girinsky et al[152] conducted a similar study in a group of 85 patients with various lymphoid or hematopoietic cancers. Each patient received TBI with a dose of 10 Gy given in a single fraction over 4 hours (average dose rate of 0.04 Gy/minute; instantaneous dose rate of 0.125 Gy/minute). Patients were randomly assigned to receive a 6 Gy or 8 Gy lung dose. The authors observed no differences in rates of overall survival or lung complications. However, chronic GVHD and infections were significantly less common in the low lung dose group. Interestingly, there were significantly more leukemia relapses in the low lung dose group. The authors speculated that the additional lung shielding may have fostered survival of leukemic cells, which led to higher rates of relapse.

Retrospective data support the benefit of shielding. Weshler et al[151] reported a series of 44 consecutive patients who received 12 Gy of TBI; the first 23 patients were treated with opposed lateral fields and had no lung shielding in place, whereas the subsequent 21 patients had half-value layer transmission blocking after 6 Gy. Pneumonitis occurred in 26% of patients without lung shielding, whereas no pneumonitis was noted in those who had lung shielding. Investigators from Wisconsin have demonstrated sparing of renal and hepatic dysfunction with shielding.[180,212]

Boosting in Total Body Irradiation

There is scant high-level evidence for integrating a boost into the radiotherapy plan involving TBI. The EBMT conducted an RCT to assess the benefit of splenic boosting before allogeneic HSCT in patients with CML in their first complete remission. Two-hundred twenty-nine participants were enrolled and stratified based on age (25 years) and T-cell depletion. Patients were randomized to receive a 10-Gy boost to the spleen (given in one, two, or three fractions) within 14 days of HSCT. Overall, there was no difference in the groups. However, in subgroup analysis, it was determined that patients who did not undergo T-cell depletion and who had more than 3% circulating basophils before transplant demonstrated a statistically significant improvement in overall survival rates.[341] At MSKCC, the testes of males with leukemia undergoing myeloablative HSCT are boosted with 4 Gy in one fraction, based on the results of a retrospective series that revealed significantly lower rates of testicular relapse with this treatment strategy.[342] These findings have never been validated in a prospective study, but other institutions have incorporated the findings in their radiotherapy strategies, as discussed by Quaranta et al.[343] In other situations, investigators have reported success in delivering an involved field boost to the central nervous system (in leukemia)[344] or bulky nodal disease (in lymphoma),[345] although the efficacy of these approaches has never been validated in prospective trials.

Total Body Irradiation in Nonmalignant Diseases

Because radiotherapy is most commonly employed in the treatment of malignant diseases dealt with in other sections of this book, special attention will be paid to the role of TBI as part of HSCT for nonmalignant diseases. Although there are reports of using TBI as part of conditioning before HSCT for nonmalignant-acquired diseases such as severe aplastic anemia, paroxysmal nocturnal hemoglobinuria, systemic amyloidosis, and the acquired immunodeficiency syndrome caused by the human immunodeficiency virus, in general TBI is avoided in these situations.

Although no RCT data exist to support the use of TBI in the conditioning regimen of patients undergoing autologous HSCT for autoimmune conditions, several pilot studies have prompted the execution of phase III studies incorporating TBI. The basis for the role of TBI lies in preclinical studies of a rat model of autoimmune arthritis treated with pseudo-autologous HSCT. When the highest tolerable doses of TBI, cyclophosphamide, or busulfan were given, TBI was the most effective single conditioning agent.[346] Saccardi et al[347] summarized the results of phase I and II trials carried out by the EBMT using HSCT for multiple sclerosis (MS), which revealed stabilization or improvement of neurologic symptoms in 63% of patients, who generally had severe or progressive disease. Collectively, TBI was part of the conditioning regimen in 16 of the 178 patients. Statistical analysis revealed that busulfan, and not TBI, was associated with transplant-related mortality. Interestingly, Nash et al[348] studied 26 patients in a pilot study using high-dose myeloablative conditioning before autologous HSCT, including 8 Gy of TBI, and found that the 3-year progression-free survival rate was 73%, with a 91% overall survival rate, with minimal toxicity. Concerns about the use of TBI in HSCT for MS were brought up by Samijin et al[349] as well as Burt et al,[350] who speculated that radiotherapy may have contributed to axonal injury or caused dysfunction of neural precursor cells, although direct evidence of this was lacking. For these reasons, the ongoing RCT to compare autologous HSCT (ASCT) with mitoxantrone drug therapy for severe MS will not involve TBI (www.astims.org/). Similar concerns regarding the toxicity of radiotherapy in patients with inflammatory bowel disease have prompted investigators to omit TBI from ongoing RCTs of autologous HSCT in Crohn disease.[351]

As in studies of MS and Crohn disease, autologous HSCT has been explored recently for patients with systemic sclerosis (SSc, scleroderma) in several pilot studies. Binks et al[352] reported the results of a phase I/II trial of autologous HSCT for poor-prognosis systemic sclerosis, using a variety of conditioning regimens, some of which included TBI. In their initial report, two of nine patients who received 8 Gy of TBI died of interstitial pneumonitis 1 and 3 months after TBI. This prompted investigators to minimize the TBI dose during further investigations of HSCT in this disease.[353] After two of

the first eight patients in a study by Nash et al[354] died of pneumonitis, these investigators shielded the lungs with five half-value layers after patients received the first 2-Gy fraction. With shielding in place, no further TBI-related pulmonary mortality has occurred; however, two patients developed myelodysplastic syndrome and a former smoker was diagnosed with stage 1 lung cancer.[355] Autologous HSCT for systemic sclerosis is currently being studied in two RCTs; in the United States, the Scleroderma Cyclophosphamide or Transplantation (SCOT) trial, NCT00114530, will incorporate 8 Gy of TBI, whereas in the Autologous Stem Cell Transplantation International Scleroderma (ASTIS) trial in Europe (www.astistrial.com), TBI will not be used.

Several inherited diseases have been successfully treated with HSCT using TBI for conditioning; however, this approach is not desirable for children, who frequently need HSCT at a young age. HSCT for thalassemia has been carried out in several Italian centers and generally does not involve TBI. However, reduced-intensity regimens involving low doses of TBI have been used in a few small series of patients undergoing HSCT for thalassemia and sickle cell disease with favorable results.[356,357] Immunodeficiency syndromes are often treated with HSCT, but TBI is not commonly employed during conditioning, probably because these syndromes are commonly caused by impaired DNA damage repair by nonhomologous end-joining. Phagocytic disorders have been treated with HSCT using myeloablative doses of TBI.[358] HSCT is considered the only curative therapy for osteopetrosis, and the first successful case involved TBI.[359] Likewise, hundreds of patients have been successfully treated for lysosomal or peroxisomal storage diseases (i.e., mucopolysaccharidoses, mucolipidoses, leukodystrophies, glycoprotein and other disorders) with HSCT, often using TBI, although this approach is undesirable in younger children.[360-362] Recent studies have focused on non–TBI-based approaches in these diseases.[363] Fanconi anemia is a disease commonly treated with allogeneic HSCT. In favorable patients with an HLA-matched sibling donor, TBI can usually be avoided. However, in patients with evidence of MDS or AML, use of TBI should be considered. TBI is typically delivered in a single fraction, given the underlying defects in DNA repair and cell-cycle checkpoint regulation in patients with Fanconi anemia. Prospective dose-escalation studies have found no benefit of doses beyond 4.5 Gy.[364]

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CHAPTER

19 Charged Particle Radiotherapy

William P. Levin and Thomas F. DeLaney

Interest in the use of charged particle radiotherapy derives from the superior dose distributions that can be achieved with these particles compared with those produced by standard photon therapy techniques, as well as the potential for higher biological effect in the tumor with heavier charged particles. Charged particles deposit energy in tissue through multiple interactions with electrons in the atoms of cells, although a small fraction of energy is also transferred to tissue through collisions with the nuclei of atoms. The energy loss per unit path length is initially relatively small and constant until near the end of the range where the residual energy is lost over a short distance, resulting in a steep rise in the absorbed dose (energy absorbed per unit mass). This portion of the particle track, where energy is rapidly lost over a short distance, is known as the *Bragg peak* (Figure 19-1).

The initial low-dose region in the depth-dose curve, before the Bragg peak, is referred to as the plateau of the dose distribution and delivers about 30% of the Bragg peak maximum dose. The Bragg peak is too narrow for practical clinical applications. For the irradiation of most tumors, the beam energy is modulated to achieve a uniform dose over a significant volume. This has traditionally been accomplished by superimposing several Bragg peaks of descending energies (ranges) and weights to create a region of uniform dose over the depth of the target; these extended regions of uniform dose are called *spread-out Bragg peaks* (SOBP; see Figure 19-1 and Techniques of Proton Delivery section). Although the SOBP beam modulation does increase the entrance dose, the proton dose distribution is still characterized by a lower-dose region in normal tissue proximal to the tumor, a uniform high-dose region in the tumor, and zero dose beyond the tumor. The protons are distributed laterally through the target volumes by a passive scattering foil, collimated with brass apertures, and contoured distally with customized range compensators to compensate for proton range differences from variable proton absorption by tissues of different radiologic density.

Increasingly, charged particle therapy is being delivered by raster scanning a pencil beam of charged particles through the deepest slab of the target volume, then reducing the energy of the particle beam and repeating the process iteratively through the target volume. The pencil beam scanning technique delivers lower proximal dose than the traditional SOBP modulation with passive scattering, can eliminate the need for machining customized apertures and range compensators, and provides greater flexibility in dose delivery including dose painting and intensity modulation.

Charged particles are generally characterized as having either high or low linear energy transfer (LET), which is the rate of energy loss by the particle in tissue. The LET influences the biologic impact of the energy deposited in tissue. X and gamma photons, protons, and helium ions are considered to be forms of low LET radiation. Heavier charged particles (e.g., neon ions, carbon ions) are considered to be forms of high LET radiation. There is an initial increase in the relative biologic effectiveness (RBE) with an increase in LET.[1] Carbon ions have an RBE of about 3, whereas the recommended RBE of protons is 1.1.[2] Higher-LET radiation is less influenced by tissue oxygenation and less sensitive to variations in the cell cycle and DNA repair. For particle radiation, the Gray equivalent dose is calculated by multiplying the physical dose administered by the RBE for that particle; the recommended nomenclature for expressing the dose is Gy(RBE) = physical dose in Gy × RBE.[3]

DEVELOPMENT OF PROTON BEAM RADIOTHERAPY

The vast majority of patients receiving charged particle therapy have been treated with protons. As of December 2012, more than 78,000 patients had received part or all of their radiotherapy by proton beams.[4] Table 19-1 lists currently operational proton beam treatment facilities worldwide. Multiple sites are scheduled to begin using proton beam therapy over the next several years.

In 1946, Robert Wilson proposed that proton beams would provide superior dose distributions over photons and should be considered for clinical radiotherapy.[5] Initially, patients were being treated at facilities designed and constructed for basic high-energy physics research, and this often meant that treatment delivery was cumbersome. The proton beams were limited to a fixed horizontal position, which meant that the patient had to be moved to align the tumor on the trajectory of the beam. This technique was in contrast to the isocentric capabilities of the modern linear accelerator, which rotates around a point in space and can effectively target any site in the body. In addition, for many of the proton machines, the energy of the beam (which defined the depth of the Bragg peak) was only sufficient to treat superficial lesions (such as those of the eye) or intermediate-depth lesions (such as those at the base of the skull). Because of these technical factors and the interests of the involved physicians, the tumors that initially received the most attention were uveal melanomas in the eye and sarcomas at the base of the skull. The major emphasis in proton therapy clinical research initially was on dose escalation for tumors for which local control with conventional (at that time, two-dimensional) radiotherapy was poor.

The development of hospital-based cyclotrons with higher-energy beams capable of reaching deep-seated tumors (up to ~30 cm with a 235-MeV beam), field sizes comparable to those of linear accelerators, and rotational gantries has greatly facilitated proton radiation therapy. Increasingly, researchers are interested in developing protocols that will reduce morbidity at sites where tumor control with photons has proven to be beneficial. At about the same time that hospital-based cyclotrons appeared in the 1990s, intensity modulated photon radiation therapy (IMRT) emerged as a technique that also facilitated dose escalation. IMRT may produce comparable or even higher conformality of the prescription dose compared to passively scattered protons, although the integral dose with protons may be ~50% to 60% lower. Intensity modulated proton radiation therapy (IMPT) can theoretically match the conformality of IMRT in the high-dose prescription volume while simultaneously reducing the integral dose, although making IMPT robust in the face of range and setup uncertainties requires careful treatment planning. For pediatric patients,

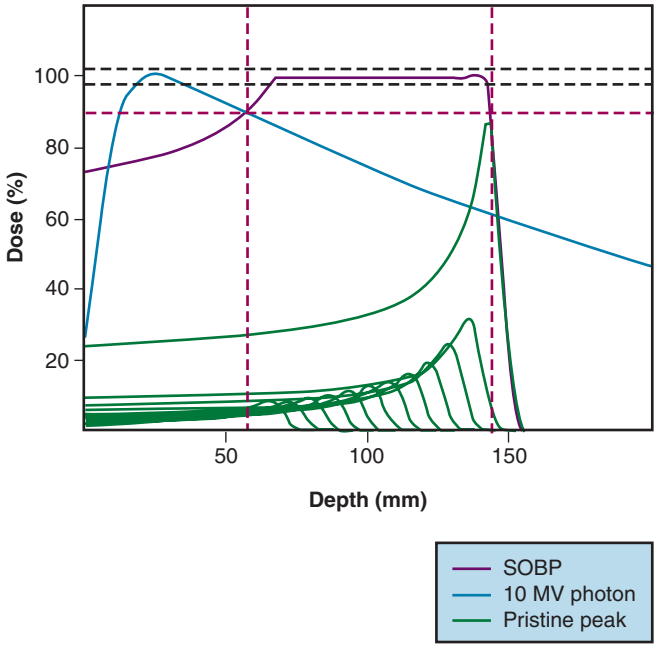


Figure 19-1 Depth-dose distributions for a spread-out Bragg peak (SOBP, *red*), its constituent pristine Bragg peaks *(green)*, and a 10-MV photon beam *(blue)*. The SOBP dose distribution is created by adding the contributions of individually modulated pristine Bragg peaks. The penetration depth, or range (measured as the depth of the distal 90% of the plateau dose), of the SOBP dose distribution is determined by the range of the most distal pristine peak. The *dashed lines (black)* indicate the clinically acceptable variation in the plateau dose of ±2%. The *dot-dashed lines (red)* indicate the 90% dose and the spatial, range, and modulation width intervals. The SOBP dose distribution of even a single field can provide complete target volume coverage in depth and lateral dimensions, in sharp contrast to a single photon dose distribution; only a composite set of photon fields can deliver an appropriate clinical target dose distribution. Note the absence of dose beyond the distal fall-off edge of the SOBP.
Reprinted, with permission, from Levin WP, Kooy H, Loeffler JS, et al: Proton beam therapy. Br J Cancer 93:849–854, 2005.

the lower integral dose with protons has led many clinicians to conclude that protons are the preferred curative radiation treatment modality for children. In fact, if the cost of proton therapy were the same as photons, it has been argued that protons would also be the treatment of choice for adult patients. Because of the greater cost of accelerating and delivering protons to the tumor, however, cost and cost-effectiveness, particularly in an era of concern about rising healthcare costs, must be considered in the selection of treatment modality. Hence, the current primary focus of discussion about and research in proton radiation therapy is the magnitude of the reduction in clinical toxicity using protons (related to its lower integral dose), at which clinical sites protons provide the greatest clinical benefit and where they are cost effective, and the optimum strategy to assess the benefits in adult patients (i.e., are randomized clinical trials of photons versus protons ethical, can other comparative strategies such as registries provide valid comparisons?). A priori, large target volumes, large target volumes relative to the involved organ (i.e., eye tumors), or sensitive adjacent normal tissues (i.e., spinal cord, critical areas of the brain), particularly in young patients, would be clinical scenarios where the elimination of exit dose would seem to be most important for the use of protons but these will need to be further validated by clinical studies.

TREATMENT OF SPECIFIC CANCERS WITH PROTON BEAM RADIOTHERAPY

Ocular (Uveal) Melanoma

Uveal melanoma is the most common primary ocular tumor. Historically, the primary treatment has been enucleation. Conventional radiotherapy is an alternative to surgery but does not ensure preservation of sight because of the proximity of nearby structures such as the cornea, lens, retina, fovea, and optic nerve. Radioactive plaque therapy is also used for its dose distribution. Because preservation of vision is of utmost importance (secondary only to tumor control), particle beam therapy, with its favorable dose distribution characteristics, has increasingly been employed in the treatment of uveal melanomas.

At Massachusetts General Hospital (MGH), in cooperation with the Massachusetts Eye and Ear Infirmary, patients have undergone placement of tantalum clips to demarcate the location of the tumor for proton radiotherapy planning. When the patient is undergoing treatment, the clips can be identified by fluoroscopy to allow for accurate daily setup. Most institutions employ a fixed horizontal beam for treatment of uveal melanomas, so the patient is able to sit upright. Immobilization is achieved with a mask and a bite block. Patients are asked to stare at a small light to help set the eye position and are monitored with a video camera during treatment. Typically, a total of 70 Gy(RBE) is administered over five fractions.

As of December 2002, more than 3000 patients with uveal melanoma had been treated with protons at MGH in collaboration with the Massachusetts Eye and Ear Infirmary.[6] The 5-year actuarial local control rate was 96% for all sites within the globe, with an 80% survival rate. The probability of eye retention at 5 years was estimated to be 90% for the entire group and 97%, 93%, and 78% for patients with small, intermediate, and large tumors, respectively. Independent risk factors for enucleation were involvement of the ciliary body, tumor height greater than 8 mm, and distance between the posterior tumor edge and the fovea. These results compare favorably with the 5-year local control rates of 93% reported with protons in Nice, France,[7] and 98.9% from the Paul Scherrer Institute in Villigen, Switzerland.[8]

Because some patients have experienced deteriorating vision after doses of 70 Gy(RBE), a randomized trial of 50 Gy(RBE) versus 70 Gy(RBE) for small and intermediate-sized lesions located within 6 mm of the optic disc or macula was conducted. Interim analysis of 188 patients, with a median follow-up of 60 months, suggested no reduction in either local control or survival rates. No significant improvement in visual outcome or complications has been observed. However, visual field analysis does show a smaller mean defect in the patients randomized to 50 Gy(RBE).[9] Hence, smaller posterior tumors that are near the macula or optic disc can be treated with 50 Gy(RBE).

Egger et al[10] reported long-term results of eye retention after treatment of uveal melanoma with proton beam therapy. A total of 2645 patients (2648 eyes) were treated at the Paul Scherrer Institute between 1984 and 1999. The overall eye retention rate at 5, 10, and 15 years after treatment was 89%, 86%, and 83%, respectively. Enucleation was related to large tumor size (mainly, tumor height), male gender, high intraocular pressure, and large degree of retinal detachment at treatment time.

Sarcomas of the Skull Base and Spine

Treatment of patients with sarcoma of the skull base is challenging because of the proximity of critical structures, notably, the brain, brainstem, cervical cord, optic nerves, and chiasm.

TABLE 19-1 Particle Therapy Facilities Currently in Operation

Facility	Particle	First Patient	Patient Total	Date of Total
Tri-University Meson Facility (TRIUMF), Vancouver, Canada	Protons	1995	170	December 2012
WPTC, Wanjie, China	Protons	2004	1,078	December 2012
Lanzhou, China	Carbon	2006	194	December 2012
Clatterbridge, England	Protons	1989	2297	December 2012
CAL, Nice, France	Protons	1991	4,692	December 2012
Center for Proton Therapy, Orsay, France (CPO)	Protons	1991	5,949	December 2012
Hahn-Meitner Institute (HMI), Berlin, Germany	Protons	1998	2,084	December 2012
RPTC, Munich, Germany	Protons	2009	1,377	December 2012
HIT, Heidelberg, Germany	Carbon, protons	2010	1,232	December 2012
Instituto Nazionale di Fisica Nucleare–Laboratori Nazionali del Sud (INFN-LNS), Catania, Italy	Protons	2002	293	November 2012
(CNAO) Pavia, Italy	Protons	2011	53	November 2012
Heavy Ion Medical Accelerator (HIMAC), Chiba, Japan	Carbon ions	1994	7,331	January 2013
National Cancer Center (NCC), Kashiwa, Japan	Protons	1998	772	December 2010
Hyogo Ion Beam Medical Center (HIBMC), Hyogo, Japan	Protons	2001	3,198	December 2011
Hyogo Ion Beam Medical Center (HIBMC) Hyogo, Japan	Carbon ions	2002	1,271	December 2011
PMRC, 2, Tsukuba University, Japan	Protons	2001	2,516	December 2012
Shizuoka, Japan	Protons	2003	1,365	December 2012
Koriyama-City, Japan	Protons	2008	1,812	December 2012
Gunma, Japan	Carbon	2010	537	December 2012
MMRI, Ibusuki, Japan	Protons	2011	490	December 2012
Seoul, Korea	Protons	2007	1,041	December 2012
Krakow, Poland	Protons	2011	15	December 2012
ITEP, Moscow, Russia	Protons	1969	4,300	December 2012
St. Petersburg, Russia	Protons	1975	1,386	December 2012
JINR, 2, Dubna, Russia	Protons	1999	922	December 2012
iThemba LABS, South Africa	Protons	1993	521	December 2011
Uppsala, Sweden (2)	Protons	1989	1,267	December 2008
Paul Scherrer Institute, Villigen, Switzerland	Protons	1984	7,045	December 2012
Crocker Nuclear Laboratory, University of California, San Francisco	Protons	1994	1,515	December 2012
LLUMC, Loma Linda University, California	Protons	1990	16,884	December 2012
MPRI, 2, Bloomington, Indiana	Protons	2004	1688	December 2012
NPTC, Boston, Massachusetts	Protons	2001	1,688	December 2012
MDACC, Houston, Texas	Protons	2006	3,909	December 2012
University of Florida, Jacksonville, Florida	Protons	2006	4272	December 2012
ProCure, Oklahoma City, Oklahoma	Protons	2009	1,045	December 2012
University of Pennsylvania, Philadelphia, Pennsylvania	Protons	2010	1,100	December 2012
ProCure, New Jersey	Protons	2012	137	December 2012
CDH, Warrenville, Illinois	Protons	2010	840	December 2012
Hampton, Virginia	Protons	2010	489	December 2012

Courtesy of Martin Jemann, PTCOG Secretary.

Accordingly, surgery and conventional photon therapy have not been successful at controlling these tumors. Because of the necessity of delivering the dose in a precise manner, the use of proton therapy is becoming the treatment of choice for these tumors.

At the Harvard Cyclotron Laboratory, MGH, physicians used a combination of protons and photons to treat patients with tumors of the skull base and cervical spine.[11] A total of 169 patients with chordoma and 165 patients with chondrosarcoma were treated. The 10-year local control rate was highest for chondrosarcomas, intermediate for males with chordomas, and lowest for females with chordoma (94%, 65%, and 42%, respectively). For cervical spine tumors, 10-year local control rates were not significantly different for chordomas and chondrosarcomas (54% and 48%, respectively), nor was there any significant difference in local control rates between males and females. In a Cox multivariate analysis, predictors of local control included gender and equivalent uniform dose, or gender and target volume, or gender and minimum target dose.[12] Five-year actuarial rates of endocrinopathy were as follows: 72% for hyperprolactinemia, 30% for hypothyroidism, 29% for hypogonadism, and 19% for hypoadrenalism. The minimum target dose (Dmin) to the pituitary gland was found to be predictive of endocrinopathy: Patients receiving 50 Gy(RBE) or more at Dmin to the pituitary gland had a higher incidence of and greater severity of endocrine dysfunction. Posterior pituitary dysfunction, represented by vasopressin activity with diabetes insipidus, was not observed.[13]

Between 1998 and 2005, 64 patients with skull base chordomas (42 patients) and chondrosarcomas (22 patients) were treated at the Paul Scherrer Institute with protons using a spot-scanning technique.[14] Patients with chordoma received a mean dose of 73.5 Gy(RBE) (range, 67 Gy[RBE] to 74 Gy[RBE]), and patients with chondrosarcoma received a mean dose of 68.4 Gy(RBE) (range, 63 Gy[RBE] to 74 Gy[RBE]). With a mean follow-up of 38 months, actuarial 5-year local control rates were 81% and 94% for chordomas and chondrosarcomas, respectively. The actuarial 5-year rate for freedom from high-grade toxicity was 94%.

Torres et al[15] performed a planning study where they compared three-dimensional (3D) conformal proton (PR) therapy, IMRT with photons (PH), and combined proton and IMRT photon (PP) irradiation of skull-base chordomas to determine the optimal technique. For each of five patients, they generated four treatment plans: (1) an IMRT plan with a 1-mm planning target volume (PH1) for stereotactic treatment; (2) an IMRT plan with a 3-mm planning target volume (PH3) for routine treatment; (3) a PR plan with beam-specific expansion margins on the clinical target volume; and (4) a plan for PP treatment. The mean percentage of planning target volume (%PTV) receiving the prescription dose of 74 Gy(RBE) was highest in the PP plans and lowest in the PH3 plans. The PR plans were the least homogeneous and conformal. The PH3 plans had the highest mean percentage of volume (%V) of brain, brainstem, chiasm, and temporal lobes above the tolerance dose for those organs. The PH1 plans had the lowest brainstem mean %V receiving 67 Gy(RBE) and temporal lobe mean %V receiving 65 Gy(RBE). Global evaluation of the plans based on objective parameters revealed that the PP plans yielded the best target coverage and conformality. This study indicates that there may be dosimetric advantages to using a combination of IMRT and 3D protons, to optimize conformality and minimize integral dose, which may be an important option until intensity-modulated proton therapy is more widely available.

As with skull-base tumors, treatment of spinal and paraspinal tumors is complicated by the proximity of the spinal cord. Radiation tolerance of the spinal cord is generally quoted at 45 Gy to 50 Gy, well below the doses necessary to reliably control most sarcomas: doses of approximately 60 Gy are needed for subclinical microscopic disease, 66 Gy for tumors with microscopically positive margins, and more than 70 Gy for gross residual disease. Proton radiotherapy, with its ability to spare adjacent tissues, offers advantages for treatment of tumors in these locations.

Hug et al[16] presented results on combined photon/proton treatment of 47 patients with osteogenic and chondrogenic tumors of the axial skeleton. Radiation was delivered postoperatively in 23 patients, preoperatively and postoperatively in 17 patients, and as the sole treatment in 7 patients. Mean radiation doses of 73.9 Gy(RBE), 69.8 Gy(RBE), and 61.8 Gy(RBE), respectively, were delivered to group 1 (20 patients with recurrent/primary chordoma or chondrosarcoma), group 2 (15 patients with osteogenic sarcoma), and group 3 (12 patients with giant cell tumors, osteoblastomas, or chondroblastomas). Five-year actuarial local control and survival rates for patients with chondrosarcoma were 100% and 100% and with chordoma, 53% and 50%. The actuarial 5-year local control rate for patients with osteosarcoma was 59%. The 5-year actuarial local control and survival rates for the group 3 patients were 76% and 87%. Overall, improved local control was noted for patients with primary versus recurrent tumors, those who underwent gross total resection, and those who received target doses of more than 77 Gy(RBE).

At the Francis H. Burr Proton Therapy Center at MGH, a Phase II study was conducted of combined photon and proton beam radiation therapy, with or without surgical resection, for patients with spinal and paraspinal sarcomas.[17] Doses of 77.4 Gy(RBE) at 1.8 Gy(RBE) per day were used for patients with gross residual disease and 70.2 Gy(RBE) for patients with microscopic residual disease. A total of 50 patients (29 with chordoma, 14 with chondrosarcoma, and 7 with other cancers) underwent gross total (25 patients), subtotal (12 patients) resection, or biopsy (13 patients). With a 48-month median follow-up, the 5-year actuarial local control, recurrence-free survival, and overall survival rates were 78%, 63%, and 87%, respectively. Two of 36 patients (5.6%) treated for primary tumors versus 7 of 14 patients (50%) treated for recurrent tumors developed local recurrence ($p < 0.001$). The spinal cord center dose was limited to 54 Gy(RBE) and the cord surface dose to 63 Gy(RBE) over a length of 5 cm or less. The cauda equina was constrained to 70.2 Gy(RBE), except for areas in direct contact with tumor, where the dose limit was 77.4 Gy(RBE). Five patients developed late radiation-associated complications; no myelopathy developed, but three grade 3 sacral neuropathies appeared after doses of 77.1 Gy(RBE) to 77.4 Gy(RBE) had been delivered. A recent update with median follow-up of 7.3 years, continues to show excellent local control in patients with primary tumors, with estimated local control at 8 years of 85% with an acceptable rate of grades 3 to 4 complications of 13% at 8 years.[18]

Recently, the MGH group reported the results on 24 patients treated with high-dose proton based definitive radiotherapy for unresected spinal chordomas.[19] Tumor locations included cervical (2), thoracic (1), lumbar (2), S1 to S2 (17), and S3 or below (2). Median total dose was 77.4 Gy(RBE). Analysis at median follow-up of 56 months showed overall survival of 91.7% and 78.1%, chordoma specific survival of 95.7% and 81.5%, local progression free survival of 90.4% and 79.8%, and metastases-free survival of 86.5% and 76.3%, at 3 and 5 years, respectively. Long-term side effects included eight sacral insufficiency fractures (none required surgical stabilization), one secondary malignancy, one foot drop, one erectile dysfunction, one perineal numbness, two worsening urinary/fecal incontinence, and four grade-2 rectal bleeding. None required new colostomy. All surviving patients remained ambulatory.

Optic Pathway Glioma

At Loma Linda University, seven children with optic pathway gliomas were treated with proton radiation therapy.[20] At a median follow-up of 37 months, all tumors were locally controlled. A reduction in tumor volume was seen in three patients, and tumor volume was stable in the other four. Visual acuity was stable in those who presented with useful vision. Proton plans were compared with 3D conformal photon plans for individual patients. With proton therapy there was a 47% reduction in the dose to the contralateral optic nerve. There was an 11% reduction in the dose to the chiasm and a 13% reduction in the dose to the pituitary gland. There was also a reduction in the dose to the temporal lobes and frontal lobes.

Astrocytoma

Between 1993 and 1998, 48 patients were treated for nonresectable grades II and III intracranial tumors at the Center for Proton Therapy in Orsay, France.[21] Mean tumor doses ranged from 63 Gy(RBE) to 67 Gy(RBE) at 1.8 Gy(RBE)/fraction. With a median follow-up of 18 months, local control rates were 97% (33 of 34 patients) and 43% (6 of 14 patients) for nonparenchymal and parenchymal lesions, respectively.

At the Harvard Cyclotron Laboratory (HCL) and MGH a Phase II study was undertaken to assess whether dose escalation to 90 Gy(RBE) with conformal protons and photons in accelerated fractionation twice a day would improve local tumor control and survival rates.[22] A total of 23 patients were enrolled, with ages of 18 to 70 years. Actuarial survival rates at 2 and 3 years were 34% and 18%, respectively. The median survival time was 20 months, with 4 patients alive 22 to 60 months after diagnosis. All patients developed new areas of gadolinium enhancement during the follow-up period. Histologic examination of tissues obtained at biopsy, resection, or autopsy was conducted in 15 patients. Radiation necrosis only was demonstrated in 7 patients, and their survival was significantly longer than patients with recurrent tumor. Tumor regrowth occurred most commonly in areas that received doses of 60 Gy(RBE)to 70 Gy(RBE) or less; recurrent tumor was found in only 1 patient in the group that received a dose of 90 Gy(RBE). The authors concluded that attempts to extend local control by enlarging the volume would likely be complicated by a high incidence of radionecrosis.

Benign Meningioma

Surgical resection of meningiomas is often limited by their location, which may be the sphenoid ridge, parasellar area, or posterior fossa. Likewise, radiation therapy for these intracranial tumors is complicated by the proximity of critical structures, notably, the visual system. Proton beam radiation, with its high degree of conformality, therefore would seem to be an attractive treatment modality.

Between 1981 and 1996, 46 patients with partially resected, biopsied, or recurrent benign meningiomas were treated with combined proton/photon radiation at HCL/MGH.[23] The median dose to the tumor was 59 Gy(RBE). Overall survival rates at 5 and 10 years were 93% and 77%, respectively, and recurrence-free rates at 5 and 10 years were 100% and 88%, respectively. Three patients presented with local tumor recurrence at 61, 95, and 125 months. One patient died of focal brain necrosis at 22 months. Neurologic complications, including memory deficits and hearing loss, were also seen. Four patients developed ophthalmologic toxicity. In all of these cases, the maximum dose to the optic structures was more than 58 Gy(RBE). Endocrine abnormalities following treatment were also seen.

Investigators from the Paul Scherrer Institute reported on the treatment of 16 patients with recurrent, residual, or untreated intracranial meningiomas.[24] The median prescribed dose was 56 Gy(RBE) (range, 52 Gy[RBE] to 64 Gy[RBE]) at 1.8 Gy[RBE] to 2 Gy(RBE) per fraction. Cumulative 3-year local control, progression-free survival, and overall survival rates were 91%, 91%, and 92%, respectively. No patient died of recurrent meningioma. Radiographic follow-up (median, 34 months) revealed an objective response in 3 patients and stable disease in 12 patients. The cumulative 3-year toxicity-free survival rate was 76%. One patient with an optic nerve sheath meningioma presented with sudden visual field deterioration of the ipsilateral eye 30 months after irradiation with 56 Gy(RBE). Another patient with optic nerve encasement by disease developed visual deterioration at 9 months. A third patient developed symptomatic brain necrosis 7 months after treatment. No radiation-induced hypothalamic/pituitary dysfunction was observed.

Paranasal Sinus, Nasal, and Nasopharyngeal Tumors

Mock et al[25] performed a planning comparison study of various photon and proton techniques for the treatment of paranasal sinus carcinoma. In five patients, proton plans were compared with conventional, conformal, and IMRT photon plans. The evaluations analyzed dose-volume histogram findings of the target volumes and organs at risk (i.e., the pituitary gland, optic pathway structures, and brain).

The mean and maximal doses, dose inhomogeneities, and conformity indexes for the planning target volumes were comparable for all techniques. Photon plans resulted in greater volumes of irradiated nontarget tissues at the 10% to 70% dose level compared with the corresponding proton plans. Compared with conventional techniques, conformal and IMRT photon treatment planning options similarly reduced the mean dose to the organs at risk. The use of protons further reduced the mean dose to the organs at risk by up to 65% and 62% compared with conformal and IMRT techniques, respectively.

Truong et al[26] performed a retrospective review of 20 patients with locally advanced primary sphenoid sinus malignant tumors treated between 1991 and 2005 with proton radiotherapy to a median dose of 76 Gy(RBE) to determine treatment outcome and prognostic factors. With a median follow-up of 27 months, the 2-year local, regional, and freedom from distant metastasis rates were 86%, 86%, and 50%, respectively. The disease-free and overall survival rates at 2 years were 31% and 53%, respectively. In multivariate analysis, oropharyngeal involvement ($p = 0.005$) and anterior cranial fossa invasion ($p = 0.02$) were predictive for poor disease-free survival rates. Brain invasion was predictive for decreased overall survival ($p = 0.05$). No grade 3 or 4 late visual toxicity was reported.

Three patients developed chronic nasal symptoms after radiotherapy, consisting of common toxicity criteria (CTC) grades 2 to 3 nasal obstruction secondary to fibrous adhesions. One patient required surgical removal of adhesions to relieve chronic nasal congestion. One patient with symptomatic CTC grade-2 brain toxicity experienced seizures and short-term memory loss. The seizures were controlled with anticonvulsant medications and a short course of steroids. Two patients experienced cerebrospinal fluid leakage after surgery and irradiation. One patient developed a CTC grade-2 cerebrospinal fluid leak from the external auditory canal, secondary to tumor shrinkage and erosion of the petrous temporal bone 5 months after radiotherapy. One patient developed a CTC grade-5 cerebrospinal fluid leak without evidence of tumor recurrence at 2 months after completion of radiotherapy. The patient underwent four surgical repairs, including transethmoid packing of the ethmoid and sphenoid sinuses and placement of a lumboperitoneal shunt. The patient subsequently died from infectious meningitis. Two patients had endocrinopathies that were medically corrected. The authors concluded that proton radiation therapy results in excellent local control in patients with advanced primary sphenoid sinus malignant disease. Brain invasion and involvement of the oropharynx and anterior cranial fossa were important prognostic factors. Nasal symptoms, brain injury, endocrinopathies, and cerebrospinal fluid leaks, however, complicated treatment.

At Loma Linda University, 16 patients with recurrent nasopharyngeal carcinoma were treated with conformal proton irradiation.[27] Patients had initially been treated with photon therapy at doses of 50 Gy to 70 Gy. Conformal proton boost radiation was then delivered to bring the total dose to 59 Gy(RBE) to 70 Gy(RBE). With a mean follow-up of 23 months, the 24-month actuarial overall and locoregional progression-free survival rates were both 50%. No central nervous system complications were observed. An update now includes data on 39 patients. Twenty-four-month actuarial overall and locoregional progression-free survival rates were 49% and 70%, respectively. When critical central nervous system structures were reirradiated, doses were low (0 Gy[RBE] to 22 Gy[RBE]); one patient experienced grade-4 central

nervous system side effects. Grade-3 late head and neck toxicity occurred in seven patients and grade-4 toxicity in two patients.

Acoustic Neuroma

Between 1991 and 1999, 30 patients with acoustic neuroma were treated with proton therapy at Loma Linda University.[28] Patients with useful hearing before treatment received 54 Gy(RBE) in 30 fractions, and patients without useful hearing received 60 Gy(RBE). Follow-up ranged from 7 to 98 months (median, 34 months), during which no patients demonstrated disease progression on magnetic resonance imaging (MRI) scans. Eleven patients demonstrated radiographic regression. Of the 13 patients with useful hearing before treatment, 4 (31%) maintained their hearing. No transient or permanent treatment-related trigeminal or facial nerve dysfunction was observed. Investigators are now interested in evaluating a reduction in tumor dose in an attempt to increase hearing preservation rates.

Carcinoma of the Prostate

Investigators at MGH completed a Phase III trial comparing 67.2 Gy of photons with 75.6 Gy(RBE) of combined photons/protons using a conformal perineal proton boost.[29] From 1982 to 1992, 202 patients with stage T3 or T4 prostate cancer received 50.4 Gy by four-field photons. Patients then received either 25.2 Gy(RBE) with conformal protons or a 16.8-Gy photon boost. No differences between the two groups were found in overall survival, total recurrence-free survival, or local recurrence-free survival rates. The local recurrence-free survival rate at 7 years for patients with poorly differentiated tumors (Gleason score of 9 or 10) was 85% for the proton arm and 37% for the photon arm. Rates of grades 1 and 2 rectal bleeding were higher in the proton arm (32% versus 12%), as were those for urethral stricture (19% versus 8%). Dose escalation to 75.6 Gy(RBE) by conformal proton boost led to increased late radiation sequelae but not to increased total survival rates in any subgroup. However, there was an improved local recurrence-free survival rate in patients with poorly differentiated tumors.

The Loma Linda University experience of conformal proton therapy for prostate cancer was reported[30] for 1255 patients treated from 1991 to 1997. The overall biochemical disease-free survival rate was 73%, and it was 90% in patients with an initial prostate-specific antigen (PSA) level of ≤4 ng/mL; it was 87% in patients with posttreatment PSA nadirs of ≤0.50 ng/mL. Rates dropped with higher initial and nadir PSA values.

In general, conformal proton beam radiation therapy was well tolerated; the rate of Radiation Therapy Oncology Group (RTOG) grade 3 or higher acute gastrointestinal or genitourinary morbidity was less than 1%. RTOG grade-3 late morbidity was seen in 16 patients (1%) and grade-4 late morbidity in two patients (0.2%). Late gastrointestinal toxicity included grade-3 bleeding and pain in two patients and a bowel obstruction requiring diverting colostomy in one patient. All cases of severe gastrointestinal toxicity presented within the first 2.5 years after treatment. The actuarial 5-year and 10-year rates for freedom from grades 3 and 4 genitourinary toxicity were both 99%.

Late genitourinary morbidity was seen more frequently than gastrointestinal morbidity. Fourteen patients developed grade-3 late toxicity, with eight of them having urethral strictures, followed by hematuria (four patients) and dysuria (two patients). The actuarial 5-year and 10-year rates for freedom from grades 3 and 4 genitourinary toxicity were both 99%. One patient developed necrosis of the symphysis, which was partially included in the treatment field. Because of the low incidence of grades 3 and 4 side effects, no statistically significant prognostic variables for toxicity could be found. These results, when accounting for length of follow-up, compare favorably with those of conformal photon therapy and intensity-modulated photon therapy.

MGH and Loma Linda University conducted a Phase III randomized dose escalation trial in patients with early-stage prostate cancer.[31] Between 1996 and 1999, 393 men with stage T1b to T2b prostate cancer and PSA levels of 15 ng/mL or less were randomly assigned to a total dose of either 70.2 Gy Gy(RBE) or 79.2 Gy(RBE). No patient received androgen suppression therapy with irradiation. Conformal radiation therapy was given in two phases. In phase I, conformal proton beams were used to treat the prostate alone. Either 19.8 Gy(RBE) or 28.8 Gy(RBE) was given in 1.8-Gy(RBE) fractions. In phase II, all men—regardless of trial arm—received 50.4 Gy delivered with photons in 1.8-Gy fractions to the prostate and seminal vesicles. Rates of local failure, biochemical failure, and overall survival were measured as outcomes. With a median follow-up of 8.9 years, men receiving high-dose radiation therapy were significantly less likely to have local failure, with a hazard ratio of 0.57. The 10-year American Society for Therapeutic Radiology and Oncology defined biochemical failure rates were 32.4% for conventional-dose and 16.7% for high-dose radiation therapy ($p < 0.0001$). This difference held when only those with low-risk disease (227 patients; 58% of total) were examined: 28.2% for conventional-dose and 7.1% for high-dose radiation therapy ($p < 0.0001$). There was a strong trend in the same direction for the intermediate-risk patients (144 patients; 37% of total; 42.1% versus 30.4%, $p = 0.06$). Eleven percent of patients subsequently required androgen deprivation for recurrence after conventional-dose radiation therapy compared with 6% after high-dose radiation therapy ($p = 0.047$). There remains no difference in overall survival rates between the treatment arms (78.4% versus 83.4%; $p = 0.41$). Two percent of patients in both arms experienced late grade 3 or higher genitourinary toxicity, and 1% of patients in the high-dose arm experienced late grade 3 or higher gastrointestinal toxicity. This randomized controlled trial shows superior long-term cancer control for men with localized prostate cancer receiving high-dose versus conventional-dose radiation. This dose escalation was achieved with protons without an increase in grade 3 or higher late urinary or rectal morbidity.

Given the significant cost difference and lack of level-1 evidence showing a clear clinical benefit, great controversy exists about the use of proton radiation for prostate cancer instead of conventional photon radiotherapy. Treatment planning studies and retrospective analyzes addressing these issues exist, but prospective head-to-head comparisons between the two treatment modalities are lacking. With that in mind, investigators at MGH and the University of Pennsylvania developed a multiinstitutional randomized trial comparing proton therapy to IMRT in the treatment of patients with low or low-intermediate risk prostate cancer.[32] Patients are randomized to receive 79.2 Gy in 1.8 Gy fractions via IMRT or proton beam therapy. The primary endpoint is post-treatment bowel function. Secondary outcomes to be examined include, quality of life, clinical efficacy, biological, and physics endpoints, and cost.

Just as IMRT radically changed the delivery of photon-based radiation for the treatment of prostate cancer, IMPT offers the possibility of a similar change in the future. IMPT relies on the use of spots scanning to deliver a more conformal dose distribution of radiation, with the potential for an even greater reduction of treatment-related toxicity in comparison

to passive scatter techniques.[33] Another approach being investigated is the use of anterior-oriented beams, which may overcome the issues of tissue heterogeneity brought on by treating through the hip joints.[34]

Gastrointestinal Tumors

Investigators at Tsukuba University in Japan have reported impressive long-term control and survival in 122 patients with primary hepatocellular carcinoma treated with proton radiotherapy.[35] The dose per fraction was 4 Gy(RBE) and the mean total dose was 72 Gy(RBE) (the Tsukuba group did not correct for RBE, so these doses are in physical Gray; hence, the biologically effective dose may have been up to 10% higher). The 7-year local control and survival rates were 94% and 27%, respectively. Proton irradiation did not cause clinically symptomatic changes in liver function. The only notable change observed was a transient increase in liver transaminase levels. In 2012, the group from Tsukuba published a retrospective analysis of 259 patients who received pencil beam therapy for hepatocellular carcinoma between 2001 and 2007.[36] Univariate analysis revealed a significant association between the percentage volume abnormal liver receiving a particular radiation dose and the liver function, as quantitated by the Child-Pugh score.

Investigators at MGH carried out a feasibility study for neoadjuvant hypofractionated proton therapy for pancreatic adenocarcinoma.[36] Tumor and normal tissue dosimetry was evaluated for a treatment regimen of 5 Gy(RBE) × 5 fractions. These plans were compared with IMRT plans with conventional fractionation generated for the same nine patients. Both techniques yielded plans with acceptable target volume coverage and dose homogeneity. Dose-volume histograms for the kidneys, liver, and small bowel were significantly better for the proton plans, and stomach and duodenum doses were similar.

In 2012, the M. D. Anderson Cancer Center (MDACC) group reported results of a prospective study of patients treated with proton beam therapy and concurrent chemotherapy for esophageal cancer.[37] Normal tissue toxicity was the primary focus of this study. Passive scattering protons with a two- or three-field beam arrangement were used. The median dose was 50.4 Gy. The median follow-up for survivors was 20 months. The most common grades 2 to 3 adverse events were dysphagia (43.6%), esophagitis (46.8%), fatigue (43.6%), nausea (33.9%), anorexia (30.1%), and radiation dermatitis (16.1%). There were two cases of grades 2 and 3 radiation pneumonitis and two cases of grade 5 toxicities. The pathologic complete response rate for the surgical cohort (n = 29) was 28%.

Lung Cancer

At Loma Linda University, a prospective study was undertaken to assess the efficacy and toxicity of conformal proton beam radiotherapy for 37 patients with medically inoperable non–small cell lung cancer.[38] Eligible patients had clinical stage I to IIIa non–small cell lung cancer and were not candidates for surgical resection either for medical reasons or because of patient refusal. Patients with adequate cardiopulmonary function received 45 Gy to the mediastinum and gross tumor volume with photons with a concurrent proton boost to the gross tumor volume of an additional 28.8 Gy(RBE). Total tumor dose was 73.8 Gy(RBE) given over 5 weeks. Patients with poor cardiopulmonary function received proton beam radiotherapy to the gross tumor volume only, with 51 Gy(RBE) given in 10 fractions over a 2-week period. Follow-up ranged from 3 to 45 months, with a median of 14 months. Two patients in the proton and photon arm developed pneumonitis that resolved with oral steroids; otherwise, no significant toxicities were encountered. The 2-year actuarial disease-free survival rate for the entire group was 63%; for stage I patients, the 2-year disease-free survival rate was 86% and the local control rate was 87%.

The MDACC group carried out a treatment planning study on 10 patients with stage IIIB non–small cell lung cancer.[39] Dose-volume histograms were generated for plans using IMPT, IMRT, and passive scattering proton therapy (PSPT). The IMRT cases were planned to 60 Gy to 63 Gy, and the proton cases were planned to 74 Gy. The possibility of increasing the total tumor dose with IMPT for each patient without exceeding the dose volume constraints (maximum tolerated dose) was also investigated. Compared with IMRT, IMPT showed improved tissue sparing for virtually every parameter measured, even with dose escalation from 63 Gy to 83.5 Gy, with a mean maximum tolerated dose of 74 Gy. IMPT also showed dosimetric advantages for those cases with complicated tumor anatomies.

Now open to accrual, RTOG 1308 is a Phase 3 randomized trial comparing proton versus photon radiation with concurrent chemotherapy for inoperable stage II-IIIB non–small cell lung cancer.[40] The primary objective is to compare overall survival between arms. Secondary end points will measure toxicity, quality of life, and cost effectiveness of treatment.

Pediatric Cancers

Investigators in Switzerland looked at the potential influence of improved dose distribution with proton beams compared with conventional or intensity-modulated (IM) x-ray beams on the incidence of treatment-induced secondary cancers in children.[41] Two children, one with parameningeal rhabdomyosarcoma and a second with medulloblastoma, were used as models for this study. After defining the target and critical structures, treatment plans were calculated and optimized, four for the rhabdomyosarcoma case (conventional x-ray, IM x-rays, 3D conformal protons, and IM protons) and three for the irradiation of the spinal axis in medulloblastoma (conventional x-ray, IM x-rays, 3D conformal protons). The secondary cancer incidence was estimated using a model by the International Commission on Radiologic Protection. This model allowed estimation of absolute risks of secondary cancer for each treatment plan based on dose-volume distributions for nontarget organs. Proton beams reduced the expected incidence of radiation-induced secondary cancers for the patient with rhabdomyosarcoma by a factor equal to or greater than 2, and for the medulloblastoma cases a factor of 8 to 15 when compared with either IM or conventional x-ray plans. Risks were higher for the patients with medulloblastoma because the target and radiated volumes were larger. This study underscores the concern with using radiation therapy in the treatment of pediatric cancers. It is the goal of clinicians to not only eradicate the primary tumor but also to minimize the risk of radiation-induced malignant tumors over the lifetime of these patients.

In a second MGH study, treatment plans were compared from standard 3D conformal photon therapy to intensity-modulated x-rays (IMRT) and 3D conformal protons for craniospinal axis irradiation and posterior fossa boost in a patient with medulloblastoma.[42] Substantial normal tissue sparing was realized with IMRT and proton irradiation of the posterior fossa and spinal axis (Figures 19-2 and 19-3). The dose to 90% of the cochlea was reduced from 101% of the prescribed posterior fossa boost dose from conventional x-rays to 33% and 2% from IMRT and protons, respectively. The dose to 50% of the heart volume was reduced from 72% for photons to 30% for IMRT and 0.5% for protons.

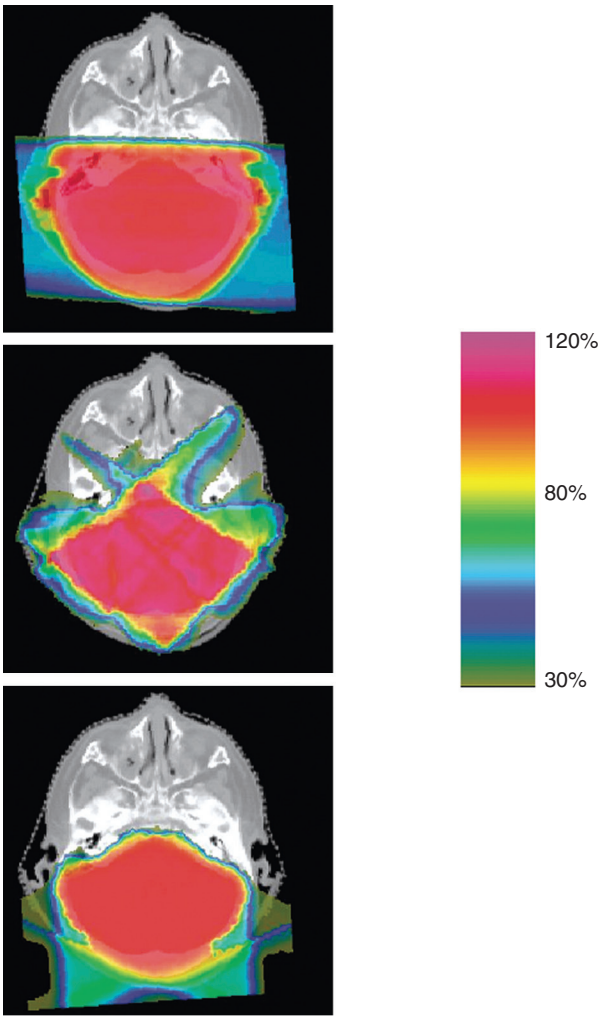


Figure 19-2 Three-dimensional conformal photon therapy *(upper panel)*, IMRT *(middle panel)*, and passively scattered proton therapy *(lower panel)* dose distributions for delivery of the posterior fossa boost in a patient with medulloblastoma. Note the absence of dose to the temporal lobes, pituitary, orbits, and cochlea that can be achieved with protons but that is not possible with three-dimensional conformal therapy or IMRT. This additional dose to nontarget normal tissues offers only potential morbidity to these young patients.
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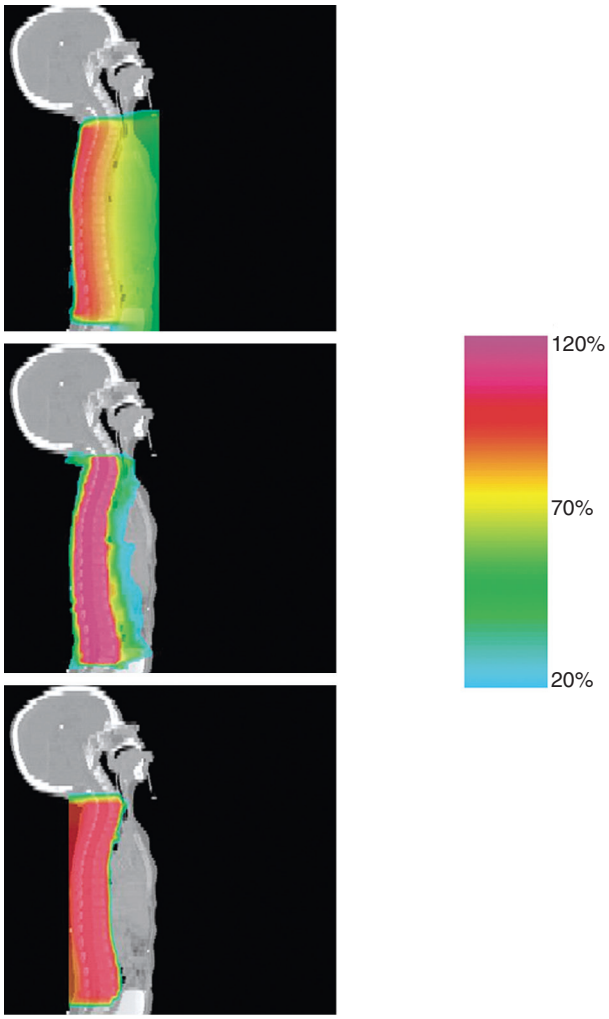


Figure 19-3 Sagittal dose displays for the spinal irradiation field in a child with medulloblastoma undergoing craniospinal irradiation with either three-dimensional conformal photons *(upper panel)*, IMRT *(middle panel)*, or passively scattered proton fields *(lower panel).* Note the absence of significant exit dose beyond the anterior border of the vertebral bodies with protons, so that the bowel, heart, and mediastinum are spared from potential side effects of radiotherapy.
Reprinted, with permission, from St. Clair WH, Adams JA, Bues M, et al: Advantage of protons compared to conventional X-ray or IMRT in the treatment of a pediatric patient with medulloblastoma. Int J Radiat Oncol Biol Phys 58(3):727–734, 2004.

Merchant et al[43] modeled the dose characteristics to critical normal tissue volumes using data from patients with four types of childhood brain tumors. 3D imaging and treatment planning data, including targeted tumor and normal tissue contours, were acquired for 40 patients, 10 each with optic pathway glioma, craniopharyngioma, infratentorial ependymoma, and medulloblastoma. Dose-volume data were collected for the entire brain, temporal lobes, cochlea, and hypothalamus from each patient. The data were averaged and compared based on treatment modality (protons versus photons) using dose-cognitive effects models. Outcomes were estimated over 5 years. The results suggested that relatively small critical normal tissue volumes such as the cochlea and hypothalamus may be spared from radiation exposure when they are not adjacent to the primary tumor volume. It was found that larger normal tissue volumes such as the supratentorial brain or temporal lobes receive less of the low and intermediate doses with protons. When applied to longitudinal models of radiation dose-cognitive effects, these differences resulted in estimated clinically significant higher IQ scores for patients with medulloblastoma and craniopharyngioma and higher academic reading scores in patients with optic pathway glioma. Extreme differences between proton and photon dose distributions precluded meaningful comparison of protons and photons for patients with infratentorial ependymoma. The authors concluded that differences in the overall dose distributions, as indicated by modeling changes in cognitive function, showed that a reduction in the lower-dose volumes or mean dose with protons would have long-term, clinical advantages for children with medulloblastoma, craniopharyngioma, and optic pathway glioma.

Loma Linda University investigators evaluated the safety and efficacy of proton beam irradiation in the treatment of

pediatric patients with intracranial low-grade astrocytoma.[44] Between 1991 and 1997, 27 patients underwent fractionated proton radiation therapy for progression of recurrent low-grade astrocytoma. Patients were 2 to 18 years old. Twenty-five of the 27 patients (92%) were treated for progressive, unresectable, or residual disease following subtotal resection. The mean target dose was 55.2 Gy(RBE) (range, 50.4 Gy[RBE] to 63 Gy[RBE]) and the fraction size was 1.8 Gy(RBE). At a mean follow-up period of 3.3 years (range, 0 years to 6.8 years), 6 of 27 patients experienced local failure within the irradiated field and 4 of 27 had died. Local control and survival rates were 87% and 93%, respectively, for centrally located tumors, 71% and 86% for hemispheric tumors, and 60% and 60% for tumors of the brainstem. All children with local control maintained their performance status except one, who developed moyamoya disease. All 6 patients with optic pathway tumors and useful vision maintained or improved their visual status.

Atypical teratoid/rhabdoid tumors (AT/RT) are rare, aggressive tumors that often affect infants. Although they can occur anywhere in the body, they are frequently found in the central nervous system. Fear of significant long-term neurocognitive sequelae in this population has historically limited the use of radiation therapy. Recently, investigators at MGH published their early clinical experience for 10 consecutive patients (median age of 2.3 years) who underwent maximal resection followed by 3D-conformal proton therapy.[45] With a median follow-up of 27.3 months, 2 patients had a distant relapse; 1 patient was successfully treated with involved field irradiation and chemotherapy, whereas the second patient died of disease. At last follow-up, 9 patients were alive without evidence of disease without major radiation therapy-related toxicities.

Investigators at Loma Linda and MGH developed a proton radiation technique for the treatment of orbital rhabdomyosarcoma. The technique, along with a dosimetric analysis for two patients was recently published.[46] Dose-volume histograms were obtained for target and nontarget regions, including the lens, bony orbit, pituitary gland, optic chiasm, optic nerves, lacrimal gland, and ipsilateral frontal and temporal lobes. Doses to 90%, 50%, and 5% of lens volume were kept at less than 1%, less than 2%, and less than 8%, respectively. At a mean follow-up of 3 years, visual acuity for both patients was excellent and there was no evidence of cataract formation. Furthermore, pituitary function was normal; cosmetically, only mild enophthalmos was noticeable. The steep dose gradient beyond the orbit minimized irradiation of normal brain parenchyma, with sparing of the pituitary gland (Figure 19-4).

The MGH group recently updated their experience for pediatric patients treated with proton irradiation for intracranial ependymoma.[47] Seventy patients with localized ependymoma were treated with conformal proton radiation using at least three fields. The median age at diagnosis was 38 months (range, 3 months to 20 years). At a median follow-up of 46 months, 3-year local control, progression-free survival, and overall survival were 83%, 76%, and 95%, respectively. In a subset of patients (n = 14), mean intelligence was 108.5 at baseline and 111.3 after a mean 2.05 years of follow-up. In a larger group of patients (n = 28), overall adaptive skills were 100.1 at baseline and 100.8 after 2.21 years of follow-up. Few patients developed evidence of growth hormone deficiency, hypothyroidism, or hearing loss (Figure 19-5).

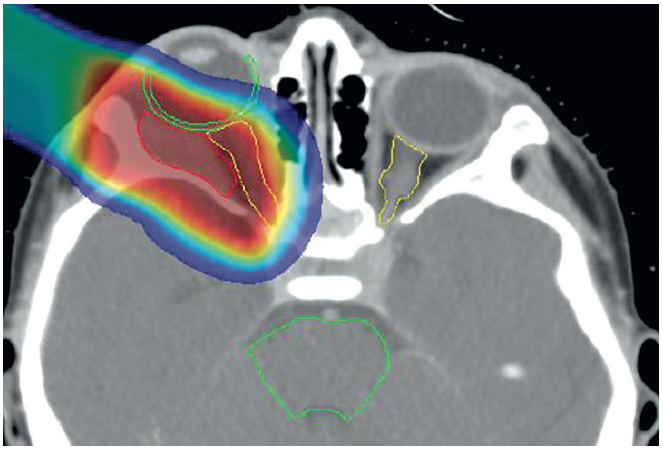


Figure 19-4 Right anterior oblique proton beam radiation therapy field for treatment of a child with a right orbital rhabdomyosarcoma. Note the absence of exit dose to the pituitary, contralateral orbit, and contralateral temporal lobe.
Courtesy Nancy Tarbell, MD, Torunn Yock, MD, and Judy Adams, CMD.

Breast Cancer

Some patients with breast cancer have anatomic configurations that make it difficult to adequately treat the breast while sparing the underlying lung and heart. A treatment planning exercise was undertaken comparing standard photon therapy with IMRT and proton therapy in the treatment of breast cancer.[48] Using computed tomography (CT) data from a patient with breast cancer, treatment plans were computed for the different treatment techniques. A dose of 50 Gy was prescribed to the target volume consisting of the involved breast and the internal mammary, supraclavicular, and axillary nodes. Comparison of plans revealed worse dose heterogeneity for the photon plan versus the other two plans. Lung dose-volume histograms for the photon and IMRT plans were comparable, whereas the proton plan showed the best sparing over all dose levels. Mean doses to the ipsilateral lung for the three plans were 17 Gy, 15 Gy, and 13 Gy, for the photon, IMRT, and proton plans, respectively. For the heart, the IMRT plan delivered the highest mean dose (16 Gy), reflecting the extra dose delivered through this organ to spare the lungs. This was reduced somewhat by the standard plan (15 Gy), with the best sparing being provided by the proton plan (6 Gy). When the IMRT plan was reoptimized with an increased precedence to the normal tissues, the mean doses to all neighboring organs at risk could be reduced but only at the cost of substantial target dose heterogeneity. Only the two-field, energy-modulated proton plan had the potential to preserve target dose homogeneity while simultaneously minimizing the dose delivered to the lungs, heart, and contralateral breast.

The MGH group recently published results of a prospective study investigating the use of proton therapy for the delivery of postmastectomy radiation.[49] The 12 patients enrolled received proton radiation to a dose of 50.4 Gy(RBE) to the chest wall and 45 Gy(RBE) to 50.4 Gy(RBE) to the regional lymphatics. The maximum skin toxicity observed was grade 2. No cases of radiation pneumonitis have been reported.

Proton therapy is also being investigated for partial breast irradiation. The Loma Linda group recently reported results of their Phase II trial.[50] Fifty patients who underwent lumpectomy for early stage breast cancer were enrolled. The median follow up was 48 months. Acute toxicities were limited to mild radiation dermatitis. Late skin toxicities included three grade 1 telangiectasias. There were no posttreatment infections or ulcerations and no cases of fat necrosis, rib fractures, radiation pneumonitis, or cardiac events. Actuarial 5-year overall survival and disease-free survival rates were 96% and 92%, respectively.

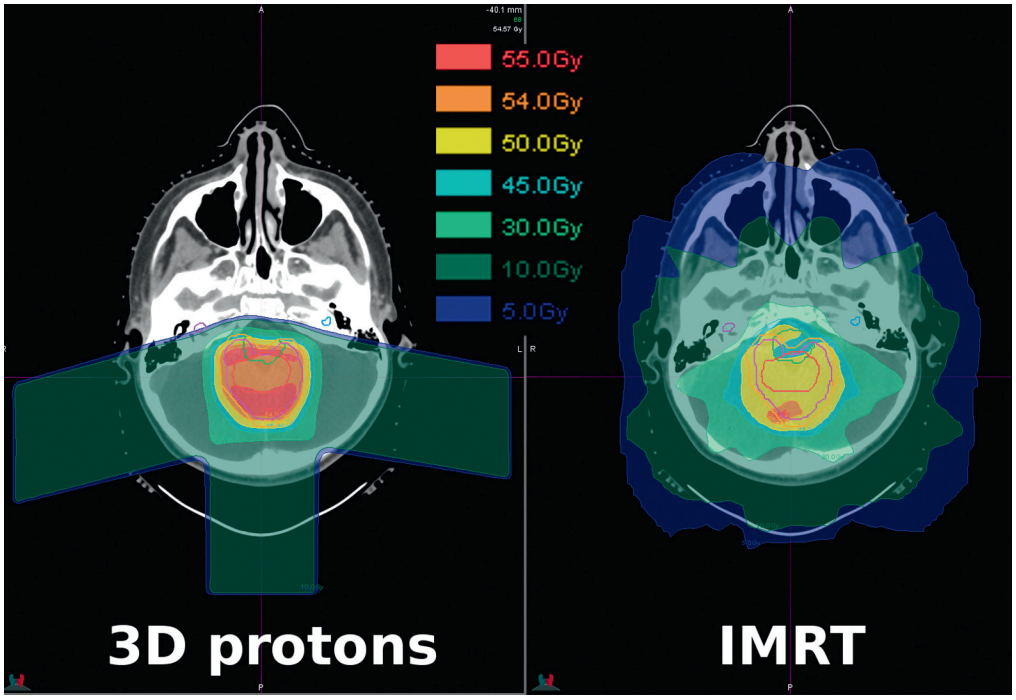


Figure 19-5 Intensity-modulated radiation therapy (IMRT) and three-dimensional proton radiation dose distributions for treatment of the posterior fossa.
Courtesy Shannon MacDonald, MD.

TECHNIQUES OF PROTON BEAM DELIVERY

Currently, most proton facilities use passive scattering for beam delivery. With this technique, a spatially uniform dose distribution is achieved by scattering and degrading the primary proton beam in a set of distributed absorbers. Passive systems use either single- or double-scattering foils. The foil is made of high-Z material such as lead, and effectively scatters the beam while keeping energy loss to a minimum. Generally speaking, double-scatter systems are preferred because larger, more uniform beams can be generated (Figure 19-6).

Beam shaping is accomplished with the use of some devices that are patient- and field-specific and some that are not. *Range modulation* refers to the concept that pristine Bragg peaks must be spread out to be clinically useful. In the passive scatter system this is done with either a propeller-shaped modulator (Figure 19-7) or a ridge filter, which is not patient-specific but may be range-specific, with a small library of range modulators available to address the different range modulator options that might be clinically desired. The Bragg peaks are spread out by placing these devices, which have variable thicknesses in the path of a given beam. The thicker the modulator, the more the beam is shifted in range.

Additional beam conformality is achieved with the use of patient-specific devices (Figure 19-8). Brass apertures are formulated to be used for a specific field for a given patient. Apertures are equivalent to the blocks used in conventional radiation therapy. In January 2010, the University of Pennsylvania Health System received approval from the Food and Drug Administration (FDA) to use multileaf collimators in their new proton facility.

A range compensator is another patient-specific beam modulator. This device is a block of plastic that is milled by a computer lathe for a specific field and is responsible for conforming the distal edge of the beam, necessary because of the variability in individual proton range secondary to differences in radiologic density in the tissue along their particular trajectory. Unfortunately, for historical reasons, a range compensator is sometimes referred to as a "bolus." But this should not be confused with the bolus that is directly applied to the patient's skin in conventional radiation therapy. This device is actually located adjacent to the brass aperture in the snout of the accelerator, above the patient.

Use of patient-specific devices that must be formulated for each beam angle is not a trivial matter in terms of labor and

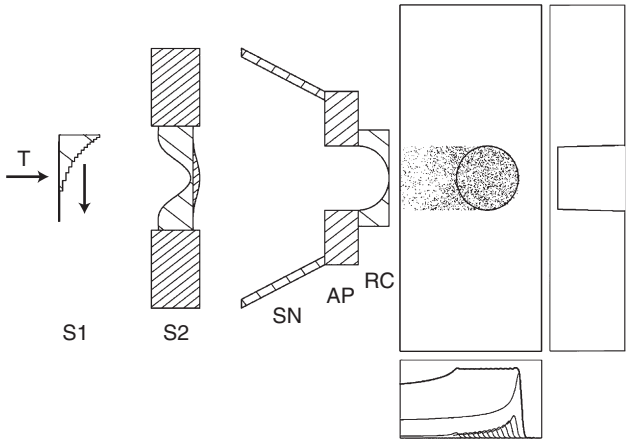


Figure 19-6 Double scattering system uses a first *(S1)* and second *(S2)* scatterer with a beamline snout *(SN)*, which shields scattered protons and permits the mounting of patient-specific apertures *(AP)* and range compensators *(RC)*. The example illustrates the effect of the range compensator in water and indicates the sharp lateral fall-off achieved by the aperture.
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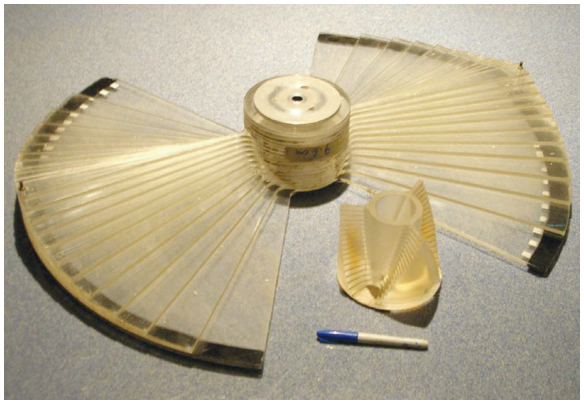


Figure 19-7 Two examples of range modulators, upstream *(small)* and downstream. Both are characterized by a "staircase" structure to achieve the differential pullback of the pristine proton beam and variable widths of the "stair steps" to achieve differential weighting of the shifted pristine peak contribution to the spread-out Bragg peaks. The downstream range modulator is large to cover the clinical area of the scattered proton beam at the downstream position.
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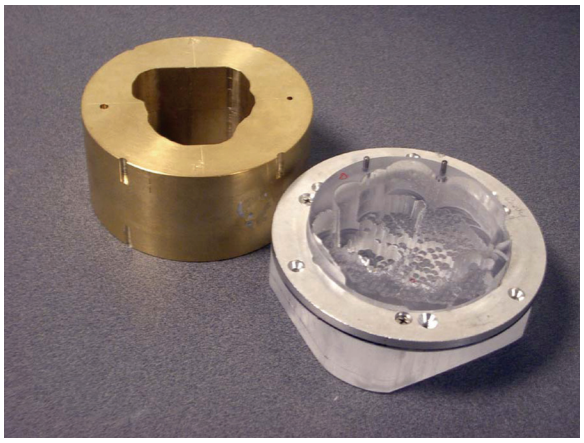


Figure 19-8 Patient-specific brass aperture to achieve lateral field confirmation to the target volume and a polymethyl methacrylate (PMMA) range compensator to achieve distal confirmation.
Reprinted with permission from Gottshalk B: Passive beam scattering. In DeLaney TF, Kooy H, editors: Proton and charged particle radiotherapy. Philadelphia, 2007, Lippincott Williams and Wilkins, Figure 5A.6, p 37.

cost. Furthermore, insertion and removal of the heavy apertures for each field is time-consuming and potentially dangerous for therapists and technicians. This process adds a significant amount of time to each patient's treatment and limits the total number of patients treated by an accelerator.

Although proton therapy has the potential to spare more healthy tissue than x-ray therapy, by virtue of physical qualities of the Bragg peak, there is a concern for increased neutron production. Neutrons can be generated whenever high-energy protons are slowed down by nuclear interactions. Such events can take place inside or outside of the patient. There is a certain amount of neutron production that takes place from proton interactions within the patient, and this is unavoidable and relatively modest. But with the passive scatter system, neutrons are primarily produced from proton interactions with scattering material and collimators in the accelerator. Hall[51] determined that this external neutron dose was more than 100 times the internal dose. Others argue that Hall's technical assumptions and calculations reflect the worst case scenario of treatment of a small target with a large amount of brass in the aperture, and still other investigators have measured substantially lower levels of neutrons, because the number of neutrons generated will be a function of the specific beam line as well as the beam-modifying hardware upstream from the patient.[52]

Chung et al[53] quantified the risk of a second malignant tumor associated with the use of proton therapy compared with photon radiation therapy. In this retrospective cohort analysis, 558 patients treated with protons at the HCL from 1973 to 2001 were matched with 558 patients from the Surveillance Epidemiology and End Results (SEER) Program database. With a median follow-up of more than 6 years, a second cancer developed in 5.2% of proton patients and 7.5% of photon patients (adjusted hazard ratio of 0.52 [0.32 to 0.85]; $p = 0.009$). Although the magnitude of neutron production and its clinical significance in contributing to radiation-induced malignant disease have been hotly debated, these data indicate that the use of proton radiotherapy was not associated with a significantly increased risk of secondary malignancies compared with photon therapy. Furthermore, active beam scanning will markedly reduce external neutron contamination, and for this reason, will be preferred over the passively scattered beam technique.

Active Scanning

The next step in the evolution of proton beam delivery is active (spot or pencil beam) scanning. With passive scanning, it is difficult to obtain large, uniform fields without significant energy loss, even with double scattering systems. In 1980, investigators in Japan first described a spot scanning system.[54] The technique was further refined by the group at the Paul Scherrer Institute in Switzerland.[55] With this technique, the beam is not spread out or scattered; rather, a narrow pencil beam is precisely steered through the treatment volume by magnets in the beam line nozzle. One of the benefits of this system is that there may not be any field-specific or patient-specific hardware; therefore, the time and cost of fabrication are avoided. Furthermore, the speed of the treatment is increased because these heavy devices do not need to be changed for each treatment field. Most importantly, neutron production is greatly diminished with the absence of this hardware.

These pencil beams deposit the dose layer by layer, with the distal edge treated first and the more superficial layers treated thereafter (Figure 19-9). Active scanning also allows for good conformation of the proximal edge of the treatment volume, which is typically not the case with passive scanning. This ability to conform the dose to the proximal tumor volume may further be enhanced with the use of IMPT. This excellent dose-shaping ability of IMPT makes it the best technique for the treatment of irregularly shaped tumors.

Perhaps the greatest concern about active scanning is the issue of organ motion. Because of this, active scanning should be reserved for tumor sites that have minimal motion and can be well immobilized, such as the head and neck, spinal cord, and low pelvis unless specific organ motion strategies are implemented. Several strategies have been developed to address the problem of organ motion. One technique is to repaint the same volume several times with the scanning beam, allowing for an averaging effect of the dose. Gating, as is used in the treatment of lung cancer, with photons is also an option. The spot size of the beam, as well as the scanning speed, can be manipulated as well.

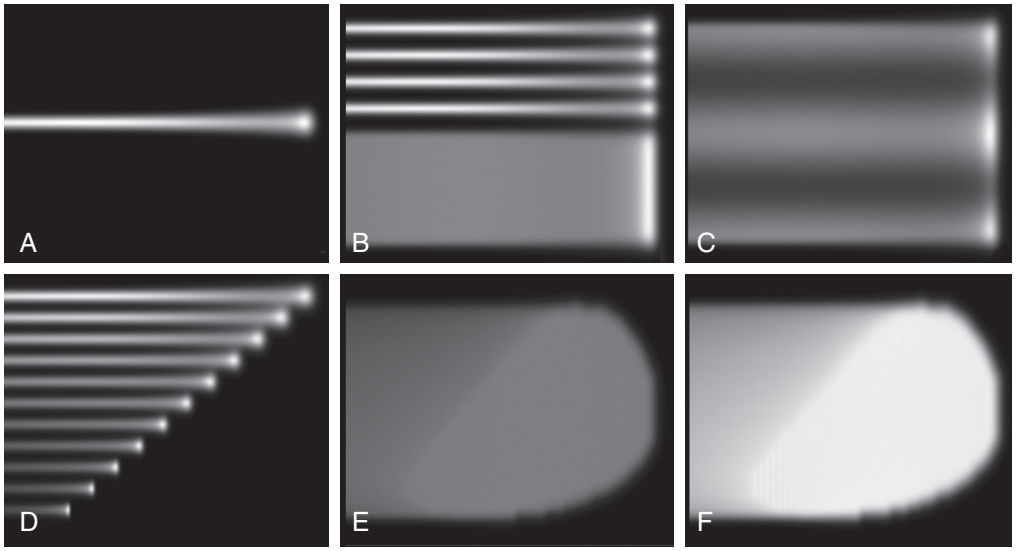


Figure 19-9 **A,** The proton pencil, with a (gaussian) spread of about 3 mm, enters into the patient. The lateral broadening of the pencil beam resulting from multiple coulomb scattering (MCS) in the patient body is small but not negligible. The dose distribution of such a pencil beam shows a sharp maximum near the end of the range and is well localized in the Bragg peak in all three dimensions within a "spot" volume of about 1 cm^3. The superposition of these spots, scanned on a three-dimensional grid in steps of ~5 mm, can be delivered to produce a three-dimensional dose distribution that conforms to the target volume in all three dimensions **(F),** albeit with an unavoidable entrance dose. **A,** Single pencil beam. **B,** Lateral scanning. **C,** The dose is shaped by changing the dosage of each spot, the speed of the scan, or the intensity of the beam. **D,** A homogeneous dose is produced by changing the energy of the beam. **E,** Repainting delivers a lower dose to the target volume per painting and is repeated to deliver the total target dose. **F,** The summation of many pencil beams in the lateral direction and in depth results in a conformal homogeneous dose distribution. *Reprinted with permission from Pedroni E: Pencil beam scanning. In DeLaney TF, Kooy H, editors: Proton and charged particle radiotherapy. Philadelphia, 2007, Lippincott Williams and Wilkins, Figure 5B-1, p 42.*

COST COMPARISONS FOR PROTON BEAM RADIOTHERAPY

All of the clinical and treatment planning results that have been reported indicate that proton beams offer a significant potential for improvements in clinical outcomes for cancer patients over a broad range of disease sites. There is hope that prospective clinical trials that have begun in the new hospital-based proton therapy facilities will establish the magnitude of these improvements. It will be important for physicians and patients and even society in general to have some sense of the cost of these benefits, to be able to place them in an appropriate context and allow comparison with other medical interventions. Goitein and Jermann[56] performed cost comparisons between proton radiation therapy and technically sophisticated photon radiation therapy in an effort to define the relative costs of the technologies. The expense of proton therapy per patient is expected to decrease as more facilities are built and greater numbers of patients are treated. The adoption of hypofractionation and beam scanning, as well as technical advances including smaller proton facilities, is expected to further reduce the cost. At the present time, when neither costs nor benefits have been adequately determined, it is not possible to carry out a reliable cost-benefit analysis. Goitein and Jermann[56] were able to estimate that the relative cost of proton beam radiation therapy compared with intensity-modulated photon beam radiation therapy was in the range of 2.4 in 2003 but might come down to 1.7 to 2.1 over time. Studies that have assessed cost-effectiveness suggest that protons will be cost-effective for pediatric malignant disease because of the reduction in late effects associated with the 50% to 60% reduction in integral dose associated with protons.[57]

CARBON ION RADIOTHERAPY

Carbon ions have a slight physical advantage over protons in that they will have a narrower penumbra than protons, particularly for deep-seated tumors.[58] On the other hand, carbon ions will also produce some spallation products deep to the Bragg peak. Whether the higher RBE and differential effect on hypoxic cells of carbon ions will translate into a clinical advantage remains to be determined, particularly because the clinical use of carbon has generally been with larger fraction sizes where there will be less RBE difference between carbon ions and protons. Because of the higher ionization and double-strand break density with carbon ions, they would logically of the greatest potential value in areas of gross tumor to minimize late normal tissue injury.

The Heavy Ion Medical Accelerator (HIMAC) in Chiba, Japan, began clinical studies in 1994. Kamada et al[59] reported the results of a Phase I/II study evaluating the tolerance and effectiveness of carbon ion radiotherapy in patients with unresectable bone and soft-tissue sarcomas. Fifty-seven patients with 64 sites of sarcomas not suited for resection received carbon ion therapy. Tumors involved the spine or paraspinous soft tissues in 19 patients, pelvis in 32 patients, and extremities in 6 patients. The total dose ranged from 52.8 to 73.6 carbon GyE and was administered in 16 fractions over 4 weeks (3.3 GyE/fraction to 4.6 GyE/fraction). Seventeen of the patients treated with the highest total dose of 73.6 GyE experienced RTOG grade-3 acute skin reactions. No other severe acute reactions (grade >3) were observed. The overall local control rates were 88% and 73% at 1 and 3 years of follow-up, respectively. The 1- and 3-year overall survival rates were 82% and 46%, respectively. It will be important to continue close follow-up to ensure that the large dose fractions are not associated with late injury of normal tissue.

Raster scanned carbon ion radiation therapy was used to treat patients at the Gesellschaft für Schwerionenforschung in Darmstadt, Germany, from 1997 to 2009, following which the program was transferred to the Heidelberg Ion Therapy Center. Between November 1998 and July 2005, a total of 96 patients with chordomas of the skull base were treated with carbon ion radiation therapy.[60] All patients had gross residual tumors. The median total dose was 60 Gy(RBE) (range, 60 Gy[RBE] to 70 Gy[RBE]), delivered in 20 fractions within 3 weeks. The mean follow-up was 31 months (range, 3 months to 91 months). Fifteen patients developed local recurrences after carbon ion radiation therapy. The actuarial local control rates were 80.6% and 70% at 3 and 5 years, respectively. Target doses in excess of 60 Gy(RBE) and primary tumor status were associated with higher local control rates. Overall survival rates were 91.8% and 88.5% at 3 and 5 years, respectively. Grade 3 toxicity was seen in 4% of patients and consisted of fat necrosis and optic neuropathy.

Kato et al[61] from Chiba, Japan, recently reported the results of a carbon ion dose escalation study for 24 patients with hepatocellular carcinoma. Fifteen fractions were delivered over 5 weeks, and total doses ranged from 49.5 Gy to 79.5 GyE. During a median follow-up of 71 months (range, 63 months to 83 months), no severe adverse effects or treatment-related deaths occurred. The overall tumor response rate was 71%. The local control and overall survival rates were 92% and 92%, 81% and 50%, and 81% and 25% at 1, 3, and 5 years, respectively.

Additional encouraging results with carbon ions have been reported for uveal melanoma, head and neck malignancies of multiple histologies, prostate cancer, and early stage non–small cell lung cancers. No clinical trials directly comparing lower LET protons with higher LET carbon ions have been completed to date but these are now under way. Randomized clinical trials of carbon ions versus protons are now being conducted at the Heidelberg Ion Therapy Center for patients with glioblastoma and skull-base chordomas and chondrosarcomas.

NEON ION RADIOTHERAPY

High-LET charged particle therapy with neon ions was studied in the treatment of glioblastoma of the brain because of the neon ion's increased biologic potential for destruction of radioresistant tumors. At the University of California, San Francisco (UCSF), and Lawrence Berkeley Laboratories (LBL), 15 patients were entered into a randomized protocol comparing two dose levels of neon ion irradiation,[62] either 20 Gy or 25 Gy in 4 weeks. However, there was no significant difference in overall survival time (13 to 14 months). Furthermore, an optimal dose level was not identified. Neon ions are not in current clinical use.

π-MESON RADIOTHERAPY

Subatomic particles called *π-mesons* provide the nuclear binding force between nuclei. These particles are produced when protons (600+ MeV) affect a target. Three types of mesons are produced: a neutral form, a positive form, and a negative form. It is the negative form, π^-, that is used for radiotherapy. When the π^- slows down, it is "captured" by a nucleus, causing it to "explode" in a "star" event, producing neutrons and charged nuclear fragments having high-LET properties[63] (Figure 19-10).

Negative π-mesons (pions) were used to treat 228 patients at the Los Alamos Meson Physics Facility between 1974 and 1981. One hundred twenty-nine patients received pion therapy only. All patients had locally advanced disease, and a number of different sites were treated. Local control was achieved in

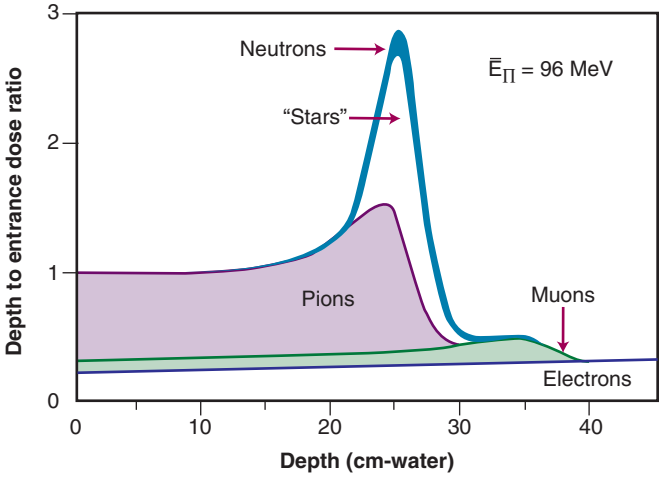


Figure 19-10 Illustration of negative π^- meson capture. When the π^- slows down, it is "captured" by a nucleus, causing it to "explode" in a "star" event, producing neutrons and charged nuclear fragments with high-LET properties.

86% of patients with prostate cancer, in 26% with head and neck cancers, and in none with pancreatic cancer. A steep rise in the complication rate was seen beyond a dose level of 3750 cGy.[64] π-Mesons are also no longer in clinical use.

HELIUM RADIOTHERAPY

A retrospective study was done at UCSF and LBL to evaluate the use of helium ions in the treatment of uveal melanomas.[65] Ten years after helium ion radiation, 208 of the 218 eyes irradiated had local tumor control (95.4%). At 10 years, 46 eyes (22%) had been enucleated; the majority resulting from anterior ocular segment complications. At 10 years, 51 patients (23%) had died of metastatic melanoma. The best corrected visual acuity after irradiation was greater than 20/40 in 21 of 93 eyes (23%) of patients who were alive and who had retained their eyes 10 or more years after treatment. Visual acuity was related to height of tumor and location near the nerve or fovea.

Schoenthaler et al[66] reported on the use of charged particle irradiation for sacral chordomas. At LBL, 14 patients with sacral chordomas were treated with charged particles, either lower LET helium or higher LET neon. All patients were treated postoperatively; 10 had gross disease. The median dose was 7565 cGy and the median follow-up was 5 years. The Kaplan-Meier survival rate at 5 years was 85%, and the overall 5-year local control rate was 55%. A trend in improved local control at 5 years was seen in patients treated with neon ions compared with patients treated with helium ions (62% versus 34%), in patients following complete resection versus patients with gross residual tumor (75% versus 40%), and in patients who had treatment courses less than 73 days (61% versus 21%). No patient developed neurologic sequelae or pain syndromes. One patient who had been previously irradiated required colostomy; 1 patient had delayed wound healing following a negative postradiation biopsy; and 1 patient developed a second malignant tumor. There were no genitourinary complications.

CONCLUSIONS

As discussed, the main benefit of protons over conventional photon beam radiotherapy is a reduction in integral dose. With intensity modulation, dose conformality with protons

and photons are comparable (assuming a small enough proton pencil beam diameter). It remains to be determined how much clinical benefit this reduction in integral dose achieves for patients. From planning studies, the greatest benefit is projected for larger targets (or larger targets relative to the size of the involved or closely approximated critical organ such as would be the case for eye tumors or skull-base tumors) and in younger patients, where studies project a reduction in second cancers[68] and other late effects to render protons cost-effective.[57] With minimization of the normal tissue dose, protons may allow for better tolerance of combined chemotherapy and radiation therapy regimens; indeed, many of the trials of pediatric proton radiation therapy employ chemotherapy in the same way that it has been commonly employed in pediatric protocol-directed therapy for solid tumors.[67]

Heavier charged particles have a sharper penumbra than protons when treating deep targets and may also confer a biologic advantage against tumor because of the higher RBE and differential effect on hypoxic cells, although comparison studies with protons are recommended to see if there indeed is a clinical advantage in using carbon ions over protons, because of the greater complexity and cost of carbon or other heavier charged particles.

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CHAPTER

20 Neutron Radiotherapy

Jason K. Rockhill and George E. Laramore

The neutron was discovered by Sir James Chadwick in 1932 during an analysis of certain nuclear reactions. Shortly thereafter, investigators proposed using it to treat various human malignant diseases. There have been two main areas of clinical investigation: fast neutron radiotherapy and boron neutron capture therapy (BNCT). We briefly describe the underlying physics of each type of therapy, summarize the historical development, and discuss current clinical usage. Space permits only a brief discussion of neutron brachytherapy using californium-252 (^{252}Cf) sources, which is in limited clinical use today. We will restrict our review to the clinical arena and not discuss ongoing basic research.

FAST NEUTRON RADIOTHERAPY

Overview

Fast neutron radiotherapy uses neutrons having typical energies of several tens of megaelectron volts (MeV) that are generated by accelerating either protons or deuterons with cyclotrons or particle accelerators and then delivering them to an appropriate target, most generally beryllium. The resulting distribution of neutrons is approximately spherically symmetric, and the beams used in therapy are collimated in much the same manner as the photon therapy beams generated by electron linear accelerators. Fission neutrons from nuclear reactors that have energies in the range of 1 MeV to 2 MeV can also be used to treat patients. Neutrons are neutral particles and interact directly with the atomic nuclei in tissue, producing recoil protons and nuclear fragments, which in turn create dense chains of ionization events. For neutrons of energies used in radiotherapy, about 85% of the deposited energy is via a "knock-on" reaction ("billiard-ball" type of collision) involving the hydrogen-1 (^{1}H) nucleus, meaning that the kinetic energy release in matter (KERMA) is larger in high-hydrogen-content tissue such as fat or myelin.

The resulting energy transfer is in the range of 20 keV/μm to 100 keV/μm compared with 0.2 keV/μm to 2 keV/μm for the megavoltage photons and electrons used in conventional radiotherapy. It is this higher energy transfer that gives rise to the different radiobiologic properties of fast neutrons, which are advantageous in certain clinical situations. The higher relative biologic effectiveness (RBE) accounts for the different clinical response observed with neutrons as opposed to conventional photon irradiation. Fast neutrons have RBEs in the range of 3 to 3.5 in terms of most normal tissue late effects, RBEs in the range of 4 to 4.5 in terms of damage to the central nervous system, and RBEs in the range of 8 for salivary gland malignant tumors.[1-3] High–linear energy transfer (LET) radiation causes a dense chain of ionizing events affecting both strands of the DNA and therefore makes DNA repair more difficult. Other cellular targets are similarly affected to a greater degree by high LET radiation. Furthermore, high-LET radiation from fast neutrons is less sensitive to the reduced cell-killing effects of hypoxia, with there being nearly equal cell killing under normoxic and hypoxic conditions.

Historical Perspective

Patients were first treated with fast neutron radiotherapy in 1938 by Robert Stone et al[4] at the Crocker Radiation Laboratory (later to become Lawrence Berkeley Laboratories). Two hundred forty patients were treated between 1938 and 1942. Many of these patients had received prior photon irradiation. There were significant radiation sequelae in the few long-term survivors such that clinical interest in fast neutron radiotherapy dropped off significantly for the next 20 years. Brennan and Phillips[5] subsequently reviewed the initial work by Stone et al and showed that an inappropriate value for the neutron RBE had been used in the dose calculations. Hence, many of those initial patients had been inadvertently overdosed.

With a better understanding of the RBE of fast neutron radiotherapy in different tissue types, in the 1970s Catterall et al[6-8] resumed neutron clinical trials at Hammersmith Hospital in London, England. Their results indicated that many advanced head and neck cancers exhibited a good response with acceptable side effects. The interest in fast neutron radiotherapy grew and to date, approximately 30,000 patients have been treated in 41 centers in North America, Europe, Asia, and Africa. Clinical utility has been elucidated through clinical trials and single-institution experiences, and neutron radiotherapy now has fairly well defined and limited indications. There are currently only four operating fast neutron radiotherapy centers throughout the world. These are listed in Table 20-1, along with some of their more important characteristics.

A summary of clinical situations and tumor histologic types for which neutrons have been shown to be advantageous compared with standard photon irradiation follows.

Salivary Gland Tumors

The therapeutic advantage of fast neutron radiotherapy compared to conventional radiotherapy is best established in salivary gland tumors. The RBE for salivary gland tumors is approximately 8, whereas for surrounding normal tissues, the RBE is 3 to 3.5.[1] A typical neutron dose for a salivary gland cancer is approximately 18 nGy (neutron Gray) to 20 nGy. The approximate equivalent photon dose is 60 Gy equivalents (GyE) to 70 GyE as far as normal tissues are concerned but it is in the range of 150 GyE to 160 GyE as far as the tumor is concerned. The therapeutic gain factor for salivary gland tumors is therefore in the range of 2.3 to 2.6.

Early single-institution studies showed neutrons to be beneficial in the treatment of salivary gland tumors. These results led to a prospective randomized trial sponsored by the Radiation Therapy Oncology Group (RTOG) and the Medical Research Council (MRC) of Great Britain.[9] Local control at 10 years was improved in the neutron arm (56% versus 17%; $p = 0.009$). The final report showed a trend toward increased median survival of about 8 months in the neutron arm, but this was not statistically significant. However, the cause of death differed between the two subgroups. Metastatic disease

TABLE 20-1 Location of Operating Fast Neutron Radiotherapy Centers, 2013

Location	Beam Reaction	Comments
United States		
University of Washington Medical Center, Seattle, Washington	50 MeV p→Be	Isocentric gantry and multileaf collimator
Europe		
Tomsk Polytechnical University, Tomsk, Russia	Cyclotron	Mean neutron energy 6.3 MeV
Technisch Universtät Munich, Munich, Germany	Fission neutrons	FRMII reactor, horizontal beam with multileaf collimator, mean neutron energy 1.9 MeV
Africa		
National Accelerator Centre, Faure, South Africa	66 MeV p→Be	Isocentric gantry and jaw collimator

Be, *Beryllium;* d, *deuteron,* FRMII, *Forschungs-Nuetronenquelle Heinz Maier-Leibnitz;* MeV, *million electron volt;* p, *proton.*

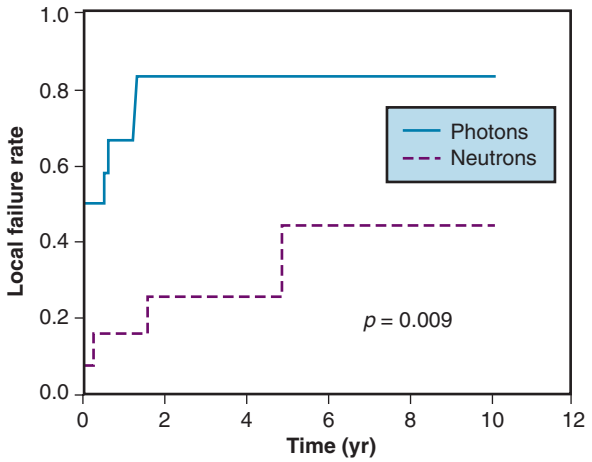


Figure 20-1 Actuarial locoregional control curves for patients with unresectable salivary gland tumors from the Radiation Therapy Oncology Group/Medical Research Council (RTOG/MRC) randomized study (80-01). The difference between the neutron curve *(purple dashed line)* and the photon curve *(blue solid line)* is statistically significant at the $p = 0.009$ level.
Adapted from Laramore GE, Krall JM, Griffin TW, et al: Neutron versus photon irradiation for unresectable salivary gland tumors. Final report of an RTOG-MRC randomized clinical trial. Int J Radiat Oncol Biol Phys 27:235, 1993.

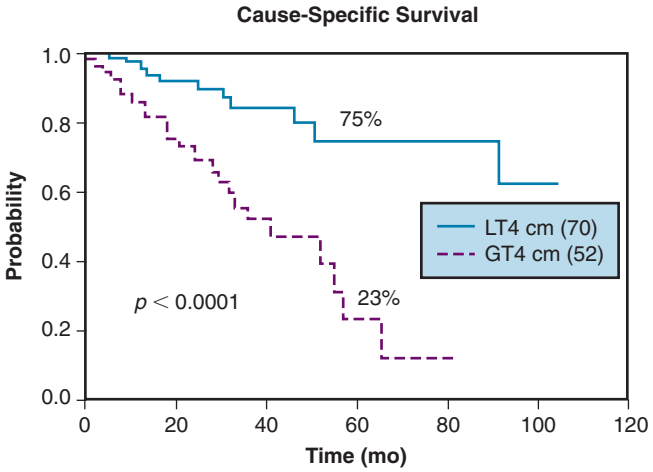


Figure 20-2 Actuarial cause-specific survival curves as a function of tumor size for patients with major salivary gland tumors treated with curative intent at the University of Washington neutron treatment facility. The *blue solid curve* depicts the results for patients with tumors smaller than 4 cm in the greatest diameter, and the *dashed purple curve* depicts the results for patients with tumors larger than 4 cm in the greatest diameter. The difference between the two curves is statistically significant at the $p < 0.0001$ level.
Adapted from Douglas JG, Lee S, Laramore GE, et al: Neutron radiotherapy for the treatment of locally advanced major salivary gland tumors. Head Neck 21:255, 1999.

was the main cause of death for the neutron patients, whereas locoregional tumor failure was the main cause of death for the photon patients. Of note, the study was stopped early for ethical reasons when 2-year survival data showed a strong trend in favor of the neutron patients. Local tumor recurrence curves for this study are shown in Figure 20-1.

The University of Washington experience was reviewed by Douglas et al.[10,11] Two hundred seventy-nine patients treated with curative intent were included in the analysis. A majority (263 patients) had evidence of gross disease, with 141 having major salivary gland neoplasms and 138 having minor salivary gland neoplasms. The 6-year actuarial cause-specific survival rate was 67%. On multivariate analysis, stage I/II disease, minor salivary gland primary tumors, lack of base-of-skull involvement, and primary (rather than recurrent) disease were associated with improved survival rates. Improved locoregional control was associated with tumors having the following characteristics: greatest diameter less than 4 cm, no base-of-skull invasion, prior surgical resection, or no previous radiation therapy. The 6-year actuarial rate for freedom from the development of metastases was 64% for patients without lymph node involvement or base-of-skull involvement. There was a 6-year actuarial rate of 10% for developing RTOG grade 3 or 4 toxicity. Cause-specific survival curves for the patients with major salivary gland cancer as a function of tumor size are shown in Figure 20-2.

The poorer outcome of salivary tumors with base-of-skull involvement appears to be the need to reduce the dose to portions of tumors that are adjacent to critical central nervous system structures (recall that the RBE for fast neutrons for central nervous system tissue is 4 to 4.5). With a standard 20 nGy dose to the involved site, the dose to the temporal tips could be approximately 80 photon GyE. Reducing the temporal lobe dose to a safe level sometimes required blocking portions of tumor. In an attempt to compensate for the reduced neutron dose, a stereotactic radiosurgical boost with photon radiation has been instituted at the University of Washington. At 40 months there was improved local control compared with historically treated patients with skull-base invasion who did not receive a stereotactic radiosurgical boost (82% versus 39%; $p = 0.04$).[12] Complications appear to be acceptable.

The use of both neutrons and photons in a composite "mixed beam" treatment has been explored by Huber et al[13] in a series of patients with advanced adenoid cystic carcinomas treated at the Heidelberg neutron facility. They found a

5-year local control rate of 75% for patients treated with neutrons alone compared with 32% for patients treated with "mixed beam" irradiation or with photons alone. It appeared that patients who had a greater portion of their treatment with neutrons fared better. Distant metastatic disease once again prevented improved local control from translating into an increase in overall survival rates.

The neutron facility in Orleans has reported similar results for 59 patients treated with fast neutron radiotherapy.[14] The 5-year local control rate was 69.5%, with a crude 5-year survival rate of 66% and a 5-year tumor-free survival rate of 64.5%.

Adenoid cystic carcinomas arising in uncommon locations are also amenable to treatment with fast neutron radiotherapy. Thirty-four patients with adenoid cystic carcinomas of the trachea received neutron radiotherapy at the University of Washington.[15] Those patients who received neutron radiotherapy as their primary treatment had a 5-year survival of 89%, whereas those who received postoperative neutron radiotherapy following surgery had a 5-year survival of 60%. There was no significant advantage to adding a brachytherapy (HDR) boost following the neutron radiotherapy. Gensheimer et al reported on 11 high-risk patients with adenoid cystic carcinomas of the lacrimal gland who were treated with fast neutron radiotherapy.[16] Most had undergone a surgical resection but gross disease was present in eight patients at the time of treatment. Disease extending to the skull base was treated with a Gamma Knife radiosurgery boost in four patients and with a proton radiotherapy boost in one1 patient. Median overall survival was 11.1 years and median disease-free survival was 6.3 years. Kaplan-Meir local control at 5 years was 80%. Long-term, ipsilateral vision preservation was not possible in most cases, although only two patients required an enucleation for treatment-related side effects.

Prostate Cancer

Prostate cancer is another tumor for which there has been significant clinical work using fast neutron radiotherapy. The National Cancer Institute (through RTOG 77-04) conducted a randomized trial for patients with T3, N0/N1 disease.[17] One arm received a mixed beam (neutron/photon) dose to 70 GyE versus a second arm that received standard photons to 70 Gy. Pelvic lymph nodes were treated to doses appropriate for microscopic disease. At the 10-year endpoint, survival rates (46% versus 29%, $p = 0.04$) were improved in the mixed beam arm. There was also improved locoregional control (70% versus 58%, $p = 0.03$) for the mixed beam subgroup. There was no difference in the rate of significant complications between the two arms. Survival curves for the patients in this study are shown in Figure 20-3.

A follow-up randomized trial was conducted that compared 70-Gy standard photon irradiation with 20.4-nGy fast neutron therapy. Pelvic lymph nodes were treated to doses appropriate for microscopic disease. This study was carried out by the National Cancer Institute (NCI)–sponsored Neutron Therapy Collaborative Working Group (NTCWG) and included patients with high-grade T2 tumors or T3 to T4, N0 to N1, M0 tumors of any grade.[18] With a median follow-up of 68 months, the 5-year actuarial locoregional failure rate was 11% for neutrons versus 32% for photons ($p < 0.01$). Actuarial overall survival and cause-specific survival rates were statistically equivalent. The incidence of severe complications was higher in the neutron group than in the photon group (11% versus 3%). Complications were fewer and less severe in the centers that had more sophisticated beam-shaping abilities. Local failure curves for the patients in this study are shown in Figure 20-4.

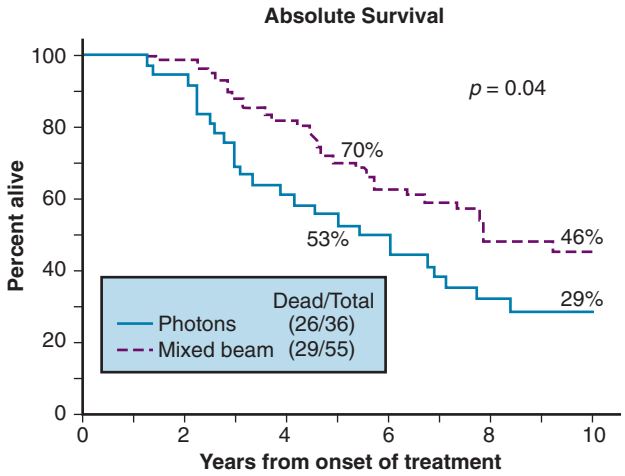


Figure 20-3 Actuarial survival curves for patients with locally advanced prostate cancer treated on Radiation Therapy Oncology Group (RTOG) protocol 77-04. The mixed (neutron and photon) beam group is shown by the *dashed purple curve,* and the photon control arm is shown as the *solid blue curve.* The difference between the curves is statistically significant at the $p = 0.04$ level.
Adapted from Laramore GE, Krall JM, Griffin TW, et al: Fast neutron radiotherapy for locally advanced prostate cancer. Am J Clin Oncol 16:164, 1993.

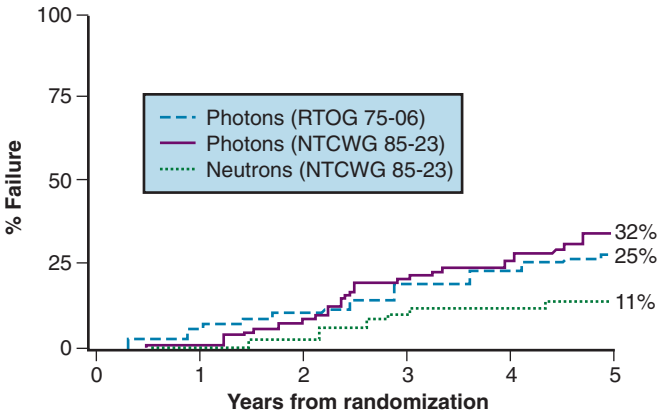


Figure 20-4 Actuarial percent local failure curves for patients with locally advanced prostate cancer treated on Neutron Therapy Collaborative Working Group (NTCWG) protocol 85-23. The group treated with neutrons is shown as the *dotted green curve,* and the group treated with photons is shown as the *dashed blue curve.* The difference between these two curves is statistically significant at the $p < 0.01$ level. A local control curve *(solid purple line)* for photon-treated patients from another Radiation Therapy Oncology Group study (RTOG 75-06) is shown for comparison. There is no statistical difference between the latter curve and the photon control arm of the neutron study.
Adapted from Russell KJ, Caplan RJ, Laramore GE, et al: Photon versus fast neutron external beam radiotherapy in the treatment of locally advanced prostate cancer. Results of a randomized prospective trial. Int J Radiat Oncol Biol Phys 28:47, 1993.

Following the randomized trials, additional studies were conducted at several centers in the United States,[19-23] Europe,[24,25] and Asia.[26,27] These single-institution results showed good locoregional control and appeared to corroborate the results of the randomized trials described previously.

Sarcomas

Sarcomas are generally considered to be among the more "radioresistant" histologic types of tumors and so would fall into the category of tumors thought to be more responsive to high-LET radiation.[1] A retrospective review by Schwarz et al[28] reports on 1171 patients with soft-tissue sarcomas from 11 European centers treated with fast neutron radiotherapy. In those patients with either inoperable tumors or gross disease after surgery, the local control rate was approximately 50%. Toxicity was higher than what was generally seen with photon irradiation. The local control rates were thought by the authors to be better than what would have been expected with standard radiotherapy. This conclusion is supported by other single-institution studies.[29]

Other Tumor Types

Fast neutron radiation has been tested on a variety of other tumor types. Generally, the rationale for the use of fast neutrons came from trying to overcome a perceived limitation of standard photon irradiation. A good example of this is malignant glioma of the brain. Dose-escalation studies with photons have failed to increase overall survival rates.[30] By definition, *glioblastoma multiforme* tumors have associated areas of necrosis that are often surrounded by regions of hypoxia, which might make the tumors more radioresistant. Studies of malignant gliomas in the 1970s and 1980s used neutrons either alone or in combination with photons.[31] None of these initial trials showed an improvement in overall survival rates with the addition of neutrons. However, with relatively high doses of fast neutrons alone, autopsy and second-look surgical data indicated that tumor cells were sterilized in the treated region.[32] Unfortunately, there was also significant coagulative necrosis caused by the neutron irradiation, which indicated too much damage to normal brain tissue. A more recent study used fluorodeoxyglucose–positron emission tomography (FDG-PET) scanning to determine the final boost volume that received 18 nGy.[33] Only 10 patients were treated and all exhibited tumor progression by 39 weeks, perhaps because of the restricted fields that were employed. Gliosis and microvascular sclerosis consistent with radiation injury were noted in regions of the contralateral brain receiving 6 nGy to 10 nGy. Much of the current interest in neutron radiotherapy for malignant gliomas is focused on boron neutron capture therapy (BNCT), which is discussed later in this chapter.

Squamous cell carcinoma of the head and neck region is another tumor for which neutrons have been used to try to overcome the relative radiation resistance of hypoxic cells. However, randomized studies and several single-institutional trials in Europe and the United States failed to show a significant improvement in locoregional control with the use of neutrons compared with standard photons. Furthermore, the side effects were generally more severe.

Summary

Neutron radiotherapy is best used in the treatment of certain tumors that exhibit a "resistance" to standard low-LET radiotherapy. The niche that it occupies is small, but it remains a highly important treatment option for a small number of patients for whom it appears to be better than more traditional forms of treatment. Examples are patients with inoperable or recurrent salivary gland malignant tumors or in high-risk situations where there has been an incomplete surgical extirpation or patients with inoperable or incompletely resected sarcomas of bone, cartilage, and soft tissue or locally advanced prostate cancers, particularly those that are not hormonally responsive. In highly selected circumstances, it may also be beneficial in the treatment of metastases from melanoma and renal cell cancer. Future research may extend these indications. The declining number of active treatment centers is attributable to the aging of the equipment and the narrow niche indications making it not economically feasible to build new centers.

BORON NEUTRON CAPTURE THERAPY

Overview

Conceptually, BNCT is a "magic bullet" approach to treating tumors. Pure beams of very low energy neutrons do not directly deposit much energy in tissue via collisions but rather interact via nuclear transmutation reactions. The basic idea is to selectively attach to the cancer cells a nuclide having a large cross section for capturing a thermal neutron. The nuclide then undergoes a nuclear reaction with the localized release of a substantial amount of energy. In principle, this kills the "tagged" cell but does not damage the surrounding "untagged" normal cells. Although there is ongoing work in developing high-current particle accelerators to produce low-energy thermal or epithermal beams for BNCT, at the present time, all clinical work is being done using moderated neutron beams from nuclear reactors. There are other nuclides besides boron-10 (^{10}B) that have a high neutron capture therapy cross section, and some of these (e.g., gadolinium-157 [^{157}Gd]) are of interest in neutron capture therapy for cancer. The ^{157}Gd neutron capture reaction produces high LET Auger electrons rather than nuclear fragments and so the agent must be in close proximity to the cellular DNA to be effective. There is little data on the clinical use of ^{157}Gd and so we will confine our discussion to BNCT. Space limitations preclude our describing ongoing research in radiobiology, compound development, or physics research into nonreactor sources of appropriate beams.

Historical Perspective

The basic idea for BNCT dates to 1936, when Locher[34] proposed treating malignant tumors with low-energy thermal neutrons via a capture process with ^{10}B. A few years later, Kruger[35] and Zahl et al[36] experimentally verified some of the basic tenets of this concept and demonstrated the high RBE of the resulting helium-4 (^{4}He) and lithium-7 (^{7}Li) fission fragments. The theoretical advantage of "tagging" the tumor-specific carrier with an innocuous substance such as ^{10}B and then activating it, rather than tagging it with a toxic compound such as ricin, is that the "binary approach" is more forgiving of other body tissues that might also display some avidity for the carrier agent.

In the real world, the thermal and epithermal beams produced by nuclear reactors are contaminated with gamma rays and fast neutrons, which can cause considerable normal tissue damage even in the absence of a high ^{10}B concentration.[37] Moreover, even in the absence of such beam contaminants, nuclear species such as ^{1}H, nitrogen-14 (^{14}N), and chlorine-35 (^{35}Cl), which are commonly found in tissue, interact with thermal neutrons via capture events of their own, and their reaction products cause biologic damage to non–^{10}B-containing normal tissues. Although the respective capture cross sections for these commonly found nuclei are much lower than for ^{10}B and other nuclear species of interest for neutron capture therapy, the concentrations of these commonly found nuclei are many orders of magnitude greater than the concentrations of ^{10}B. Hence, reactions involving these nuclides can result in an appreciable tissue dose, even in the absence of ^{10}B. The key to BNCT as a practical therapy is the development of compounds that localize specifically in tumors and deliver

sufficient ^{10}B concentrations to yield a significant therapeutic advantage compared with the radiation doses delivered to normal tissues.

Early Clinical Studies

The first set of human clinical trials was carried out in the 1950s at Brookhaven National Laboratory using ^{10}B-enriched, boric acid derivatives.[38,39] These compounds yielded high concentrations of ^{10}B in the blood at the time of irradiation and unfortunately produced relatively low ^{10}B levels in the tumors. This resulted in considerable blood vessel endothelial damage and no therapeutic benefit from treatment either in these trials or in subsequent trials that were carried out in the 1960s.[40-42] Interest in the technique waned until Hatanaka et al in Japan[43] reinstituted BNCT for malignant gliomas using a different ^{10}B-carrier, ^{10}B-sodium-mercaptoundecahydrododecaborate (BSH). This compound produced better tumor-to-blood boron ratios than the compounds used in the prior Brookhaven National Laboratory studies and the treatments caused less damage to normal brain tissue. Favorable reports regarding the efficacy of BSH[43-45] led to renewed worldwide interest in the technique.

Many patients have received BNCT treatments using thermal neutron beams from various reactors in Japan, but to date, no randomized clinical trials have been carried out. An analysis of the RTOG database by Curran et al[46] demonstrated that there are some subsets of patients with high-grade gliomas who will do well with conventional photon irradiation. A few years ago, an analysis of a subset of patients from the United States who were treated with BNCT in Japan showed no improvement over that which would have been expected with conventional therapy after correcting for the appropriate prognostic factors.[47] A comparison of the survival rates of these patients with a pseudo-matched group from the RTOG database is shown in Figure 20-5. The prognostic factors identified by Curran et al[46] were used to generate these curves. There is no statistical difference between the two curves.

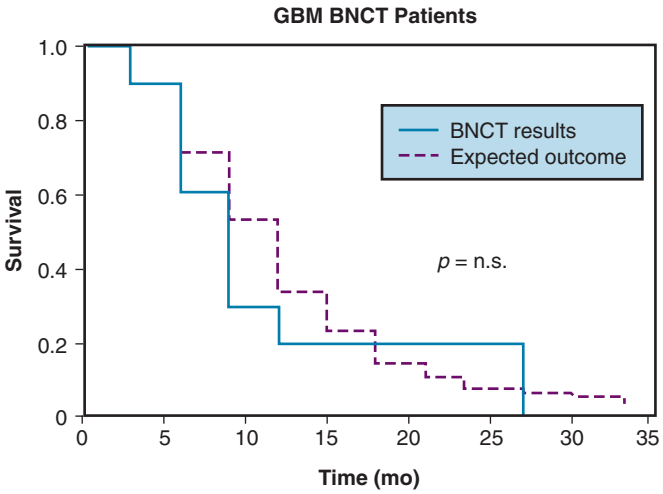


Figure 20-5 Actuarial survival curves for a group of 10 patients from the United States with glioblastoma multiforme (GBM) histology who were treated with boron neutron capture therapy (BNCT) *(solid blue curve)* and the expected survival curve for a matched cohort who received conventional treatment according to various Radiation Therapy Oncology Group study (RTOG) protocols *(dashed purple curve)*. There is no statistically significant difference between the two curves.
Adapted from Laramore GE, Spence AM: Boron neutron capture therapy [BNCT] for high grade gliomas of the brain. A cautionary note. Int J Radiat Oncol Biol Phys 36:241, 1996.

Moreover, review of the data for the entire group of evaluable patients showed that in all except one patient there was a documented tumor recurrence within the primary radiation field.[47] The only long-term survivor in this group of American patients had an anaplastic astrocytoma and fell into the most favorable category I of Curran et al.[46]

There is no doubt that many aspects of the early Japanese BNCT clinical research program were suboptimal. The use of a poorly penetrating beam of thermal neutrons meant that an open craniotomy was required to expose the tumor bed. Because of the low neutron fluxes, treatment times of 4 to 8 hours were required to deliver a surface fluence of approximately 10^{13} neutrons/cm^2, and during treatment the patient had to be under general anesthesia with the brain exposed in a converted operating room adjacent to the nuclear reactor. Although BSH is conceptually attractive as a ^{10}B-carrier agent in that it is excluded from normal brain tissue by the blood-brain barrier, typical tumor boron concentrations for glioblastoma multiforme were in the range of only 15 μg/g to 25 μg/g. It is now possible to improve on many of these shortcomings.

Modern Clinical Trials

In the modern era, clinical trials have been conducted in Japan, Europe, Argentina, and the United States. Most of this work has dealt with the treatment of malignant brain tumors and metastatic melanomas, but there is increasing interest in using this modality to treat recurrent head and neck cancers and high-grade meningiomas

In Japan, there have been three reactor facilities involved in patient treatments: (1) KURRI in Osaka, (2) MITR in Musashi, and (3) JRR-4 at the Japan Atomic Energy Research Institute in Ikargi.[48] Although most patients have been treated using thermal neutron beams, the KURRI facility has been modified to produce a higher-energy epithermal beam allowing treatment through the intact skull. The majority of the patients have been treated for various types of brain tumors using BSH as the ^{10}B-carrier agent and with a single fraction of neutron radiation. A report by Nakagawa et al[49] shows that in the subset of glioblastoma multiforme patients, 12% of treated patients lived longer than 2 years. Depending on other prognostic factors, this may or may not be better than expected with more conventional forms of treatment. A report by Kawabata et al shows a modest survival benefit in 21 glioblastoma patients treated with either BNCT alone or in combination with standard photon radiotherapy when compare to patients having similar RTOG prognostic factors.[50] Currently only the KURRI and JRR-4 reactors are treating patients.

There were several reactor facilities in Europe with BNCT clinical programs for malignant brain tumors, all using epithermal neutron beams. The program that treated the most patients was based at the HFR reactor in Petten (the Netherlands) and was directed by the European Collaboration on Boron Neutron Capture Therapy. BSH at 100 mg/kg was used as the ^{10}B-carrier. Researchers conducted a phase I dose-searching study restricted to the subsets of patients with glioblastoma multiforme whose expected median survival time with conventional radiotherapy would be less than 10 months. Unlike the other ongoing treatment regimens, which employed a single BNCT treatment, the Petten program used four fractions requiring multiple administrations of the boron-carrier compound. BNCT dose reporting is complex, and the Petten group has chosen to specify each component of the radiation field separately rather than state a Gray-equivalent dose.[51] The starting dose from the ^{10}B component was set at 80% of the dose that produced neurologic changes in a dog brain study, D_B = 8.6 Gy. The other components of the radiation dose were limited

to $D_n < 0.9$ Gy, $D_N < 1.1$ Gy, and $D_g < 5.8$ Gy, where D_n is the neutron-absorbed dose delivered by the thermal, epithermal, and fast neutrons and the charged particles produced by their reactions, D_g is the gamma ray absorbed dose, and D_N is the absorbed dose from the protons produced by the ^{14}N capture reaction. Twenty-five patients were entered into the initial dose arm of the study, with 21 actually receiving BNCT treatment.[52] The median survival time of the BNCT-treated patients was 31 weeks, with 6 patients alive at the time of a preliminary report. All 21 patients exhibited tumor recurrence.

A second BNCT program is based at the FiR No. 1 reactor in Helsinki, Finland. The initial protocol was a Phase I dose-searching study that used l-*para*-boronophenylalanine (BPA) in a fructose solution at 290 mg BPA/kg as the B-carrier. Only a single treatment was given using two radiation fields. Thus far, 10 patients have been treated with tumor doses between 35.1 and 66.7 GyE. This effective dose has been determined using weighting factors for each of the radiation components (see Kankaanranta et al[53] for specific details). With a median follow-up of 9 months, 7 of 10 patients had recurrent or persistent tumor, with the median time to tumor progression being 8 months.[53] The toxicity in both of the European trials was thought to be acceptable, making future escalation of the radiation dose possible. Small numbers of patients were also treated at Studsvik Medical AB in Uppsala University[54] and at the Nuclear Research Institute in the Czech Republic.[55] Currently, only the FiR No. 1 reactor is treating patients.

After approximately a 30-year hiatus, the first "modern era" BNCT clinical program in the United States was begun at the Massachusetts Institute of Technology (MIT) research reactor in collaboration with Tufts Medical Center. The first patient was treated in September 1994. This project was under the clinical direction of the New England Deaconess Hospital. Treatments were delivered using an epithermal beam with BPA as the ^{10}B-carrier agent. Between 1996 and 1999, a total of 22 patients with intracranial lesions, either glioblastoma multiforme or metastatic melanoma, were treated.[56] The initial clinical trial was a dose-searching toxicity study with the target dose ranging between 8.8 GyE and 14.2 GyE. At the higher radiation doses, the time required to deliver the dose ranged up to 3 hours. At the higher dose levels, significant skin and mucosal reactions were observed. No adverse effects were noted because of the BPA administration, and no long-term complications relating to the BNCT treatment were noted. Some tumor responses were noted in the patients with metastatic melanoma, but there was no obvious prolongation of survival rates in either group of treated patients. This facility is no longer treating patients.

A second clinical BNCT program focusing on high-grade gliomas of the brain was initiated at Brookhaven National Laboratory. This program differed from the Japanese glioma program in two main respects: (1) a higher-energy epithermal neutron beam was used instead of a thermal neutron beam, and (2) a different ^{10}B-carrier agent (BPA) was used rather than BSH. The epithermal beam meant that patients could be treated without recourse to a craniotomy and intraoperative irradiation and that more deeply located tumors could be given adequate doses. It was expected that BPA would produce higher tumor ^{10}B concentrations than could be achieved with BSH. Based on ^{10}B blood levels, it appeared that tumor ^{10}B concentrations of approximately 35 μg/g to 50 μg/g were achieved. However, unlike BSH, BPA is not excluded from the normal brain by the blood-brain barrier, and tumor enrichment depends on other mechanisms of selective uptake (perhaps relating to an enhanced amino acid transport system). A dose-escalation approach was used. Before June 1996, all patients were treated using a simple appositional field with a single treatment fraction being given. A critique of this early Brookhaven National Laboratory treatment technique indicated significant deficiencies in the basic approach relating to the inability to achieve a tumor dose adequate to sterilize glioblastoma multiforme tumors using a single appositional field.[57]

Between September 1994 and May 1999, 53 patients with primary glioblastoma multiforme received BPA-fructose–mediated BNCT at Brookhaven National Laboratory using one, two, or three irradiation fields on a sequential, dose-searching protocol. The median age for the subjects treated with one field was 56.5 years, with a median tumor volume of 20.5 cm^3 (2 cm^3 to 70 cm^3) and a median Karnofsky Performance Status (KPS) of 80. The volume-weighted average radiation dose to normal brain (ABD) varied from 1.9 GyE to 4.1 GyE for one field, from 4.1 GyE to 6.6 GyE for two fields, and from 6.7 GyE to 9.5 GyE for the three-field group.

Fifty of the 53 subjects have exhibited tumor persistence/recurrence within the treatment volume.[58] The median time to progression was independent of dose. In fact, there was a significant trend toward worse local control in subjects treated using three fields. Survival as an endpoint was found to be more dependent on the aggressiveness of the postrecurrence treatment than the BNCT dose given and, as such, was not a useful indicator of treatment-dependent tumor control. The functional brain tolerance was reached in the three-field group. All except one patient treated with three fields exhibited significant acute or subacute functional neurologic toxicity at average brain doses as low as 6.7 GyE. This may indicate a "volume effect" in that multiple fields generally treat a larger volume of normal brain to a lower dose compared with when a single field is used. The early stopping criterion of a more than 20% incidence of grade 3 or 4 toxicity (RTOG and European Organization for Research and Treatment of Cancer [EORTC] criteria) was reached during this study. However, no significant tumor response was observed in the patients treated to minimum tumor doses above those predicted by Laramore et al to be therapeutic.[57,58] We also note that preclinical studies using a 9-L rat gliosarcoma model showed significant tumor response of the tumor to BPA-fructose–mediated BNCT at comparable doses.[59] Hence, neither the preclinical radiobiologic studies nor the mathematical modeling based on fast neutron data provided an accurate guide to the necessary therapeutic dose. The Brookhaven National Laboratory clinical program is no longer in operation.

In parallel with the BNCT program for malignant gliomas, a second area of major interest is the treatment of malignant melanoma metastatic to the brain. This work was instigated by Mishima et al[60,61] in Japan. They used BPA as the ^{10}B-carrier agent with a single treatment fraction of thermal neutrons. BPA acts as a dopamine analog in the melanin synthetic pathway and concentrates well in pigmented tumors. Initial reports describe good clinical results with this treatment,[62,63] but no randomized trials have been performed. Reports from the MIT/Massachusetts General Hospital program indicate that responses are better in this setting than in the treatment of glioblastoma multiforme, which is consistent with BPA being better suited to the treatment of pigmented tumors. Under the auspices of the Atomic Energy Commission of Argentina, a program for the treatment of metastatic melanoma has been instituted at the RA-6 research reactor in San Carlos de Bariloche, and this program is still clinically active.[64] An updated report showed an overall response rate of 69% in treated skin nodules with an additional 31% of nodules showing stable behavior.[65]

A third area of increasing interest in the BNCT community is the treatment of patients with recurrent head and neck cancers. A report on 26 patients treated at the KURRI and JRR-4 reactors using both BSH and BPA as boron carrier agents

showed an overall response rate of 85% although there were three instances of osteoradionecrosis and one case of brain necrosis.[66] The majority of these patients was treated for tumor recurrence after having received previous standard radiotherapy and therefore represent a high-risk population with respect to complications. Thirty patients with recurrent head and neck cancers were treated in Finland between 2003 and 2008 using the FiR 1 reactor. Like the Japanese work, a combination of BSH and BPA was used to maximize the boron concentration in the tumors. Two portals were irradiated and the mean boron dose was 19.6 μg/g for the first portal and 16.4 μg/g for the second portal.[67] For 29 evaluable patients, 76% had some response and the 2-year locoregional control rate was 27%. There were 3 patients who developed osteoradionecrosis and 1 patient who developed a soft-tissue necrosis.

Kawabata et al recently reported on using BNCT to treat 20 patients with recurrent, high-grade meningomas who had failed surgery followed by one or more courses of radiotherapy.[68] Either BPA alone or combined with BSH was used as the boron carrier agent. The radiation dose to normal brain was restricted to 15 Gy-equivalent or less in the planning process. With a median follow-up duration of 13 months, 6 patients were still alive and only 3 deaths were as a result of in-field failure. The majority of deaths were the result of systemic metastases or cerebrospinal fluid (CSF) dissemination indicating the aggressive nature of the tumors that were treated. The authors noted a rapid tumor shrinkage in many of the treated patients.

An interesting approach to the treatment of liver metastases was begun at the University of Pavia in Italy. The patient is infused with BPA, and the diseased liver is extirpated and irradiated in the reactor and then reimplanted into the patient. Two patients have been treated in this manner, with one long-term survivor at 3 years from the time of the procedure. Model calculations indicate that it may be possible to perform this treatment without first removing the liver.[69] There is continued work on this concept through EORTC 11001. This biodistribution trial showed that BPA is taken up preferentially in liver metastases of colorectal adenocarcinoma to an extent that is high enough for therapeutic BNCT whereas BSH does not preferentially accumulate.[70]

Summary

To date there is no convincing evidence that BNCT offers a therapeutic advantage over conventional treatments for glioblastoma multiforme. Reactor-based treatment centers are sufficient in number to conduct well-designed clinical trials to provide a "proof of concept" but certainly will not be adequate to treat large numbers of patients in the event that a therapeutic advantage is demonstrated. In this event, accelerator-based sources must be designed and placed in hospital settings. The main hurdle at the present time is the lack of tumor-specific ^{10}B-carrier agents. Besides BSH and BPA, only one other boron compound, GB-10 ($Na_2B_{10}H_{10}$), is approved for human trials. GB-10 and BSH are global agents with no specific tumor cell targeting, whereas BPA has some specificity for certain types of tumors. All three are suboptimal for clinical use. Support of research in compound development is key to further development of the field.[71-73]

CALIFORNIUM 252 BRACHYTHERAPY

Californium was the sixth transuranium element that was produced by a team at the Lawrence Berkeley Laboratories in 1950 by bombarding a curium target with α particles. The particular isotope used in radiotherapy, californium-252 (^{252}Cf), is produced in high-neutron flux reactors and is made available for peaceful uses by the U.S. Department of Energy. ^{252}Cf is a neutron-rich isotope that has a half-life of 2.647 years. It decays either by α-particle emission or by spontaneous fission with a branching ratio of 96.9% to 3.1%. It is a highly prolific neutron emitter with a spectrum of energies similar to that produced by nuclear reactors. Although its use in medicine requires significant radiation protection precautions, it is theoretically attractive for brachytherapy applications wherein high-LET radiation is advantageous from a radiobiologic aspect. It has also been proposed as a hospital-based teletherapy source for BNCT applications.

Gynecologic applications of ^{252}Cf brachytherapy were explored by Maruyama et al,[74] who developed appropriate dosing schedules. More recently, Tacev et al[75] reported on long-term results of a randomized trial for patients with advanced cervical cancer (stages IIB and IIIB) that compared ^{252}Cf brachytherapy with a supplementary gamma ray boost of 16 Gy with conventional brachytherapy alone with gamma ray–emitting radium-226 (^{226}Ra) or cesium-137 (^{137}Cs) sources following 40-Gy external beam radiotherapy. Using an RBE of 6 for the ^{252}Cf neutrons, point A doses of 56 GyE were given with the implants. Two hundred seventy-seven patients were entered into the study, and there was an improved 5-year survival rate in the group receiving the ^{252}Cf implant (75.2% vs. 56.3%; $p < 0.001$).

Also of note is a pilot study using ^{252}Cf interstitial brachytherapy in 56 patients with high-grade gliomas of the brain.[76] After surgical debulking, catheters were placed under CT guidance followed by ^{252}Cf placement. A dose of 3 Gy was given over 4 to 6 hours to the residual tumor, and then patients received 60-Gy to 70-Gy doses of conventional external beam radiotherapy. The median survival time was only 10 months, and recurrent tumor was found in all patients who died and were autopsied. Given the dose inhomogeneties and the relatively small amount of neutron radiation given, this outcome is not surprising.

Summary

^{252}Cf sources offer a means of performing brachytherapy with neutrons. Conceptually, this is intriguing for tumors in which hypoxia is thought to be a factor in limiting tumor control with standard treatment and which lend themselves to brachytherapy approaches. There has been one randomized study for advanced cervical cancer showing benefit compared with standard brachytherapy with gamma ray sources, but this field still requires considerable development. Remote afterloading devices allow implementation of this technique without high risk to medical personnel. A recent review shows that there are 21 ^{252}Cf brachytherapy systems being used in China today.[77]

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CHAPTER

21 Hyperthermia

Mark Dewhirst, Paul R. Stauffer, Shiva Das, Oana I. Craciunescu, and Zeljko Vujaskovic

The biological rationale for hyperthermia (HT) as a cancer treatment is based on several mechanisms, particularly relating to its combination with other therapies: (1) HT is directly cytotoxic. (2) When used with radiotherapy (RT), HT inhibits potentially lethal- and sublethal-damage repair and has complementary cytotoxicity with reference to the cell cycle. Hyperthermic killing is not influenced by hypoxia, whereas hypoxia has a significant effect on radiosensitivity. HT causes reoxygenation, which can increase RT sensitivity. (3) HT increases drug uptake into cells, enhances DNA damage, and partially or completely reverses drug resistance. (4) HT improves delivery of nanoparticle drug carriers, such as liposomes, and macromolecular drugs, such as antibodies and drug-carrying polymers. (5) The process of thermal adaptation (thermotolerance) may enhance exposure of tumor cell antigens to immune cells and increase innate immunity, thereby augmenting host immune responses against tumor cells.

Despite strong biological rationale, delivery of HT presents significant challenges. The goal is to be able to heat tumor tissue volumes reproducibly and to do so using methods that are clinically practical. A significant impediment to this goal is that current thermometry is invasive. Consequently, definition and calculation of thermal dose is not well defined. Priorities in the area of engineering and physics center on improvements in technologies to deliver HT, to measure thermal dose noninvasively, and to use such data to control power to the tumor in real time.

Despite the technical difficulties in delivering HT, however, several positive randomized trials using HT in combination with RT and chemotherapy in human patients with cancer have been published in addition to three positive canine randomized trials. The majority have demonstrated local control or survival advantages with therapies involving HT. These trials have involved patients with cervix cancer, primary brain tumors, head and neck cancers, esophageal cancer, chest wall recurrences of breast cancer, bladder cancer, melanoma, and most recently, high-grade soft-tissue sarcomas.

In this chapter, the biological rationale for using HT will be examined in more detail, a survey of methods used to heat tissues will be provided, and a comprehensive overview of key Phase III studies will be presented. The emerging discipline of thermal ablative technologies will also be presented briefly because it is approved for treatment of a range of diseases and is used widely by interventional radiologists and surgeons.

THE BIOLOGY OF HYPERTHERMIA

Definition of Hyperthermia

Hyperthermia means elevation of temperature to a supraphysiologic level, between 40°C and 45°C. Typical durations of hyperthermia treatment are 30 minutes to 60 minutes a session. Temperatures in the range of 50°C to 100°C for a few minutes per session are used for thermal ablation.[1]

The Arrhenius Relationship and Thermal Isoeffect Dose

Arrhenius found a temperature dependence of sucrose hydrolysis in the presence of various acids that was a logarithmic function of the absolute temperatures at which the reactions were conducted.[2] These observations were physiologically relevant in that the rate of cellular metabolism increases as temperature rises in cells or tissues, up to a point where thermal damage is created. The principles discovered by Arrhenius extend to cell killing by HT as well. The temperature dependence of the rate of cell killing is referred to as the "Arrhenius relationship."

The temperature dependence of the rate of cell killing has been used as a method for thermal dosimetry. This is done by plotting temperature versus log of the slope of the survival curve ($1/Do$). Do is analogous to a Do in a radiation survival curve (the dose to reduce survival to 37% of a starting value on the exponential portion of the survival curve). In the case of HT, "dose" is the number of minutes at a specified temperature (Figure 21-1). Typically, Arrhenius plots have a biphasic curve and the point at which there is a change in slope is referred to as a *breakpoint*. Above the breakpoint for nearly all cell types, a change in temperature of 1.0°C doubles the rate of cell killing. Acquired resistance to HT killing (thermotolerance) that occurs during HT is responsible for the change in slope of the heat cell survival curve at longer heating times for temperatures below 43°C (see Figure 21-1, *A*). Arrhenius plots for human cell and rodent lines are well described. The breakpoint for human cells is near 43.5°C, and the slope below the breakpoint, which is caused by thermotolerance induction during heating, is between 2 and 4. The slopes of Arrhenius plots derived from in vivo studies are virtually identical to those that are derived from in vitro studies.[4]

Sapareto and Dewey[5] proposed using the Arrhenius relationship to normalize thermal data from HT treatments. The rationale came from the observations that time-temperature histories are not stable, that they vary from patient to patient, and that temperatures within tumors were almost always nonuniform. Using the Arrhenius relationship, it would be possible to convert all time-temperature data to an equivalent number of minutes at a standard temperature (defined as 43°C). The formulation takes the following form.

$$\text{CEM } 43^\circ\text{C} = t R^{(43-T)} \qquad \text{Equation 1}$$

Where CEM 43°C = cumulative equivalent minutes at 43°C (the temperature most commonly used for normalization), t is the time of treatment, T is the average temperature during desired interval of heating, and R is a constant. When above the breakpoint, which is assumed by convention to be 43°C, $R = 0.5$. When below the breakpoint, $R = 0.25$

For a complex time-temperature history, the heating profile is broken into intervals of time t length, where the temperature remains relatively constant. CEM 43°C is calculated using the average T (T_{avg}) for each interval, and the resultant data

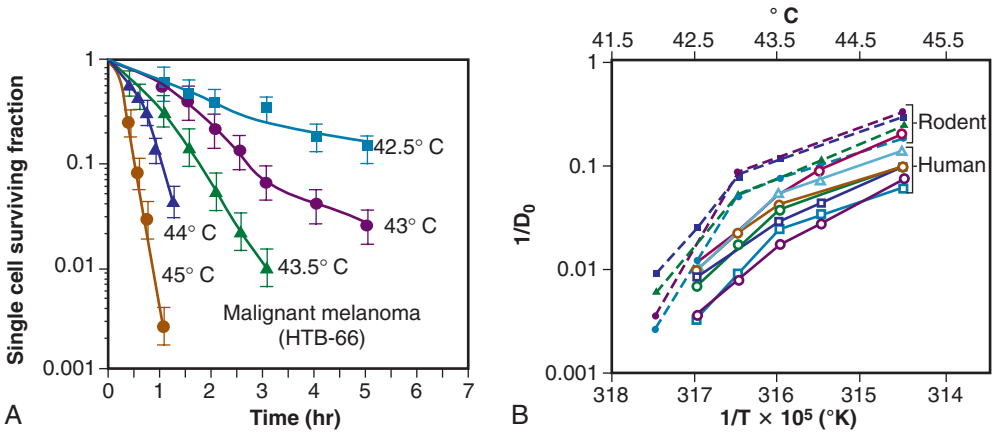


Figure 21-1 **(a)** Cell survival curves for human melanoma cells, plotted as log of surviving fraction as a function of time of heating at a defined temperature. **(b)** Arrhenius plots derived from survival curve data of several human and rodent tumor lines. Note change in slope (known as the "breakpoint") of Arrhenius plots for both types of cells. For human cell lines, this appears to be around 43.5° C, whereas for rodent lines it is approximately 43° C.
Data reproduced from Roizin-Towle,[3] with permission of the publisher and author.

are summed to give a final CEM 43°C for the entire heating regimen.

$$\text{CEM } 43^\circ\text{C} = \Sigma t R^{(43-T_{avg})} \qquad \text{Equation 2}$$

The CEM 43°C (thermal isoeffect dose) formulation has been used extensively and successfully in clinical trials to assess the efficacy of heating. This is despite that the *R* values and breakpoints have historically been derived from studies done in rodents, which are somewhat different from the parameters derived from human cells.[4]

There appears to be a relatively common threshold for thermal coagulation, which is used for thermal ablation. CEM 43°C >240 minutes is sufficient to achieve full coagulation of most tissues.[1]

Mechanisms of Hyperthermic Cytotoxicity

Cellular and Tissue Responses to Hyperthermia

Protein Is the Primary Target for Hyperthermic Cytotoxicity

When cells are exposed to elevated temperatures (≥41.0°C), damage is inflicted in multiple sites, but the predominant molecular target appears to be protein. The heat of inactivation for cell killing and thermal damage to tissues is in the range of that necessary for protein denaturation (130 kcal/mole to 170 kcal/mole).[6] Additional evidence for proteins as being the primary target for cell killing is the importance of heat shock proteins in protecting thermotolerant cells from thermal damage. One of the primary functions of heat shock proteins is to refold other proteins that have been damaged.[7]

Some organelles are especially important in controlling thermal response. For example, modification of membrane lipid content or use of membrane active agents, such as alcohols, can sensitize cells to heat killing, but the sensitization is probably related to destabilization of the membrane as it relates to lipid-protein interactions.[8] The cytoskeleton of cells is particularly heat sensitive.[9] When it is collapsed by heat, there is disruption of cytoskeletal-dependent signal transduction pathways as well as inhibition of cell motility.[10,11] The heat sensitivity of the centriole leads to chromosomal aberrations following thermal injury.[12] Finally, the DNA repair process is heat sensitive, and this may be one of the mechanisms that leads to heat-induced radio- and chemosensitization.[13]

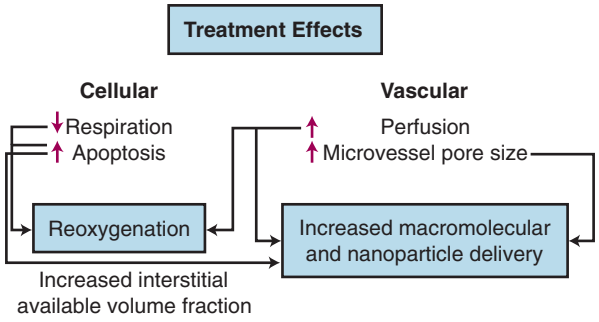


Figure 21-2 Overview of the beneficial physiologic and metabolic effects of HT.

Physiologic Response to Hyperthermia

Tumor blood flow and metabolism have important influences on the efficacy of HT, and conversely, the physiologic consequences of HT can influence the efficacy of other treatments.

As temperatures are increased, there is an increase in blood flow. The temperature threshold for this change is 41°C to 41.5°C in skin.[14] Changes in vascular permeability also occur, leading to edema formation in the heated volume. At higher thermal doses, vascular stasis and hemorrhage develop. The change in normal tissue perfusion upon heating is much greater (10-fold) than one sees in tumors (1.5- to 2-fold).[15] Mechanisms underlying vascular stasis may include arteriovenous shunting, thrombus formation, and leukocyte plugging.[16] Importantly, physiologic changes occur in tumors at temperatures below those that damage normal tissue (Figure 21-2).

Taking Advantage of Physiological Response to Hyperthermia

Improvement in Macromolecular and Liposomal Drug Delivery. A liposome is a small lipid vesicle (≈100 nm diameter) that contains water or saline in the center. Drugs can be loaded into liposomes at high concentration. HT increases microvascular pore sizes preferentially in tumor microvessels, which leads to enhanced liposomal accumulation in tumor.[17] The threshold for increased liposomal extravasation is 40°C

and increases by a factor of two for every degree temperature rise until vascular damage occurs.[18] The effects of HT on liposomal extravasation have been studied extensively in preclinical models, but 2-fold to 13-fold enhancement in accumulation occurs in spontaneous soft-tissue sarcomas of pet cats, an encouraging result that may translate to human tumors.[19] HT also increases the available volume fraction (fraction of tissue not occupied by cells or stromal fibers), which may develop as cells undergo either necrosis or apoptosis following heat treatment.[20] This increases the tissue space available for nanoparticles to be deposited. The increase in liposomal drug delivery achieved with HT has been shown to result in increased antitumor effect in many preclinical studies.[21] HT has been used in conjunction with liposomal doxorubicin and radiation in one small clinical series of patients with chest wall recurrences of breast cancer and encouraging results were obtained.[22]

Selective delivery of drug to a targeted tumor volume can be enhanced by using thermosensitive liposomes. These liposomes undergo a phase transition from a solid to a liquid state as they are heated.[23] When the phase transition occurs, the liposomes become permeable and release their contents. The phase transition temperature can be modified by changing the lipid composition. The original idea for a thermosensitive liposome is attributed to Dr. Milton Yatvin,[24] but the phase transition temperature of his formulation was too high and the rate of drug release was too slow for clinical use.[24] Needham developed the first low temperature, rapid release thermosensitive liposome, which exhibited complete doxorubicin release in <20 seconds upon reaching a transition temperature of 41.3°C.[25] Since then, other formulations have been reported that exhibit similar properties.[26,27] A key feature of this liposome is the fact that the majority of drug delivery achieved is via intravascular drug release (Figure 21-3). This feature essentially creates a local drug infusion within the heated volume that drives the drug down its concentration gradient and into the tumor interstitial space. This feature yields significantly greater drug penetration than can be achieved by increasing pore sizes to solid liposomes.[28] The Needham doxorubicin-loaded formulation yielded 5-fold higher accumulation of drug following HT treatment of 60 minutes at 42°C than the nonthermally sensitive Doxil formulation and 25-fold higher accumulation than free drug. The antitumor efficacy of the Needham formulation with HT was substantially greater than the liposomal drug without HT or free drug with HT in several different tumor lines.[29] The degree of enhancement in antitumor properties was directly proportional to the amount of drug accumulation in tumor.[30]

For relatively small chemotherapeutic drugs, there is no advantage gained via increased vascular permeability to macromolecules or nanoparticles, unless the drugs are protein-bound.[31] For drugs with molecular weight <1000 mw, the primary mechanism that governs drug transport is diffusion,[32] which is not highly temperature dependent. In contrast, the primary driving force for transport of macromolecules with >1000 mw is convection, which is controlled by the pressure gradient across the vessel wall. Accordingly, HT can augment the transvascular delivery of agents such as monoclonal antibodies[33] and polymeric peptides that carry drugs or radioisotopes.[34] Dreher et al used a novel peptide polymer that undergoes an inverse phase transition at 41°C, to "pump" polymer into tumors. The inverse phase transition refers to a

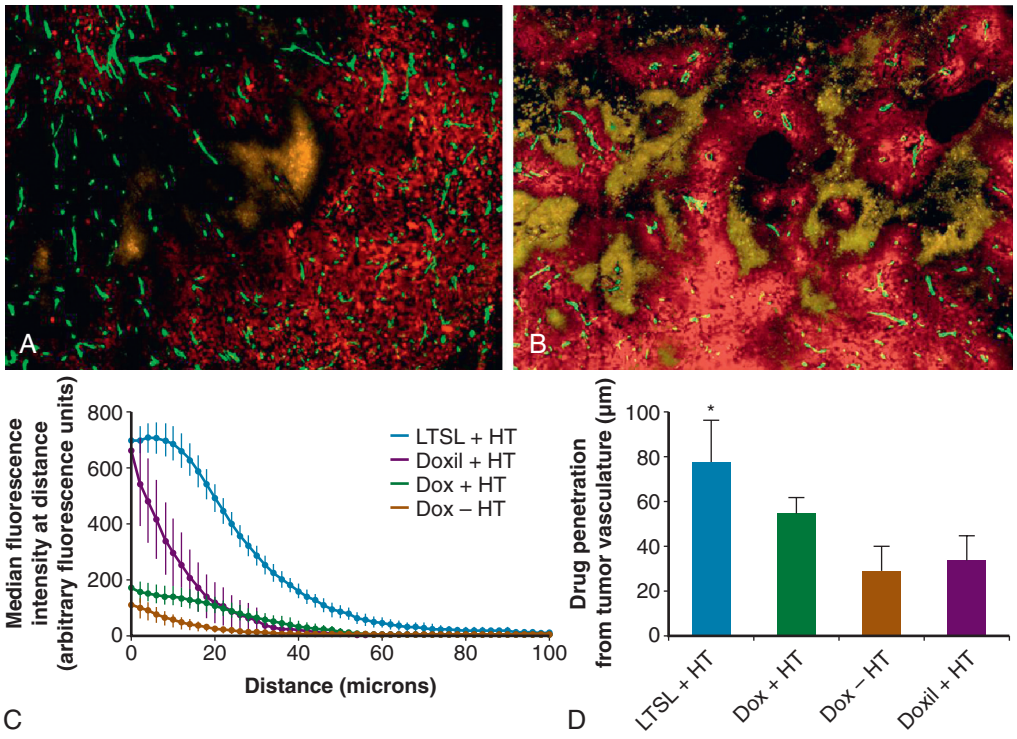


Figure 21-3 Immunohistochemistry images of doxorubicin penetration (red fluorescence) from vessels in the FaDu head and neck tumor xenograft. **A** and **B,** histology images following free doxorubicin with 42°C heating **(A)** and thermosensitive doxorubicin containing liposome (Dox-LTSL) with heating **(B).** Microvessels were stained with CD31 (green), and tissues assessed for hypoxia, using EF5 *(yellow)*. Qualitatively, the drug penetration is far greater with Dox-LTSL than with free drug. Quantification of penetration distance from nearest blood vessel shows that Dox-LTSL + heat delivers more drug at all distances from vessels compared with Doxil™ and free doxorubicin with heat **(C).** Doxorubicin delivered with Dox-LTSL penetrates twice as far as Doxil™ liposomes (78 vs. 34 mm; $p = 0.0106$) **(D).**
Data reproduced from Manzoor et al.[28] with permission of the publisher and author.

physical feature of the polymer that renders it to be water soluble below 41°C; above this temperature, the polymer comes out of solution in aggregates. The aggregation occurs primarily intravascularly but is reversible. Thus, when the tissue is cooled down, the particles rapidly disaggregate and diffuse into the tissue down their concentration gradient.[35] Additional nanoparticles have been designed since this work, which also have attractive thermal properties that would enhance drug delivery.[36,37]

Effects of HT on Tumor Metabolism and Oxygenation. Heat also modulates cell metabolism, by switching it toward glycolysis. This reduces oxygen consumption rate, which, in combination with increased perfusion, may contribute to heat induced reoxygenation.[38] Decreases in ATP concentration after HT are inversely related to the temperatures achieved during HT in preclinical models and canine sarcomas[39,40] and are related to pathologic CR rate in human sarcomas.[39] Decreases in ATP and increases in lactate concentration occur following tumor blood flow reduction after HT.[41] In human patients with soft tissue sarcomas who were treated preoperatively with HT and radiation therapy, reduction in ATP/Pi ratio (measured using ^{31}P magnetic resonance spectroscopy; Pi = inorganic phosphate) was significantly correlated with a higher probability for pathologic complete response.[39] These results are consistent with the theory that tumor respiration decreases after HT treatment.

Several pre-clinical studies have shown that mild temperature heating (between 40°C and 42°C for an hour) can lead to improvements in tumor pO_2 up to 24 hours after heating.[42] However, in some models, the extent of reoxygenation is quite heterogeneous between and even within individual tumors.[43] It has been reported that HT improves tumor oxygenation in canine and human soft tissue sarcomas, with reoxygenation being associated with greater probability for pathologic complete response (pCR) in human tumors.[44,45] In a canine study, median temperatures <44°C improved oxygenation, whereas median temperatures >44°C for 60 minutes led to decreased oxygenation.[44] In a follow up study with canine sarcomas, reoxygenation 24 hours after the first heat treatment was associated with increased likelihood for reduction in tumor volume at the end of therapy.[46] In patients with locally advanced breast cancer who were treated in a phase II study with preoperative HT + radiotherapy and taxol, there was a significantly increased likelihood for achieving pCR if the tumors reoxygenated 24 hours after the first HT treatment. The probability for achieving a pCR was greater when the median temperatures were below 41.5°C.[47] Improvement in oxygenation does not occur in all tumors, however, and currently there is no method for predicting which tumors will show this effect.[48] In summary, mild temperature elevations during HT will benefit some patients if HT induces reoxygenation. To take full advantage of this effect it will be necessary to utilize methods to enhance the reoxygenation effect, such that it occurs in the majority of patients. Song and Griffin have suggested that the addition of hyperoxic gas breathing after HT, but during radiotherapy, may achieve this goal.[49,50]

Hyperthermia and Metastases

HT causes abrupt changes in tumor microvascular function, as described above, which could enhance tumor cell shedding from the heated site. Pre-clinical studies are mixed on this issue. One report showed that local HT alone enhanced the metastatic rate of B16 melanoma.[51,52] When curative doses of radiotherapy were added to HT in the B16 melanoma model, however, the incidence of lymph node and lung metastases was decreased, compared with controls.[52] The combination of curative doses of radiation and HT has generally been reported in other tumor models to reduce the incidence of metastases,[53,54] although in a few models, simultaneous administration of HT with radiation has been reported to increase metastases.[53,54]

The question of whether local HT increases the risk for metastasis is difficult to answer in clinical trials unless the primary therapy has a high probability for local control. This is because of the problem of competing risks. In a phase III trial of canine patients with primary malignant melanomas treated with the combination of HT and radiation or radiation alone, no difference in the likelihood for metastasis between the two groups was seen.[55] However, local recurrence was a common event, and its onset was frequently followed by appearance of distant metastases. In a phase III randomized trial of human melanomas treated with thermoradiotherapy vs. radiotherapy alone, there was significant improvement in the likelihood for survival when the local tumor was controlled. Since the use of HT in that trial resulted in improved local control, the implication is that the combination therapy reduced the probability for metastases.[56,57] In a study comparing graded doses of radiation ± HT for treatment of canine soft-tissue sarcomas, higher normal tissue temperatures in the region of the tumor were correlated with lower likelihood for distant metastases.[58] A large series of patients (N = 95) with previously untreated high-grade soft tissue sarcomas who were treated preoperatively with HT and radiation achieved a local control rate near 90%, but 50% developed distant metastases.[59] This rate of metastasis is essentially identical to that seen with preoperative RT alone, however, suggesting that HT had an undetectable influence on metastases.[60]

The conclusion is that with the exception of one study with the B16 melanoma murine model involving HT alone, there is not any evidence from pre-clinical models or human trials that local-regional HT causes an increase in metastases, particularly when HT is combined with radiotherapy.

Normal Tissue Damage from Hyperthermia

Thresholds for thermal damage depend on the tissue type being heated and the severity of the injury. Mild damage can merely lead to edema, whereas more severe injury can lead to massive necrosis and organ failure. This subject has been reviewed in detail.[1,3] The ranking of tissue thermal sensitivities does not follow classical principles derived from other cytotoxic agents, such as radiation or chemotherapy. With such agents the most sensitive tissues are those with the highest proliferative potential or activity. For HT the most sensitive tissue classification includes brain, which is comprised of cells with almost no proliferative potential, as well as testis, which has high proliferative potential. There has been speculation as to whether tumor tissues might be more sensitive to thermal damage than normal tissues. Many studies have compared tumor to normal cells, in vitro. There is no inherent difference in the thermal sensitivity. However, the microenvironment of tumors, which is often acidotic and nutritionally deprived, leads to an increase in thermal sensitivity that has been reported in a clinical series.[61]

Radiation and Hyperthermia

Rationale for Combining Hyperthermia with Radiotherapy

When radiation is combined with HT, complementary effects occur. Cells in S-phase are radioresistant, but sensitive to HT. Hypoxic cells are three-fold more resistant to radiation, compared to aerobic cells, but there is no difference in thermal sensitivity between aerobic and hypoxic cells. As discussed

earlier, HT can lead to reoxygenation, which will further improve radiotherapy response.[42,45,46,62] Finally, HT inhibits the repair of both sublethal and potentially lethal damage by inactivating crucial DNA repair pathways.[63-65]

Factors to Consider When Combining Hyperthermia with Radiotherapy

The interaction between radiation and HT is described by the "thermal enhancement ratio" or TER, which is defined as the ratio of doses of radiation to achieve an isoeffect for RT/RT + HT. TERs for local tumor control have been estimated for a number of human tumors using historical control data for radiation alone.[66] In most tumor types examined, these ratios were >1. Assessment of normal tissue TER has not been attempted except in a few cases. For those examples, TER values for normal tissue damage have been less than those for tumor in the same patient population, suggesting potential for therapeutic gain for RT + HT compared with RT alone.[66] Prospective randomized trials in dogs with spontaneous tumors have also shown evidence for improved local tumor control with RT + HT compared with RT alone[58,67-69] with no observable increase in the frequency of clinically relevant late normal tissue complications. In one canine trial enhancement of late radiation damage (as assessed histologically) was reported and the duration of acute radiation complications was prolonged.[69] There is clinical evidence, however, that excessively high intratumoral temperatures (i.e., >45°C for 60 minutes) can lead to damage to surrounding normal tissues, an effect that is often caused by rapid tumor regression.[67,70] Such damage is not easily repaired and can lead to chronic tissue consequences, such as fibrosis, fistulae formation, and bone necrosis.

Two cases of fatal pelvic necrosis have been reported as a late complication in patients with locally advanced cervix cancer treated with thermoradiotherapy.[71] There was speculation as to whether the complication was the result of HT. More recently, however, this rare complication has been reported following chemoradiotherapy treatment of cervix cancer.[72,73] Thermal doses achieved in the HT series were several degrees lower than has been reported to be associated with enhancement of normal tissue complications by radiotherapy, which strongly suggests that these two cases were not the result of HT, but more likely a result of the radiotherapy treatment, perhaps complicated by a heavy smoking history associated with both patients.[71]

In summary, most available data from pre-clinical and clinical studies indicate that therapeutic gain is achievable for the combination of HT with RT. There is very little evidence to suggest that HT enhances the incidence or severity of late normal tissue complications from radiotherapy, particularly when excessively high intratumoral temperatures are avoided.

Hyperthermia and Chemotherapy

Rationale for Using Hyperthermia with Chemotherapy

Many chemotherapeutic agents have been shown to exhibit synergism with HT, including cisplatin and related compounds, melphalan, cyclophosphamide, nitrogen mustards, anthracyclines, nitrosoureas, blyeomycin, mitomycin C, and hypoxic cell sensitizers.[31] The mechanisms that underlie the synergy may include: (1) increased cellular uptake of drug, (2) increased oxygen radical production, (3) increased DNA damage and inhibition of repair, and (4) reversal of drug resistance mechanisms.[74-77] Hypoxia and pH are also important in the thermochemotherapeutic response.[78-82] There are some classes of drugs, such as etoposide and vinca alkaloids, that do not synergistically interact with HT.[31]

Rationale for Using Hyperthermia with Targeted Agents

(MAP) Kinase, Heat Shock Response and HIF-1

It has been reported that hyperthermia can increase expression of HSP40 (40 KD heat shock protein) via the ERK1/2 (MAP) kinase pathway.[83] The upregulation of HSP40 protects against heat killing, but blockade of MAP kinase activation by SiRNA or by targeted drugs sensitizes tumor cells to hyperthermic cell killing.

HIF-1 is also upregulated by hyperthermia in a process mediated by ERK1/2 transcription of NADPH oxidase in tumor cells.[38] The increased production of peroxide by NADPH oxidase stabilizes the labile subunit, HIF-1α. Increased levels of HIF-1α bind to its heterodimer, HIF-1β, leading to HIF-1 mediated gene transcription. The increased transcriptional activity of HIF-1 upregulates: (1) production of VEGF (vascular endothelial growth factor), which promotes angiogenesis and (2) PDK-1, (pyruvate dehydrogenase lipoamide kinase isozyme 1) which promotes a switch to anaerobic metabolism. Both of these responses and other HIF-1 regulated genes promote survival of tumor cells. The upregulation of HIF-1 mediated transcripts has been verified clinically in canine sarcomas after treatment with thermoradiotherapy.[84] Further, inhibition of HIF-1 after radiotherapy has been shown to enhance growth delay.[85] Thus, there is rationale to inhibit the HIF-1 response after hyperthermia particularly when combined with radiotherapy.

Genomic Analyses

Genomic analysis of U937 cells, a human myelomonocytic tumor, exhibited differential expression in approximately 1000 genes, following a non-cytotoxic treatment of 41°C for 30 minutes.[86] A higher thermal exposure of 42°C for 90 minutes led to more significant change in pro-apoptotic signaling pathways,[87] in addition to the expected heat shock response in both cases. Genome-wide analysis has also been done on one rat tumor line in vivo, following local heating (43°C for 60 minutes).[88,89] The effects of hyperthermia were rather pleiotropic, involving over 1200 genes and a host of cellular responses, including apoptosis regulation, cell cycle control, MAP kinase and calcium regulated cell signaling and genes involved in angiogenesis and metabolism regulation. There was also substantial downregulation of a number of genes involved in immune function at 3 hours after treatment, which recovered to baseline by 24 hours. These results suggested that HT does not adversely affect immune function. The fact that hyperthermia appears to augment pro-apoptotic signaling pathways suggests that it could work additively to with targeted agents that promote apoptosis.

Chi et al conducted the first clinical study comparing gene expression patterns and functional imaging (diffusion weighted MRI) prior to and 24 hours after the first HT fraction during a course of thermoradiotherapy for spontaneous canine soft tissue sarcomas.[84] Patterns of gene expression change of VEGF, DNA repair and inflammation were correlated with response, as assessed by changes in diffusion weighted MRI. Using connectivity mapping, the differential in gene expression was found to be linked to several drugs, the most promising of which was geldanomycin, an HSP90 inhibitor. The authors went on to show that this drug sensitizes cells to thermoradiotherapy, in vitro. This provides rationale for such combinations in future human clinical trials.

PARP-1 (Poly [ADP-ribose] Polymerase 1) Inhibitors

It has recently been reported that mild hyperthermia (41°C and 43°C) inhibits double strand DNA break repair after

radiotherapy.[90] This is due to downregulation of BRCA2 accumulation at double strand break sites of DNA. BRCA2 is a protein that is essential for completion of homologous recombination. Based on prior knowledge that cells deficient in BRCA2 are sensitive to PARP-1(Poly [ADP-ribose] polymerase 1) inhibitors, the authors went on to show that inhibition of PARP-1 sensitizes tumor cells to killing by hyperthermia. The authors termed this strategic approach an "induced synthetic lethality." Given that PARP inhibitors are currently in clinical trials <http://clinicaltrials.gov/ct2/results?term=PARP+inhibitor&Search=Search>, this therapeutic approach may be rapidly translated to trials involving hyperthermia.

It has been reported that HT can induce autophagy via activation of NFκB, as a protective mechanism against cell death.[91,92] Thus it would make sense to consider combining agents that inhibit NFκB activation with HT as a means to enhance thermal cell killing. Alternatively, the combination of 43°C hyperthermia with increased oxidative stress can increase cell killing via inhibition of the Akt pathway and induction of irreversible autophagy.[92] Pajonk et al reported that inhibition of proteasome activity in combination with (44°C for 60 minutes) hyperthermia was particularly effective in augmenting apoptosis, in addition to causing substantial radiosensitization.[93]

In summary, there appears that there is emerging rationale for targeting various signal transduction pathways and other cellular adaptation processes as a means to enhance cell killing when combined with hyperthermia.

Factors to Consider when Combining Hyperthermia with Chemotherapy

Temperature Dependence

The degree of enhancement of cytotoxicity has been shown to be temperature dependent for many drugs.[94] Combinations of camptothecins with HT have not shown consistent results in vitro. The interaction between these agents and HT is schedule and temperature dependent.[95,96] In one report, temperatures up to 41.8°C increased the activity of topoisomerase II, which may be the explanation for the increased activity of these drugs at elevated temperatures.[95]

In Vitro Results May not Predict In Vivo Activity

Tubulin binding agents, such as taxol, show no evidence for interaction in vitro,[97] but studies in combination with radiation therapy in vivo are more encouraging.[98] There may be physiologic consequences of the combination of taxol and HT that make the combination work better than predicted from in vitro studies.

Sequencing

For most drugs (excluding 5-FU and perhaps other antimetabolites), the optimal sequence between heat and drug is to administer them simultaneously or to give the drug immediately before the onset of heating. For platinum-containing drugs, the tissue extraction rate is increased with HT, further substantiating the rationale for use of this sequence.[99] It has been shown recently that thermal enhancement of cisplatin uptake by cells is the result of multimerization of the CTR1 transporter (otherwise known as the copper transporter).[100] Most antimetabolites do not interact with HT when given concomitantly.[31] However, 5FU has been shown to interact supra-additively with HT by controlling temperatures to be between 39°C and 41°C. Temperatures in this range lead to enhanced conversion to active metabolites, thereby increasing drug cytotoxicity. In addition, continuous infusion protocols with this drug may lead to cell cycle block in S phase, a relatively sensitive part of the cell cycle to HT.[101]

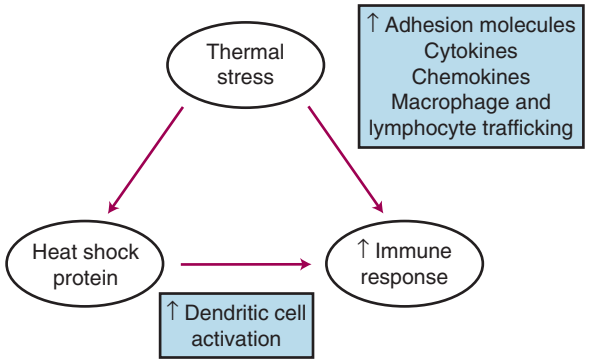


Figure 21-4 Summary of known beneficial immunological effects of mild temperature hyperthermia.

Immunological Effects of HT

Heat shock proteins have been recently recognized for their potential role in regulating immune responses. There are several recognized functions of these proteins: (1) They are known to bind, in a non-covalent fashion, to immunogenic peptides. (2) When tumor cells are exposed to HT, HSP-peptide complexes are presented on the cell surface. These complexes can be recognized by antigen-presenting cells (dendritic cells) via MHC class I molecules. Once dendritic cells have received this type of stimulus, they migrate to lymph nodes, where they prime T-cell lymphocytes to be cytotoxic toward cells that express the peptide-HSP complex. Hyperthermia has been shown to enhance the rate of dendritic cell migration.[102] (3) Heat shock proteins also induce dendritic cell maturation and pro-inflammatory cytokine release.[103,104] (4) Cell membrane localization of heat shock proteins also activates the innate immune system by activating natural killer cells (NK cells).[105] Other sources of cellular stress—such as viral infection, fever, hypoxia, and radiation exposure—have been shown to upregulate heat shock proteins as well. Because this process appears to occur naturally, there have been efforts to exploit the use of hyperthermia to produce tumor-derived vaccines and to augment the in vivo response to such vaccines.[104] HT has also been reported to upregulate a number of pro-inflammatory cytokines and adhesion molecules that facilitate immune cell trafficking across endothelial cells to gain access to tumor interstitium.[106] Additionally, shed heat shock proteins, with or without associated peptides, may act as chemokines to attract immune cells (particularly macrophages) toward a region tissue that has undergone heat stress.[107] A summary of some key immunological effects of HT is shown in Figure 21-4. Note that a special issue of the International Journal of Hyperthermia was recently published, which covers this subject in detail.[108]

HYPERTHERMIA PHYSICS/ENGINEERING

Clinical HT is usually achieved by exposing tissues to non-ionizing radiation (e.g., electromagnetic [EM] or ultrasonic [US] fields) or by conducting heat into tissue from a heated source (e.g., hot pad or needle). Although these modalities deposit energy in tissue by different physical mechanisms, they have general similarities. Uniformity of heating is sensitive to the heterogeneity of tissue properties, geometry of blood flow, and practical problems of coupling the energy source into tissue. Hyperthermia can be delivered non-invasively with externally applied power sources or invasively by placing heat sources either interstitially or inside natural body cavities. An overview of non-invasive methods is provided below and is summarized in Table 21-1. Invasive

TABLE 21-1 Summary of Methods Used to Heat Tissues

Class	Method	Power Directed to Tumor Site?	Frequency	Coupling Medium	Invasive Thermometry Requirements	Advantages	Disadvantages
ELECTROMAGNETIC							
Superficial							
	Capacitive radiofrequency	Partially, by changing position and relative size of electrodes	5-30 MHz	Saline	RF-shielded EMI-resistant probes and readout electronics	Simple to operate	Superficial fat heats; use limited to thinner patients
	Microwave waveguide	Yes, by placing waveguide over tumor	433, 915, 2450 MHz	Water	Non-perturbing EMI-resistant fiberoptic probes or high-resistance lead thermistors	Simple to operate	Limited depth of heating; heat pattern dependent on tissue properties and applicator coupling
	Microwave array	Yes, by adjusting relative power to multiple antennas	433, 915, MHz	Water	Non-perturbing EMI-resistant fiberoptic probes or high-resistance lead thermistors	Adjustable size, shape and location of heating; available in planar or conformal arrays	Limited depth of heating
Deep							
	Magnetic induction	No	0.05-15 MHz	Air	RF-shielded EMI-resistant probes and readout electronics	Simple to operate; focus with implanted particles or seeds	Eddy currents follow path of least resistance; heating pattern controllable with particles or seeds
	Capacitive radiofrequency	Partially, by changing position and temperature of electrodes	5-30 MHz	Saline	RF-shielded EMI-resistant probes and readout electronics	Simple to operate	Superficial fat heats; use limited to thinner patients
	Phased radio-frequency arrays	Partially, by adjusting phase and amplitude of power from different antennas	70-150 MHz	Water	Non-perturbing EMI-resistant fiberoptic probes or high-resistance lead thermistors	Ability to focus heat at depth and move the heat focus around	Limited control over size and location of heat focus
ULTRASOUND							
Superficial							
	Planar non-focused ultrasound transducer	Partially, by placing transducers over tumor	1-5 MHz	Degassed water	Metal probes required; avoid plastic	Simple to operate	Good coupling to soft tissue required—air and air prohibit penetration and can lead to pain
	Planar non-focused ultrasound transducers—multiple	Yes, by adjusting relative power and/or frequency of transducers	1-5 MHz	Degassed water	Metal probes required; avoid plastic	Improved control of size, shape and perhaps depth of heating	Good coupling to soft tissue required—air and air prohibit penetration and can lead to pain
Deep							
	Focused transducer array	Yes, by adjusting relative power, phase and/or scanning of transducers	0.5-2 MHz	Degassed water	Metal probes required; avoid plastic	Precise steerable focus possible at depth	Practical limit on size and location of appropriate acoustic window, air and bone prohibit penetration and can lead to pain

methods have been developed extensively and include radiofrequency (RF) electrodes, microwave antennas, ultrasound transducers, hot water tubes, and inductively heated ferromagnetic implant rods or seeds. Further details on all methods are available elsewhere.[109-118]

Electromagnetic Heating

The primary mechanism of EM heating varies with frequency. For radiofrequency (RF) fields below about 30 MHz, the EM field induces a net movement of free electrons and power deposition results from resistive (ohmic) losses due to electric currents through lossy tissue. The term "lossy" means that the tissue is both a poor conductor and poor insulator. As such, electromagenetic fields are absorbed as they traverse the tissue. At microwave frequencies above about 150 MHz, heating results primarily from friction between polar water molecules that oscillate to maintain alignment with the time-varying field. This is called "dielectric loss." Improved penetration is obtained for lower frequencies with longer wavelengths, but the ability to localize EM energy in a desired target improves with higher frequency and corresponding shorter EM wavelengths. Accordingly, there is a trade-off between depth of penetration and ability to focus energy. In practice, heating may be localized in tumor targets within 2-4 cm from a microwave applicator at >430 MHz, whereas lower frequency multiple antenna phased arrays are used to heat larger regions that include tumor deep in the body.

Considering the effects described earlier, electromagnetic heating devices are quite different for superficial heat applications with effective penetration less than 4 cm than they are for deep heating of tissue more than 4 cm. Superficial heat applicators include waveguides (Figure 21-5) and microstrip or patch antennas (Figure 21-6) operating at microwave frequencies of 433, 915, or 2450 MHz. These devices can be separated into two categories: superficial applicators with effective penetration into tissue <4 cm, and deep heating devices that have effective penetration >4 cm. Superficial devices include waveguides (Figure 21-5) and microstrip or patch antennas (Figure 21-6) operating at microwave frequencies of 433, 915, or 2450 MHz.[115-117,119-121] Microwave energy is usually coupled into tissue through a temperature-controlled deionized water bolus to maintain skin temperature below 44°C.

In order to heat at depths >4 cm, radiofrequencies between 5 and 200 MHz are used. There are three basic techniques for EM deep heating: inductively coupled magnetic fields, capacitively coupled electric fields, and radiated fields from multiple antenna phased arrays.

Magnetic Induction Heating

Magnetic induction heating uses a 0.05-15 MHz magnetic field to induce eddy currents in conductive tissue.[122] The magnetic field can penetrate to the body center but heating is caused by eddy currents in lossy tissue that depend on tissue type and geometry of the induction coils and tissue load.[123] Heating may be concentrated deep in the body around implanted ferromagnetic seeds or particles that couple into the external magnetic field more effectively than surrounding tissue. Without insertion of ferromagnetic material into the body, the distribution of power deposition in tissue directly from induced eddy currents is not adjustable. By inserting ferromagnetic seeds or particles in the tumor, the distribution



Figure 21-5 Example of a commercial microwave waveguide applicator heating system for superficial hyperthermia treatments. Typical systems operate at 915 MHz or 430 MHz for heating 2-4 cm depth. Energy is usually coupled into tissue through a thin layer of deionized water, which is temperature controlled to maintain the skin surface below 44°C. A single waveguide applicator provides no control of power distribution in the x-y plane, aside from what can be achieved by physically moving the applicator. The arrow indicates the aperture of the waveguide. The water bolus would be attached to the waveguide in this location.

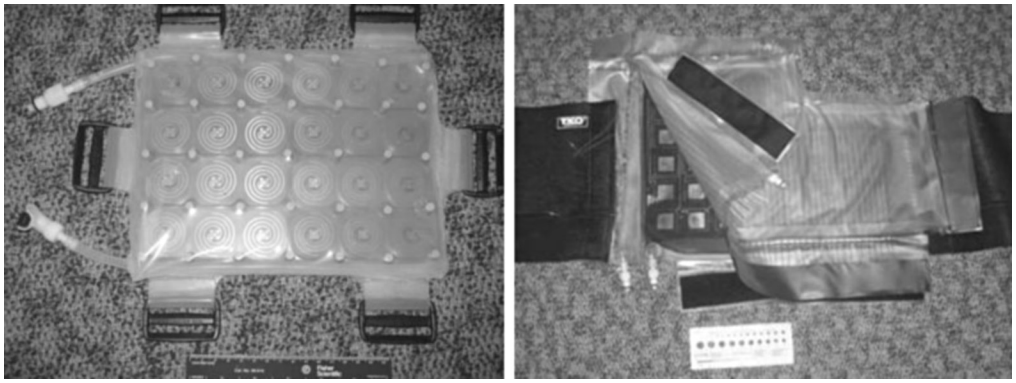


Figure 21-6 Two examples of thin and flexible microstrip antenna array applicators currently under development for superficial hyperthermia. A <1 cm thick temperature controlled deionized water bolus is used to couple microwaves into tissue and maintain the skin surface below 44°C. These conformal array applicators are driven with 8 or more microwave power sources to provide adjustment of the power distribution across the tissue surface.

of heating may be adjusted by changing the density of implanted material. There has been a resurgence of interest in ferromagnetic materials for hyperthermia. See recent special edition of the International Journal of Hyperthermia for more details.[123]

Capacitive Heating

Capacitive heating uses radiofrequency fields between 5 and 30 MHz to generate electric current between two or more conductive electrodes. Heating tends to be concentrated nearest the electrodes, but temperature-controlled saline boluses are used to reduce hot spots on the skin surface and help cool superficial fat.[124] Using different size electrodes, the maximum power deposition may be shifted toward the smaller electrode. This technique can be used with large electrodes on the skin[125,126] and one or more small intracavitary electrodes such as a balloon electrode for esophageal tumors.[127] The thickness of the superficial fat layer is a significant factor for this method because of extra heating in high resistance fat tissue relative to deeper lying high conductivity soft tissues. To date, RF capacitive heating has been used most widely in Asia, where patients tend to be thinner.

Radiofrequency Phased Array

The third option for heating with electromagnetic fields is the radiofrequency phased array.[128-131] These devices consist of an array of RF antennas arranged in a geometric pattern surrounding the target body region. Antennas are driven with multiple independently controllable power amplifiers but using a common radiofrequency source, allowing phase addition fields from all antennas to add together to form a heat focus in the center of the array. The focus can be shifted off center and around the tumor by variation of relative phase of the drive signals from each amplifier. For a multiple antenna phased array deeper power deposition into tissue is possible than using several independent antennas without phase addition. The phased array technique has more flexibility for controlling power deposition pattern than direct tissue magnetic induction and capacitive techniques which are altered significantly by heterogeneous tissue properties and few power control variables. Figure 21-7 shows one example of a 12 antenna annular phased array applicator mounted on the patient table of a magnetic resonance imaging (MRI) system. This MR compatible 100 MHz RF phased array applicator fits inside the bore of 1.5 T magnet allowing MR imaging of temperature to rise inside the body during hyperthermia treatment.

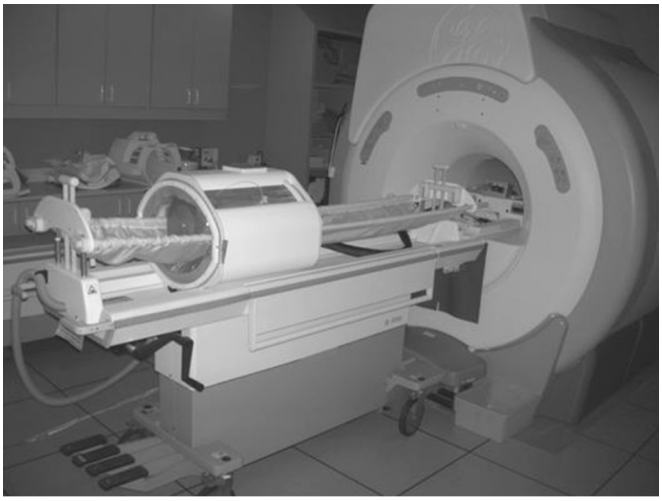


Figure 21-7 Example of 12 antenna radiofrequency phased array applicator for deep regional hyperthermia treatments. This array is driven at 100 MHz and has appropriate filtering to enable use inside a magnetic resonance (MR) imaging system for monitoring deep tissue temperatures with proton resonance frequency shift based MR thermal imaging. The large focus of heating inside the phased array applicator may be guided into the tumor by adjusting phase and amplitude of the 12 antennas, in response to real-time feedback from the MR thermal images.

Ultrasound Heating

Energy transfer from an ultrasound acoustic pressure field results from viscous friction within the tissue caused by successive compression and expansion from the high and low pressure wavefront. As with electromagnetic sources, heating falls off exponentially with distance from a single source, and penetration of the ultrasound field decreases with increasing frequency. However, because the wavelength of an US field is several orders of magnitude smaller than that of EM fields, and on the order of mm, ultrasound energy may be focused into small volumes deep in the body, given sufficient number of transducers to spread out the surface power density over a large surface. In practice, it is anatomic geometry and tissue heterogeneity (air reflects and bone preferentially absorbs ultrasound) that restrict the utility of US for heating large tumor volumes at depth. The availability of an adequate "acoustic window" (a path unobstructed by bone or air proximal and distal to the target) is the primary concern in clinical HT with ultrasound, wherein the entry window and acoustic gain to the target determines the maximum size and depth of the target volume.

Energy is coupled into tissue using temperature-controlled degassed water. Single and multiple transducer unfocussed devices have been designed for superficial tumor (2-5 cm) heating which typically operate in the 1-5 MHz range.[132-135] Deep heating with ultrasound is accomplished by using electrically or mechanically scanned focused transducers, phased arrays, or multiple scanned focused transducers, normally in the 0.5 to 2 MHz range.[135]

High intensity focused ultrasound systems are now available with high density multiple transducer arrays that are integrated into magnetic resonance imaging systems for simultaneous anatomic imaging, real-time thermal monitoring and beam steering control, and immediate post treatment assessment of ablation volumes. These systems produce a tight focus inside the cranium[136] or torso,[137] and are used most often for high temperature thermal ablation treatments.[139] For some treatment sites, additional localization is obtained using transducer arrays implanted in interstitial or intracavitary catheters. Excellent reviews of the physics and clinical aspects of focused ultrasound therapy have been published.[138-141] Focused ultrasound has also been tested extensively for its potential to augment nanoparticle delivery. This includes applications to open the blood brain barrier.[142-145]

Measurement of Temperatures during Hyperthermia

Invasive Thermometry

Invasive thermometry is the current standard for most hyperthermia treatments, involves physically placing thermometry probes into the tumor within implanted needles or catheters to read subsurface temperatures.[146-148] Although the accuracy of invasive thermometers is sufficiently precise (typically ± 0.3°C) to resolve important differences in thermal dose (as described earlier), this type of thermometry has many disadvantages. Disadvantages include discomfort to the patient and

risk of hemorrhage and/or infection, the expense of physician time required for catheter placement, and necessity for imaging to verify placement of thermometers in the target volume. In addition, the sparse nature of the data obtained makes it difficult to spatially control power deposition or alter treatment to improve temperature distributions.[149,150] The most common method for doing invasive thermometry is to insert blind ended catheters into a tumor, using either ultrasound or CT guidance.[147] Alternatively, for deep-seated tumors, thermometers may be placed inside orifices that are surrounded by tumor, such as the rectum, urethra, bladder, or cervix.[151] The probes can be multipoint sensors that remain fixed in place, or sensors are moved cyclically during treatment to record temperatures at many points along the catheter. There are guidelines published for how these measurements should be taken for all HT devices.[147,151-154] In spite of its sparse nature, invasive thermometry can provide valuable information about the quality of a treatment. A number of clinical reports have correlated temperature-related parameters to clinical response.[67,155-160]

Noninvasive Thermometry

Noninvasive thermometry is emerging in answer to the critical need for volumetric thermometry to visualize complete 3D temperature distributions in real time during deep hyperthermia treatments. In typical treatments using radiofrequency phased array applicators monitored only by invasive probes the number of thermal monitoring points is insufficient to adequately characterize the heating pattern. Parts of the tumor are unheated whereas too much heat is sometimes generated in surrounding normal tissues. Similarly, multiple element array superficial hyperthermia applicators require more temperature measurements than are possible with a limited number of invasive probes to monitor and control all independently powered heat sources. Insertion of multiple interstitial probes is clinically impractical. For superficial tumors (<1.5 cm depth), thermal dosimetry is often limited to probes placed in fixed positions on the skin or mapped through catheters lying on the skin to characterize the distribution of heating across large area disease as a prediction of subsurface temperatures.

To address the shortcomings of invasive thermometry, a number of noninvasive techniques are under investigation. Infrared thermography has been available for years for monitoring surface temperature distributions.[161] Although spatial resolution and accuracy are excellent, the method requires open access to visualize the surface so is not compatible with most heating technologies. A new approach for monitoring 2D surface temperature distributions even when the surface is buried under a water-bolus coupled applicator involves use of high density arrays of fiberoptic sensors mounted in a large surface-conforming Thermal Monitoring Sheet (TMS).[162,163] Other noninvasive thermometry approaches under development include electrical impedance tomography (EIT) sometimes called applied potential tomography,[164-165] ultrasonic temperature imaging using change in backscattered energy,[166-167] electron paramagnetic resonance (EPR),[168] active microwave imaging or tomography,[169] microwave radiometry,[170-176] and real-time multislice magnetic resonance thermal imaging (MRTI).

While there are clinical applications for each of these technologies, MRTI is being studied most intensively for volumetric characterization of temperature distributions and control of radiofrequency beam steering for deep tissue hyperthermia. Although several MR tissue parameters are sensitive to changes in temperature, attention has focused on investigation of the change in water proton resonance frequency shift (PRFS),[138,177-179] even in tissues with low water content like breast.[180,181] Use of noninvasive MR thermometry should translate into improved treatment efficacy by providing quantitative volumetric thermal dosimetry in real-time to assist the delivery of improved quality HT treatments. Figure 21-8 shows an example of non-invasive thermometry with MRTI during heat treatment of a lower leg sarcoma with a four antenna 140 MHz mini annular phased array applicator. The method has yielded a temperature resolution of better than 1.0°C compared with calibrated with invasive sensors in human patients.[182] Moreover, MR imaging offers opportunities for validation of treatment planning systems,[183-185] dynamic control of treatment delivery,[186-189] and posttreatment assessment of tissue damage.[190] The use of MRTI has been increasing rapidly in recent years for clinical applications in both moderate temperature hyperthermia and high temperature thermal ablation therapy such as radiofrequency, laser, and high intensity focused ultrasound.[191] The International Journal of Hyperthermia summarized the status of MR thermometry in a

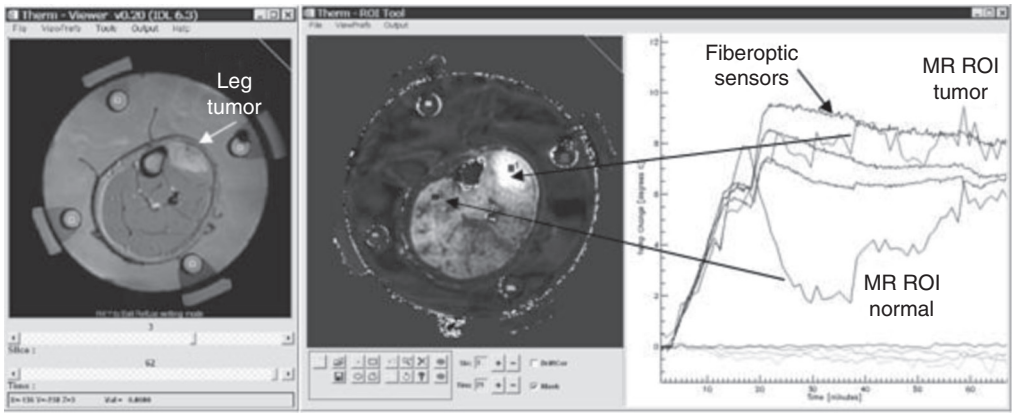


Figure 21-8 Real-time display during MR monitoring of heat treatment. Left panel shows anatomical image of leg in 24 cm diameter phased array applicator. The central image shows a typical differential temperature image display at about 20 minutes into heat treatment, after the phase of the four 140 MHz twin dipole heating antennas had been adjusted to move the heat focus into the tumor at upper right of leg. The PRFS calculated temperature rise is displayed on the same plot as invasive fiberoptic sensors in the tumor. The dramatic refocusing of power deposition at 18 minutes into treatment is seen to shift heating away from normal tissues in upper left of image and into the tumor at upper right, as indicated qualitatively by the brightness of the temperature image and quantitatively in the calculated temperature rise for tumor in the plot at right.

special issue.[192]; additional background can be found in review articles by Rieke and Butts[193] and MacFall and Soher.[178]

In a paper by Craciunescu et al[182] the critical steps were presented to attain rapid volumetric real-time image-guided hyperthermia treatments. With update times of the order of minutes, the claim of real-time treatment control agrees with an accepted definition of "real-time" given for thermal therapies by Rieke and Butts,[193] as "an update time that is small compared to significant changes in temperatures during treatment." This update time is different in hyperthermia applications (minutes or more) versus ablation therapies (a few seconds to minutes). This whole process lends credibility to the idea that future hyperthermia systems will use image feedback to control beam steering and focus heating in tumor targets.

CLINICAL HYPERTHERMIA

General Considerations

HT Alone

HT alone has been studied in the treatment of superficial tumors. While an occasional response is noted, the duration is typically quite short.[194,195] No long-term tumor control has been described with the use of HT as a sole treatment modality. HT alone remains widely practiced in certain alternative and complementary medicine clinics. Its use, however, is not supported by any peer-reviewed published scientific data.

Thermal Ablation

In contrast to effects of mild to moderate temperature hyperthermia, thermal ablation can yield durable long-term results. A meta-analysis was conducted of four phase III trials (766 patients) comparing percutaneous ethanol injection to radiofrequency ablation (RFA) for patients with liver metastases. Survival and local control rates were superior for RFA with a hazard ratio of 0.66 for survival.[196] However, the complication rate and costs of application were higher for RFA. RFA is generally used when patients are not suitable surgical candidates.[196-199]

HT with Radiotherapy

A large number of reports attest to the efficacy of HT in combination with radiotherapy (RT). The majority of publications have been from phase II trials involving patients with superficial malignancies (and thus more amenable to heating) as a component of more generalized disease, such as local recurrence of breast carcinoma on the chest wall. With the addition of HT to radiation, clinical response rates have approximately doubled from 25% to 35% with radiation alone to 50% to 70% with RT + HT.[200] In addition to phase II studies, several phase III trials have now been conducted worldwide with approximately two-thirds published in the English literature. These trials generally have been positive, lending additional validity to the information obtained from phase II studies.

HT with Chemotherapy

Published data on the efficacy of locoregional HT in conjunction with chemotherapy (CT) is much less frequent. Both animal and human data have been reviewed.[200] Particularly encouraging phase II results were reported for sarcomas,[201] which led to a recently completed phase III trial (see section on phase III trials for outcomes on the sarcoma trial and a small esophageal cancer trial).

Wessalowski et al recently reported results of a phase II study, conducted on 44 children ranging in age from 7 months to 16 years who had refractory or recurrent germ cell tumors.[202] All of these patients had received cisplatin previously as part of their initial treatment. They were treated with a combination of cisplatin, etoposide, and ifosphamide, where HT was given twice weekly in three cycles. The objective response rates were similar to what is expected from front line therapy. The 5-year overall survival rate was 62%. The results were better than anticipated given the likelihood that the majority had drug resistant tumors. As discussed earlier, hyperthermia reverses drug resistance. This effect may have played a role in the overall success of the trial.

Trimodality Therapies with HT, RT, and CT

A small randomized phase III trial involving patients with esophageal cancer showed a higher pathologic CR rate when HT was added to chemoradiotherapy compared with chemoradiotherapy alone.[203] More recently, the combination of HT + cisplatin + radiotherapy has been evaluated in patients with locally advanced cervix cancer. Twelve patients were treated in this series, with local control being achieved in ten. The two patients with local failure presented with local recurrence following hysterectomy.[204] In a follow-up report, Westermann et al combined results of this trial (with longer follow-up) with results from several other institutions that had conducted similar studies.[205] A total of 68 patients were included in the analysis. Of these, 61 achieved a complete response. At a median follow up of 538 days, 74% of patients were disease free. This is a favorable outcome, compared with historical controls. To date, however, a confirmatory phase III trial has not been reported.

The combination of 5FU, HT, and radiation therapy yielded favorable responses in patients with locally advanced colorectal cancer in a phase II study.[206] In a retrospective study comparing sphincter sparing in patients with locally advanced rectal cancer, those who received HT in addition to RT and chemotherapy tended to have a higher sphincter preservation rate, compared with those who were treated with radiochemotherapy.[207] To date, no phase III trials have been reported comparing the addition of HT to chemoradiotherapy for locally advanced rectal cancer.

Normal Tissue Damage from HT

HT does not significantly increase early or late toxicity of radiation.[67-69] The most common toxicities of HT are superficial or subcutaneous tissue burns. They are usually first or second degree and small in volume. Such burns occur in approximately 5% of patients treated in the Duke experience; characteristically they do not exceed 3 to 4 cm in maximum diameter. Third-degree burns are infrequently observed (<1% incidence). Complications from thermometry catheters are infrequent if the catheters are removed following each HT treatment.[208] When catheters are left in place throughout the course of HT (e.g., for several weeks), the frequency of complications rises significantly, particularly secondary infections.[209]

There are potential medical contraindications to deep-regional HT related to the physiological stress. Guidelines for patient selection for deep hyperthermia have been developed.[154,211]

Relationship between Thermal Dose and Outcome

Quality assurance for delivery and measurement of temperatures during hyperthermia are essential to identify quantifiable thermal dose parameters. Negative phase III clinical trials conducted by the RTOG in the 1980s were attributed to this issue.[212-214] Quality assurance standards as well as data acquisition procedures were subsequently established by both the

The maximum size that one can ablate in a single session is <5 cm. Recurrence at the margin can occur, which may require additional treatments. Feasibility of performing ablation can be affected by proximity of the lesion to thermally significant vessels[199] or other key structures that should be avoided (e.g., diaphragm, bile ducts). The FDA has granted 510K approval for three commercial RFA devices. High intensity focused ultrasound can also be used for thermal ablation. The FDA recently approved one system for use in treatment of painful bone metastases. The approval is specifically for patients in whom radiotherapy is not an option <http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/DeviceApprovalsandClearances/Recently-ApprovedDevices/ucm327521.htm>.

RTOG[147] and European Society of Hyperthermic Oncology (ESHO).[210,211,215] The biological underpinning for thermal dosimetry was discussed previously in the biology section of this chapter.

Dosimetry for hyperthermia is distinctly different from that for radiation therapy in that the amount of energy deposited does not correlate with the degree of damage. This is because damage is related to the amount of temperature rise and the time of exposure, both of which are governed by the net balance between how much energy is deposited vs. how much is carried away by thermal conduction and perfusion. In the case of hyperthermia, the dosimetric unit used most often has been one that was derived empirically from evaluation of the Arrhenius relationship for cell killing in vitro as well as from numerous studies of degree of tissue damage as a function of temperature and time of exposure.[1] As was described in detail previously, the unit most often used has been equivalent minutes at 43°C (CEM 43°C). Application of this concept to the clinic, however, requires integration of non-uniform temperature history data with CEM43°C.

Since temperatures during hyperthermia treatment are non-uniform, it is necessary to derive descriptive parameters from the temperature distribution to which the CEM43°C parameter can be applied. A number of clinical parameters have been described based on simple descriptions of the multipoint thermometry, such as minimum temperature, average temperature, etc. Parameters that have proven useful for describing temperature distributions are the 10th percentile of the temperature distribution, which is commonly referred to as the T_{90} (90% of measured points exceed this value) or the T_{50}, which is the median temperature. Use of these types of parameters leads to dosimetry that is comparable across patients and studies, as long as quality assurance guidelines are followed with respect to the placement and number of thermometers used. The resultant units are referred to as CEM43°CT_{90} or CEM43°CT_{50}.

Retrospective evaluation of many phase II and phase III trial results have shown positive relationships between measures of thermal dose and treatment outcome, suggesting that higher thermal doses will yield better responses when HT is combined with radiotherapy.[156,158-160] In all positive studies reported to date, thermal analysis was performed retrospectively. It has been more difficult to correlate variations in thermal dose administered a priori and clinical outcome. Two studies compared various numbers of heat treatments given in combination with fractionated RT,[216,217] using the assumption that more treatments would yield greater cumulative thermal dose. Neither study showed any benefit with higher numbers of HT fractions, which could in part be due to the fact that there was considerable overlap in thermal doses between the treatment arms. This is because temperature is a stronger determinant of thermal dose than time-at-temperature (see biology section previously). A canine study compared radiation therapy combined with whole body HT + local HT compared with local HT alone. The CEM43°CT_{90} was higher in the group that received whole body hyperthermia, but there was no difference in duration of local control between the two treatment arms.[218] One potential explanation for the lack of improvement in local control might have been the induction of thermotolerance during the whole body HT, which was administered prior to application of local heating.

The first attempt to prospectively control thermal dose, as prescribed by the CEM43°CT_{90}, was a study of preoperative RT + HT for soft tissue sarcomas.[59] The outcome variable was pCR assessed at the time of surgery, and the percentage of patients predicted to achieve a pCR as a result of achieving CEM43T_{90} > 10 minutes was predicted to be 75%, based on prior phase II studies.[158] The pCR rate in this study was 54%, which was below the 95% confidence level for the projected rate. A number of explanations are possible for failing to achieve the projected pCR rate, including the sparseness of the temperature information gained. Recently, it was reported that other mitigating physiologic factors may have confounded the results of this study.[219]

Two additional phase III trials have been completed by the same group—one in patients with superficial tumors and the other in pet dogs with soft tissue sarcomas. In both of these trials there was clear separation in thermal doses between the two treatment arms.[156,220] Most importantly, improved response and duration of local control was observed in the groups that prospectively received the higher thermal dose. These are the first two and only trials conducted in which prospective control of thermal dose has yielded demonstrated improvement in local tumor response and/or control. They clearly indicate that better prospective control of thermal dose may ultimately lead to methods to truly optimize hyperthermia treatment. A recent study by this same group evaluated the question of how many fractions of HT (1 vs. 4 fractions/week) should be delivered in conjunction with fractionated RT.[46] The cumulative thermal dose was kept equal between the two arms. In prior clinical trials, the number of hyperthermia treatments has been restricted to no more than 2/week, because of concerns about persistence of thermotolerance between HT fractions. However, heat radiosensitization is not affected by thermotolerance, thus it was reasoned that giving 4 fractions of HT/week might yield superior results to giving 1 fraction/week. Surprisingly, giving 1 fraction/week was significantly better than 4, based on tumor response at the end of therapy.

Phase III Clinical Trials Overview – HT + RT

Phase III trials have involved a wide variety of diseases, including superficial malignancies and tumors deep within the body. Trials have been conducted with either palliative or curative intent. A summary of the most important of these trials is presented in Table 21-2.

Breast Cancer

Chest wall recurrences of breast cancer are difficult to control with conventional approaches, and many patients develop such recurrences despite prior adjuvant radiotherapy or systemic therapy. Since they are superficial tumors, they have been amenable to HT trials. Five separate phase III trials were combined for analysis in an international collaborative study by Vernon et al.[221] Patients were randomized to either RT alone or RT with HT. Treatment was prescribed according to ESHO and RTOG guidelines. HT techniques differed somewhat between institutions but are well documented, as is information concerning temperature distributions and thermal dosimetry.[160] Overall, the five trials demonstrated a significant improvement in the complete response rate for patients receiving HT + RT (59%) compared with RT alone (41%), with an odds ratio of 2.3 (95% CI 1.4-3.8) (see Table 21-2). The greatest effect was observed in patients with recurrent lesions in previously irradiated areas where further irradiation was of necessity limited to low doses. No survival advantage was seen.

Other Superficial Malignancies

A study was conducted by the RTOG in the 1980s comparing RT alone with RT + HT in superficial measurable tumors (RTOG 8104).[213,214] Three hundred seven patients were included in the study; approximately half of the patients had head and neck tumors, one-third had breast carcinoma (chest wall recurrences), and the remaining had a variety of superficial malignancies. Patients treated with RT + HT had a

TABLE 21-2 Key Phase III Trials: Hyperthermia Combined with Radiotherapy

Author	Tumor Type/ Location	Type of Trial	N	RX Arm: RT	RX Arm: RT + HT	RT Dose (Gy)	# Fx	Mean Tx Time	Hyperthermia: # Fx	Hyperthermia: Thermal Dose Goals/ reported data	End Points: Control Arm (RT)	End Points: Treatment Arm (RT + HT)	Significance ($p < 0.05$)
van der Zee[227]	Pelvic*	Dutch multicenter	358	176	182	—	—	—	1/wk, ≤5 Fx (1-4 hr post RT	Target = 60 min @ 42C; avg total HT, 90 min	CR 39% (3 mo) 3-y OS 24% 3-y LC 26%	CR 55% (3 mo.) 3-y OS 30% 3-y LC 38%	Yes Yes Yes
	Cervix subgroup	Dutch multicenter	114	56	58	≥42	23-28	48 d	Same	Same	CR 57% (3 mo) 3-y OS 27% 3-y LC 41%	CR 83% (3 mo.) 3-y OS 51% 3-y LC 61%	Yes Yes Yes
Sneed[226]	GBM (after RT)	Single institution	68	33	35	59.4 Gy EBRT + BT 60 Gy	33 1	32 d 100 hr	2Fx (pre-post BT)	Median CEM 43°T90: 14.1 Median CEM 43°T50: 74.6	TTP, median 33 weeks TTLTP 35 wks 2-y OS 15%	TTP, median 49 weeks TTLTP 57 wks 2-y OS 31%	Yes Yes Yes
Emami[212]	Various (HN, pelvis, other)†	RTOG multicenter	173	87	86	Prior + BT study dose <100 Gy	—	1 d (BT)	1-2 pre or post BT	Goal: Tmin 43° C for 60 min	CR 54% 2-y LC 37% 2-y OS 29%	CR 57% 2-y LC 43% 2-y OS 36%	No No NR
Vernon[221]	Breast	Multicenter	306	135	171	29-50 Gy +/– boost	Varied	2-5 wks	1 to 8	Goal: T > 42.5°C Q 30 min	CR 41% 2-yr OS 40%	CR 59% 2-yr OS 40%	Yes No
Overgaard[57]	Melanoma	Multicenter 70 pts, 134 sites	68	65	63	24-27	3	8 d	3	Goal: 43°C Q 60 min	CR 35% 3 mo 5-y LC 28%	CR 62% 3 mo 5-y LC 46%‡	Yes Yes
Kitamura[225]	Esophagus	Single institution	66	34*	32*	30 Gy	13	3 wks	6	42.5–44.0° C Q 30 min	Downstg, 44% CR 8% 3-y OS 24%	Downstg, 69% CR 26% 3-y OS 50%	Yes Yes NR
Valdagni[223,224]	Head and neck nodes	—	41	21/22 nodes	16/18 nodes	64-70 Gy	NR	30 d	2 vs 6 Fx	Goal: Tmin + 42.5°C Q 30 min	5-yr LC 24% 5-y OS 0%	5-yr LC 69% 5-y OS 53%	Yes Yes
Perez[214]	Misc. superficial	RTOG 8104 multicenter	307	117	119	32 Gy	8	4 wks	8	Goal: 42.5°C Q 60 min BIW	CR total 30% CR for lesions <3 cm 25%	CR total 32% CR for lesions <3 cm 52%	No No
Datta[222]	Head and neck	Single institution	65	32	33	50 Gy + boost	25	5 wks	BIW	Goal: 20 min @ 42.5°C	CR 31% @ 8 wk	CR 55% @ 8 wk§	Yes

Wks, *Weeks;* d, *days;* Q, *every;* hr, *hour;* RX, *treatment;* RT, *radiation;* Fx, *fractions;* HT, *hyperthermia;* CT, *chemotherapy;* CR, *complete response;* 3-y, *3-year;* downstg, *downstage;* LC, *local control;* OS, *overall survival;* DFS, *disease-free survival;* FU, *follow-up;* HN, *head and neck;* TTP, *time to progression;* TTLTP, *time to local tumor progression;* Rec, *recurrent;* GBM, *Glioblastoma multiforme.*

**Rectal and bladder subgroup data (non-significant difference in outcomes).*

†HN and pelvic subgroup date (no significant difference in outcomes).

‡RR (RT + HT vs RT alone): CR = 4.01; 2 yr local control = 1.73.

§DFS, no difference total gp but advantage to RT + HT for Stage III-IV pts.

complete response rate of 32% compared with 30% for those receiving RT alone. Subgroup analysis revealed significant improvements in duration of local control only in patients with tumors less than 3 cm in depth and in those with breast and/or chest wall recurrences. It was postulated that the better outcome in smaller tumors was a consequence of better heating. This trial was plagued by highly variable heating techniques and crude thermal dosimetry. These problems led to the development of subsequent RTOG guidelines for performing HT.[147]

Head and Neck Cancer

There are two randomized series demonstrating an advantage to HT combined with RT (see Table 21-2). The first study by Datta et al randomized 65 patients to radiation alone vs. RT and HT.[222] RT doses consisted of 50 Gy in 5 weeks to the primary site and regional lymphatics followed by 10 to 15 Gy given to sites of gross disease in daily fractions of 2 Gy. HT was given twice a week with 72 hours between each session. The HT + RT arm showed significant improvement in response in patients with stage III and IV disease. For example, patients with stage III disease receiving combined treatment had a 58% CR compared with 20% in the RT alone group. There was no benefit for patients with stage I and II disease, with greater than 90% of these patients achieving a CR with either treatment. This trial from India evaluated both the primary site as well as neck nodes, despite the recognized difficulties of effectively delivering heat to most primary head and neck tumors.

A second trial from Italy by Valdagni et al restricted treatment and evaluation to metastatic cervical lymph nodes. This study randomized 41 patients with advanced local regional squamous cell carcinoma of the head and neck to treatment with either RT alone or RT combined with HT.[223,224] Long-term follow-up allowed for analysis of response, duration of local control, and survival. The five-year actuarial local control in the neck with RT alone vs RT + HT was 24 vs 69%, and 5-yr OS was 0 vs. 53%; all of these differences were statistically significant. There was no clear enhancement of toxicity or any clear relationship between thermal dose received and outcome. Nonetheless, this well-executed and described phase III trial, despite the relatively small number of patients, is an important component of the evidence suggesting the value of HT.

A trial of interstitial hyperthermia was carried out primarily in head and neck patients by the RTOG.[212] This trial entered 173 patients with persistent or recurrent tumors after prior radiotherapy and/or surgery that were amenable to interstitial radiotherapy. The lesion site was the head and neck in approximately 45% of patients, the pelvis in approximately 40%, with miscellaneous sites accounting for the rest. The patients were randomized to receive interstitial RT alone ± interstitial HT. Overall there was no difference in complete response rates or 2-year survival. There were major quality assurance issues with this trial. Only one patient in the entire group was considered to have had adequate HT. This trial, as well as the previously mentioned RTOG trial, provided impetus for the subsequent development of HT guidelines by the RTOG.[153]

Esophagus Cancer

Two randomized studies demonstrated an advantage to the addition of HT to chemoradiotherapy or chemotherapy alone in the neoadjuvant treatment of esophagus cancer. In the first study by Kitamura et al 66 patients with squamous cell carcinoma of the thoracic esophagus were randomized to preoperative HT, RT, and CT, compared with chemoradiotherapy alone.[225] The chemotherapy (bleomycin) and HT were given concurrently 1 hour prior to the radiation in a 3-week regimen with a total RT dose of approximately 32 Gy. Clinical complete responses and pathologic responses were significantly improved in the tri-modality arm, with a pathologic CR of 26% combined in the tri-modality group vs. 8% in the chemoradiotherapy group (see Table 21-2).

In a follow-up study, an additional 40 patients were treated with chemotherapy alone (bleomycin and cisplatin) or combined with HT.[225] No RT was given in this trial. Again, an improvement in histopathologic response was noted favoring the HT group (19% vs. 41%).

Malignant Melanoma

A major multicenter trial was conducted in patients with metastatic melanoma by Overgaard et al.[57] Seventy patients with 134 metastatic or recurrent malignant melanoma lesions were randomized to receive RT ± HT. Overall there was a significant benefit for the addition of HT with a 2-year local control of 46% in the combined group compared with 28% for those receiving RT alone (see Table 21-2). Quality assurance issues were problematic in this trial, with only 14% of treatments achieving the protocol objective of 43°C for 60 minutes. Despite this, positive benefits were seen.

Glioblastoma Multiforme

A University of California San Francisco study by Sneed et al evaluated interstitial HT combined with a brachytherapy boost for selected patients with glioblastoma multiforme.[226] One hundred twelve patients were entered into this trial, which randomized patients whose tumor was implantable following external beam RT and chemotherapy to receive brachytherapy ± HT. Seventy-nine were randomized; 33 patients were dropped from the protocol due to disease progression. Both time to tumor progression and survival were significantly improved for the HT patients compared with those treated with brachytherapy alone (see Table 21-2). Two year survivals in the two groups were 31% and 15%, respectively. Toxicity appeared to be slightly greater in the HT patients, with seven grade 3 toxicities reported compared with one in the brachytherapy alone group. Thermal dose data showed that good heating was achieved in most patients. No significant correlation was seen between thermal dose and response.

Pelvic Tumors (Cervix, Bladder, Colorectum)

The Dutch hyperthermia group conducted a study by Van der Zee et al in which 358 patients with previously untreated locally advanced pelvic tumors were randomized to receive RT alone or RT + HT (see Table 21-2).[227] HT treatments were given once weekly for a total of five treatments. Generally, thermal goals were not achieved, but detailed thermal dose analyses have not been published. There were approximately equal numbers of patients with bladder, colorectal, and cervical carcinomas. Complete response rates were 39% and 55% after RT alone and RT + HT, respectively ($p \leq 0.001$). Duration of local control was also significantly improved with RT + HT. Patients with cervical carcinoma benefited the most. Three year survivals were 27% and 51% in the RT and RT + HT groups, respectively ($p = 0.003$). This study has been criticized for suboptimal therapy in the control arm, namely RT alone as opposed to the combination of RT + CT. At the time the trial was initiated in 1990, the role of chemotherapy in cervix carcinoma was not established. Subsequently, a number of studies published in 1999/2000 have demonstrated a survival advantage for concurrent cisplatin-based chemotherapy in cervical carcinoma.[228-232] Additional phase III trials are needed to establish whether there is an advantage to thermochemoradiotherapy compared with chemoradiotherapy for locally advanced cervix cancer.

TABLE 21-3 Key Phase III Trials: Hyperthermia Combined With Chemotherapy

Author	Tumor type	Trial	No. Pts	Therapy	# cycles	Thermal Dose Goals/ reported data	END POINTS
Colombo[234,235]	Rec or primary bladder	Multicenter	83	Mitomycin C	8 weekly + 4 monthly	42 +/– 0.2°C Q 1 hour	23/41 relapses,control arm vs 6/42, combined arm
Issels[233]	Locally advanced STS	EORTC Multicenter	341*	Etoposide, ifosfamide, doxorubicin; optional postop RT*	4 cycles before and after local therapy	42°C 60 minutes Q 1 hour	Local progression*, median 34 mo FU: CT + HT 56/169; CT, 76/172

Postop RT, *Postoperative irradiation;* HT, *hyperthermia;* CT, *chemotherapy;* STS, *soft tissue sarcoma (extremity, retroperitoneal).*
**125 of 339 evaluable patients did not receive postop RT as a component of local therapy.*

Phase III Clinical Trials Overview – HT + CT

Soft Tissue Sarcoma

The EORTC recently reported on results of a phase III trial by Issels et al that compared neoadjuvant thermochemotherapy to chemotherapy (etoposide, ifosfamide and doxorubicin; Table 21-3).[233] A total of 341 patients were enrolled. Patients received four cycles of neoadjuvant treatment before receiving definitive surgery and/or radiotherapy for the primary tumor. The hazard ratio for local PFS, the primary outcome variable, was 0.58 for patients receiving thermochemotherapy (p = 0.003). At 2-year follow-up, the combined arm had a 15% higher rate of PFS. DFS analysis showed a hazard ratio for the combined arm of 0.7 (p = 0.011). For those patients who completed the combined arm treatment, the hazard ratio for OS was 0.66 (p = 0.038).

Bladder Cancer

Colombo et al conducted a randomized phase III trial for recurrent superficial bladder cancer, which utilized intravesicular mitomycin C with and without bladder HT, using an intravesicularly placed microwave antenna to heat the bladder contents and wall (see Table 21-3).[234] A large majority of these patients had already failed mitomycin C previously. Eighty-six patients were enrolled and 75 completed therapy and were evaluable. Treatment of the bladder commenced after surgical removal of the tumor. The hazard ratio for local control after chemotherapy alone vs. thermochemotherapy was 4.8 (p = 0.0002). The heated group had a higher rate of complications, particularly related to thermal damage to the posterior bladder wall. Most of this damage resolved quickly, with only one patient experiencing a prolonged several month recovery period. Long term follow-up data from this trial has recently been reported (88% of patients in prior trial available).[235] The 10 year disease free survival rates were 53 and 15%, in favor of the addition of HT to mitomycin C (p = 0.001). Bladder preservation rates were comparable between the two arms.

There has been increasing interest in using HT for treatment of non-muscle invasive bladder cancer, as a result of the Colombo trial.[236-239] A recently completed pilot trial using the BSD2000 to heat the bladder noninvasively, in combination with mitomycin C, demonstrated that this approach was feasible and well tolerated.[240] This may prove to be an effective alternative approach to the intravesicular microwave antenna used by Colombo.

Summary of Clinical Trials

Results of the published phase III trials above are intriguing. Apart from the RTOG trials, they all appear to demonstrate substantial benefits with the addition of HT to RT or HT with chemotherapy. However, several of the trials were associated with significant design and implementation problems, including relatively small numbers of patients, thermal dosimetry information that was highly variable in nature, thermal goals that were often not achieved, and control arms that may not have represented optimal standard therapy. Despite these difficulties, the positive clinical outcome of these trials and the sound scientific rationale for adjuvant hyperthermia justify continued efforts in technological refinements and the conduct of well-designed clinical trials.

CHALLENGES/CONTROVERSIES/ FUTURE POSSIBILITIES

There are significant challenges to the continued development of hyperthermia. These can be roughly categorized into three types: (1) improvements are needed to make the treatment less technically challenging, (2) widespread establishment of chemo-radiation for many locally advanced cancers have reduced the potential population of patients who could benefit from thermoradiotherapy, and (3) emphasis on development of targeted therapies, such as tyrosine kinase inhibitors and anti-angiogenic drugs, which show promise for selective targeting of tumors while greatly minimizing normal tissue toxicities are easier to implement than HT. It is important to consider how hyperthermia can fit into this rapidly changing landscape of oncology research and practice and this is discussed next.

Technical Challenges

The FDA recently approved the use of deep heating with the BSD-2000, in combination with radiotherapy, to treat women with recurrent cervix cancer, where chemotherapy is not an option <http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/DeviceApprovalsandClearances/Recently-ApprovedDevices/ucm286404.htm>. Aside from this orphan designation, the use of hyperthermia for deep-seated tumors is still experimental in the United States. In Europe, deep hyperthermia has been more widely accepted and is approved in The Netherlands, Germany, and Italy as an adjunct therapy with radiotherapy and chemotherapy. Regardless of whether it is approved or not, it is technically challenging and expensive to administer, because it requires time of a dedicated team involving highly skilled physicists, engineers, physicians, and nurses to perform it safely and accurately. Invasive thermometry requires dedicated physician time to place thermometry catheters, and imaging is

needed to document thermometry placement. Currently, control of applied power requires significant technical skill and experience. These issues place important constraints on the promulgation of hyperthermia to the broader medical community. Progress will continue to be impeded until the technology is made more user-friendly. Advances in noninvasive thermometry, as discussed above, hold great promise for reducing the burdens associated with invasive temperature measurements.

Thermal Dose Prescription

Even if noninvasive thermometry were available, until recently there has been no information on what target temperature ranges are needed to optimize this therapy. Such information is the second key for providing a quantitative assessment of hyperthermia treatment adequacy (i.e., establishes a method for writing a hyperthermia prescription). In spite of extensive phase II data suggesting that higher temperatures yield improved likelihood for effective therapy, until recently there have been no successful prospective trials showing that escalation of thermal dose yields improved antitumor effect. However, two clinical trials have been reported where thermal dose was controlled during application of hyperthermia.[156,220] These trials set the stage for establishing realistic goals for how to administer this treatment in combination with radiotherapy.

These two trials were designed to perform a "test" hyperthermia treatment first, to determine whether the tumor was heatable, as defined by pre-established criteria. If the tumor was "heatable" then the patient was randomized to receive either a low cumulative thermal dose or a high thermal dose that was at least 10-fold higher than the low dose group. The inclusion of the "test" treatment was key in both studies, as about 12% of all eligible patients were excluded from randomization because their tumors could not be heated. The first trial was in patients with superficial tumors and the second was in pet dogs with spontaneous soft tissue sarcomas. Both trials demonstrated that cumulative thermal doses >10CEM 43°CT_{90} yielded improved tumor responses and durations of local control[156,220] (Figure 21-9). To put this into perspective, this cumulative thermal dose is equivalent to achieving a temperature of 40°C for 1 hour, once or twice a week, at the 10th percentile of the temperature distribution. Importantly, this thermal goal was reached in >90% of patients who randomized to the high thermal dose group.

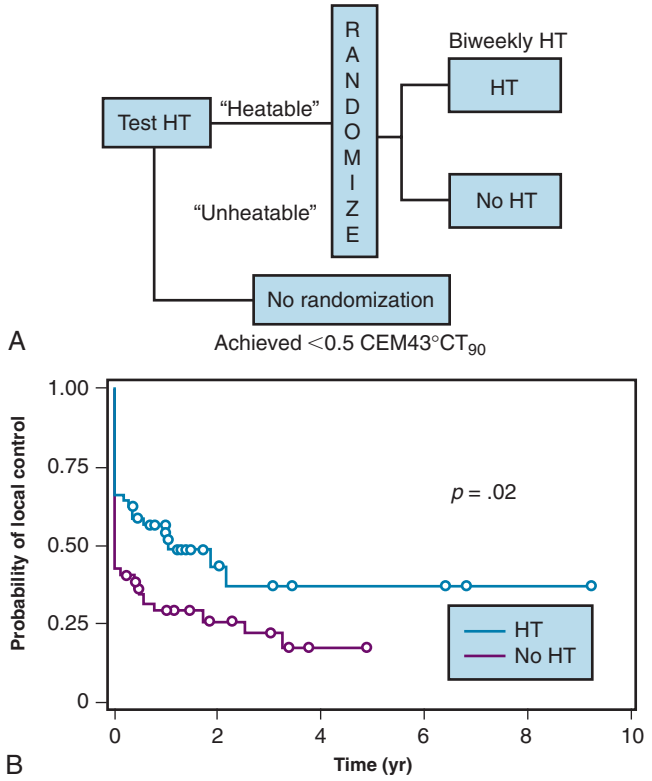


Figure 21-9 **A,** Clinical trial design. **B,** Duration of local control in patients with superficial tumors treated with a low vs. high cumulative thermal dose combined with RT. The difference in CR rate was significant.
Figure reproduced with permission of the author and publisher Jones, 2105.[156]

Future Directions

Tri-Modality Therapies

There are important observations that have been made about hyperthermia that provide strong rationale for its continued development. First, although the addition of chemotherapy to radiation therapy has improved treatment outcome for many diseases, there is still a long way to go. The addition of hyperthermia to chemoradiotherapy protocols may be what is needed to push the therapies further toward the goal of reaching 100% local control. Since hyperthermia provides synergistic interaction with many chemotherapeutics, some targeted drugs as well as radiation therapy, this general approach is compelling.

Augmentation of Drug Delivery

Drug delivery to tumors remains a major challenge due to physiologic barriers such as high interstitial fluid pressure and heterogeneous perfusion. As noted earlier, hyperthermia has been shown to augment macromolecule and nanoparticle drug delivery by increasing blood flow, available volume fraction, and tumor vascular permeability. Furthermore, local hyperthermia can be used as a trigger for temperature-sensitive drug delivery systems such as liposomes, polymers, and hydrogels.[23,28,34,36,241] In this manner, site-specific bioavailability can be achieved. For example, a temperature-sensitive liposome containing doxorubicin (ThermoDox™) has been developed to release rapidly at clinically achievable temperatures of 40°C to 42°C. This formulation has shown dramatic improvement in tumor drug concentration and anti-tumor efficacy in preclinical studies[23,242] and is currently being investigated in phase I/II/III clinical trials for chest wall recurrences of breast cancer and radiofrequency ablation of liver metastases, respectively. As thermal technology and liposomal formulations advance, this method has the potential for precise control of drug delivery independent of tumor phenotype and drug composition.

Newer applications of thermosensitive liposomes have contained both drug and MR contrast agents and this tandem has been used to monitor drug delivery to heated tumors in real time, as the MR contrast agents change the MR signal when released from the liposomes[243-245] (Figure 21-10). There is increasing interest in using the dual MR/drug containing liposomes in combination with high intensity focused ultrasound to enhance drug delivery to a variety of tumor sites, including brain.[23,26,27,145,246-251]

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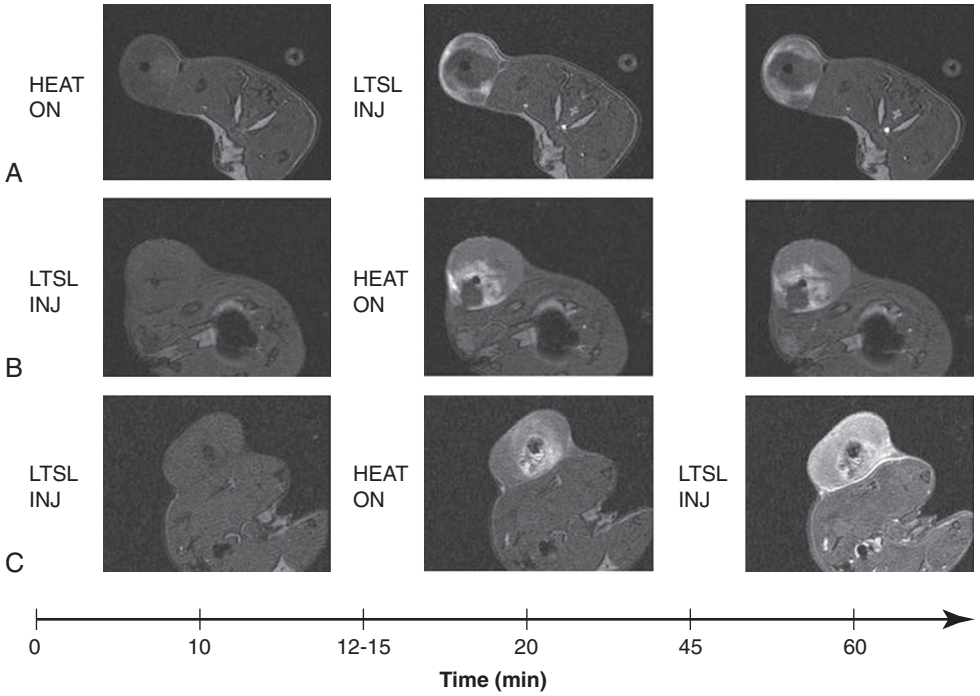


Figure 21-10 Example of monitoring drug delivery in real time, using liposomes containing an MR contrast agent (MnSO4) and doxorubicin. Calibration studies showed that the change in T1 relaxation time, induced by the Mn^{++}, is linearly proportional to drug concentration, in vivo. HT is delivered to the tumor using a catheter containing circulating hot water at the center of the tumor (shows as a dark spot near the center of each tumor). **(A)** When HT is administered, prior to and during drug administration, drug deposition is highest at the periphery of the tumor. **(B)** When drug is administered first, followed by HT, the drug accumulates around the cathether, yielding a centralized drug deposition pattern. **(C)** When drug dosing is split in half and given prior to HT and after HT has started, a more uniform drug deposition pattern is seen. Interestingly, the peripheral drug delivery pattern was most efficacious.[243] *LTSL*, Thermally sensitive liposome.

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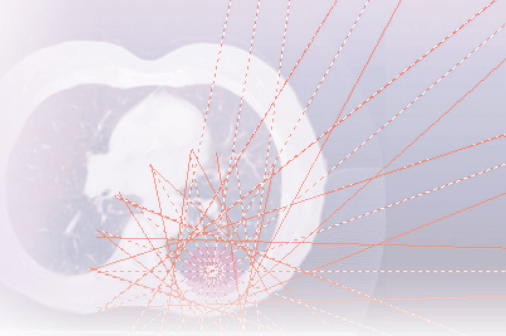
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CHAPTER

22 Targeted Radionuclide Therapy

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Selective delivery of radionuclides to cancer cells using an antibody or other conjugate has been under investigation for >20 years. In 2002, the first Food and Drug Administration (FDA) approval was issued for a radiolabeled antibody. Initially this form of radionuclide therapy mainly involved the use of antibodies, or antibody-derived constructs as carriers of radionuclides and is therefore called *radioimmunotherapy (RIT)*. However, because the concept also includes binding to nonantigen receptors, targeted radionuclide therapy (TaRT) is a more comprehensive term, and Paul Wallner coined the acronym *STaRT* for systemic targeting. The development of TaRT has required the cooperation of basic scientists in the areas of radiation biology, chemistry, physics, and immunology with multiple clinical specialists. With the exception of some gene therapy approaches, TaRT differs from external beam radiation therapy in that selective targeting can be at the cellular rather than target volume level. Among its potential applications, TaRT provides a means of irradiating multiple tumor sites throughout the body with relative sparing of normal tissues. A number of challenges hampering the use of TaRT have been overcome, whereas others are areas of active investigation. Many of these are covered in more detail in other reviews.[1-16] A more extensive version of this chapter can be found on the Expert Consult website. The supplemental text contains tables, figures, and references that enhance the print version of this chapter.

TUMOR TARGETING

Antibodies

The efficacy of TaRT is dependent on a number of factors including properties of the targeted antigen or receptor, tumor, and targeting agent. Antigen/receptor variables include affinity, avidity, density, availability, shedding, and heterogeneity of expression.[17] Tumor factors include vascularity, blood flow, and permeability. Antibody features to consider are specificity of the binding site, which affects selective tumor uptake; immunoreactivity, which can affect localization; stability in vivo; and both avidity and affinity.[18-20] Affinity can be described by an intrinsic association constant K that characterizes binding of a univalent ligand (formation of a stable antibody-antigen complex) and can be calculated from the ratio of the rate constants for association and dissociation. Because intact antibodies and most antigens are multivalent, the tendency to bind depends on the affinity, number of binding sites, and other nonspecific factors involved in aggregation. The term *avidity* encompasses all of these factors and is therefore used to describe the overall tendency of antibody to bind to antigen.

A wide variety of antibodies have been made against a number of tumor-specific and tumor-associated antigens, that although present on some normal cells, are usually expressed at lower levels than on the targeted tumor cells. Most RIT trials have used monoclonal antibodies (Mabs), and many have used intact murine immunoglobulin G (IgG) antibodies. Early on, the immunogenicity of the nonhuman antibodies was recognized as a serious limitation of TaRT.[32] With the exception of patients with lymphoma, who are less prone to develop an immune response to murine antibodies (human antimouse antibody [HAMA] response), >80% of patients usually develop an immune response against a therapeutically administered murine or other species antibody after a single injection of antibody.[32] Such an immune response can occur even after doses as small as 1 mg used for imaging studies or following administration of antibody fragments or smaller constructs (but with less frequency than found following administration of intact IgG). Administration of antibody in a patient with a HAMA response can result in a severe immune reaction and rapid blood clearance, limiting tumor uptake of radiolabeled antibody.[33] Several approaches have been employed in an effort to ameliorate the problem of antibody immunogenicity such as: (1) the development of less immunogenic (chimeric and humanized) antibodies, (2) the use of immunosuppression by cyclosporine or deoxyspergualin to prevent an immune response, (3) the removal of HAMA directed to the therapeutic antibody by administration of an excess of unlabeled antibody before the administration of the radioimmunoconjugate, or (4) posttreatment removal of immune complexes by passing the patient's blood through an extracorporeal immunoadsorption column.[34-37] Genetic engineering has been successful in providing numerous targeting agents with reduced immunogenicity and has allowed for optimization of other aspects of the therapy.[38-40] Genetic constructs have been produced that vary in specificity and can be altered by conjugating them to other agents (e.g., cytokines, toxins, or radiosensitizers) to form fusion proteins.[41,42]

Technologic advances have provided a wide variety of antibodies and constructs varying in specificity, size and number of antigen combining sites, rapidity of distribution, immunogenicity, and immunological function.[43] Use of small antibody constructs such as single-chain antigen binding proteins may be most useful for diagnostic studies or for multistep targeting strategies.[44] The decreased immunogenicity of fragments/constructs and human and humanized antibodies now allows for administration of repeat courses or fractionated TaRT dosing.[45] As immunogenicity of antibodies has been ameliorated, some investigators have had concern about the potential immunogenicity of other components of therapy. For example, as more macrocyclic chelators have been developed to improve stability of conjugates, some data suggest that these molecules may be immunogenic as has been the streptavidin used in some pretargeting schemes.[46-48] Thus, immunogenicity of the various components of TaRT remains a challenge that requires further innovation.

Nonantibody Targeting

Several of the factors affecting antibody development and efficacy for TaRT are also pertinent to nonantigen targeting such as receptor density, availability, affinity, shedding, and heterogeneity of receptor expression, as well as features of the tumor including vascularity, blood flow, and permeability. The discovery more than a decade ago that many tumors overexpress receptors for peptide hormones opened the field for TaRT and other forms of targeted therapy. Radiolabeled peptide analogs such as those for somatostatin, bombesin, calcitonin, oxytocin,

ABBREVIATIONS

ADCC = antibody-dependent cellular cytotoxicity
AML = acute myeloid leukemia
APL = acute promyelocytic leukemia
ASCT = autologous stem cell transplant
BED = biologic equivalent dose
BMT = bone marrow transplantation
BU = busulfan
CLL = chronic lymphocytic leukemia
CR = complete response with no evidence of disease for ≥1 mo
CTCL = cutaneous T-cell lymphoma
CY = cytoxan or cyclophosphamide
DLCL = diffuse large cell lymphoma
EGFR = epidermal growth factor receptor
FU = fluorouracil
HACA = human antichimeric antibodies
HAMA = human antimouse antibodies
HSG = histamine-succinyl-glycine
ID = injected dose
LDR = low dose rate
IP = intraperitoneal
IV = intravenous
KPS = Karnofsky performance status
LET = linear energy transfer
Mab = monoclonal antibodies
MDS = myelodysplastic syndrome
MHC = major histocompatibility complex
MIRD = Medical Internal Radiation Dose Committee of the Society of Nuclear Medicine
MR = minor response of 25% to 49% decrease from baseline in overall tumor size for ≥1 mo
MW = molecular weight
NA = not available
NHL = non-Hodgkin's lymphoma
NED = no evidence of disease
OS = overall survival
PCR = polymerase chain reaction
PEG = polyethylene glycol
PFS = progression-free survival
PML/RAR-α = promyelocytic leukemia gene/retinoic acid receptor-α
PR = ≥50% decrease from baseline in overall tumor size for ≥1 mo
PRRT = peptide receptor radionuclide therapy
PSMA = prostate-specific membrane antigen
RBE = relative biologic effectiveness
RIT = radioimmunotherapy
ROI = regions of interest
RT = reverse transcriptase
SCT = stem cell transplant
scFv = single chain monovalent constructs
SPECT = single photon emission tomography
TaRT = targeted radionuclide therapy
TBI = total body irradiation
TLDs = thermoluminescent dosimeters
TMZ = temozolomide
$T_{1/2}$ = half time
V_H = variable heavy regions
V_L = variable light regions

Increased antibody affinity or avidity does not always correlate with increased in vivo efficacy and the optimal level of affinity remains controversial.[21,22] One might expect that higher affinity antibodies would result in increased tumor uptake, retention, and improved efficacy.[23-25] High affinity antibodies, however, may preferentially bind to perivascular regions in the periphery of tumors, whereas antibodies of lower affinity are able to penetrate deeper into tumors.[26,27] Hence, the optimal affinity of an antibody is likely to depend on a number of factors including level of target antigen expression, vascular permeability, and bulkiness of disease.[28]

In many cases, targeting of radiolabeled antibodies to tumor can also be improved through preinfusion of unlabeled antibody, which decreases splenic and urinary uptake of radiotracer.[29] The optimal amount of unlabeled antibody remains undetermined for most agents, but relatively high doses have been as good or better than lower doses in most imaging studies.[29,30] Efforts by the Seattle transplant team to optimize the amount of unlabeled antibody for individual patients by tracer studies with varying amounts often showed the highest concentration studied to be as good or better for direct RIT with iodine-131 (^{131}I)-antibody conjugates.[31]

and epidermal growth factor have been studied. Analogs of somatostatin are the most studied to date, with radiolabeled peptides being used for detection and treatment of a variety of neuroendocrine tumors.[10,49-51] Initial treatment of tumors expressing somatostatin receptor subtype 2 was with higher doses of the diagnostic agent (^{111}In-DTPA)-octreotide.[52] Subsequently the higher affinity (DOTA, Tyr^3) octreotide and (DOTA, Tyr^3) octreotate were introduced and used with yttrium-90 (^{90}Y) and ^{177}Lu labeling as the therapeutic beta emitter for peptide receptor radionuclide therapy (PRRT). (Tyr^3) octreotate differs from octreotide by substitution of tyrosine as the third residue and the replacement of threoninol by threonine. Early studies show impressive response rates, and that fractionation of administered dose as well as infusion of amino acids has ameliorated the dose-limiting renal toxicity.[3,53-55] Various multicenter studies have been conducted for optimization of ^{90}Y-(DOTA, Tyr^3) octreotide, ^{177}Lu-(DOTA, Tyr^3) octreotate, and ^{90}Y-(DOTA) lanreotide, another somatostatin analog.[56] In addition to objective clinical response rates often >25% and improved survival, clinical benefit in terms of decreased symptoms has usually been observed in the majority of patients with progressive neuroendocrine tumors.[14,51,54,57,58] Although PRRT is not FDA approved in the United States, its use continues in Europe.[59] Radiolabeled peptides targeting tumor neovasculature are also under investigation and may provide therapy for nonendocrine malignancies[60] with promising results in preclinical models.[61] The use of liposomes or nanoparticles as alternative targeting mechanisms for radionuclides is currently under investigation; however, these agents are still in the preclinical stage.[62-64] There continues to be progress on strategies that are independent of tumor type such as targeting tumor vasculature and the broad applications of nanoparticles.[65-67]

SELECTION OF RADIONUCLIDES

Early reviews provide detail on radionuclide selection, primarily with regard to the radiolabeling of whole immunoglobulins with beta-emitters.[68-70] Some later publications have focused on the selection of radionuclides for use with smaller, engineered antibody-derived constructs[71-73] and small nonantibody targeting delivery entities.[74] Alpha-emitters are also of increasing use.[62,75-80] The utility of a given radionuclide for TaRT is influenced by a number a radionuclide-specific factors such as half-life, emission profile, path length, efficiency of energy transfer, and ease of conjugation to its targeting ligand, as well as disease-related factors such as bulkiness of disease and heterogeneity of antigen expression. In a one-step RIT, administration using directly labeled antibodies, matching of the physical half-life of the radionuclide with the initial peak of tumor-to-nontumor antibody concentration was reported to be the most important factor for optimal radionuclide selection.[68] For example, a good therapeutic ratio would not be obtained if one used a radionuclide that decays within several hours linked to an antibody that has a circulation time of several days because most of the radiation exposure would have occurred before the radiolabeled antibody localized in the tumor. In this case, the resulting radiation dose to normal tissues would be nearly as great as that to the targeted tumor. Pretargeting strategies, discussed in more detail in the Optimization section, allow for use of radionuclides with shorter half-lives because unlabeled methods of tumor targeting precede administration of the radionuclide.[76]

The emission profile of radionuclides determines their suitability for therapy and imaging. A variety of radionuclides have been used in TaRT including alpha-emitters; low-, medium-, and high-energy beta-emitters; and those that work through electron capture or internal conversion (Auger electrons). Gamma-emitters, on the other hand, are more appropriate for imaging.[13] Some radionuclides such as ^{131}I have beta and gamma emissions that allow for both therapy and imaging. The therapeutic effect from such radionuclides is primarily the result of the beta radiation, whereas the gamma component allows for imaging but contributes substantially more to normal tissue toxicity than efficacy. Features of some of these radionuclides are compared in Table 22-1.

Tumor characteristics such as size (e.g., micrometastases vs. bulky masses) and the level and heterogeneity of antigen expression help dictate the efficacy of a given radionuclide for TaRT. Beta-emitters (e.g., ^{131}I and ^{90}Y) have been the most popular radionuclides for clinical TaRT trials to date. These radionuclides have the advantage of not needing to target every individual tumor cell because the mean radiation range is approximately 0.4 mm and 2.5 mm, respectively. This long path length allows for "cross fire" (e.g., killing of nonantigen-expressing tumor cells); however, it can also be associated with increased levels of normal tissue toxicity. Hence, beta-emitters may be more effective for sizable tumors and those with heterogeneous antigen expression but be less useful in the setting of micrometastatic disease. Auger electron emitters, such as iodine-125 (^{125}I), may be suitable for treatment of micrometastases that abundantly express internalizing antigen on every cell because targeting of the nucleus is necessary for effective cell killing with this very short range emitter (mean path length, 10 nM).

Compared with beta-emitters, alpha-emitters typically have shorter path lengths (40 μM to 80 μM), higher linear energy transfer (LET), and higher kinetic energies.[88] Together these features allow alpha-emitters to efficiently kill tumor cells by inducing double-stranded DNA breaks over a radius of several cells, even when antigen expression is heterogeneous. Hence, alpha-emitters may be most useful for the treatment of micrometastatic disease, such as leukemia in bone marrow, minimal intraperitoneal disease, and intratumoral

TABLE 22-1 Comparison of Selected β-Emitting Radionuclides Used in TaRT

Isotope	$T_{1/2}$ (d)	γ Energy (kev)	Percent γ Intensity	β Range in Tissue (mm)		Advantages	Disadvantages
				Maximum	Mean		
^{90}Y	2.7			11.9	2.5	Long β range	Chelator, bone seeker
^{131}I	8.0	364	81	2.4	0.3	No chelator needed	Dehalogenation, toxicity from γ
^{186}Re	3.7	137	9	5.0	0.9	Less γ than ^{131}I	Chelator, scarce
^{67}Cu	2.5	184	48	2.2	0.4	Less γ than ^{131}I	Chelator, scarce
^{177}Lu	6.7	208/113	11 and 7	2.2	0.3	Less γ than ^{131}I	Chelator, scarce
^{125}I	60.4	35	7	0.02	—	Low-normal tissue toxicity	Does not image well
^{188}Re	0.8	155	15	11.0	2.4	Long β range	Chelator, scarce

The development of labeling and chelation chemistry for the production of stable radioconjugates has greatly facilitated TaRT. Iodine-131 (^{131}I) can be directly attached to antibody without a chelator. However, if a targeted antigen/receptor undergoes modulation (internalization), the tumor cells can dehalogenate the conjugate and release free iodine. ^{131}I can also be attached by a secondary molecule conjugated through an iodinatable linker rather than directly linked to antibodies. These radioimmunoconjugates appear to be more resistant to dehalogenation.[81] A variety of increasingly stable chelators have been developed for yttrium-90 (^{90}Y) and other metal radionuclides, but some have been found to be immunogenic (probably partly as a result of aggregation).[46,48] The chemistry, stability, and in vivo processing of radioimmunoconjugates also have implications for toxicity. The filtration of small radioconjugates or their metabolites through the kidneys may result in considerable radiation to the kidneys. Renal toxicity has been reported to be the dose-limiting toxicity for some small MW peptide conjugates and alpha-emitter conjugates.[78,82] Hepatic uptake, metabolism of radioimmunoconjugates, and retention of ^{90}Y-complexes in the liver, are potentially dose limiting in myeloablative TaRT.[83] Designing chelators with special characteristics can also affect radionuclide "matching" with the targeting agent. For example, selective degradation of a cathepsin-sensitive chelate reduced liver uptake of radiometal.[84] The use of such chelators may allow for dose escalation of radiometal conjugates such as copper-67 (^{67}Cu) that otherwise would be limited by hepatic toxicity. Other conditionally cleavable chelators are also under study.[85] The synthesis of the TCMC chelator has allowed progress in the use of lead-212 (^{212}Pb).[86] Macrocyclic chelators such a DOT, which have been developed for stable chelation to ^{90}Y, and other beta-emitting radiometals have shown acid lability with ^{212}Pb, and likely other alpha-emitters.[87] To overcome this, the bifunctional chelating agent 2-(4-isothiocyanotobenzyl)-1,4,7,10-tetraaza-1,4,7,10-tetra-(2-carbamonyl methyl)-cyclododecane (TCMC) was synthesized, characterized, and subsequently used in several animal studies.[86]

delivery.[89] These favorable characteristics of alpha-emitters have led to considerable progress in their use in clinical trials as well as improving their availability.[78,80,90-92] The National Laboratories of the USA have established cooperation to increase the supply of actinium-225 (^{225}Ac), and AREVA Med has developed the ability to ship ^{212}Pb generators all over the world.[93,94]

The alpha-emitters bismuth-213 (^{213}Bi) and ^{225}Ac have been conjugated to anti-CD33 antibodies and have shown promising results in Phase I and Phase II clinical trials in acute myeloid leukemia (AML), with ^{225}Ac recently advancing to the multiinstitutional setting.[95-97] Alpha-emitters also have increasing use in the treatment of metastatic prostate cancer. Radium-223 (^{223}Ra) is an unconjugated alpha-emitting calcium-mimetic that accumulates in areas of high bone turnover by physiologic rather than ligand-guided targeting.[98] The alpha-particles emitted by ^{223}Ra are high energy and have a relatively short path length of 10 μM, which allows efficient tumor cell killing with minimal marrow suppression.[99] In a recent Phase III clinical trial, treatment with ^{223}Ra has shown a survival benefit in patients with metastatic prostate cancer. Similar results have not been achievable with bone-targeted beta-emitters such as strontium-89, which are limited by marrow suppression, presumably because of their longer path lengths.[98-100] These results, along with considerable experience in Europe, led to FDA approval for ^{223}Ra in 2013, making it the first alpha-emitter to receive such approval.

RADIOBIOLOGY

Biological effects of TaRT may be associated with both the radionuclides and their carriers, either alone or in combination.[101-103] This is particularly true for certain antibody carriers that may have antitumor efficacy alone (e.g., anti-CD20 antibodies). Another important determinant of efficacy may be whether or not the antibody in internalized.[104] Antibody-induced responses can include apoptosis, complement-dependent cytotoxicity, and antibody-dependent cell-mediated cytotoxicity.[105] Radiation effects can result in cell death during mitosis or by apoptosis, necrosis, or a metabolic cell death. The relative importance of these types of cell death depends on factors such as the inherent genetic makeup of the cells. For lymphomas, apoptosis is an important mechanism of cell death, whereas apoptosis usually plays less of a role in killing solid tumor cells. Lymphomas are especially sensitive to apoptosis induced not only by radiation, but by a variety of cytotoxic agents including antibody therapy alone.[106-109] Several signal transduction pathways have been found to be associated with radiation-induced apoptosis. These have been reviewed by Hernandez and Knox.[101] Antibody-induced intracellular signaling may also function to enhance the effects of TaRT and dose rate effects, as well as the relative biological effectiveness of the associated radiation (e.g., high LET of alpha-particle emitter labeled monoclonal antibodies) may be important to the efficacy of TaRT as well.[110,111]

Several studies have shown that cells exposed to either continuous or exponentially decreasing low dose rate (LDR) radiation arrest in the radiosensitive G_2/M phase of the cell cycle and undergo apoptosis.[112-115] This G_2/M block from LDR radiation as delivered via TaRT may also sensitize tumor cells to killing by other therapies such as external beam radiation.[116] Data from some experiments showing this effect suggest that therapy may be optimized by using TaRT before external beam radiation.[116,117] External beam radiation has also been given before TaRT to increase tumor uptake of radionuclide conjugates. In addition, regulating cell-cycle distribution or altering the underlying apoptotic potential by drugs or biologic response modifiers in tumor cells can affect the susceptibility of such cells to radiation-induced apoptosis.[118] Recent studies include the exploration of the use of gene transfer technology to induce expression of high affinity membrane receptors to enhance the specificity of radioligand localization or the use of genetically engineered antibody molecules (e.g., diabodies: noncovalent single chain F_v dimers) as carriers for TaRT that may be able to enhance the efficacy of this therapy.[119-122]

Although there is usually a positive correlation between the level of radiation-induced cell killing and dose rate, an inverse dose rate effect has been reported with LDR irradiation in the range of about 0.3 Gy/hour, with some cell types being more sensitive to this inverse dose rate effect than others.[123] Knox et al showed lymphoma cells to be sensitive to ^{131}I-labeled antibody LDR radiation in a direct comparison to high dose rate external beam irradiation.[124] At least one mechanism for this observation appears to be greater arrest in the G_2/M phase of the cell cycle. Another mechanism of lymphoma radiation sensitivity may be less efficient DNA repair among lymphomas compared to some other cell types.[101,102]

CLINICAL RESULTS

A wide variety of human malignancies have been treated with RIT in the setting of clinical trials. Antibodies carrying radionuclides have targeted tumor-associated antigens, growth factor receptors, and other cell surface markers, usually expressed at a high level on malignant cells and to a lesser extent on subsets of normal cells. Nonantibody targeting has primarily been against neuroendocrine receptors. Several routes of administration have been employed including intravenous, intraarterial, intrathecal, intraperitoneal, intratumoral, and rarely, intrapleural administration. The most prevalent route of administration has been intravenous for systemic therapy. However, for localized disease, regional or intracavitary administration may be advantageous. Intraperitoneal RIT has generally been more efficacious than intravenous RIT for the treatment of small volume disease confined to the peritoneal cavity, but there are conflicting reports concerning the relative merits of arterial and venous routes of administration of radiolabeled antibodies for other sites.[125-129]

RADIOIMMUNOTHERAPY OF NONHEMATOLOGIC MALIGNANCIES

RIT for solid tumors continues to be actively investigated as a form of systemic targeted radiation therapy in a variety of tumor types and clinical settings. Initial clinical efforts were with polyclonal antibodies.[130] With the development of hybridoma technology, large-scale production of clinical grade Mabs selected against specific tumor-associated antigens became possible and greatly expanded the number of agents evaluated in clinical trials. Subsequent molecular engineering efforts allowed for the customized design of antibody constructs with properties better optimized for therapy.

RIT demonstrated initial promise in animal models with dozens of studies in tumor-bearing animal models documenting significant tumor growth delay and cures in a wide variety of solid tumor types.[6,131-134] Tumor doses often exceeded 10 Gy to 15 Gy after a single infusion.[135,136] In some preclinical studies RIT achieved comparable tumor growth delays as equivalent doses of single fraction or conventionally fractionated external beam radiation therapy[135-140] or equitoxic doses of chemotherapy.[141] Initial clinical trials evaluating biodistribution and pharmacokinetics confirmed tumor targeting and demonstrated that therapeutic doses of radiation to tumor were potentially achievable.[142-147] Table 22-2 provides an overview of Mabs that have been evaluated in clinical trials. RIT has been evaluated in most major disease sites, including gastrointestinal, breast, brain, ovarian, head and neck, medullary

Ongoing studies will help elucidate the radiobiology of TaRT, which will facilitate optimization of TaRT therapy in the future, and provide the prerequisite understanding of underlying biological mechanisms to determine how best to use TaRT in combination with other treatment modalities.

TABLE 22-2 Examples of Monoclonal Antibodies Evaluated for RIT of Nonhematologic Malignancies

Malignancy	Antigen	Antibody
Colorectal cancer	CEA	cT84.66, hMN-14, A5B7, F6
	TAG-72	B72.3, CC49
	A33	anti-A33
	EpCAM	NR-LU-10, NR-LU-13, 17-1A
	DNA histone H1	chTNT-1/B
Breast cancer	MUC1	huBrE-3, m170
	L6	chL6
	TAG-72	CC49
	CEA	cT84.66
Ovarian cancer	MUC1	HMFG1
	Folate receptor	cMov18
	TAG-72	B72.3, CC49
Prostate cancer	PSMA	huJ591, CYT-356
	TAG-72	CC49
Lung cancer	DNA histone H1	chTNT-1/B
	TAG72	CC49
Head and neck cancer	CD44v6	U36, BIWA4
Gliomas	EGFR	425
	Tenascin	816C, BC4
Melanoma	p97	96.5
	chondroitin sulfate proteoglycan	9.2.27
Renal cancer	G250 glycoprotein	cG250
Pancreatic cancer	PAM4 reactive mucin	hPAM4
	CEA	KAb201
Medullary thyroid	CEA	cT84.66, hMN-14, NP-4
Neuroblastoma	Ganglioside GD2	3F8
	NCAM	UJ13A, ERIC-1

thyroid, melanoma, renal, lung, and prostate cancers. Results from selected solid tumor trials evaluating systemically administered nonmyeloablative doses of RIT as single modality are summarized in eTable 22-1, available in the expanded chapter on the Expert Consult website. Early efforts used Mabs labeled with ^{131}I because of availability and ease of labeling, with subsequent trials using radiometals such as ^{90}Y, rhenium-186 (^{186}Re), and lutetium-177 (^{177}Lu), and several alpha-emitters. Almost all of the antibodies studied have been administered at low protein doses (~5 mg to 50 mg), have had no significant clinical immunomodulatory or antitumor properties, and have therefore served primarily as a delivery vehicle for radiation. Dose-limiting toxicities have primarily been thrombocytopenia and leukopenia. Results have been comparable regardless of disease site or a particular radionuclide-antibody combination.

Until recently, most of the clinical experience involved Phase I trials, evaluating RIT as monotherapy in patients with advanced, bulky, chemotherapy refractory disease progressing into therapy. As expected in this patient population, partial and complete responses have been infrequent regardless of disease type,[148-158] with most antitumor effects reported as stable disease and serologic, mixed, or minor responses.[159-181] This is in contrast to clinical results observed with RIT in hematologic malignancies with objective responses ranging from 30% to 85%.[29,182-189]

A number of factors have been put forth to explain the limited responses seen. With hematologic malignancies, at least some of the observed response rates can be attributed to the immunologic effects of the antibody itself,[190] which is not the case for most radiolabeled antibodies directed against solid tumors. Other factors involve those that restrict antibody targeting and uptake to tumor more so for solid tumors than lymphomas. These include differences in tumor physiology, tumor vascularity, antigen accessibility, and heterogeneity of antigen expression.[191,192] However, these factors probably play a minor role because the clinical literature demonstrates no significant differences in estimated RIT dose to tumor between solid tumors and hematologic malignances. This suggests that the difference in radiosensitivity between solid tumors and hematologic malignancies is the major factor in explaining the difference in RIT response rates.

eTable 22-2, available in the expanded chapter on the Expert Consult website, compares tumor doses achieved after single administration of nonmyeloablative activities of RIT for solid tumors and lymphomas and demonstrates that tumor doses are comparable for most antibodies evaluated in the clinic. Median and mean doses are approximately 10 Gy to 20 Gy, with select tumors occasionally achieving doses of 20 Gy to 70 Gy or greater. For example, with ^{90}Y-cT84.66 anti-CEA RIT, approximately 25% of tumors achieve tumor doses >15 Gy to 20 Gy after single infusion. These data support the hypothesis that the differences in response rates between solid tumors and hematologic malignancies are largely the result of differences in radiosensitivity rather than differences in tumor antibody uptake. This is even after accounting for effects of unlabeled antilymphoma antibodies because clinical trials have demonstrated no significant response rates with unlabeled antibodies such as Lym-1,[193,194] but in the case of ^{90}Y-ibritumomab, there was a 24% increase in response rate was observed with the addition of radiolabeled antibody compared to unlabeled antibody alone in a recent randomized trial.[190] Similarly for tositumomab, there was significant improvement in all therapeutic outcomes by additional ^{131}I-labeled antibody.[195]

Although tumor doses with RIT are a fraction of what can be delivered by standard teletherapy or brachytherapy, doses currently achievable are at levels that can potentially result in clinically important antitumor effects in solid tumors if applied in the appropriate clinical setting, particularly in patients with subclinical or microscopic disease. In a review of the literature for conventionally fractionated external beam radiotherapy given as adjuvant therapy for solid tumors, Withers et al[196] noted an inverse linear relationship between radiation dose and tumor recurrence rate with doses ranging from 2000 to 5000 cGy. No threshold effect was seen, and doses in the range of 2000 cGy had measurable effects in the adjuvant setting. Clinical trials have also demonstrated important antitumor effects in rectal cancer with doses in the range of 3000 cGy.[197,198] Finally, doses as low as 3000 cGy conventionally fractionated have been combined with chemotherapy in esophageal and anal cancer resulting in pathologic complete responses.[199-201] Therefore, cGy doses to tumor achievable through RIT may have more clinical importance in low tumor burden situations or as an additional agent added to a multiagent systemic therapy approach.

To further improve RIT clinical outcomes in solid tumors requires increasing radiation dose to tumor or increasing the antitumor effect of the targeted dose. Strategies to achieve this goal include (1) improving the antibody delivery system to either increase antibody targeting to tumor or decrease uptake to critical organs; (2) decreasing dose-limiting toxicity (usually marrow toxicity) that would allow for escalation of administered activity; (3) altering the tumor environment to enhance

eTABLE 22-1 Select Systemic Monoclonal Antibody RIT Clinical Trials in Nonhematologic Malignancies

Study (First Author)	Year	Radiolabeled Antibody	Antigen	Study Type	Patient No.
Breitz[149]	1992	^{186}Re-NR-CO-2 F(ab′)$_2$	CEA	I	26
Lane[150]	1994	^{131}I-A5B7 intact/F(ab′)$_2$	CEA	Pilot	19
Meyer[279]	2009	^{131}I-A5B7	CEA	I/II	12
Yu[169]	1996	^{131}I-COL-1	CEA	I	18
Ychou[154]	1998	^{131}I-F6 F(ab′)$_2$	CEA	I/II	10
Ychou[181]	2008	^{131}I-F6 F(ab′)$_2$	CEA	II	13
Mittal[744]	1996	^{131}I-NP4	CEA	I/II	6
Juweid[168]	1996	^{131}I-NP4 F(ab′)$_2$	CEA	I	13
Behr[151]	1997	^{131}I-NP-4	CEA	I/II	57
Juweid[153]	1997	^{131}I-MN-14	CEA	I	14
Juweid[172]	1998	^{186}Re-MN-14	CEA	I	11
Juweid[156]	1999	^{131}I-MN-14 F(ab′)$_2$	CEA	I/II	15
Hajjar[228]	2002	^{131}I-hMN-14	CEA	I	17
Behr[155]	1999	^{131}I-hMN-14	CEA	I	12
Behr[287]	2002	^{131}I-hMN-14	CEA	II	21
Behr[745]	2002	^{131}I-hMN-14	CEA	II	9
Liersch[289]	2007	^{131}I-hMN-14	CEA	II	23
Liersch[290]	2008	^{131}I-hMN-14	CEA	II	32
Wong[176]	2000	^{90}Y-DTPA-cT84.66	CEA	I	22
Wong[231]	2006	^{90}Y-DOTA-cT84.66	CEA	I	13
Sultana[746]	2009	^{131}I-KAb201	CEA	I/II	19
Meredith[159]	1992	^{131}I-cB72.3	TAG-72	I	12
Meredith[161]	1994	^{131}I-CC49	TAG-72	II	15
Murray[162]	1994	^{131}I-CC49	TAG-72	II	15
Wheeler[164]	1994	^{131}I-CC49	TAG-72	II	15
Divgi[212]	1995	^{131}I-CC49	TAG-72	I	24
Divgi[747]	1995	^{131}I-CC49	TAG-72	I	6
Mulligan[166]	1995	^{177}Lu-CC49	TAG-72	I	9
Meredith[265]	1996	^{131}I-CC49+ 131 I-COL-1	TAG-72 CEA	II	14
Macey[266]	1997	^{131}I-CC49	TAG-72	II	15
Slovin[267]	1998	^{131}I-CC49	TAG-72	II	14
Meredith[268]	1999	^{131}I-CC49	TAG-72	II	14
Breitz[149]	1992	^{186}Re-NR-LU-10	EpCAM	I	15
Weiden[160]	1993	^{186}Re-NR-LU-13	EpCAM	I	9
Meredith[165]	1995	^{125}I-chimeric 17-1A	EpCAM	I	28
DeNardo[170]	1997	^{90}Y-BrE-3	MUC1	I	6
O'Donnell[177]	2001	^{90}Y-m170	MUC1	I	17
Welt[163]	1994	^{131}I-A33	A33	I/II	23
Welt[748]	1996	^{125}I-A33	A33	I/II	21
Chong[229]	2005	^{131}I-huA33	A33	I	15

Tumor Type	Objective Responses (%)	Minor/Mixed Response or Stable Disease (%)	Comments
Colorectal, lung, breast	1/31 (3)	11/31 (35)	Hepatic arterial infusion in five patients
CEA+	2/19 (11)		
GI		1/10 (10)	RIT combined with combretastatin (CA4P)
GI		4/18 (22)	
Colon	1/9 (11)	3/9 (33)	Autologous marrow infused in five patients
Colorectal	DFS 12 months OS 50 months		Adjuvant RIT after R0 resection of liver mets
Colorectal	1/6 (13)	5/6 (88) ↓ CEA	Liver mets, hyperthermia combined with RIT
CEA+		4/13 (31)	Small volume disease
CEA+	1/57 (2)	4/57 (7)	
Ovary	1/14 (7)	2/14 (14)	
Colon, pancreas			Given in two to three divided doses every 3 to 4 days
Thyroid	1/12 (8)	11/12 (92)	
Colorectal, GI			
Colorectal	2/11 (16)	5/11 (45)	Small volume lesions ≤2.5 cm
Colorectal	3/19 (16)	8/19 (42)	Small volume liver mets ≤3.0 cm
Colorectal	7/9 NED 24-36+ months		Adjuvant RIT after R0 resection of liver mets
Colorectal	DFS 18 months OS 59 months		Adjuvant RIT R0 resection liver mets
Colorectal	DFS 18 months Adjuvant RIT DFS 6 months Non-adjuvant RIT		Resected liver mets 24 patients received two cycles RIT 16 no gross residual (adjuvant) 16 gross residual (nonadjuvant)
CEA+		12/22 (54) 7/22 >50% ↓ CEA (33)	DTPA infusion post RIT
CEA+		5/13 (38)	DOTA conjugated antibody DTPA infusion post-RIT
Pancreatic	6% (1/18)		Human-sheep chimeric antibody 50-75 mCi IV (9 pts) or IA (10 pts)
Colorectal		4/12 (33)	12-18 mCi/m^2 weekly × 2-3
Prostate		10/15 (67) 5/15 >50% ↓ PSA (33) 6/10 ↓ bone pain (60)	
Colorectal		3/14 (21)	
Colorectal		5/15 (33)	IL-1 to reduce hematopoietic toxicity
Colorectal		6/24 (25)	
Colorectal			15 mCi/m^2 biweekly × 4
Colorectal, breast, lung		2/9 (22)	
Colorectal		4/14 (29)	Alpha-interferon
Breast	1/15	5/15 (33)	Alpha-interferon
Prostate		4/14 (29)	Gamma-interferon
Prostate		8/14 (57) 5/6 ↓ pain (83) 3/14 >50% ↓ PSA (21)	Alpha-interferon
Colorectal, lung, breast			
GI, lung, breast		2/9 (22)	
Colorectal		10/28 (36)	
Breast		3/6 (50)	
Prostate		8/13 ↓ pain (62) 7/17 stable PSA (41)	
Colorectal		3/20 (15)	
Colorectal		14/20 (70)	
Colorectal		4/15 (27)	

Continued

eTABLE 22-1 Select Systemic Monoclonal Antibody RIT Clinical Trials in Nonhematologic Malignancies—cont'd

Study (First Author)	Year	Radiolabeled Antibody	Antigen	Study Type	Patient No.
Gulec[322]	2011	^{90}Y-hPAM4	PAM4-reactive mucin	I	20
Sharkey[749]	1994	^{131}I-Mu-9	Colon specific antigen-p	I	25
Chen[750]	2004	^{131}I-Hepema-1	Glycoprotein	I	32
Deb[167]	1996	^{90}Y-CYT-356	PSMA	I	12
Kahn[173]	1999	^{90}Y-CYT-356	PSMA	II	8
Milowsky[179]	2004	^{90}Y-huJ591	PSMA	I	29
Bander[180]	2005	^{177}Lu-huJ591	PSMA	I	35
Tagawa[346]	2013	^{177}Lu-huJ591	PSMA	II	47
Allen[90]	2011	^{213}Bi-9.2.27	Melanoma chondroitan sulfate proteoglycan	I	38
Colnot[174]	2000	^{186}Re-chimeric U36	CD44v6	I	13
Borjesson[178]	2003	^{186}Re-hu BIWA 4	CD44v6	I	17
Divgi[171]	1998	^{131}I-G250	G250	I/II	33
Steffens[157]	1999	^{131}I-cG250	G250	I	8
Divgi[751]	2004	^{131}I-cG250	G250	I	27
Brouwers[752]	2005	^{131}I-cG250	G250	I	15
Street[230]	2006	^{131}I-chTNT-1/B	DNA Histone H1	I	21
Chen[158]	2005	^{131}I-chTNT-1/B	DNA Histone H1	II	107
Van Zanten-Pryzbysz[175]	2000	^{131}I-cMOv18	Folate receptor	Pilot	3
DeNardo[152,668]	1997	^{131}I-chL6	L6	I	10
Lashford[148]	1987	^{131}I-UJ13A	NCAM	Pilot	5
Carasquillo[753]	1984	^{131}I-anti-p97	p97	Pilot	10

ADCC, *antibody dependent cellular cytotoxicity*; CR, *complete response;* DFS, *disease free survival;* DOTA, *1,4,7,10-tetraazacylcodecane-N, N′,N″,N‴-tetraacetic acid;* DTPA, *diethylenetriaminepentaacetic acid;* IL-1, *interleukin-1;* IL-2, *interleukin-2;* IL-2R, *interleukin-2 receptor;* NED, *no evidence of disease;* OS, *overall survival;* PR, *partial response.*

Tumor Type	Objective Responses (%)	Minor/Mixed Response or Stable Disease (%)	Comments
Pancreas	3/20 (15)	4/20 (20)	
Colorectal, pancreas			
Hepatocellular	1 yr. survival 31% Median survival 4 mos.	4/20 (20) normal AFP 13/20 (65) > 50% ↓ AFP	
Prostate		2/12 ↓ pain (17)	
Prostate (rising post-op PSA)		4/8 stable PSA (50)	
Prostate	2/29 (7) PR	6/29 (21) stable	
Prostate		4/35 > 50% ↓ PSA 16/35 stable PSA	16 patients two to three cycles
Prostate	1/12 (8) PR	5/47 ≥ 50% ↓ PSA 17/47 ≥ 30% ↓ PSA	
Melanoma	10% PR	40% SD	
Head and neck		1/13 (8)	
Head and neck		4/17 (24)	
Renal		17/33 (52)	
Renal	1/8 (13)	1/8 (13)	
Renal		8/15 stable	Given in three to seven divided doses every 2-3 days
Renal		5/27 stable	20 patients given second cycle
Colorectal		5/21 (24)	
Lung	4/107 (3.7) CR 33/107 (30.8) PR Median survival 11.7 mos.	59/107 (55.1) stable	IV or intralesional
Ovary		3/3 (100)	
Breast	4/10 (40)	2/10 (20)	200 mg cold Mab prior to RIT, resulting in ↑ serum IL-2, IL-2R, C3, C4, and ADCC, and twofold to threefold ↑ tumor Mab uptake
Neuroblastoma	1/5 (20)	1/5 (20)	
Melanoma	1/3 (33)	1/3 (33)	

eTABLE 22-2 Tumor Doses and Objective Response Rates from Selected Solid Tumor and Lymphoma RIT Trials

Study (First Author), Year	Radionuclide-Antibody	Tumor Type	No. Tumors Analyzed	Tumor Dose (cGy/Cycle)	Objective Response Rate (%)
Meredith,[161] 1994	^{131}I-CC49	Prostate	4	208-1083	0
Juweid,[168] 1996	^{131}I-NP4 F(ab′)$_2$	Colorectal, lung, pancreas, thyroid	4	511-6476	0
DeNardo,[152] 1997	^{131}I-chL6	Breast	7	120-3700 (~1300 mean)	40
Van Zanten-Pryzbysz,[175] 2000	^{131}I-cMOv18	Ovary	3	600-3800	0
Breitz,[149] 1992	^{186}Re-NR-CO-2 F(ab′)$_2$	Lung, colorectal, breast, ovary, renal	5	500-2100	4
Postema,[754] 2003	^{186}Re-hu BIWA 4	Head and neck	16	380-7610 (1240 median)	0
DeNardo,[170] 1997	^{90}Y-BrE-3	Breast	16	442-1887	0
Wong,[312] 2003	^{90}Y-cT84.66	Colorectal	31	46-6400 (1320 mean)	0
Chong,[229] 2005	^{131}I-huA33	Colorectal	NS	1170-3180 (2119 mean)	0
Divgi,[751] 2004	^{131}I-cG250	Renal	20	320-2330	0
Street,[230] 2006	^{131}I-chTNT-1/B	Colorectal	8	365-4560	0
Wiseman,[755] 2000	^{90}Y-2B8	Non-Hodgkin's lymphoma	18	580-6700 (1700 median)	67
Vose,[447] 2000	^{131}I-anti-B1	Non-Hodgkin's lymphoma	NS	795 mean	57
Kaminski,[463] 1996	^{131}I-anti-B1	Non-Hodgkin's lymphoma	NS	141-2584 (925 mean)	79
Lamborn,[756] 1997	^{131}I-Lym-1	Non-Hodgkin's lymphoma	45	16-1485 (241 median)	54
Vose,[757] 2000	^{131}I-LL2	Non-Hodgkin's lymphoma	NS	166-861	33

NS, *Not stated.*

radiolabeled macromolecule targeting; and (4) increasing the tumoricidal effect of the targeted radiation dose. Clinical trials evaluating these optimization strategies are summarized in this chapter. Those that have been studied include regional administration, combined modality approaches, and therapy in the minimal tumor burden or adjuvant setting. Pretargeting antibody based delivery strategies that seek to amplify the differences between tumor and normal organ uptake also continue to be explored and remain promising. There has also been increasing interest in the use of high LET α-emitters in patients with solid tumors.

Autologous Stem Cell Support
(See eTable 22-1)

Because hematologic toxicity is dose-limiting, groups have explored dose intensification strategies using stem cell reinfusion after myeloablative doses of radiolabeled Mabs. Most have been Phase I studies treating a limited number of patients. Stem cell supported RIT studies primarily in breast cancer have reported objective responses.[202,203] Other studies have reported fewer or no objective responses.[83,154,202-206] Stem cell reinfusion has permitted higher myeloablative doses to be administered, but it appears that dose intensification alone will not result in the level of objective response rates initially hoped for and will need to be combined with other optimization strategies.

Fractionation of Administered Activity
(See eTable 22-1)

Fractionated RIT usually involves administration of the total activity through divided infusions spaced days to a week apart instead of as a single infusion and takes advantage of the differences in uptake and clearance kinetics of activity between tumor and normal tissues, such that with the appropriate fractionation schedule the ratio between tumor dose and marrow dose can be amplified. The optimum schedule therefore may be dependent on a complex interplay of multiple factors including uptake and clearance kinetics of the antibody construct, decay kinetics of the radionuclide, tumor size, radiosensitivity of tumor and organs, and clearance kinetics of the individual patient. A number of groups have reported in animal models reduced hematopoietic toxicity and greater antitumor effects with fractionation.[207-210] Meredith et al[211] used a fractionated RIT schedule with ^{131}I-chimeric B72.3 in patients with colorectal cancer who received 28 mCi/m^2 or 36 mCi/m^2 in two to three weekly fractions of 12 mCi/m^2 to 18 mCi/m^2. There was a modest but statistically significant ($p = 0.04$) decrease in hematopoietic toxicity adjusted for whole-body dose when compared to a similar population treated in a previous trial who received similar doses of ^{131}I-chimeric B72.3 as a single infusion.[211] Divgi et al[212] also evaluated a fractionated schedule with the anti-TAG-72 antibody CC49 radiolabeled with ^{131}I. Six patients with colorectal cancer received 15 mCi/m^2 biweekly for up to a maximum of four infusions. This schedule was well tolerated with no dose-limiting toxicities observed.

Engineered Immunoconstructs

Molecular engineering of antibodies with properties optimized for therapy continue to be pursued. Reducing antibody immunogenicity to permit multiple administrations has been successful in the clinic. Murine derived Mabs have the disadvantage of being recognized as foreign by the patient's immune system, which can lead to the formation of HAMA in 50% to 100% of patients after single administration,[213-216] resulting in faster blood clearance of subsequently administered antibody and potentially compromised efficacy.[216-217] Reduction in antibody immunogenicity has been observed with the use of immunosuppressive agents, such as cyclosporine A.[34,218,219] Others have reduced antibody immunogenicity through modification of the antibody molecule using recombinant DNA techniques to replace murine with human antibody domains (e.g., chimeric antibodies, where the murine variable domains are retained, and humanized antibodies, where only the murine complementarily determining regions CDR antigen recognition sites are retained; see eTable 22-3, available in the expanded chapter on the Expert Consult website).[152,174,178,220-231]

Recombinant antibodies can be designed with improved biodistribution and pharmacokinetic properties to optimize their use for therapy. Antibody fragments and other smaller molecular weight antibody constructs may ultimately prove superior for therapy because of their faster clearance, greater tumor penetration,[26] more uniform distribution in tumor,[232] higher initial dose-rate in tumor,[233] decreased immunogenicity,[234] higher tumor to background ratios,[132] and potential for higher administered activities and tumor doses for the same level of toxicity. Initial efforts evaluated radiolabeled Fab and F(ab')$_2$ fragments generated from whole immunoglobulin through enzymatic digestion (see eTable 22-1).[149,150,154,168,235] Unfortunately, antitumor effects appeared to be no better than with radiolabeled intact antibody. Although blood clearance may be more rapid with fragments, retention time in tumor is also reduced, resulting in no significant improvement in radiation dose to tumor over the intact antibody for equitoxic administered activities.

More recent efforts have used recombinant DNA technology to genetically engineer antibody constructs with properties to improve tumor to normal organ biodistribution, enhance in vivo stability, reduce immunogenicity, aid in conjugation and radiolabeling, and increase clearance kinetics. Constructs have ranged from approximately 25 kDa to 160 kDa in size. The genes encoding the antibody's variable light (V_L) and variable heavy (V_H) domains can be cloned and linked by a contiguously encoded peptide into a single chain (sc) Fv construct. This small monovalent scFv, 28 kDa, clears rapidly from the circulation increasing the tumor-to-blood ratio, making them attractive as potential imaging agents.[236,237] However, the absolute peak uptake and retention time in tumors are often reduced, limiting their use as therapy agents.[236-239] In addition, low-molecular-weight constructs can filter through the renal glomeruli, resulting in increased kidney uptake and radiation dose compared to higher molecular weight constructs. A more suitable construct for therapy might be bivalent, of intermediate molecular weight, and exhibit uptake and retention in tumor comparable to intact antibodies, but with faster clearance times than an intact Mab, resulting in an improved therapeutic ratio. Multivalent, intermediate molecular weight constructs have been produced through covalent linking of monovalent fragments.[209,238,240-248] Alternatively, single chain monomers can be engineered with properties that promote spontaneous formation of dimeric and trimeric species. For example, Figure 22-1 shows an engineered series of recombinant fragments derived from the intact anti-CEA T84.66 MAb.[249] This cognate family of anti-CEA constructs was radioiodinated and evaluated in animal biodistribution studies. The minibody (80 kDa), formed by the self-association of two scFv-C_H3 single chain monomers, was potentially suitable for therapy and resulted in peak tumor uptakes of more than 20% to 30% injected dose per gram, which exceeded that of the diabody and F(ab')$_2$ and approached that of the intact antibody.[250]

A pilot imaging trial[251] evaluating the biodistribution and tumor targeting properties of the ^{123}I-cT84.66 minibody in 10 patients with colorectal cancer demonstrated faster blood

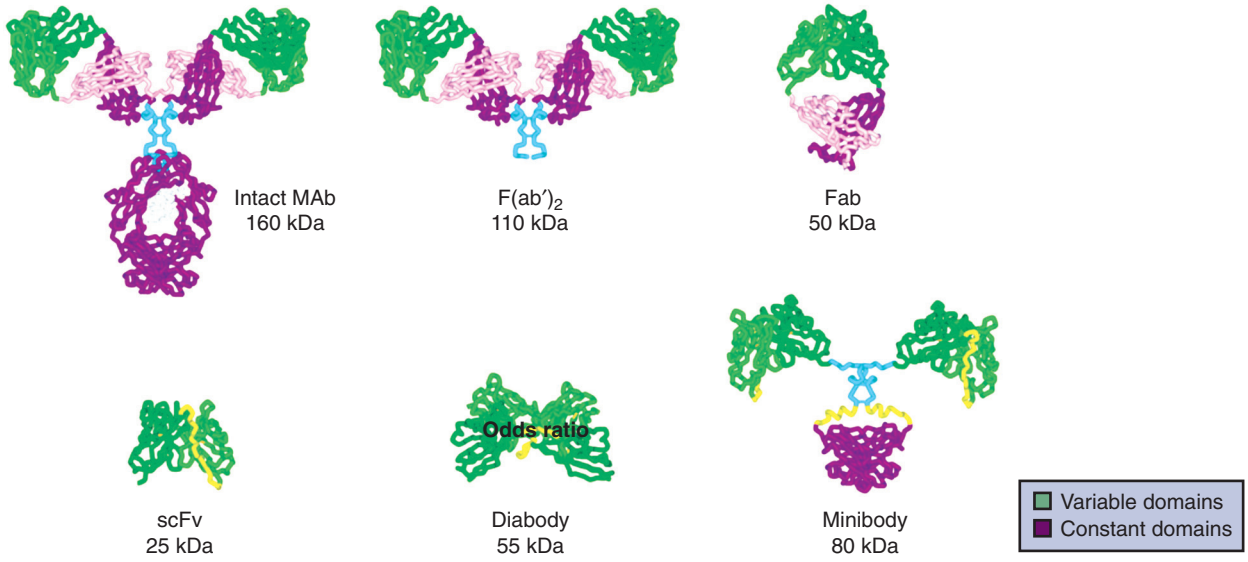


Figure 22-1 Comparison of the variable and constant domains for six types of engineered antibodies.

clearance than intact cT84.66.[145] To further evaluate its potential as a therapy agent, a follow-up pilot study evaluated ^{111}In-DOTA-cT84.66 minibody, with 4 of 5 patients demonstrating tumor imaging. Predicted mean radiation dose to liver was 19.6, kidney 33.3, lung 1.5, and marrow 2.2 cGy/mCi ^{90}Y. Mean tumor dose was 12.4 (6.8 to 25.1) cGy/mCi ^{90}Y. Tumor dose to marrow dose ratio was 5.6, comparable to that seen in murine models, but less than the ratio of 10.5 seen for intact ^{90}Y-DTPA-cT84.66[176] and 11.6 for ^{90}Y-DOTA-cT84.66[231] seen in previous Phase I trials.

Other groups have investigated similar strategies.[239,252-256] Forero et al reported on a 153 kDa ^{131}I labeled humanized C_H2 domain deleted construct (HuCC49ΔCH_2) derived from CC49 anti-TAG72.[257] Blood clearance $T_{1/2}$ was 20 hours, comparable to cT84.66 minibody. Early results from a Phase I dose escalation therapy trial in metastatic colorectal cancer indicated reduced hematologic toxicity compared to intact murine ^{131}I-CC49. At the initial dose level of 75 mCi/m^2, only 25% of patients (one of four) developed more than grade 3 hematopoietic toxicity, compared to >60% of patients with ^{131}I-murine CC49 in a previous trial.[258]

Modifying Tumor Environment
(See eTable 22-1)

Upregulation of tumor antigen expression as a means of increasing antibody targeting and radiation dose to tumor has been explored. Alpha- and gamma-interferon have been shown to increase CEA and TAG-72 expression,[259-262] resulting in increased tumor antibody uptake and RIT efficacy in animal models.[263,264] In the clinic, interferon has also increased tumor antigen expression and antibody uptake in breast, colorectal, and prostate cancers.[265-268] However, antitumor effects remain modest with this strategy alone, leading investigators to now combine this approach with other optimization strategies.

Strategies to modify the tumor vasculature to increase blood flow or vascular leakage, using vasoactive agents, vasoactive immunoconjugates, radiation therapy, or hyperthermia, have been explored primarily in experimental models.[269] Interest has focused on an emerging class of agents directed against the tumor neovasculature. Jain et al[270] and others[271] have proposed using antiangiogenic agents, such as anti-vascular endothelial growth factor (VEGF) antibodies, to "prune" or normalize the tumor vasculature, decrease tumor interstitial pressure, and increase tumor perfusion, which should increase macromolecule delivery. In some experimental models tumor oxygenation is also increased,[271] which can further enhance antitumor effects of RIT. In a similar strategy Burke et al have looked at using cyclic RGD peptide, which recognizes the αvβ3 integrin receptor on tumor neovasculature. In a tumor-bearing breast cancer mouse model, the combination of RGD peptide and ^{90}Y-chimeric L6 RIT resulted in higher tumor uptake of antibody and a greater percentage of mice cured than either therapy alone.[272,273] In mice with colorectal cancer, Kinuya et al[274] combined the antiangiogenic agent 2-methoxyestradiol with ^{131}I-A7 RIT and demonstrated prolonged survival with the combination, compared to either agent alone. Bodet-Milin et al[275] combined ^{131}I-F6 anti-CEA RIT and bevacizumab (anti-VEGF) in mice with medullary thyroid cancer and reported an increase in tumor growth delay with the combination compared to either agent alone.

Agents that increase vascular permeability also have been evaluated. A response-selective peptide agonist to human C5a, resulted in an increase in ^{131}I-B72.3 anti-TAG72 Mab and a two-fold increase in colon cancer xenograft growth delay in vivo.[276] The vascular disrupting agent combretastatin A-4-phosphate (CA4P) has been shown to increase tumor retention of ^{131}I-AB7 anti-CEA antibody, resulting in increased radiation dose to tumor[277] and a significant increase in tumor growth suppression compared to ^{131}I-AB7 RIT alone.[278] A Phase I/II trial was initiated and preliminary results reported.[279] Twelve patients received ^{1311}-A5B7 anti-CEA Mab given on day 1 and CA4P on days 2 and 3. Dynamic contrast-enhancing magnetic resonance imaging (MRI) demonstrated reduction in tumor vascular kinetics in 9 of 12 patients. Dose-limiting hematopoietic toxicity was observed at ^{131}I-A5B7 administered activities of 43.2 mCi/m^2 and CA4P of 54 mg/m^2. Of ten evaluable patients one had stable disease.

Minimal Tumor Burden Setting
(See eTable 22-1)

Tumor size plays a dominant role in influencing antibody uptake and clinically important outcomes are predicted if systemic RIT is applied in the subclinical or microscopic disease setting. Jain et al[26,280] have identified key physiologic factors

that limit uptake of macromolecules. These factors include spatial heterogeneity of tumor vascularity, increased interstitial pressure in poorly vascularized areas, and limited diffusion distances of macromolecules, which work to significantly limit the ability of the antibody to reach all sites within the tumor. These factors are amplified as the tumor grows, resulting in an exponential decrease in tumor antibody uptake, that has been demonstrated in vivo[281-284] and in clinical trials.[285,286] Given this inverse exponential relationship, a very modest reduction in tumor size will result in a substantial increase in antibody uptake.

RIT should therefore have its greatest impact in the adjuvant setting and in the treatment of minimal or microscopic disease. For example, Behr et al[155] and Vogel et al[208] successfully demonstrated improved survival and prevention of liver metastases in animal models with RIT delivered with adjuvant intent. Subsequent clinical trials evaluated this strategy in patients with small volume disease. Behr et al[155] reported initial Phase I trial results in 12 patients with colorectal cancer with metastatic lesions ≤2.5 cm. Patients received a single administration of 50 mCi/m^2 to 70 mCi/m^2 ^{131}I-hMN14 anti-CEA RIT. Of 11 evaluable patients, 2 partial responses and 5 minor/mixed responses of up to 12 months duration were observed (see eTable 22-3). This was followed by a Phase II study of 30 patients with colorectal cancer and liver metastases who received a single administration of ^{131}I-hMN14 anti-CEA RIT (60 mCi/m^2).[287] Of 19 evaluable patients who had small volume disease of ≤3.0 cm, 3 experienced a partial response of 3 to 15 months' duration and 8 patients had a minor response of 3 to 14 months' duration. Five patients received a second cycle at time of progression at 8 to 16 months, which resulted in partial responses in 2 patients. In addition, 9 patients received RIT for microscopic disease similar to the results in an adjuvant setting after a complete resection of hepatic metastases. Seven of 9 remained disease free at more than 24 to 36 months, which compared favorably to historical controls at the same institution receiving 5-fluorouracil (5-FU) based regimens posthepatic resection (see eTable 22-1).

These initial encouraging observations led to a Phase II adjuvant RIT trial of ^{131}I-hMN14 administered after resection of colorectal cancer liver metastases.[288] In a subsequent report, 23 patients who underwent R0 resection of liver metastases from colorectal cancer, received a single administration of 40 mCi/m^2 to 60 mCi/m^2 of ^{131}I-hMN14 anti-CEA (see eTable 22-1).[289] Results were compared to a contemporaneous control group of 19 patients from the same institution treated postresection with 5-FU–based chemotherapy regimens. Median follow-up for the RIT group was 91 months and for the control group, 51 months. A statistically significant improvement in median overall survival in the RIT group (58 months versus 31 months) was reported. Median disease-free survival was greater for the RIT group (18 months versus 12 months), but the difference did not reach statistical significance. The investigators concluded that a prospective randomized trial to evaluate ^{131}I-hMN14 as adjuvant therapy in this patient population was warranted given the suggestion of a survival advantage. This same group evaluated administering two courses of RIT after resection of liver metastases in patients with colorectal cancer.[290] Thirty-two patients received a 40 mCi/m^2 to 50 mCi/m^2 ^{131}I-hMN14 anti-CEA, with 24 receiving a second RIT administration. Sixteen patients had no residual disease detectable after surgery and comprised the group that received adjuvant RIT. With follow-up of 21 months, disease-free survival was 18 months for the adjuvant group and 6 months for the nonadjuvant group. The authors concluded that a second cycle of RIT is feasible with acceptable toxicity.

An adjuvant RIT trial in colorectal cancer was carried out by Ychou et al[181] who administered a preoperative dose of ^{131}I-F6 F(ab')$_2$ anti-CEA (8 mCi to 10 mCi) prior to planned surgery to 22 patients with one to four liver metastases. After complete resection (R0) resection, 13 patients, including 10 who had tumor to liver uptake ratios of >5, received 180 mCi/m^2 to 200 mCi of ^{131}I-F6 F(ab')$_2$ anti-CEA RIT. With a median follow-up of 127 months, median disease-free survival was 12 months and median overall survival was 50 months. One patient remained disease free at 93 months. The investigators concluded that RIT is feasible after surgery in this poor prognostic group and that RIT combined with chemotherapy should be further evaluated in this clinical setting.

At City of Hope, a Phase I trial evaluated the feasibility and toxicities of ^{90}Y-cT84.66 anti-CEA RIT combined with hepatic arterial fluorodeoxyuridine (FUdR) and systemic gemcitabine in patients with colorectal cancer after resection and or radiofrequency ablation of liver metastases. No dose-limiting toxicities were observed in 16 patients with FUdR of 0.1 to 0.2 μg/kg/d × 14 days, gemcitabine 105 mg/kg and RIT 16.6 mCi/m^2. Median time to progression was 9 months, with two patients still progression free at 38 and 90 months (see eTable 22-1). Encouraging results in the minimal tumor burden setting are also promising with regional administration of RIT and are detailed below.

In summary, preclinical studies predict that RIT should have its greatest impact in the minimum tumor burden or adjuvant setting. Initial clinical trials remain promising and demonstrate feasibility of RIT alone or in combination with chemotherapy in the posthepatic resection setting. Further trials are warranted to better define the potential benefits of this approach.

Combined Modality Approaches (eTable 22-4)

RIT and Chemotherapy

Multiple preclinical studies have documented additive or supraadditive antitumor effects when RIT is combined with radiation enhancing chemotherapy or other systemic agents, including gemcitabine,[291-293] taxanes,[294,295] cisplatin,[296] 5-FU,[297-299] doxorubicin,[300] halogenated pyrimidines,[301] topoisomerase inhibitors,[299,302,303] tirapazamine,[304,305] epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors,[306] and anti-EGFR Mabs.[307] A growing number of clinical trials are evaluating the feasibility and potential improved efficacy of concomitant chemotherapy and RIT, either by adding chemotherapy to maximum tolerated doses of RIT or adding RIT as additional therapy to established chemotherapy regimens. RIT-chemotherapy trials have been performed in a number of different solid tumor types including ovarian, breast, prostate, medullary thyroid, and colorectal cancers and are summarized in eTable 22-4, available on the Expert Consult website.[205,235,308-321] In some studies, the strategy of chemotherapy and RIT has often been combined with other strategies, including regional delivery, interferon, and hematopoietic stem cell support.

Radiolabeled anti-CEA Mabs have been evaluated in Phase I trials in combination with single-agent chemotherapy. One of the first reported Phase I trials combined ^{90}Y-cT84.66 at MTD doses of 16.6 mCi/m^2 (defined from a previous trial[176]) with 5-day continuous infusion 5-FU at doses escalating from 700 mg/m^2/day to 1000 mg/m^2/day.[312] One mixed response and 11 patients with stable disease of up to 8 months' duration were reported in 21 patients treated with up to two courses of combination therapy. 5-FU did not appear to alter the pharmacokinetics and biodistribution of cT84.66. human anti-chimeric antibody (HACA) responses were more than 50% less frequent compared to that seen with ^{90}Y-cT84.66 alone,[176] suggesting that the 5-FU may have played a role in reducing immune response to the chimeric antibody. This was followed

eTABLE 22-3 Antibody Immunogenicity after Single Administration (Selected Solid Tumor RIT Trials)

Study (First Author, Year)	Antibody	Type	No. of Patients	Anti-Antibody Response (%)
Breitz,[149] 1992	^{186}Re-NR-LU-10	Murine	15	100
Meredith,[161] 1994	^{131}I-CC49	Murine	15	100
Welt,[163] 1994	^{131}I-mAb A33	Murine	23	100
Mulligan,[166] 1995	^{177}Lu-CC49	Murine	9	100
Yu,[169] 1996	^{131}I-COL-1	Murine	18	83 prevented add'n RIT in 2
DeNardo,[170] 1997	^{90}Y-BrE-3	Murine	6	83 prevented add'n RIT in 3
Behr,[151] 1997	^{131}I-NP-4	Murine	32	94
Juweid,[156] 1999	^{131}I-MN-14	Murine	14	100
Divgi,[171] 1998	^{131}I-mG250	Murine	33	100
Ychou,[181] 2008	^{131}I-F6 F(ab′)$_2$	Murine	13	77
Meredith.[211] 1992	^{131}I-cB72.3	Chimeric	12	58
Weiden,[160] 1993	^{186}Re-NR-LU-13	Chimeric	8	75
Meredith,[165] 1995	^{125}I-17-1A	Chimeric	15	13
DeNardo,[152] 1997	^{131}I-chL6	Chimeric	10	80 prevented add'n RIT in 4
Steffens,[157] 1999	^{131}I-cG250	Chimeric	12	8
Zanten-Przybysz,[175] 2000	^{131}I-cMOv18	Chimeric	3	0
Colnot,[174] 2000	^{186}Re-U36	Chimeric	12	42
Wong,[176] 2000	^{90}Y-DTPA-cT84.66	Chimeric	21	52 prevented add'n RIT in 8
Wong,[231] 2006	^{90}Y-DOTA-cT84.66	Chimeric	13	62 prevented add'n RIT in 5
Street,[230] 2006	^{131}I-chTNT-1/B	Chimeric	19	37
Sultana,[746] 2009	^{131}I-KAb201	Chimeric	19	100
Kramer,[225] 1998	^{111}In-huBrE3	Humanized	7	14
Hajjar,[228] 2002	^{131}I-hMN-14	Humanized	15	47
Bander,[180] 2005	^{90}Y-huJ591	Humanized	35	0
Gulec,[322] 2011	^{90}Y-hPAM4	Humanized	21	10
Wong, 2013 (unpublished)	^{90}Y-M5A T84.66	Humanized	16	13
Borjesson,[178] 2003	^{186}Re-BIWA 4	Humanized	20	10
Chong,[229] 2005	^{131}I-hu-A33	Humanized	15	27

eTABLE 22-4 Select RIT Trials Using Combined Modality Approaches

Study (First Author, Year)	Study Type	Antibody	Antigen	Route	Tumor Type
Wong,[205] 1999	I	^{90}Y-cT84.66	CEA	IV	CEA+ Breast
Wong,[312] 2003	I	^{90}Y-cT84.66	CEA	IV	Colorectal
Sharkey,[318] 2005	I	^{90}Y-hMN-14	CEA	IV	Medullary thyroid
Shibata,[321] 2009	I	^{90}Y-cT84.66	CEA	IV	CEA+
Wong, unpublished	I	^{90}Y-cT84.66	CEA	IP	CEA+
Wong, unpublished	I	^{90}Y-cT84.66	CEA	IV	Colorectal
Wong, unpublished	I	^{90}Y-cT84.66	CEA	IV	CEA+ stage III non–small cell lung
Buchegger,[235] 2000	Pilot	^{131}I-F(ab′)$_2$ mab 35 mab B7 mab B93	CEA	IV	Colorectal with limited liver mets
Carabasi,[308] 1999	Pilot	^{131}I-CC49	TAG-72	IV	Prostate, breast
Meredith,[309] 2001	I	^{177}Lu-CC49	TAG-72	IP	Ovary (recurrent/persistent tumor ≤5 cm after second-look lap)
Alvarez,[310] 2002	I	^{90}Y-CC49	TAG-72	IP	Ovary (recurrent/persistent tumor ≤5 cm)
Forero,[316] 2005	I	^{90}Y-CC49	TAG-72	IV	Lung (NSLC) stage IIB and IV
Meredith,[403] 2012	I	^{90}Y-CC49 ^{177}Lu-CC49	TAG-72	IP	Ovary (recurrent/persistent tumor ≤5 cm)
Ocean,[323] 2012	I/II	^{90}Y-hPAM4	PAM4 positive mucin	IV	Pancreas
DeNardo,[315] 2005	I	^{90}Y-m170	MUC1	IV	Prostate
Richman,[317] 2005	I	^{90}Y-m170	MUC1	IV	Prostate, breast
Anderson,[311] 2003	pilot	^{131}I-chTNT-1/B	DNA histone 1	IV	Carcinoid, leiomyosarcoma, colorectal
Wygoda,[319] 2006	II	^{125}I-425	EGFR	IV	Primary grade 3/4 gliomas. RT vs. RT + RIT

Pt. No.	No. Cycles	Objective Responses	Other Antitumor Effects	Comments
8	1		4/8 MR/SD 3-14 mos.	Cisplatin 25 mg/m^2 days 1-4 Gemcitabine 100 mg/m^2 days 2,8 RIT 15 mCi/m^2-31.4 mCi/m^2 day 2 DTPA post RIT Autologous stem cell reinfusion
21	13-1 cycle 8-2 cycles		1 MR 11 SD 3-8 mos.	5-FU 700 mg/m^2/d-1000 mg/m^2/d × 5 cont. infusion RIT 16/6 mCi/m^2 DTPA post RIT
14	1	1/14 PR	2/14 MR 4/14 SD	Doxorubicin 60 mg/m^2 day 3 Autologous stem cell supported RIT 20 mCi/m^2-50 mCi/m^2
32	25-1 cycle 4-2 cycles 3-3 cycles	1/32 PR	10/32 SD	Gemcitabine 30-165 mg/m^2 days 1,3 RIT 16.6 mCi/m^2 DTPA post RIT
5	1		2/5 SD	IP gemcitabine 40 mg/m^2 days 1,4,8 IP RIT 19 mCi/m^2 DTPA post RIT
16	15-1 cycle 1-2 cycles	2 pts no progression (38 and 90+ mos.)		RIT 16.6 mCi/m^2 DTPA post RIT Intraarterial FUdR 0.1 μg/kg/d-0.2 μg/kg/d × 14 d Gemcitabine 105 mg/m^2 days 9,11 Liver met resection
11	1 cycle	3 pts progression free at 5, 14 and 70+ mos.		EBRT (60 Gy) Chemotherapy (cisplatinum/etoposide or carboplatin/paclitaxel)
6	1		1/6 MR 3/6 SD 5/6 ↓ CEA	Whole liver RT (20 Gy) RIT 186 mCi (mean) (127 mCi-227 mCi)
12	1	4/12 PR	1/9 MR	RT (TBI 13.2 Gy) RIT 100 mCi/m^2-150 mCi/m^2
44	1	4/17 PR (measurable disease)	Median TTP 13 months 4/27 non-measurable disease progression free 18+, 21+, 21+, 37+ mos.	IP paclitaxel 25 mg/m^2-100 mg/m^2 α-interferon RIT 32 mCi/m^2-45 mCi/m^2
20	1	Measurable disease 2/9 PR 5/9 SD	Nonmeasurable disease 4/11 progression free 15+ to 23+ months	IP paclitaxel 100 mg/m^2 α-interferon RIT 14 mCi/m^2-24.2 mCi/m^2
34	1		13/34 SD	Paclitaxel 60 mg/m^2-80 mg/m^2 α-interferon RIT 8 mg/m^2-20 mCi/m^2 EDTA or DTPA post RIT
92	1	Significant ↑ in time to progression for tumors <2 cm and age <60		IP paclitaxel 100 mg/m^2 α-interferon ^{90}Y-CC49 RIT 14mCi/m^2-24.2 mCi/m^2 ^{177}Lu-CC49 RIT 32-40 mCi/m^2
38	weekly	6/38 PR	16/38 SD	^{90}Y-hPAM4 6.5mCi/m^2-15 mCi/m^2 weekly Gemcitabine 200 mg.m^2 weekly
23	1		9/19 ↓ bone pain 9/23 ↓ PSA velocity	Paclitaxel 75 mg/m^2 + autologous stem cells (6 pts) RIT (5 mCi/m^2-20 mCi/m^2)
12	1		2/6 prostate 50% ↓ PSA and bone pain 2/6 breast MR	Paclitaxel 75 mg/m^2 (5 pts) RIT 12 mCi/m^2 prostate RIT 22 mCi/m^2 breast with autologous stem cells
6	1			Radiofrequency ablation RIT 0.35 mCi/kg or 0.71 mCi/kg
18	3 weekly		Median survival 14 mos	RT (60 Gy) No difference between two groups. 136 mCi per cycle

Continued

eTABLE 22-4 Select RIT Trials Using Combined Modality Approaches—cont'd

Study (First Author, Year)	Study Type	Antibody	Antigen	Route	Tumor Type
Bartolomei,[313] 2004	I/II	Pretargeting three-step BC-4-biotin Avidin ^{90}Y-biotin	Tenascin	IC	GBM recurrent/progressive
Boiardi,[314] 2005	II	Pretargeting three-step BC-4-biotin Avidin ^{90}Y-biotin	Tenascin	IC	GBM recurrent
Reardon,[320] 2008	pilot	^{131}I-m81C6	Tenascin	IC	Gliomas, primary
Reardon,[406] 2006	I	^{131}I-ch81C6	Tenascin	IC	Gliomas, primary and recurrent

AA, *Anaplastic astrocytoma;* CR, *complete response;* DTPA, *diethylenetriaminepentaacetic acid;* EDTA, *ethylenediaminetetraacetic acid;* FUdR, *fluorodeoxyuridine;* GBM, *glioblastoma multiforme;* IP, *intraperitoneal;* RT, *radiotherapy;* MR, *mixed or minor response;* OS, *overall survival;* PFS, *progression free survival;* PR, *partial response;* SD, *stable disease;* TMZ, *temozolomide;* TTP, *time to progression.*

Pt. No.	No. Cycles	Objective Responses	Other Antitumor Effects	Comments
73 38 RIT alone 35 RIT + TMZ	Median 3 (2-7)	1	RIT alone OS 17.5 months PFS 5 months RIT and TMZ OS 25 months PFS 10 months ($p < 0.01$)	Temozolomide (TMZ) 150-200 mg/m^2/d × 5 d Median 6 cycles with RIT RIT 10 mCi-25 mCi Surgery prior to RIT
26 20 RIT + mitoxantrone 6 RIT alone	2	2	RIT + mitoxantrone PFS 8 months OS 20 months RIT alone PFS 8 moths OS 22 months	PCV chemotherapy every 6 weeks × 3 IC mitoxantrone 4 mg every 20 d Surgery prior to RIT RIT 5 mCi-25 mCi
21 (16 GBM 5 AA)	1		AA Median OS not reached GBM median OS 90.6 weeks	Temozolomide, irinotecan, etoposide, or lomustine RT (55 Fy-60 Gy) Surgery
47 (38 GBM)	1		GBM median OS 86.1 weeks primary 48.9 weeks recurrent	Temozolomide, irinotecan, etoposide, or lomustine RT (55 Gy-60 Gy) Surgery

by a Phase I trial of similar design combining ^{90}Y-cT84.66 at doses of 16.6 mCi/m^2 on day 1 with gemcitabine 30 mg/m^2 to 165 mg/m^2 on days 1 and 3. The maximum tolerated dose (MTD) of gemcitabine was 150 mg/m^2. Of 32 patients treated with one to three courses of therapy, one partial response, and 10 patients with stable disease were observed.[321] HACA response was less frequent than with ^{90}Y-cT84.66 alone,[176] suggesting that, as with 5-FU, the addition of gemcitabine may have reduced the incidence of HACA.

RIT using ^{90}Y-cT84.66 anti-CEA has also been combined with standard radiotherapy and chemotherapy regimens. Phase I trials using autologous stem cell support with full intensity chemotherapy have also been reported (eTable 22-4). The established chemotherapy regimen of gemcitabine and cisplatin was combined with a single infusion of ^{90}Y-cT84.66 (15 mCi/m^2 to 31.4 mCi/m^2) in 8 patients with metastatic breast cancer. Four patients demonstrated mixed responses or stable disease of 3 to 14 months' duration.[205] More recently, ^{90}Y-cT84.66 RIT was administered to 11 patients with unresectable stage III non–small cell lung cancer in combination with standard radiotherapy (60 Gy) and chemotherapy (cisplatin/etoposide or carboplatin/paclitaxel). RIT was administered concomitantly with radiochemotherapy in 4 patients (10 mCi/m^2) or 6 weeks after completion of radiochemotherapy in 7 patients (8 mCi/m^2 to 12 mCi/m^2) (Wong, unpublished data). Three patients remain progression free at 5, 14, and 70+ months (eTable 22-4).

^{90}Y-hPAM4 has been evaluated with gemcitabine in patients with pancreatic cancer. The initial Phase I trial established an MTD of 20 mCi/m^2 when administered as a single infusion in 20 patients with advance pancreatic cancer, with 3 patients demonstrating a partial response (see eTable 22-1).[322] A successor Phase I/II trial combined fractionated (weekly) ^{90}Y-hPAM4 with low dose gemcitabine (200 mg/m^2 weekly).[323] The MTD was established at 12 mCi/m^2 weekly for 3 weeks for the first cycle and ≤9 mCi/m^2 weekly for 3 weeks for subsequent cycles. Of 38 patients with stage III/IV pancreatic cancer, 13 received more than one cycle of therapy. Partial responses were observed in 6 patients (16%) and stable disease in 16 patients (42%) (see eTable 22-4). In medullary thyroid cancer, escalating doses (20 mCi/m^2 to 50 mCi/m^2) of ^{90}Y-hMN-14 anti-CEA were combined with single cycle doxorubicin at 60 mg/m^2 in 14 patients, with 1 partial response, 2 mixed responses, and 4 with stable disease observed.[318]

Taxanes have shown promise in combination with systemic and intraperitoneal (IP) RIT. ^{90}Y-m170 at 5 mCi/m^2 to 20 mCi/m^2 with paclitaxel 75 mg/m^2 has been evaluated in prostate and breast cancers.[315,317] ^{90}Y-CC49, paclitaxel 60 mg/m^2 to 80 mg/m^2, and interferon, to increase tumor antigen expression, was administered to 34 patients with stage IIB and IV non–small cell lung cancer with 13 demonstrating stable disease. Regional combined modality approaches remain promising. In patients with ovarian cancer with recurrent or refractory microscopic disease or macroscopic disease <5 cm, combination therapy was evaluated, consisting of a single cycle of IP ^{177}Lu-CC49 RIT, IP paclitaxel, and subcutaneous alpha-interferon.[309] Four of 17 patients with CT measurable disease had a partial response, and 4 of 27 patients with nonmeasurable disease remained progression free at 18+ to 37+ months. A subsequent Phase I study of the same design evaluated IP ^{90}Y-CC49 in combination with IP paclitaxel and alpha-interferon.[310] Two of 9 patients with measurable disease demonstrated a partial response and 4 of 11 with nonmeasurable disease remained progression free at 15+ to 23+ months. A pilot study of IP ^{90}Y-cT4.66 anti-CEA RIT and IP gemcitabine in patients with CEA-expressing cancers with disease primarily confined to the peritoneal cavity demonstrated that the combination was well tolerated with no dose-limiting toxicities observed (see eTable 22-4, unpublished data). Results were encouraging with 4 of 7 patients demonstrating antitumor effects (1 with mixed response and 3 with stable disease of 2 to more than 15 months). One had complete resolution of malignant ascites, whereas another had >50% reduction of ascites, no longer requiring frequent abdominal paracenteses. Regional RIT is also actively being evaluated in combination with chemotherapy in patients with high-grade gliomas.

In summary, combining RIT with single agent or multiagent chemotherapy regimens is feasible with acceptable toxicity and has resulted in antitumor activity in heavily pretreated patients. Similar efforts should continue in the appropriate patient populations and should consider combining RIT with established chemotherapy regimens in less heavily pretreated patients with minimal tumor burden.

RIT and External Beam Radiotherapy

RIT in combination with external beam radiation therapy is an attractive concept for a number of reasons.[324] The two modalities combined may deliver a higher cumulative radiation dose to the tumor than either modality alone. If external beam radiotherapy precedes RIT, radiolabeled macromolecule uptake can potentially be increased through reduction in tumor size,[325] increase in vascular permeability,[326,327] or increase in antigen expression.[328-330] If RIT precedes external beam radiation, low dose-rate RIT irradiation has been shown to potentiate tumoricidal effects of subsequent external beam radiotherapy in vitro through mechanisms that involve a G_2 block,[331] or through a phenomenon termed *protracted exposure radiosensitization* as described by Williams et al.[332]

A limited number of external beam radiotherapy and RIT combined therapy efforts have been reported (see eTable 22-4). Markoe et al[333] treated 53 patients with ^{125}I-17-1A anti-Ep-Cam antibody in a phase I study. Forty-six patients with liver metastases also received 1500 cGy whole liver radiotherapy in 10 daily fractions to increase RIT uptake to hepatic lesions. No significant hepatotoxicity was reported. One partial response, 1 mixed response of 12 months duration and 10 patients with stable disease of 3- to 8-months' duration were observed. Buchegger et al[235] combined ^{131}I-anti-CEA F(ab')$_2$ RIT with liver radiotherapy (20 Gy in 2-2.5 Gy daily fractions) in 6 patients with metastatic colorectal cancer. Hematopoietic toxicity was the primary toxicity and grade 1-3 transient elevations in liver transaminases and alkaline phosphatase were observed. One minor response, 3 patients with stable disease and 5 patients with a decrease in CEA were reported. Clinical trials combining local regional external beam radiotherapy with RIT have been completed with acceptable toxicity in patients with hepatobiliary cancers[333-336] and high-grade gliomas.[337-339]

Combining total body irradiation as a form of systemic external beam radiotherapy with RIT in a myeloablative transplant setting has also been performed by one group in patients with breast and prostate cancers.[308] Twelve patients received 1320 cGy total body irradiation in 8 fractions over 4 days combined with a single infusion of 100 mCi/m^2 to 150 mCi/m^2 of ^{131}I-CC49 anti-TAG72 RIT, followed by autologous hematopoietic cell reinfusion, with four partial and one mixed responses observed.

Although the experience is limited, combining RIT with external beam radiotherapy appears to be feasible and is associated with acceptable toxicity. Efforts evaluating RIT as an adjunct to external beam radiotherapy should continue to be evaluated.

RIT Using Antibodies with Immunomodulatory or Biologic Activity

Although most Mabs evaluated to date have had no significant biologic activity, there have been some exceptions. In a

RIT and Hyperthermia

Hyperthermia has demonstrated promise in experimental models as a means of enhancing the efficacy of RIT through a number of possible mechanisms, which include increasing tumor antigen expression,[340,341] increasing tumor blood flow or vascular permeability, decreasing tumor interstitial pressure, radiosensitization by inhibition of sublethal damage and potentially lethal damage repair,[342-344] and direct cytotoxic effects on tumor. Mittal et al[345] treated mice with LS174T colon cancer with ^{131}I-anti-CEA C110, followed 2 days later with 42.5°C for 45 minutes hyperthermia. Greater tumor growth delay was seen when hyperthermia was added to RIT. The same group then performed a Phase I/II combined therapy trial of ^{131}I-NP4 anti-CEA RIT combined with hyperthermia in six patients with liver metastases. RIT (30 mCi/m^2 or 60 mCi/m^2) was administered intravenously followed 24 hours later by 42°C interstitial hyperthermia to the liver lesions. One partial response was observed and two of three patients had resolution of abdominal pain after therapy.

pilot trial of 10 patients with breast cancer, unlabeled chL6 (200 mg) was administered before the ^{131}I-chL6 therapy dose. chL6 resulted in an increase in serum interleukin-2 and interleukin-2-receptor levels, a decrease in serum C3 and C4 complement levels, and an increase in antibody dependent cellular cytotoxicity (ADCC) activity. In addition approximately a two-fold increase in radiolabeled antibody uptake to tumor was seen, which the authors hypothesized was secondary to changes in tumor vascular permeability as a result of chL6 bioactivity.[152] This may explain, in part, the higher than usual response rate on this trial, with four partial and two mixed responses reported (see eTable 22-1).

HuJ591, which recognizes an external domain of prostate specific membrane antigen (PSMA), may have similar bioactivity. HuJ591 has been radiolabeled with ^{90}Y and ^{177}Lu and evaluated in Phase I RIT trials with encouraging results (see eTable 22-1).[179,180] In a Phase II trial, 47 patients with hormone refractory prostate cancer received 65 mCi/m^2 to 70 mCi/m^2 of ^{177}Lu-HuJ591.[346] A total of 10.6% of patients experienced ≥50% decline in prostate-specific antigen (PSA) and 36.2% experienced ≥30% decline in PSA. Median overall survival was 22.2 months for those with any PSA decline compared to 11.4 months for those with no decline. Unlabeled huJ591 has also been evaluated in several trials in patients with hormone refractory metastatic prostate cancer. The initial Phase I trial treated 14 patients with 4 weekly doses of huJ591 with dose levels of 25 mg/m^2, 50 mg/m^2, 100 mg/m^2, or 200 mg/m^2.[347] PSA stabilization was observed in 3 patients. This was followed by a pilot trial of 14 patients with each patient receiving four escalating doses of unlabeled Mab of 10 mg, 25 mg, 50 mg, and 100 mg.[348] Increasing ADCC activity was seen with increasing antibody dose. One patient demonstrated >50% reduction in PSA. Given the ability of huJ591 to mediate ADCC, a Phase II trial of huJ591 and low dose IL-2 therapy has been initiated with stabilization of PSA observed in some patients.[147]

Using radiotherapy and RIT as a means to enhance immunotherapy through other mechanisms has also received recent attention.[349,350] Tumor cell death after irradiation can release antigens that can then activate or potentiate an immune response against tumors.[349] Radiation therapy can alter the tumor cell phenotype, by increasing expression of tumor associated antigens, such as CEA, upregulate tumor chemokines and adhesion molecules,[351] and upregulate Fas and major histocompatibility complex (MHC) molecules expression, which can work in concert to enhance immune recognition.[352] Low-dose total body irradiation (TBI) in murine models can enhance effects of subsequent adoptive transfer of tumor-specific T cells by selectively depleting cell populations that compete for needed cytokines.[353] Charkraborty et al[354] evaluated the combination of anti-CEA RIT (^{90}Y-COL-1) and vaccine therapy in a transgenic mouse with colon cancer model for human CEA. The combination resulted in a significant increase in survival compared to either therapy alone. RIT resulted in an upregulation of Fas by tumor cells and an increase in infiltrating CEA-specific CD8$^+$ T cells in tumor.

Antibodies now used as part of standard regimens in nonhematologic malignancies are also being evaluated as potential radioimmunotherapeutics. This concept is attractive because these antibodies have known antitumor effects that can add to the cytotoxic effects of RIT. Trastuzumab (Herceptin) is one the first Mabs to be approved for use in the treatment of nonhematologic malignancies and recognizes epidermal growth factor receptor 2 (HER2/neu), which is overexpressed by 20% to 30% of breast cancers. Trastuzumab radiolabeled with the β-emitters ^{90}Y, ^{177}Lu, and ^{188}Re, the Auger electron emitter ^{111}In, and α-particle emitters ^{212}Pb, ^{211}At, and ^{225}Ac has been evaluated in in vitro and in vivo preclinical therapy studies with encouraging results.[89,355-361] Imaging doses of ^{111}In-trastuzumab were administered to 17 patients with metastatic Her2 overexpressing breast cancers.[357] The tumor detection rate was 45% with new tumor lesions detected in 13 of 15 evaluable patients.

Cetuximab, a monoclonal antibody directed against epidermal growth factor receptor (EGFR), is used in the treatment of head and neck cancers with radiotherapy and in colorectal cancer in combination with standard chemotherapy regimens. The antitumor effects of the antibody may also enhance the efficacy of radiotherapy,[362-364] although the exact mechanism is unclear. Preclinical in vivo studies have also reported increased RIT efficacy when combined with EGFR inhibiting agents.[306,365] Radiolabeled anti-EGFR Mabs have been evaluated in animal models and in a limited number of clinical trials to assess biodistribution, tumor targeting, and their potential as radioimmunotherapy agents. Goldenberg et al[366] evaluated biodistribution and tumor localization of ^{111}In-labeled murine 225 anti-EGFR in mice bearing a high EGFR-expressing vulvar squamous cell cancer tumors. This was followed by an imaging and biodistribution trial with ^{111}In-Mab 225 in 19 patients with squamous cell lung cancer.[367] At the 300-mg level, mean %ID of tumor was 3.1%, liver 21.6%, heart 4.3%, and bowel 24.5%. The low tumor uptake and low tumor to organ uptake ratios appear to limit the potential of Mab 225 as a RIT agent. In contrast to this, Milenic et al[368] evaluated ^{111}In-cetuximab in mice bearing a variety of tumor xenografts. For the human colon cancer line LS174T, tumor uptake at 72 hours was high at 52 %ID/g, with blood uptake of 10.6 %ID/g and liver uptake of 7.9 %ID/g. The authors concluded that ^{111}In-cetuximab may be a useful radioimmunoconjugate for therapy.

Bevacizumab, an anti-VEGF Mab, has been introduced as part of standard systemic therapy regimens for metastatic colorectal, lung, and breast cancers.[369,370] Preclinical models also report that bevacizumab combined with RIT can potentially increase antitumor effects compared to RIT alone.[275] Evaluation of bevacizumab as a possible radioimmunoconjugate for imaging and therapy is in the preclinical stages. Stollman et al[371] performed imaging and biodistribution studies in mice with LS174T colon cancer administered ^{111}In labeled bevacizumab. At 3 days postadministration, mean tumor uptake of ^{111}In-bevacizumab was 19.4 %ID/g, which is comparable to the levels observed for ^{111}In-anti-CEA antibodies evaluated in the same tumor-bearing mouse model. Bevacizumab labeled with zirconium-89 (^{89}Zr) or alpha-particle emitting radionuclides[372,373] have also been evaluated in vivo and have demonstrated targeting to tumor and successful tumor imaging.

Pretargeting Delivery Systems

Pretargeting or multistep approaches may overcome the limitations of direct-radiolabeled antibody therapy approaches. Pretargeting separates the antibody's slow pharmacokinetics from the rapid delivery of a therapeutic radionuclide ligand. The end result is an increase in the therapeutic ratio primarily through a decrease in radiation dose to marrow and normal tissue, allowing for increased administered activities. This strategy is described in more detail elsewhere in this chapter. Pioneering work used the high-binding affinity streptavidin- or avidin-biotin system in which an antibody-streptavidin conjugate or a biotinylated antibody is coupled to a reciprocal ligand bearing the therapeutic radionuclide.[374-376] Results using pretargeted approaches have been promising in animal models[377,378] and have been studied in the clinic.[48,379-386] However, immunogenicity to the bacterial-derived reagents, such as streptavadin, has limited the ability to deliver multiple administrations.

Bispecific antibodies provide an attractive alternative for pretargeting by fusing antitumor targeting to the capture of

the small molecular weight hapten.[387] Bispecific antibodies have one arm of the antibody recognizing the tumor antigen and the other recognizing the radiolabeled ligand. Although initial studies used chemically conjugated[388] or quadroma fusions,[389] recombinant DNA technology has enabled the production of human or humanized molecules to lower the potential for immunogenicity. The antihapten antibody can be highly specific for the radiometal-chelate complex, exhibiting vastly reduced binding affinity if a different metal is used to coordinate the complex.[390] To circumvent this metal specificity, antibodies against the hapten peptide, histamine-succinyl-glycine (HSG), have been generated, which is independent of the radionuclide or chelate.[391] This provides a platform technology that enables multivalency and multifunctionality, where for example, two antitumor Fabs can self-assemble with an anti-HSG Fab.[392]

eTable 22-5, available in the expanded chapter on the Expert Consult website, summarizes some of the clinical therapy trials performed to date using pretargeting approaches. Trials in colorectal, ovarian, lung, medullary thyroid, and brain cancers have been carried out with most trials reporting objective responses. Chatal et al[393] reported on 29 patients with metastatic medullary thyroid cancer treated using a bispecific anti-CEA Mab. The median overall survival for high-risk patients with a calcitonin doubling time of <2 years was 110 months, which compared favorably to the 61 months for historical controls. Recently, the same group reported on 42 patients with medullary thyroid cancer. A complete response was seen in 1 patient, stable disease in 31 patients, and significant increases in doubling times or decreases in levels of calcitonin or CEA were observed in 21 patients.[394] Grana et al,[384] using the anti-tenascin Mab BC-4, reported on 37 patients with newly diagnosed high-grade gliomas. After standard therapy of surgical resection and external beam radiotherapy, 19 patients received adjuvant intracavitary RIT. There was a significant improvement in median overall survival for grade-4 gliomas of 33.5 months with RIT versus 8 months without RIT. Results from pilot Phase I/II trials using pretargeting approaches are encouraging, and this approach warrants further investigation.

Regional Administration

Regional administration (intraperitoneal, intracavitary, intralesional, and intraarterial) to optimize uptake at the tumor site relative to dose-limiting normal organs has been extensively explored with the most encouraging results in the minimal tumor burden and adjuvant setting. eTable 22-6, available in the expanded chapter on the Expert Consult website, summarizes RIT trials that have administered therapy through the intraperitoneal (IP) route. Preclinical[395] and clinical[396] studies indicate that IP administration has pharmacologic advantages over intravenous administration for cancers confined to the peritoneal cavity because of reduced circulating activity and lower hematologic toxicity secondary to increased antibody uptake in tumor, particularly for small volume disease.[397,398]

The agent most extensively studied is ^{90}Y-HMFG1. Epenetos et al[399] first evaluated HMFG1, along with a panel of other antiovarian cancer antibodies radiolabeled with ^{131}I in patients with ovarian cancer after debulking surgery, first-line chemotherapy, and second-look laparoscopy. Objective responses were more frequent in patients with smaller tumors or lower tumor burden. This led to a Phase II trial evaluating adjuvant IP ^{90}Y-HMFG1 at 18 mCi/m^2 in patients with initial stage Ic-IV after surgery, first-line chemotherapy and negative second-look laparoscopy.[400] With a median follow-up of 59 months, a 5-year actuarial survival of 80% was reported that was significantly better than the 55% observed for a matched historical control group (p = 0.0035). This was followed by a multinational Phase III trial entering 447 patients with stage Ic-IV ovarian cancer with negative second-look laparoscopy after surgery and platinum-based chemotherapy. Patients were randomized to standard treatment versus standard treatment plus a single IP infusion of RIT (18 mCi/m^2).[401] With a median follow-up of 3.5 years, there was no significant difference in time to relapse, relapse-free survival, or overall survival between the two arms. The overall survival at 5 years was 55% to 60%, less than that reported in the Phase II study. The authors put forth a number of factors to explain the lack of benefit with RIT, including the fact the type of standard treatment varied with each center and that more patients received consolidative chemotherapy on the control arm than the RIT arm (19.7% versus 12.5%). A subsequent analysis reported a significant decrease in IP time to relapse and IP recurrence rates, which was offset by a significant increase in extraperitoneal time to relapse and recurrence rates.[402]

Strategies to improve on IP RIT in this population may involve more effective systemic therapy delivered concomitantly with IP RIT, multiple administrations of IP RIT or combined IP RIT-chemotherapy approaches that are currently being evaluated by a number of groups (see eTable 22-6). Meredith et al recently reported their long-term results of IP RIT in patients with ovarian cancer.[403] Ninety-two patients with persistent disease after debulking surgery and chemotherapy received IP ^{90}Y labeled or ^{177}Lu labeled CC49 either alone, combined with interferon to increase tumor TAG-72 antigen expression or combined with interferon and paclitaxel. A statistically significant improvement in progression free survival was seen in patients <60 years of age or with tumor nodules <2 cm in size. Use of interferon and paclitaxel, development of a HAMA response and use of ^{90}Y was associated with a trend toward improvement which did not reach statistical significance.

Regional delivery of RIT has also been evaluated in central nervous system (CNS) malignancies, primarily high-grade gliomas (eTable 22-7, available in the expanded chapter on the Expert Consult website). Studies have investigated intracavitary administration after surgical resection, intralesional, intraarterial, or intrathecal administration. Early efforts in patients with recurrent disease were encouraging, leading to trials evaluating this approach as adjuvant therapy in combination with standard surgical resection, external beam radiotherapy, and chemotherapy in patients with newly diagnosed high-grade gliomas. Reported toxicities have been acceptable and were primarily hematologic and neurologic, including temporary headache, seizure and worsening of neurologic symptoms, with a few studies reporting irreversible neurologic symptoms in a small subset of patients at maximum tolerated doses.[338,404] Intracavitary and intralesional delivery of radioiodinated antibodies against tenascin, an extracellular matrix protein expressed by gliomas, but not by normal brain tissue, has been evaluated as single-cycle therapy by investigators at Duke University and as multicycle therapy in Italy. Bigner et al have evaluated single administration of intracavitary ^{131}I-81C6[404,405] in recurrent and newly diagnosed high-grade gliomas (see eTable 22-7). This led to a Phase II adjuvant RIT trial.[338] Thirty-three patients with previously untreated high-grade gliomas received a single administration of 120 mCi ^{131}I-81C6 directly into the surgical resection cavity, followed by conventional radiation therapy and 1 year of alkylator-based chemotherapy. The average radiation dose from RIT to the 2-cm rim around the resection cavity was 48 Gy. A median survival of 86.7 weeks for all patients and 79.4 weeks for glioblastoma patients was observed.

A pilot study with ^{131}I-murine 81C6 was completed (see eTable 22-4)[320] where RIT was combined with standard therapy

eTABLE 22-5 Select RIT Trials Using Pretargeting Approaches

Study (First Author, Year)	Phase	Antigen	No. of Steps	Tumor Type
Kraeber-Bodere,[379] 1999	I/II	CEA	2 step Bispecific anti-CEA × anti-DTPA ^{131}I-bivalent hapten di-DTPA TL	Recurrent medullary thyroid
Vuillez,[380] 1999	I/II	CEA	Two step Bispecific anti-CEA × anti-DTPA ^{131}I-bivalent hapten di-DTPA TL	Small cell lung cancer
Kraeber-Bodere,[758] 2006	I	CEA	Two steps Bispecific anti-CEA × anti-DTPA ^{131}I-bivalent hapten di-DTPA TL	Medullary thyroid, colorectal, lung
Chatal,[393] 2006	Retrospective analysis	CEA	Two steps Bispecific anti-CEA × anti-DTPA ^{131}I-bivalent hapten di-DTPA TL	Medullary thyroid
Salaun,[394] 2012	II	CEA	Two steps Bispecific anti-CEA × anti-DTPA ^{131}I-bivalent hapten di-DTPA TL	Medullary thyroid
Grana,[386] 2004	pilot retrospective	CEA, TAG-72 and Mov18	Three step Biotinylated Mabs IP Avidin IP ^{90}Y-DOTA-biotin IP or IV	Ovarian; recurrent
Breitz,[759] 1998	I	Ep-CAM	Three step NR-LU-10-streptavidin HSA-galactose-biotin clearing agent ^{90}Y-DOTA-biotin	Adenocarcinoma (colon, prostate, breast, ovary)
Knox,[48] 2000	II	Ep-CAM	Three step NR-LU-10-streptavidin HSA-galactose-biotin clearing agent ^{90}Y-DOTA-biotin	Colon
Forerro-Torres,[709] 2005	Pilot	TAG-72	Three step Tetrameric scFv CC49-streptavidin Biotin clearing agent ^{90}Y-DOTA-biotin	Colorectal
Paganelli,[579] 1999	I	Tenascin	Three step BC4-biotinylated IV Avidin/streptavidin ^{90}Y-DOTA-biotin	Glioma, grade 3/4; recurrent
Paganelli,[382] 2001	I	Tenascin	Three step intracavitary therapy BC4-biotinylated Avidin ^{90}Y-DOTA-biotin	Recurrent gliomas
Grana,[384] 2002	Pilot	Tenascin	Three step BC4-biotinylated IV Avidin/streptavidin ^{90}Y-DOTA-biotin	Glioma, grade 3/4; newly diagnosed

CR, *complete response;* MR, *mixed or minor response;* OS, *overall survival;* PR, *partial response;* SD, *stable disease.*

No. of Pts	Objective Response	Other Antitumor Effects	Comments
26	0/17	4/17 ↓ calcitonin 5/17 ↓ pain 5/17 MR	RIT 24 mCi/m^2-60 mCi/m^2
14	2/12 PR (1 near CR)	1/12 SD	RIT 32 mCi-180 mCi
22		9/20 SD	RIT 40 mCi/m^2 or 75 mCi/m^2
29		For high-risk patients with calcitonin doubling time <2 years median OS 110 months for RIT vs. 61 months ($p < 0.03$) for untreated historical controls. If bone marrow involved survival at 10 years 83% vs. 14% ($p < 0.023$)	RIT 38 mCi-112 mCi
42	1/42 CR	31/42 SD 21/27 ≥ 100% ↑ in calcitonin or CEA doubling time or prolonged decrease in calcitonin or CEA	RIT 63 mCi-109 mCi
38	3/38 CR + PR	12/38 SD	RIT 10 mCi-100 mCi
40	2/40 PR	4/40 MR	RIT 10 mCi/m^2-140 mCi/m^2
25	2/25 PR	4/25 SD	RIT 110 mCi/m^2 GI toxicity dose limiting
6		2/6 SD	RIT 10 mCi/m^2
48	3/48 CR 5/48 PR	4/48 MR 25/48 SD Median survival 11 months grade 4 19 months grade 3	RIT 60 mCi/m^2-80 mCi/m^2 2 cycles
24	2/24 PR	2/24 MR 12/24 SD	RIT 15 mCi-30 mCi 2 cycles Surgical debulking prior to RIT
37 (17 grade 3 and 20 grade 4)		Grade 4: median survival 33.5 months with RIT vs. 8 months no RIT Grade 3; median survival not reached with RIT vs. 33 months no RIT. Differences significant	All treated with total resection and RT 19 received adjuvant RIT 18 no RIT RIT 60 mCi/m^2

eTABLE 22-6 Select Intraperitoneal RIT Trials

Study (First Author), Year	Antibody	Antigen	Phase	Tumor Type
Stewart,[399] 1989	^{131}I-HMFG1, AUA1, HMFG2, HE17E2	Variety	I/II	Ovary (after surgery, chemotherapy and second-look laparoscopy)
Stewart,[760] 1990	^{90}Y-HMFG1, AUA1	MUC1	I/II	Ovary (after surgery, chemotherapy, and second-look laparoscopy)
Hird,[713] 1993	^{90}Y-HMFG1	MUC1	I/II	Ovary (after surgery, chemotherapy, and second-look laparoscopy)
Nicholson,[400] 1998	^{90}Y-HMFG1	MUC1	II	Ovary (after surgery, chemotherapy, and negative second-look laparoscopy)
Epenetos,[570] 2000	^{90}Y-HMFG1	MUC1	II	Ovary (after surgery, chemotherapy, and negative second-look laparoscopy)
Verheijen,[401] 2006	^{90}Y-HMFG1	MUC1	III	Ovary (after surgery, chemotherapy, and negative second-look laparoscopy) then randomized to standard therapy vs. standard therapy + RIT
Meredith,[761] 1998	^{177}Lu-CC49	TAG-72	I	Ovary (residual disease at second-look laparoscopy)
Rosenblum,[762] 1999	^{90}Y-B72.3	TAG-72	I	Ovary, fallopian tube, papillary serous
Muto,[763] 1992	^{131}I-OC125 F(ab′)$_2$	CA-125	I	Ovary (refractory)
Mahe,[764] 1999	^{131}I-OC125 F(ab′)$_2$	CA-125	II	Ovary (<0.5 cm residual after second-look laparoscopy)
Jacobs,[712] 1993	^{186}Re-NR-LU-10	Ep-CAM	I	Ovary (recurrent or persistent)
Crippa,[714] 1995	^{131}I-Mov18	Folate receptor	I	Ovary (<0.5 cm residual after second-look laparoscopy)
Riva,[765] 1991	^{131}I-FO23C5, BW494/32, B72.3,AUA1	CEA TAG-72	II	Colorectal
Wong (unpublished)	^{90}Y-cT84.66	CEA	I	GI, pseudomyxoma
Buckman,[766] 1992	^{131}I-mab 2G3	Mucin	I/II	Malignant ascites—ovary, breast

OS, *Overall survival;* CR, *complete response;* PR, *partial response;* NED, *no evidence of disease;* IP, *intraperitoneal.*

Patient No.	Objective Responses	Other Antitumor Effects
36	0/10 if >2 cm tumors 2/15 PR if <2 cm tumors 3/6 CR if positive cytology 4/4 NED at 6-12 months if negative cytology	
25	0/3 if >2 cm 1/10 PR if <2 cm 0/1 if positive cytology 10/11 NED at 6-15 months if negative cytology	
52	median survival 11 months if >2 cm at second look (n = 14) median survival IIB pts with negative second look (n = 15) not reached and significantly better compared to matched historical controls	
25	5 yr actuarial survival 80% vs. 55% matched historical controls (p = 0.0035)	
21	73% survival 10 years median survival not reached	
447	no difference in OS or time to relapse between two arms	RIT resulted in a significant ↓ in IP recurrence but an offsetting ↑ in extraperitoneal recurrences in the subgroup with residual disease after primary surgery (Oei, Verheijen et al. 2007[422])
27	1/12 PR if >1 cm 3/15 NED for 3-5 years if <1 cm or positive cytology	
58	2/57 CR 9-12 mos. (both <3 cm)	2/57 minor 30/57 stable median 6 mo.
29		1/28 NED at 41 mo.
6		3/6 stable
17	4/7 PR if ≤1 cm 0/10 if >1 cm (p < 0.05)	4/13 ↓ CA-125
16	5/16 CR	6/16 stable
16	2/15 CR (6-12 mo) 2/15 PR (3-16 mo)	3/15 stable 6/10 ↓ CEA
13		5/13 stable 2/13 resolution of ascites
9		3/4 temporary ↓ ascites if >50 mCi administered

eTABLE 22-7 Select CNS RIT Trials

Study, Year (First Author)	Phase	Antibody	Antigen	Route	Tumor Type
Brady,[419] 1990	I	^{125}I-425	EGFR	IA	Glioma, grade II-IV recurrent
Li,[422] 2010	II	^{125}I-425	EGFR	IV	Glioma, IV newly diagnosed
Kim,[423] 2013	II	^{125}I-425	EGFR	IV	Glioma, III newly diagnosed
Kalofonos,[418] 1989	I	^{131}I-EGFR1 or H17E2	EGFR, Placental alkaline phosphatase	IV or IA	Glioma, grade III/IV Recurrent
Casaco,[412] 2008	I	^{188}Re-h-R3	EGFR	IC	Glioma, grade III/IV recurrent
Bigner,[405] 1998	I	^{131}I-81C6	tenascin	IC	Recurrent glioma or metastases amenable to surgery
Cokgor,[404] 2000	I	^{131}I-81C6	tenascin	IC	Glioma, grade III/IV newly diagnosed
Reardon,[338] 2002	II	^{131}I-81C6	tenascin	IC	Glioma, grade III/IV newly diagnosed
Reardon,[767] 2006	II	^{131}I-81C6	tenascin	IC	Glioma, grade III/IV recurrent
Zalutsky,[91] 2008	I	^{211}At-ch81C6	tenascin	IC	Glioma, grade III/IV recurrent
Riva,[407] 1995	I	^{131}I-BC-2 and BC-4	tenascin	IC and Intralesional	Glioma, grade III/IV recurrent and newly diagnosed
Riva,[768] 1999	I/II	^{131}I-BC-2 and BC-4	tenascin	IC and Intralesional	Glioma, grade III/IV recurrent and newly diagnosed
Goetz,[410] 2003	Pilot	^{131}I or ^{90}Y-BC-4	tenascin	IC	Glioma, grade III/IV newly diagnosed
Brown,[416] 1996	I	^{131}I-81C6	tenascin	IT or IC	High-grade glioma, ependymoma, medulloblastoma
Papanastassiou,[413] 1993	pilot	^{131}I-ERIC-1	NCAM	IC	Glioma, grade III/IV recurrent
Hopkins,[414] 1995	pilot	^{90}Y-ERIC-1	NCAM	IC	Glioma, grade III/IV recurrent
Shapiro,[411] 2006	I	^{131}I-chTNT-1/B	DNA Histone H1	intralesional	Glioma grade III, IV recurrent
Shapiro,[411] 2006	II	^{131}I-chTNT-1/B	DNA Histone H1	intralesional	Glioma grade III, IV recurrent, newly diagnosed
Kemshead,[417] 1996	pilot	^{131}I-HMFG-1, Mel-14, M340,	multiple	IT	Meningeal disease carcinomas, melanoma and PNET
Pizer,[415] 1991	pilot	^{131}I-UJ181.4, M340, UJ13A, Mel-14	multiple	IT or intra-ventricular	Relapsed medulloblastoma

C, *Chemotherapy;* CR, *complete response;* IA, *intraarterial;* IC, *intracavitary;* IT, *intrathecal;* IV, *intravenous;* NED, *no evidence of disease* PR, *partial response;* RT, *external beam radiotherapy;* S, *surgery;* TMZ, *temozolomide.*

Patient No.	Other Therapies	Antitumor Effects	Median Overall Survival
15		1/12 CR 11/12 stable	8 mos. median for whole group
192	S, RT, C (59 pts) TMZ (60 pts)		15.7 mos.
80	S, RT		55.6 mos.
10			1/10 NED for 3+ years;
11	S	2/11 CR 1/11 PR	6.1 months for whole group
34	S	14/33 stable	60 weeks for whole group 56 weeks for grade IV
42	S, RT, C		79 weeks for whole group 69 weeks for grade IV
32	S, RT, C		86.7 weeks for whole group 79.4 weeks for grade IV
43	S		69 weeks for whole group 64 weeks for grade IV
18	S		54 weeks for grade IV 52 weeks for grade III
50	S, RT	3/50 CR 6/50 PR 11/50 stable 11/50 NED mean 13 mos.	20 months for whole group 18 months recurrent 23 months newly diagnosed
111	S, RT, C (56 pts)	1/74 CR 9/74 PR 10/74 stable 23/74 NED	19 months for grade IV
37	S, RT		17 mos. for grade IV For grade III, median not reached, estimate 85% 5 year survival
31		1/31 PR 13/31 stable	
7		3/7 stable	
15			6 mos. median for whole group 3 alive at 4,6, and 26 months
12			27.3 weeks for grade IV 138 weeks for grade III
39			23 weeks for grade IV, recurrent
27		3/7 CR carcinoma pts 7/18 PR in PNET	
14		2/11 CR 2/11 PR 1/11 stable	

in 21 patients with newly diagnosed high-grade gliomas. After surgical resection, RIT was administered into the surgical cavity to deliver 44 Gy to the cavity rim, followed by 55 Gy to 60 Gy external beam radiotherapy and chemotherapy. Toxicities were acceptable demonstrating the feasibility of this combined modality first-line therapy approach. With a median follow-up of 151 weeks, the median overall survival was 90.6 weeks for patients with glioblastomas. A Phase I study evaluated a ^{131}I labeled chimeric version of 81C6 in a similar combined modality approach also demonstrating encouraging results (see eTable 22-4).[406] Finally, chimeric 81C6 radiolabeled with the α-emitter ^{211}At is being evaluated in a Phase I setting.[91] Riva et al in Italy have also investigated intracavitary and intralesional radiolabeled antitenascin RIT in patients with resected high-grade glioma (see eTable 22-7).[407-410] Recent efforts have focused on pretargeting approaches combined with chemotherapy (see eTable 22-4).[313,314] In a Phase I/II trial of 73 patients with recurrent glioblastomas, 38 received RIT alone versus 35 who received RIT and temozolomide. A median of three cycles of therapy were administered. With RIT and temozolomide the overall survival was 25 months and progression-free survival 10 months, which compared favorably to the RIT alone group with overall survival of 17.5 months and progression-free survival of 5 months.

Other antibodies have also been evaluated in a similar approach[411,412] with mean doses to the cavity rim of 5120 cGy[413] and 5500 cGy.[414] In addition, regional intrathecal administration has been evaluated in meningeal carcinomatosis and medulloblastoma with objective responses observed.[415-417] CNS malignancies have also been treated through intraarterial, intravenous, and intracavitary approaches using antibodies directed against EGFR.[412,418,419] Brady et al[337,412,418-421] have administered ^{125}I-Mab 425, an internalizing murine IgG_{2a} directed against EGFR, in patients with high-grade gliomas (see eTable 22-7). A Phase II study was conducted in 192 patients with newly diagnosed glioblastoma multiforme who received adjuvant RIT using ^{125}I-Mab 425 6 weeks after conventional radiotherapy and debulking surgery.[422] Approximately 31% received nitrosoureas and another 31% temozolomide. The median survival was 15.7 months. For the subgroups receiving ^{125}I-Mab 425 alone versus ^{125}I-Mab 425 and temozolomide, the median survival was 14.5 versus 20.2 months, respectively. Median survival for 80 patients with anaplastic astrocytoma was 55.6 months and 5 year survival 47% (eTable 22-7).[423]

Finally, hepatic arterial delivery of RIT in hepatocellular carcinoma has been investigated. Zeng et al reported their single-institution experience and observed a significantly higher rate of conversion to resectability for the group receiving hepatic arterial ^{131}I-Hepama-1 RIT compared to patients receiving hepatic arterial 5-FU, cisplatin, and doxorubicin[424] or chemoembolization and 46 Gy external beam radiotherapy.[425] A 5-year survival rate of 28.1% for the RIT group was reported, which compared favorably to 9.1% for the chemotherapy group. In a recent multicenter Phase I/II trial, 134 patients with unresectable hepatoma received one to two cycles of ^{131}I-metiximab via the hepatic artery, with a reported 8.2% partial response rate and median survival of 19 months.[426]

High LET Alpha-Particle Emitters

There has been increasing interest in evaluating RIT using α-particle emitters in patients with nonhematologic malignancies. The high LET of alpha particles increase the radiobiologic effect of the targeted dose. Although their short range may limit efficacy in large macroscopic tumors, there may be use in the setting of microscopic or small volume disease. Their short range limits dose to normal tissues, potentially reducing dose-limiting toxicities traditionally associated with RIT using β-emitting radionuclides.

Zalutsky et al evaluated the feasibility and safety of intracavitary administration of the antitenascin chimeric antibody ^{211}At-ch81C6 in 18 patients with recurrent grade II/IV gliomas after surgical resection (see eTable 22-7).[91] No dose-limiting toxicities were observed. Median survival for patients with glioblastoma multiforme was 54 weeks. Andersson et al administered ^{211}At-MX35 $F(ab')_2$ to 9 patients with recurrent ovarian cancer in complete clinical remission after second-line chemotherapy and after negative second-look laparoscopy.[427] The antigen recognized by MX35 is a sodium dependent phosphate transport protein overexpressed by ovarian cancers (NaPi2b). No dose-limiting toxicities were observed. Absorbed dose to the peritoneum was 15.6 and red marrow 0.14 mGy/MBq/L. The authors concluded that therapeutic doses to microscopic IP disease were achievable without significant toxicity. Finally, Meredith et al at the University of Alabama are evaluating in a Phase I trial IP ^{212}Pb-trastuzumab in HER-2 positive intraperitoneal cancers.

Allen et al have evaluated systemic α-particle RIT using ^{213}Bi-cDTPA-9.2.27 in patients with stage IV metastatic melanoma or in-transit metastases (see eTable 22-1).[428] Thirty-eight patients were treated with 1.25 mCi to 25 mCi in this Phase I study. Partial responses were observed in 10% and stable disease of at least 8 weeks' duration seen in 40%. Intralesional administration of ^{213}Bi-cDTPA-9.2.27 has been reported by the same group in 16 patients.[429]

Summary of Solid Tumors

As one of the first forms of targeted therapy, the introduction of radiolabeled antibodies into the clinic was understandably accompanied with high expectations. What has been learned through preclinical and clinical studies is a better understanding of the limitations and the challenges associated with RIT, many of which apply to both nonhematologic as well as hematologic malignancies. As with other emerging therapies, RIT will likely find its role not as monotherapy, but rather as a therapy used rationally in combination with other modalities. Although a number of strategies to increase tumor uptake and antitumor effects of these agents have proven encouraging, it is likely that no one strategy will be sufficient and that multiple strategies will be needed to realize clinically important results in the solid tumor setting. As clinical trials suggest, RIT will likely be best defined in the minimal tumor burden or adjuvant setting.

RIT OF LYMPHOMA AND LEUKEMIA

RIT has been most successful for the treatment of lymphoma and leukemia. Representative clinical trials using RIT for B-cell NHL and T-cell lymphoma and leukemia have been summarized in eTables 22-8[29-31,186,188,430-455] and 22-9[456-459] (available in the expanded chapter on the Expert Consult website) in terms of general study design (nonmyeloablative versus myeloablative), radionuclide and antibody used, number of treatments, number of treated evaluable patients, and responses. Myeloablative studies have included bone marrow or peripheral stem cell collection and reinfusion. These trials differ in terms of eligibility criteria, antibody and radionuclides used, dose, number of treatments, doses of unlabeled antibody preinfused or coinfused, and the biodistribution or dosimetry estimations required for administration of a therapeutic dose of radiolabeled antibody. The results summarized in eTable 22-8 are particularly promising and show a relatively high response rate with a number of durable PRs and CRs, with a subset of these responses ongoing at ≥5 yrs, and many

eTABLE 22-8 Radioimmunotherapy Trials for Relapsed B-Cell Lymphoma

Antibody (Cumulative mg)	Radionuclide (Cumulative mCi)	Treatments	No. of Evaluable Patients	Responses	References
NONMYELOABLATIVE					
LYM-1 (8-676)	^{131}I (26-1044) ^{131}I (40/m^2/ treatment-100/m^2/ treatment)	1-16 1-4	57 21	11 CR, 20 PR 7 CR, 4 PR	Lewis,[435] DeNardo,[439] DeNardo[769]
LYM-1 (30-67)	^{131}I (50-267)	1-2	13	4 PR	Kuzel,[433] Meredith[434]
LYM-1 (17-290)	^{67}Cu (40-438) ^{90}Y (0.185 GBq/ m^2-0.370 GBq/m^2)	1-4 1	12 8	1 CR, 4 PR, 2 MR 5 PR or SD	O'Donnell,[443] O'Donnell,[444] O'Donnell[446]
LL2- (epratuzumab) (1.1 mg IgG-157 mg F(ab^1)$_2$)	^{131}I (15-343)	1-7	17	2 CR, 2 PR, 2 MR	Juweid[188]
LL2 (N/A)†	^{186}Re (0.5 GBq/ m^2-2.0 GBq/m^2)	1	15	1 CR, 4 PR	Postema[454]
Humanized LL-2 (41-139)	^{131}I (15-59) ^{90}Y (15 mCi/ m^2-22.5 mCi/m^2)	1 1	13 13	1 CR, 1 PR 8 objective responses	Juweid[442] Chatal[455]
LL2 (0-160)	^{131}I (30 mCi/ m^2-120 mCi/m^2)	2-8	21	5 CR, 2 PR	Vose[438]
MB-1 (40)	^{131}I (25-161)	1	10	1 CR, 2 PR, 1 MR	Kaminski[431]
OKB7 (25)	^{131}I (90-200)	3-4	18	1 PR, 12 MR	Czuczman[432]
Anti-idiotype (1000-4050)	^{90}Y (10-54)	1-4	9	2 CR, 1 PR, 1 MR	Parker,[430] White[437]
Tositumomab (2-110)	^{90}Y (14-22)	1	4	1 CR, 1 PR	Knox[29]
Tositumomab (10-518)	^{131}I (33-161)	1	59	20 CR, 22 PR	Kaminski[445]
Tositumomab (484-487)	^{131}I (45-177)	1	47	15 CR, 12 PR	Vose[447]
Tositumomab (450-506)	^{131}I (0 ≤ 198)	1	60	10 CR, 29 PR	Kaminski[449]
Tositumomab (485)	^{131}I (N/A)	1	42	14 CR, 9 PR	Davis[453]
Tositumomab (485)	^{131}I (N/A)	1	38	8 CR, 14 PR	Horning[450]
Chimeric C2B8 (Rituximab; cumulative mg N/A)	^{90}Y (51-109)	1	7	3 CR, 1 PR, 2 MR	Weiden[448]
Ibritumomab Tiuxetan 2B8 (55-294)	^{90}Y (20-53)	1-2	14	5 CR, 6 PR	Knox[29*]
Ibritumomab Tiuxetan 2B8 (Rituximab; 100-250 mg/m^2 × 2)	^{90}Y (12-32)	1	50	13 CR, 21 PR	Witzig[30]
Ibritumomab Tiuxetan 2B8 (Rituximab; 250 mg/m^2 × 2)	^{90}Y (≤32)	1	73	25 CR, 33 PR	Witzig[190]
Ibritumomab Tiuxetan 2B8 (Rituximab; 250 mg/m^2 × 2)	^{90}Y (N/A)	1	54	8 CR, 32 PR	Witzig[452]
Rituximab	^{131}I (200)	1	24	3 CR, 2 PR	Kang[466]
Rituximab	^{131}I (≥200, median 501)	1-6	31	13 CR, 8 PR	Kang[467]
Rituximab	^{177}Lu-DOTA (740 mBq/ m^2-1850 mBq/m^2)	1	29	6 CR, 9 PR	Forrer[468]

Adapted from Knox SJ: Radioimmunotherapy of the non-Hodgkin's lymphomas. Semin Radiat Oncol 5(4):331–341, 1995.

**A Phase I dose escalation trial; two patients required stem cell reinfusion of four patients treated at the highest dose (50 mCi).*

†*N/A, not available.*

CR, *complete response;* MR, *minor response;* PR, *partial response.*

eTABLE 22-9 Radioimmunotherapy Trials for T-Cell Lymphoma and Leukemia

Radionuclide (Cumulative mCi)	Antibody (Cumulative mg)	Treatments	No. of Evaluable Patients	Responses	References
NON-MYELOABLATIVE					
^{131}I (25-50)	T101 (10)	1	4	0[a]	Zimmer[36] [b]
^{131}I (100-150)	T101 (10-16)	1[c]	6	2 PR, 4 MR	Rosen[457]
^{90}Y (N/A)[d]	T101 (N/A)[d]	1	6	3 CR	Raubitschek[458] [e]
^{90}Y (5-15)	Anti-Tac (2-10)	1-9	16	2 CR, 9 PR	Waldmann[459] [f]

Adapted from Knox SJ: Radioimmunotherapy of the non-Hodgkin's lymphomas. Semin Radiat Oncol 5(4):331–341.

CR, *complete response;* MR, *minor response;* PR, *partial response.*

[a]*No objective clinical responses were observed; however, a transient decrease in peripheral blood lymphocytes was observed in 1 patient.*

[b]*CLL, chronic lymphocytic leukemia.*

[c]*Three patients were subsequently retreated, but responses shown are for the first treatment with a single dose of ^{131}I-T101.*

[d]*N/A, not available.*

[e]*CLL, Chronic lymphocytic leukemia; CTCL, cutaneous T-cell lymphoma.*

[f]*Adult T-cell leukemia.*

patients experiencing remissions of longer duration than had been achieved with previous chemotherapy. The highest overall response and CR rates and the longest remission durations have been reported in patients treated with high doses of radiolabeled antibody in single doses in conjunction with autologous bone marrow transplantation (BMT) or stem cell transplantation (SCT).[31,436,441,460,461] Although higher doses of RIT have tended to be more efficacious, there has not been a direct correlation between dose and response in most reported studies. These results are particularly encouraging because all of the patients treated in these trials have had recurrent disease following at least one form of conventional therapy. Many of the patients had failed multiple courses of therapy, and some were unable to tolerate additional chemotherapy for a variety of reasons.

Two anti-CD20 Mabs conjugated to either ^{131}I (^{131}I-tositumomab or Bexxar) or ^{90}Y (^{90}Y-ibritumomab tiuxetan or Zevalin) have been approved by the FDA for patients with relapsed or refractory low-grade or transformed B-cell NHL,[447,449,451] and have demonstrated efficacy in patients even after the use of rituximab (Rituxan).[450,452] ^{90}Y-ibritumomab was also approved for upfront treatment of previously untreated patients with low-grade B-cell NHL in 2009. The Bexxar (tositumomab and ^{131}I-tositumomab) regimen consists of the sequential administration of a dose of unlabeled murine Mab, tositumomab, to optimize biodistribution and increase tumor localization of the ^{131}I-tositumomab that is administered thereafter.[184,462] An initial biodistribution study uses a dosimetric dose to allow for the calculation of a patient specific therapeutic dose to deliver an absorbed whole-body dose of 75 cGy in patients with a platelet count of ≥150,000/μL. FDA approval was based on a study in 40 patients with relapsed/refractory disease after rituximab therapy and was further supported by the demonstration of durable responses in four other studies enrolling 190 patients with relapsed/refractory disease following chemotherapy. Objective tumor responses occurred in approximately 60% of patients, with CRs in approximately 30%. Median response durations have been in excess of 12 months, with occasional durable complete responses lasting for years.[447,449,463,464] Despite these encouraging results, manufacturing of ^{131}I-toxitumomab was discontinued in 2014 because of its limited clinical use.

The ^{90}Y-ibritumomab tiuxetan or Zevalin regimen uses the chimeric anti-CD20 antibody rituximab for predosing. The pivotal study that supported FDA approval of Zevalin randomized 143 patients to receive either rituximab alone (four weekly doses of 375 mg/m^2, as it is used as a therapeutic agent) or RIT with a lower dose (250 mg/m^2) of rituximab for purposes of optimizing the biodistribution of Indium-111 (^{111}In)-labeled ibritumomab tiuxetan for an imaging/dosimetry study. Seven days later patients received 250 mg/m^2 rituximab followed by 0.4 mCi/kg ^{90}Y-labeled ibritumomab tiuxetan. Based on the International Workshop NHL Response Criteria, the overall response rate was 80% for ^{90}Y-ibrutuomab tiuxetan versus 56% in the rituximab arm ($p = 0.002$). CRs were achieved in 30% of patients with ^{90}Y-ibrutuomab tiuxetan versus 16% for rituximab ($p = 0.04$).[190] Of those patients who have since progressed, the time to next therapy was 11.5 months after ^{90}Y-ibrutuomab tiuxetan and 7.8 months after rituximab.

Two randomized studies of either ^{90}Y-anti-CD20 Mab[190] or ^{131}I-anti-CD20 Mab[453] versus unlabeled anti-CD20 Mab have demonstrated the importance of the radiation associated with RIT as a determinant of both the efficacy and toxicity of the RIT treatment. The radiobiology of RIT targeting the CD20 antigen is critical to tumor and normal tissue effects associated with this therapy and has been reviewed.[101] Retreatment with radiolabeled anti-CD20 Mab has also been reported to be well tolerated and efficacious in a subset of patients.[29,438,465]

The optimal time to use RIT in the course of NHL has not been defined.[12,469] A trial using ^{131}I-tositumomab as primary therapy for low-grade disease in 76 previously untreated follicular lymphoma patients has shown impressive results, with a response rate of 95% and evidence of conversion to molecular negativity by polymerase chain reaction (PCR) testing for Bcl-2 rearrangements in 80% of patients with a complete response. Actuarial 5-year survival was 59% with a median PFS of 6.1 years.[470] Patients who have failed BMT have experienced excellent tumor responses to RIT as well.[455,471] In addition, RIT is also being studied in other histologies, such as diffuse large cell lymphoma (DLCL), mantle cell lymphoma,[472] early-stage extranodal indolent ocular adnexal lymphoma,[473] and multiple myeloma[474] with encouraging results.[475-477] For example, in a study of 104 patients with relapsed B-cell DLCL following treatment with either chemotherapy alone, or chemotherapy and rituximab, the overall response rate was 44%, with median overall survival of approximately 22 months for patients previously treated with chemotherapy, and 4.6 months for patients who had failed chemotherapy plus rituximab.[475]

RIT has also been useful as a preparatory regimen for transplantation.[31,436,441,460,461] In a clinical trial comparing high dose RIT with conventional high dose chemotherapy with hematopoietic SCT, the RIT group had higher overall survival and progression-free survival than the group of patients who received the conventional preparatory regimen for transplantation.[478] Other trials of ^{131}I-tositumomab combined with etoposide, cyclophosphamide, and autologous stem cell transplant (ASCT) compared with TBI combined with etoposide, cyclophosphamide, and ASCT also demonstrated improved overall survival and progression-free survival in the group receiving RIT.[479] The same regimen has yielded encouraging results in patients with mantle cell lymphoma, with 3-year progression-free survival of 61%.[480] ^{131}I-tositumomab has also been studied in combination with BCNU, etoposide, Ara-C, and melphalan (BEAM) followed by ASCT. Toxicity was similar to BEAM alone. The CR rate was 57% and overall response rate was 65%, with 3-year event-free survival 39% and overall survival 55%.[481] However, when conditioning with standard doses of ^{131}I-tositumomab added to BEAM before ASCT was compared to rituximab and BEAM in 224 patients with relapsed diffuse large B-cell lymphoma, no difference in progression-free survival or overall survival was seen.[482] The lack of benefit may be the result of decreased administered activity of ^{131}I compared to other myeloablative transplant approaches. In another study, ^{131}I-rituximab combined with BEAM conditioning and ASCT for relapsed/refractory aggressive non-Hodgkin's lymphoma resulted in a very high CR rate (15/16), with 12 out of 16 patients alive and disease-free at a median of 44 months posttransplant.[483]

A similar approach using ^{90}Y-ibritumomab with BEAM has also yielded promising results.[484] In a matched-cohort analysis of ^{90}Y-ibritumomab with BEAM versus 12-Gy fractionated TBI with etoposide and cyclophosphamide as a conditioning regimen for ASCT in diffuse large cell lymphoma, the 4-year cumulative incidence of relapse/progression was similar, but overall survival at 4 years was 81% for the RIT group compared with 52.7% for the TBI group, perhaps as a result, in part, of the lower incidence of cardiac toxicity in the TBI group.[485] Another study of ^{90}Y-ibritumomab, fludarabine, and 2 Gy TBI as a conditioning regimen for allogeneic transplantation for patients with persistent high-risk B-cell lymphoma resulted in an estimated 30-month survival, progression-free survival, and nonrelapse mortality of 54.1%, 31.1%, and 15.9%, respectively, with an acceptable toxicity profile.[486] ^{90}Y-ibritumomab therapy with stem cell support is also being studied with encouraging early results in studies of RIT as part of a reduced intensity conditioning regimen for allogeneic

^{131}I-rituximab has also been studied in patients with relapsed/refractory B-cell non-Hodgkin's lymphoma, with a response rate of 46%, and median progression-free survival of 4.5 months in patients with low-grade B-cell lymphoma, compared with only a 9% response rate and 1.3 month progression-free survival in patients with diffuse large B-cell lymphoma.[466] Repeat treatment with ^{131}I-rituximab was well tolerated and resulted in a two-fold increase in response rate and median duration of response.[467] Recently, ^{177}Lu-DOTA-rituximab was also studied for safety and feasibility for the treatment of follicular and mantle cell lymphoma with encouraging results.[468]

stem cell transplant.[487,488] Investigators at M. D. Anderson Cancer Center found a 3-year progression-free survival of 87% for chemosensitive patients with relapsed follicular lymphoma after conditioning with ^{90}Y-ibritumomab tiuxetan, fludarabine, and cyclophosphamide and an 80% 3-year progression-free survival for patients with chemo-refractory disease.[489] A variety of extended Phase II trials using RIT combined with high-dose chemotherapy are ongoing to better define the safety and efficacy of this therapeutic approach, which may be further improved by radiobiological optimization of RIT for stem cell transplantation.[490]

Other approaches to increase the efficacy of RIT in B-cell NHL include the use of a pretargeting regimen using an anti-CD20-fusion peptide, which is discussed later in this chapter.[385] This approach is based on the dissociation of the delivery of antibody from the delivery of radionuclide, with a clearing agent used in between to eliminate unbound circulating antibody that if radiolabeled, would be a source of nonspecific radiation and therefore toxicity. Proof of principle for this platform technology has been demonstrated in a clinical trial with significantly increased tumor-to–whole-body, tumor-to-blood, and tumor-to-normal organ ratios than achievable with directly labeled Mab.[385]

Another area of active investigation is the study of RIT as part of a combined modality approach with either nonmyeloablative chemotherapy or conventional radiation therapy.[491,492] For example, the combination of low-dose–involved field radiation therapy to sites of active disease ≥2.5 cm prior to RIT in patients with relapsed/refractory B-cell lymphoma was well tolerated, did not add toxicity to that of RIT alone, and resulted in excellent progression-free survival, especially in patients with a CR.[493] In addition, a small study of 18 Gy whole brain radiation combined with RIT following CNS chemotherapy resulted in a 100% CR rate, with no relapses after 12 to 20 months and no associated neurocognitive function decline.[494] Numerous trials have explored the combination of RIT with a variety of chemotherapy drugs. The combination of RIT, CHOP, and involved field radiation therapy in aggressive DLCL (SWOG 0313) was reported to result in outcomes that compared favorably to historical experience with relatively short follow-up.[495] Additionally, combination fludarabine or CHOP chemotherapy with RIT as upfront therapy in Phase II trials has resulted in high overall response and excellent progression-free survival.[496] In a recent Phase II trial (SWOG 9911) of CHOP chemotherapy combined with ^{131}I-tositumomab as consolidation in 90 patients newly diagnosed with follicular non-Hodgkin's lymphoma (NHL), the CR rate was 39% with CHOP alone and 69% for patients receiving both CHOP and RIT, respectively. Five-year progression-free survival and overall survival was 67% and 87%, respectively, for patients receiving the combination therapy.[491] These results provided the rationale for a Phase III trial (SWOG 0016) comparing CHOP plus rituximab with CHOP followed by ^{131}I-tositumomab. In this trial, with a median follow up of 4.9 years, the 2-year estimated progression-free survival was 76% for the CHOP-R arm and 80% for the CHOP-RIT arm (p = 0.11), with 2-year overall survival 97% for CHOP-R and 93% for CHOP-RIT (p = 0.08).[497] Chemotherapy combined with RIT has also been studied in 20 previously untreated elderly patients with DLBCL, using CHOP and ^{90}Y-ibritumomab tiuxetan.[498] In this Phase II trial the overall response rate was 100%, with 95% CRs. Importantly, four of five patients with an initial PR to CHOP alone, converted to CRs following consolidative RIT. With median follow-up of 15 months, 2 year progression-free survival is 75% with 2-year overall survival of 95%. A randomized Phase III study of induction chemotherapy followed by observation or ^{90}Y-ibritumomab in 409 patients with advanced stage follicular NHL, with a median of 7.3 years follow up, demonstrated that ^{90}Y-ibritumomab consolidation after PR or CR/CR$_u$ following induction resulted in a 3-year benefit in median progression-free survival, with a durable 19% progression-free survival advantage at 8 years, and improved median time to next treatment by 5.1 years.[499]

Other studies have investigated the role of ^{90}Y-ibritumomab therapy as consolidative therapy following CHOP, and CHOP/rituximab therapy, respectively, in early stage disease. In a Phase II trial of R-CHOP followed by ^{90}Y-ibritumomab in patients with previously untreated stages I and II diffuse large cell NHL (ECOG E3402), 88% of patients who received both R-CHOP and RIT were progression free with ongoing complete responses, and 98% were alive at 4 years.[500] Other data suggests that consolidative RIT with ^{90}Y-ibritumomab tiuxetan may prolong survival of patients with chemosensitive mantle cell lymphoma who achieve a clinical response after chemotherapy.[501] Indeed, data from multiple trials have demonstrated that consolidative RIT increases rates of complete remission and duration of response.[502] Encouraging results have also been reported in patients with untreated mantle cell lymphoma using ^{90}Y-ibritumomab following four cycles of rituximab/CHOP with a 75% RR (43% CR) and 93% overall survival at 18 months.[472] It is noteworthy that patients with NHL who undergo RIT therapy can well-tolerate subsequent chemotherapy regimens or ASCT with toxicity from subsequent therapy being similar to that observed in patients not previously treated with RIT.[503] More recently, RIT is being studied in combination with biological response modifiers, such as bortezomib, to try to further increase the therapeutic index of RIT.[504] RIT has also been studied in combination with immunostimulatory C$_p$G 7909 oligodeoxynucleotide in relapsed B-cell lymphoma with promising results.[505]

Results from clinical studies of RIT for the treatment of patients with recurrent Hodgkin lymphoma have been encouraging. These studies have used ^{131}I[506] or ^{90}Y[182,507-509] labeled antiferritin antibody. Overall, 134 patients with recurrent Hodgkin's disease have been treated in five different studies with radiolabeled antiferritin antibody.[510] Results obtained with ^{90}Y-antiferritin antibody were better than those obtained with ^{131}I-antiferritin antibody. ^{90}Y-antiferritin antibody therapy resulted in a response rate of 60%, with a CR rate of 30%. The extent of response was associated with survival, with 50% of patients with CR, PR, and progressive disease alive at 2 years, 1 year, and 4 months, respectively.[510] Responses in these studies were more common in patients with disease histories longer than 3 years, tumor volumes less than 30 cm^3, and in patients receiving at least 0.4 mCi/kg of ^{90}Y-labeled antiferritin antibody.[510] ^{131}I-tositumomab has also been studied in recurrent lymphocytic-predominant Hodgkin lymphoma.[511] More recently, ^{90}Y-anti-CD25 Mab therapy in patients with refractory and relapsed Hodgkin lymphoma yielded encouraging results with seven PRs and 12 CRs in 30 patients.[512]

A variety of radiolabeled antibodies have also been safely administered to patients with advanced acute leukemias and have been shown to have significant antileukemic activity and to enhance the antileukemic effects of SCT conditioning regimens (e.g., beta-emitting ^{131}I-anti-CD33, ^{90}Y-anti-CD33, ^{131}I-anti-CD45, and ^{188}Re-anti-CD66c) (eTable 22-10).[513] Radioimmunoconjugates that emit alpha-particles with a very short range (e.g., ^{213}Bi) may be most useful for low volume or microscopic residual leukemic disease.[78,514] Studies using RIT targeting the CD33 antigen, which is expressed on early myeloid progenitor cells and myeloid leukemia cells, have yielded promising results that may improve the efficacy of marrow transplantation. In a dose escalation trial of ^{131}I-murine anti-CD33 (M195) in patients with relapsed or refractory myeloid leukemias,[515] 8 of 24 patients treated with 50 mCi/m^2 to 210 mCi/m^2 in divided doses had sufficient marrow

eTABLE 22-10 Selected Clinical Trials Using RIT for AML and MDS

Author, Year	Agent	Phase of Study	Antigen	Isotope Dose
Schwatz,[515] 1993	^{131}I-M195	I	CD33	50 mCi/m^2-210 mCi/m^2
Burke,[519] 2003	^{131}I-M195, ^{131}I-Lintuzumab	I	CD33	120 mCi/m^2-230 mCi/m^2
Appelbaum,[183] 1992	^{131}I-p67	Pilot	CD33	110-mCi 330 mCi
Matthews,[520] 1999	^{131}I-BC8	I	CD45	76 mCi-612 mCi
Pagel,[522] 2006	^{131}I-BC8	I/II	CD45	102 mCi-298 mCi
Pagel,[524] 2009	^{131}I-BC8	I	CD45	246 mCi-1084 mCi
Bunjes,[770] 2001	^{188}Re-BW 250/183	I/II	CD66	10.3 GBq (mean)
Jurcic,[95] 2002	^{213}Bi-Lintuzumab	I	CD33	0.28 mCi/kg-1 mCi/kg
Rosenblat,[529] 2010	^{213}Bi-Lintuzumab	I/II	CD33	0.5 mCi/kg-1.25 mCi/kg
Jurcic,[97] 2011	^{225}Ac-Lintuzumab	I	CD33	0.5 μCi/kg-4 μCi/kg

AML, *acute myeloid leukemia;* BMT, *bone marrow transplantation;* BU, *busulfan;* CR, *complete response;* CRp, *complete response with incomplete platelet recovery;* CY, *cyclophosphamide;* DFS, *disease-free survival;* Flu, *fludarabine;* MDS, *myelodysplastic syndrome;* OS, *overall survival;* PR, *partial response;*TBI, *total body irradiation.*

No. of Patients	Results	Comments
24	CR in 3 of 8 patients receiving BMT	5 patients received autologous BMT; 3 received allogeneic BMT
31	24/25 evaluable patients had marrow remissions; long-term DFS in 3 patients	Used with BU/CY before allogeneic BMT
9	75% CR; 3 of 4 patients treated with therapeutic doses relapsed	Given with CY/TBI before BMT; many patients had unfavorable biodistribution
44	7 of 25 patients with AML or MDS had long-term DFS	Given with CY/TBI before BMT
46	3-yr DFS, 61%	Given with BU/CY prior to allogeneic BMT to patients in first remission
58	100% CR, 1-yr DFS, 41%	Given to older patients with advanced AML/MDS with Flu/low-dose TBI as part of reduced-intensity transplant
57	47% DFS at median of 26 months	Given as part of preparative regimen prior to BMT
18	14 patients had reductions in marrow blasts; no CRs	First demonstration of safety of α-particle therapy
31	2 CRs, 2 CRp, 2 PRs	Given after partial cytoreduction with cytarabine
18	10 patients with reductions in marrow blasts; 3 with ≤5%	

cytoreduction to proceed to BMT, and 3 of these patients achieved marrow remission, but 37% of assessable patients developed HAMA. ^{131}I-M195 (120 mCi/m^2 to 230 mCi/m^2) was combined with busulfan (BU) and cyclophosphamide (CY) in an effort to intensify therapy prior to first or second BMT.[187] All patients engrafted, and 18 achieved CRs. Six patients relapsed, and 10 patients died in CR of transplant-related complications.[187] HAMA occurred in 37.5% of evaluable patients. Next, a study was performed with ^{131}I-M195 (50 mCi/m^2 or 70 mCi/m^2) in 7 patients with relapsed acute promyelocytic leukemia (APL) in second remission following treatment with all-trans retinoic acid.[516] Two of 6 patients with detectable promyelocytic leukemia gene/retinoic acid receptor-α (PML/RAR-α) messenger RNA after all-trans retinoic acid therapy had negative reverse transcriptase-PCR determinations following ^{131}I-M195. Median disease-free survival was 8 months, which compared favorably with other approaches for the treatment of relapsed APL.[516] Because of the immunogenicity of the murine M195 antibody, a humanized M195 antibody was developed that had avidity 4 to 8.6 times higher than the murine antibody.[517] This humanized M195 (HuM195, also known as lintuzumab) was subsequently used in a Phase 1B trial,[518] in which patients with relapsed or refractory myeloid leukemia were treated at dose levels of 0.5 mg/m^2 to 10.0 mg/m^2 and patients received six doses over 8 days. Optimal biodistribution occurred at 3 mg/m^2, and HAMA responses were not observed.[518] ^{131}I-labed M195 and lintuzumab, its humanized counterpart, have been studied in combination with BU and CY as a conditioning regimen for allogeneic transplant. Absorbed doses to the bone marrow ranged between 272 cGy and 1470 cGy. Median survival was 4.9 months (range 0.3 to 90+), and 3 patients with relapsed AML have ongoing CRs at 59+ to 90+ months following BMT. These results demonstrate the feasibility of using radiolabeled anti-CD33 in combination with a standard BMT preparatory regimen, but randomized trials will be needed to determine whether or not there is a statistically significant benefit to intensified conditioning with RIT.[519]

Other encouraging results have been achieved using RIT targeting the CD45 antigen with ^{131}I-anti-CD45 (BC8 antibody) combined with CY and TBI as a marrow transplant regimen for acute leukemia and myelodysplastic syndrome (MDS).[520] Forty-four patients received a biodistribution dose of 0.5 mg/kg ^{131}I-anti-CD45, which delivered 6.5 cGy/mCi ± 0.5 cGy/mCi to the marrow, with a mean dose to the spleen of 13.5 cGy/mCi ± 1.3 cGy/mCi. Doses to liver, lung, kidney, and total body were significantly less, and 84% of patients had a favorable biodistribution of antibody, with higher estimated radiation absorbed doses to the marrow and spleen than to normal organs. Thirty-four patients received a therapeutic dose of ^{131}I-anti-CD45 labeled with 76 cGy/mCi to 612 mCi ^{131}I in addition to CY and TBI. The maximum tolerated dose delivered 10.5 Gy to the liver. Seven out of 25 treated patients with AML/MDS survived disease-free for a median of 26 to 100 months posttransplant, and 3 of 9 patients with acute lymphoblastic leukemia (ALL) were disease-free 34 to 82 months posttransplant. This study demonstrates that RIT with ^{131}I-anti-CD45 can be used safely to deliver additional targeted radiation to bone marrow (approximately 24 Gy) and spleen (approximately 50 Gy) when combined with CY/TBI.[520]

A subsequent study with this preparative regimen in patients with relapsed AML following first remission or advanced MDS suggested that marrow doses >7 cGy/mCi may lead to lower posttransplant relapse rates.[521] This was followed by a trial of ^{131}I-anti-CD45 combined with BU and CY in 49 patients with AML in first remission.[522] In this study, the estimated mean dose to marrow was 11 Gy with almost 30 Gy to spleen. The results were superior to that expected for treatment with BU and CY alone (≥30% relapse rate), with a relapse rate of only 20% and estimated 3-year disease-free survival after transplantation of 61%.[523] The use of ^{131}I-anti-CD45 as part of a reduced intensity conditioning regimen along with fludarabine and TBI (2 Gy) was also examined in 58 patients older than age 50 years with advanced AML and high-risk MDS. Eight-six percent of patients had more than 5% blasts at the time of transplantation. All patients attained remission. Seven patients died of nonrelapse causes by day 100. The probability of recurrence at 1 year was 40%, and the 1-year survival rate was 41%, suggesting that this approach warrants further study.[524] More recently, a pretargeting approach using an anti-CD45 antibody-streptavidin conjugate and radiolabeled DOTA-biotin has been studied in patients with high-risk acute leukemia or MDS undergoing allogeneic stem cell transplantation.[525] ^{90}Y- and ^{188}Re-labeled anti-CD66 have also been studied as part of a dose reduced conditioning regimen for patients ≥55 years of age with acute leukemia and MDS, with a cumulative risk of relapse of 55% at 30 months posttransplant.[526,527]

In an effort to overcome the limitations of using beta emitting radionuclides for the treatment of leukemia, alpha-emitting radioimmunoconjugates have been studied with promising results. Alpha-emitters have the potential to increase the efficacy of RIT, without the nonspecific effects of beta-emitting radionuclides and also have promise for treatment of patients in a minimal disease state. In an early study using an alpha-emitter, ^{213}Bi, was conjugated to lintuzumab. ^{213}Bi has a $t_{1/2}$ of 45.6 minutes and emits high LET alpha particles (8 MeV) with a path length of approximately 60 μm to 90 μm in tissue. Therefore, ^{213}Bi-labeled Mab can theoretically kill leukemia cells with one or two alpha-particles with minimal bystander effect. A Phase I dose escalation study at Memorial Sloan Kettering Cancer Center using ^{213}Bi-lintuzumab in patients with refractory and relapsed myeloid leukemias demonstrated rapid targeting of disease sites within minutes, with evidence of antileukemic effects even at low dose levels.[528] In a study of 18 patients with relapsed and refractory AML or chronic myelomonocytic leukemia treated with 37.0 MBq/kg of ^{213}Bi-lintuzumab, there was no significant extramedullary toxicity. The median time to hematological recovery was 22 days. Target-to-background and target-to–whole-body ratios were greatly enhanced compared to those seen with immunoconjugates using beta emitters in this patient population. With this therapy 78% of patients had a decrease in the percentage of bone marrow blasts.[78] When ^{213}Bi-lintuzumab was used sequentially with cytarabine in patients with AML, significant reductions in marrow blasts were seen at all dose levels. Among patients treated at the maximum tolerated dose or higher, responses were seen in 24%, with a median duration of 6 months.[529] With the further development of chelator chemistry for linking alpha-emitting radionuclides to antibodies, it has become possible to use other alpha-emitters, with longer half-lives, and potentially longer marrow residence times than that achievable with ^{213}Bi.

Use of actinium-225 (^{225}Ac) offers several advantages over ^{213}Bi, including a longer half-life (10 days). Additionally, intracellular decay of ^{225}Ac to short-lived therapeutic daughter alpha-emitters (^{221}Fr, ^{217}At, ^{213}Bi) significantly increases the effectiveness of ^{225}Ac as compared to ^{213}Bi constructs.[530] A Phase I trial investigating the use of ^{225}Ac-lintuzumab for patients with relapsed and refractory AML was conducted in 18 patients with relapsed or refractory AML. Dose-limiting toxicity was prolonged myelosuppression, and there was no evidence of radiation-induced nephrotoxicity, despite the known uptake of free ^{213}Bi by the kidneys. Bone marrow blast reductions were seen in 10 of 15 evaluable patients (67%), including three patients who achieved marrow blast

reductions to 5% or less.[531] ^{225}Ac-lintuzumab is now being investigated in a multicenter Phase I/II trial in combination with low-dose cytarabine for older patients with AML.

The use of alpha-particle therapy may play a role as conditioning for SCT as well. Investigators at the Fred Hutchinson Cancer Research Center studied ^{213}Bi-labeled Mabs against CD45[532] and the T-cell receptor (TCRαβ)[533] before DLA-identical SCT in a canine model. Administration of both constructs along with additional immunosuppressive agents resulted in engraftment of transplanted marrow and stable mixed chimerism. Transient myelosuppression and liver enzyme abnormalities were observed. In similar studies, dogs receiving ^{213}Bi-anti-CD45 Mab achieved a high level of donor chimerism after receiving haploidentical grafts.[534] The use of ^{213}Bi for this application in humans may be limited by the high activities required to attain engraftment, as well as the short half-life and the need for an on-site generator to prepare drug immediately prior to administration. Subsequently, these investigators have shown in preclinical models that ^{211}At-anti-CD45 can produce sufficient immunosuppression to allow stable long-term engraftment in a canine SCT model.[535] Additionally, ^{211}At-labeled anti-CD25 and anti-CD30 Mabs are being studied as potential new antileukemia therapeutics, which have the additional advantage of being expressed by a high proportion of targeted neoplastic cells, but not normal resting cells.[536,537]

TOXICITIES ASSOCIATED WITH TaRT AND METHODS TO AMELIORATE THESE EFFECTS

There are a number of well-established factors that influence radionuclide toxicity. Among these are genetic makeup, immune factors, physiologic conditions, age, gender, radionuclide characteristics, dose rate, heterogeneous dose distribution, other prior and concomitant therapies, recovery from prior therapy, and radioprotector/sensitizer use. Many of these have been discussed in more detail in prior reviews.[538-540]

Bone marrow suppression has been the primary dose-limiting toxicity of most conventional systemic and IP TaRT. That is changing, however, with the increasing use of small molecule radionuclide delivery. Among multiple factors that may influence the extent and duration of myelosuppression, marrow reserve, recovery from prior therapy, and radioconjugate stability appear to be predominant determinants of this effect.[541,542] Hematologic support with transfusions and growth factors has been helpful, and bone marrow or peripheral stem cell reinfusion has allowed dose escalation of radioconjugates to at least three-fold over the dose that resulted in dose-limiting hematopoietic toxicity.[478] Interleukin-1 and GM-CSF have been reported to have radioprotective effects on the hematopoietic system.[543,544] The adjuvant use of these cytokines with TaRT has resulted in modest protection. Additionally, the radioprotector, amifostine, has been helpful in preclinical radionuclide studies, for the therapy of thyroid disease with ^{131}I,[545,546] and for reduction of renal toxicity from small molecule conjugates.[547] Similar effects with other radioconjugates are expected, but this potential effect has not yet been well studied. Adjuvant use of chelating agents in combination with unstable metal radioconjugates can help to minimize toxicity, but some have had only a minor protective effect on myelosuppression when used with stable chelators.[316,548,549] In addition to chelators that remove unbound radioactivity from the blood, "chasing" the radiolabeled antibody with a second unlabeled antibody directed against the radiolabeled antibody, has been reported to modestly decrease toxicity.[550] Pretargeting approaches, which dissociate and delay the delivery of the radionuclide from that of the targeting agent, can decrease toxicity and are discussed in more detail in the "Optimization" section. Although the second dose-limiting organ toxicity for myeloablative TaRT may vary with radionuclide, cardiopulmonary and liver toxicity has been reported for ^{131}I and anticipated for ^{90}Y immunoconjugates, respectively.[83,436,551]

The importance of stable chelators also impacts other potential toxicities as demonstrated with alpha-emitters. Renal accumulation leading to nephrotoxicity has been noted from a ^{212}Bi conjugate with an unstable chelator and may be dose-limiting for some applications. This was reported by Macklis et al after IP administration of ^{212}Bi-anti-Thy 1.2 IgM conjugate to mice with EL-4 tumor cells.[87] In the Macklis study, 8% of the injected radioactivity was in the cardiac blood pool by 2 hours and accumulation to kidneys was similar to that of free ^{206}Bi, indicating instability of the ^{212}Bi conjugate with the DTPA chelator. Subsequently, nephrotoxicity has been reduced with stable chelate-conjugates, including clinical experience in patients with AML receiving up to 1 mCi/kg ^{213}Bi.[78] Additionally, nephrotoxicity resulting from free ^{213}Bi could be mitigated by the use of adjuvant agents, including dithiol chelators and renin-angiotensin-aldosterone system inhibitors, as demonstrated in preclinical models.[552,553]

Acute symptoms from systemic RIT are usually related to administration of antibody products, not the radioactivity. The symptoms have usually been mild and have included rash, fever, chills, myalgia, diaphoresis, pruritus, nausea, vomiting, diarrhea, nasal congestion, and hypotension.[554] These side effects are transient and usually respond to antihistamines, acetaminophen, and nonsteroidal antiinflammatory agents. Rarely, more severe symptoms including rigors, bronchospasm, or laryngeal edema have been noted. These often respond quickly to steroids, antihistamines, oxygen, and meperidine. With CNS administration, various transient symptoms have been described, which are usually mild but can include cerebral edema, nuchal rigidity, aseptic meningitis, increased intracranial pressure, and seizure. Steroids have usually ameliorated these symptoms. A serum sickness type phenomenon has been commonly observed with IP administration of murine antibody conjugates (affecting about one third of patients), but is rare among patients receiving intravenous RIT, even with the same radioimmunoconjugate. Serum sickness–like symptoms occur about 2 weeks after treatment and may persist more than a week. Variations in the manifestation of symptoms may depend, in part, on the particular radioimmunoconjugate used because skin rash has been noted by the Hammersmith group, whereas fever with joint or muscle aches, but no rash, has been common among patients treated at the University of Alabama at Birmingham with a different radiolabeled monoclonal antibody.[399,555]

Other acute effects can include a temporary increase in bone pain for radionuclide targeting of bone metastases, as well as gastrointestinal disturbance, which usually manifests as nausea. Nausea has been more commonly associated with peptide receptor radionuclide therapy (PRRT) than conventional RIT. However, nausea from PRRT may be more related to the amino acid infusion given to reduce renal toxicity than to the radionuclide therapy itself. The targeting of receptors along the gastrointestinal tract may also contribute to nausea in PRRT. Nausea and vomiting can occur after oral ^{131}I as used in thyroid ablation or treatment of metastatic disease sites. ^{131}I therapy can also lead to sialadenitis, taste changes, transient swelling and pain at sites of metastasis, ocular dryness, nasolacrimal duct obstruction, and bone marrow suppression.[556] Radiation sickness has been reported with doses in excess of 300 mCi.[557] There are various reports concerning how fertility is impacted by the ^{131}I thyroid therapy. Short-term gonadal function may be impaired and the incidence of miscarriages

increased but there appears to be no increase in malformed offspring.[558,559] Also, the risk for development of certain malignancies shifts after ^{131}I thyroid therapy, with increases for some organs with excess exposure such as stomach and salivary glands but decreases for cancer of lung and cervix.[556,560]

In TaRT using small molecules such as peptides or radionuclide conjugates used in pretargeting approaches, kidney and bladder usually receive much higher doses than other normal organs. For these therapies, renal, rather than bone marrow toxicity can be dose-limiting.[10,48,53,55] Fractionated radionuclide delivery may reduce toxicity and increase efficacy.[10,14,561] Limited clinical studies as well as radiobiologic considerations of fractionated TaRT have been reviewed elsewhere.[210] Fractionation of dosing has been helpful for decreasing toxicity associated with peptide-radionuclide therapy and has been investigated in other TaRT applications.[210] Acute symptoms from PRRT are often related to adjuvant agents (amino acids with amifostine) used to decrease renal toxicity, rather than "foreign substance reaction" that may occur with larger immunoglobulin products. The nausea and vomiting commonly associated with use of the adjuvant agents may be ameliorated with antiemetics and other measures.

The importance of dose rate in urinary tract (renal and bladder) toxicity is suggested by early experience with PRRT and in patients with myeloma receiving holmium-166 (^{166}Ho). Although the calculated renal dose from high dose ^{166}Ho-DOTMP was only 710 cGy when 40 Gy was delivered to marrow, 30% of patients experienced grades 2 to 4 renal toxicity, with severe thrombotic microangiopathy. The risk of hemorrhagic cystitis was decreased by continuous bladder irrigation during the ^{166}Ho infusion.[562]

Unexpected rates of renal toxicity were also noted in early use of PRRT. Although the mean renal doses were well below tolerance limits for fractionated external beam radiation, the rapid accumulation of the radioactivity in the renal cortex, resulted in higher doses in that area, that were delivered at a relatively high dose rate. Further study has shown that renal toxicity of PRRT is associated with risk factors such as prior renal insufficiency and diabetes, whereas adjuvant infusion of amino acids and amifostine can help to prevent toxicity.[55,72] Incorporation of "protective" measures in PRRT regimens has allowed escalation of the fractionated radioactivity administered by as much as 50%.[547] The impact of the administration of lysine was shown in an animal study directly comparing autoradiographs of the same radionuclide conjugate with and without amino acid infusion (see eFigure 22-1, available in the expanded chapter on the Expert Consult website).[563] A 40% reduction of ^{111}In-octreotide accumulation in rat kidney was obtained in animals treated with either intravenous or oral lysine compared with controls. A similar illustration of the impact of lysine administration is demonstrated in single photon emission tomography (SPECT) images of a patient by Valkema et al.[547,563] Other efforts to understand and ameliorate the problem of renal toxicity by more accurate prediction of dose parameters includes publication of six age-dependent Medical Internal Radiation Dose (MIRD) Committee models that allow subregion radionuclide dose calculation,[564] a continuing education session at the 2003 Society of Nuclear Medicine Meeting from which contributions have been published, and MIRD suborgan modeling.[565,566] MIRD #20 examines renal toxicity from radionuclide therapy by modeling effects of (1) dose rate (BED), (2) heterogeneity of activity distribution over time, and (3) correlation of absorbed radiation dose and BED with observed clinical toxicity. The impact of application of patient specific dosimetry on renal toxicity is illustrated by Barone et al.[567]

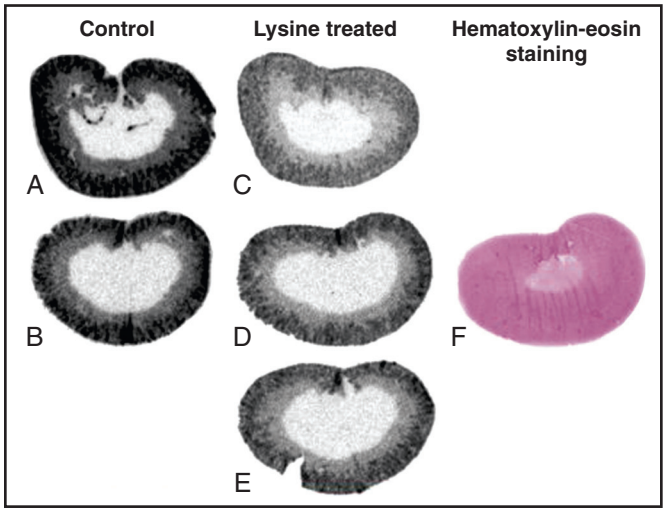
Nonsystemic administration of radionuclides has been associated with other types of toxicity, dependent on the site of administration and other factors. Late bowel toxicity after IP RIT has been infrequent, which is an advantage compared with nonspecific radionuclide therapy (e.g., ^{32}P chromic phosphate solution). However, the most severe toxicities of ^{32}P therapy includes fibrosis and necrosis of bowel or body wall, and are the result of misplacement of the therapeutic agent into bowel lumen, loculation sac, or body wall rather than the IP space (FDA Medwatch). Even with proper administration, there has been an increased risk of bowel complications compared to chemotherapy, especially among patients who also received external beam radiation to the pelvis. Although nearly three quarters of postsurgery patients with ovarian cancer receiving 15 μCi ^{32}P IP in an early GOG trial (#7602) reported no side effects, some of the remaining patients had mild to moderate gastrointestinal symptoms. One developed bacterial peritonitis and four developed bowel obstruction.[568] A later GOG study compared cyclophosphamide/cisplatin to IP ^{32}P after surgical debulking. More patients treated with ^{32}P as compared to chemotherapy had bowel problems. Some had suboptimal distribution of the radionuclide within the peritoneal cavity with areas of loculation and likely would not currently have been considered candidates for IP therapy.[569] With targeted therapy using antibody carriers for radionuclides and pretreatment scans to rule out loculation, severe bowel toxicity has been infrequent.[309,310,570] In >90 patients treated at the University of Alabama at Birmingham with IP ^{90}Y- or ^{177}Lu-CC49 antibody therapy for relapsed ovarian cancer, no incidences of bowel toxicity severe enough to require surgery were observed, although a portion of patients who underwent surgery for recurrent disease were found to have areas of palpable fibrosis.[571] Specimen analysis after IP alpha-emitter administration has not shown tissue changes and early clinical experience with alpha-emitter conjugates have not reported peritoneal toxicity.[572-574]

^{32}P has also been injected into malignant lesions and other cavities, such as the pleural space for treatment of malignant effusions, and intraarticular spaces for hemarthoses.[557] Relatively high concentrations of ^{32}P injected directly into malignant lesions have been well-tolerated locally and have occasionally resulted in dose-limiting toxicity in other organs such as stomach and lungs from shunting. To overcome this potential hazard, pretreatment scans have been obtained to assess trace radionuclide distribution prior to administration of a therapeutic dose.[575] ^{32}P injected directly into subcutaneous nodules and pretargeted interstitial administration of ^{90}Y-radionuclide into more diffuse areas of chest wall recurrence of breast cancer have been well-tolerated.[576] In contrast, accidental delivery of radionuclide to subcutaneous tissues from intravenous infiltration has resulted in local necrosis.[577] ^{32}P applied as a skin patch for treatment of basal cell carcinoma has been well-tolerated and effective.[578]

Higher concentrations of beta- and alpha-emitters have been injected into glioma cavities than could be tolerated systemically with infrequent reports of severe toxicity.[91,577] Edema and seizures are the most common adverse events reported. Intrathecal radionuclide therapy has resulted in aseptic meningitis and occasion seizure activity.[580]

There are a number of other organs at risk for toxicity that have not been extensively addressed. For instance, cataracts would be anticipated as a risk after high dose total body radiation based on external beam data but have not been reported in long term follow-up studies.[581] Lung fibrosis is of concern for ^{131}I therapy of lung metastases and is under study in animals after plutonium inhalation.[582,583] Animal model radium inhalation studies have shown an increased risk of lung cancer that is enhanced by smoking.[584]

Thus far, late organ dysfunction following RIT with ^{131}I-labeled antibodies has been uncommon except for



eFigure 22-1 Ex vivo autoradiograms of renal tissue slices of control rats (**A** and **B**) and lysine-treated rats **(C-E)** 24 hours after injection of [^{111}In-DTPA]-octreotide, 3 MBq/0.5 μg. Greatest reduction of renal radioactivity was seen in rats treated with intravenous lysine coninjected with tracer **(C)** or lysine (400 mg/kg) orally 60 minutes before tracer **(D).** Increasing the interval between oral lysine (400 mg/kg) and tracer to 120 minutes **(E)** did not lead to greater renal reduction. **(F)** Hematoxylin- and eosin-stained section adjacent to **D** shows high uptake of radioactivity in cortex and outer medulla but almost no uptake in inner medulla.
Reproduced with permission from Verwijnen S, et al: J Nucl Med 46:2057, 2005.

abnormal thyroid function.[441] Despite measures to block thyroid uptake, elevated thyroid-stimulating hormone levels occurred in 59% of patients treated with myeloablative doses of ^{131}I-anti-CD20 antibodies, at a median of 6 months after treatment.[441] Some patients who received nonmyeloablative doses of ^{131}I have also had elevated thyroid-stimulating hormone levels at later times. Salivary gland inflammation and damage can be an acute or late toxicity. Parotiditis, which may result in xerostomia, has been more common with treatment of thyroid cancer than high dose radioconjugate therapy. However, this remains a potential toxicity of ^{131}I-antibody therapy.[585]

Risk of a second malignancy is of concern even if it has not been noted for any particular radionuclide therapy. A small percentage of patients treated with high-dose RIT for lymphoma have developed second malignancies. Myelodysplasia is the potential TaRT treatment related toxicity of most concern in the treatment of hematologic malignancies. Some lymphoma patients who were diagnosed with myelodysplasia after TaRT had evidence of dysplasia prior to radionuclide therapy.[449,586,587] These patients were also considered at increased risk for myelodysplasia because of prior alkylating agents with or without conventional external beam radiation. The risk of second malignancy for RIT lymphoma patients has been modest at 0.5% a year compared to that of patients with neuroendocrine tumors receiving ^{131}I-metaiodobenzylguanidine (MIBG).[499,588] Leukemia risk for adults treated with ^{32}P for polycythemia appears dose related whereas leukemia has been noted after lower doses (0.6 mCi to 1.5 mCi) of intraarticular ^{32}P administration in children (FDA Medwatch).[589] Second malignancies will be especially of concern as more radionuclide therapy is developed for children (e.g., MIBG, ^{90}Y-Ibritumomab) because an age effect in malignancy induction has been noted for thyroid cancer and other malignancies after ^{131}I exposure and MDS has been observed after MIBG (BEIR).[590]

DOSIMETRY

Dosimetry is the process of relating the administered amount of radioactivity to the absorbed radiation dose in tumors, organs, or the whole body. Dosimetry is important for dose correlation with clinical results, and in some instances, for treatment planning to avoid excess toxicity. In general the doses calculated for TaRT are less accurate than for external beam radiation therapy for a variety of reasons. These include limited radiation dose input data (e.g., few sample points for a therapy using continuous exponentially decreasing irradiation), inhomogeneous dose distributions, and the assumptions/calculation methodology used to estimate TaRT absorbed doses.[591] Dose calculation is also more complicated for internally distributed radionuclides than for external beam irradiation. Alpha particle dosimetry adds the complication of decay scheme cascade and daughter products that may have a different distribution than the parent radionuclide.[77,592,593] Additionally, the higher relative biologic effectiveness (RBE) delivered by alpha- compared to beta-radionuclide therapy needs to be considered.[594] Data required for TaRT dose estimate calculations include the mass of tumors and normal organs, the cumulative radioactivity taken up by organs and tumors, and the pharmacokinetics of the administered radioactivity.[595] Data is usually acquired by serial gamma camera imaging. Bone marrow dose estimates are based on imaging studies of bony regions of active marrow such as the spine or blood pharmacokinetics.[596-598]

Bremsstrahlung images from radionuclides that do not have gamma emissions are generally of suboptimal quality, making accurate quantitation difficult. However, progress with sophisticated methods has provided good images that have been useful for dose estimates.[599] As an alternative appropriate for many circumstances, estimates are often made for nongamma-emitters from tracer studies using a gamma-emitter that has a similar chemistry to that of the therapeutic radionuclide. Because animal studies have shown that the biodistribution is similar, although not usually identical, for ^{111}In and ^{90}Y, tracer/dosimetry studies with ^{111}In-labeled antibody have frequently been performed in conjunction with ^{90}Y-labeled antibody therapy to estimate the subsequent biodistribution/dosimetry of the ^{90}Y-immunoconjugate.[83,600,601] Quantitative immuno-PET with ^{89}Zr-labeled antibody has shown good correlation with ^{111}In-labeled antibody biodistribution and may be useful as a positron-emitting surrogate for ^{90}Y-labeled antibody therapy.[602] Position emission tomography (PET) scanning with ^{124}I-labeled conjugates can be useful for radionuclide dosimetry.[603,604] PET images from ^{89}Zr-cG250 antibody have been superior to those of ^{111}In-cG250 antibody in an animal model and compare favorably with ^{124}I.[605,606] Other examples include use of ^{99m}Tc-antibody for imaging/dosimetry studies in conjunction with ^{186}Re-antibody therapy.[607] Another variable in estimating the expected dose from therapeutic TaRT using a preliminary biodistribution/dosimetry is that even when a small amount of a therapeutic agent is used, the correlation between doses predicted and later delivered has ranged up to ~30% between estimated absorbed doses for the two procedures in the same patient.[162,436,551,608] With continued progress in refinement of methodology, improved correlation is anticipated. For instance, quantitative SPECT reports accuracy within 5% to 15% for diagnostic or therapeutic levels of radionuclide.

For many dose estimates, conjugate views of the whole body and regions of interest (ROI) (e.g., tumors and normal organs such as liver) are obtained.[596] The activity for each ROI is measured from the counts in that region at multiple time points. The counts in each ROI are corrected for background. Attenuation correction factors are calculated for each patient and a sample of the administered radionuclide is used for calibration so that counts per minute can be converted to units of radioactivity (mCi or MBq). Scatter correction may also be applied. SPECT for ROIs can provide superior definition and quantitation.[609] Despite expansion of this technology, SPECT has not yet become the standard for most quantitation as it is more time consuming than planar conjugate view methodology.[610,611] Absorbed radiation doses can be calculated from radioactivity quantitation and the specific absorbed fraction for the target. The specific absorbed fraction takes into account the type and energy of radiation emissions, the fraction of energy from the source absorbed by the target and mass of the target.[612] The mass of each ROI is usually determined by estimating volumes from computed tomography, MRI, or other methods such as 99mTc-sulphur colloid liver scans, and converting volume to mass by assuming a unit density of 1 g/mm^3 for most soft tissues. Accounting for excretory routes is needed in quantitating changes in radioactivity distribution over time. For radionuclides such as ^{131}I where the major route of excretion is renal, urinary activity measurements can provide an estimate of total body clearance if it is not feasible to obtain whole-body counts.

The MIRD Committee is one entity that provides guidance for methods to calculate radiation absorbed dose estimates for the whole body and organs.[613] This methodology has been adapted for TaRT, with continuing effort by this committee and others to further improve the models and methods available.[564,595,598,609,613-624] A Java applet was created, in collaboration with the MIRD Committee to provide worldwide access (http://mirdcell.njms.rutgers.edu/) to new software that facilitates multicellular dosimetry and biological-response modeling. In addition to MIRD publications and information

posted through the SNM.org website, other informational publications, websites, and computer programs have been developed to assist with dosimetry calculations.[624-627] Among websites available, www.doseinfo-radar.com was developed to provide information in a number of areas including standardized dose estimates, decay data, and absorbed fractions. With fusion of anatomic and physiologic images, dose estimates can be calculated in three dimensions at the voxel level, taking into account heterogeneity of radioactivity distribution within an organ.[628-633]

The relationship between outcome and radiation dose-related factors has been variable, with some studies showing a strong correlation, whereas others show no correlation.[639-642] Some of the factors making it more difficult to establish a dose response relationship for TaRT, as compared to external beam radiation therapy, may include relative uncertainty associated with TaRT dose calculations, the heterogeneity of dose deposition that occurs with TaRT, dose rate effects, and agent/patient variation in excretion/clearance. Whereas most normal organ tolerance levels for external beam radiation have been established using high dose rate radiation, and vary as a function of fraction size, the dose rate is often low and variable with TaRT, limiting the validity of extrapolating from high dose rate tolerance levels to those expected with TaRT. Fractionation of TaRT, as with external beam, can increase the total radionuclide dose tolerated.[53,210] Several studies have demonstrated how biologic factors affect tolerance but are not accounted for in standard dose/toxicity reporting. Many of these have been summarized in a review.[539] Improved dose/toxicity correlations for marrow suppression has included adjustment of calculated absorbed marrow dose for levels of a biomarker involved in hematopoiesis, as well as cellularity and patient specific marrow mass.[542,643,644] Although data suggests the presence of a relationship between TaRT radiation dose and tumor response, early analyses with relatively small numbers of patients receiving a limited dose range fail to show strong correlation between these two factors.[611,645] As dosimetry accuracy has improved and nondosimetry factors (that affect biologic response) have been considered, better correlation has been observed between dose delivered and tumor control.[639,646] Despite the progress toward improving accuracy of dosimetry and need for individualized dose administration,[603,611,647-651] most studies are still being done without required organ or tumor dosimetry in the nontransplant setting. Activity is usually given per kg or per square meter as is common with chemotherapy. For one of the FDA-approved agents (^{131}I-tositumomab), whole body effective half time is used to individualize administered activity, but no organ or tumor dosimetry is required.[647] As better correlation is achieved between dosimetry results and clinical outcome, additional tumor dosimetry may be required, as has usually been needed for high-dose therapy followed by stem cell rescue.[652-654] Individualized kidney dosimetry has been important in predicting toxicity of PRRT.[655] Like marrow dose versus toxicity studies, adjustment for diseases, conditions, and factors that influence kidney function such as hypertension have resulted in better correlation of calculated kidney dose and renal toxicity in peptide TaRT therapy.[648]

OPTIMIZATION OF TaRT

Encouraging results have been obtained in TaRT studies using a variety of targeting agents, radionuclides, and study designs.[14] The success with lymphomas has spurred much investigation to further optimize this form of therapy in NHL and other malignancies, including use as consolidation.[6,133,476,499,656-658] Although much progress has been made, especially in reducing immunogenicity of antibody-derived targeting, adding nonantibody-targeting agents and improving radionuclide conjugate chemistry, many challenges remain.[66,476] Information about overcoming some of the challenges has been included in the "Solid Nonhematologic Tumor" section.

One of the main limitations of systemic TaRT has been the low uptake of radioactivity (generally <0.001% ID/g) in tumors. This low uptake is affected by such factors as tumor vascularity, size, charge, affinity and avidity of the targeting agent, and the interstitial pressure in tumors.[659] The use of small targeting agents may improve tumor penetration with more rapid tumor uptake but are generally limited by a relatively short retention time/half life.[660,661] Other approaches for increasing tumor uptake of radiolabeled antibody include the use of external beam therapy to increase vascular permeability and expression of target antigens.[324,662] In patients the combination of external beam therapy with TaRT increased the objective response rate of liver tumors to RIT and was well tolerated in the setting of relapsed/refractory B-cell lymphoma with 11 of 13 patients treated achieving a complete response.[663] This combined approach has used both local as well as TBI in stem cell rescue studies during which radiolabeled antibody was still circulating.[308,334] In head and neck cancers, RIT has been combined with proton therapy in preclinical studies.[664] The use of hyperthermia and vasoactive cytokines such as IL-2 and tumor necrosis factor have also resulted in higher tumor uptake of radiolabeled antibody in early studies.[665-668] Of note, hyperthermia can have multiple effects including increased antigen expression, direct cytotoxic activity, inhibition of radiation repair at medium and low dose rates, and reduced interstitial fluid pressure.[669-672] Neovascular targeting is also a promising approach to use in combination with TaRT (e.g., upregulated receptors on new tumor vessels).[60,272,673,674] Antiangiogenic agents can also be combined with TaRT.[64,274] For example, a selective peptide agonist of humanC5a, given before and after radiolabeled antibody therapy to increase vascular permeability of tumor capillaries, improved the therapeutic outcome of TaRT in xenograft tumors,[276] and combining bevacizumab with ^{131}I-labeled anti-CEA antibodies significantly improves treatment response in a mouse model of medullary thyroid cancer.[394] Fractionation of TaRT dosing has generally been favorable in many preclinical investigations and in limited clinical experience.[3,210,675] However, more study is needed as some preclinical studies have shown decreased vascular permeability with fractionation, which could have a deleterious effect.[676] As previously discussed, high-affinity antibodies have been reported to improve antibody uptake, but not necessarily intratumor distribution, and in some cases high-affinity antibodies have produced a more favorable therapeutic ratio. Clinical trials using high affinity antibodies have been performed for cancer of the colon, breast, prostate, lung, and ovary.[161,162,677,678] Targeting may also be enhanced by increasing antigen expression on target cells.[679] Several studies show that interferon can increase the expression of some common tumor-associated antigens including CEA, TAG-72, and an antigen expressed on melanomas.[680,681] Applications of this approach in vivo using human tumor xenografts in mice have shown greater tumor growth inhibition with interferon administration before RIT compared to similarly treated mice without interferon.[264] Human tumor biopsy material has also confirmed increased antigen expression following interferon administration. Benefit from adjuvant interferon in clinical trials has been difficult to demonstrate. Potential benefit may be inferred because increased tumor antigen expression was demonstrated by biopsy, and imaging of antibody localization in known sites of disease was improved by interferon compared to results obtained in other trials with similar radiolabeled antibody that did not use interferon.[268,679] Targeting of two antigens with separate antibodies

Biopsy results are infrequently used for as a sole measure for dosimetry. Although biopsy provides a direct measurement and can be used for autoradiography, it is invasive, and not practical for most tumor or organ dosimetry. Biopsy data is of interest to correlate with other methods of dosimetry, but it is often of limited value alone because of the small sample size, which may not be representative, and is usually only done once. Thus biopsy dosimetry usually does not allow a time-activity curve to be generated. However, the development of alpha cameras now allows activity over time to be measured.[628,630,634-636] Implanted thermoluminescent dosimeters (TLD) and other devises have also been used for quantitation in experimental preclinical studies and in limited clinical trials.[637] When used in patients with ovarian cancer treated with intraperitoneal TaRT, TDL-obtained dose measurements were in the range of those estimated with other methods.[607] As with biopsy, TLDs provide a direct measurement of absorbed dose but also usually require an invasive procedure for placement that has the disadvantage of potentially introducing a sampling error. Like most other dosimetry methods, TLDs do not account for dose rate, which may be an important determinant of dose response relationships. Another implantable dosimeter has been developed and applied to external beam radiation that can give real-time wireless feedback to a computer. This technology should be applicable to radionuclides but, similar to TLDs, will only provide data from a small area.[638]

As experience grows and dosimetry techniques improve, insight may be provided for tolerance of new agents that become available. An example is the marrow studies pertinent to alpha-emitter ^{223}Ra.[630]

is also promising. Studies of unlabeled veltuzumab, a humanized anti-CD20 antibody, combined with ^{90}Y-epratuzumab, an anti-CD22 antibody, enhances the therapy response of lymphoma in mouse studies, and this has progressed to clinical trial, where it has been well tolerated in the initial Phase I experience.[682,683] Use of the nonidentical unlabeled antibody may promote apoptosis in conjunction with the radiolabeled antibody, but eliminate the potential for competition between additional unlabeled antibody when using the same antibody for unlabeled predose and as a radionuclide conjugate.[682] Although not a mechanism to increase uptake, removal of unbound radiolabeled agent decreases toxicity and can allow dose escalation.[684]

Several pretargeting methods have been proposed to overcome some of the limitations of conventional one-step TaRT where prolonged radiation exposure of the bone marrow results in dose-limiting marrow suppression.[685,686] As previously mentioned, pretargeting approaches dissociate the delivery of unlabeled antibody, or other targeting entity, from the delivery of the radionuclide. Ideally this approach delays the delivery of the radioactivity until the ratio of tumor-bound to nontumor-bound targeting agent has reached its maximum. Because the radionuclide is usually given conjugated to a small hapten that interacts with the targeting entity, any nonbound radioactivity will clear quickly because of the small molecular weight of the radionuclide conjugate. Thus, the pretargeting approach has the potential to improve tumor-to-normal tissue ratios several fold over that achieved with directly labeled antibodies by minimizing circulation time of unbound radionuclide. Proof-of-principle of the pretargeting approach has been established in multiple preclinical and early phase clinical trials while studies continue for further optimization.[48,378,385] Application of pretargeted radioimmunotherapy in a high-risk group of patients with medullary thyroid cancer improved survival compared to contemporaneous untreated controls.[393] A recently reported Phase II of pretargeted radioimmunotherapy in a similar population showed rates of disease control rates over 75% but with a 54% rate of grade III/IV hematologic toxicity, which was more pronounced in patients with diffuse bone marrow involvement.[394]

In an effort to increase the efficacy of TaRT in relatively radioresistant malignancies, TaRT is being studied in conjunction with other agents or therapies (e.g., external beam radiation that may increase targeting by affecting tumor vasculature while causing G_2/M arrest in a radiosensitive phase of the cell cycle). With G_2/M arrest during this radiosensitive phase of the cell cycle, tumors will receive prolonged low dose rate radiation from radionuclide emissions associated with TaRT. Other approaches include the use of radiosensitizers and radioprotectors,[724] but these combined modality approaches have generally not been optimized (e.g., dose sequence and timing).[725] Optimization of these regimens may vary with tumor and radionuclide systems.[726-731] Polyethylene glycol (PEG) modification of targeting agents is an example of an optimization strategy under study that provides multiple carrying sites for molecules such as radiosensitizers.[732,733] TaRT has been studied in combination with a variety of agents including the radiosensitizer SR2508, intercalating agents, and the hypoxic cytotoxin, SR 4233 (tirapazamine).[671] A variety of chemotherapy agents have also been studied as radiosensitizing agents in conjunction with TaRT.[296,303,312,728,734,735]

The taxanes radiosensitize tumors by arresting cells in the G_2/M cell cycle phase and have demonstrated synergistic effects in preclinical TaRT studies. Subsequently, they have been studied in clinical trials in combination with TaRT.[309,725] Cisplatin has also been shown to have a supraadditive effect in combination with low dose rate radiation and has been systematically studied with TaRT in murine xenograft model.[728,736] Buchsbaum et al have reported increased growth inhibition in human tumor xenografts in nude mice when bromodeoxyuridine, which is incorporated into the DNA in place of thymidine, was given for 4 days with a 1 day washout before RIT.[301] Tirapazamine-potentiated cytotoxicity by RIT in mice with human tumor xenografts.[304,671] Caffeine as well as poly ADP ribose polymerase (PARP) inhibitors have also been shown to modulate sensitivity to RIT in a variety of cell lines.[108,737,738] Although sensitization may be achieved with low doses of adjuvant agents, it has been feasible to use nearly full doses of each agent with acceptable toxicity in some trials.[309,316] Patients with recurrent glioblastoma were given the combination of locoregional pretargeted TaRT with temozolomide without significant neurologic toxicity or severe hematologic toxicity.[739]

At the preclinical level, gene therapy can enhance the efficacy of TaRT. Gene transfer methods have been used to genetically induce tumor cells to express enhanced levels of cell surface tumor-associated antigens or receptors, which have resulted in increased tumor uptake of radiolabeled antibody or peptides in animal models.[740] This approach could potentially result in enhanced therapeutic efficacy.[741] There is also the potential to use gene transfer techniques to radiosensitize tumors by knocking out genes involved in DNA repair, signal transduction, and control of the cell cycle that would result in sensitization of tumors to TaRT. Alternatively, gene therapy may be used to provide radioprotection of bone marrow. The combination of toxin-gene delivery and TaRT also offers the potential for improved therapeutic efficacy.[740] For example, specific genes can be targeted with short range radionuclides such as Auger emitters as demonstrated by ^{125}I-labeled triplex forming oligonucleotides.[742]

FUTURE CONSIDERATIONS

TaRT is a promising therapeutic modality and ongoing work in this area will result in expansion of indications and improved efficacy. In addition to acceptance of TaRT as a component of the standard armamentarium for lympho-hematopoietic malignancies, its efficacy for selected nonhematologic entities is continually being improved. It is expected that for many diseases, TaRT will be most useful as a component of multimodality therapy.[96,312,469,491] Future studies should define how to optimally combine TaRT with other therapeutic modalities. More investigation is needed to determine agents/schedules that result in synergistic antitumor activity without significantly greater toxicity. TaRT has been useful both as a component of early therapy, and as a salvage therapy (e.g., improved survival of patients with glioma).[743] It is also being studied in lymphoma as an adjunct to other agents in an effort to further improve therapeutic outcome.[469,499] Active areas of investigation include studies of TaRT using alpha particles, small non-antibody targeting agents, gene therapy, and other approaches for increasing tumor uptake of radionuclide and enhancing efficacy.[276]

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A number of pretargeting designs have been devised and others are in development.[687-689] To date, the most popular are based on the use of bifunctional antibodies or biotin-streptavidin interactions, with these components complexed to a targeting agent and radionuclide.[8,378] Less common pretargeting approaches include the use of antibody-oligonucleotide conjugates, a prodrug/enzyme strategy, and DNA/DNA systems.[690,691] Other mechanisms that allow for amplification/enhancement of targeting are under study.[689,692] Common to all methods is the desire for (1) high specificity and retention of the targeting agent, without shedding or internalization, (2) high specificity of the radionuclide conjugate for the bound targeting agent, and (3) rapid clearance of radionuclide that does not localize to target.

Bifunctional antibodies have been constructed by cross-linking Fab' fragments from two antibodies that have different specificities.[388,693-695] For RIT, one end of a bifunctional antibody contains an unlabeled fragment directed toward a tumor-associated antigen/receptor, whereas the other binding site reacts with a hapten linked to a radionuclide. Sharkey et al have designed a "universal" system by making one Fab' fragment specific for the chelating agent that is conjugated to the radionuclide.[694-696] Thus, different radionuclides can be used as long as they are complexed to that chelating agent. Bivalent nonantibody peptides have also been developed.[694,697]

Advantages of the biotin-streptavidin system include not only the small molecular weight of biotin, which can quickly circulate throughout the body, but also the high binding affinity between biotin and avidin or streptavidin (10^{15} M^{-1}). Streptavidin is tetravalent (has four biotin binding sites) and can thereby increase the amount of radionuclide localization in tumor. On the other hand, a disadvantage of the biotin/streptavidin system is the immunogenicity of streptavidin or avidin. Polyethylene glycol modification can reduce this immunogenicity, but may also decrease the binding capacity of biotin.[694,698]

Although the concept of pretargeting does not require a clearing step between administration of the targeting agent and radionuclide, use of a clearing agent can further enhance the tumor-to-normal tissue ratio. Theoretical and experimental pharmacokinetic modeling studies suggest that pretargeting approaches using a two-step method will result in a two- to three-fold enhancement of efficacy compared to conventional one-step RIT.[694,699] Use of a clearing agent can further improve tumor-to-normal tissue ratios severalfold. A variety of clearing mechanisms have been studied to date including use of an antibody that reacts with the targeting agent, plasmapheresis/extracorporeal immunoadsorption, and large molecular weight agents that react with the targeting agent in the circulation, or other agents that are primarily confined to vasculature.[700-703] The primary objective of clearing strategies is to remove unbound targeting agent from the circulation without affecting that bound to tumor. Clearing designs for biotin-streptavidin systems have usually used three to five steps to promote clearance of unbound targeting agent to which the radionuclide-complex would otherwise bind.[384] By using a three-step approach, a mean tumor/marrow ratio of 19 was achieved in patients with glioma. Using this three-step pretargeting approach, 12 of 48 patients with glioma with residual or recurrent disease after conventional therapy achieved a greater than 25% reduction in tumor, with 8 of 48 patients in remission at 12 months.[579,704] Efficacy has been reported by Paganelli and his European Institute of Oncology colleagues using this biotinylated antibody in a three-step approach for therapy in patients with other solid tumors as well.[704,705] One of the most efficient clearing agents is a complex of galactosamine-biotin molecules that bind streptavidin-antibody and are extracted via the liver. After optimal tumor targeting, antibody complexes were efficiently removed such that blood concentrations of streptavidin were reduced by >95% within 6 hours of administration of a synthetic mono-biotin poly-N-acetyl-galactosamine compound developed by NeoRx Corp. investigators.[385,706] Extraction of clearing agent from blood occurs via interaction with Ashwell receptors in the liver. Use of clearing agents that complex with the targeting agent and are trapped in the liver has allowed dose escalation as high as 140 mCi/m^2 ^{90}Y, whereas the MTD for conventional RIT of ^{90}Y-antibody conjugates is usually <30 mCi/m^2 because of myelosuppression.[48,316,707] This synthetic mono-biotin poly-N-acetyl-galactosamine compound has been used with antibodies conjugated chemically with streptavidin and more recently with fusion proteins.[385,708] The genetically engineered Fusion proteins have been produced by fusing single chain antibody fragments with streptavidin. This has provided tetrameric products with four binding sites for the bivalent antibody and four binding sites for biotin.[42] Early study of an anti-CD20/streptavidin fusion protein in a pretargeted approach with the synthetic biotin-poly-N-acetyl-galactosamine compound has resulted in an average tumor to whole-body radiation dose ratio of 49, with most patients having no significant hematologic toxicity at 15 mCi/m^2 of ^{90}Y.[385]

The pretargeting approach is promising for treating solid tumors where efficacy has been limited primarily by the inability to deliver sufficient tumor doses with acceptable toxicity. Meaningful responses in a variety of nonmyelogenous solid tumors as well as lymphomas have been achieved with pretargeting.[48,379,380,703,709] Several reviews provide additional details of pretargeting development.[5,8,378,393,694,696] A new technique for partial breast treatment involves pretargeting of the tumorectomy cavity by intraoperative injection with avidin, followed later by intravenously radiolabeled biotin.[710,711]

Use of regional or direct injection of TaRT into tumors or tumor cavities has allowed dose escalation for treatment of relatively radioresistant tumors, with encouraging results as discussed in the Solid tumor section.[91,128,309,399,403,415,416,548,712-717] Other approaches that may improve uptake of radiolabeled antibody in tumors include the use of unlabeled antibody to bind circulating antigen and nonspecific binding sites, and the use of cocktails or mixtures of antibodies reactive with different tumor-associated antigens.[682,718-720] An advantage of antibody mixtures has been confirmed in animal studies, which showed superior detection and localization to smaller tumors and greater tumor growth inhibition with the combination of two ^{131}I-labeled antibodies than either antibody alone using the same total amount of radionuclide.[721,722] Several human trials have used two or more antibodies simultaneously. However, it has not been possible to make a direct comparison of one versus more than two antibodies in patients because most trials did not test one antibody alone compared to a combination of antibodies in the same study.[268] When optimized, antibody cocktails may include the combination of whole antibodies with smaller constructs, or use of different radionuclides. Radionuclides are chosen on the basis of their physical half-life, radiation emission characteristics, and pharmacokinetics in a manner that would complement one another and will be matched with the half-life of the antibody or antibody constructs. In addition, the use of antibodies with different affinities or the use of genetically engineered antibodies with greater avidity may also increase the targeting and retention of radioimmunoconjugates in tumors. Use of two radionuclides, even with the same carrier, shows improved results in a rat model of PRRT ^{90}Y and ^{177}Lu and in initial clinical experience.[72,73,723]

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CHAPTER

23 Stereotactic Irradiation: CNS Tumors

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The term *radio-surgery* was possibly first used in a medical context more than 90 years ago, when Dr. Francis Hernaman-Johnson described in a lecture to the Royal Society of Medicine an assortment of indications where x-ray therapy might be combined with surgery for benign and malignant indications. From the modern perspective, Dr. Hernaman-Johnson's oration is quaint but wonderfully lyrical, at times invoking Biblical metaphors and Greek fables.[1] Prophetically, though, he concluded with the message that "no human mind can compass the whole field of medicine. Hence the hope of the future lies in specialism [*sic*] tempered by co-operation."

Fast-forward to the mid-20th century, and with the loss of a hyphen along the way, the term *radiosurgery* was repurposed to describe the procedure now widely used as treatment for a variety of benign and malignant intracranial neoplasms as well as a few selected functional disorders. Applying principles of stereotactic surgery and harnessing the tissue- and tumor-ablative potential of ionizing radiation, the Swedish neurosurgeon Lars Leksell designed the first prototype unit for stereotactic radiosurgery (SRS), opening up new clinical opportunities and launching a Hernaman-Johnsonian interspecialty cooperation between neurosurgeons and radiation oncologists that continues to provide valuable clinical service to patients and new insights into tumor and normal tissue biology.

In this chapter we review the distinct technical aspects of SRS, the current understanding of SRS radiobiology, and clinical outcomes after SRS for common indications.

DEFINITION AND TECHNICAL PRINCIPLES OF STEREOTACTIC RADIOSURGERY

In the half-century following Leksell's pioneering work in SRS, numerous other investigators around the world made important contributions to the technical development of SRS. Whereas Leksell eventually settled on a design involving a hemispherical pattern of multiple cobalt-60 sources shielded and arranged so that their output gamma rays would converge on the target, in the 1980s and 1990s various linear accelerator-based SRS platforms were also developed.[2,3] Many of these newer commercially available systems are also capable of delivering other forms of radiotherapy, and there came a period of time when the commonly used terminology describing SRS and non-SRS forms of radiotherapy were somewhat loosely interchanged. Ultimately, the American Association of Neurological Surgeons (AANS), the Congress of Neurological Surgeons (CNS), and the American Society for Radiation Oncology (ASTRO) agreed that a uniform description of SRS was required to avoid confusion, and the consensus definition is as follows[4]:

> *Stereotactic Radiosurgery is a distinct discipline that utilizes externally generated ionizing radiation in certain cases to inactivate or eradicate (a) defined target(s) in the head or spine without the need to make an incision. The target is defined by high-resolution stereotactic imaging. To assure quality of patient care the procedure involves a multidisciplinary team consisting of a neurosurgeon, radiation oncologist, and medical physicist.*
>
> *Stereotactic Radiosurgery (SRS) typically is performed in a single session, using a rigidly attached stereotactic guiding device, other immobilization technology and/or a stereotactic image-guidance system, but can be performed in a limited number of sessions, up to a maximum of five.*
>
> *Technologies that are used to perform SRS include linear accelerators, particle beam accelerators and multisource Cobalt 60 units. In order to enhance precision, various devices may incorporate robotics and real time imaging.*

Contained within this definition are references to several essential ingredients of SRS. The treatment is noninvasive and involves external radiation sources or beams. As it is also elaborated in other ASTRO statements concerning SRS,[5] the adjective *stereotactic* implies that the target lesion is localized relative to a fixed three-dimensional spatial coordinate system, using either a rigid head frame or reliable internal fiducial markers (bony landmarks or implanted markers). And, most importantly, SRS is a multidisciplinary endeavor in which the quality of patient care is of paramount importance.

Regarding the issue of patient safety, in 2011 ASTRO issued a white paper concerning quality and safety considerations for SRS and the extracranial application of high dose-per-fraction irradiation, stereotactic body radiation therapy (SBRT).[6] This report highlights structure and process elements that are essential for establishing and operating a clinical program with the proper recognition of the risks involved and attention to detail that maximizes the chance for successful treatment while minimizing the chance of error.

As for any clinical activity involving radiation therapy, developing a culture of safety is crucial.[7] Collegiality and a nonjudgmental atmosphere can contribute to an environment that fosters proactive recognition of ways to avoid systematic problems that might produce potentially harmful errors. In the context of SRS, mistakes can be magnified beyond what might be seen in conventionally fractionated radiotherapy treatments. The fact that an entire treatment course is delivered in only a single or perhaps a few fractions means that a targeting inaccuracy greatly increases the odds of tumor progression via geographic miss. Furthermore, the fact that each individual treatment involves a large amount of ionizing radiation dose deposition means that the risk of injury to normal tissue may be escalated beyond an acceptable range if the delivered dose hotspots drift into adjacent normal brain parenchyma rather than remain in the target volume. A thorough discussion of quality assurance methods in SRS is outside the scope of the present chapter. Among the high-priority tasks are accurate initial commissioning and periodic calibration of the treatment delivery technology, proper personnel training, and various patient-specific preparation routines.[6]

Common to all delivery technology for SRS is the use of multiple nonopposed radiation beams that converge on a

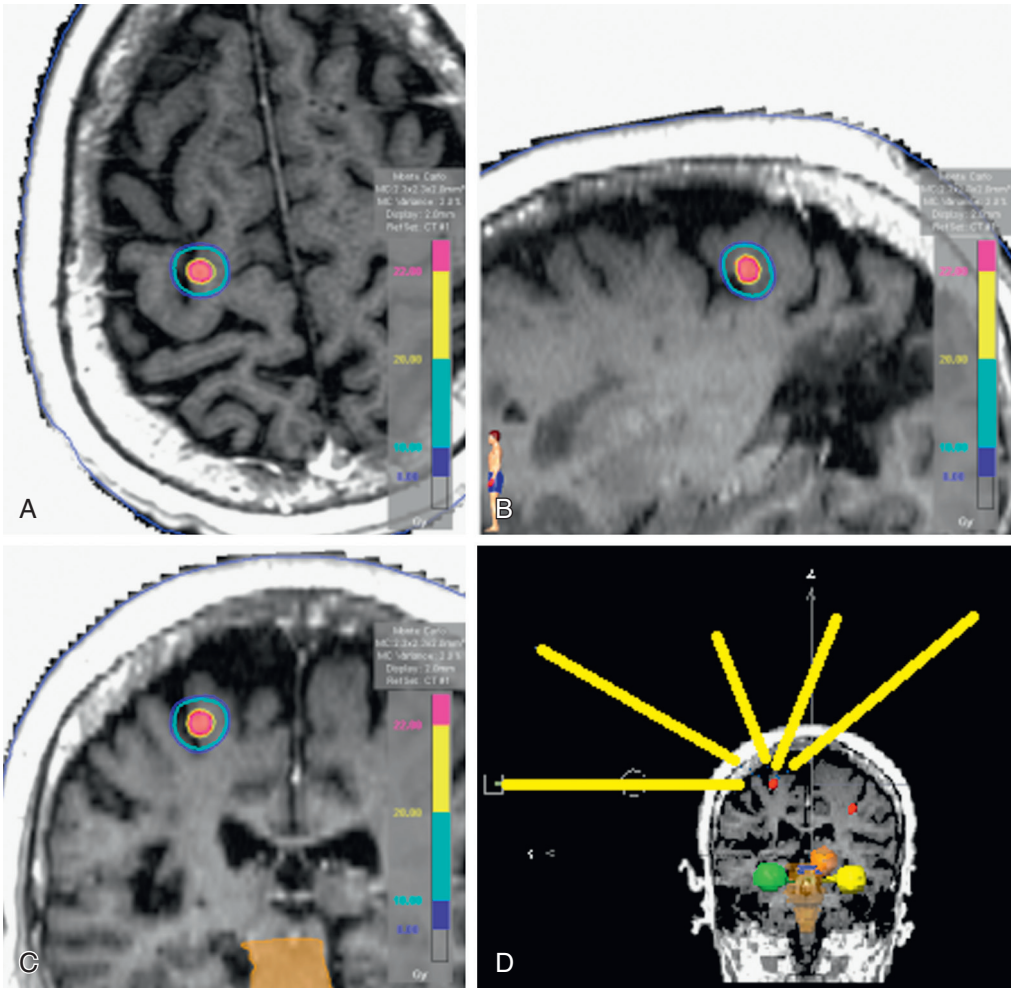


Figure 23-1 Example of an SRS treatment of a right parietal lesion to a prescription dose of 20 Gy, illustrating good conformality. The target is outlined in red and shaded in pink. The 20-Gy prescription isodose volume is outlined in yellow and is shown on axial **(A)**, sagittal **(B)**, and coronal **(C)** planes through the center of the lesion, in all views tightly surrounding the target. The treatment was delivered on a linear accelerator, and panel D is a coronal view showing the angles through which the arcs passed *(yellow lines)*. The beam angles were achieved by table rotations. A separately treated left-sided lesion is also seen in red in that panel, and several normal tissue structures are also outlined.

target in the brain, thus avoiding a high dose to normal tissues in the entrance and exit paths of the beams while depositing an ablative dose within the target volume. The ideal treatment delivery plan achieves a high level of conformality, implying that the volume receiving the prescription dose closely approximates the target volume, thus minimizing the volume of normal tissue exposed to a high dose (Figure 23-1). Unlike the case in some applications of conventionally fractionated radiation therapy, wherein dose homogeneity within the target volume is clinically valuable for cosmetic or other endpoints,[8] for SRS it is generally advantageous to allow for a dose hotspot to be present within the target volume, both for the purpose of increasing the intensity of therapeutic effect and also steepening the gradient of dose falloff into surrounding normal tissues in the brain. This latter goal in particular is often best achieved under the conditions whereby the beam's eye view of the tumor nearly surrounds the contour of the target itself, perhaps with even a "negative margin" where the beam is slightly smaller than the target in cross section—effectively exploiting the fact that the maximum slope of dose falloff outside the beam is generally at the midpoint of the lateral penumbra, a consideration also applicable in SBRT.[9]

THE RADIOBIOLOGY OF STEREOTACTIC RADIOSURGERY

Upon recall of the classic "4 R's" of radiobiology, it is readily apparent that SRS involves considerations that depart from the traditional views of conventionally fractionated radiotherapy. For a single treatment course, the interfraction processes of repair, repopulation, redistribution, and reoxygenation are not relevant realities. Furthermore, for single or extremely hypofractionated regimens, the utility of the popular linear-quadratic model of radiobiological potency has been challenged given the lack of agreement with some preclinical observations and emerging awareness of dose threshold effects that impact tumor and normal tissue responses via vasculature-related events.

By the 1980s SRS had become appreciated as a safe and effective therapy for arteriovenous malformations (AVMs),[10,11] and efforts were initiated to understand the nature of the therapeutic histologic effect on blood vessels in particular. Interestingly, a wide variety of animal models of SRS have been employed to study normal tissue effects including a goat, baboon, and cat, among others.[12-14] Some of these early reports

included experimental single fraction doses on the order of 150 Gy to 200 Gy, and thus their relevance to modern clinical practice, which frequently uses doses an order of magnitude smaller, is uncertain. However, using a dose more closely in line with current human clinical practice, Acker et al at Duke University studied the pial vasculature in a rat using a window chamber model that allowed for repeated direct visual inspection of the in vivo microcirculation.[15]

The experimental setup at Duke included a 4-MV linac fitted with a 2.2-mm diameter collimator. Doses in the range of 15 Gy to 30 Gy were administered in a single exposure, and serial observations were made to characterize the effect on blood flow, vessel density, and leukocyte-endothelial cell interactions. Acute reductions in vessel length density and blood flow were observed at 24 hours postirradiation and continued to become more pronounced 30 days after exposure, without a suggestion of dose-dependence above the level of a 15-Gy dose. Notably foreshadowing a future area of intense focus by others, morphologic changes that included extensive sections of endothelial cell loss were also observed within weeks after irradiation. The authors found this apparently apoptotic effect to be somewhat curious, speculating on its relationship to changes observed in white blood cell interactions with the vessel walls and hypothesizing that platelet-activating factor might play an important role.

This possibility that the tumor vasculature is an important target of radiotherapy is not an especially modern concept and was suggested at least as long ago as 1930, when James Ewing commented that with regard to certain tumors whose cells were thought to be relatively radioresistant, "it seems to me highly probable that the influence is mainly upon the blood vessels, which eventually shrink and cut off the blood supply."[16] However, there was rather limited investigation into this topic specifically between that statement and the SRS-inspired work of the late 20th and early 21st centuries. Many of these studies are cataloged in a recent review by Park et al, who concluded that there appears to be a suggestion of a threshold effect occurring at a fraction size on the order of 10 Gy, above which there appears to be substantial vascular damage that contributes indirectly to a tumoricidal effect.[17]

Perhaps best exemplifying these studies, while also adding fundamental mechanistic insights, is the work of Garcia-Barros et al from Memorial Sloan-Kettering Cancer Center.[18] In the experiments reported in 2003, these investigators implanted MCA/129 fibrosarcomas and B16F1 melanomas into mice that were either genetically wild type or deficient in acid sphingomyelinase (asmase), an enzyme needed for endothelial cell apoptosis. For both tumor cell types, host asmase deficiency was associated with radioresistance as evidenced by significantly enhanced tumor growth delay after a single dose of 15 Gy. Confirmatory assays of endothelial apoptosis reported in the same paper demonstrated that the effect occurs acutely, peaking within 3 to 6 hours after exposure. Additionally, there is an apparent threshold dose for inducing endothelial apoptosis between 7 Gy, where essentially zero apoptosis was seen, and 11 Gy, where the percentage of apoptotic cells in asmase wild type jumped up to approximately 20%. There was a continued increase in percentage of apoptotic endothelial cells up to approximately 60% with a dose of 25 Gy, the upper limit of dose evaluated in this study. As will be discussed, the profound vascular effects of SRS are also well illustrated clinically by the frequently successful obliteration of complex intracranial AVMs when using single fraction doses in the upper range of what was tested here preclinically.

For fractionated radiotherapy the most frequently applied mathematical model to relate radiation dose to expected tumor cell kill is the linear-quadratic (LQ) model, based on a formula that first appeared in Lea and Catcheside's description of the relationship between radiation dose and incidence of chromosomal translocations, using a plant model.[19] Although this model has been the most popular in recent decades and is discussed elsewhere in this book, sometimes overlooked in the original publication by Lea and Catcheside is recognition that for high dose exposure, there would in principle need to be a correction applied to the LQ model that accounted for a decaying effect when the dose is delivered over a prolonged interval, presumably related to what amounts to intrafractional repair as some radiation-induced single-stranded breaks recombine without translocation. Experimental data supporting this possibility in mammalian cells may be found in the work of Eley et al, who used a glioma cell line and modeled SRS-type dose effects, comparing radiosensitivity when the same 12-Gy dose was given either in a single brief exposure or else in a series of smaller exposures spread out over 1 hour.[20] The intent was to simulate SRS treatments that might be delivered clinically using multiple beam angle and table position changes, thus effectively prolonging the time of dose delivery. The results revealed that the cells underwent detectable cell cycle arrest at the G2/M after the first subfraction in intermittent exposure conditions and that this effect was associated with relative radioresistance, consistent with the Lea-Catcheside predictions.

In view of the vascular threshold dose effects and possible intrafraction repair effects, among other differences from fractionated radiotherapy, an argument can be made that alternatives to the LQ model are needed.[21] Indeed, numerous groups have proposed alternative models to characterize the relationship between radiation dose and tumor cell kill when doses in the realm used for SRS or SBRT are employed. For example, Guerrero and Li proposed a modified LQ (MLQ) model based largely on the lethal-potentially lethal model of Curtis,[22] except they proposed a new term, δ, to account for repair kinetics related to dose rate. In a model that combines elements of LQ formalism and a multitarget model, Park et al at the University of Texas–Southwestern Medical Center have described a "universal survival curve" (USC) that involves a step function: LQ estimates apply below a certain dose per fraction, but above a transition dose, D_T, there is a correction that effectively straightens the curve to maintain a linear relationship between dose and log cell kill above D_T.[23] The purpose of this construct is to match the true relationship between high dose exposure and log cell kill, which tends to be overestimated by the LQ model. The USC model may be used to derive a convenient index of radiobiological potency, the single fraction equivalent dose (SFED), by which different SRS or SBRT regimens might be compared. When the dose per fraction, d, exceeds D_T, SFED is calculated as follows:

$$SFED = D - (n-1)D_q$$

where D is the total dose, D_0 is the dose required to reduce the surviving fraction of cells to 37%, n is the total number of fractions, and D_q is the quasi-threshold dose of the multitarget model. The SFED metric has been demonstrated to describe a dose-control relationship for a variety of tumor types treated with SBRT.[24,25]

To gauge the true dose-related normal tissue toxicity risk in clinical settings, even the best predictive mathematical models are not a substitute for careful analyses of actual clinical data. The QUAntitative estimates of Normal Tissue Effects in the Clinic (QUANTEC) project was sponsored jointly by the American Association of Physicists in Medicine (AAPM) and ASTRO. Medical physicists, radiobiologists, and radiation oncologists from across North America, Europe, and Asia participated. The group's charge was to catalog, review, analyze,

and summarize all published literature concerning the quantitative relationship between dose of ionizing radiation and injury to normal tissues, with the intent of identifying practical guidelines for normal tissue dose constraints based not on models but on actual patient observations. Of direct relevance to SRS are the QUANTEC reports on radiation effects in the brain, brainstem, and optic nerves and chiasm.[26-28]

In each case there are acknowledged limitations concerning the quantitative data available for analysis; nevertheless the QUANTEC papers do offer dose-volume parameters that are clinically useful in the design and evaluation of SRS treatment plans for individual patients. Largely influenced by the synthesis of numerous reports involving the treatment of AVMs and subsequent risk of radionecrosis, the authors of the QUANTEC brain paper concluded that toxicity increases rapidly once the volume of the brain exposed to >12 Gy is >5 cm^3 to 10 cm^3.[26] An added caveat is that eloquent areas of the brain such as the brainstem or corpus callosum require extra caution.

The QUANTEC brainstem summary is mainly concerned with tolerance to fractionated radiotherapy, given the larger number of studies available for that setting relative to the setting of brainstem SRS and, in particular, the paucity of long-term reports after SRS to brainstem metastases.[27] One clinical indication for SRS in which long-term follow-up is typically available is for the treatment of acoustic schwannomas, a benign condition with negligible risk of mortality to the patient. Here, the dose to the brainstem is primarily just a glancing focus of scattered dose away from the actual target; a maximum point dose of less than 12.5 Gy is associated with a low risk of new cranial neuropathy in that setting. Regarding injury to the optic nerves or chiasm, the QUANTEC reviewers found that the risk of radiation-induced optic neuropathy in the more modern context of MRI-aided planning is low, with a maximum point dose of ≤12 Gy to the optic apparatus.[28] Figure 23-2 provides an illustration of a patient treated with SRS where the tumor approached the chiasm, necessitating caution with the optic chiasm dose.

CLINICAL OUTCOMES

In Leksell's report describing the first 762 cases treated with SRS at the Karolinska Institute, the three most common diagnoses were AVMs, Cushing disease, and acoustic neuromas.[29] No brain metastases were treated, and a large percentage of the cases were functional disorders such as trigeminal neuralgia, intractable pain elsewhere in the body, or pituitary tumors. Nowadays, the most common indication for SRS is brain metastases. Although many of the diagnoses treated in the early years by Leksell are still managed by SRS today, others such as Parkinsonism or anxiety or obsessive-compulsive disorder are managed with other interventions.

Pituitary Tumors

It is difficult to summarize the full spectrum of literature on SRS, primarily because there have been so many papers involving so many patients. In an encyclopedic review of recent series, Sheehan et al identified 25 separate reports published between 2002 and 2013 concerning SRS for nonfunctioning pituitary tumors alone.[30]

A representative series, that is also the largest published experience, would be the multicenter retrospective study of the North American Gamma Knife Consortium.[31] Among 512 patients with nonfunctional pituitary adenomas, 94% had prior resection and 7% had prior fractionated radiotherapy, the median age at the time of SRS was 53 years. Most patients had some degree of baseline pre-SRS hypopituitarism. The median SRS dose to the tumor margin was 16 Gy. The actuarial rate of tumor control, assessed radiographically, was 95% and 85% at 5 and 10 years post-SRS, respectively. New or worsened hypopituitarism after SRS was noted in 21% of patients, most commonly manifest as thyroid or cortisol deficiencies. Prior fractionated radiotherapy and higher tumor dose were associated with a higher risk of endocrinopathy. New or progressive cranial nerve deficits occurred in <10% of patients. In multivariate analysis, decreasing age, increasing volume, prior fractionated radiotherapy, and prior pituitary axis deficiency were predictive of new or worsening cranial nerve dysfunction. No patient died as a result of tumor progression. The authors concluded that SRS is effective and well-tolerated for recurrent or residual nonfunctional pituitary adenomas. A marginal dose of 16 Gy to 18 Gy, lower if needed to constrain the maximum point dose to the optic pathway structures below 10 Gy to 12 Gy, appears a reasonable consideration in this setting.

Functioning pituitary adenomas are also commonly treated with SRS, and likewise there have been dozens of studies published since 2000.[30] A key difference in both clinical goal and follow-up evaluation is that the intent is to achieve endocrine normalization that is evaluable by serum or other assay. Table 23-1 includes a summary of the five largest series of SRS for Cushing disease or acromegaly published since 2007. Note that the doses employed are typically higher than for nonfunctioning tumors; prescription doses on the order of 20 Gy to 25 Gy are considered reasonable. Also, there is typically a delay of 1 to 2 years after SRS before the endocrine remission is achieved. Limited data suggest that it might be advantageous to discontinue pharmacological suppression of pituitary hormonal secretion at the time of SRS, possibly because the octreotide reduces the metabolic activity and proliferative activity within tumor cells, allowing opportunity for repair of radiation damage.[40]

AVM

Steiner et al at the Karolinska Institute are credited with the first use of SRS in the management of an AVM.[41] A dose of 25 Gy was prescribed in an effort to obliterate the fistulous point of a sizeable AVM. Success was achieved, and since then. SRS has emerged as an important modality in the treatment of AVM. Numerous centers have reported clinical outcomes in large series, not infrequently including 500 or more patients.[30] Representative series from the University of Pittsburgh and the University of Virginia document an obliteration rate in the range of 70% or higher with a low risk of serious toxicity, with doses in the range of 20 Gy to 25 Gy for small lesions (<4 cc), and somewhat lower doses for larger lesions.[42,43] In the latter analysis, factors associated with a favorable outcome included no prior hemorrhage, AVM in a noneloquent location, and AVMs with a volume of less than 4 cc. When the target volume exceeds 10 cc to 12 cc, consideration is given to a staged treatment regimen, whereby portions of the lesion are treated to a dose of 16 Gy to 18 Gy, followed by a break of 4 to 6 months, and then SRS to another portion.[44]

Meningiomas and Other CNS Tumors

SRS can play an important role in the management of intracranial and skull-based meningiomas. Although most are benign low-grade tumors, these neoplasms may develop in locations that can cause symptoms indirectly via mass effect on eloquent areas such as the brainstem or motor cortex or can directly cause pain and threaten cranial nerve functional compromise if located along the skull base. Numerous single-institutional experiences have been published on this

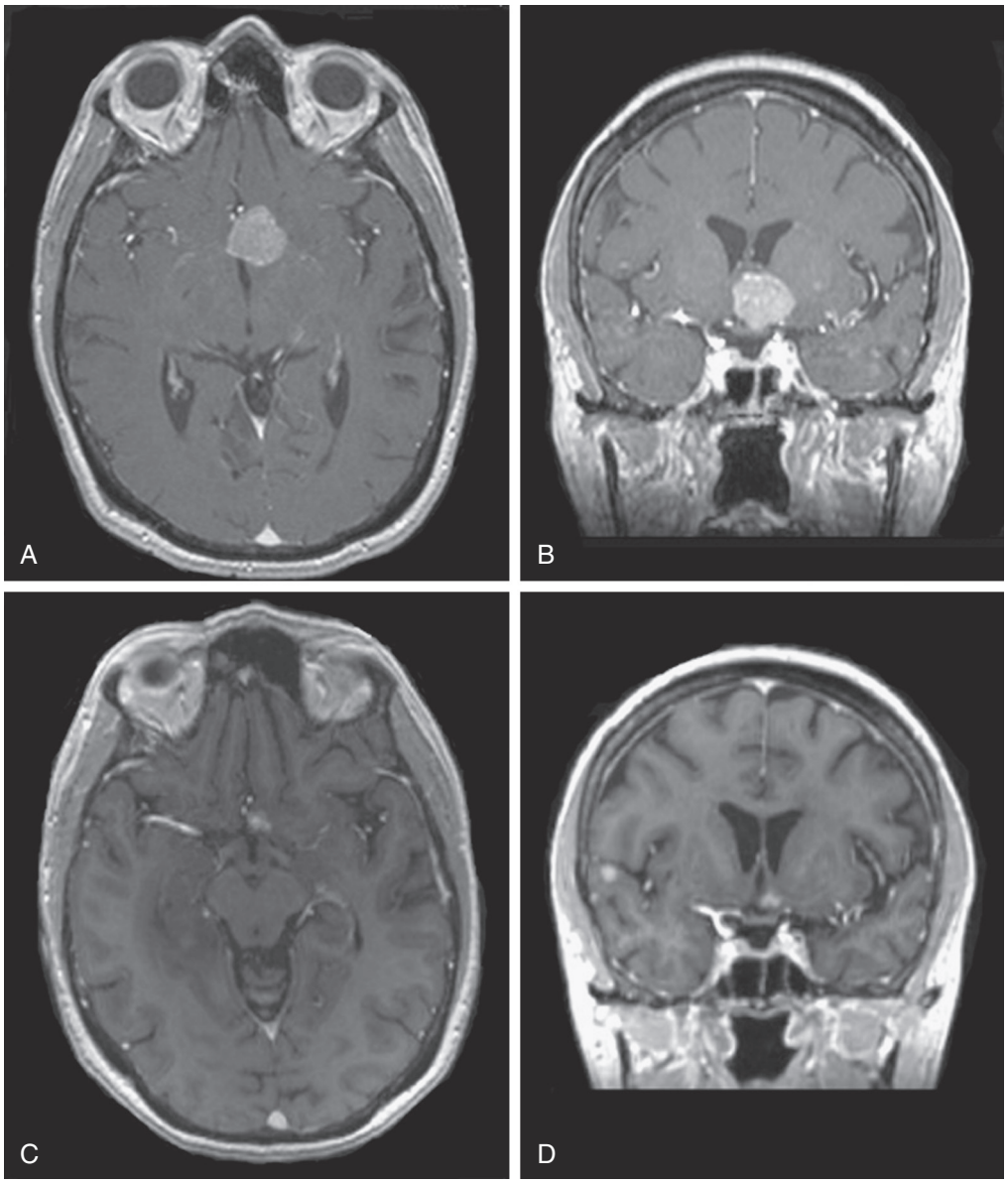


Figure 23-2 The patient is a 54-year-old woman with a history of metastatic non–small cell lung cancer. She underwent stereotactic radiosurgery (SRS) to treat a left perioptic brain metastasis. The tumor was treated in a single session with a margin dose of 16 Gy and a maximum point dose to the optic pathway of 12 Gy. The metastatic lesion is shown on the pre-SRS postcontrast axial **(A)** and coronal **(B)** magnetic resonance imaging (MRI). Six months later, the patient's visual fields and acuity were stable. Her tumor had markedly regressed as demonstrated by the follow up postcontrast axial **(C)** and coronal **(D)** MRIs. Of note, **D** shows a new metastatic lesion in the right Sylvian fissure region that was later treated with SRS.

TABLE 23-1 Summary of Selected Recent Series of Stereotactic Radiosurgery (SRS) for Cushing Disease or Acromegaly

First Author [Reference]	Number of Patients	Mean or Median Follow-Up, Months	Mean or Median Margin Dose, Gy	Endocrine Remission (%)
SRS for Cushing Disease				
Castinetti[32]	40	54.7	29.5	42.5
Jagannathan[33]	90	45	23	54
Petit[34]	33	62	20	52
Wan[35]	68	67.3	23	27.9
Sheehan[36]	82	31	24	54
SRS for Acromegaly				
Jagannathan[37]	95	57	22	53
Losa[38]	83	69	21.5	60.2
Wan[35]	103	67.3	21.4	36.9
Sheehan[36]	130	31	24	53
Franzin[39]	103	71	22.5	60.7

Adapted from Sheehan JP, Yen C-Y, Lee C-C, Loeffler JS: Cranial stereotactic radiosurgery: current status of the initial paradigm shifter. J Clin Oncol 32(26): 2836-2846, 2014.

indication for SRS. A representative example is the most recent update of the Mayo Clinic experience, in which Pollock et al reported on 251 patients treated between 1990 and 2008.[45] The mean patient age was 59 years. Most of the tumors were located in the skull base or tentorium. The mean treatment volume was approximately 8 cc, and the mean tumor margin dose was 16 Gy. After a mean follow-up of more than 5 years, only 3 patients had manifested in-field tumor progression. There was radiographic evidence of tumor size decrease in more than 70% of patients, and no patient died of radiation-related complications. No radiation-induced tumors were observed.

Santacroce et al reported a large European multicenter experience of SRS for meningiomas in 2012.[46] A total of 15 centers contributed data to the retrospective analysis. The median tumor volume was 4.8 cm^3, and median dose to tumor margin was 14 Gy. The median imaging follow-up was 63 months. Similar to the Mayo Clinic experience, the volume of treated lesions was noted to decrease in 58% of cases and remained unchanged in another 34.5%, for a crude local control rate of 92.5%. Tumor control was higher for imaging-defined tumors, female gender, and for skull base compared to convexity tumors.

Prescription dose selection is often influenced by tumor location. For lesions near the cerebellopontine angle, a marginal dose on the order of 13 Gy to 14 Gy is generally advisable,[47] especially considering the need to respect adjacent normal tissue dose constraints. The QUANTEC recommended limit for maximum point dose to the brainstem is 12.5 Gy.[27] For locations where critical structures are not dose-limiting, a marginal dose in the range of 15 Gy to 16 Gy is reasonable.

SRS can also play a role in an assortment of less common indications. This includes recurrent hemangiopericytomas[48-50] and recurrent high-grade glioma,[51,52] among others. Acoustic neuromas (also called vestibular schwannomas) are also commonly treated with SRS[53]; an example case is shown in Figure 23-3.

Brain Metastases

By far the most common current indication of SRS is in the management of brain metastases. In this regard, there are abundant retrospective and also numerous prospective clinical studies.

Because a patient who develops one or more brain metastases is then known to have a risk of manifesting other lesions later, one clinical question that has been asked often asked is whether adjuvant whole brain radiation therapy (WBRT) provides clinical benefit by eradicating occult micrometastases in the brain present at the time of diagnosis with brain metastases. Table 23-2 contains a summary of the four randomized studies performed in the last decade that compared the outcomes of patients who had initial SRS or surgical resection (S) followed by observation or WBRT.[54-57] In addition to the criteria shown in the table, in each study, eligibility typically required good performance status and stable systemic disease. The SRS dose employed was in the range of 18 Gy to 25 Gy. The lack of survival benefit with the addition of WBRT is generally explained by the success of salvage therapy for subsequent brain relapse, which effectively equalizes the chance for durable survival. Additionally, in the study by Chang et al at the M. D. Anderson Cancer Center, the primary endpoint was cognitive decline, and the trial had to be stopped early because of excessive neurocognitive toxicity 4 months after treatment in the WBRT arm. Likewise, in the European Organization for Research and Treatment of Cancer (EORTC) study, a secondary analysis of Health-related Quality of Life (HRQOL) revealed that patients in the observation only arm reported better HRQOL scores than did patients who received WBRT.[58] The differences were statistically significant and clinically relevant, especially during the early follow-up period. Taken together, these studies support a strategy of initial S or SRS for patients with limited brain metastases, followed by close surveillance and salvage therapy later as needed.

Another question commonly asked with regard to SRS for brain metastases is whether there is an upper limit of lesions above which SRS is not appropriate and WBRT should be employed instead. Although the diagnosis-specific graded prognostic assessment index includes number of lesions as a component for certain histologies, it does not address how those patients are ideally managed.[58a] Numerous recent reports have indicated that a patient's prognosis, when treated by SRS, is predominantly driven by performance status and other factors and not the number of lesions. For example, in the M. D. Anderson experience reported by Likhacheva et al, a total of 251 patients underwent SRS for initial treatment of brain metastases.[59] SRS was used as the sole management for most patients but was combined with salvage treatment with SRS, WBRT, or resection on about one third of cases. The median number of brain metastases was 2 (range, 1 to 9). The median overall survival (OS) was 11.1 months. On multivariate analysis, statistically significant predictors of OS were

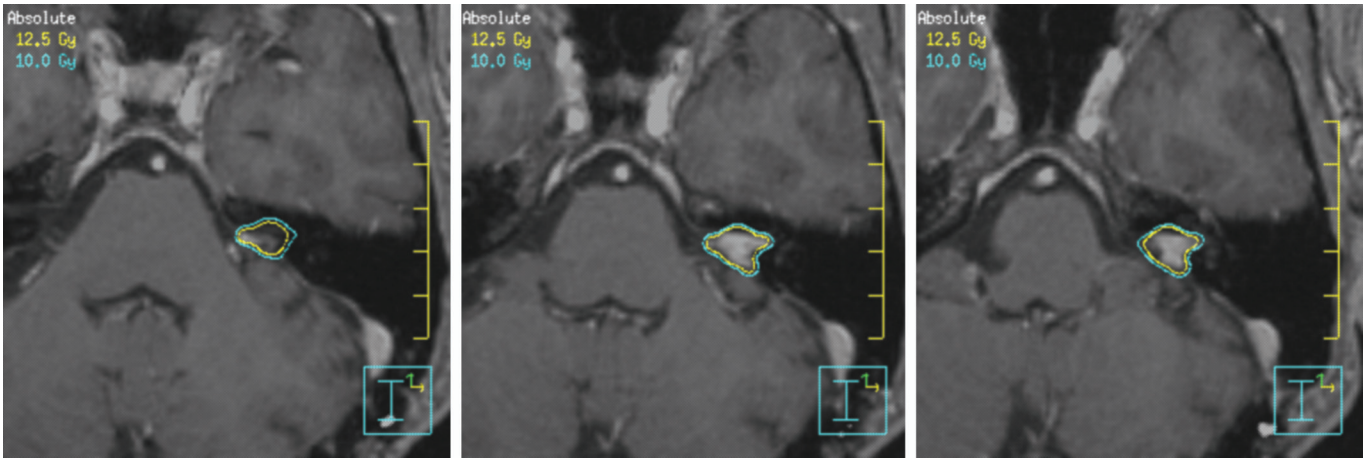


Figure 23-3 Three selected axial cuts through a vestibular schwannoma showing the resulting conformal treatment plan using four different isocenters. The gadolinium contrast enhanced thin slice T1-3D-SPGR MRI data set has been fused to the underlying stereotactic computed tomography (CT) to visualize the vestibular schwannoma. The 12.5-Gy treatment isodose line and the 10-Gy isodose line are shown.

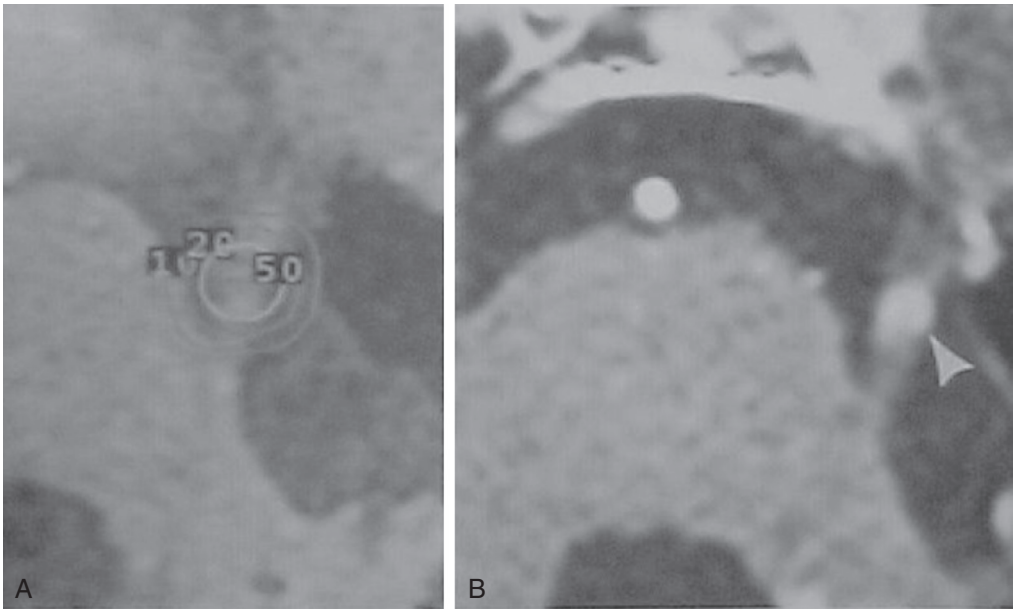


Figure 23-4 **(A)** Typical Gamma Knife radiosurgery dose distribution for trigeminal neuralgia targeted at the root entry zone of cranial nerve V (CN V). The prescription dose is typically 70 Gy to 90 Gy prescribed to the 100% isodose line. **(B)** Magnetic resonance imaging (MRI) 6 months after radiosurgery demonstrating radiographic changes on CN V.

TABLE 23-2 Randomized Studies of Stereotactic Radiosurgery (SRS) versus SRS or Surgery (S) Plus Whole Brain Radiation Therapy (WBRT) for Patients with Brain Metastases

First Author [Reference]	Eligibility	Number of Patients	Median OS (mo.) No WBRT	Median OS (mo.) + WBRT	Comment
Aoyama[51]	1-4 lesions <3 cm diameter	132	8.0	7.5	
Muacevic[52]	1 resectable lesion <3 cm diameter	70	10.3	9.5	SRS vs S + WBRT
Chang,[53] MDACC	1-3 lesions <3 cm diameter	58	15.2	5.7	Trial stopped early because of neurocognitive toxicity in WBRT arm
Kocher,[54] EORTC	1-3 lesions <3.5 cm if 1 <2.5 cm if >1	359	10.9	10.7	SRS or S alone or plus WBRT

EORTC, *European Organization for Research and Treatment of Cancer;* MDACC, *M. D. Anderson Cancer Center;* OS, *overall survival.*

presence of extracranial disease, total tumor volume greater than 2 cc, age ≥60 years, and diagnosis-specific graded prognostic assessment. The number of brain metastases was not predictive of OS or distant brain failure.

Other data indicating that there does not appear to be a number of brain metastases above which SRS is contraindicated are recently reported Japanese experiences. The Japanese Leksell Gamma Knife (JLGK) Society undertook a prospective study of SRS without WBRT (JLGK 0901) to establish evidence that such a treatment strategy is feasible for 5 to 10 brain metastases. A preliminary report showed that the overall survival for patients with 5 to 10 brain metastases was almost the same as that of patients with two to four brain lesions.[60] More recently reported analyzes are confirmatory.[61]

Functional Disorders

Although a variety of functional disorders have been treated with SRS over the years, the currently most common and widely accepted functional indication for SRS is for medically refractory pain from trigeminal neuralgia.[62] The typical dose given is 70 Gy to 90 Gy prescribed to a point located near where the fifth cranial nerve exits the brainstem (Figure 23-4). In a representative study from the University of Maryland, 112 patients were treated with SRS to a median prescription dose of 75 Gy (range, 70 Gy to 80 Gy).[63] Among 95 who were compliant with follow-up surveys, the median follow-up was 5.6 years (range, 1 year to 10 years). Before SRS 88% of patients had inadequate control or severe pain on medication, whereas the remainder described some pain but controlled on medication. After SRS 64% reported no pain and no requirement for medications, 5% had no pain but were still on medication, 12% had some pain controlled on medication, and the rest still had inadequate pain control. The median time to response was 2 weeks (range, 0 weeks to 12 weeks), and the median response duration was nearly 3 years. The actuarial rates of freedom from treatment failure at 1, 3, 5, and 7 years were 60%, 41%, 34%, and 22%, respectively. Response duration was significantly better for those who had no prior invasive treatment versus those in whom a previous surgical intervention had failed (32 versus 21 months, $p < 0.02$).

CONCLUSIONS

SRS is an established method of ablating brain metastases and AVMs as well as treating certain benign intracranial neoplasms and trigeminal neuralgia. Careful patient selection is important and is best done within the context of a multidisciplinary team approach involving the radiation oncologist, neurosurgeon, and other caregivers involved in the patient's management. With proper attention to technique and an especially thoughtful respect for normal tissue dose tolerances, SRS achieves a clinically valuable result in the majority of patients and has a low risk of serious toxicity.

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CHAPTER

24 Stereotactic Body Irradiation: Extracranial Tumors

Brian D. Kavanagh and Robert D. Timmerman

The success of stereotactic radiosurgery (SRS) for intracranial lesions spawned interest in applying the same principles of narrowly focused high-dose per-fraction irradiation in the management of selected extracranial tumors. The transition included an initial effort to design and implement a surgically placed rigid frame for spine immobilization,[1] but soon thereafter noninvasive means to target lung, liver, and other non-brain lesions were developed.[2,3]

Stereotactic body radiation therapy (SBRT) is the current American Medical Association Common Procedural Terminology (CPT) name applied in the United States to describe the management and delivery of image-guided high-dose radiation therapy with extracranial tumor-ablative intent within a course of treatment that does not exceed five fractions. Other labels that have been used in the past include extracranial stereotactic radiosurgery and various vendor-created nicknames, and a moniker that has been used in recent years is stereotactic ablative radiotherapy, which emphasizes the ablative potential of the treatment and has an appealingly onomatopoetic acronym (SABR). For simplicity the acronym *SBRT* will be used throughout.

In this chapter we review technical considerations, radiobiological implications, and normal tissue dose constraints for SBRT. Clinical outcomes after SBRT for common indications will be presented. The radiation physics of SBRT are discussed in a separate chapter in the textbook (Chapter 7).

SAFETY CONSIDERATIONS AND TECHNICAL ASPECTS OF STEREOTACTIC BODY RADIATION THERAPY

Relative to cranial SRS, the major additional practical hurdle that must typically be overcome to target an extracranial tumor with SBRT accurately and precisely involves accounting for breathing-related motion, present to some extent for nearly all cases apart from largely immobile spine and paraspinous tumors. Periodic breathing motion displacements have been both quantified and, if necessary, controlled with equipment and procedures used for simulation/planning and consistently applied toward treatment. Positioning errors (e.g., misalignment) either during a treatment or between treatments would also otherwise require expansion of targets. Numerous linear accelerator manufacturers now offer SBRT-ready treatment delivery systems that integrate a high performance linear accelerator with one or another form of image guidance technology, thus ensuring proper target relocalization and beam alignment. Collectively, these SBRT systems and procedures allow the use of considerably smaller fields compared with conventional radiation therapy without missing the target.

The American Society for Radiation Oncology (ASTRO) has issued guidelines on SBRT,[4] and the American Association of Physicist in Medicine (AAPM) Task Group 101 report expanded and augmented the ASTRO guidelines.[5] More recently, ASTRO also produced a white paper on quality and safety in SRS and SBRT.[6] In addition to describing the personnel and training requirements, the reports highlight key features of the quality assurance (QA) measures necessary to ensure the safety of the procedure.

The complete process of care for a patient receiving SBRT involves a multistep process that can involve patient immobilization, motion assessments (and motion-management if necessary), planning computed tomography (CT) image acquisition, analysis and processing of any four-dimensional image sets, fusion of the planning images with relevant diagnostic image sets, target delineation, dosimetric planning, patient-specific quality assurance testing, patient setup on the treatment couch, acquisition of guidance images to allow target relocalization, deployment of any motion-managing techniques or devices, proper initialization and commencement of the patient's unique beam and/or arc sequence, real-time monitoring of the integrity of the treatment delivery process, and the patient's stability and tolerance. At each step along the way are opportunities for systematic errors, miscalibrations, miscalculations, and any number of operator mistakes.

Regarding the possible purely technical sources of errors such as impaired performance of gantry motion or incorrect registration of pretreatment cone beam CT scans with the planning images in the image guidance software, careful initial commissioning and subsequent regular maintenance checks of individual components of the system are mandatory. Additionally, it is strongly recommended that there be end-to-end testing that incorporates all of the linked component parts to ensure that the additive impact of numerous small errors do not accumulate to a clinically relevant systematic targeting error whereby the planning target volume is not properly irradiated for any combination of reasons. The possibility of human error can never be completely eliminated. However, as noted in the chapter on stereotactic irradiation of central nervous system tumors, steps to reduce the chance of errors include the use of checklists and the development of a general culture of safety in which communication flows freely and nonjudgmentally among colleagues, with the common goal of quality patient care.[7]

SBRT requires proper patient repositioning, target localization, and management of breathing-related motion. Commercially available immobilization devices include several types of body frames with external fiducial markers, but these or any frameless system must always be used with accompanying image guidance that involves ultrasound, kV radiographs, CT scan, or magnetic resonance imaging (MRI) to verify the location of internal targets relative to the beams to be used (Figure 24-1). Because SBRT treatment sessions take more time than conventional external beam treatments, patient comfort is an important issue to lessen the chance that the patient might shift his or her position between the time of image guidance and treatment delivery.

Breathing motion management can be accomplished in one of several ways. Motion-dampening techniques involve light to moderate abdominal compression coupled with thoughtful patient coaching intended to transfer the predominant breathing forces from primarily abdominal (diaphragmatic contraction) to primarily chest wall (external intercostals, scalene, and sternocleidomastoid contraction). In this way, breathing forces

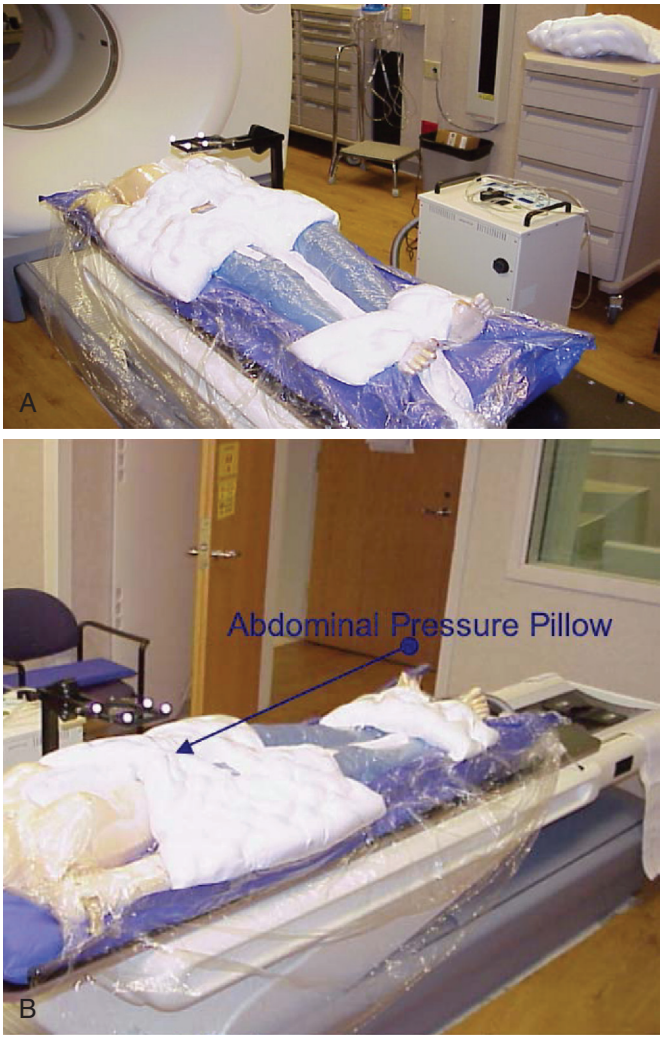


Figure 24-1 An example of a patient immobilization device for SBRT.

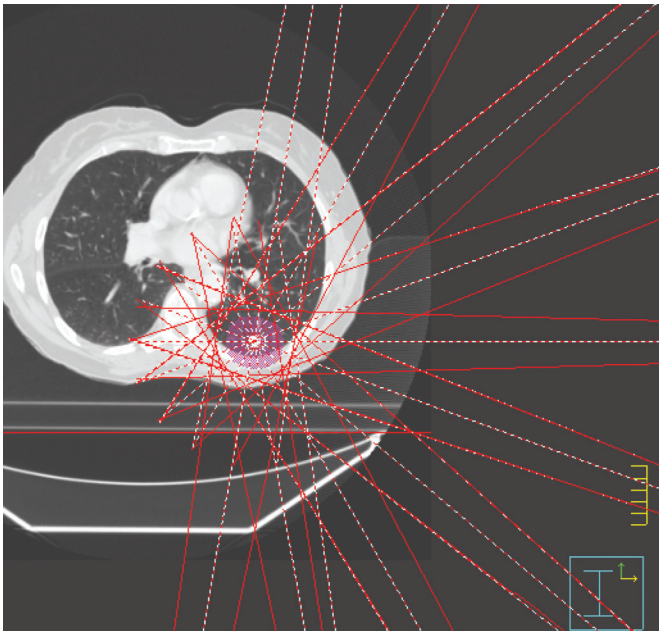


Figure 24-2 Typical beam arrangement and dose distribution for SBRT to a peripheral stage I lung cancer.

that otherwise put a tumor into motion with larger displacements are reduced while still facilitating an adequate tidal volume. Also within this category are coached breath hold maneuvers to "freeze" the tumor in space by drawing in and holding a constant tidal volume (e.g., deep inspiration) and holding that volume while the radiation beam is engaged. Gating systems may be used for SBRT in the same manner as for conventionally fractionated radiotherapy: the movement of external surface markers is correlated with phases of the breathing cycle, and beam output is triggered only when the markers are located within a preselected segment of the breathing cycle, implying tumor location within the expected range of motion. Tracking or "chasing" systems move the radiation beam to follow the movement of the tumor. Both breath hold and gating methods have a duty cycle whereby the beam is turned on and off for periods of time, thus lengthening the total treatment time. To some degree these motion management techniques can be used in conjunction (e.g., abdominal compression and gating) to reduce the overall target displacements or duty cycle.

Most clinical implementation of SBRT thus far has involved high-energy photons as the source of therapeutic radiation. However, charged particles could also be used. There is no absolute standard or consensus class solution for the combination of beam or arc angles best suited for any given clinical situation, and each case can present idiosyncratic challenges. In general, though, to achieve a tightly focused high-dose distribution within the planning target volume (PTV) and rapid dose fall-off outside the PTV, a combination of multiple (often 7 to 10) noncoplanar beams or multiple arcs is often required (Figure 24-2). Intensity modulation across the individual beams or arc segments can be incorporated within SBRT, but it is important to bear in mind that as for cranial SRS, it is typically advantageous to allow for a dose hotspot to accumulate inside the PTV to steepen the dose falloff outside the target, exploiting the natural gradient of the lateral beam penumbra to some extent in this regard. One notable exception to this practice would be in the case of prostate SBRT, where it is important to avoid a hot spot in the region of the urethra.

CLINICAL RADIOBIOLOGY AND NORMAL TISSUE DOSE CONSTRAINTS

The emerging knowledge about high-dose per-fraction irradiation is reviewed in more detail in the chapter on stereotactic irradiation of CNS tumors. Briefly, the mathematical models established to describe the relationship between radiation dose and biological effect in tumor and normal tissue that are generally reliable for conventionally fractionated radiotherapy are less stable in the setting of high-dose per-fraction irradiation. The linear quadratic model tends to overestimate the in vitro cytotoxicity of doses on the order of 8 Gy to 10 Gy or higher, and yet there is added uncertainty with regard to the in vivo effects of doses in this range because of the suspected extra effect of endothelial cell apoptosis, which can lead to tumor cell death via an early antiangiogenic mechanism as well as likely more late-fibrosing vascular effects. Given these caveats concerning traditional radiobiological models, for the purpose of predicting the effect of SBRT on tumors and normal tissues, it is best to rely whenever possible on empiric observations that relate dose or dose-volume parameters to directly observed rates of tumor control or normal tissue toxicity.

SBRT Dose versus Tumor Control

There are numerous reports that support the concept of a dose-tumor control relationship over the range of doses that have been explored for lung and liver SBRT. For example, McCammon et al reviewed the records of 141 consecutive patients with 246 lung or liver lesions treated with three-fraction SBRT regimens.[8] Lesions treated to a nominal dose of 54 Gy or greater had a 3-year actuarial local control rate of 89.3% compared with 59.0% and 8.1% for those treated to 36 Gy to 53.9 Gy and less than 36 Gy, respectively.

Similarly, Olsen et al reviewed the records of 130 patients who underwent definitive lung cancer SBRT to a single lesion, receiving 18 Gy × 3 fractions for peripheral tumors (n = 111) and either 9 Gy × 5 fractions (n = 8) or 10 Gy × 5 fractions (n = 11) for tumors that were central or near critical structures.[9] The observed local control after 1 or 2 years were, respectively, 75% and 50% for 9 Gy × 5, 100% and 100% for 10 Gy × 5, and 99% and 91% for 18 Gy × 3. No difference in local control or overall survival (OS) was found between the 10 Gy × 5 and 18 Gy × 3 groups, but treatment with 9 Gy × 5 was the only independent prognostic factor for reduced local control on multivariate analysis.

In yet another study that was particularly robust because of the structured dose escalation within a prospective trial, Rule et al treated patients with hepatic metastases in three consecutive dose-escalation cohorts: 30 Gy in three fractions, 50 Gy in five fractions, and 60 Gy in five fractions.[10] Twenty-seven patients, 9 in each cohort, with 37 lesions were enrolled and treated: 17 men and 11 women; median age 62 (range 48 to 86) years. The most common site of primary disease was colorectal cancer. The 2-year actuarial local control rates were 56%, 89%, and 100% for the 30 Gy, 50 Gy, and 60 Gy cohorts, respectively. There was a statistically significant difference for local control between the 60 Gy and 30 Gy cohorts (p = 0.009) but not between the 60-Gy and 50-Gy cohorts (p = 0.56) or the 50-Gy and 30-Gy cohorts (p = 0.091). Thus, taken together, the results of these studies support that SBRT doses in the range of 50 Gy to 54 Gy or higher in three to five fractions provide superior local control rates than less aggressive regimens for liver and lung lesions.

Normal Tissue Dose Constraints

There is a growing literature of reports characterizing SBRT dose-effect relationships in normal tissues, notably for liver, lung, and intestinal tissue. In an effort to analyze these data in aggregate to search for consistent trends across series, the AAPM has supported a working group initiative involving dozens of volunteers charged with cataloging all of the published SBRT studies that include clinical information, treatment details, and rates of toxicity. Although the results of this effort might eventually illuminate correlations not appreciated when only smaller numbers of patients in individual reports are considered, there are already strong indicators of effects that are routinely observed after high-dose per-fraction irradiation above given thresholds of dose or volume, some considered clinically harmless and others associated with toxicity.

One feature of the normal tissue effect of liver SBRT consistently observed within the first few months after SBRT is a zone of hypodensity observed on follow-up CT scans corresponding to the volume that received approximately 30 Gy in three to five fractions. This phenomenon, first described by Herfarth et al following single dose liver SBRT,[11] is related to a local veno-occlusive effect.[12] There is no clinical consequence associated with the finding per se, and it will resolve over time, but the Herfarth effect can obscure the assessment of tumor response within the first few months after liver SBRT. Of greater utility for this purpose would likely be a positron emission tomography (PET) scan, but here it should be appreciated that it will take months for the full effect of treatment to mature and lower the standardized uptake value (SUV) of target lesions.[13]

For conventionally fractionated radiotherapy, it has been observed that the risk of significant radiation-induced liver disease (RILD) characterized by ascites, anicteric hepatomegaly, and elevated liver enzymes is well correlated to the mean liver dose.[14] Fortunately, RILD is an exceedingly rare complication after liver SBRT because the mean dose to uninvolved liver parenchyma is generally well below what has been given in the past using conventional techniques. Indeed, normal tissue complication probability (NTCP) models established for conventional fractionation have not reliably predicted toxicity after liver SBRT, typically overestimating the risk.[15]

The QUANTEC (Quantitative Analyses of Normal Tissue Effects in the Clinic) summary recommendations for liver SBRT given in a three fraction regimen are to constrain the mean normal liver dose (liver minus gross tumor volume) to less than 13 Gy for primary liver cancer and less than 15 Gy for metastases and to ensure that at least 700 mL of normal liver receive less than 15 Gy.[14] This latter recommendation is based on a so-called *critical volume model*. Relevant for organs of parallel structure, this construct requires recognizing how much volume of the organ is essential and must be protected from functional ablation. The estimate for liver that at least 700 mL should receive less than 15 Gy during a three-fraction SBRT course was originally derived from a combination of prior reports of outcomes after partial hepatectomy documenting approximate minimum volumes required and good faith estimates of the effects of that dose of radiation extrapolated from prior reports of conventionally fractionated treatment.[16]

Analogous to the Herfarth reactions after liver SBRT are observations of lung inflammation and fibrosis in and near the zone of high dose irradiation after lung SBRT. Diot et al studied post-SBRT follow-up CT scans of 62 patients who received lung SBRT prescribed to a median dose of 54 Gy (range, 30 Gy to 60 Gy) in three to five fractions. The surrogate marker of parenchymal injury was an increase in Hounsfield Units (HU), presumed here to represent postinjury scar tissue. Across a range of follow-up intervals, the HU values linearly increased with dose until 35 Gy and were constant thereafter. For 3, 18, 24, and 30 months, the rate of HU increase with per dose was consistent; however, at 6 months the rate was similar below 20 Gy but then doubled above this threshold, suggesting a phase of peak post-SBRT inflammation that subsides at later time points. These observations largely validated the quantitatively similar contemporaneous work of Palma et al, who also noted an independent effect on promoting lung fibrosis with larger PTV.[17]

Radiation pneumonitis, characterized clinically as cough, fever, shortness of breath and chest pain, and associated radiographically with a geometric alveolar infiltrate corresponding to irradiated volumes, is an uncommon event after lung SBRT. In the Radiation Therapy Oncology Group (RTOG) 0236 study in which patients with medically inoperable early stage lung cancer were treated with SBRT to a nominal dose of 60 Gy in three fractions (recalculated as 54 Gy in three fractions when accounting properly for tissue heterogeneity), the incidence of grade 3 radiation pneumonitis was 4%, with no grade 4 or 5 radiation pneumonitis.[18] A subsequent analysis of the same study documented no clinically significant changes in pulmonary function after treatment.[19] For a large cohort of patients treated at the M. D. Anderson Cancer Center, Chang et al found on multivariate analysis that only the mean dose to ipsilateral lung (lung minus gross tumor volume) was a significant predictor of grades 2 to 3 radiation pneumonitis after lung SBRT,

with a sharp increase in incidence when this metric exceeded approximately 9 Gy.[20] It has also been noted that tumor location might have a substantial influence on risk of toxicity, with a higher rate of severe toxicity observed for centrally located tumors in the initial Indiana University experience.[21]

The intestinal tract is a thin-walled structure that is susceptible to injury from high-dose per-fraction irradiation. For the major segments of the gastrointestinal tract studied to date (esophagus, duodenum, and rectum), the most significant predictor of post-SBRT late toxicity is a dose-volume metric whereby toxicity is triggered when the amount of tissue receiving a certain dose exceeds a threshold volume.[22-24] For example, in the esophagus, after a single fraction exposure, there is an escalated risk of grade 3 or higher toxicity if the volume receiving 12 Gy exceeds approximately 4 cc[22]; similarly, the risk for duodenal toxicity, grade 2 or higher, escalates sharply if the volume receiving a single fraction of 15 Gy exceeds approximately 9 cc.[23] In an analysis of a dose escalation study of prostate SBRT, the risk of grade 3 or higher late rectal toxicity was significantly elevated when the volume of rectal wall receiving 50 Gy exceeded 3 cc.[24]

CLINICAL INDICATIONS AND OUTCOMES

Lung Cancer

An important unmet medical need provided the impetus for much of the early development of SBRT. Until the advent of SBRT, a patient with medically inoperable stage I lung non–small cell lung cancer (see Chapter 44) would derive rather limited clinical benefit from conventionally fractionated radiotherapy (CFRT). The Surveillance, Epidemiology, and End Results (SEER) registry indicated a median survival of a little more than a year is typical without any radiotherapy, extending to approximately 21 months with CFRT, with an expected 3 year OS on the order of 30%.[25] The challenge for these patients was that CFRT did not achieve a high rate of local control and was poorly tolerated in a patient population especially susceptible to pulmonary toxicity. The typical single-institution analysis from centers of excellence revealed 3-year local control rates of approximately 50%, with consistently disappointing median survival of less than 2 years.[26,27]

Breakthrough improvements relative to this baseline were achieved in studies performed contemporaneously in separate multiinstitutional studies on two continents. In the Nordic Group study from Europe and the RTOG study from North America, SBRT was employed to treat patients with medically inoperable early stage lung cancer to a dose of 45 Gy to 54 Gy in three fractions, achieving a local control of more than 90% and a 3-year OS of approximately 60%.[18,28] These results are roughly twice what was typically achieved historically with CFRT, establishing a new standard of care in this setting.

In addition to its well-established role in medically inoperable early stage lung cancer, SBRT has gained traction as an acceptable approach for a variety of other indications. Primary prostate, pancreas, and hepatocellular cancers may be well treated with SBRT. Additionally, SBRT can serve as a noninvasive means of ablating oligometastatic tumor deposits in the lung and liver as well as controlling challenging para-spinal tumor deposits.

Prostate Cancer

King et al have reported tumor control outcomes and prospectively collected patient-reported quality of life effects in 1100 patients who had been enrolled in prospective trials and registries of SBRT for prostate cancer[29,30] (see also Chapter 53). The median follow-up was 3 years and 194 patients remained evaluable at 5 years. After a median dose of 36.25 Gy in four to five fractions, the 5-year biochemical relapse free survival rate was 95%, 83%, and 78% for patients with Gleason Score 6, 7, and 8, respectively, and 95%, 84%, and 81% for low-, intermediate-, and high-risk patients, respectively. A temporary decline in self-reported urinary and bowel function was observed within the first 3 months after SBRT which returned to baseline status or better within 6 months and remained so beyond 5 years. A decline in sexual quality of life was observed predominantly within the first 9 months, with no significant impact from androgen deprivation or patient age. SBRT for prostate cancer is less costly than other forms of radiation therapy.[31,32] However, an analysis of the experience of early adopters of this technology suggested there the rate of genitourinary toxicity after SBRT for prostate cancer might be slightly higher than for CFRT,[32] and so continued analyses of ongoing prospective studies will be important to understand what metrics are important for optimizing the quality of care in this setting.

Gastrointestinal Cancers: Pancreatic and Hepatocellular

Regarding the use of SBRT for locally unresectable pancreatic cancer, in an early Danish study, a large volume of bowel received a high dose (30 Gy or higher in three fractions), leading to substantial toxicity.[33] Learning from that experience, investigators from numerous institutions have reported the safe administration of SBRT to tightly focused fields around the primary pancreatic tumor, often sandwiching cycles of chemotherapy around the SBRT with minimal interruption of the chemotherapy, achieving survival and toxicity rates that compare favorably with CFRT[34-36] (see also Chapter 48).

Yet another domain in which SBRT has been explored is the primary treatment of hepatocellular cancer (HCC) (see also Chapter 49). Here, as for the other primary cancers noted previously, SBRT is an appealingly noninvasive therapy. SBRT can be administered either as definitive therapy or as a bridge to liver transplant.[37] In the Indiana University experience, 60 patients with liver-confined HCC were treated with SBRT to doses adjusted according to pretreatment liver function.[38] For Child-Pugh (CP) class A patients, the majority of patients received a prescription dose of 48 Gy in three fractions; in contrast, for CP class B patients, the dose was reduced to 40 Gy in five fractions. With a median follow-up time of 27 months for the 60 patients treated (36 CP A, 24 CP B), the 2-year local control, progression-free survival, and OS were 90%, 48%, and 67%, respectively. Twenty-three patients underwent transplant a median of 7 months post-SBRT. There was no grade 3 or higher nonhematologic toxicities, although 20% of patients experienced a progression in CP class within 3 months of treatment. This latter toxicity was similar to what was noted by the Princess Margaret Hospital group in their prospective studies.[39] In a large Japanese retrospective study, patients treated with SBRT had CP A or B status and a single primary or recurrent HCC lesion 5 cm or less in maximum diameter.[40] The prescribed dose was 40 Gy for CP A and 35 Gy for CP B, given in five fractions, with a dose reduction if more than 20% of the liver received more than 20 Gy. A 5-Gy dose reduction was required if the proportion of the liver receiving ≥20 Gy exceeded 20%. For the entire cohort of 185 patients (n = 48 in the 35-Gy group; n = 137 in the 40 Gy-group), the 3-year local control and OS rates were 91% and 70%, respectively.

Oligometastases

Ever since Hellman and Weichselbaum coined the term *oligometastases* and suggested a role for conformal radiotherapy in

this context,[41] there has been steadily increasing interest in ablating limited foci of metastatic disease radiotherapeutically or by other local intervention. A full discussion of this topic is beyond the scope of the present chapter, but there are numerous reviews summarizing the canon of literature that documents durable disease-free survivorship following surgery, radiotherapy, or other local ablative modality for many patients with limited deposits of metastatic disease.[42,43] A recent example of one of the evolving paradigms in which this approach appears to have a role is in the setting of oligoprogressive disease in a patient on therapy with a novel targeted agent, where the strategy is to "weed the garden" of resistant clonogens while extending the patient's access to an agent that is still providing systemic benefit. Gan et al described the use of local ablative therapy for patients with anaplastic lymphoma kinase-positive lung cancer receiving crizotinib.[44] Among 33 patients who progressed while taking crizotinib, those with progression outside the central nervous system (n = 14) received SBRT or equivalent local ablative therapy. The 6- and 12-month actuarial local lesion control rates with SBRT were 100% and 86%, respectively. Crizotinib was continued after local ablative therapy. The use of local ablative therapy allowed a longer duration of the use of crizotinib. Patients continuing to take crizotinib for >12 months versus ≤12 months had a 2-year OS of 72% versus 12%, respectively ($p < 0.0001$).

CONCLUSIONS

SBRT has emerged as a technology with the potential to benefit cancer patients in many ways. SBRT has an established role as a standard therapy for medically inoperable early stage lung cancer and is a viable alternative to surgery and other forms of radiation therapy for numerous other malignancies. There remain opportunities to refine the technical aspects of treatment delivery as well as our understanding of the ideal patients to treat.

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CHAPTER

25 Metastatic Disease: Bone, Spinal Cord, Brain, Liver, and Lung



Kenneth Y. Usuki, Michael T. Milano, Marc David, and Paul Okunieff

Local tumor control is now achieved with modern combined modality therapy. Metastatic disease therefore dominates the survival outcomes of patients with cancer. Metastases to the bone commonly cause pain, whereas those to the lung, liver, and brain cause organ dysfunction with substantial changes in quality of life. Metastases to any of these organs can lead to a shorter life. Although palliative care comprises a large part of the clinical practice of oncology, studies show that cancer pain is often inadequately managed.[1,2]

Among painful metastases, osseous metastases[3] remain the most common cause of intractable pain in patients with cancer. Bone is the third most common site of metastases after lung and liver.[4] Metastases usually become apparent after the diagnosis of the primary tumor, but in up to 23% of patients they are the presenting problem. Bone pain results in immobility, anxiety, and depression and severely impacts a patient's quality of life. Thus, treatment of bone pain is a high priority.

Brain metastases are a devastating site of metastatic disease. Most patients with brain metastases succumb to metastatic disease within a few months.[5,6] Relatively few are candidates for open surgery, which can carry the risk of severe sequelae. The advent of radiosurgical techniques and high-quality magnetic resonance imaging (MRI) of the brain has greatly changed the outcomes for some patients with brain metastases. Patients can have improved duration of cognitive performance, with some enjoying prolonged survival.[6] The success of this approach is limited to patients with tumors in favorable regions of the brain. Among patients with lung cancer, the actuarial incidence of brain metastases can exceed 70%.[7,8] Other cancers can also have high rates, including 19% of women with metastatic breast cancer. Regarding therapy, local therapies such as surgery or radiosurgery are often supplemented by elective whole brain irradiation in patients with more than one lesion.[9]

Liver metastases are common in many cancers, and like brain metastases are usually associated with a limited median survival. Liver metastases occur in 40% to 70% of patients with progressive colorectal cancer and in a similar range of patients with progressive breast cancer or progressive lung cancer.[10,11] Treatment for liver disease, like pain, is often difficult and therefore inadequately managed. More recently there has been an effort to treat liver metastases using localized therapies. These include stereotactic radiation techniques, radiofrequency ablation, hyperthermia, and embolic therapy in addition to resection. There has been satisfactory success with many of these treatments, which appear to be improving patient outcomes. International consensus increasingly favors stereotactic liver irradiation as a local treatment for liver metastases.[12,13]

BONE METASTASES

Table 25-1[14] shows the prevalence of skeletal metastases in several autopsy series. The marked variation may be attributed to differences in the thoroughness of the pathologic examination of the skeleton. Bone scintigraphic surveys have, in general, reported higher rates of bone metastases. In a study by Tofe et al,[15] bone scans of 1143 patients with a nonosseous primary tumor were examined; 61% of the patients had an abnormal bone scan finding, and 33% had breast, lung, or prostate primary cancer.

In a prospective series of hospital patients with bone metastases, the tumors carrying the highest risk of bone metastases were those originating in the prostate (32.4%), breast (21.9%), kidney (16.4%), thyroid (11.7%), lung (10.9%), and testes (10.2%).[2] The incidence of patients developing bone metastases by primary site is shown in Table 25-2.[15]

The distribution of skeletal metastases from breast cancer is shown in Table 25-3. Similar distributions have been noted from prostate, lung, and breast primary cancers.[16-19]

Pathophysiology

Tumor cells gain access to the systemic circulation, primarily through the capillary system, but some gain access through the lymphatics; only a few of these cells are able to successfully establish a metastatic focus.[20] Indeed although circulating tumor cells are common,[21,22] they do not reliably portend metastases and when included in American Joint Committee on Cancer (AJCC) staging are considered M0-like in choice of therapy. The process of developing a hematogenous metastasis from a primary tumor includes many steps; steps that are rarely achieved by any individual circulating tumor cell.[23] The tumor must dissociate from the primary mass, gain access to the circulation, survive the immune system and circulatory shear forces, identify a host organ, and develop an exit passage to that organ. Once it enters an organ it must retain reproductive potential, proliferate, generate a vasculature, and grow. The molecular expression profiles that dictate which tumor cells can produce a metastasis, at what frequency, and in which organs are of great research interest.[24]

Cancer cells metastasize to bone mostly via hematogenous spread. Skeletal blood flow accounts for only 4% to 10% of the cardiac output,[25] and some authors believe that the incidence of skeletal metastases is higher than expected based on perfusion alone. A mechanism explaining the high incidence has been described by Weiss.[26] The microstructure of the hematopoietic marrow renders it particularly vulnerable to tumor cell accumulation and ultimate invasion. Nutrient arteries to the bone tend to subdivide into capillaries as they near the endosteal margin of the bone. These capillaries become continuous with a rich venous sinusoidal system, with a capacity six to eight times that of the osseous arterial system. More important, the circulation comes to a near standstill at this point, allowing tumor cells more time to invade the matrix.

To sustain growth, a colony of tumor cells needs to obtain its own vascular supply once it has been established. A hypothesis is that a tumor angiogenesis factor attracts

TABLE 25-1 Prevalence of Skeletal Metastases at Primary Site

Primary Site	Prevalence (%)
Breast	47-85
Prostate	54-85
Thyroid	28-60
Kidney	33-40
Bronchus	32-40
Esophagus	5-7
Other gastrointestinal	3-11
Rectum	8-13
Bladder	42
Cervix	0
Ovaries	9
Liver	16

Data from Galasko CSB: Incidence and distribution of skeletal metastases. Clin Orthop 210:14–22, 1986.

TABLE 25-2 Incidence of Bone Metastases According to Primary Site

Primary Site	No. of Patients	Patients with Bone Metastases (%)
Breast	6423	17
Prostate	144	16
Esophagus	451	6
Lung	589	5
Bladder	172	5
Rectum	274	4
Thyroid	107	4
Uterine cervix	1981	3
Uterine corpus	509	3
Head and neck	2860	2
Ovaries	586	1
Colon	153	1
Stomach	118	1

Data from Tubiana-Hulin M: Incidence, prevalence and distribution of bone mets. Bone 12:S9–S10, 1991.

TABLE 25-3 Distribution of Skeletal Metastases in 212 Breast Cancer Patients

Anatomic Site	At Presentation (%*)	At Any Time (%*)
Lumbar spine	52	59
Thoracic spine	35	57
Pelvis	31	49
Ribs	18	30
Femur	15	24
Skull	12	20
Cervical spine	11	17
Humerus	8	13
Other	3	3
Diffuse	1	12

Data from Tubiana-Hulin M: Incidence, prevalence and distribution of bone mets. Bone 12:S9–S10, 1991.
**Of all patients.*

endothelial cells to a small tumor colony that would otherwise be dependent on local tissue circulation and incapable of further invasion.[27] The production of such tumor angiogenesis factor may be partly blocked by the immune responses, presumably mediated through lymphocytes. Therefore, an established micrometastasis may attract vasculature required for growth several years later. This theory may explain the late appearance of metastases long after definitive treatment of the primary.

Some tumors, notably of breast, prostate, lung, renal, and thyroid, produce and secrete humeral mediators that stimulate osteoclast activity. These include transforming growth factor, platelet-derived growth factor, tumor necrosis factor, prostaglandins, procathepsin D, interleukins, parathyroid hormone-related protein, and granulocyte-macrophage colony-stimulating factors.[28,29]

The distribution of metastases in the skeletal system is not uniform. Bone metastases tend to involve the axial skeleton more often than the appendicular skeleton. Considering the distribution of marrow in the axial and appendicular skeleton, this higher predilection argues for specific bone marrow-derived growth factors that fertilize the soil of the bone for tumor growth.[25]

Diagnosis

Laboratory

The biochemical parameters include alkaline phosphatase, urinary hydroxyproline, and the urinary hydroxyproline-creatinine ratio lack specificity, and are of no value in the diagnosis of skeletal metastases.[30,31]

Imaging

Skeletal scintigraphy is usually the first-line imaging technique used for detecting skeletal metastases. A bone scan is more sensitive than plain radiographs and has the advantage of examining the entire skeleton. Most lesions evoke an osteoblastic response, which shows up as an increased tracer uptake.[32] Occasionally, metastases may show up as areas of decreased uptake. This may be observed in rapidly growing lesions, when bone destruction far exceeds new bone formation, or secondary to an infarction. Highly vascular metastases, such as those from a renal primary cancer, may be seen on the early vascular phase of the bone scan. Metastases not detected by a bone scan include tumors that do not evoke an osteoblastic response such as myeloma, some lymphomas, and very small deposits.[33]

Widespread metastatic disease may be misinterpreted as a normal scan with symmetric uptake. In these situations, a reduction in urinary excretion of isotope and faint or absent renal uptake with decreased bladder activity are clues of an abnormal scan.[34]

Most skeletal metastases develop in the medulla and involve the cortex later on; therefore, plain radiographs are generally insensitive.[34] Within the spine, the vertebral body is affected first, although the radiologic findings of pedicle destruction are noted first.[35]

Computed tomography (CT) scanning has been found to differentiate between metastases and degenerative joint disease, even though the two coexist, and the latter is a common cause of increased uptake on a bone scan. Muindi et al[36] reported that 50% of patients with breast cancer with a positive bone scan and a normal radiograph had obvious skeletal metastases on a CT scan, 25% had a benign cause, and 25% had a negative CT. None of the patients with a CT scan that was negative for metastases subsequently experienced metastases. CT scan is also valuable in evaluating soft-tissue involvement and can be combined with myelography for

detecting extradural tumor spread in patients unable to undergo MRI.

More recently, MRI has been described as the method of choice for examining the spine. It is more sensitive than a bone scan for detecting early metastases within the medulla, but both T1- and T2-weighted images are required.[37] It is the procedure of choice when neural compression is suspected[31] because it is less invasive than CT myelography, and a small incidence of acute deterioration of neurologic function has been reported by CT myelography.[38] When cord impingement is suspected, imaging of the entire spine should be considered because approximately 10% of patients have multiple levels of cord impingement.[39] It is also used in discriminating between benign and malignant vertebral collapse. In the future whole-body MRI could emerge for metastasis screening.[40] Disadvantages of an MRI include its high cost, exclusion of patients with metal implants, patients with severe claustrophobia, and inferior visualization of the cortex compared with a CT scan. Treatment response using MRI and CT can be difficult to evaluate.

Positron emission tomography (PET) with 18F-fluoride or 2-fluoro-deoxy-D-glucose (FDG) is used for the initial staging of many malignancies and is helpful in the diagnosis of bony metastasis. 18F-fluoride is a bone-imaging agent and forms fluoroapatite in osteoblastic cells. Uptake of 18F-fluoride is higher than for 99Tc used for bone scintigraphy.[41] This sensitivity can lead to inadvertant overdiagnosis of bone metastases, but can be useful for diagnosis, tumor localization, and assessment of treatment response. FDG is a tumor-imaging agent that uses the higher glycolysis activity in the tumor cells.[42] FDG-PET scan compared to bone scintigraphy shows a similar high sensitivity (range from 74% to 95%) but a higher specificity (range of 90% to 97%).[43-47] Limitations include traumatic, infectious, and inflammatory processes that can also accumulate glucose. Accumulation of FDG requires the tumor to have an adequate metabolic rate. Neoplasms, like prostate adenocarcinoma, are not consistently seen using PET scans.[48,49] PET images provide poor anatomic imaging but are extremely useful when employed with a concurrent CT or fused MRI image.[41,50,51]

Biopsy

Bone biopsy is not necessary routine. It is helpful in patients with no history of malignancy, in patients with a solitary lesion (in whom a more aggressive treatment approach may be indicated), and in patients with more than one suspected primary lesion.

Treatment

The primary goal of therapy is to improve quality of life. To achieve this goal, we need to decrease or eliminate pain and improve or maintain skeletal function. The complexity, duration, and cost of therapy should be low, and complications should be avoided.

Treatment recommendations must be individualized. A key consideration is patients' overall prognosis. This assessment should be based on an understanding of the natural course of the specific disease. Although the survival of patients with bone metastases is generally poor, potential long-term survivors must be identified. Long-term survivors require a more durable relief of pain, but they are also at more risk for a late, treatment-related complication. The Radiation Therapy Oncology Group (RTOG) trial[52] studied longevity among patients with bone metastases. The median survival in patients with solitary and multiple bone metastases was 36 and 24 weeks, respectively. Patients with breast and prostate primaries survived significantly longer (30 weeks to 73 weeks), whereas patients with lung cancer died within a median of 12 weeks to 14 weeks. Patients with renal cell carcinoma with solitary metastasis are also likely to be long-term survivors. Kjaer[53] monitored 25 such patients for 10 years to 14 years. The median survival was 4.3 years, with 5-year overall survival (OS) of 36%, and 10-year OS of 16%.

Pharmacologic Treatment

Systemic therapy remains the mainstay of treatment for metastatic disease, including bone metastases. For asymptomatic bone metastases not at immediate risk of fracture, disease-appropriate systemic therapy including chemotherapy, hormonal therapy, and biologic therapy is indicated. Patients may also benefit from bisphosphonate therapy.

Bisphosphonates

The discovery of compounds inhibiting calcium phosphate precipitation in plasma and urine led to an interest in the use of bisphosphonates as therapeutic agents. The inhibitory activity was attributed to inorganic pyrophosphate, but the use of this agent was limited because of its rapid hydrolysis when given parenterally. Subsequent research led to the development of pyrophosphate analogs resistant to endogenous phosphatases, now known as bisphosphonates.

Bisphosphonates inhibit osteoclast-mediated bone resorption. The exact mechanism is likely multifactorial, including direct biochemical effects on the osteoclast, prevention of osteoclast attachment to the bone matrix, and inhibition of differentiation of osteoclast precursors and recruitment.

Four Phase II trials of intravenous pamidronate every 2 weeks to 4 weeks as the sole treatment of osteolytic bone metastases in breast cancer reported similar results.[54-57] Relief of pain was noted in approximately 50% of patients, and approximately 25% showed radiographic evidence of bone healing. Similar results for bone pain have also been reported in patients with prostate cancer.

In more recent studies, one Phase II[58] and one Phase III[59] showed equivalence between zoledronic acid and pamidronate. Rosen conducted a three-arm study for patients with bone lytic or mixed disease from either breast cancer or multiple myeloma.[59] One thousand six hundred forty-eight patients received intravenous pamidronate 90-mg zoledronate in 4 mg or 8 mg every 3 weeks for 13 months. The primary endpoint was the incidence of a skeletal event and secondary endpoints were pain relief and performance status (ECOG). All treatment groups showed equivalence with a similar frequency of skeletal events at 12 months and with pain scores decreased by an average of 0.5 on a scale of 5. This randomized trial led to modification of the ASCO 2003 and the Cochrane Breast Cancer Review Group update recommendations on the use of bisphosphonates in breast cancer.[60,61] Both boards now recommend either pamidronate 90 mg intravenously (IV) over 2 hours or zoledronate acid 4 mg IV over 15 minutes for patients with an abnormal bone scan and abnormal imaging by plain radiographs on CT scan or MRI. Bisphosphonates have not yet been formally tested in patients with early, asymptomatic bone metastasis.

Zoledronic acid has also been used in prostate cancer to treat blastic metastasis.[62] Saad et al randomized 643 patients to placebo or to zometa 4 or 8 mg IV infusion every 3 weeks for 15 months. Results show a reduction in skeletal-related events from 44% to 33% with a significant p value of 0.021. Pathological fractures were reduced from 22% to 13% (p = 0.015). Onset of the events occurred at a median time of >420 days (median not reached) in the group receiving zometa and at 321 days in the placebo group. Time to disease progression or survival was similar in both groups. The need for local field radiation was not significantly different in the two groups.

Zometa has also been evaluated for the treatment of bone metastases from other disease sites; 773 patients with lung, renal, head and neck, thyroid, and unknown primaries received either a placebo or zometa 4 or 8 mg.[63] Skeletal events including hypercalcemia were significantly reduced from 47% to 38% ($p = 0.039$) and the median time to the first event was longer in the zometa group (225 days versus 155 days, $p = 0.023$).

Although zoledronic acid is well tolerated, the treating physician is advised to monitor serum creatinine before each administration. Caution is also advised for patients receiving concomitant aminoglycoside or loop diuretic because of an increased risk of hypocalcemia. Ruggiero published a retrospective review of 63 patients on bisphosphonates who suffered osteonecrosis of the jaw[64]; 57% received pamidronate and 21% zoledronic acid. Surgical treatment was required. Oral agents, such as clodronate, have low bioavailability (2%) and produce gastrointestinal side effects.

Analgesics

The optimal management of pain begins with careful assessment of the degree of pain, site, functional limitations, and concurrent neurologic symptoms.[65] The World Health Organization (WHO) analgesic ladder for cancer pain management provides guidelines for analgesic use.[66]

Step I. Nonopioid with or without adjuvant therapy
Step II. Opioid for mild to moderate pain plus nonopioid with or without adjuvant therapy
Step III. Opioid for moderate to severe pain with or without nonopioid with or without adjuvant therapy

Step I nonopioid analgesics include acetaminophen, aspirin, and other nonsteroidal antiinflammatory drugs (NSAIDs). The dose of acetaminophen should not exceed 4 g/day. Step II opioids include codeine, dihydrocodeine, hydrocodone, oxycodone, and propoxyphene. Step III opioids include morphine, oxycodone, hydromorphone, and fentanyl.

Attention should be paid to selecting the appropriate analgesic, dose, route, and schedule. Continuous, slow-release medications are generally preferred over short-acting medications. The latter can be effectively used for breakthrough pain. Allowing pain to recur between doses causes unnecessary suffering and may allow tolerance to develop. When prescribing oral opioids, the dose is about two times that of the subcutaneous dose and three times that of the intravenous dose. For patients unable to take oral medications, suppositories and transdermal patches are good options. When combining drugs, it is important to use drugs that act at different levels of the pain pathway (Figure 25-1). The combined effect can be additive and at times synergistic.

The pain of bone metastases is generally only partially responsive to opioids.[67] Many osseous metastases produce prostaglandins that induce osteolysis. NSAIDs alleviate pain by inhibiting the synthesis of prostaglandins. Corticosteroids prevent the formation of arachidonic acid (the precursor of prostaglandins) from cell membrane phospholipids. The use of NSAIDs or corticosteroids combined with morphine is usually effective.

Corticosteroids can be used when pain is caused by nerve compression. They decrease edema and reduce the pressure on the nerve. Pain relief can be achieved within 48 hours. Corticosteroids can be used as a temporary measure before a more definitive decompression is achieved with radiotherapy or surgery.

Side effects associated with the use of opioids include nausea, vomiting, constipation, urinary retention, dysphoria, mental clouding, tolerance, and addiction. Nausea and vomiting are usually self-limiting and resolve during the first week. Side effects should be anticipated, prevented, and managed aggressively.

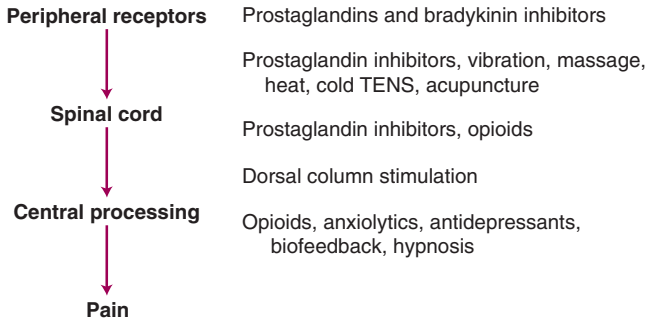


Figure 25-1 Pain pathway and analgesia interventions. *TENS*, Transcutaneous electrical nerve stimulation.

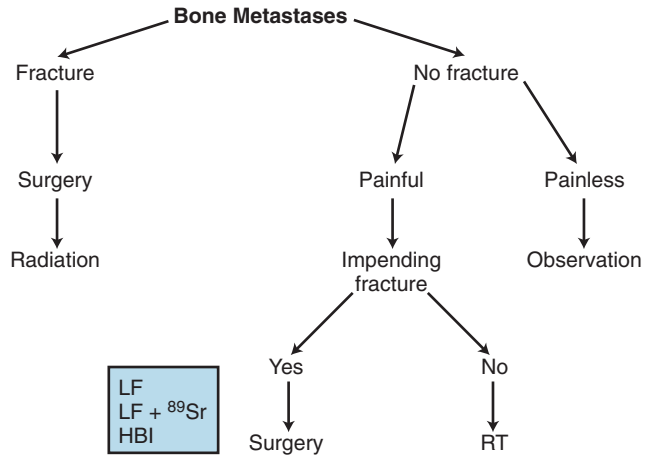


Figure 25-2 **Treatment algorithm for bone metastases.** *LF*, Local field; *LF + ^{89}Sr*, Local field plus strontium-89; *HBI*, hemibody irradiation; *RT*, radiation therapy.

Surgery

Surgery should be considered for patients with pathologic fractures or impending fractures (Figure 25-2). In the former situation, fixation can reduce pain and expedite healing. In the latter, prophylactic fixation may prevent a fracture, thereby eliminating the functional loss and reducing the risk of nonunion of a fracture.

To understand the role of surgery better, we need first to elaborate on the biomechanics of pathologic fractures. Cortical defects weaken bone, especially in the setting of torsional stress. The two general categories of cortical defects are (1) stress riser, a defect with dimensions less than the diameter of the bone, and (2) open-section defect, a discontinuity of dimensions greater than the diameter of the bone.[68] By creating a nonuniform distribution of stresses in bone, stress risers can decrease bone strength by 60% to 70%.[69] An open-section defect has a greater impact on decreasing shear and torque-loading resistance. The volume of bone able to resist the load is significantly decreased compared with a closed section. A 90% reduction in load to failure and energy storage to failure is noted in torsion testing of the human adult tibia with open section.[70] Torsional or rotational forces occur in various daily movements such as getting out of a chair. Bone is weakest during torsion. A single quarter-inch hole made for a bone biopsy can decrease torsional strength by 50%.[71]

The nature of the metastatic lesion affects the overall bone strength. Both lytic and blastic lesions dramatically alter bone elasticity; lytic lesions reduce bone strength more than blastic lesions. Irregular lesions are not necessarily more detrimental to the bone than smooth lesions, but elongated lesions drastically reduce bone strength.[72]

The distribution of pathologic fractures is shown in Table 25-4. Several series have examined various criteria predicting the risk of a pathologic fracture. Keene et al[73] evaluated 2673 patients with breast cancer in an attempt to predict pathologic fracture of the femur using clinical and radiologic criteria. Only 26 (13%) of 203 patients with evaluable proximal femur metastasis had pathologic fractures. They were unable to correlate lesion size and risk of pathologic fracture. No other risk factor was identified. The authors concluded that plains radiographs are insufficient diagnostic tools for identifying high-risk lesions. Of note is that this study was limited to single anteroposterior (AP) films.

Mirels[75] designed a score system to predict the risk of a pathologic fracture (Tables 25-5 and 25-6). Of 78 patients, 51 experienced a fracture and 27 did not. The mean score for the nonfracture group was 7 versus 10 for the fracture group. This system provides a useful tool to evaluate patients for prophylactic fixation. Patients with a score of 10 to 12 should undergo surgery. Patients with scores of 7 or less are not likely to benefit from such therapy. In patients with a "gray zone" score, the status of surrounding bone and lifestyle (old, osteoporotic woman vs young athlete) should be considered.

TABLE 25-4 Distribution of Pathologic Fractures[74]

Location	No.	%
Femur	258	65.0
Femoral neck	69	17.0
Peritrochanteric	50	13.0
Subtrochanteric	84	21.0
Femoral shaft	38	10.0
Supracondylar	17	4.0
Acetabulum	34	8.5
Tibia	31	7.5
Humerus	68	17.0
Forearm	8	2.0
Total	399	100.00

From Mirels H: Metastatic disease in long bones: A proposed scoring system. Clin Orthop 249:256, 1989.

TABLE 25-5 Scoring System by Mirels

	Points		
Variable	**1**	**2**	**3**
Site	Upper extremity	Lower extremity	Peritrochanteric
Pain	Mild	Moderate	Mechanical
Radiograph	Blastic	Mixed	Lytic
Size (% of shaft)	0-3	34-67	68-100

From Mirels H: Metastatic disease in long bones: A proposed scoring system. Clin Orthop 249:256, 1989.

TABLE 25-6 Pathologic Fracture Rate

Score	No. of Patients	Fracture Rate (%)
0-6	11	0
7	19	5
8	12	33
9	7	57
10-12	18	100

From Mirels H: Metastatic disease in long bones: A proposed scoring system. Clin Orthop 249:256, 1989.

The following guidelines may help make a decision regarding prophylactic fixation. Because each patient has unique circumstances, these guidelines cannot replace sound clinical judgment on the part of the attending physician.

1. Life expectancy is longer than 3 months.
2. Patient is medically fit to tolerate major surgery.
3. Procedure planned is expected to expedite mobilization.
4. Quality of bone both proximal and distal to the lesion is adequate to support any fixation device.
5. There is cortical bone destruction of 50% or more.
6. Lesion measuring 2.5 cm or larger is located in the proximal femur.
7. There is pathologic avulsion fracture of the lesser trochanter.
8. Stress pain persists after irradiation.

The following principles govern the surgery of impending fractures:

1. Maximum effort is made to avoid disrupting the surrounding soft tissue to preserve the periosteal blood supply. This is of particular importance in these patients because the endosteal circulation has usually been disrupted by the metastatic deposits.
2. Highly vascular lesions (metastasis from renal cell carcinoma, for instance) should be considered for possible embolization before open curettage.
3. Defects that include the entire circumference of the cortex should be plugged by acrylic cement at fixation to reduce the biomechanical risks associated with stress risers or open-section defects.
4. When large, thin-walled lesions exist, the intramedullary nailing techniques should be augmented by direct reinforcement of the lesion using methyl methacrylate. This will enhance fixation of the distal long bone, particularly with regard to the torsional stability, and will also prevent shortening of the bone.

Pathologic fractures of the humerus commonly occur in the diaphysis followed by the proximal humerus. Fractures of the diaphysis can be fixed using an intramedullary interlocking device, such as a Brooker-Wills nail, which provides excellent strength and effective resistance against varus, torque, and distraction forces.[76] Proximal humerus fractures commonly require a prosthesis. These patients usually achieve a limited flexion and abduction of about 90 degree to 100 degree and enjoy good overall function, joint stability, and pain relief.[68]

Fixation of the femoral neck–intertrochanteric area can be achieved with the use of a compression hip screw and side plate. Fractures involving the femoral neck may be better treated with prosthetic replacement because they are rarely amenable to internal fixation.[77] Subtrochanteric, femoral shaft, and supracondylar femoral lesions are amenable to internal fixation, but large cortical lesions may benefit from an intramedullary acrylic cement filling.

The common problem encountered in acetabular lesions is the failure to appreciate the extent of bone lysis radiographically. Extensive destruction of bone may render efforts to reinforce such lesions with bone graft fruitless. Pathologic fractures of the acetabulum should be managed by total hip arthroplasty.

The spine is the most common site of skeletal metastases. The vertebral body is typically affected first, although pedicle destruction is noted first radiographically. In the absence of a

blastic lesion, 30% to 50% of the vertebral body needs to be destroyed before any destruction can be noted on a radiograph. Vertebral metastases are often asymptomatic. Symptoms are usually a result of one of the following: (1) an enlarging mass within the vertebral body that breaks through the cortex and invades the paravertebral soft tissues, (2) a mass compressing or invading local nerve roots, (3) a pathologic fracture, (4) spinal instability secondary to a pathologic fracture (in particular when the posterior elements are involved), and (5) spinal cord compression.

An aggressive surgical approach to spine metastases is usually not warranted.[78] Spinal stabilization is a major surgery involving multiple risks and prolonged recovery. Most patients with spinal metastases do not have progressive spinal instability or neurologic involvement and can be treated with radiation, hormones, chemotherapy, or temporary bracing. Even patients with vertebral body compression fractures can be treated with temporary bed rest and soft bracing. Indications for surgical intervention include (1) progressive spinal canal impingement and cord compression by a radioresistant tumor or a recurrence after maximum tolerable radiation dose to the intended area; (2) bone or soft-tissue detritus extruded into the canal as a result of progressive spinal deformity, with or without spinal instability; (3) progressive spinal deformity; (4) progressive kyphotic deformity associated with posterior disruption and shear deformity; and (5) solitary metastases of a histology that is unlikely to be controlled long term with tolerable doses of irradiation.

Vertebroplasty of bone metastasis was first described in 1987 and consists of direct injection of the affected vertebra with cement. Polymethylmethacrylate (PMMA) is active through several pathways and produces pain relief in 80% of the patients.[79] The procedure is done under intravenous sedation or general anesthesia. Pain-receptors destruction is achieved with exothermic reaction of the polymonomer and compressive effect on small nerves. Vertebroplasty effects are not modified by external-beam radiation (EBRT) and PMMA conserves its properties despite radiation[79] Vertebroplasty and radiation are complementary, both providing pain relief, the former providing more structural benefit of weak bones, and the later offering more durable tumor control of larger tumors.

Radiotherapy

Local Field Radiotherapy

The vast majority of patients can be managed successfully with EBRT. A large body of clinical evidence documents the effectiveness of such therapy.[80] The optimal dose and fractionation schedule is still not resolved. A summary of the major prospective clinical trials that addressed these issues is provided in Table 25-7. The results of these studies should be interpreted with caution because the inherent heterogeneity within the randomization groups may have precluded detection of significant differences, even when such differences could have existed. The use of different pain scoring systems (physician based versus patient based) and different handling of concomitant use of analgesics, chemotherapy, or hormonal therapy precludes meaningful comparison of the results of these studies.

Between 1974 and 1980, the RTOG conducted a large national study to determine the effectiveness of five different dose fractionation schedules.[52] A total of 1016 patients were entered, 266 into a solitary metastasis stratum and 750 into a multiple metastasis stratum. The former were randomly assigned to treatment with 40.5 Gy in 15 fractions or 20 Gy in 5 fractions. The latter were assigned to 30 Gy in 10 fractions, 15 Gy in 5 fractions, 20 Gy in 5 fractions, or 25 Gy in 5 fractions. A quantitative measure of pain, based on severity and frequency of pain and the type and frequency of pain medications used, was devised to evaluate response. Overall, 89% of patients experienced at least minimal relief, 83% achieved partial relief, and 54% obtained complete relief. There were no significant differences between the treatment arms in both strata. The initial pain score was found to be a useful predictor; patients with high scores were less likely to respond and less likely to experience a complete response. Patients with breast and prostate cancer were significantly more likely to respond than those with lung or other primary lesions. Patients completing their treatment as planned had a significantly higher rate of complete response than those who did not. Although some pain relief was experienced almost invariably within the first 4 weeks, complete relief was first reported later than 4 weeks after the start of treatment in about 50% of patients. The

TABLE 25-7 Summary of Prospective Clinical Trials of Radiotherapy for Painful Osseous Metastases

Study	No. of Patients	Total Dose (Gy)	No. of Fractions	Overall Response (%)	Complete Response (%)
Tong et al[52]	1016	40.5	15	85*	61*
		20.0	5	82*	53*
		30.0	10	87	57
		15.0	5	85	49
		20.0	5	83	56
		25.0	5	78	49
Price et al[81]	288	8.0	1	82	45
		30.0	10	71	28
Hoskin et al[82]	270	4.0	1	44	36
		8.0	1	69	39
Okawa et al[83]	92	30.0	15	76	—
		22.5	5	75	—
		20.0	10 (bid)	78	—
Madsen et al[84]	57	24.0	6	47	—
		20.0	2	48	—
Steenland et al[85]	1157	8.0	1	71	—
		24.0	6		—
Sze et al[86] (review)	3621	Varies	1	60	34
			>1	90	32

median duration of minimal and complete pain relief was 20 and 12 weeks, respectively. There were no significant differences in the duration of pain relief between the different arms. The authors concluded that all treatment dose schedules were equally effective.

Blitzer[87] performed a reanalysis of the RTOG study. Using a stepwise logistic regression, he examined the effect of the number of fractions, the dose per fraction, and solitary versus multiple metastases on the probability of attaining complete pain relief and the need for retreatment. This multivariate technique allowed patients with solitary and multiple metastases to be analyzed together. The number of fractions was the only variable that was significantly associated with outcome. There was no correlation of the time-dose factor (TDF)[88] with outcome. It was concluded that the more protracted schedules resulted in improved pain relief.

The concept of TDF has long been replaced by the linear quadratic model. Using this model, and assuming an α/β of 10 for tumor, we calculated the biologically effective dose (BED) for the various schedules tested by the RTOG. Figures 25-3 and 25-4 depict pain response and freedom from retreatment as a function of BED, respectively. The solid lines are the regression functions, and the dotted lines represent the 95% confidence intervals. The results suggest that schedules with higher BED resulted in better pain relief and reduced the need for retreatment.

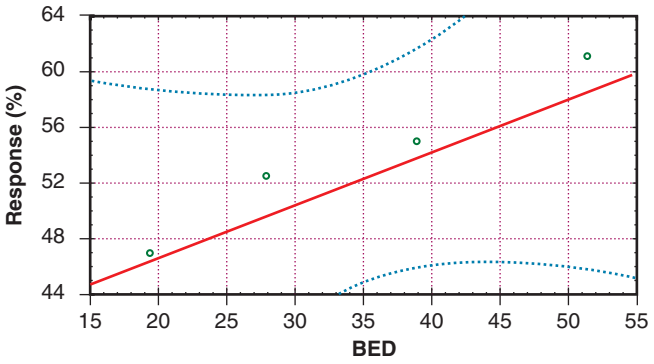


Figure 25-3 Pain response as a function of biologically effective dose (BED) by means of linear regression analysis. Response = 39.1 + 0.38 × BED; $r = 0.74$; $P = 0.15$. The *solid red line* indicates the regression function, and the dotted blue lines indicate 95% confidence intervals.

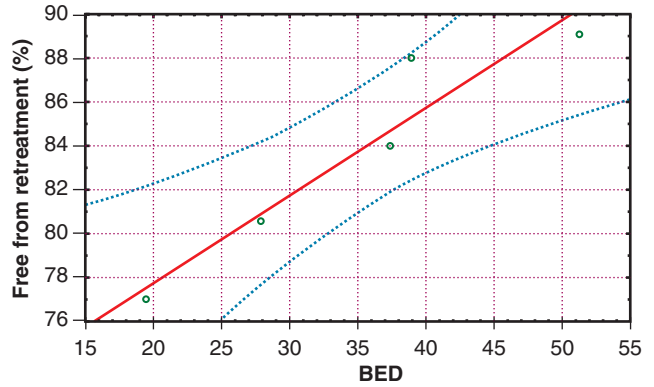


Figure 25-4 Freedom from retreatment as a function of biologically effective dose (BED) by means of linear regression analysis. Response = 69.7 + 0.4 × BED; $r = 0.95$; $P = 0.05$. The *solid red line* indicates the regression function, and the dotted blue lines indicate 95% confidence intervals.

Price et al[81] randomized 288 patients to receive either 8 Gy in one fraction or 30 Gy in 10 daily fractions. Pain was assessed using a daily questionnaire completed by the patient at home. No differences were found in the probability of attaining pain relief, speed of relief, or duration of relief between the two arms.

Hoskin et al[82] randomized 270 patients to receive either 4 Gy or 8 Gy in one fraction. Pain (assessed by the patient) and analgesic usage were recorded before treatment and at 2, 4, 8, and 12 weeks. At 4 weeks, the response rates were 69% for 8 Gy and 44% for 4 Gy ($p < 0.001$). The duration of the effect was independent of dose.

Additional studies have evaluated single- and multiple-fraction regimens. A Danish randomized trial of 241 patients showed no significant difference with regard to pain relief or quality of life after receiving either 8 Gy in a single fraction or 20 Gy in five fractions.[89] Wu et al performed a meta-analysis of 16 trials including 5455 patients[90] and proclaimed equivalence between single and multiple fractions. Van der Linden et al recently published a reanalysis of a Dutch Bone Metastasis Study that included 1171 patients.[91] This study randomized patients to either single 8 Gy or 24 Gy in six fractions. Mean time to retreatment was shorter (13 weeks versus 21 weeks) with a single fraction. It was also more frequent: 24% after a single fraction and 6% after 6 fractions ($p = 0.001$). An initial high pain score also influenced the need for retreatment.

Treatment Techniques

The target volumes for EBRT should be defined after review of all appropriate diagnostic studies. Attention should be paid to soft-tissue masses, which are often associated with bone metastases and at times responsible for the observed symptoms. Such lesions are best assessed by CT or MRI. The target volumes are treated with appropriate margins. Depending on the treatment site and volume, suppression of the bone marrow should be anticipated. In patients for whom chemotherapy is planned, treatment volumes should be kept to a minimum to preserve marrow reserves. Because many patients have repeated courses of therapy, all previous ports and radiation records must be reviewed. To minimize late radiation damage, overlap of radiation fields should be avoided. Depending on the clinical circumstances, overlapping retreatment may be appropriate in patients with short life expectancy.

Hemibody Irradiation

Most patients with bone metastases have multiple sites of involvement. As many as 76% of patients receiving therapy to a local field require additional treatment for pain at other sites within 1 year.[92] Historically, wide-field radiotherapy was used to address this problem. Although large-field radiation is less commonly used is the era of systemic therapy, it remains a treatment option. A summary of results of this form of therapy is provided in Table 25-8. Response rates are similar to those observed with local-field radiotherapy, but the onset of relief is more rapid, occurring often within 24 hours of treatment. Hemibody irradiation (HBI) is mentioned here for completeness but is rarely employed. It may require hospitalization for hydration and premedication with steroids and antiemetics and tends to be associated with substantial morbidity. Most patients experience acute gastrointestinal toxicity, with nausea, vomiting, and diarrhea persisting for 24 to 48 hours. Myelosuppression is commonly observed but is rarely of clinical significance. Radiation pneumonitis is rare at doses below 7 Gy to the lungs.

The RTOG conducted a Phase III study to evaluate the efficacy of HBI in addition to local-field irradiation.[92] A total of 499 patients were randomized to receive either HBI or no

TABLE 25-8 Wide-Field Radiotherapy for Painful Osseous Metastases

Study	No. Fields Treated	Dose (Gy)		Response (%)
		Upper	*Lower*	
Fitzpatrick[93]	570	3-6	10	55-72
Rowland et al[94]	96	7.5	10	80
Qasim[95]	129	7-8*	7-8*	76
Salazar et al[96]	168	6	8	73
Wilkins et al[97]	141	6	8	82
Poulter et al[92]	229	8	8	93

**3 Gy to 4 Gy in multiple myeloma patients.*

further therapy after completion of local-field irradiation to a symptomatic site. Entry was stratified by extent of metastatic disease (solitary or multiple) and the targeted hemibody area (upper, middle, or lower). Local-field irradiation consisted of 30 Gy in 10 fractions. HBI consisted of 8 Gy in 1 fraction given within 7 days of completion of the local field. Partial transmission blocks were used to reduce the dose to the lungs to 7 Gy. Time to disease progression, time to new disease, and time to new course of therapy were significantly longer in the HBI arm. Progression of disease was faster in patients with involvement of the upper and middle hemibody (compared with lower hemibody) and in patients with multiple metastases (compared with solitary tumor). As expected, toxicity was significantly higher in the HBI arm, but there were no fatalities and no occurrences of radiation pneumonitis. Although an impact of HBI on clinically occult metastatic disease was demonstrated, the long-term benefit was relatively small. The ultimate progression rates were not significantly different between the arms, and at 1 year 60% of the patients in the HBI arm had to be retreated.

Stereotactic Radiosurgery of the Spine

The spinal column is a common site of metastatic spread where pernicious disease progression threatens the spinal cord. Although conventional palliative fractionated radiotherapy has proven to be effective in both pain relief and short-term local control, the dose is limited by the close proximity of the spinal cord. As treatment improves and metastatic patients survive longer, progression of spine disease after fractionated radiation therapy becomes a serious issue. Stereotactic radiosurgery (SRS) allows for the delivery of a single, ablative dose fraction of radiation using highly conformal techniques with enhanced targeting accuracy. Generally, the delivery of two to five fractions of radiation, using the same techniques, is referred to as stereotactic body radiation therapy (SBRT). SBRT and SRS offer advantages over traditional fractionated therapy. Including the convenience of one to five treatments versus several days of treatment for patients with limited life expectancy in significant pain, improved long-term local control that is less histology dependent, and a safe effective radiation retreatment modality.

The ability to safely deliver ablative doses of radiation depends on accurate localization and immobilization. Using MRI imaging, a planning CT scan, and in some situations spinal myelogram and PET scan, accurate identification of anatomical dosing gradients is achieved. During treatment, image guidance using the bony vertebra as a high fidelity fiducial for both the lesion and the spinal cord may be used. Immobilization of the bony vertebral body structure may be achieved using gravity in the supine position, usually combined with a variety of other immobilization techniques. Modern treatment planning achieves a sharp dose gradient that allows the technique to achieve an ablative dose of radiation to the PTV while reducing significant dose delivery to critical structures, most importantly the spinal cord, but also the esophagus, lungs, kidney, bowel, and bone marrow of adjacent vertebral bodies.

SBRT or SRS technique can be used as the sole initial treatment for spinal metastatic disease, particularly in tumor histologies that are known to have a poor response to traditional fractionated palliative radiation technique, patients with oligometastatic disease, and patients with a long life expectancy. SRS can also be used as a boost treatment after the delivery of conventional radiation (generally prescribed to 20 Gy to 40 Gy in 2.5 Gy fractions to 4 Gy fractions), postoperatively as adjuvant treatment,[98] and as salvage treatment in patients previously irradiated (generally >3 to 6 months prior) for spine metastases.

Spinal SRS is most ideally performed on intravetebral body lesions without extension into the canal allowing for distance between the PTV and the spinal cord. If there is posterior cortical compromise of the vertebral body by the lesion, conventional fractionated radiation therapy should be considered in radiosensitive histologies. Radioresistant histology patients with limited systemic disease should be considered for surgery followed by radiation.

Generally with SRS/SBRT technique, the pain control and local tumor control is on the order of 85%.[99-104] Garg et al[105] showed local control for single fraction SRS in previously unirradiated tumors to be 88% at 18 months. There appears to be a dose response, with greater palliation with prescribed isocenter doses of ≥14 Gy.[106] Although traditional palliative spine radiation fields encompass the involved vertebral body plus a vertebral body above and below, SRS and SBRT generally treat only the involved vertebral body or a portion of the involved vertebral body. This typically equates to the anterior vertebral body with or without the posterior elements and pedicles in those with more posterior extension. In a study from Henry Ford Hospital (Detroit, MI), subsequent metastases to adjoining vertebral bodies after SRS was rare (~5%) and associated with progression of disease elsewhere.[100] In a study from M. D. Anderson Cancer Center (Houston, TX), in-field failures occurred in ~25% of recurrences, and roughly half of the recurrences were in the epidural space, which was attributed to underdosing this region to maintain spinal cord dose constraints. Patients also failed in other regions not included in the treatment volume (of any given patient) including the pedicles, posterior elements, and pre- and paravertebral regions.[98] The presence of paraspinal disease and using SRS doses <16 Gy increased risk of marginal recurrence is discussed in a paper by Koyfman el al.[107] Recent clinical data has shown spine SRS and SBRT to be tolerable, albeit with limited patient follow-up,[108] because patients with spine metastases generally have a poor survival, even those with solitary spine metastases.[109] It appears that myelopathy and radiculopathy rarely occur.[63,108] For single-fraction SRS, most institutions try to achieve a spinal cord maximum dose below 10 Gy.[57] In the University of Pittsburgh experience of spine SRS in 393 patients with 500 lesions, for which the cord maximum was kept below 8 Gy, no acute or late neurotoxicity was observed, and no late toxicity was reported after a follow-up of 3 to 53 months (median, 21 months).[100] In Garg et al[105] the dose to the spinal cord was limited to no greater than 0.01 cm^3 of the spinal cord receiving >10 Gy and the spinal cord plus 2 mm was limited to receiving 12 Gy. These constraints yielded limited toxicity with only 3% of patients suffering grade-3 neurotoxicity with some patients' prescription doses as high as 24 Gy. Sahgal et al[110] looked at dose-volume histogram results for nine cases of spine SBRT, treated at multiple institutions, where radiation myelopathy was

reported and compared them with a cohort of 66 spine SBRT patients without radiation myelopathy. They found a risk of radiation myelopathy of 5% or less when limiting the thecal sac Pmax volume to 12.4 Gy in a single fraction, 17.0 Gy in two fractions, 20.3 Gy in three fractions, 23.0 Gy in four fractions, and 25.3 Gy in five fractions. Several institutions have demonstrated that spinal cord maxima of 12 Gy[102] to 20 Gy[108,111] are tolerated in some patients, though from a multiinstitutional pooled analysis, radiation myelopathy has only been documented to occur after exceeding a fractional dose maximum of 10 Gy to the spinal cord.[112] From this study, dose-volume parameters such as maximal dose and mean and median dose to 0.1 mL to 5 mL of spinal cord significantly correlated with the risk of radiation myelopathy. From the RTOG 0631 study (which is a randomization of spine SRS delivered with 16 Gy versus conventional radiation delivered in one fraction of 8 Gy), spinal cord dose constraints are: 10% and 0.35 mL of spinal cord <10 Gy, and 0.035 mL <14 Gy, with the spinal cord volume defined as 5 mm to 6 mm above and below the target, based on T2- and T1-weighted MRI.

The use of SRS is attractive in the setting of progression after conventional fractionated radiation for spine metastases. With a repeated course of standard fractionated radiation, there is concern about exceeding residual cord tolerance, while affording inferior local control versus SRS. A study of spinal cord tolerance in a rhesus monkey model by Ang et al[113] suggested that the spinal cord has remarkable ability to recovery from previous radiation when treated 1 to 3 years later. Mahadevan et al[114] showed SBRT salvage after normal fractionated palliative radiation was effective. The dose used was 8 Gy × 3 = 24 Gy when the tumor did not touch the spinal cord and 5 Gy to 6 Gy × 5 = 25 Gy to 30 Gy when the tumor abutted the cord. The cord surface received up to the prescription dose. In this group, 93% of patients had stable or improved disease, whereas 7% of patients showed disease progression. With 65% of patients gaining significant pain relief, there was no significant toxicity other than fatigue. A spine SRS/SBRT retreatment study by Sahgal et al[110] looked at patients from multiple institutions, given salvage SRS/SBRT, with one to five fractions, at least 5 months after conventional palliative radiotherapy. They compared dose volume histograms of patients who developed radiation myelopathy to patients who did not develop radiation myelopathy. They found that a thecal sac Pmax nBED of 20 Gy to 25 Gy 2/2 appears to be safe provided the total Pmax nBED does not exceed approximately 70 Gy 2/2, and the SBRT thecal sac Pmax nBED comprises no more than approximately 50% of the total nBED.

The use of SRS/SBRT for spinal metastatic tumors is increasing. Standard field palliative radiation has been a standard option in the treatment of spinal metastatic lesions where the dose delivered was limited by the sensitivity of the spinal cord and surrounding critical structures. Spinal SRS emerged with modern techniques of improved localization, immobilization, and dose gradients within a treatment plan. This relatively new radiation modality affords patients with metastatic spine lesions a safe, effective, and convenient therapy.

Systemic Radionuclide Therapy

The first report on the use of systemic radionuclides for the treatment of bone metastases was published by Pecher more than 50 years ago.[115] Using this modality, all involved osseous sites can be addressed simultaneously. Selective absorption into bone metastases limits irradiation of normal tissues and increases the therapeutic ratio. Administration as a single intravenous injection in the outpatient clinic is a further advantage for many patients.

Systemic radionuclides should be considered in the following circumstances:

1. In patients with widely metastatic disease, as adjuvant to EBRT
2. In patients with pain but without a predominantly painful site, as a first-line therapy
3. There is no evidence of imminent epidural cord compression, pathologic fracture, or mechanical instability
4. In patients with good marrow reserve with a white blood cell count of greater than 2400 and a platelet count of greater than 100,000
5. Patients for whom the value of future marrow toxic chemotherapy is limited.

Historically, phosphorus-32 was the first radionuclide to be widely used in the treatment of bone metastases,[116] although this isotope is now rarely used for bone disease as a result in part of myelosuppression with pancytopenia and an increased incidence of acute leukemia.[92] Phosphorus-32 has since been replaced by newer, less toxic radionuclides (Tables 25-9 and 25-10).

Strontium 89. Strontium 89 decays by beta emission to yttrium 89 with a half-life of 50.6 days. The average beta energy is 1.46 MeV. Chemically similar to calcium, strontium 89 is quickly taken up into the mineral matrix of bone. The fraction of strontium 89 retained is proportional to the metastatic tumor burden and varies between 20% and 80% of the administered dose.[126] Accumulation is preferred in and around metastatic deposits, where active bone formation takes place, which is likely adjacent to but not in the site of malignancy.[126-128] Once incorporated into the metastatic lesion, strontium 89 is not removed metabolically and remains deposited for as long as 100 days.[126] Accurate tumor dosimetry is difficult and usually based primarily on the location of tracer accumulation. Estimates of the total dose absorbed within the metastatic lesion vary between 0.9 cGy and 231 cGy per megabecquerel (MBq), with the typical mean total dose at 23 cGy/MBq and high doses usually corresponding to superscans.[127-130] Typical doses are 1.5 MBq/kg, leading to a nominal tumor dose of 20 Gy to 25 Gy. Elimination is through the kidneys, and careful disposal of urine is needed for 7 days to 10 days after administration. Extra care is advised for incontinent patients. Because strontium 89 emits extremely little gamma radiation, the patient is not a radiation hazard to family members or hospital staff.

The efficacy of strontium 89 has been well documented in dose-seeking studies.[118,119,126,130-134] Laing et al[118] reported on the

TABLE 25-9 Physical Characteristics of Various Radionuclides

Radionuclide	Physical Half-Life	Beta Energy (MeV)	Gamma Energy (keV)	Chelate
Phosphorus-32	14.3 d	1.71	—	Orthophosphate
Strontium 89	50.6 d	1.46	—	Chloride
Rhenium 186	90.6 h	1.07	137	HEDP
Samarium 153	46.3 h	0.84	103	EDTMP

EDTMP, *Ethylenediaminetetramethylene phosphonate;* HEDP, *hydroxyethylenediphosphonic acid.*

TABLE 25-10 Summary of Clinical Trials with Systemic Radionuclides

Radionuclide	Response Rate (%)	Complete Response (%)	Response Duration
Phosphorus-32[117]	60-80	—	–5 mo
Strontium 89			
Laing et al[118]	75	22	6 mo
Robinson et al[119]	80	11	NA
Quilty et al[120]	65-70	30*	NA
Rhenium 186			
Maxon[121-123]	77	21	5 wk
Samarium 153			
Collins et al[124]	76	NA	2.6
Ahonen et al[125]	80	54	2-17 wk

NA, *Not applicable.*
**Substantial or dramatic response, estimated from a graph.*

results of a dose-escalation study. The optimal dose was found to be 1.5 MBq/kg with no appreciable increment in efficacy above this dose. Of 83 patients treated with at least 1.5 MBq/Kg, 75% had partial relief of pain and 22% were rendered pain free. Pain relief began 10 days to 20 days after treatment and peaked at 6 weeks. Response was maintained for a median of 6 months (range, 4 months to 15 months). The RTOG conducted a dose escalation study and concluded that the maximum tolerated dose of strontium 89 is 6.5 mCi (approximately 3.4 MBq/kg).

Toxicity of strontium 89 is mainly hematologic. Platelet depression is dose dependent and can be prolonged. Most patients have a 20% to 50% drop in their counts after doses of 3 mCi to 4 mCi (1.5 MBq/kg to 2 MBq/kg). Grade 3 toxicity is rare. Other adverse effects include a transient increase in bone pain in up to 10% of patients and rarely facial flushing. The pain flare occurs 1 week to 2 weeks after treatment, may last a few days, and usually heralds a favorable response.

Porter et al[135] reported the results of the Trans-Canada study. This trial evaluated the efficacy of strontium 89 adjuvant to local-field EBRT in patients with hormone-refractory prostate cancer. A total of 126 patients were randomized to local-field radiotherapy (20 Gy in 5 fractions or 30 Gy in 10 fractions) followed by placebo or by strontium 89 (10.8 mCi). Overall and complete responses (relief of pain at the index site) were higher in the treatment arm, but the differences did not reach statistical significance. At 3 months after treatment, 58.7% and 34% of patients in the treatment arm and control arm, respectively, were free of new painful metastases. The median time to further radiotherapy was 35.3 weeks and 20.3 weeks in the treatment and control arms, respectively. Hematologic toxicity was, as expected, higher in patients treated with strontium 89.

Samarium 153. Samarium 153 is a man-made radionuclide that emits beta particles of 0.81 MeV (20%), 0.71 MeV (30%), and 0.64 MeV (50%) and gamma photons of 103 keV (28%). It has a relatively short half-life of 46.3 hours and, consequently, a relatively high dose-rate. Samarium 153 has been chelated to a phosphonate, ethylenediaminetetramethylene (EDTMP), to produce a bone-seeking complex. About 50% of an intravenously administered dose is retained in bone.[136,137] Absorbed dose in bone and red marrow has been estimated at 2.5 cGy/MBq and 0.57 cGy/MBq, respectively.[137] In a Phase I/II clinical trial,[124] the maximally tolerated dose (MTD) was determined to be 2.5 mCi/kg. The principal toxicity observed was hematologic; maximum myelosuppression occurred at 3 weeks to 4 weeks. A flare of bone pain occurred in 12% of patients. The overall pain relief rate was 74%, with a median duration of palliation of 2.6 months. In responders, relief was obtained promptly within 7 days to 14 days of treatment. Response rates were significantly higher with 2.5 mCi/kg than with 1.0 mCi/kg.

Rhenium 186. Rhenium 186 emits beta particles of 1.07 MeV and a 137-keV gamma ray and has a short half-life of 3.8 days. Like samarium 153, it has been complexed to a bone-seeking phosphonate, hydroxyethylenediphosphonic acid (HEDP). Retention in bone is about 50% of the injected dose; the rest is excreted through the kidneys into the urine.[121] Rhenium 186 has been studied in a small number of patients with metastatic cancer of the prostate, breast, colon, and lung.[122] After administration of 33 mCi to 35 mCi, 75% to 80% of patients experienced pain relief, most often within 2 weeks.[121-123] The therapeutic efficacy of rhenium 186 has been confirmed in a double-blind, crossover comparison with placebo.[123] Myelosuppression begins 2 weeks after treatment, peaks at 4 to 6 weeks, and resolves by 8 weeks.[122] A pain flare occurs in 10% of patients 2 days to 3 days after treatment and resolves within 1 week.

Choice of Radiotherapeutic Approaches

In the United States, the usual approach to painful osseous metastases includes fractionated EBRT to index painful sites. Asymptomatic sites are less commonly irradiated. Patients with multiple lesions will commonly receive radionuclides in addition to EBRT to cytoreduce occult metastases and reduce the need for future local radiation. Radionuclides alone and hemibody radiation are less common in the United States, although the latter is often used in Europe and Canada. The advent of improved external-beam targeting technologies and the earlier discovery of patients with limited metastases have spawned efforts for local targeting of bone metastases. The utility of these high-dose treatments to achieve improved tumor control with reduced marrow and other toxicity is under investigation.[138]

SPINAL CORD COMPRESSION

Malignant spinal cord compression occurs in 5% of all patients with malignant disease and in approximately 20% of patients with metastases to the vertebral column.[139] More than 95% of spinal cord compressions are the result of extramedullary malignancy, most commonly secondary to involvement of the vertebral column anterior to the spinal cord, less frequently by tumors posterior to the spinal cord, and occasionally by invasion of the epidural space. Thankfully, the frequency of severe spinal cord compressions leading to paralysis and incontinence is decreasing with the availability of high-quality MRI technologies.[140]

Any tumor that metastasizes to the bone can eventually result in a cord compression. Most commonly seen primaries include lung, breast, prostate, kidney, lymphoma, myeloma, sarcoma, and unknown primaries.

Clinical Manifestation and Patient Evaluation

The majority of patients present with pain, motor loss, autonomic dysfunction, and sensory loss.[141] Pain is often radicular for weeks or months before the onset of neurologic symptoms, offering ample time for early diagnosis. Autonomic dysfunction may occur early and manifest as hesitancy and urgency. Weakness usually precedes sensory loss; incontinence, paraplegia, and paralysis are late effects. Pain was the initial symptom in 96% of the patients but is a poor indicator of spinal-epidural involvement.[142] In contrast, 75% of patients with major neurologic involvement have involvement of the epidural space.

Diagnosis

Early diagnosis is essential because recovery of neurologic function is related to the degree of loss. A careful history and physical examination focusing on neurologic assessment with a high index of suspicion in patients with known malignancy is key to early diagnosis. MRI is the diagnostic study of choice. Distortion of the theca by extradural lesions and soft-tissue abnormalities can be easily identified.[142,143] In case of compression fracture, protrusion of the vertebral body or tumor into the spinal canal is seen clearly, as is the impingement of nerve roots and neural foramina.[144] Approximately 10% of patients have multiple sites of cord compression and perhaps benefit from imaging of the entire spine.

Treatment

A multidisciplinary approach is recommended to treat spinal cord compression. High-dose steroids should be administered after a clinical diagnosis. An initial dose of 20 mg of dexamethasone (Decadron) followed by 4 mg four times daily improves pain and neurologic symptoms in most patients. Steroids should be tapered gradually after completion of radiation. Patients receiving dexamethasone should be placed on H_2 blockers and monitored for hyperglycemia, hypertension, and electrolyte imbalances.

A randomized trial comparing laminectomy followed by radiation versus radiation alone in the treatment of spinal epidural metastasis showed no significant difference in the effectiveness of treatment in regard to pain relief, improved ambulation, and improved sphincter function.[145] Although most cases of spinal cord compression can be managed with steroids and radiotherapy, patients without a histologically proven cancer, radioresistant tumors, previously radiated sites, or mechanical instability should be seen by a neurosurgeon for a laminectomy (Figure 25-5).

In a multiinstitutional randomized study[146] of patients with symptomatic spinal cord compression from vertebral metastases, 50 patients were randomized to receive decompressive surgery followed by radiation and 51 were randomized to receive radiation alone (30 Gy in three Gy fractions for both arms). The study was closed early because of the superiority in outcomes of surgery plus radiation versus radiation alone. Compared to patients receiving radiation alone, following surgery and radiation, significantly more patients were able to walk, patients retained the ability to walk significantly longer, significantly more patients regained the ability to walk, and the need for corticosteroids and analgesics was significantly reduced. Patients undergoing surgery also had a significantly longer survival time. Table 25-11 summarizes the results from this landmark study.

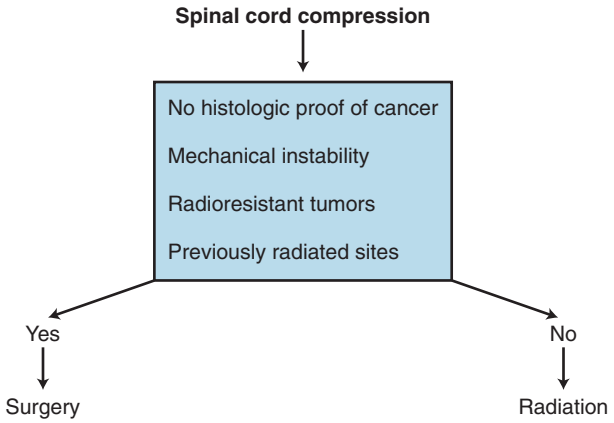


Figure 25-5 Treatment algorithm for spinal cord compression.

TABLE 25-11 Treatment Results for Spinal Cord Compression

Variable	Radiation Alone	Radiation and Surgery	*p* Values
All patients			
Able to walk after treatment	29/51 (57%)	42/50 (84%)	0.001
Retained ability to walk	median 13 days	median 122 days	0.003
Maintenance of continence	median 17 days	median 156 days	0.016
Maintenance of muscle strength	median 72 days	median 566 days	0.001
Dexamethasone dose	median 4.2 mg	median 1.6 mg	0.0093
Morphine dose	median 4.8 mg	median 0.4 mg	0.002
Survival time	median 100 days	median 126 days	0.033
Initial ambulatory patients			
Maintained ability to walk	26/35 (74%)	32/34 (94%)	0.024
Retained ability to walk	median 54 days	median 153 days	0.024
Initial nonambulatory patients			
Regained ability to walk	3/16 (19%)	10/16 (62%)	0.010
Retained ability to walk	median 0 days	median 59 days	0.024

Treatment outcome is dependent on pretreatment function. In a study of 137 patients with malignant spinal cord compression, 81% of patients who were ambulatory pretreatment remained ambulant, whereas only 16.5% of those who were nonambulant before treatment became ambulant after treatment. Pain improved after treatment in 73% of the patients regardless of their ambulatory status.[139] This was confirmed by Zelefsky et al in a retrospective review of 42 patients.[147] They also reported that the presence of a compression fracture of greater than 50% at the level of the spinal cord compression was associated with poor response on refluoromyelography (RFM). Sixty-seven percent with severe compression fractures had no response on RFM versus 11% without compression fracture ($p = 0.01$).

Irradiation Technique and Doses

The depth of the tumor mass can be determined by MRI. If the MRI is unavailable at the time of simulation, a lateral film taken at simulation can help determine the prescription depth. The width of the field is dependent on the extent of the soft-tissue mass as determined by the MRI.

Treatment fields are dependent on the site of involved spinal cord. The cervical spine is usually treated using opposed laterals to avoid the oral cavity. For the thoracic spine, a posterior field alone can be used. When treating the lumbar spine or when the target appears to be more midline, a parallel opposed anteroposterior/posterior-anterior (AP/PA) beam arrangement may be preferred. For either the thoracic or lumbar spine, acceptable alternative techniques include paired posterior obliques or PA and paired laterals. For nonemergent cases, wherein there is sufficient time for treatment planing, IMRT or arcing technique can produce reduced normal tissue consequences, particularly in the neck and thoracic regions where esophageal irradiation can be symptomatic.

The dose of irradiation used for the treatment of spinal cord compression is dependent on both the histopathologic findings and the clinical situation (ambulatory versus nonambulatory, solitary versus multiple metastases, systemic therapy options and efficacy, etc.). The typical dose is 30 Gy in 10 fractions over 2 weeks or 20 Gy in 5 fractions. If life expectancy exceeds a few months, a more protracted regimen (35 Gy to 40 Gy in 3 to 4 weeks) is reasonable with regard to the issue of spinal cord tolerance.

BRAIN METASTASES

Brain metastases are the most common intracranial brain tumor and a common complication of systemic cancer. The incidence ranges from 20% to 40% of all patients diagnosed with cancer.[148] Cancers known to generate systemic disease are the most common primary tumors involved: lung, breast, colon, and melanoma. Current improvements in systemic therapy have improved survival significantly for several cancers but may leave untreated tumor cells beyond the blood-brain barrier and increasing the incidence of brain metastasis in some solid tumors. More precise diagnostic tools, such as MRI, also have an impact on the increasing discovery of brain metastases.

The prognosis of brain metastases is poor and the impact on the patient's quality of life is important as a result of the functional neurologic deficits associated. Symptom management is successful in most patients and efforts can be concentrated on improving the outcome of the patients.[148]

Arterial hematogenous spread results in tumor emboli growth at the gray-white junction[149]; the most common neuroanatomical sites are the cerebral hemispheres (80%), the cerebellum (15%), and the brainstem (5%),[150] with this distribution approximately mirroring blood flow volumes. However, data shows that the distribution of intracranial metastases based solely on the model of arterial embolization and blood volume does not likely depict the full biological basis of spatial distribution of brain metastases. It has been found that patients with non–small cell lung cancer lesions are more likely to be located in the parieto-occipital lobes and cerebellum. Breast cancer lesions have a greater probability to be located in the cerebellum.[151] Multiple metastases are more common than single metastasis and the contribution of MRI to this statistic has reached 80% to 90%.[148]

Presenting symptoms are various and require that any new neurologic symptom be investigated in a patient known to have cancer. Symptoms reflect increasing intracranial pressure and focal neurologic deficit—headache, nausea, lateralized weakness, seizures, modified higher neurologic function. In most patients, the cancer is already diagnosed, but in as many as 20%, it may be the first manifestation; histologic confirmation is then necessary.

Contrast-enhanced MRI is the diagnostic modality of choice. The radiologic differential diagnosis includes primary brain tumor, inflammatory lesion, abscess, and brain infarction or hemorrhage. CT may also be used, but it is less specific and warrants MRI confirmation in the case of a single metastasis. Patchell et al[152] reported a false-positive rate of MRI of 11%, confirmed by histology.

Treatment

Palliative treatment of brain metastases requires rapid control of the symptoms, which are decreasing the patient's quality of life. Collaboration with colleagues in neurology is preferable. Pharmacologic treatment includes corticosteroids and antiepileptic drugs, although antiepileptic drugs should not be used prophylactically in patients without prior seizure.[153] Rapid regression of cerebral edema is the first step and can be achieved with intravenous corticosteroids. Optimal dosage is unknown, but the general practice is to administer a loading dose of Decadron (8 mg to 32 mg) followed by oral medication (4 mg four times a day).[154] Side effects are numerous, and a tapering dose schedule should be planned as symptoms improve. As a single modality, corticosteroids achieve poor survival results of 1 month to 3 months.

Treatment depends on several prognostic factors; Gaspar et al[155] have evaluated results of RTOG trials to produce a recursive partitioning analysis. Pretreatment and treatment-related variables were analyzed. Class 1 (Karnofsky Performance Status [KPS] >70, age <65 years, and controlled primary tumor) patients have a better median prognosis of 7 months. Class 2 (KPS <70, age >65 years, or uncontrolled primary tumor) patients have a median prognosis of 4 months. Class 3 (KPS <70, age >65 years, and uncontrolled primary tumor) patients have a median of 2 months. Other factors, such as histology of the tumor and the number and size of metastases, are important in the initial evaluation. Treatment options are evolving and now include whole brain radiotherapy (WBRT), surgical resection, and radiosurgery (linear accelerator or gamma knife).

Patients with a single brain metastasis in recursive partitioning analysis (RPA) Class 1 are treated aggressively with either surgical resection or SRS with or without WBRT. Multiple metastases from any RPA class receive standard WBRT alone. Patients with up to three metastases in Class 1 or 2 may be considered for local modality surgery or SRS.

Whole Brain Radiotherapy

WBRT is the treatment of choice for many patients because of the high incidence of multiple metastatic brain sites.[148,154,155] The goal of WBRT is to limit tumor progression, sterilize

microscopic disease preventing future brain metastasis[156] and to limit corticosteroid dependency. Classically, WBRT is thought to have some response in around 50% of patients and is histology dependent with small cell and breast cancers being the most sensitive. Renal cell and melanoma histologies are thought to be the most resistant. A study by Nieder et al[157] showed complete remission was observed in 37% of metastases from small-cell carcinoma, 35% of those from breast cancer, 25% of those from squamous-cell carcinoma, and 14% of those from nonbreast adenocarcinoma. The rate was 52% for metastases <0.5 cm^3 and 0% for those >10 cm^3. Sneed et al[158] showed WBRT for patients with unresected brain metastases results in symptomatic response in about 50% of patients and improvement in median survival from 3 months to 6 months compared to historical controls. The optimal dose of radiation is unknown, but in clinical practice, the range is 20 Gy in 5 fractions over 1 week to 40 Gy in 20 fractions over 4 weeks.[148]

Complications of treatment include alopecia, transient worsening of neurologic symptoms, and otitis. Continuing use of corticosteroids during WBRT may limit the incidence of most side effects. Long-term side effects such as memory loss, dementia, and decreased concentration are possible in survivors but are not expected to materialize in the majority of poor prognosis patients.

At our institutions, WBRT is becoming less commonly employed in patients with one to three metastatic lesions. Studies by Aoyama et al[156] and Chang et al[159] have shown that WBRT does not add to survival in this subset of patients and may even be detrimental, compared to SRS alone as shown in the study by Chang et al. The authors attributed this finding to patients treated with WBRT receiving less salvage treatment and less systemic therapy. In the Chang et al[159] study, there was a greater risk of significant decline in learning and memory function at 4 months in the SRS with whole brain group compared to SRS alone.

Because of this association of WBRT and cognitive decline, RTOG 0933, a single-arm Phase II study, looked at hippocampal sparring WBRT, using IMRT technique, compared to a historical control of WBRT without hippocampal avoidance. The dose received by the entirety of the hippocampus did not exceed 10 Gy, and the maximum dose did not exceed 17 Gy. The results showed that avoidance of the hippocampus during WBRT is associated with memory preservation at 4 months and 6 months. Only 4.5% of patients had progression in the hippocampal avoidance region.[160] The RTOG is planning a study of hippocampal sparing prophylactic cranial irradiation in patients with small cell lung cancer. Further study is needed to define the role and optimization of WBRT in the modern era.

Technique of WBRT

The patient is undergoing simulation for palliative treatment and therefore should be conscious and cooperative. Agitated or unresponsive patients should be stabilized before this step to decrease the risk of injury. Simulation is done in a supine position with a head rest, and immobilization is achieved with a custom mask or at least tape between the forehead and table. CT simulation requires the use of a mask.

Portal films with the gantry at 90 degrees and 270 degrees will give parallel-opposed lateral fields. The collimator should be rotated to allow the inferior border to parallel the base of skull. The field borders should go beyond the skull anterior, superior, and posterior bony limits by 2 cm to allow dosimetric homogeneity. The inferior border can be set from the bony canthus to the C1 to C2 intervertebral space and should cover the base of skull with a 1-cm margin. CT simulation is now commonly used with the same parameter but allows for a custom-block design to avoid irradiation of the lens and facial structures. All fields are treated daily. Megavoltage energy of 4 MV to 6 MV is used.

Surgical Resection

The role of surgery has evolved over the past decade. Three randomized controlled trials comparing WBRT alone versus surgery plus WBRT in patients with a single brain metastasis have been published.[152,161,162] Two demonstrated a survival advantage of the combined modalities over WBRT alone (Table 25-12). All three trials addressed the issue of single metastasis, and one cannot extrapolate the results to multiple lesions. The negative results of Mintz contradict those of others, but this trial also contained a large crossover rate, poor KPS patients, lower complete surgical resection rate, and lower WBRT dose.[162] These trials established the increased effectiveness of combination therapy of WBRT and surgical resection. Patchell et al[163] examined the effectiveness of postoperative WBRT after complete resection in patients with a single brain metastasis. They found that although whole brain did not improve survival in this group of patients it did improve local control at the site of resection, decreased the risk of general brain recurrence and decreased the risk of dying from neurological causes.

Radiosurgery

Numerous papers have been published showing the efficacy of SRS with excellent survival and local control in patients with one to three brain metastases. SRS does not require WBRT[163] to achieve excellent local control at the metastatic site, likely because of the penumbra dose beyond the periphery of the metastatic lesion sterilizing microscopic disease. In our institution, surgical resection of a single brain metastasis is trending toward being reserved for symptomatic tumors resistant to steroid treatment, larger lesions more than 4 cm where giving an ablative dose of radiation using a stereotactic technique would be deleterious and establishing diagnosis of metastatic disease when indicated.

Stereotactic radiosurgery is an accepted alternative to resection in patients with limited metastatic lesions that meet size criteria. SRS may be offered to patients with one to three brain metastases and 4 cm or less in size.[164-179]

TABLE 25-12 WBRT Alone or Plus Surgical Resection in the Management of Brain Metastases

Trial	Treatment	Radiotherapy Schedule	*n*	Median Survival (mo)	*p* Value
Patchell[152]	Biopsy + WBRT	36 Gy/12	23	4.2	<0.01
	S + WBRT	36 Gy/12	25	10	
Vecht[161]	WBRT	40 Gy/10 bid	31	6.5	NA
	S + WBRT	40 Gy/10 bid	32	10.8	
Mintz[162]	WBRT	30 Gy/10	43	6.3	0.24
	S + WBRT	30 Gy/10	41	5.9	

S, *Surgery;* WBRT, *Whole brain radiotherapy.*

RTOG 9508 study randomized 333 patients with 1 to 3 brain metastases to WBRT (37.5 Gy in 2.5 Gy fractions) versus WBRT plus SRS within 1 week of completing WBRT.[168] All metastases were ≤4 cm in size and only one metastasis could be >3 cm. The dose was dependent on the lesion size based on the RTOG 9005 Phase I study 2: 24 Gy to lesions ≤2 cm, 18 Gy for lesions >2 to ≤3 cm, and 15 Gy to lesions >3 Gy to ≤4 cm. In both RTOG 9005 and RTOG 9508, the prescription dose covering the gross tumor was the 50% to 90% isodose line, equating to central doses of 1.1 to 2 times the prescription dose. The RTOG 9508 trial demonstrated a significant survival advantage with the use of SRS in patients with a single unresectable metastasis, with a median survival of 4.9 months versus 6.5 months ($p = 0.0393$). The addition of SRS resulted in improved performance status and reduced extent of steroid use. The authors conclude that SRS should be used for patients with an unresectable solitary metastasis and considered for patients with one to three metastases.

SRS alone (without WBRT) in patients with one to three unresectable brain metastases is an alternative approach that remains actively investigated.[180,181] In retrospective studies, the 1-year local control rate is generally on the order of 80% to 95% with WBRT with SRS,[165,170,172,174,175,177] versus 80% to 90% with SRS alone.[172,177-179] At 2 years, the local control is on the order of 80% to 85% versus 50% to 70%. Thus, WBRT does lower the risk of brain failure, and the equivalence in survival likely reflects the need for more salvage therapy in the patients who underwent SRS only. In a study published by the University of Alabama (Birmingham, AL), the risk of new brain metastases in 100 patients treated with SRS alone was significantly correlated to the number of brain metastases (hazard ratio [HR] of 3.3 in patients with >3 metastases, $p = 0.004$), poorly controlled extracranial disease (HR of 2.16, $p = 0.04$), and melanoma histology ($p = 2.14$, $p = 0.02$).[182] Retrospective data suggest similar local control, overall survival, and neurologic death with SRS alone versus resection with WBRT.[183,184] Interestingly, in some series the reported local control with SRS is greater than that after resection,[185,186] probably reflecting the radiosurgical penumbra dose around the tumor periphery that treats microscopic disease.[187]

A multiinstitutional, pooled retrospective analysis examined 569 patients treated with SRS alone compared to SRS with WBRT.[167] Among the patients treated with SRS alone, 37% underwent salvage therapy at a median of 5.7 months after SRS versus 7% after a median of 8 months following WBRT with SRS. This study did not differentiate between salvage for local failures and distant central nervous system (CNS) failures. Survival was not significantly different (~8 month median survival in both arms). In a randomized study from M. D. Anderson Cancer Center (MDACC; Houston, TX), 58 patients were randomized to receive SRS alone versus SRS plus WBRT.[159] Patients treated with SRS alone had a significantly inferior 1-year tumor control (67% versus 100%, $p = 0.012$) and distant brain tumor control (45% versus 73%, $p = 0.020$), but had a significantly improved 1-year survival (63% versus 21%, $p = 0.003$), with a >2 HR of death from neurologic causes as well as systemic causes. Postulated reasons for the improved survival of the SRS-only group is the earlier administration of systemic therapy as well as the high rate of salvage therapy (87%) for brain metastases.

Avoiding WBRT can potentially prevent acute and late toxicity from WBRT and allow WBRT to be used as salvage therapy if needed. During WBRT, patients acutely experience alopecia and may develop skin erythema and mild desquamation. Less commonly, otitis media may develop. More concerning is the late toxicity from WBRT, occurring months to years after radiation, which may be relevant in the population of patients with a solitary metastasis who have a potential for cure. Late toxicity includes cataract formation, dry eye, and neurocognitive defects such as memory loss and dementia.[188-190] The extent to which WBRT causes neurocognitive defects is not well reported.[191] Neurocognitive decline may in part be because of the poor function of many patients who present with brain metastases and the general deterioration of patients whose cancer progresses.[192,193] In the randomized study of SRS versus WBRT with SRS from Japan, there was not a significant difference in the posttreatment change in neurocognitive function between the two study groups, although those patients in the SRS-alone group experienced a more rapid decline in neurocognitive function, presumably as a consequence of brain failure (local failure or distant brain failure).[194] Patients treated with WBRT did experience a continued decline in neurocognitive function, as a result of tumor recurrence or effects from WBRT. In the previously discussed trial from MDACC, Chang et al employed the most sophisticated cognitive testing to date in a randomized trial. The trial was prematurely closed because of the significantly greater likelihood of decline in learning and memory function for patients undergoing WBRT with SRS versus SRS alone.

LIVER METASTASES

Liver metastases are a common cause of morbidity and mortality. They can occur in patients with tumors of many common cancer types, are difficult to treat, and often lead to short survival periods. The liver is also protected from some cytotoxic agents because of its natural detoxification function and its relative hypoxic state. In contrast to the 80% perfusion of the normal liver by the portal venous system, most liver tumors obtain blood flow almost exclusively through the hepatic arterial system. This phenomenon necessitates novel interventional radiological techniques. Likewise, advances in imaging have allowed for more definitive anatomic localization of liver metastases, leading to new minimally or noninvasive treatments for these tumors.

Clinical Manifestations and Patient Evaluation

Common symptoms of liver metastasis include nausea, vomiting, changes in bowel habits, distension, and bloating associated with ascites, jaundice, and pain as a result of distension of the liver capsule. Some patients experience petechia, night sweats, and weight loss.

Diagnosis

Most liver metastases are discovered with routine metastatic surveys. Biphasic and triphasic helical CT is the optimal method for the detection of liver metastases. During the portal venous phase of the scan, the tumor is hypointense because of its dependence on hepatic arterial perfusion, while tumors can be enhanced on arterial phase images. Approximately 90% of lesions greater than 1 cm are detected by portal phase images alone; approximately 10% more lesions are detected when the arterial images are used in combination.[195] These imaging characteristics are also useful for distinguishing metastatic disease from many other benign small lesions commonly seen in the liver, including cysts and hemangiomas.[196] An MRI can also help detect liver metastases; however, MRIs are expensive, can have motion artifacts, and have less well-defined tumor borders. They are generally employed when a patient has a contraindication to a contrast CT scan, or when a CT is inconclusive. MRI can distinguish solid hepatic metastasis from fatty change, cysts, and hemangiomas. On T1-weighted images, hepatic metastases have low-signal intensity, whereas on T2-weighted images tumors have inhomogeneously

high-signal intensity. Other methods of tumor detection include ultrasound and incidental detection during procedures done for benign diagnoses.

Treatment

Most treatments for liver metastases are systemic. Liver metastasis can respond well to chemotherapy and hormone therapy, but most remissions are short-lived. The response to these treatments can be mixed, with some tumors progressing while others subside. Aggressive local treatments for liver metastases can also provide substantial benefits. Although liver transplantation is not recommended, resection of lesions can lead to long-term survival, particularly among patients who respond to chemotherapy.[197,198] Benefits for patients who respond to chemotherapy occur even among those who were initially unresectable because of nodes, number or location of lesions, or lesion size.[198] Generally, resections are limited to patients with disease in a single lobe peripheral to the portal region. This limitation is also true for many other localized techniques, including radiofrequency ablation and cryotherapy.

Chemoablation has arisen as an effective form of therapy. In this invasive radiological technique, the artery feeding the tumor is infused with chemotherapy, usually after an injection of contrast material defined by the tumor vasculature, followed by vascular ablation to trap the drug and asphyxiate the tumor.[199-203] Chemoablation is suitable for patients with a limited number of tumors and for whom vascular access is possible.

Irradiation Technique and Doses

Radiation techniques for liver metastases include whole liver radiation, stereotactic liver radiation, and selective internal radiation-therapy methods. Radiotherapy is often used to palliate liver-capsule pain and treat patients with chemotherapy-resistant disease. In addition, it can be used on patients with poor liver function, who have an expected survival of more than 3 months.

Whole Liver Irradiation

Normal liver has poor tolerance to EBRT if the entire liver is irradiated, and clinical liver failure can arise from low to moderate doses of whole-liver radiation (20 Gy to 30 Gy in 1.8- Gy to 2-Gy fractions). Higher doses have not been shown to be superior to lower doses. Care is taken to avoid exposure of the kidneys. Radiation has not had a significant role in the treatment of liver metastases in most institutions. It should be noted, however, that the risk for radiation-induced liver disease (RILD) is low if the whole liver dose is restricted to 30 Gy or less in fractions of 2 Gy or less.

Liver radiation for metastatic disease can be of palliative benefit, as found in an RTOG Phase II trial of 100 patients in whom palliation of pain was noted in 55%.[204] Survival for more than 6 months was significantly correlated with colorectal primary, good initial performance status, and lack of extrahepatic metastases. Median survival however even when these criteria are employed is only 4 months to 4.5 months.[205] Addition of chemotherapy provides little if any additional benefit.[206] Bydder used 5 Gy × 2 fractions and found improvement at 6 weeks in abdominal pain (63%), distention (30%), night sweats (63%), and nausea (44%). This abbreviated treatment provided results similar to those seen with more protracted courses and may be recommended for patients with poor performance status.[207]

Selective Internal Irradiation (SIRT)

Liver metastases can be treated with one of several embolization techniques, in which microscopic spheres (microspheres) are administered via the liver's arterial supply. Specific techniques include "bland embolization" in which the microspheres are not embedded with cytotoxic agents, transarterial chemotherapy embolization (TACE) in which the microspheres are embedded with chemotherapeutic agents, and SIRT in which the microspheres are embedded with radioactive Yttrium-90 (Y-90). It remains controversial as to which embolization technique is preferred for any given patient. Y-90–labeled microspheres have also been used in the treatment of hepatocellular carcinoma.[208]

Specifically, radioembolization is a highly conformal method of delivering radiation using the radioactive, beta emitter, isotope Y-90 embedded in a glass or resin microspheres. An interventional radiologist delivers these microspheres using the hepatic artery and the microsphere size allows it to become embedded in the tortuous vasculature of metastatic liver tumors. The high stopping power of the beta particle (maximum energy 2.28 MeV, average energy 0.94 MeV) allows for an average penetration range of about 2.5 mm in soft tissue. SIR-Spheres, a Y-90 labeled biocompatible resin microspheres (20 micrometers to 40 micrometers in diameter), is the only Y-90 radioembolization product approved in the United States for the treatment of unresectable liver metastases from primary colorectal cancer.

A study from Northwestern University (Chicago, IL) investigated 137 patients who underwent 227 administrations of Y-90–labeled microspheres for chemotherapy refractory liver metastases.[209] Fifty-nine percent of patients had >4 tumors. Most patients (>80%) had <25% of the liver involved. For all lesions in all patients, 87% experienced a biologic response. Toxicity was acceptable. Fifty-one patients had colorectal cancer; their median survival was about 15 months. Another study from Northwestern University demonstrated the safety and efficacy of Y-90–labeled microspheres in patients with liver metastases.[210]

In an early study from Australia of mostly patients with hepatic colorectal metastases, the combination of a single injection of Y-90–labeled microspheres plus regional hepatic artery chemotherapy was substantially more effective in increasing tumor responses and progression-free survival than the same regimen of hepatic artery chemotherapy alone. Clinical tumor response, carcinoembryonic antigen (CEA) level, and survival were all significantly improved with the addition of Y-90–labeled microspheres.[211] In another study by the same group, adding Y-90–labeled microspheres to systemic therapy yielded improved response rates and acceptable toxicity.[212] A Phase III trial published in 2010 comparing protracted intravenous fluorouracil infusion with or without Y-90 resin microsphere radioembolization for liver-limited metastatic colorectal cancer refractory to standard chemotherapy showed that Y-90 microspheres plus fluorouracil is well tolerated and improves time to liver progression 2.1 versus 5.5 (p = 0.003).[213] A pooled analysis combined 19 studies that specifically investigated patients receiving Y-90–labeled microspheres for liver metastases from colorectal cancer. The reported median survival ranged from 10.8 months to 29.4 months.[208]

Liver metastases from neuroendocrine tumors also appear to be effectively treated with Y-90–labeled microspheres. In the study from Northwestern University, 19 patients had neuroendocrine carcinomas. Among these patients, the median survival was 26 months and the 2-year survival was 69%.[209] In a multiinstitutional report, 148 patients with liver metastases from neuroendocrine tumors underwent 185 administrations of Y-90 microspheres.[148] After treatment, 23% had stable disease, 61% partial response, 3% complete response, and 5% progressive disease. The 2-year survival was ~75% and the median survival was ~70 months. In another multiinstitutional study, 42 patients underwent Y-90 microspheres for liver

metastases from neuroendocrine tumors.[214] Greater than 90% achieved stable disease or a partial response. The median survival was on the order of 2 years. In an Australian study, 34 patients with liver metastases from neuroendocrine tumors were treated with Y-90 microspheres. Radiologic liver responses were observed in 50% of patients and included 6 (18%) complete responses and 11 (32%) partial responses; the mean overall survival was 29 months. Symptoms from the tumor were improved in 50%. The differences in survival between these studies demonstrate a heterogeneous patient population. Also, the survival without Y-90–labeled microspheres treatment cannot be determined in these patients, with a condition that is often slowly progressive. Only one of these studies addressed the potential of Y-90 microspheres treatment to alleviate symptoms from carcinoid tumors.

Evidence is accumulating supporting Y-90 use for hepatic metastatic tumor treatment in a wide variety of primary cancer histologies including breast, pancreatic, lung, renal, esophageal, ovarian, and intrahepatic cholangiocarcinoma.[215,216] Because of the expense and the limited data at this time, Y-90 is usually reserved for unresectable liver dominant metastatic hepatic disease with a projected life expectancy of at least 3 months. The prework-up of this procedure is relatively intensive and includes a pretreatment planning angiogram, microsphere angiography of the liver, and a 99m-Tc macroaggregated albumin scan that demonstrates lung shunting or flow to the gastrointestinal tract. A consensus statement addressing patient eligibility for Y-90–labeled microspheres states, "Patients considered for radioembolization therapy would include those with (1) unresectable hepatic primary or metastatic cancer, (2) liver-dominant tumor burden, and (3) a life expectancy of at least 3 months … Contraindications for radioembolization therapy may include (1) pretreatment 99m-Tc macro-aggregated albumin (MAA) scan demonstrating the potential of ≥30 Gy radiation exposure to the lung or flow to the gastrointestinal tract resulting in extrahepatic deposition of 99m-Tc MAA that cannot be corrected by catheter embolization techniques, (2) excessive tumor burden with limited hepatic reserve, (3) elevated total bilirubin level (≥2 mg/dL) in the absence of a reversible cause, and (4) compromised portal vein, unless selective or superselective radioembolization can be performed. Patients with prior radiotherapy involving the liver should be carefully reviewed on a case-by-case basis. It is unclear whether capecitabine chemotherapy treatments represent a contraindication to Y90 treatment.[217]

SBRT

Because the liver's regenerative powers make localized high-dose radiation achievable with minimal toxicity, SBRT has become popular for patients with a limited number of metastases and minimal extrahepatic tumors.[12,13,218,219] As with most SBRT approaches, respiratory arrest or gating is preferred, but four-dimensional CT has also achieved good results. Large and portal lesions can be treated safely, and most studies show local control rates of more than 70%.[218,219] No clear dose response has been measured, but all radiation doses and schedules have produced similar results.

Liver Tolerance

Although lethal RILD can occur when the median liver dose exceeds 37 Gy in standard fractionation, little or no toxicity is seen when more than 50% to 70% of the liver is maintained under 30 Gy.[220,221] Patients primarily report decreased appetite and gastritis; moreover, patients with cirrhosis may experience exacerbation of hepatitis, and those with subdiaphragmatic tumors can have asymptomatic right pleural effusions. After radiation, tumors often become hypointense on CT scans, and surrounding hepatic damage may correspond to the 37-Gy isodose line. These radiographic changes can be confused with tumor progression because tumors reach a maximum size at 6 weeks to 3 months after irradiation and recover at 6 months to 9 months. The contralateral lobe of the liver commonly hypertrophies to compensate for the lost liver mass; however, total liver volume usually maintains normal levels.

LUNG METASTASES

Disease can occur in the parenchyma and in mediastinal or hilar nodes. Metastases in the lung bases are more common than in upper regions.[11] Although peripheral lesions are often asymptomatic, central tumors can cause airway obstruction. Other signs and symptoms include cough, respiratory discomfort, shortness of breath, superior vena cava syndrome, and in severe cases hemoptysis or dysphagia. High-speed helical CT allows for high-precision detection of lung tumors smaller than 1 cm. Malignancy can be confirmed using PET/CT for glucose-avid tumor types, including colorectal, lung, and breast cancers.

Treatment

Standard treatment for pulmonary metastases is systemic chemotherapy. Tumor response to chemotherapy can be substantial, but it is usually short lived and oftentimes results in eventual recurrence. Minimally invasive surgical techniques paired with advanced imaging of the lung have made it possible to remove many small lesions. Although rarely employed for adult cancers, resection by open or minimally invasive techniques is commonly used for many childhood malignancies.[222,223] As with liver metastases, radiofrequency ablation and radiosurgical techniques are also employed.

SBRT

Use of pulmonary SBRT for metastasis to the lung has greatly increased with the advent of imaging technologies capable of identifying very small metastatic tumors. The more widespread availability of PET/CT has improved our ability to distinguish these small tumors from benign nodules. The incremental gain for patients, as with metastectomy, has been difficult to prove; still, as with surgical approaches, local control rates are consistently higher than 80% or 90%. New metastases in the lungs are also commonly low, and quality of life is improved with maintenance of pulmonary function. Additionally, most studies show increased long-term and disease-free survival, which indicates the potential for a cure.

The ability to give hypofractionated ablative doses of radiation relies on decreasing the size of the planned treatment volume to spare normal tissue from damaging penumbra. In the lung, the most severe limitation of a parsimonious PTV that covers the lesion is respiratory motion. Several methods for increased PTV accuracy include real-time imaging of the lesion during respiration, gating, and methods to decrease the severity of motion (breath hold, quiet breathing, real-time breathing feedback, and diaphragmatic immobilization). Radiation doses range from 30 Gy to 66 Gy given in 3 fractions to 10 fractions to 48 Gy to 60 Gy given in 10 fractions to 12 fractions.[224-227] Despite the wide variation in dose and fractionation, the results have been uniformly excellent with high control rates. Higher fraction sizes do not necessarily produce higher control rates for metastases, but grade-3 to grade-5 toxicity is most common with larger fraction sizes and central tumor locations.[225] In Rusthoven et al's[227] report on patients, with one to three metastases with a cumulative diameter under 7 cm, who were given 48 Gy to 60 Gy in 3 fractions: 63 lesions were treated in 38 patients with a local control rate of

96% at 2 years and 8% grade 3 and no grade 4 toxicity. Okunieff et al[224] report local failures in 8 of 125 lesions (local control rate of 94%) treated and followed for a minimum of 1 year. Tumors were up to 7.7 cm, and the dose was 50 Gy in 10 fractions. The progression-free survival progression-free survival (PFS) was 16% at 2 years. Grade-3 toxicity was seen in only 2% of patients; there was no grade-4 toxicity.

Most patients have already failed several courses of standard chemotherapy before being offered SBRT. Nevertheless, excellent tumor control with minimal toxicity and unexpectedly high rates of PFS suggest that SBRT improves morbidity and mortality.

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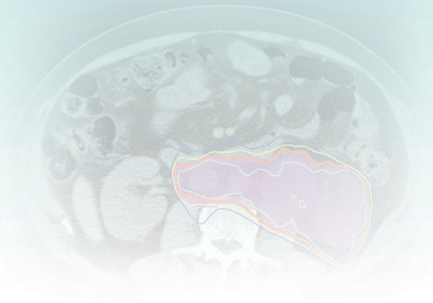
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Overview



Minesh P. Mehta

Since the last edition of this book, significant advances in neurooncology have been made that have changed the standard of care for several central nervous system (CNS) neoplasms, and these are reviewed in detail in the following chapters. The purpose of this overview is to present the "headlines" relative to these major practice events, which will then set the stage for the reader to delve into greater detail in the ensuing chapters.

SPECIFIC TUMORS: GLIOMAS AND LYMPHOMA

For *glioblastoma*, despite a name change from the prior glioblastoma multiforme (GBM), few true advances in survival prolongation have been identified. Two major efforts, focused at dose-intensifying temozolomide and incorporating antiangiogenic strategies, have failed to prolong survival. However, for recurrent glioblastoma, antiangiogenic agents have become well-established in practice, and newer technologies such as alternating electric field devices are emerging as options. More importantly, an explosion of molecularly driven knowledge has opened up several avenues, for example, the recognition that the benefit of temozolomide in methyl-guanine methyl transferase (MGMT)-unmethylated tumors might in fact be a reflection of undetected methylated tumors; that some subsets of GBM might actually benefit from antiangiogenic strategies (based on preliminary analysis); and the rapidly emerging investigation of immune checkpoint inhibitors and vaccine-based strategies. Management of elderly patients with GBM, always a major challenge, is also being rapidly refined, with the understanding that as far as single agent therapy alone is being contemplated, temozolomide might be superior to radiotherapy for methylated tumors, with the converse being true for the unmethylated tumors.

For *anaplastic gliomas*, the role of combined modality chemoradiation has now become truly established with the recognition of a major benefit in overall survival with procarbazine/CCNU/vincristine (PCV) plus radiotherapy especially in the 1p19q co-deleted tumors. Further, it appears that the survival benefit seen with concurrent chemoradiation in the 1p19q non codeleted anaplastic oligodendroglioma might in fact be limited to the cohort of patients with mutated isocitrate dehydrogenase (IDH), and in fact IDH mutations might supplant 1p19q analysis in this context. In practice, this has posed a major conundrum, because of practitioner preference for temozolomide, which is currently being compared to PCV in a randomized trial, with only limited prospective data supporting the use of temozolomide in this context. More importantly, even though there are no categorical data to support such an approach, there is an emerging trend to withhold radiotherapy from some of these patients, driven in large measure because the long-term survival of these patients raises the specter of delayed radiotherapy toxicities. However, advances in the realm of intensity-modulated radiotherapy (IMRT) have now convincingly demonstrated improved cognitive sparing and such techniques are rapidly being adapted in practice. The significant increase in the number of proton centers is also allowing greater access to this technology, which is also associated with clear dosimetric advantages, the clinical benefits of which remain to be categorically demonstrated.

For *low-grade gliomas*, chemotherapy historically had no role; recent results from seminal trials conducted by the Radiation Therapy Oncology Group (RTOG) and other North American cooperative groups with long-term follow-up now provide convincing evidence of major survival benefit from combined chemoradiation, compared to radiotherapy alone for all patients older than the age of 40, and for patients who are subtotally resected, irrespective of age. This survival benefit also comes from PCV chemotherapy, and limited data supporting similar possible outcomes are beginning to emerge when PCV is replaced with temozolomide. Whether radiotherapy could be withheld or not remains an investigational question and data from a recently completed prospective randomized European Organisation for Research and Treatment of Cancer (EORTC) trial will likely provide the answer in the near future. The role of molecular fingerprints determining the extent of benefit and identifying appropriate subsets is being unraveled, and as would be expected, MGMT, 1p19q, IDH, and several others are being intensively interrogated. Clearly, for most gliomas, therefore, the landscape appears to be shifting in favor of combined chemoradiation, and especially in the context of molecular subtyping to identify tumors most likely to benefit.

For *lymphomas* of the CNS, major survival gains have been made with high-dose methotrexate-based regimens, and biological agents such as rituximab in conjunction with chemotherapy are rapidly being incorporated into practice based on the results of two recent clinical trials.

IMAGING

Despite the superb detail provided by today's high-resolution high-field magnets, a major limitation of magnetic resonance imaging, especially for infiltrative neoplasms, is definition of the true extent and range of spread, something that no established imaging technique comes even close to estimating with precision. The unusual phenomena of pseudo-progression, and more recently, pseudo-response, rarely seen outside the

CNS continue to pose a further diagnostic conundrum, and new and more sophisticated biologically based imaging is being developed for this purpose.

The success of local therapies such as surgery and radiotherapy is comprehensively dependent on accurate estimation of tumor extent. As several studies have now demonstrated, current imaging is simply inadequate for this, especially for detecting microscopic infiltration, which in CNS neoplasms can assume extremely complicated patterns, such as along fiber tracts, along subependymal planes, through the cerebrospinal fluid, by exhibiting "skipping" and "multifocality," and more recently the presumed phenomenon of "cooption."

PRIMARY THERAPY: SURGERY AND IRRADIATION

The surgical challenges in the CNS remain immense. Unlike other anatomic sites, the concept of "redundant" tissue simply does not exist in the brain and spinal cord, and therefore, every surgical procedure is technically risky, and en bloc oncologically complete resections with wide margins are almost impossible. Before the advent of pre- and intraoperative neuronavigation with three-dimensional (3D) navigating capabilities, intraoperative microscopes, the availability of brilliant illumination, improved instrumentation and techniques for hemostatsis, as well as neuroanesthetic advances, aggressive resections with an intent to remove all visible tumors were infrequently undertaken. The consequences of this were multiple. Many tumors remained "imaging and clinical diagnosis," for example, skull-base meningiomas, vestibular schwannomas, brainstem gliomas, and presumed pineal germ cell tumors. Inclusion of these tumors, with uncertain diagnosis, as well as uncertain clinical behavior, makes interpretation of generalized treatment results inaccurate. Further, a tendency toward "small" biopsies was common, adding to diagnostic uncertainty. And most importantly, although level 1 evidence is sparse, an increasing body of literature suggests that more complete resections are important for almost all CNS neoplasms, a trend that has clearly increased in practice in the last decade. Agents to guide complete resection through tumor-specific visualization have already been approved in Europe and remain under investigation in the United States; their advent could be practice changing.

Advances in radiotherapeutic techniques over the last two decades have had a major impact in neurooncology. Because the majority of cell populations within the CNS have a low mitotic index, and proliferate slowly, they are the prototypical "late-responding tissues" of conventional radiobiologic literature. Consequently, the effects of CNS radiation are sometimes not apparent for years, and even then, the historic approach has assumed that "all brain is equally sensitive," with a nascent appreciation of compartment and cell-type specific radiosensitivity. This, too, is changing rapidly, and the advent of 3D conformal, stereotactic, IMRT, image-guided radiotherapy (IGRT), and proton solutions now offers unique opportunities for altering the therapeutic index in CNS tumors. Some elegant and practical examples include the avoidance of the optic apparatus during stereotactic radiosurgery (SRS) to prevent blindness, cochlear sparing with IMRT in children with medulloblastoma to spare hearing, minimizing the dose to the hypothalamic-pituitary axis to avoid endocrinopathies, the emerging hypothesis of compartmental stem cell sparing to retain neurogenesis and hence memory, etc. The recent QUAntitative estimates of Normal Tissue Effects in the Clinic (QUANTEC) analysis provides a new dataset for normal tissue tolerance, and although still limited in scope, it is substantially improved over what was available just 3 years ago for the treating physician. This should help standardize dose-selection practices.

SUMMARY

In the series of detailed chapters that follow, a team of internationally acclaimed authors, infused with this newfound enthusiasm in neurooncology, review the issues I have highlighted in considerable detail. This will provide the treating physician with an up-to-date resource that is practical, comprehensive, and thoroughly referenced, which we hope will ultimately serve our patients' needs.

CHAPTER

26 Low-Grade Gliomas



Paul D. Brown, Michael D. Chan, Edward G. Shaw, and Martin J. van den Bent

EPIDEMIOLOGIC AND ETIOLOGIC FINDINGS

The estimated annual incidence of low-grade gliomas in the United States is 2000 cases. Etiologic factors are unknown. These tumors are seen with increased frequency in patients with types 1 and 2 neurofibromatosis.

PATHOLOGIC FINDINGS

The most common pathologic types include pilocytic astrocytoma (World Health Organization [WHO] grade I), diffuse fibrillary astrocytoma, oligoastrocytoma, and oligodendroglioma (WHO grade II).

BIOLOGIC CHARACTERISTICS

Combined 1p and 19q deletions are associated with a superior outcome and are most common in oligodendrogliomas. *TP53* mutations are more common in diffuse astrocytomas and are mutually exclusive from 1p/19q co-deletions. *IDH1* mutations occur in the vast majority of low-grade gliomas and are found both in tumors with *TP53* mutations and in tumors with 1p/19q codeletions.

CLINICAL MANIFESTATIONS AND PATIENT EVALUATION

The mean age at presentation is 37 years. Most patients do not have any signs of their disease (i.e., they are neurologically "intact"). The most common symptom is seizure.

Age is the most powerful clinical prognostic factor for survival. Children have a significantly better outcome than adults. Other prognostic factors associated with better overall or progression-free survival (PFS) rates include oligodendroglioma histology, normal mental status, and smaller tumor size.

The imaging features vary by pathologic type. Pilocytic astrocytomas are well circumscribed and contrast enhancing. Diffuse fibrillary astrocytomas are poorly circumscribed and typically nonenhancing, best seen on a T2-weighted or fluid attenuated inversion recovery (FLAIR) magnetic resonance imaging (MRI) scan.

PRIMARY THERAPY

Maximum surgical resection is associated with a more favorable outcome.

In pediatric low-grade gliomas, observation is recommended after gross total resection. After subtotal resection or biopsy, treatment (radiation therapy, chemotherapy) is usually deferred until symptomatic or imaging progression.

In adults, after gross total resection of a pilocytic astrocytoma, observation is recommended. After gross total or subtotal resection (or biopsy) of a low-grade glioma, irradiation may be given postoperatively or deferred until progression occurs.

The recommended radiotherapy (RT) dose is 45 Gy to 54 Gy in 25 fractions to 30 fractions, treating the MRI-defined tumor volume with a 2-cm margin.

Early results from one large randomized clinical trial suggest disease and outcomes are similar for either temozolomide or RT for 1p/19q-deleted tumors although RT may have a superior PFS for 1p-intact tumors; however, the period of follow-up in this trial is immature and not yet adequate to make definitive treatment recommendations.

Long-term follow-up of a large randomized clinical trial of 251 patients with less than gross total tumor resection or older than 40 found significantly better PFS and overall survival (OS) for those treated with RT followed by procarbazine, CCNU, and vincristine (PCV) compared to those treated with RT alone (RTOG 98-02). These results confirm a benefit for RT followed by chemotherapy for select low-grade glioma populations.

RECURRENT DISEASE

Several challenges constrain recommendations in this setting. It is difficult to differentiate recurrence from radionecrosis by clinical symptoms or signs alone or by conventional MRI or positron emission tomography (PET). Further, at recurrence, consideration must be given to the possibility that these tumors could have transformed to malignant gliomas, which are treated differently.

Low-grade gliomas are a pathologically and clinically diverse group of uncommon central nervous system (CNS) tumors that occur primarily in children and young adults. The prognosis is principally affected by patient age and pathologic type of tumor. Studies assessing proliferation and molecular genetics may provide additional insight into prognostic groups that are at higher risk for developing recurrence and therefore may benefit from adjunctive treatments such as radiation therapy and chemotherapy. In general, more extensive resection is associated with better prognosis. The optimal timing of irradiation is best determined by weighing all prognostic factors, favoring "early" (or postoperative) irradiation for high-risk patients and delaying irradiation for lower-risk patients. The importance of chemotherapy in the treatment of low-grade glioma is growing based on a number of clinical trials.[1]

In this chapter, a comprehensive overview of low-grade glioma is provided with an emphasis on adults. Topics covered include epidemiology, etiology, pathology, biology, clinical manifestations, patient evaluation, management (including surgery, radiation therapy, and chemotherapy), and toxicity.

EPIDEMIOLOGY AND ETIOLOGY

Annually in the United States, it is estimated that 23,130 CNS tumors will be diagnosed,[2] of which approximately 20,000 will arise in the brain.[3] Of these, approximately 2000 will be low-grade gliomas.[4]

Etiologic factors for low-grade gliomas are largely unknown. Low-grade astrocytomas have been associated with von Recklinghausen disease (type 1 neurofibromatosis) and type 2 neurofibromatosis.[3] In addition, a direct link has been made between subependymal giant cell astrocytoma, an uncommon pathologic type of low-grade astrocytoma, and tuberous sclerosis.[5]

PATHOLOGY

Pathologic Classification

Historically, low-grade gliomas have been considered a homogeneous group of neoplasms associated with a more favorable natural history.[6] In reality, they are a diverse group of tumors found throughout the CNS, the outcome of which depends on a number of anatomic, pathologic, biologic, host, and treatment factors.

Table 26-1 summarizes the current World Health Organization (WHO) classification of primary CNS tumors as it applies to low-grade gliomas.[7] Grade I tumors must be separated from grade II tumors because they have a different molecular background. These tumors are well circumscribed, are considered benign, and if completely resected, they are typically cured. The pilocytic astrocytomas, which comprise nearly all of the grade I cerebral astrocytomas, tend to be better circumscribed and rarely transform.[8] Although pilocytic astrocytomas occur more commonly in the cerebellum of children (juvenile pilocytic astrocytoma), they also occur in the cerebral hemispheres and in particular near the optic pathway.

The diffusely infiltrative low-grade astrocytomas (WHO grade II) are the most common and include astrocytoma, oligodendroglioma, and mixed oligoastrocytoma.[7] Grade II gliomas are diffusely infiltrating tumors and are capable of undergoing anaplastic transformation with an incidence as high as 80%.[8,9] Remaining are the uncommon low-grade glioma variants, including the pleomorphic xanthoastrocytomas, subependymal giant cell astrocytomas, and others, which are briefly discussed later in the chapter.

TABLE 26-1 Low-Grade Gliomas* Included in World Health Organization (WHO) Classification of Gliomas

Type	WHO Grade
ASTROCYTIC TUMORS	
Subependymal giant cell astrocytomas	I
Pilocytic astrocytomas	I
Pleomorphic xanthoastrocytomas	II
Pilomyxoid astrocytoma	II
Diffuse astrocytoma	II
OLIGODENDROGLIAL TUMORS	
Oligodendrogliomas	II
OLIGOASTROCYTIC TUMORS	
Oligoastrocytomas	II

Louis DN, Ohgaki H, Wiestler OD, et al: The 2007 WHO classification of tumors of the central nervous system. Acta Neuropathol 114(2):97-109, 2007.
**Exclusive of ependymal and glioneuronal neoplasms.*

Grading Systems

The concept of dividing astrocytomas into discrete grades associated with a distinct clinical prognosis dates back to the mid-1920s and early 1930s to the work of Bailey and Cushing, who recognized a subset of astrocytomas that had a more favorable outcome than glioblastoma.[10] There have been many grading systems (e.g., Kernohan, St. Anne-Mayo, and Ringertz systems) in the past, which assess nuclear abnormalities, mitoses, endothelial proliferation, and necrosis. Currently, the most widely used and accepted grading system is the WHO system.[7] WHO grade I lesions are well circumscribed and have low proliferative potential, with the possibility of cure following surgery alone. Grade II neoplasms are infiltrative, as a rule recur, and tend to progress to higher grades of malignancy (e.g., grade II astrocytoma transforms to grade III anaplastic astrocytoma) despite initial low-level proliferative activity. All histopathological grading schemes are limited by their need to separate gliomas artificially into three or four groups, when in actuality they exist along a biologic continuum and the diagnoses are subject to considerable interobserver variation.[11] For the present, this somewhat outdated method is still used in both therapeutic decision making and prognostication, but it is fully anticipated that in the near future reiterations of the WHO grading system will incorporate imaging and genetic testing.

BIOLOGIC CHARACTERISTICS AND MOLECULAR BIOLOGY

Since the 1990s, our understanding of the biology of low-grade gliomas has increased. This has included studies of tumor proliferation, and both cytogenetic and molecular genetic studies.

Studies of Proliferation

Tumor proliferation can be assessed with Ki-67 labeling. A large review on Ki-67 labeling revealed increasing values of Ki-67/MIB-1 labeling index with increasing grade of malignancy.[12] The MIB-1 labeling index differentiates diffuse astrocytomas (WHO grade II) from anaplastic astrocytomas (WHO grade III) and glioblastoma (GM) tumors. Similar findings have been reported in oligodendrogliomas.[13] Although the MIB-1 labeling index is a clear prognostic factor in low-grade glioma, the absence of agreed-on low versus high cut-off values and interobserver variation between various institutions prevents its routine use.

Genetic and Other Molecular Studies

About 50% to 60% of astrocytomas have *TP53* mutations, and this figure may be even higher in gemistocytic astrocytoma.[14,15] In contrast, low-grade oligodendrogliomas typically have combined loss of 1p/19q, and the genotype is actually an unbalanced t(1;19)(p10;q10) peri-centromeric translocation.[16] *TP53* mutations and 1p/19q codeletions are mutually exclusive, and most mixed oligoastrocytomas carry either the typical oligodendroglial 1p/19q codeletion or a *TP53* mutation, suggestive of an astrocytic lineage.[17] Therefore, at the molecular level, mixed oligoastrocytomas are not true mixed tumors but are of either astrocytic or oligodendroglial lineage.

The recently identified *IDH1* mutations (an enzyme that participates in the citric acid cycle) occur in 70% to 80% of low-grade gliomas, both in tumors with *TP53* mutations and in tumors with the 1p/19q loss.[15,18] The current data and the absence of the acquisition of *IDH1* mutations over time suggest that the *IDH1* mutation is an early event in the tumorigenesis

of *IDH1*-mutated tumors[19] and distinguishes primary from secondary glioblastoma.[18]

Methyl-guanine methyl transferase (MGMT) is a DNA-repair enzyme that removes alkyl groups from the O_6 position of guanine in DNA and therefore repairs damage induced by alkylating agents (e.g., temozolomide). MGMT promoter methylation in IDH-mutated tumors is highly associated with the CpG Island methylated phenotype (CIMP) that is induced by the metabolic alterations induced by IDH mutations.[20] It is currently unclear if MGMT promoter methylation can be used for treatment decisions in low-grade gliomas; recent data suggest that MGMT promoter methylation may have different significance in IDH-mutated versus IDHwt tumors.[21] Lastly, a concept of "triple negative" low-grade glioma is emerging, low-grade astrocytomas without either IDH mutations, TP53 mutation, or 1p/19q co-deletion. Of all grade II diffuse glioma these tumors tend to have the worst survival.[22]

The PI3K/mTOR pathway is activated in most adult low-grade gliomas, with methylation of the promoter region of the PTEN gene in one third of patients.[23] One study observed that p14(ARF) hypermethylation and MGMT hypermethylation constitute distinct molecular pathways of astrocytoma progression, with more frequent progression in p14(ARF) hypermethylation cases.[24]

Prognostic and Predictive Molecular Factors

Molecular and cellular biologic characterization of low-grade gliomas may help to predict which patients are more likely to require earlier and more aggressive therapy. Conversely, it may help to determine which patients may be observed initially, withholding treatment until the time of disease progression. To date, molecular findings are still infrequently used for clinical decision making primarily because most lack prospective validation. Today, most of the observed findings are primarily prognostic and are not predictive for outcome to specific treatments. For example, the presence of IDH1 mutations have a major favorable prognostic impact in low-grade astrocytomas but does not affect outcome with temozolomide treatment.[15,25] However, recent studies show that molecular profiling holds more prognostic information in low-grade glioma compared to classical histology.[25] Moreover, the upcoming molecular analyses of recently completed large Radiation Therapy Oncology Group (RTOG) and European Organisation for Research and Treatment of Cancer (EORTC) Phase III studies on low-grade gliomas are expected to change the prognostic nature of these molecular features to predictive factors, similar to the recent developments in anaplastic glioma.

The presence of the 1p/19q codeletion also confers a favorable prognosis, with slower growth rates, compared with non–codeleted low-grade gliomas.[26,27] In a study of patients with low-grade glioma enrolled on two North Central Cancer Treatment Group (NCCTG) protocols, the median OS time and 5-year OS were 13 years and 96% in oligodendroglioma patients with 1p/19q codeleted tumors versus 10.8 years and 70% in those without codeletion.[16] For oligoastrocytomas, the median OS and 5-year OS were 11 years and 90% for 1p/19q codeleted tumors and 8.3 years and 62% for tumors without the 1p/19q codeletion. Several studies noted improved outcome with chemotherapy of 1p/19q codeleted tumors as opposed to 1p/19q intact (oligodendroglial) tumors.[28]

CLINICAL MANIFESTATIONS AND PATIENT EVALUATION

In this section, information is reviewed on the clinical presentation and imaging of supratentorial low-grade gliomas based on the literature.[29]

TABLE 26-2 Symptoms of Low-Grade Gliomas

Symptom	Frequency (%) Mean	Range
Seizure	65	30-92
Headache	36	5-48
Weakness	30	6-53
Visual loss or change	15	4-16
Personality change	14	5-16
Focal symptom, NOS	13	6-20
Language dysfunction	13	4-17
Altered sensation	10	8-11
Nausea and vomiting	10	4-14
Altered mental status	9	7-12
Altered consciousness	8	4-20
Cranial neuropathy, NOS	7	—

Data from Levin VA, Gutin PH, Leibel S: Neoplasms of the central nervous system. In DeVita V, Hellman J, Rosenberg S, editors: Cancer: principles and practice of oncology, ed 4, Philadelphia, 1993, JB Lippincott.
NOS, *Not otherwise specified; data reported in only one series.*

Clinical Presentation

Low-grade gliomas are generally a disease of patients in their 20s, 30s, or 40s, with a mean age at presentation of 37 years. Cases have been reported in patients as young as 7 months and as old as 78 years. Low-grade gliomas are more common in men than in women by a ratio of 1.4:1.

The symptoms of low-grade gliomas are shown in Table 26-2. The most common symptom is seizure, occurring in two thirds of patients. Focal seizures are more common than generalized ones. Generalized tonic-clonic, simple partial, and complex partial seizures occur in 43%, 23%, and 34% of patients, respectively. Seizures are particularly common in patients with tumors located in the temporal and frontal lobes, insula, and perirolandic cortex.[30] Headache and weakness occur in approximately one third of patients. The remaining symptoms occur in 15% or fewer patients. The median duration from onset of symptoms to diagnosis is between 6 and 17 months, with a range of 1 day to 17 years.

Neurologic signs associated with low-grade gliomas have not been as rigorously reported in the literature. Focal neurologic deficits are related to the tumor location. About 50% of affected patients have a normal neurologic examination. The frequency of other signs at presentation is as follows: sensory or motor deficit, 42%; altered mental status, 23%; papilledema, 22%; aphasia, dysphasia, or decreased memory, 20%; focal deficit, 15%; altered consciousness, 8%; and motor deficit, 8%. Neurologic function is considered normal or mildly symptomatic or impaired in 63% of patients, moderately symptomatic or impaired in 25% of patients, and severely symptomatic or impaired in the remaining 12%. Less than 5% of low-grade gliomas are discovered incidentally (generally because of work-up of head trauma). These tumors appear to have improved outcomes compared to symptomatic tumors.[31]

Prognosis by Clinical Presentation

Age, gender, symptoms, signs, and neurologic function have all been significantly associated with survival in univariate and multivariate analyses from a number of retrospective studies in the literature. Both preoperative and postoperative neurologic function and performance status are correlated with outcome.[32] Brown et al conducted an analysis of baseline (before radiation therapy) Mini-Mental State Examination (MMSE) scores collected in patients with low-grade glioma on a prospective, intergroup clinical trial and found that the

TABLE 26-3 Survival of Children with Low-Grade Astrocytoma

Series	No.	Age (yr)	5-yr OS (%)	10-yr OS (%)
Pollack et al[35]	71	≤18	95	93
Youland et al[36]	351	<20	95	90
Merchant et al[33]	78	<20	99	96

No., *Number;* OS, *overall survival;* yr, *year.*

presence of an abnormal baseline MMSE score (26 or less) was a strong predictor of worse outcome. Patients with an abnormal baseline MMSE score had worse 5-year PFS (27% versus 60%) and OS (31% versus 76%) compared with those with a normal score.

After grade, the most powerful predictor of survival in patients with low-grade glioma is age, with much better survival rates in pediatric patients compared with adults. Table 26-3 shows the survival rate of children with low-grade astrocytoma. In a Phase II trial of 78 pediatric patients with low-grade glioma treated with RT (54 Gy), the 5- and 10-year OS were 99% and 96%, respectively.[33] For adult patients with low-grade astrocytoma, there is also an association between age and survival. Those younger than 40 years of age have a better survival than older patients.[34]

Of all the neurologic symptoms associated with low-grade astrocytoma, seizures, particularly when preceding the diagnosis by 6 months or more and in the absence of other neurologic symptoms, are associated with a better prognosis. In one series, the 5-year OS was 47% in patients presenting with seizures, 33% in those with headaches, 20% in those with altered mental status, and 0% when stupor was the presenting symptom.[37] In another series, the 5-year OS was 64% in patients with low-grade glioma who had seizures versus 14% in those without seizures.[38] Recent evidence suggests that low-grade gliomas presenting with seizures as first symptom may correlate with the presence of *IDH* mutations.[39]

Patients who present with a history of chronic epilepsy resulting from an underlying cerebral neoplasm are frequently found to have a low-grade astrocytoma. These patients are usually children or young adults (30 years of age or younger) whose seizure disorder and underlying tumor are often cured by a complete resection.[40]

Imaging of Low-Grade Gliomas

Table 26-4 shows the imaging characteristics of supratentorial low-grade astrocytomas based on multiple series in the literature.[41] On computed tomography (CT), the typical low-grade astrocytoma is lobar in location, involves the frontal or temporal lobes, is larger than 5 cm in diameter, and is nonenhancing. Because of the infiltrative nature of low-grade astrocytomas, the CT appearance of a typical nonenhancing tumor is a poorly defined area of low attenuation (Figure 26-1, *A*).

MRI (see Figure 26-1, *B*) provides superior visualization. FLAIR and both T2- and T1-weighted images (without and with contrast) provide anatomic detail that is useful in defining the extent of the tumor and in planning for surgical and radiation therapy. An understanding of these imaging-based anatomic-histopathologic relationships is important for both the neurosurgeon and the radiation oncologist. Removal of the poorly defined area of low attenuation (increased T2 or FLAIR signal) in a functionally intact area of brain (Figure 26-2) may lead to significant neurologic morbidity.

The radiographic features of low-grade gliomas have been correlated with prognosis in a number of retrospective series.

TABLE 26-4 Imaging Characteristics of Supratentorial Low-Grade Astrocytoma

Characteristics	Frequency (%) Mean	Range
LOCATION		
Lobar	80	50-90
Deep/midline*	20	4-40
Right	50	42-55
Left	50	41-60
Bilateral	5	1-11
Hemispheric†	0.5	—
LOBAR SITES		
Single	84	—
Multiple	16	13-38
Frontal	44	38-65
Temporal	37	8-61
Parietal	18	5-40
Occipital	3	0-10
OTHER		
Enhancement	34	22-58
Size ≥5 cm	66	21-88
Calcification	10	3-18
Cyst	15	6-29
Mass effect‡	—	12-84

From Shaw EG, Scheithauer BW, Dinapoli PR: Low-grade hemispheric astrocytomas. In Black PM, Loeffler JS, editors: Cancer of the nervous system. Cambridge, UK, 1997, Blackwell Scientific.

**Deep/midline sites include thalamus, basal ganglia, hypothalamus, third ventricle, and corpus callosum.*

†Only one series presented data on hemispheric involvement.[42]

‡Only two series presented data on mass effect.[43,44]

Although the presence of contrast enhancement on a CT or MRI scan in nonpilocytic low-grade gliomas would seemingly be associated with a worse prognosis because of presumed higher-grade elements or malignant transformation, data from prospective trials have not found the presence of contrast enhancement to be a predictor of outcome.[45,46] This may be related to the type of enhancement. Nodular enhancement as opposed to faint, patchy enhancement appears to be related to decreased survival times.[47] Other imaging findings, such as tumor size greater than 5 or 6 cm, or tumor crossing the midline (Figure 26-3), have been consistently associated with worse outcome.[34,45] Although the relationship between enhancement and prognosis has been controversial in the literature, two series assessing the likelihood of malignant transformation in low-grade gliomas based on the presence of enhancement have demonstrated a statistical association between enhancement and earlier malignant transformation.[48,49]

Imaging alone cannot reliably distinguish between grade II astrocytomas and oligodendrogliomas, though there are some imaging characteristics that may suggest that a tumor has an oligodendroglial component. Oligodendrogliomas are the most frequent primary brain tumor to calcify and have calcifications in 70% to 90% of cases.[50] They also tend to have cortical involvement and heterogeneous signal. There is also emerging evidence that oligodendroglioma and astrocytoma may have distinct signatures on perfusion MRI as the relative cerebral blood volume (rCBV) was found in one study to be significantly higher in low-grade oligodendroglioma than in low-grade astrocytoma.[51]

Pignatti et al[34] developed a prognostic scoring system using imaging, patient, and tumor characteristics derived from the

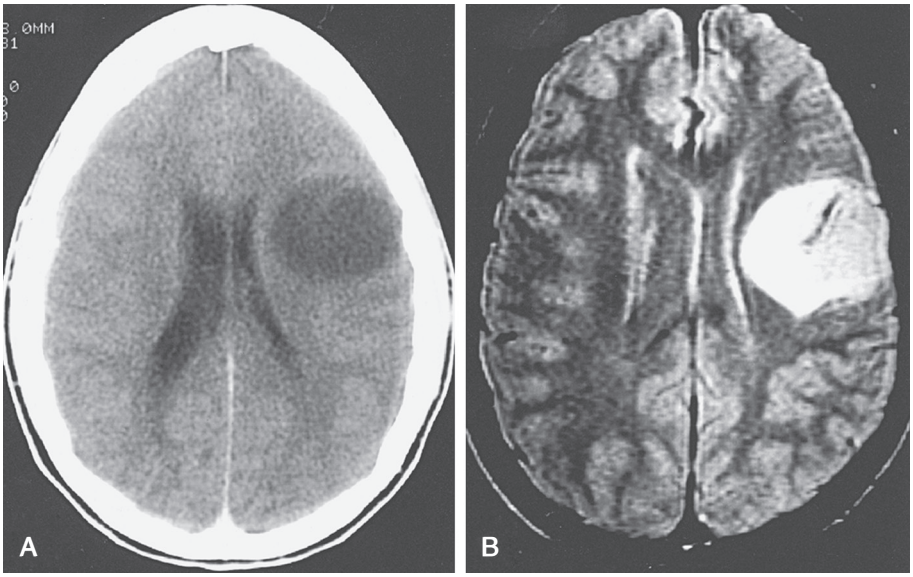


Figure 26-1 Postcontrast CT **(A)** and a noncontrast MRI **(B)** of an adult with a nonenhancing posterior left frontal WHO II astrocytoma.

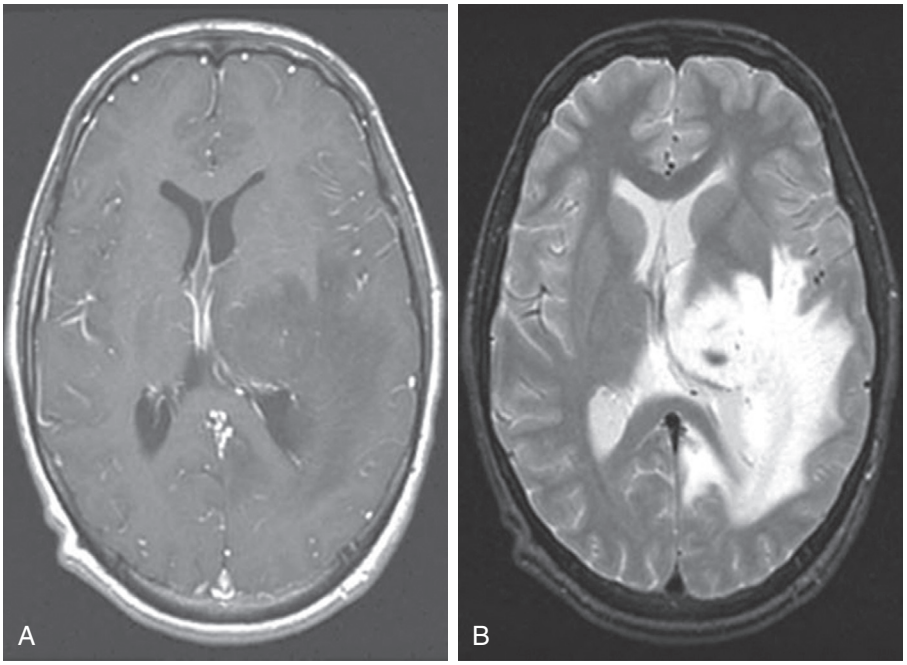


Figure 26-2 Postgadolinium T1-weighted **(A)** and T2-weighted **(B)** MRI scans of an adult with a WHO II astrocytoma of the left parietal lobe.

databases of two large Phase III adult low-grade glioma trials (EORTC trials 22844 and 22845). By means of Cox regression analysis, they identified and validated the following negative risk factors: age 40 years or older, astrocytoma histology subtype, largest diameter of the tumor of 6 cm or more, tumor crossing the midline, and presence of neurologic deficit before surgery. The total number of unfavorable factors present was found to be useful in predicting outcome. The presence of two of these factors or fewer identified a low-risk group (median survival, 7.7 years), whereas three risk factors or more identified a high-risk group (median survival, 3.2 years). A more recent meta-analysis of the four available large Phase III studies using only data on centrally confirmed low-grade astrocytoma found that both PFS and OS were adversely influenced by the presence of baseline neurological deficits, a shorter time since first symptoms (<30 wk), an astrocytic tumor type, and tumors larger than 5 cm in diameter. Age was no longer of prognostic significance.[52]

PRIMARY THERAPY

Observation

The decision to observe a patient with low-grade glioma has been justified in the literature for several reasons. These reasons include the relatively favorable natural history of the disease, the lack of proven benefit for invasive interventions such as surgical resection or radiation therapy, and the potential morbidities of treatment. Patients who are observed should be monitored at regular intervals (e.g., every 6 months) to detect radiologic progression before new signs and symptoms occur.

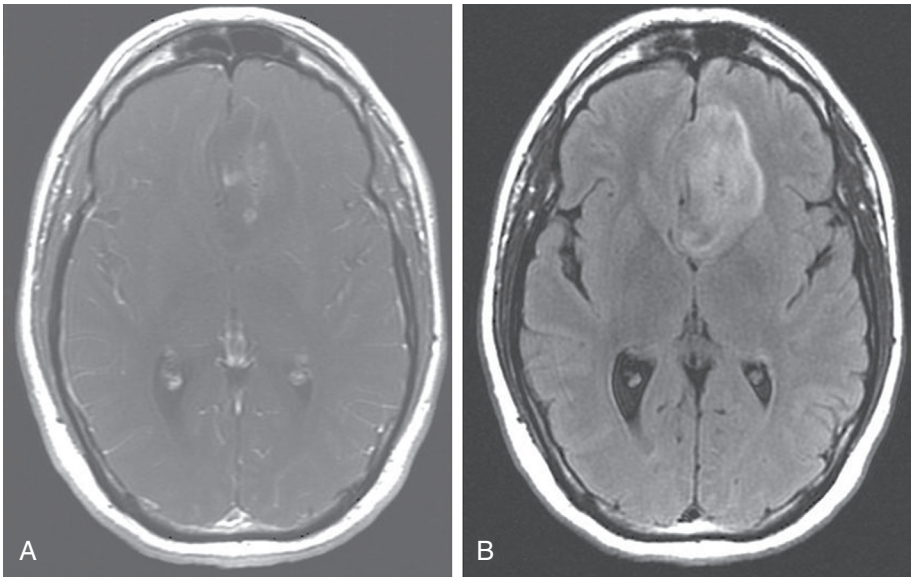


Figure 26-3 Postgadolinium T1-weighted **(A)** and FLAIR **(B)** MRI scans of an adult with a WHO II oligoastrocytoma of the left frontal lobe with midline involvement.

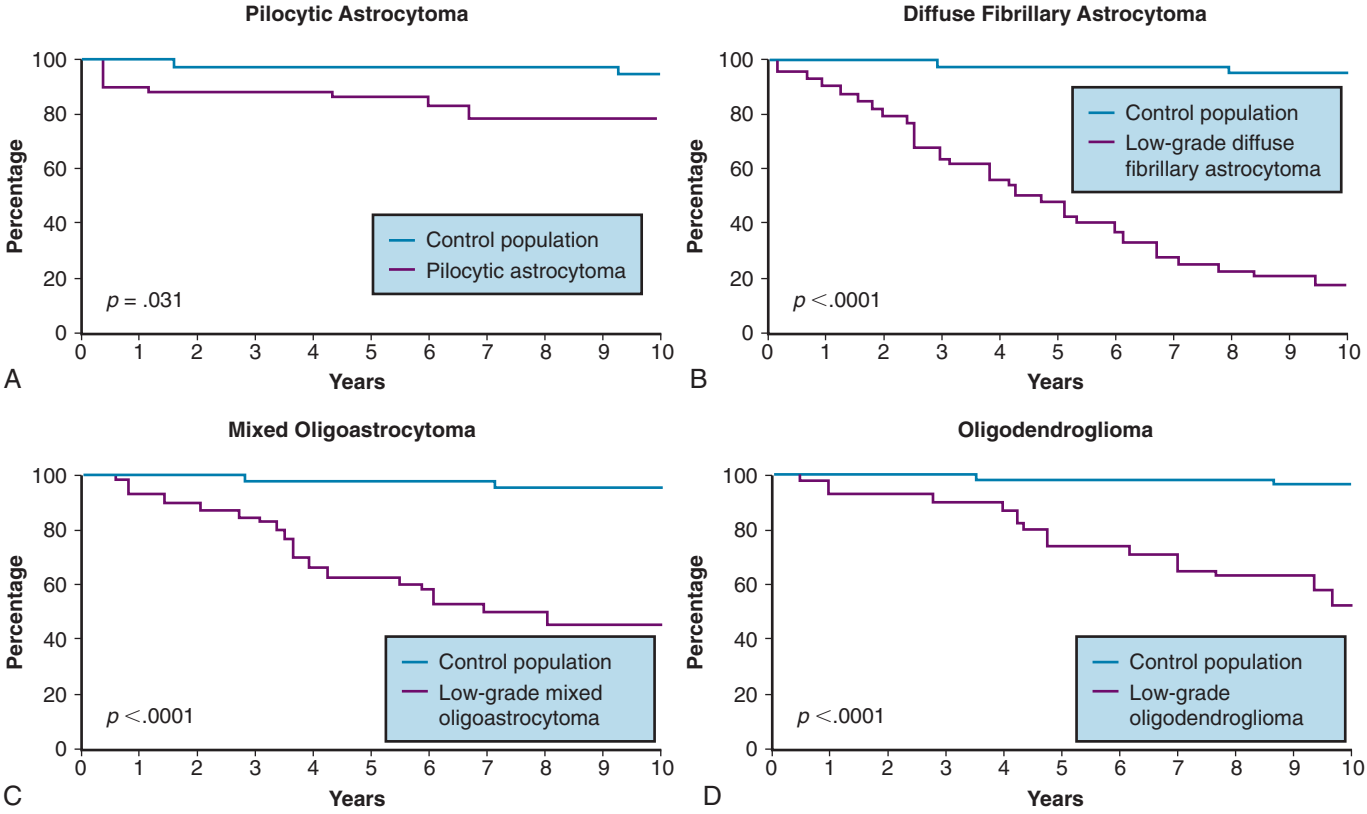


Figure 26-4 Survival curves for patients with the various subtypes of low-grade glioma compared with curves for an age- and sex-matched control population. **A,** WHO I (pilocytic) astrocytoma. **B,** WHO II (diffuse fibrillary) astrocytoma. **C,** WHO II (mixed) oligoastrocytoma, **D,** WHO II oligodendroglioma.
A *to* ***D,*** *Adapted from Shaw EG: The low-grade glioma debate. Evidence defending the position of early radiation therapy. Clin Neurosurg 42:488-494, 1995.*

Despite the favorable survival rates observed in certain subsets of patients with low-grade gliomas, the natural history of all pathologic types of supratentorial low-grade gliomas, including the pilocytic astrocytomas (WHO grade I), diffuse astrocytomas, oligoastrocytomas, and oligodendrogliomas (WHO grade II), is significantly worse than that of an age- and sex-matched control population, for which the expected survival rate is greater than 95% (Figure 26-4).[53] Based on this observation, some have argued that all such patients should undergo maximal safe surgical resection followed by

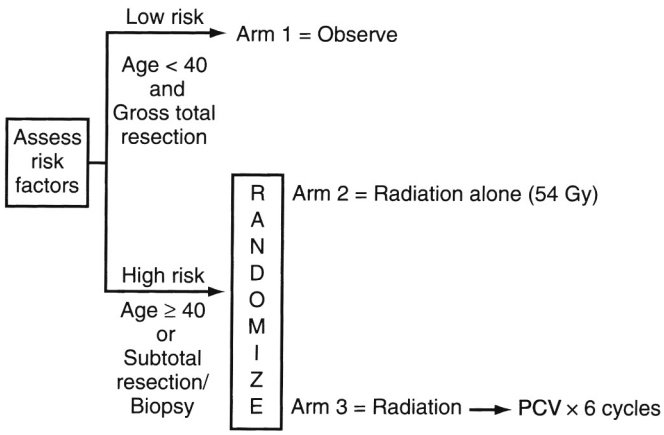


Figure 26-5 Schema of the Radiation Therapy Oncology Group Intergroup Low-Grade Glioma Trial 98-02. PCV, procarbazine, CCNU, and vincristine.

postoperative radiation therapy or chemotherapy, although a survival benefit for treatment, with either aggressive surgery, chemotherapy, or radiation therapy has not been demonstrated in prospective clinical trials.

The RTOG Phase II portion of protocol 9802 (Figure 26-5) prospectively observed 111 patients with low-risk (age younger than 40 years and neurosurgically defined gross total resection) low-grade gliomas.[46] In this "low-risk" population, the 5-year OS was 93%. Astrocytoma histology, residual tumor of 1 cm or more according to MR imaging, and preoperative tumor diameter of 4 cm or more were found to be predictive of a poorer PFS. In patients with all three unfavorable prognostic factors, the 2- and 5-year rates of PFS were 60% and 13%, respectively. In patients with none of the three unfavorable prognostic factors, the 2- and 5-year rates of PFS were 100% and 70%, respectively. These data suggest that observation is a reasonable strategy for the most favorable subset (<1 cm residual tumor, preoperative tumor diameter <4 cm, and oligodendroglioma histology) of younger patients after a gross total resection (GTR).

An EORTC Phase III trial (22845) of 311 adults with supratentorial low-grade gliomas randomized patients to either observation with radiation therapy at progression (which should be considered a delayed RT arm because two thirds of the patients in the observation group received RT at the time of progression) or initial radiation therapy using 54 Gy to localized treatment fields.[54] The 5-year rate of PFS was significantly better for patients receiving initial radiation therapy (55% versus 35%). However, the median OS was not affected (7.4 years versus 7.2 years). In patients who were progression free at 2 years, there were no differences with respect to cognitive deficits, performance status, and headache. These data suggest that observation is a reasonable strategy in adults with asymptomatic supratentorial low-grade glioma.

Surgery

The key surgical issues in the management of supratentorial low-grade gliomas are twofold. The first issue is whether to perform a biopsy on a patient whose clinical presentation and imaging studies suggest a low-grade glioma, and the second is extent of resection.

Although one series in the literature suggests that the survival rate of patients irradiated for presumed low-grade glioma is comparable to that of patients irradiated for histologically verified low-grade astrocytoma,[55] the possibility of inappropriate management in up to 50% of cases[56] diagnosed by imaging underscores the need for histologic verification if a therapeutic intervention is planned. For instance, patients with higher-grade astrocytomas typically receive high-dose external beam radiation therapy in addition to alkylating agents (e.g., temozolomide), whereas GTR without adjuvant radiation therapy constitutes curative treatment for a ganglioglioma.

Extent of Resection

A number of retrospective studies have suggested a benefit for greater extent of resection recognizing the inherent bias associated with extent of resection and tumor location (e.g., more favorable "lobar" lesions are resectable and unfavorable brainstem lesions are unresectable) that makes any definitive conclusions about extent of resection dubious.[57] Nonetheless, some retrospective trials have attempted to further assess this issue.

Investigators from the University of California San Francisco (UCSF) measured tumor volumes based on FLAIR imaging in 216 patients with low-grade gliomas.[58] Patients with at least 90% extent of resection had an 8-year OS of 91% whereas patients with less than 90% extent of resection had an 8-year OS of 60%. After adjusting for age, Karnofsky performance status (KPS) score, tumor location, and tumor subtype, OS and PFS outcomes were both predicted by postoperative tumor volume. One limitation of this study was the relatively short follow-up (median, 4.4 years).

A long-term follow-up (median, 13.6 years) study from the Mayo Clinic reviewed 314 adult patients with low-grade gliomas and found on multivariate analyses significantly improved OS and PFS rates with GTR or nearly GTR. Almost 50% of patients after GTR or nearly GTR were free of recurrence 10 years after diagnosis.[59]

Prospective trials have also found a benefit for greater extent of resection. The Phase II portion of RTOG 9802 (see Figure 26-5) prospectively observed 111 low-risk cases after neurosurgically defined GTR.[46] Review of the postoperative MRI emphasized the importance of postoperative imaging to confirm the extent of resection because a substantial minority of patients had residual disease (32% with 1 cm to 2 cm of residual disease and 9% with more than 2 cm of residual tumor). The crude incidence of tumor recurrence was 26% with a residual tumor of less than 1 cm, 68% with a residual tumor of 1 to 2 cm, and 89% with a residual tumor of more than 2 cm.

Although there are no randomized trials that directly assess the impact of maximal tumor resection in low-grade gliomas, a review of the literature suggests a benefit for maximal *safe* tumor resection, recognizing the importance of achieving this with as little morbidity as possible.[60-62]

External Beam Irradiation

The key external beam irradiation (EBRT) issues in the management of supratentorial low-grade gliomas are timing of radiation (postoperative versus at time of recurrence) and the appropriate dose and treatment volume. The timing of radiation therapy has best been addressed by the Phase III randomized trial EORTC 22845[54] and the RTOG intergroup trial 98-02,[46] as previously reviewed.

Radiation, however, has several other beneficial effects besides the potential delay in tumor recurrence. In a small series of 25 patients with medically intractable epilepsy resulting from an underlying cerebral low-grade glioma, 19 (76%) achieved a significant reduction (>50% decrease) in seizure frequency after RT.[63] In the EORTC Phase III randomized trial 22845, there were no differences in seizure control at baseline,

but at 1 year there were significantly fewer seizures in the irradiated group (25%) than in the observation group (41%).[54]

It has been suggested that radiation therapy may either increase or decrease the likelihood of malignant transformation or may delay its onset. However, in the EORTC Phase III randomized trial 22845, there were no differences in the malignant transformation rate (observation group, 66% versus 72% in the irradiated group) between the study arms at the time of progression.[54] These data imply that irradiation neither increases nor decreases the likelihood of malignant transformation, suggesting that dedifferentiation is a biologic phenomenon observed in low-grade gliomas independent of the treatment.

EBRT Dose-Volume Considerations

Regarding the potential benefit of higher doses of radiation therapy compared with lower doses, two prospective randomized clinical trials (EORTC 22844 and NCCTG 86-72-51) failed to show improved outcome with higher radiation therapy doses.[45,64] The EORTC trial randomized 379 patients to receive moderate-dose (45 Gy) or higher-dose (59.4 Gy) radiation therapy and found no difference in survival rates between the two doses but did find worse quality of life in the higher-dose arm with lower levels of functioning (i.e., emotional and leisure time functioning) and a more extensive symptom burden, including fatigue, malaise, and insomnia.[65] The NCCTG trial compared 50.4 Gy with 64.8 Gy and also failed to demonstrate a difference in survival rates between the two doses. Taken together these trials (along with EORTC 22845) support moderate doses in the range of 45 Gy to 54 Gy using localized fields.[54]

Several series analyzing failure patterns in irradiated patients with low-grade hemispheric gliomas suggest that when tumor progression occurs, it almost always is at the site of the primary tumor within the treatment volume, which implies that partial brain irradiation is appropriate. This was confirmed in the prospective dose-response trial NCCTG 86-72-51 with 92% of failures occurring in the treatment field, 3% within 2 cm of the treatment field, and 5% more than 2 cm beyond the treatment field.[45] These data support the appropriateness of partial brain irradiation.

Other Radiation Modalities

Several other radiation modalities (e.g., stereotactic radiosurgery, proton therapy) have been used selectively in patients with low-grade gliomas with growing interest especially in proton RT. Because proton RT reduces the amount of radiation to the normal surrounding brain it is hoped this will decrease late toxicity. To date only small studies have been conducted and more clinical trials are needed to evaluate the efficacy and safety of protons in this setting.[66]

Chemotherapy

Several Phase II chemotherapy studies have shown efficacy of both temozolomide and PCV chemotherapy in both newly diagnosed and in progressing low-grade gliomas[67-73] (Figure 26-6). The studies on newly diagnosed tumors show that the response assessment may be difficult, and that most cases have radiologically stable disease or a minor response as their best response to chemotherapy (at times, even despite clinical improvement and improved seizure control).[67] As a result, the PFS appears to be a more informative endpoint than objective response rate in unenhancing tumors.[74]

Trials that investigated recurrent tumors with enhancing disease report high response rates both in relapsing oligodendrogliomas and astrocytomas even in the absence of 1p/19q deletion.[72,73] For example a study of 58 patients with dedifferentiated low-grade astrocytomas treated with temozolomide found a response rate of 50% and 6- and 12-month rates of PFS in 67% and 25% of patients, respectively.[75]

The potential role of chemotherapy in newly diagnosed low-grade glioma is better defined based on the results of two large Phase III chemotherapy studies. RTOG intergroup trial 98-02 (see Figure 26-5) randomized patients with low-grade gliomas at high risk for recurrence (age of 40 years or older or subtotal resection/biopsy) between radiation therapy alone or radiation therapy followed by six cycles of PCV.[1,76] With a median follow up of 12 years the patients in the RT and PCV arm had significantly longer median PFS (10.4 years versus 4.0 years, $p = 0.002$) and OS (13.3 years versus 7.8 years, $p = 0.03$) compared with the radiotherapy alone arm. These

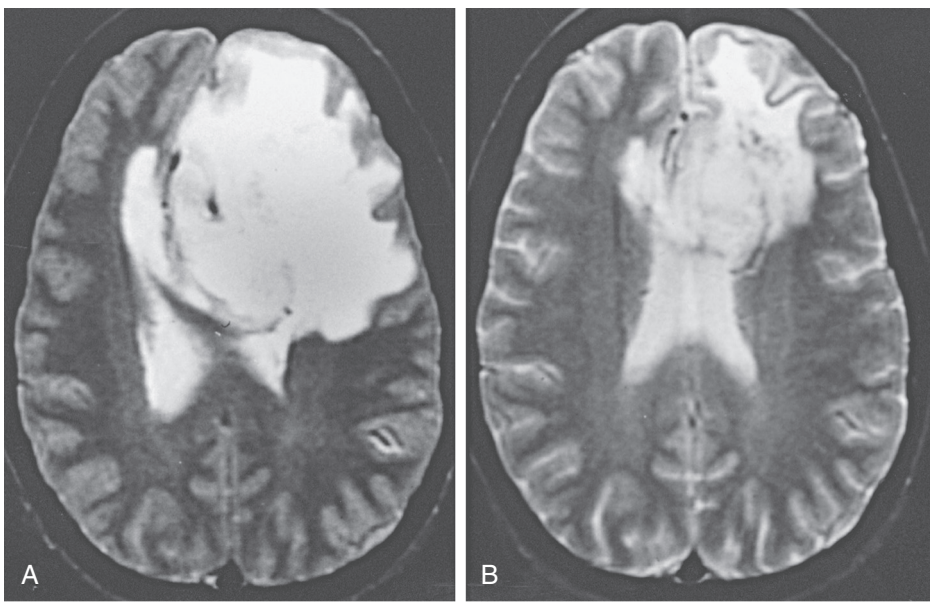


Figure 26-6 Prechemotherapy **(A)** and postchemotherapy **(B)** T2-weighted MRI of a young adult with a WHO II oligodendroglioma of the left frontal lobe.

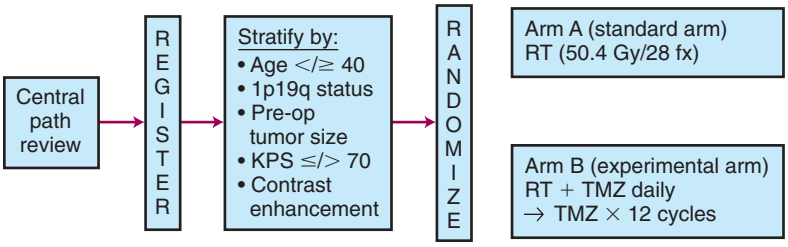


Figure 26-7 Schema of the Eastern Cooperative Oncology Group Intergroup Phase III trial E3F05 of radiation therapy with or without temozolomide for symptomatic or progressive low-grade gliomas. *fx*, Fraction; *KPS*, Karnofsky performance scale; *RT*, radiotherapy; *TMZ*, temozolomide.

results confirm a benefit for RT followed by PCV for selected low-grade glioma populations.

An EORTC trial addressed the role of temozolomide in newly diagnosed patients with high-risk low-grade gliomas.[77] This trial, with PFS as the primary endpoint, randomized patients with progressive disease, uncontrolled seizures despite anticonvulsants, or neurologic symptoms to either standard radiation therapy or daily low-dose temozolomide. Initial results suggest that in 1p-intact tumors RT may confer an improved PFS (p = 0.06), whereas in 1p-deleted tumors temozolomide may be equivalent to RT. At the time of the first report, OS data were still immature. Further follow-up reports of this study must confirm whether a strategy to treat with early chemotherapy and delay administration of RT will translate into better long-term cognitive functioning. An intergroup Phase III trial (Figure 26-7) with similar eligibility criteria and stratification factors investigated the efficacy of combined chemoradiation with temozolomide compared with RT alone although the results of this trial are not yet available. Of note a RTOG Phase II study of RT plus concurrent and adjuvant temozolomide for high-risk low-grade gliomas did find improved OS compared to a historical control of RT alone.[78]

FAVORABLE LOW-GRADE GLIOMA VARIANTS

One group of primary CNS tumors with a distinctly more favorable prognosis than WHO grade II low-grade gliomas includes the pilocytic astrocytomas (WHO grade I) and the other low-grade glioma variants, such as pleomorphic xanthoastrocytomas, subependymal giant cell astrocytomas, and subependymomas. Three other primary CNS tumors of neuronal or mixed neuronal-glial origin are often grouped with the low-grade glioma variants because of their similar presentation and favorable prognosis, including the gangliogliomas, central neurocytomas, and dysembryoplastic neuroepithelial tumors. Other than the pilocytic astrocytomas, which make up approximately 20% of supratentorial low-grade gliomas and 80% of cerebellar gliomas,[41] the other six variants are uncommon, accounting for approximately 1% or less of primary CNS tumors. From an imaging standpoint, they are typically well circumscribed, enhancing, and sometimes cystic or calcified, or both.[7]

Pilocytic Astrocytomas

Pilocytic astrocytomas typically occur in children and young adults, with common locations being the cerebellum, optic pathways, hypothalamus/third ventricle, and cerebral hemispheres. They are the most common primary brain tumor occurring in patients with type 1 neurofibromatosis.[79,80] The 10-year OS rate is 80% or greater, independent of location in the brain, although rarely, they behave more aggressively.[8] In patients undergoing GTR, the 10-year disease-free survival and OS approach 100%.[8]

For patients who have subtotal resection, particularly children, a reasonable strategy is observation with close follow-up because there is no apparent survival benefit for routine postoperative radiation therapy, and a second surgical procedure accomplishing GTR appears curative.[81] Radiation therapy is usually reserved for symptomatic subtotally resected or unresectable tumors, usually in the setting of tumor recurrence. This paradigm was tested and proved to be successful in an NCCTG prospective clinical trial of 20 adults with supratentorial pilocytic astrocytomas observed after gross or subtotal resection or treated with irradiation after biopsy.[8] The 10-year rate of PFS and OS was 95%. When pilocytic astrocytomas require irradiation, the recommendation is to treat localized fields (enhancing tumor with a 4-mm to 5-mm margin using image-guided radiotherapy [IGRT]) with moderate doses (45 Gy to 54 Gy). Radiosurgery (e.g., 13 Gy or 15 Gy marginal dose) has also been used in the treatment of pilocytic astrocytoma, although it is most frequently used in the salvage setting after prior fractionated RT.[82,83] The recurrence rate seems to be higher with radiosurgery when compared to fractionated RT, which may be as a result of patient selection, dose inadequacy, or margin inadequacy.

Pleomorphic Xanthoastrocytomas

Pleomorphic xanthoastrocytomas occur in children and young adults, usually presenting with seizures caused by an underlying tumor in the cerebral cortex (temporal lobes), sometimes with adjacent meningeal and, rarely, craniospinal leptomeningeal involvement. Despite their pleomorphism, these tumors often behave in an indolent manner.[7] An analysis of BRAF V600E mutation in 1320 CNS tumors found BRAF mutations in several tumor types (e.g., pilocytic astrocytoma, ganglioglioma) with an especially high frequency (66%) in pleomorphic xanthoastrocytoma, possibly providing a new therapeutic window for BRAF-targeted therapies although this will require future clinical trials.[84] Treatment recommendations depend on the grade of the astrocytic component. When GTR has been achieved of a pleomorphic xanthoastrocytoma that contains a low-grade diffuse astrocytoma (WHO grade II), observation is appropriate, although local tumor recurrence, sometimes with malignant transformation, can occur. Indications for radiation therapy (doses and treatment fields are similar to those of the more common forms of WHO grade II low-grade gliomas) include pleomorphic xanthoastrocytomas that contain an anaplastic astrocytoma or glioblastoma (WHO grades III/IV), symptomatic subtotally resected or unresectable tumors, or recurrent tumors, particularly if their astrocytic component dedifferentiates.[85]

Central Neurocytomas

Central neurocytomas contain neuronal elements that are usually mature. They are classified as WHO grade II tumors. By definition, they arise in the ventricular system (although an extraventricular neurocytoma with similar clinical behavior

is described in the fourth edition of the WHO classification), usually as large tumors in the lateral ventricular system, and they rarely have been reported to disseminate craniospinally. The typical age at presentation is the late 20s, although these tumors can occur in children or adults.[7] Subtotally resected tumors have been reported to respond to radiation therapy.[86]

A review of 45 patients with central neurocytoma treated with various combinations of surgery, radiation therapy (median dose, 55.8 Gy), and chemotherapy found a 10-year OS of 83%.[86] The 5-year local control rate was 100% for patients who received radiation therapy compared with 51% for those who did not ($p = 0.045$); however, there was no difference in 5-year OS, likely because of the effectiveness of salvage irradiation. Therefore, patients are observed after GTR with consideration of observation after subtotal resection of typical neurocytomas. Patients with unresectable tumors, recurrent tumors, or select patients with subtotally resected tumors (especially, "atypical neurocytomas") are usually offered radiation therapy postoperatively. A systematic review of radiosurgery identified 64 central neurocytomas with a tumor control of 91% at a mean follow-up of 59 months after radiosurgery (median marginal dose 12 Gy to 16 Gy).[87] Although this review was limited by small patient numbers, radiosurgery appears to be an effective treatment for highly selected patients with recurrent or residual disease.

Other Favorable Variants

Gangliogliomas consist of neoplastic ganglion (neuronal) cells and neoplastic glial (astrocytic) cells. They can occur in children and adults, although most are present in the first two to three decades of life. Gangliogliomas can develop anywhere in the CNS, but they tend to occur in the supratentorial brain, most often in a temporal location, and enhance on MR images with contrast medium. Like pleomorphic xanthoastrocytomas, the glial component can be a low-grade tumor (WHO grade I) or a higher-grade tumor (WHO grade III).[7] A review of 402 patients found no local control or survival benefit with postoperative RT after GTR but did find improved local control (but not survival) after subtotal resection for both low and high-grade tumors.[88] Treatment principles are similar to those of pleomorphic xanthoastrocytoma from both a surgical and radiotherapeutic standpoint.[89]

Dysembryoplastic neuroepithelial tumors, like gangliogliomas, also contain a mixture of neuronal and glial elements, although the neuronal component is mature and the glial component is well differentiated and has astrocytic or oligodendroglial tissue. As such, the tumors are classified as WHO grade I tumors. Typically, these tumors occur in a temporal location, are characteristically multinodular, and arise during the first two decades of life. Treatment principles are similar to those of pilocytic astrocytomas from both a surgical and radiotherapeutic standpoint, although irradiation is rarely necessary.[7]

Subependymal giant cell astrocytomas (SEGA) occur in patients with tuberous sclerosis, often during the first two decades of life but sometimes later.[5] Characterized by large astrocyte-like cells, they are classified as WHO grade I tumors, like the pilocytic astrocytomas. Typically, they arise in an intraventricular or periventricular location (e.g., lateral ventricles, foramen of Monro) and on MR images appear as intraventricular enhancing masses. Treatment recommendations parallel the pilocytic astrocytomas; that is, GTR is considered curative.[90] However the role of RT for symptomatic progression or relapse has been diminished even more with the recognition that tuberous sclerosis is associated with constitutive activation of mammalian target of rapamycin (mTOR). Prospective placebo-controlled trials[91] have shown the efficacy and safety of mTOR inhibitors (e.g., everolimus) in the treatment of SEGA, even in the long term.[92]

Subependymomas are also classified as WHO grade I ependymal tumors. They contain both low-grade astrocytic and ependymal-like cells, and they usually arise in an intraventricular location (lateral or fourth ventricles, particularly in and around the foramen of Monro) in adults near the age of 50 years. Treatment recommendations parallel those of pilocytic astrocytomas, both surgically and radiotherapeutically. Subtotally resected and recurrent tumors have been reported to respond to radiation therapy.[93]

RECURRENT DISEASE AND PALLIATION

The vast majority of patients with a low-grade diffuse glioma die of their disease. As such, at some point in his or her illness, the typical patient with a low-grade glioma likely has the combination of progressive neurologic symptoms and signs in the face of neuroimaging evidence of tumor recurrence. Most of the time the lesion progresses at the original site, but uncommon patterns of treatment failure can occur in patients with recurrent low-grade gliomas such as infiltration across the deep, dense white matter tracts of the brain. Leptomeningeal failure has also been reported, though this is more likely to occur in the pediatric low-grade glioma population.

At the time of progression, often (in up to 70% of patients) the lesion has dedifferentiated to a higher grade of malignancy.[54] This is revealed on the MRI scan by areas of enhancement, which can be preceded for 6 months to 12 months by a local increase in regional cerebral blood volume (e.g., Figure 26-8). The clinical and radiographic features of a high-grade tumor recurrence can be difficult to distinguish from radiation necrosis by conventional MRI. Advanced imaging techniques such as PET,[94] single-photon emission CT,[95] MRI spectroscopy,[96] perfusion and diffusion-weighted MRI[97] may prove to be more useful in this regard (Figure 26-9), though there is not yet a consensus as to the most accurate imaging technique for distinguishing transformation from treatment-related imaging changes. As such, tissue must be obtained, although even pathologic findings can be difficult to interpret.

In Forsyth et al,[98] 51 previously irradiated patients (40 of whom had Kernohan grade 1 or grade 2 astrocytoma, oligoastrocytoma, or oligodendroglioma) underwent stereotactic biopsy for suspected recurrence. Pathologic examination revealed the presence of tumor only in 30 biopsies (59%), tumor plus necrosis in 17 biopsies (33%), radionecrosis in three instances (6%), and one case of a radiation-induced sarcoma (3%). In patients in whom tumor was found, it was of a high grade in 63%. Median survival time after biopsy was 10 months in patients with tumor only, a finding significantly worse than the 22-month median survival time in those with tumor plus necrosis. No deaths occurred among the patients whose biopsies showed radionecrosis alone.

In general, survival after tumor recurrence is poor. In one series, patients with recurrent low-grade astrocytoma after treatment with surgery and postoperative irradiation were treated with temozolomide and had a 1-year OS of 60%.[75] Typically, survival in patients with recurrent oligodendroglioma showing a 1p/19q codeletion will be better. In the series Leighton et al[99] conducted before the 1p/19q era, the median survival time after recurrence was 39 months for all patients, 16 months for those with recurrent low-grade diffuse astrocytomas, and 60 months for those with recurrent low-grade oligodendrogliomas.

Treatment options for recurrence include surgery, reirradiation (e.g., EBRT, brachytherapy, stereotactic radiation

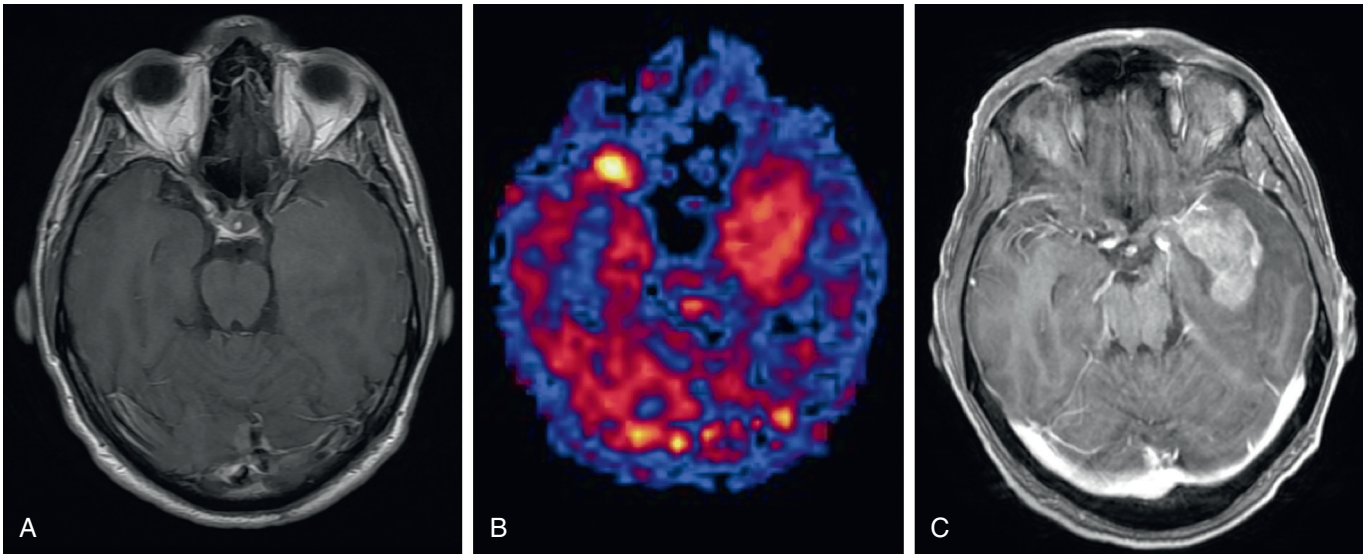
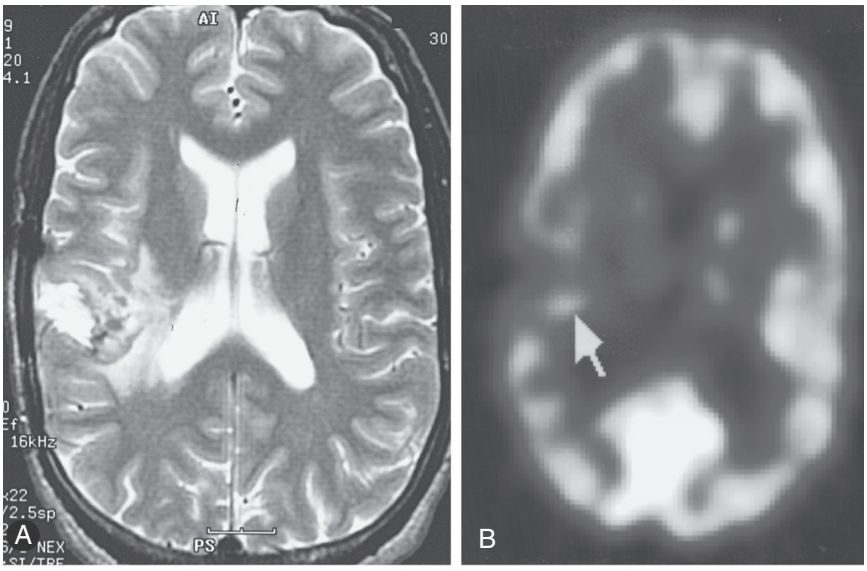


Figure 26-8 **A,** Axial T1-weighted MRI of diagnostic imaging of WHO grade II diffuse astrocytoma demonstrating nonenhancing mass in the left medial temporal lobe. **B,** Axial arterial spin labeling MRI of the same patient acquired simultaneously with image A and showing increased perfusion in the left temporal lobe mass. **C,** Axial T1-weighted MRI performed at 6-month interval showing increased enhancement in the left temporal lobe. Subsequent biopsy demonstrated malignant transformation to WHO grade IV glioblastoma.



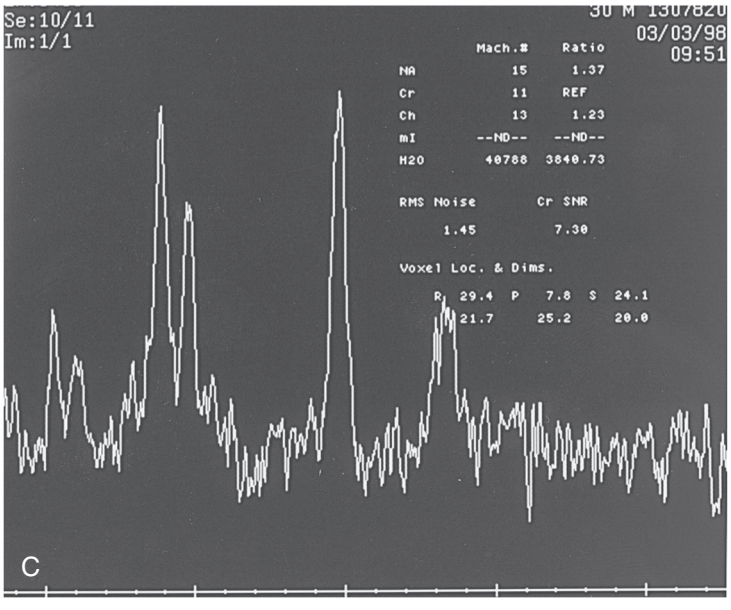


Figure 26-9 Postgadolinium T1-weighted MRI of a young adult with a WHO grade II oligoastrocytoma after subtotal resection, 50.4-Gy external beam radiation therapy, and 18 Gy given in a single fraction in stereotactic radiosurgery for recurrent disease at the medial edge of the resection cavity. **A,** An area of increased contrast enhancement at the site of the stereotactic radiosurgery. **B,** Positron emission tomography using fluorodeoxyglucose showed increased uptake at the site of the contrast enhancement *(arrow).* However, MRI spectroscopy **(C)** was more suggestive of radiation necrosis because the choline-to-creatine ratio was less than 2 and the lactate peak was elevated. Subsequent biopsy demonstrated radiation necrosis.

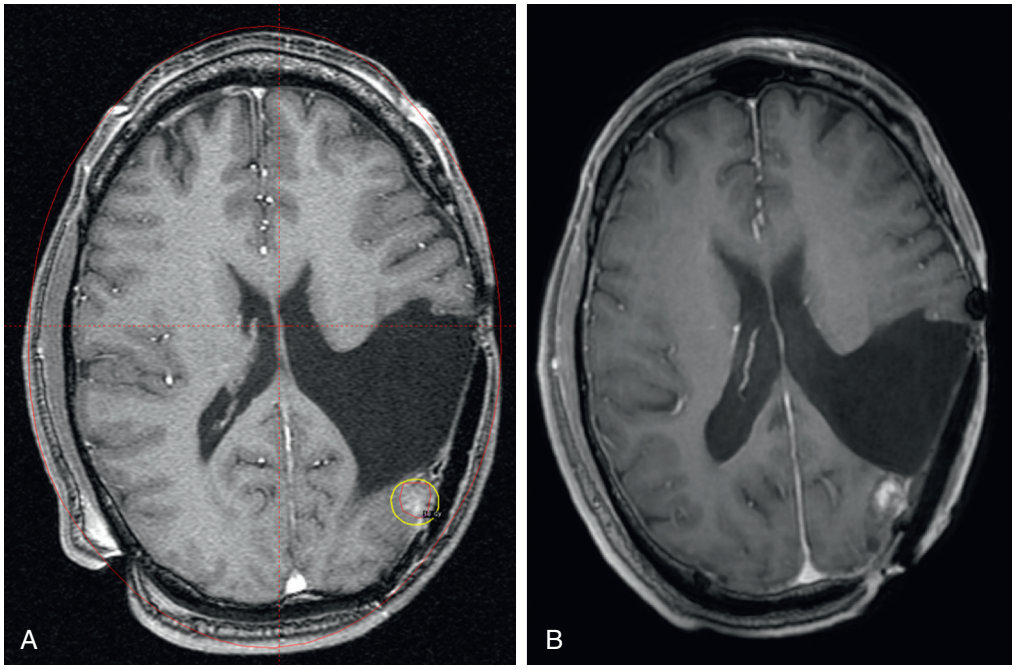


Figure 26-10 **A,** Axial T1-weighted MRI depicting treatment plan for single fraction radiosurgery of multiply recurrent WHO grade II oligodendroglioma treated with 18 Gy to the 50%. **B,** Axial T1-weighted MRI depicting 10-year follow-up imaging confirming long-term local control of previously treated lesion.

therapy, radiosurgery) and chemotherapy (or second-line chemotherapy). Patients must be managed on an individual basis, depending on the timing of the relapse, previous treatments, and accessibility for clinically significant surgery. In one series, 63 patients with recurrent low-grade gliomas were treated with a second course of conventionally fractionated RT (median dose 36 Gy in 2 Gy fractions) in which the enhancing and FLAIR abnormality was encompassed within the RT volume.[100] From time of reirradiation, median survival and PFS were 23 and 12 months, respectively. Hypofractionated reirradiation has also been reported for recurrent low-grade gliomas.[101]

A concern for stereotactic radiosurgery (SRS) as a treatment option for recurrent low-grade glioma is the likely infiltrative nature of these tumors and the limitations of SRS to a smaller treatment volume. There have been several reported series of salvage SRS, and although durable local control is not the rule, there likely exists a population of patients that may benefit from this modality. In a University of Pittsburgh SRS series, PFS was 81.5% at 5 years after SRS for patients with recurrent grade II oligodendroglioma.[83] In a separate SRS series from the same institution in patients with recurrent grade II astrocytoma, only 54.1% remained progression free at 5 years.[102] Figure 26-10 depicts a patient treated with SRS for a nodular resection cavity recurrence of grade II oligodendroglioma along with a 10 year follow-up MRI documenting continued local control.

Salvage chemotherapy appears to have a modest effect after failure of low-grade glioma that has progressed beyond either prior RT or prior first-line chemotherapy. Retrospective series appear to suggest that neither PCV nor temozolomide have significant activity after a low-grade glioma has failed the other regimen as first-line therapy.[103,104] The EORTC is currently assessing the efficacy of adding bevacizumab to temozolomide in a randomized Phase II study in progressive non 1p/19q codeleted grade II and grade III tumors.

IRRADIATION TECHNIQUES AND TOXICITIES

EBRT Volume Considerations

Because the vast majority of treatment failures after partial brain irradiation occur in the field, treatment of the tumor plus a margin of normal tissue is considered the standard of care. With the identification of tumor cells up to several centimeters beyond the margin of the tumor identified by T2-weighted MRI,[105] the appropriate irradiation volume should include the MRI extent of tumor as defined by T2-weighted or FLAIR MR images with a 2-cm to 3-cm margin. A 2-cm margin may be acceptable if some form of IGRT is used (Figure 26-11).

EBRT Dose and Technique Issues

As previously outlined, three prospective randomized clinical trials (EORTC 22844, EORTC 22845, and NCCTG 86-72-51) support moderate RT doses in the range of 45 Gy to 54 Gy.[45,54,64] In an effort to improve conformality and possibly better spare normal structures, many centers use intensity-modulated radiation therapy (IMRT), especially in select situations such as tumors involving the inferior temporal lobes or tumors with irregular or complex shapes. However, a disadvantage of IMRT is the increased dose heterogeneity because in low-grade gliomas, much of the target is an admixture of tumor cells and normal brain tissue.[106] As an example, if IMRT is used with a prescription of 54 Gy in 30 fractions, this may result in heterogeneity of 10% or more in the target. This increased heterogeneity results in an increased daily dose per fraction and an increased total dose such that the biologically equivalent dose approaches that of the high-dose arm in NCCTG 86-72-51 (e.g., 64.8 Gy) and therefore increases the risk of radiation necrosis.[45] Selecting a slightly lower dose (e.g., 50.4 Gy) is a reasonable strategy because even with

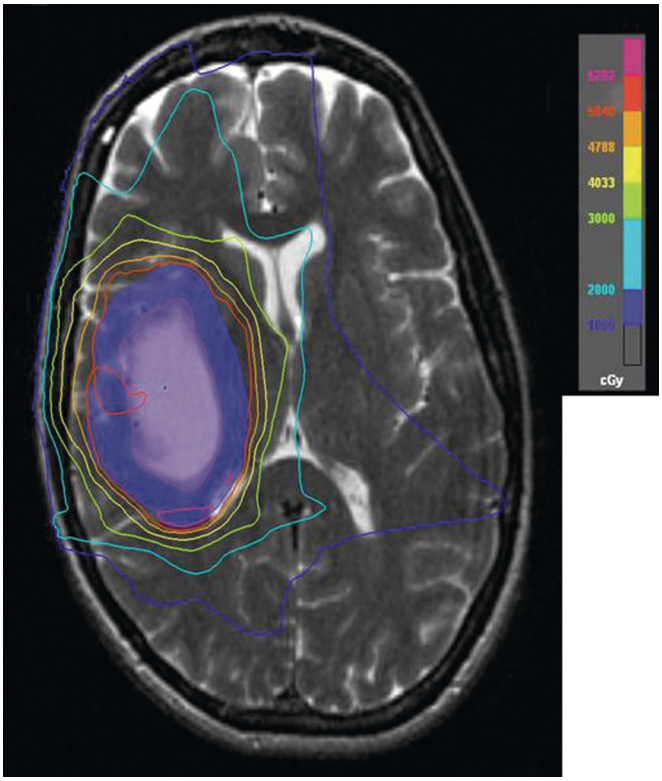


Figure 26-11 Fractionated stereotactic radiotherapy (50.4 Gy in 28 fractions), using daily image-guided radiotherapy (IGRT), in the treatment of a WHO grade II oligoastrocytoma involving the posterior insular cortex and superior temporal gyrus.

heterogeneity of 10% the hot spots are within the range of what is considered to be a low risk of radiation necrosis. Accordingly, a dose of 50.4 Gy was chosen for the current intergroup low-grade glioma trial (E3F05) (see Figure 26-7). Because modern IMRT techniques tend not to have this degree of dose heterogeneity, the issue will likely become less significant with better treatment planning techniques.

Toxicities of Radiation Therapy

A spectrum of radiation-induced toxicities can occur in patients receiving therapeutic brain irradiation. These range from cognitive sequelae, the pathogenesis of which is likely white matter injury, to overt radiation necrosis, which is probably a consequence of vascular injury.[107] The incidence of overt radiation necrosis after irradiation for a cerebral low-grade glioma is approximately 3% based on data from surgical series in which reoperation data were reported.[43,108] This is consistent with findings from NCCTG 86-72-51 (50.4 Gy versus 64.8 Gy), in which the 2-year actuarial incidence of severe, life-threatening, or fatal radionecrosis was 1% at 50.4 Gy and 5% at 64.8 Gy.[45] Examples of the clinical presentation, imaging changes, time course, management, and outcome of the spectrum of severe or worse radiation toxicities seen in patients with cerebral low-grade gliomas are shown in Figures 26-12 to 26-14.

Prospective Quality-of-Life and Neurocognitive Analyses

Several studies have focused on the neurocognitive effects of radiation therapy in patients who are long-term recurrence-free survivors, most of whom were irradiated for supratentorial low-grade gliomas. To assess the toxicity of irradiation, it is also important to understand the neurologic and cognitive dysfunction that results from having a cerebral low-grade glioma.[109] To assess the impact of early intervention on quality of life (QOL), investigators from the University Medical Center Utrecht matched 24 patients with suspected low-grade gliomas (based on imaging and clinical history) to 24 patients with proven low-grade gliomas, who had undergone early surgery, and 24 healthy controls.[110] Both patient groups scored worse on QOL and cognitive function scales than healthy control subjects. Unoperated patients with suspected low-grade gliomas scored better on most items than patients who had undergone surgery and had tissue with proven low-grade gliomas. This study suggests that observation is a reasonable option for a select population. In addition, this study emphasizes the need for baseline (i.e., before surgery or RT) cognitive testing because the tumor itself causes cognitive deficits.

Because there is no convincing evidence that early radiation therapy improves OS, deferring irradiation until there is evidence of symptomatic tumor growth is an acceptable practice. The primary rationale for delaying irradiation is to reduce the risk of radiation-induced neurocognitive damage. Some retrospective studies have found increased neurocognitive difficulties after cranial radiation therapy. However, these studies have several deficiencies[109] although the most serious is the lack of baseline neurocognitive testing because the brain tumor itself is often the primary cause of cognitive difficulties. In contrast, a number of studies have prospectively performed extensive neuropsychological testing on adult patients with low-grade neoplasms before (baseline) and after radiation therapy (up to 6 years after radiation therapy) and have not found significant neurocognitive deficits when compared with either baseline[111,112] or a cohort of patients with low-grade brain neoplasms not treated with irradiation[113,114] (Table 26-5). For example, in NCCTG 86-72-51, a subset of 20 of the 203 adult study patients who received either 50.4 Gy or 64.8 Gy underwent psychometric testing before and up to 5 years after localized radiation therapy.[112] No significant loss in general intellectual function, new learning, or memory was seen. However, four patients, all in the 64.8-Gy arm, had a mild decline in one or more of the domains (immediate verbal memory, learning, and spatial problem solving) assessed. Therefore the weight of evidence indicates a low incidence of neurocognitive difficulties after focal, conventionally fractionated (1.8 Gy to 2 Gy) radiation therapy using modern techniques to deliver moderate doses in adults.[109]

In children, the risk of cognitive injury after irradiation appears to be most closely associated with younger age (i.e., developing brain) at the time of treatment and secondarily with the volume of brain irradiated.[115] The effects of surgery and other therapies for these tumors are also associated with a risk of cognitive injury, which can make assessments after RT difficult.[116,117] To better assess the cognitive impact of RT in children St Jude Children's Hospital evaluated late effects in 78 patients with low-grade gliomas after treatment with more *modern* techniques (54-Gy conformal EBRT with a 10-mm clinical target volume margin).[115] Through 5 years of follow-up for the entire group (baseline testing after surgery and serial evaluations), only a decline in spelling scores was clinically significant. Thirteen of the patients had neurofibromatosis 1 (NF-1) and were found to have worse function at baseline compared with other pediatric patients with low-grade gliomas. In addition, the patients with NF-1 had worsening function over time whereas patients without NF-1 had stable function over time. Age had a significant impact on cognitive function over time, such that a 10-point decline in IQ 5 years after irradiation would be expected for a child age

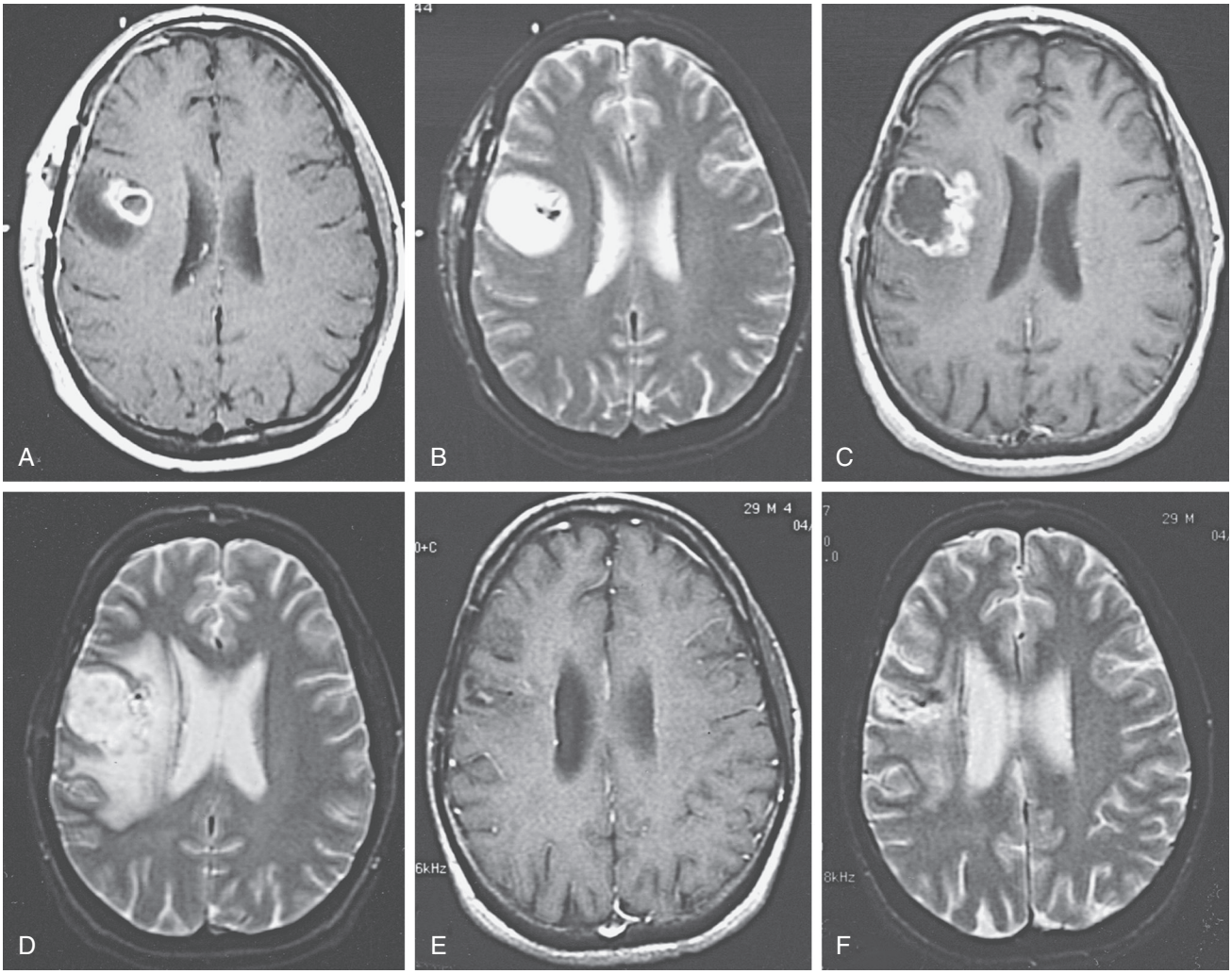


Figure 26-12 Preirradiation, postgadolinium T1-weighted **(A)** and T2-weighted **(B)** MR images of an adult with a WHO grade II oligodendroglioma of the right frontotemporal lobes. Seven months after 64.8-Gy external beam radiation therapy, the patient developed headaches. Postgadolinium T1-weighted **(C)** and T2-weighted **(D)** MR images are shown. The differential diagnosis considered recurrent tumor and radiation necrosis. After a brief course of oral corticosteroid medications, the imaging abnormalities resolved, a finding supporting the diagnosis of transient radiation necrosis. Postgadolinium T1-weighted **(E)** and T2-weighted **(F)** magnetic resonant images are shown.
Adapted from Daumas-Duport C, Scheithauer BW, Kelly PJ: A histologic and cytologic method for spatial definition of gliomas. Mayo Clin Proc 62:435-449, 1987; and Kelly PJ, Daumas-Duport C, Scheithauer BW, et al: Stereotactic histologic correlations of computed tomography and magnetic resonance imaging-defined abnormalities in patients with glial neoplasms. Mayo Clin Proc 62:450-459, 1987.

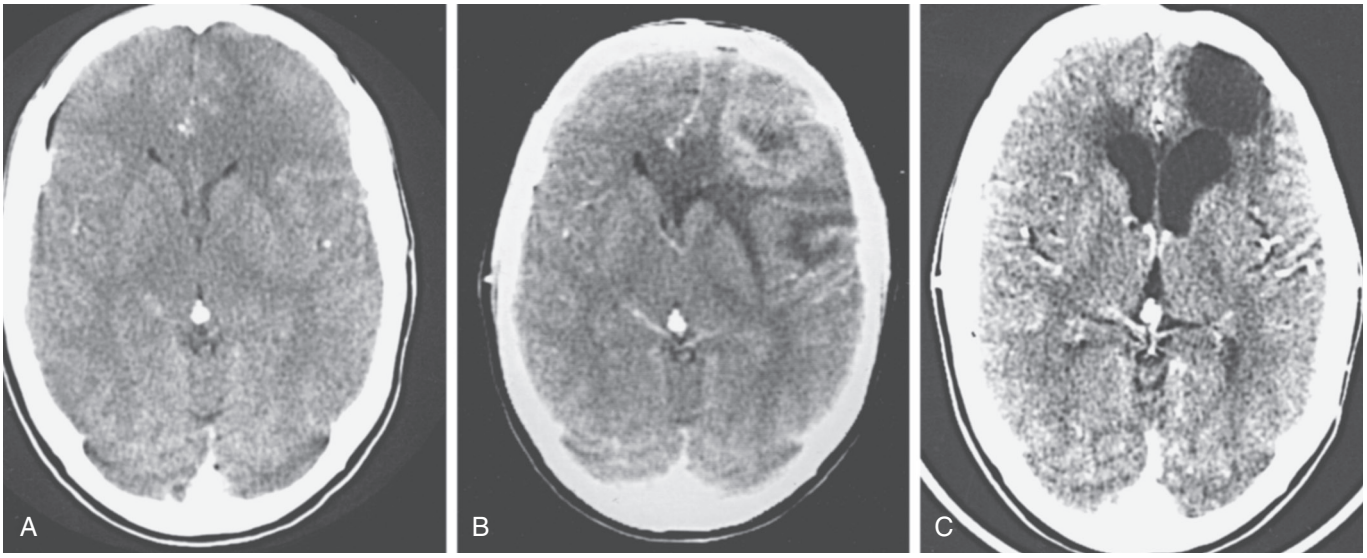


Figure 26-13 Contrast-enhanced CT demonstrates the progress of a left frontal WHO grade II astrocytoma in an adult patient. **A,** Before 64.8-Gy external beam radiation therapy. **B,** After irradiation, the patient had headaches. **C,** Eighteen months after gross total resection of what proved to be a combination of radiation necrosis and persistent low-grade astrocytoma, the patient had no evidence of further radiation necrosis or tumor.

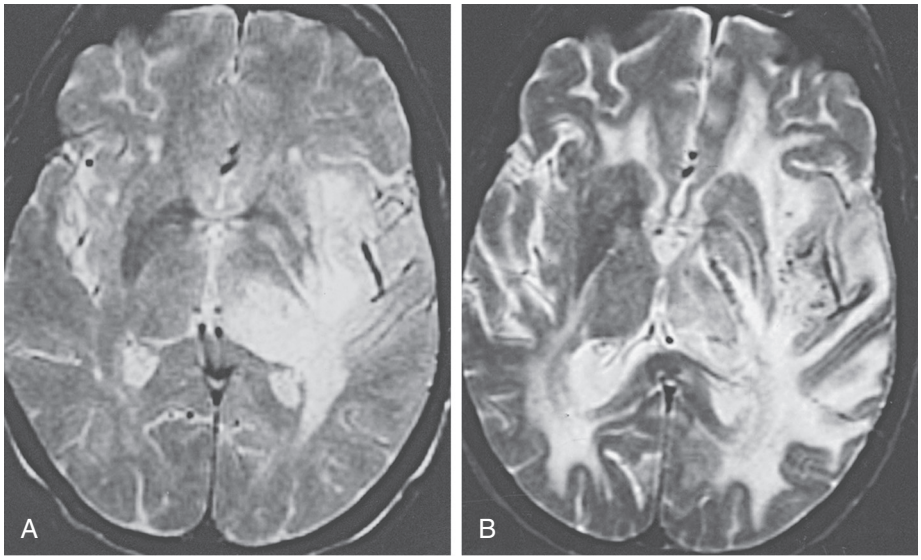


Figure 26-14 **A,** T2-weighted MRI scan of an older adult with an infiltrative, poorly defined WHO grade II astrocytoma the epicenter of which was in the left temporal lobe. Six months after completing 64.8-Gy external beam radiation therapy, the patient developed a significant decline in cognitive function and overall performance status. **B,** Repeat MRI showed dramatic white matter changes. The patient subsequently died, and an autopsy showed radiation necrosis with a persistent low-grade astrocytoma.

TABLE 26-5 Prospective Trials with Baseline and Serial Cognitive Testing in Adults with Low-Grade Neoplasms

Author	Histology (No. with RT)	RT: Total Dose/ Fraction (Gy)	Mean FU (yr)	Neurotoxicity after RT
Vigliani et al[114]	LGG, AA (17)	Focal RT 54/1.8	4	No; transient decline in RcT
Armstrong et al[111]	LGG, pituitary, pineal, meningioma (26)	Focal RT mean 54.6/1.8-2	3	No; mild decline in visual memory after 5 yr
Torres et al[113]	Meningioma, LGG, GBM, ependymoma, adenoma (15)	Focal RT mean 54/1.8	2	No; decline in memory and attention only if tumor progression
Laack et al[112]	LGG (20)	Focal RT 50.4/1.8 or 64.8/1.8	3	No; mild decline in 64.8-Gy arm in immediate verbal memory, learning, and spatial problem solving

AA, *Anaplastic astrocytoma;* CGE, *cobalt Gray equivalent;* FU, *follow-up;* GBM, *glioblastoma multiforme;* LGG, *low-grade glioma;* NFS, *neurologic function scores;* RcT, *reaction time;* RT, *radiation therapy.*

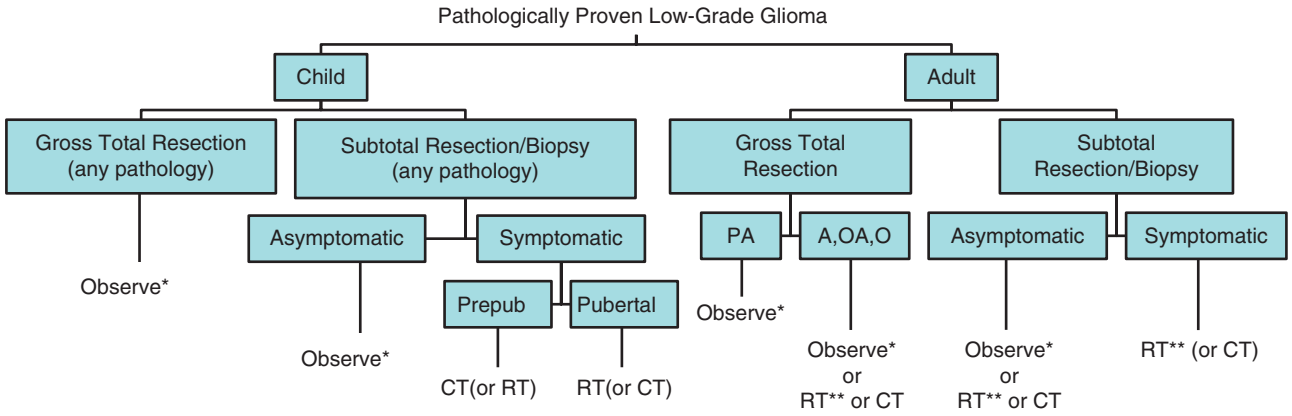


Figure 26-15 Treatment algorithm for low-grade glioma. *Treatment is deferred until the time of symptomatic or imaging progression. Appropriate treatment at the time of progression may include surgery, chemotherapy, or radiation therapy. ** For patients with less than gross total tumor resection or older than 40 consider radiotherapy followed by procarbazine, CCNU, and vincristine. *A*, Astrocytoma; *CT*, chemotherapy; *O*, oligodendroglioma; *OA*, oligoastrocytoma; *PA*, pilocytic astrocytoma; *RT*, radiation therapy.

5 years at the time of irradiation. Each year of increasing age significantly reduced the decline in IQ. The authors noted that cognitive function was largely preserved after conformal RT using modern techniques, but RT should be delayed if possible for younger patients.

CONCLUSIONS, TREATMENT ALGORITHM, AND FUTURE POSSIBILITIES

Low-grade gliomas are a heterogeneous group of CNS neoplasms, and their natural history depends primarily on pathologic type and tumor size. A treatment algorithm for low-grade gliomas is provided in Figure 26-15. Despite having been considered "benign," most of these tumors behave in an aggressive manner, even after surgery and radiation therapy.

Prospective trials confirm the role of chemotherapy for select low-grade glioma populations. Long-term follow-up of RTOG 98-02 (high-risk patients with less than gross total tumor resection or older than 40) found significantly better PFS (10.4 years versus 4.0 years, $p = 0.002$) and OS (13.3 years versus 7.8 years, $p = 0.02$) for those treated with RT followed by PCV chemotherapy compared to those treated with RT alone.

Translational research, including studies of proliferation, cytogenetics, and molecular genetics, will provide much needed insight for the next generation of biologically based therapies.

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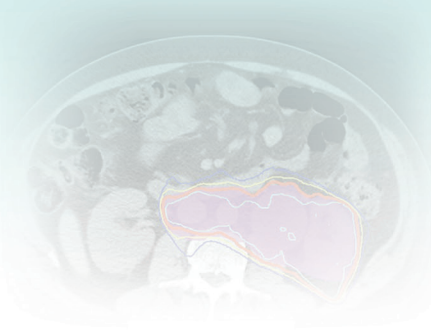
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CHAPTER

27 High-Grade Gliomas



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INCIDENCE

There are approximately 68,000 new cases of brain tumors diagnosed in the United States each year. Gliomas now account for nearly 80% of malignant brain tumors. Glioblastoma (GBM) is the most common primary malignant brain tumor.[1]

BIOLOGIC CHARACTERISTICS

A better prognosis is associated with grade III tumors (as classified by the World Health Organization [WHO]) when compared with grade IV tumors (i.e., GBM) and for oligodendrogliomas when compared with astrocytomas. A better response to therapy and higher rates of survival are associated with oligodendroglial tumors manifesting 1p19q codeletions and IDH mutations. Methylation of the promoter for the *MGMT* gene predicts for increased sensitivity to DNA alkylating agents such as temozolomide and is prognostic for overall survival (OS) in patients with GBM, especially older patients.

STAGING EVALUATION

Optimal imaging is carried out with contrast-enhanced magnetic resonance imaging (MRI). Computed tomography (CT) scans are primarily used as an infrastructure for radiation treatment planning before fusion with MRI images. On the first postoperative day, an MRI study should be obtained to evaluate the extent of resection and as a basis for radiation treatment planning.

PRIMARY THERAPY AND RESULTS

The standard of care for the definitive treatment of newly diagnosed GBM in patients aged 18 years to 70 years is the delivery of approximately 60 Gy of fractionated partial brain radiotherapy following maximal safe surgical debulking. Irradiation (most commonly administered with conformal strategies) should be accompanied by concurrent temozolomide chemotherapy. Adjuvant temozolomide is also administered for at least 6 months following the end of radiotherapy unless disease progression occurs.

Temozolomide has not been established as a component of standard therapy for newly diagnosed WHO grade III gliomas; ongoing trials are investigating this issue.

Prospective randomized trials could not define a role for either brachytherapy or radiosurgery in the initial management of high-grade gliomas.

LOCALLY ADVANCED DISEASE AND RECURRENCE

Bevacizumab has been approved for salvage of failures following definitive therapy for GBM. If chemotherapeutic options are not available in the setting of recurrence, creative radiotherapeutic strategies (e.g., radiosurgery, intensity-modulated radiation therapy [IMRT], brachytherapy) may be considered.

High-grade gliomas are almost universally fatal. Although recently discovered combined-modality approaches have prolonged survival, many patients succumb relatively quickly, and cure remains elusive for the majority.

New protocols have recently emerged after decades of limited progress in the management of these tumors. New chemotherapeutic drugs, such as temozolomide, have found application in GBM. Bevacizumab is effective in recurrent disease and prolongs radiographic disease control in first-line regimens. In the future, molecular profiling may also allow tailoring of specific treatment to the patients most likely to benefit.

ETIOLOGY AND EPIDEMIOLOGY

Most malignant brain tumors are high-grade gliomas, and most of these are GBM, a WHO grade IV tumor. The remainder are WHO grade III tumors such as anaplastic astrocytoma, anaplastic oligodendroglioma, and anaplastic oligoastrocytoma. Men are more commonly affected than women. The peak incidence occurs in the age range of 65 years to 75 years, and the median survival time is inversely proportional to age; these findings have prompted a redoubling of efforts in elderly subpopulations.[1]

There has been concern for cancer development following exposure to electromagnetic fields, but definitive evidence is lacking. More recently, the use of cellular telephones has been studied extensively in Europe,[2] but its importance as a risk factor has not been established. In terms of chemical exposure, nitrosamines have long been regarded as culpable, but causality is far from proven.[3] Brain tumors have also been linked with previous exposure to therapeutic ionizing radiation.[3] However, the absolute risk is low.

Most gliomas are sporadic, but genetic susceptibility is suspected based on the occurrence of multiple brain tumors in families with germline mutation of the *TP53* suppressor gene and patients with neurofibromatosis type I as well as the rare patients who have been diagnosed with Turcot's syndrome. A heritable syndrome contributes to less than 5% of GBMs.[4]

PREVENTION AND EARLY DETECTION

No viable strategy for screening or early detection of glial tumors has been developed. There is also no convincing evidence demonstrating either improved survival when high-grade gliomas are found early, or a clear rationale for prophylactic strategies to reduce the incidence of these aggressive tumors.[3]

BIOLOGIC CHARACTERISTICS AND MOLECULAR BIOLOGY

Investigators around the world are searching for the molecular biologic characteristics of gliomas in an effort to improve therapy. For example, work by the Cancer Genome Atlas Research Network[5] and others[6,7] suggests that at least three molecular subclasses of GBM exist with potential therapeutic and prognostic implications. Mouse modeling has also demonstrated the oncogenic importance of abnormalities in receptor signaling (e.g., epidermal growth factor receptor [EGFR] and platelet-derived growth factor receptor [PDGFR]), signal transduction cascades (e.g., RAS and AKT), and cell cycle regulation.[8]

In the early 1990s, it was recognized that deletion of the short arm of chromosome 1 (1p) and the long arm of chromosome 19 (19q) occurs in most oligodendrogliomas.[9] Codeletion of 1p and 19q is prognostic for longer survival,[10-12] although until recently controversy existed as to whether this finding should alter therapy.[13] It is now recognized that an unbalanced chromosomal translocation underlies 1p/19q codeletion,[14,15] but the specific genes involved and their mechanism of action remain elusive. More recently, mutations in the isocitrate dehydrogenase 1 and 2 *(IDH1* and *IDH2)* genes, occurring most often in low-grade gliomas but also in a minority of WHO grades III and IV tumors have been described,[16,17] and are prognostic for longer survival.[12,16,18,19] Methylation of the *MGMT* promoter (see the section on chemotherapy) is emerging as a potential but imperfect predictive and prognostic factor in the treatment of newly diagnosed GBMs.

With the exception of 1p19q codeletion in anaplastic tumors, it is not yet clear how to best incorporate molecular data into the treatment of individual patients. Detailed discussions of the biologic characteristics of glioma and their clinical relevance are beyond the scope of this chapter and can be found elsewhere.[20]

PATHOLOGY AND PATHWAYS OF SPREAD

The WHO classification system[21] is derived in part from the correlation between pathologic findings and survival rates observed by Bailey and Cushing[22] and published in the early 1900s. In current parlance, *low grade* refers to WHO grades I to II tumors and *high grade* to WHO grades III to IV tumors (Figure 27-1). However, the WHO grade I gliomas (e.g., juvenile pilocytic astrocytomas) are biologically different tumors from the others, infrequently occur in adults, and may be amenable to surgical cure. *Anaplastic* in the context of gliomas refers to WHO grade III tumors such as anaplastic astrocytomas, anaplastic oligodendrogliomas, and anaplastic oligoastrocytomas. GBM is a WHO grade IV astrocytoma, although the most recent WHO classification scheme does account for other rare subtypes, including GBM with oligodendroglial components.

WHO grades II to IV gliomas are characterized by a tendency to directly infiltrate adjacent brain tissue. Lesions with direct access to the corpus callosum may extend across the midline and configure themselves in a classic "butterfly pattern" (Figure 27-2). MRI underestimates the extent of invasive disease, and the diffusely infiltrative nature of these tumors makes complete removal of all tumor cells impossible. This "misleading appearance of enucleability" was described more than 80 years ago.[22] Leptomeningeal spread occurs occasionally (Figure 27-3). Hematogenous and lymphatic spread are exceedingly uncommon.[23]

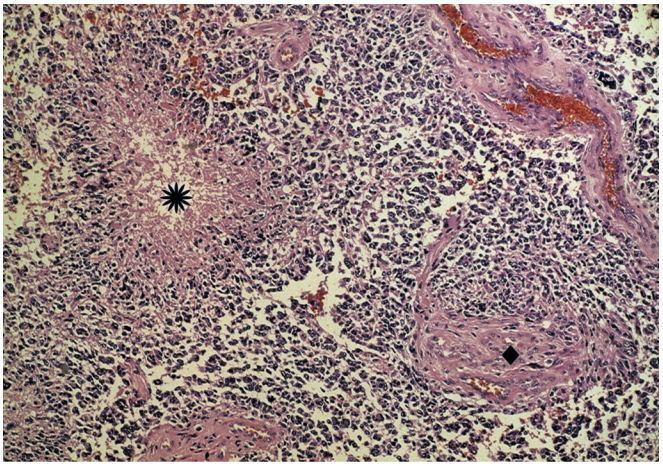


Figure 27-1 Highly cellular astrocytic glioma with foci of microvascular proliferation *(asterisk)* and pseudopalisading necrosis *(diamond)* consistent with glioblastoma.

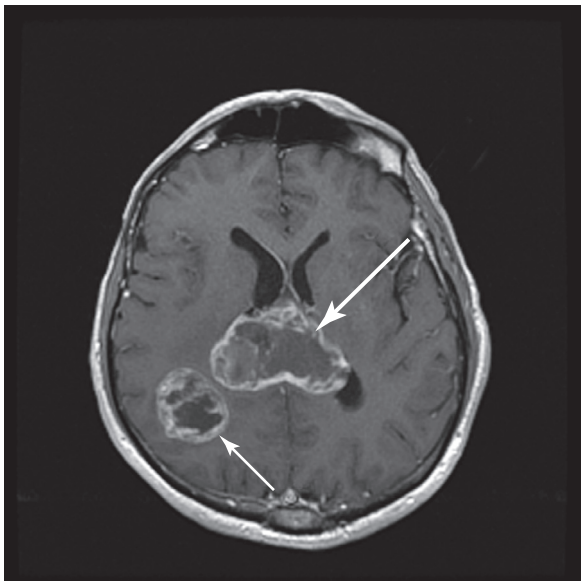


Figure 27-2 "Butterfly" glioblastoma *(long arrow)*; a separate satellite lesion in the right parietal lobe *(short arrow)* is also apparent. The contrast enhancement with central necrosis is classic for a glioblastoma, which was histologically confirmed by biopsy.

CLINICAL MANIFESTATIONS, PATIENT EVALUATION, AND STAGING

No specific symptom constellation is pathognomonic of high-grade glioma. Typically, patients present with some combination of headaches, neurologic deficits, nausea, and vomiting, depending on tumor size and location. It is not unusual for patients to present with or subsequently develop seizures. Tissue for pathologic diagnosis can be obtained via stereotactic biopsy, open biopsy, or gross resection in the context of craniotomy. More complete resection improves diagnostic accuracy, provides additional tissue for molecular analyses, and is increasingly thought to improve OS.

The typical imaging appearance of a GBM is a ring-enhancing or heterogeneously enhancing lesion. The differential diagnosis may include stroke, brain metastasis, primary central nervous system lymphoma, demyelination, and even infectious or other inflammatory diseases. If a brain metastasis

is suspected, it is prudent to perform an appropriate extracranial evaluation to identify the primary malignant tumor. If there is a high index of suspicion for primary central nervous system lymphoma, such as in multifocal, periventricular, or homogenously enhancing lesions,[24] corticosteroids should be withheld preoperatively unless herniation is imminent because their use may confound the histologic diagnosis.

Nearly all GBMs demonstrate contrast enhancement. However, up to 10% of anaplastic gliomas will not manifest such a pattern on imaging. Background uptake in the brain (an organ with an inherent avidity for glucose) significantly compromises the use of glucose-based positron emission tomography (PET) as a diagnostic tool for high-grade gliomas.

An algorithm for the evaluation and management of patients with GBM is shown in Figure 27-4.



Figure 27-3 T1 contrast-enhanced sagittal view from a magnetic resonance imaging showing rare leptomeningeal spread from a glioblastoma surrounding the spinal cord.

PRIMARY THERAPY

Prognostic and Predictive Factors

Historically, all high-grade gliomas were lumped together in most clinical trials, thereby confounding results because of maldistribution of patients with differing prognoses. In 1993, Curran et al[25] published a landmark paper describing a prognostic classification scheme based on clinical variables. Data from three Radiation Therapy Oncology Group (RTOG) trials that enrolled nearly 1600 patients with high-grade glioma from 1974 to 1989 were used. This recursive partitioning analysis (RPA) methodology builds decision trees to model predictors by examining all possible "cut points" for all variables included in the model. Patients were segmented into six distinct groups with different survival outcomes. The key variables included patient age, performance status, histologic tumor type (i.e., anaplastic astrocytoma versus GBM), mental status, symptom duration antecedent to diagnosis, extent of resection, neurologic function, and radiotherapy dose. Median survival ranged from 4.6 months for class VI patients to almost 5 years for class I patients, underscoring heterogeneity. The European Organization for Research and Treatment of Cancer (EORTC) demonstrated that the prior RTOG RPA classification remained valid among patients in a more recent Phase III trial.[26] An RPA for anaplastic oligodendroglial tumors has also been proposed.[27]

One of the more controversial factors in the setting of high-grade gliomas has been the extent of surgical resection. Bailey and Cushing observed longer survival following resection in their 1926 publication,[22] as did others in the 1960s.[28] Numerous series since then also support more complete resection as a prognostic factor.[29-33] One of the largest involved more than 400 patients at the M. D. Anderson Cancer Center and demonstrated improved median survival (13 versus 8.8 months; $p < 0.0001$) following at least 98% resection, as defined by postoperative MRI scans.[34] One small randomized study of 30 patients older than 65 years demonstrated improved survival rates following resection versus biopsy alone.[32] Use of 5-aminolevulinic acid fluorescence intraoperatively improves the likelihood of gross total resection,[29] but the effect on survival is debated.

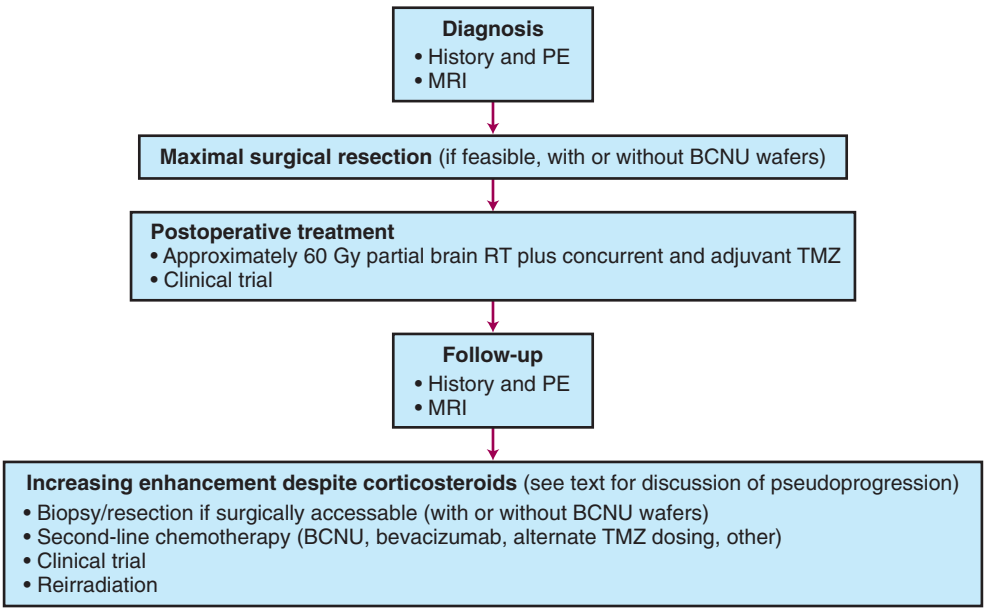


Figure 27-4 Algorithm for diagnosis and treatment of glioblastoma. See text for details. *BCNU,* Carmustine; *MRI,* magnetic resonance imaging; *PE,* physical examination; *RT*, radiotherapy; *TMZ,* temozolomide.

Surgery

Patients can often undergo a craniotomy where the goal is the safe removal of the largest possible volume of tumor to establish a diagnosis and relieve mass effect. High-grade gliomas are not surgically curable because of their extensive infiltration.

If biopsy rather than resection is pursued, choices include stereotactic options with CT or MRI guidance or open craniotomy and biopsy. Some have employed metabolic imaging such as magnetic resonance spectroscopy (MRS) to better select the biopsy sites most likely to contain the most aggressive portions of the tumor, but this is not widely used. Usually, stereotactic biopsy can be performed using either frame-based or frameless neuronavigation systems. The pathologist can review the frozen section to make an immediate preliminary diagnosis and confirm tissue adequacy.

When craniotomy is contemplated, meticulous planning is invested in the scalp incision and flap design. Special care must be taken to preserve the vascular supply of the scalp. The bony opening is devised to be sufficiently large to facilitate resection without needlessly exposing adjacent brain to the risk of injury. After opening the scalp, burr holes are placed and connected with a craniotomy. The bone flap is removed and the dura mater is opened. As a rule, the bone flap is reattached at the end of the resection, although some surgeons prefer not to reattach the bone flap.

Although tumors on the brain surface are immediately visible after exposure, subcortical lesions are harder to discern. Frameless image-guided neuronavigation systems are employed to localize subcortical tumors along with intraoperative ultrasound and MRI. Tumors that are situated near "eloquent" areas of cortex, such as those harboring motor and speech function, are mapped intraoperatively via electrical cortical stimulation to achieve maximal tumor debulking without operative morbidity. Resection of gliomas in the dominant hemisphere is often carried out under local anesthesia with supplementary sedation to allow speech mapping.

Occasionally, tumors may be removed en bloc via circumferential dissection, but more frequently, resection is effected in piecemeal fashion. A cavitational ultrasonic surgical aspirator (CUSA) facilitates removal of a firm, adherent, or calcified tumor.

Patients are routinely monitored in an intensive care unit following a craniotomy. The first MRI is obtained within 24 hours to 48 hours after surgery before postoperative changes set in. The extent of resection can be determined in this manner.

External Beam Irradiation

External beam irradiation (EBRT) has historically been the cornerstone of the therapeutic approach to GBM (and anaplastic astrocytoma) for the past half-century, and its use in brain tumors was already described by the 1920s.[35] In the 1970s and early 1980s, categorical level I data became available from several studies,[36] including prospective Phase III trials conducted by the Brain Tumor Study Group (BTSG)[37,38] (Table 27-1).

The radiotherapeutic approach to high-grade glioma has evolved. Initially, large opposed lateral fields were employed to cover the entire brain volume. In 1989, Shapiro et al[42] published data from Brain Tumor Cooperative Group trial 80-01, in which the randomization was altered during the trial to compare partial brain irradiation with whole-brain radiotherapy (WBRT). No difference in OS or change in the patterns of failure was seen. Accordingly, WBRT is generally not advocated, except perhaps in the scenario of a widespread intracranial process such as gliomatosis cerebri.[43]

Several lines of evidence have influenced the trend to treat the gross tumor volume along with a margin of approximately 2 cm. In a classic paper published in 1980, Hochberg and Pruitt[44] used CT scans to determine that nearly 90% of GBM recurrences occurred within 2 cm of the primary tumor site (although this may be changing with the use of bevacizumab). Wallner et al[45] assessed the patterns of recurrence in 32 patients with unifocal malignant gliomas who were treated with primary surgery and postoperative irradiation. Nearly 80% of patients manifested recurrence or progression within 2 cm of the original tumor. Even when 80 Gy of partial brain irradiation was used in a prospective Phase I trial,[46] 90% of patients failed within the high-dose region.

It has been demonstrated on biopsy and autopsy studies that the abnormality detected on T2 or fluid-attenuated inversion-recovery (FLAIR) images harbors microscopic tumor extension. Accordingly, 45 Gy to 50 Gy is generally delivered, in 1.8-Gy to 2-Gy fractions, to the T2/FLAIR abnormality seen

TABLE 27-1 Positive Phase III Trials Evaluating the Role of Irradiation, Chemotherapy, or Chemoradiation in the Treatment of Malignant Gliomas

Study	No. Patients	Treatment Arm	Median (mo)	18 mo	24 mo	5 yr
BTSG 69-01*[37]	VSG		—			
	31	Observation	3.2	0	0	0
	51	Carmustine	4.3	4	0	0
	68	Radiation therapy	8.3	4	1	NA
	72	Radiation therapy plus carmustine	7.9	19	5	NA
BTSG 72-01†[38]	VSG		—			
	81	Semustine	4.8	10	8	NA
	94	Radiation therapy	8.3	15	10	NA
	92	Radiation therapy plus carmustine	11.8	27	15	NA
	91	Radiation therapy plus semustine	9.7	23	12	NA
EORTC/NCI-C‡[39-41]	286	Radiation therapy	12.1	21	11	2
	287	Radiation therapy plus temozolomide	14.6	39	27	10

BTSG, *Brain Tumor Study Group;* EORTC, *European Organization for Research and Treatment of Cancer;* NA, *not available;* NCI-C, *NCI Canada;* VSG, *valid study group;* yr, *year.*

*p = *0.001 for radiation therapy versus observation/supportive care and radiation therapy plus carmustine versus observation/supportive care.*

†p ≤ *0.003 for radiation therapy, radiation therapy plus carmustine, and radiation therapy plus semustine versus semustine alone.*

‡p < *0.0001. Most patients randomized to radiation therapy alone crossed over to temozolomide at time of relapse or progression.*

on the image, followed by a boost to raise the total dose to 60 Gy based on the T1-enhancing abnormality. The MRI abnormalities, however, remain quite nonspecific in terms of histopathologic confirmation, and even when novel strategies such as MRS are used for radiotherapy planning, there can be over or underestimation of the true extent of microscopic spread.[47]

A novel view of target definition has recently been proposed.[48,49] This approach posits that neuroprogenitor cells in the subventricular zone (SVZ) play a role in tumor recurrence. In retrospective analyses of dose distribution among patients with GBM, investigators found that the deposition of high dose (e.g., >40 Gy) in the ipsilateral SVZ was associated with a significantly improved progression-free survival (PFS) and OS in patients who also achieved gross total resection of their tumors. To validate this hypothesis, prospective clinical trials will need to be conducted to determine if cancer stem cells will need to be encompassed when delineating the targets for irradiation of high-grade glioma.

Rationale for Current Total Irradiation Dose

A pooled analysis of three successive randomized trials conducted by the Brain Tumor Study Group (BTSG 66-01, 69-01, 72-01, respectively) generated data to support doses in excess of 50 Gy.[50] A stepwise improvement in survival was observed with doses ranging from less than 45 Gy to 60 Gy, consistent with dose response. A comparison of 70 Gy versus 60 Gy demonstrated no survival or local control advantage for the 70-Gy dose.[51,52] These results established 60 Gy as the standard of care.

Dose escalation has remained an important investigational option because there is still a pattern of failure characterized by local progression or recurrence. There are now multiple techniques for dose escalation, including three-dimensional conformal irradiation, radiosurgery, and brachytherapy, but these have not yielded higher rates of disease control or survival. Increasing the radiotherapy dose or reirradiation with radioprotective or antiangiogenic agents may be a useful strategy in the future.[53]

Altered Fractionation

The RTOG has systematically and rigorously studied hyperfractionation for high-grade gliomas. In RTOG 83-02, patients were randomized to one of four dose arms (64.8 Gy, 72 Gy, 76.8 Gy, or 81.6 Gy) using twice-daily fractions of 1.2 Gy. Initial results suggested the superiority of 72 Gy,[54] but a subsequent Phase III trial demonstrated no improvement.[55] Prados et al[56] used an elegant randomization to assess not only a hyperfractionation schedule, but also to determine the activity of difluoromethylornithine (DFMO), a compound that inhibits sublethal and potentially lethal damage repair. Unfortunately, neither intervention improved survival.

Stereotactic Irradiation

Two provocative small-scale experiences prompted the design of Phase III trials to formally evaluate radiosurgery for high-grade gliomas.[57,58] Loeffler et al[57] reported on 37 patients treated with 59.4-Gy fractionated radiotherapy followed by a stereotactic radiosurgery (SRS) boost to a median dose of 12 Gy. After a median follow-up period of 19 months, a 76% survival rate was reported. Sarkaria et al[58] described 115 patients with high-grade glioma who received conformal radiation therapy and a SRS boost; median survival time was 96 weeks. These results called into question whether they represented a benefit from SRS or simply selection bias.

RTOG 93-05 compared conformal irradiation plus carmustine with or without a SRS boost for newly diagnosed GBM. No differences were observed in terms of OS (median, approximately 13 months in each arm) or quality of life.[59]

SRS may still have a role in the treatment of recurrent disease, particularly if a focal region of recurrence can be defined.[53] However, this has not been tested in prospective trials.

Brachytherapy

Brachytherapy, the use of implanted radioactive material at the site of the tumor offers a mechanism for focal dose escalation. Both permanent and temporary radioactive implants have been used. Early positive results by Gutin et al[60] suggested a potential survival benefit in a Phase II trial. These findings were not reproduced in subsequent randomized trials.[61,62]

Interest in this modality was rekindled when the GliaSite radiation therapy system (Proxima Therapeutics, Alpharetta, Georgia) received approval by the Food and Drug Administration (FDA) in 2001. This intracavitary device is implanted at the time of tumor debulking, and a solution of iodine-125 (^{125}I) is injected into an expandable closed-catheter balloon. A retrospective study suggested reasonable safety and promising efficacy.[63] A Phase I study was conducted.[64] However, the implant induces changes in imaging that complicate determination of disease progression.[65]

Chemotherapy: Concurrent with EBRT, Maintenance, and Other

Early randomized trials of chemotherapy were individually negative, but meta-analysis of these trials showed that 15% to 20% of patients treated with radiation therapy (RT) and nitrosoureas survived at least 18 months versus 5% treated with radiotherapy alone (Table 27-1).[37,38,66,67] Nitrosoureas, especially carmustine, were the most commonly used drugs, although procarbazine was also used extensively.[68] The combination of procarbazine, lomustine (CCNU), and vincristine (PCV)[69] had no clear benefit (yet much greater toxicity) versus carmustine for anaplastic astrocytoma,[70] and this regimen has been largely abandoned for nonoligodendroglial tumors.

Intratumoral delivery of chemotherapy for residual postoperative disease is most commonly in the form of carmustine-eluting (Gliadel) wafers. Patients undergoing wafer implantation during surgery for recurrent GBM survived approximately 2 months longer than patients without wafers in one study ($p = 0.02$).[71] Treatment of newly diagnosed disease also yielded a 2-month prolongation of average survival.[72,73] However, this was not statistically significant when the analysis was restricted to patients with GBM histology. Of note, wafer delivery of carmustine versus systemic administration has not been compared for safety or efficacy. Gliadel does, however, carry an FDA label for implantation during resection of recurrent GBM and newly diagnosed malignant glioma. Attempts to treat residual visible or microscopic disease with other local chemotherapies delivered through implanted catheters and using convection-enhanced migration of drug have generally failed.[74]

Currently, the most widely used chemotherapeutic agent is temozolomide. Whether it is more effective than nitrosoureas has not been investigated, but it is unquestionably better tolerated with significant myelosuppression in less than 20% of patients.[39,40] Temozolomide was first approved for use in the United States in recurrent anaplastic astrocytomas following a phase II study.[75] A randomized study also demonstrated superior efficacy to procarbazine in recurrent GBM.[76]

Temozolomide for newly diagnosed GBM has been studied both when given before RT[77] and when combined with RT in various dosing schedules.[78,79] Its role for newly diagnosed GBM was established by Stupp et al[39,40] on the basis of the EORTC 26981/22981 and NCIC CE.3 trial (Figure 27-4). In

this Phase III multicenter study, 573 patients with newly diagnosed GBM received RT alone or RT with concurrent temozolomide followed by six adjuvant cycles of temozolomide. The patients who received the combined-modality regimen had significantly longer OS and PFS without significantly more toxicity (Table 27-1). The 5-year OS was 10% among those receiving temozolomide versus 2% among those receiving RT alone ($p < 0.0001$).[39] Patients in the most favorable RPA class had a 5-year OS rate of 28% following combined therapy.[39] In a companion paper, Hegi et al[41] reported that methylation of the promoter for the O_6-methylguanine DNA methyltransferase *(MGMT)* gene, which encodes the DNA repair enzyme O_6-alkylguanine DNA alkyltransferase (AGT or AGAT, but now commonly also referred to as MGMT), was correlated with prolonged survival and patients with *MGMT* methylated tumors benefited the most from temozolomide.

MGMT repairs DNA damage induced by temozolomide, and methylation of the *MGMT* promoter silences expression of the protein, thereby accentuating the antineoplastic effects of temozolomide. However, the mechanism by which *MGMT* promoter methylation leads to an improved outcome is more complex. For example, some patients with tumors that did not demonstrate MGMT methylation also benefited from temozolomide although it is increasingly recognized that the initial test probably scored some "methylated" tumors as either "unmethylated" or "unknown."[39-41] Accordingly, it remains unclear whether MGMT analysis should categorically alter treatment, although this situation remains somewhat fluid. In addition, patients with tumors harboring methylated *MGMT* survived longer following treatment with RT alone than patients who did not have tumors harboring methylated *MGMT* treated identically.[39,40] Others reported similar findings in GBM[80] and other malignant gliomas.[81] Moreover, MGMT protein expression by immunostaining does not predict outcome.[82]

Several groups have explored intensifying the temozolomide dosing schedule in an attempt to overcome *MGMT*-mediated resistance.[83,84] The intensified regimens are designed to deplete MGMT activity as suggested by previous studies.[85] RTOG 0525 was a Phase III randomized placebo controlled study that compared standard temozolomide dosing following completion of radiotherapy (150 mg/m^2 to 200 mg/m^2 body surface area days 1 to 5 of 28) versus an intensified regimen (75 mg/m^2 to 100 mg/m^2 body surface area days 1 to 21 of 28). This prospectively validated that *MGMT* promoter methylation is a favorable prognostic factor regardless of treatment.[86] However, "dose-dense" temozolomide was more toxic than standard dosing and did not significantly alter PFS or OS regardless of *MGMT* status.[86]

Therefore, *MGMT* promoter methylation is prognostic but the mechanism remains unclear. In addition, there are now several different methodologies to test for *MGMT* promoter methylation, which may lead to discordant results.[87] It is possible that *MGMT* is a marker of more global hypermethylation and is only one of multiple genes mechanistically involved in resistance to alkylator chemotherapy and prognosis in tumors harboring the recently described Glioma CpG island methylator phenotype (G-CIMP).[88,89]

Another major area of investigation has been the use of vascular endothelial growth factor receptor (VEGFR) signaling inhibitors. Bevacizumab (Avastin) is a monoclonal antibody against VEGF that competitively inhibits binding of the ligand to VEGFR and targets tumor vascularity. It is the most widely studied of these antiangiogenic strategies.

Based on encouraging response rates and prolongation of PFS in recurrent GBM, two major Phase III studies, RTOG 0825 and Avastin in Glioblastoma (AVAglio) sponsored by F. Hoffmann La Roche, were launched nearly simultaneously. Following maximal safe surgical resection, both randomized patients to receive RT and temozolomide plus either bevacizumab or placebo. Although there were subtle differences in trial design with respect to extent of resection (e.g., biopsy-only patients not permitted in RTOG 0825 but allowed in AVAglio, timing of treatment, etc.), both demonstrated prolongation of PFS (median 10.7 versus 7.3 months, $p = 0.007$ for RTOG 0825; median 8.4 versus 4.3 months, $p < 0.001$ for AVAglio).[90,91] However, neither demonstrated a difference in OS (median 15.7 versus 16.1 months, $p = 0.21$ for RTOG 0825; median 16.8 months versus 16.7 months for AVAglio, $p = 0.10$). Both permitted cross-over from placebo to bevacizumab that was offered as part of the study design to participants in RTOG 0825 and permitted but not offered routinely in AVAglio.

These results have not categorically settled the issue of whether bevacizumab should be used for newly diagnosed GBM. In RTOG 0825, the prolongation of PFS did not meet the prespecified statistical level (30% reduction in hazard, $p = 0.004$ required for significance), whereas it did for AVaglio (23% improvement, $p = 0.01$ required for significant difference in PFS). In addition, quality of life measures in RTOG 0825 did not demonstrate a "Net Clinical Benefit," in fact it was worse for those who received bevacizumab, whereas improvement was observed in AVAglio.[90,91] In the context of these results, some practitioners consider using bevacizumab for patients with unresectable large deep tumors with surrounding edema, and especially patients with poor performance status, but such patients would have been excluded from the Phase III trials.

Other antiangiogenic therapies also have not improved survival. For example, the EORTC in collaboration with the Canadian Brain Tumor Consortium conducted the Phase III CENTRIC (CilENgitide in combination with Temozolomide and Radiotherapy In newly diagnosed glioblastoma Phase III randomized Clinical trial) study to evaluate the integrin inhibitor cilengitide that has reported antiangiogenic properties.[92] Based on encouraging Phase II results among the subset of patients with *MGMT* methylated tumors,[93] CENTRIC randomized such patients with newly diagnosed GBM to standard RT and temozolomide with or without cilengitide.[94] Median survival was unchanged (26.3 months in both arms, hazard ratio [HR] 1.02, $p = 0.86$).[94] There was also no significant improvement in PFS (13.5 months versus 10.7 months, HR 0.93, $p = 0.48$) as evaluated by the treating investigator.[94] A study of cediranib for newly diagnosed GBM (RTOG 0837) is ongoing; however, the failure of cediranib to demonstrate meaningful efficacy in recurrent GBM is concerning.

Two studies have evaluated antiangiogenic therapy in particular for patients with *MGMT* unmethylated tumors. The ongoing CORE (Cilengitide in patients with newly diagnosed glioblastoma multifoRme and unmethylated *MGMT* genE promoter) randomized such patients to RT and temozolomide with or without cilengitide. Results are not available yet. The German GLARIUS Phase II trial randomized cases with ummethyalted *MGMT* 2:1 to RT and concurrent bevacizumab followed by maintenance temozolomide for six cycles.[95] The primary endpoint was 6-month PFS determined by central review (generally considered somewhat unconventional), with 80% power to detect an increase from 40% to 60%. Results favored the bevacizumab arm (79.6% versus 41.3%, $p < 0.0001$). Median PFS (9.7 versus 6.0 months, HR 0.3, $p < 0.0001$) and OS (16.6 versus 14.8 months, HR 0.60, $p = 0.031$) also significantly favored the experimental arm.[95] These results require maturation and further validation, but begin to suggest a subgroup of patients who may benefit from addition of bevacizumab containing chemotherapy in lieu of temozolomide for newly diagnosed GBM. Notably, OS did not favor the bevacizumab group in RTOG 0825 or AVAglio,[90,91] but these trials were not intended for comparison.

Anaplastic Gliomas

Anaplastic astrocytomas, anaplastic oligodendrogliomas, and anaplastic oligoastrocytomas represent the most common WHO grade III tumors.[1,21] In anaplastic gliomas, resection appears to improve survival relative to biopsy, as it does for GBM.

Anaplastic Astrocytic Neoplasms

It is generally accepted that RT should be administered postoperatively for astrocytomas. In a German study (NOA-04), early analysis demonstrated that survival was equivalent whether chemotherapy or RT was used first among patients with anaplastic astrocytomas, oligodendrogliomas, and mixed tumors.[12] However, time to progression following RT was longer than after chemotherapy, and initial radiation therapy achieved more complete and partial responses than initial chemotherapy, suggesting the superiority of RT.[96] In addition, the data were relatively immature at initial publication, and longer follow-up may demonstrate the importance of primary RT more fully among anaplastic astrocytomas, or mixed oligoastrocytomas without 1p19q codeletion.

Regarding chemotherapy, Combs et al[97] reviewed the outcome of 191 patients with grade III astrocytic tumors treated at the University of Heidelberg with either RT alone or RT in combination with temozolomide during a 20-year period (from 1988 to 2007). In this retrospective study, no significant advantage in rates of OS or PFS could be attributed to the combination. RTOG trial 9813 randomized patients with anaplastic astrocytomas (or oligoastrocytomas) to RT with concurrent nitrosourea (carmustine or lomustine) or with temozolomide, and results are pending.

The ongoing Concurrent vs. Adjuvant Temozolomide for NON 1p19q co-deleted anaplastic gliomas, also called EORTC 26053-22054 (CATNON) Intergroup trial randomizes patients to receive postoperative RT alone, concurrent temozolomide and RT without adjuvant temozolomide, RT (without concurrent temozolomide) followed by adjuvant temozolomide, or RT with both concurrent and adjuvant temozolomide (Figure 27-5). Although technically this study allows any WHO grade III glioma without 1p/19q codeletion, the majority of the tumors will be anaplastic astrocytomas.

Anaplastic Oligodendroglial Tumors

Long-term follow-up is now available for patients enrolled on RTOG 94-02[10,98] and EORTC 26951.[11,99] In these studies, radiation was compared to radiation with PCV chemotherapy. The RTOG trial entailed administration of chemotherapy before irradiation (intensified PCV[100] for up to four cycles in the combined-modality arm) whereas the reverse sequence (i.e., RT alone versus 59.4 Gy followed by up to six cycles of standard dose PCV) was used in the EORTC trial. With median follow-up in excess of 10 years in both studies, there was a dramatic improvement in OS associated with combined chemotherapy and radiotherapy (irrespective of sequence) among patients with anaplastic oligodendroglioma or anaplastic mixed oligoastrocytoma whose tumors contain allelic loss of chromosomes 1p and 19q, compared with radiation alone. For example, in RTOG 9402, median survival was 14.7 years versus 7.3 years ($p = 0.03$, HR 0.59 for chemoradiotherapy) and in EORTC 26951 median survival was not reached versus 9.3 years ($p = 0.0594$, HR 0.56 for chemoradiotherapy). In addition, patients with *IDH* mutant but not 1p19q codeleted tumors also benefited from chemotherapy, although the magnitude was lower than for those with tumors that harbored both codeletion and *IDH* mutation.[101] Those with *MGMT* promoter methylation[87] or ATRX expression[101] may also benefit regardless of 1p19q deletion status.

The applicability of these findings in an era where PCV is no longer popular remains debatable, especially because temozolomide has almost entirely replaced PCV in routine practice[102] despite the lack of a clear efficacy equivalence. What is clear, however, is that RT alone is inadequate for treatment of patients with codeleted tumors, and likely those with *IDH1* or *IDH2* mutated tumors, regardless of deletion status.

In addition, the role of RT for newly diagnosed anaplastic oligodendroglioma is becoming the subject of controversy because of the tumor's reported sensitivity to chemotherapy,[100] especially tumors with 1p/19q codeletion.[103] Neither RTOG 9402 nor EORTC 26951 used chemotherapy alone, which was recommended by 42% of clinicians (typically with temozolomide)[13] and used in 55% of patients from 2005 to 2007 in a retrospective series of codeleted tumors, without prospective data supporting such usage.[102] The ongoing CODEL (for 1p/19q CO-DELeted tumors) trial now randomizes patients to RT followed by PCV versus RT plus concurrent and adjuvant temozolomide, versus temozolomide alone (Figure 27-6).

The CATNON and CODEL study designs are premised on the belief that the 1p/19q chromosomal status may be more important than the histologic subtype for WHO grade III lesions. However, scientific advances in the interim may outpace the questions posed by these trials as it becomes apparent that *MGMT* promoter methylation[81,87] and *IDH* gene mutation[12,18,101] are also powerful markers of outcome in anaplastic gliomas. There is a clear need to move beyond histologic information (e.g., WHO subtyping) because important advances in prognostication have been made.[104]

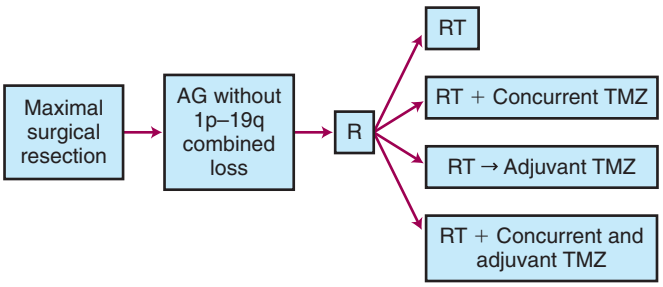


Figure 27-5 Schema from the CATNON study (Intergroup phase III, EORTC 26-53, RTOG 0834). *AG*, Anaplastic glioma; *R*, randomization; *RT*, radiotherapy; *TMZ*, temozolomide.

Special Topics

Toxicities of Radiation Therapy

Acute and late effects of irradiation, including brain necrosis are discussed in a subsequent section on Irradiation Techniques and Toxicities.[45,97,105-107]

Elderly Patients with GBM

More than 44% of GBMs occur in patients older than 65 years of age,[1] but prospective trials often exclude elderly patients.[39,40]

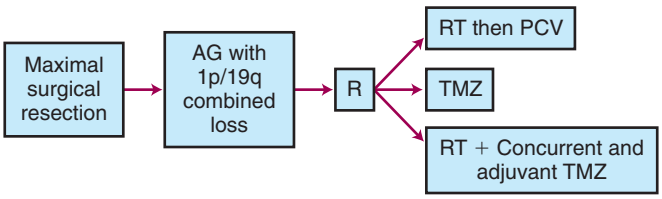


Figure 27-6 Schema from the CODEL trial (NCCTG NO0557/RTOG 0670). *PCV*, Procarbazine; *TMZ*, temozolomide.

Because these patients often have a worse outcome than younger patients, there has been some uncertainty with regard to the aggressiveness of treatment, and the definition of "elderly" is highly variable.

A Finnish randomized study of 30 patients older than age 65 years with imaging consistent with malignant gliomas demonstrated longer median survival following craniotomy than following biopsy (5.7 versus 2.1 months; $p = 0.035$).[32] The Association of French-Speaking Neuro-Oncologists[106] conducted a randomized trial comparing RT alone (50 Gy in conventional fractionation) versus supportive care among patients older than 70 years of age. The trial was discontinued after 85 patients were registered when it became apparent that RT was associated with a statistically advantageous outcome (median survival time, 29 versus 17 weeks; $p = 0.002$).

Efforts to abbreviate the duration of RT have been conducted. For example, a randomized study in patients older than age 60 years demonstrated that 40 Gy in 15 fractions was not inferior to 60 Gy in 30 fractions.[107]

A Phase II study of temozolomide alone in 32 patients older than age 70 years with newly diagnosed GBM demonstrated a response rate of 31%, median PFS time of 5 months and median survival time of 6.4 months, comparable to RT alone.[108,109] A single-arm 77-patient Phase II study for those older than age 70 with poor performance status (Karnofsky Performance Status [KPS] <70)[110] demonstrated median survival of approximately 6 months, with 26% becoming functionally independent (KPS at least 70).[111] Among those with *MGMT*-promoter methylated tumors (13 of 31 tested) median OS was approximately 7 months, and *MGMT* status was a statistically significant prognostic factor.[111]

In the NOA-08 trial conducted by the German Neuro-Oncology Working Group,[112] 373 patients older than age 65 with KPS of at least 60 with anaplastic astrocytoma or GBM (in 89%) were treated following randomization with RT (60 Gy) or an intensive schedule of temozolomide (100 mg/m^2 days 1 to 7 and 15 to 21 of every 28) without RT. If patients did not tolerate treatment or if they demonstrated progression, then cross-over (or surgical intervention) was triggered. Survival was slightly shorter following chemotherapy alone (8.6 months versus 9.6 months), but did not reach the prespecified statistical endpoint for declaring it inferiority (i.e., it was noninferior, based on accepting a certain level of survival loss designated as "noninferior"). Among patients with *MGMT* unmethylated tumors, RT was statistically superior (4.6-month versus 3.3-month event-free-survival). In addition, in *MGMT*-methylated cases, treatment with temozolomide was superior (8.4-month versus 4.6-month event-free survival). Analyzed differently, *MGMT* status did not influence event-free survival following RT (4.6 months regardless of *MGMT* status). However, *MGMT* status clearly and strongly influenced event-free survival following temozolomide alone (8.4 months versus 3.3 months for methylated versus unmethylated). Accordingly, among those with *MGMT*-methylated tumors, RT alone was an inferior treatment to temozolomide, and similarly, temozolomide alone was an inferior treatment to RT in those with unmethylated tumors. Many have presumed by implication that temozolomide in lieu of RT could be considered a reasonable treatment strategy in the elderly, but this supposition does not take into account the fact that results with combination RT and temozolomide are superior in almost all trials, and in the U.S. trials, even patients in their 80s were enrolled. Accordingly, monotherapy should be reserved for patients with poor KPS. Further, the intense schedule of temozolomide was excessively toxic and more standard schedules of temozolomide, commonly used in the United States were not studied in this trial,[112,113] and as eluded to previously, the combination of RT and temozolomide (the standard of care for patients younger than age 70 in Europe, and no age limit imposed in U.S. clinical trials, including enrollment patients, even in their 80s, as long as KPS was >70)[39,40] was not studied. It must further be underscored that NOA-08 had a noninferiority design, which included a definition of inferiority of temozolomide as a greater than 25% difference in survival endpoints, which arguably represents too much latitude and insufficient statistical rigor to allow clinicians to conclude that a new standard of care has emerged, especially given that there are few other comparable scenarios in oncology, where 25% loss of survival is accepted as noninferior.

In a Phase III trial from the Nordic Clinical Brain Tumour Study Group, 291 patients were randomized to standard dose temozolomide, standard (60 Gy) RT, or hypofractionated RT (10 fractions of 3.4 Gy each), and similar to the NOA-08 trial, there was no combined-modality therapy arm.[114] The trial has been criticized for its inclusion criteria of 60-year-olds under the rubric of "elderly" in view of the fact that the median age for the diagnosis of GBM is closer to 65 in the contemporary era.[115] Nonetheless, in an unplanned posthoc subset analysis of patients older than 70 years of age ($n = 123$), standard irradiation was associated with inferior survival in comparison to the other therapeutic arms; there was no difference in outcome between temozolomide and short-course RT, with fewer cytopenic toxicities in the short-course RT arm. The Nordic trial, much like the German study, revealed that *MGMT*-promoter methylation predicted for better outcomes in those treated with temozolomide alone, and once again it must be noted that the trial was not initially powered for this assessment as a primary observation. These trials are still open to interpretation at this juncture. The case could be made that for those patients in whom for reasons of poor performance status or inability to commute for long-course RT, temozolomide alone or short-course RT without temozolomide is an acceptable alternative; for patients who might be at higher risk of infection, short-course RT would induce fewer cytopenic episodes and might actually be preferred over temozolomide. For *MGMT*-methylated tumors in patients for whom daily radiation treatments for 6 weeks or so may impose unacceptable burden, temozolomide alone could be considered. This is not to say that RT is not an effective option for elderly patients, especially for patients with unmethylated-promoter *MGMT*. Indeed, an important next step will be to investigate chemoradiation strategies using a shortened course of irradiation, especially in the elderly poor KPS subset of patients; this is the subject of an ongoing trial by the EORTC and NCI Canada (NCT00482677).

It should also be noted that intravenous temozolomide has recently became available as an option for elderly or otherwise impaired patients who cannot swallow capsules or comply with an oral regimen.[116]

Pseudo-Progression

Pseudo-progression confounds interpretation of imaging performed in the first several months following completion of RT. Descriptions of "pseudo-progression" appeared as early as 1979, when Hoffman et al[117] described patients treated with RT and carmustine. Among patients thought to have experienced disease progression immediately following irradiation, nearly half were shown to have improvement or at least stabilization on subsequent brain imaging.

A report in 2004 described that approximately one third of patients with gliomas stabilized or improved with no change in management.[118] Chamberlain et al[119] reported histologically proven treatment injury rather than disease progression in approximately 50% of patients with symptomatic resectable lesions felt to represent worsening disease

following concurrent RT and temozolomide. The incidence of pseudo-progression has been reported to be as high as 75%, in selected subsets of patients with GBM.[84,120,121] Pseudo-progression rather than "true" progression may also correlate with *MGMT*-promoter methylation,[120] although this has not yet been prospectively validated.

Multiple imaging techniques have been explored to delineate radiographic pseudo-progression from true progression.[120,122-126] However, at this time, histologic analysis is the only validated method of distinguishing the two diagnoses, and even that has its limitations because of sampling issues, and difficulty in interpreting tumor cell viability posttreatment.[127]

It is presumed that the incidence of pseudo-progression is higher following concurrent RT and temozolomide than that following RT alone, although supportive evidence is equivocal.[128] As chemoradiotherapy is now the accepted standard of care for newly diagnosed GBM, no prospective study is likely to study this definitively. One approach to dealing with this issue involves using the MRI study done following RT as a new baseline, unless there is surgical documentation of recurrent disease or clear worsening outside of the RT portal. This remains an area of active study.[129] It is also worth noting that the "stabilization" of the peritumoral vasculature induced by antiangiogenic agents can possibly lead to a reduction in the pseudo-progression event rate, and has sometimes been used to manage florid imaging changes, with or without clinical deterioration.

RECURRENT DISEASE

Chemotherapy

Efforts to treat recurrent disease with single agents, either cytotoxics or molecular-targeted agents, have generally been unsuccessful, at least in part because of the innate resistance, poor drug penetrability, and molecular complexity of the disease.[130] Some studies suggest the key may lie in identifying the patients most likely to respond based on molecular profiling of tumor tissue at recurrence.[131]

An exception is the use of agents that target vascular endothelial growth factor (VEGF) or VEGFRs. Bevacizumab, a monoclonal antibody against VEGF, is the most widely studied of these antiangiogenic strategies.

The "BRAIN" trial was a noncomparative Phase II study for recurrent GBM that randomized 167 patients to either bevacizumab alone or bevacizumab combined with irinotecan,[132] the latter regimen adopted from activity of that combination in colon cancer.[133] The 6-month PFS was 43% with bevacizumab and 50% with bevacizumab plus irinotecan.[132] Similar results were seen in a single-arm Phase II study conducted by the NCI.[134] None of these trials however provided categorical evidence of improved OS.

These results are far superior to those of prior available therapies. For example, the 6-month PFS following carmustine is approximately 15% to 20%.[135] Emerging data from the randomized Dutch BELOB (BEvacizumab vs. LOmustine in glioBlastoma, Or Both) study demonstrate the superiority of bevacizumab (10 mg/kg days 1 and 15 of 28) combined with lomustine (90 mg/m^2 to 110 mg/m^2 every 6 weeks) versus either alone in terms of 6-month PFS (16% for bevacizumab, 13% for lomustine alone, >40% for lomustine with bevacizumab).[136] Based on these results, EORTC 26101 has been redesigned to compare lomustine alone (110 mg/m^2) versus bevacizumab with lomustine (90 mg/m^2), specifically seeking a survival benefit in a Phase III context for recurrent GBM.

Trials of other VEGF/VEGFR inhibitors have been negative. For example, REGAL (Recentin in Glioblastoma Alone and With Lomustine) was a Phase III trial[137] that tested efficacy of Recentin (cediranib), a direct oral pan-VEGFR inhibitor after a prior promising Phase II study.[138] An interim analysis demonstrated median PFS was longer following cedirinib (92 days) or cedirinib and lomustine (125 days) than lomustine (plus placebo, 82 days). However, median OS was not longer with cediranib (8.0 months versus 9.4 months versus 9.8 months), and the PFS benefit did not reach the prespecified improvement goal; accordingly, the trial was declared negative and accrual terminated.[137]

Therefore, despite increased response rates and improved PFS, to date there are no data clearly demonstrating a survival advantage for the use of bevacizumab, and its major potential toxicities include thromboembolic disease, hemorrhagic consequences, and hypertension. In addition, almost all salvage treatments following progression on bevacizumab are ineffective,[41,139] and therefore, the timing of bevacizumab for either first or later recurrence remains controversial. Recent data suggest that deferring bevacizumab to a second or later recurrence does not shorten survival.[140] The potential toxicity, as well as the fear of inducing a more invasive tumor phenotype also tempers enthusiasm for use of this agent in newly diagnosed disease, especially in light of lack of survival benefit from the RTOG 0825[90] and AVAglio trials.[91]

Alternating Electric Fields

Finally, one nonchemotherapy approach has been explored using alternating electric fields, tumor treatment fields (TTF) generated by a current source on the scalp (NovoTTF). This therapy is hypothesized to affect the mitotic spindle and thereby reduce proliferation. A Phase III trial suggested noninferiority when compared to any one of several possible physician-chosen chemotherapy regimens (median survival 6.6 months versus 6.0 months, HR 0.86 [95% CI, 0.66 to 1.12], $p = 0.27$; 6-month PFS 21.4% versus 15.1%, $p = 0.13$) with less toxicity than chemotherapy.[141]

Favoring a role for the device in treatment of glioblastoma, in addition to the similarly of survival and fewer side effects, more responses were seen in the TTF arm, although the difference was not significant and the response rate was low regardless of treatment. These results led to accelerated FDA approval. It should also be noted that 31% of patients received bevacizumab as the comparator chemotherapy during treatment on study, and approximately 20% of patients in both arms had a bevacizumab refractory tumor, suggesting benefit of the device in such patients.

However, it should be noted the trial was formally negative. The primary endpoint was improvement in survival. The statistical design had 80% power to detect a 60% increase in survival (HR 0.63, $p \leq 0.05$), and this was not achieved. The study was neither designed nor powered for a noninferiority endpoint, and the lack of a difference in survival in this study is not necessarily the same as true noninferiority.

In addition, the requirement for device approval is less stringent than for a drug, and the trial design and results have been heavily criticized. For example, there was no placebo device used as a control. One explanation is the questionable ethics of randomizing patients to no treatment whatsoever had the design been chemotherapy compared with NovoTTF compared with placebo device. However, that could have been ameliorated by randomizing patients to a specific chemotherapy (such as a nitrosourea or bevacizumab or both) in combination with either NovoTTF or placebo device.

Therefore, a clear interpretation remains elusive. The device appears reasonably safe, and it may well be that NovoTTF was noninferior to various chemotherapies. However, it is equally plausible that neither the device nor the chemotherapies were

beneficial to the patients. A Phase III study for newly diagnosed GBM (without placebo control) is ongoing, and a trial evaluating survival benefit in bevacizumab refractory GBM is being designed through the RTOG Foundation.

Reirradiation

Focal RT approaches are often employed with limited volume recurrences. In a retrospective analysis of 95 patients with recurrent gliomas treated with the GliaSite device, the median survival time was 36 weeks.[142,143] However, whether this is a function of true benefit or patient selection has not been determined.

Fractionated RT to treat larger-volume recurrent disease has also been employed. Although there has been speculation from animal studies that neural tissue will recover from previous irradiation to a large extent once some time has elapsed (e.g., 1 year to 3 years),[144] no firm data quantify the degree to which one can assume that a "dose discount" exists. It is most likely that the damage from reirradiation is underestimated because the majority of patients do not live long enough to express such damage. A small study showed good short-term tolerance to intensity-modulated radiation therapy (IMRT) delivered in six daily fractions of 5 Gy each.[145] A recent single-arm trial from the Memorial Sloan Kettering Cancer Center (MSKCC) demonstrated reasonable safety and efficacy of combined bevacizumab and reirradiation using IMRT for small recurrent malignant gliomas.[50] No radionecrosis was observed and survival appeared to be prolonged relative to historic controls, suggesting that bevacizumab may not only treat radionecrosis[146] but might protect against it. Another approach was recently reported by investigators from Jefferson Medical College[147] who treated 147 patients with recurrent high-grade glioma to 35 Gy in 3.5-Gy fractions with stereotactic radiation therapy. This hypofractionated stereotactic radiation therapy (HSRT) approach was associated with a median survival time in excess of 10 months.

Based on the promising results from the MSKCC and Jefferson trials, RTOG 12-05 was recently opened for patients with recurrent GBM. The Phase II study, which will enroll approximately 180 patients who are bevacizumab-naive with recurrent disease, compares concurrent bevacizumab plus reirradiation (using a hypofractionated RT schema of 35 Gy in 10 fractions) to bevacizumab alone.

IRRADIATION TECHNIQUES AND TOXICITIES

Whole-brain radiation therapy (WBRT) has been replaced with partial brain techniques by consensus for almost all gliomas. Although the dose computation component of treatment planning requires CT imaging, effective image registration with MRI has made this the modality of choice for contouring. The notion of a dedicated MRI simulator has also been proposed as a valuable adjunct in the radiotherapeutic management of high-grade gliomas.[148] However, treatment plans based only on MRI are not able to take into account tissue electron-density variations, which may lead to slightly inaccurate dose calculations.

Patients are usually simulated after surgical wound apposition is reasonably stable and free of infection (generally, 10 days to 14 days after the operation). An immobilization mask is fashioned to reduce motion during and between fractions. The planning CT scan is extended to encompass the head and neck region to allow sufficient anatomic areas for proper image fusion and generation of high-quality digitally reconstructed radiographs (DRRs) and to permit the introduction of noncoplanar beams; ideally, the slice thickness should match that of the MRI used for fusion.

For high-grade gliomas, especially GBM, T1 contrast-enhanced sequences are used to define the gross tumor volume (GTV) and the T2 or FLAIR sequences plus a margin define the microscopic disease extent, or clinical target volume (CTV), which reflects the bulk of microscopic infiltration. To arrive at a planning target volume (PTV), both organ motion and setup error must be taken into account. Organ motion in the brain is quite minimal during therapy (e.g., <1 mm). The PTV may be further modified to exclude normal tissue in areas where gliomas are unlikely to infiltrate. Bokstein et al[149] recently demonstrated that when anatomic barriers such as the temporal bone can serve as a border to impede tumor spread, failure is likely to be seen in less than 5% of cases even when the customary 2-cm margins are *not added* to the abnormalities seen on MRI (Figure 27-7).

In general, there are two major schools of thought (with numerous institutional variations based on these) that provide guidance for the prescription of the radiation regimen. The RTOG approach is a biphasic technique that includes an initial PTV (PTV 1) followed by a second PTV (PTV 2) that represents the cone down. In the lexicon of the RTOG, the PTV 1 includes the T2 or FLAIR CTV with a margin and is treated to 46 Gy in 2-Gy fractions. The PTV 2 includes the T1-enhancing GTV with a margin and is treated to an additional 14 Gy. The EORTC recommends a single-phase technique using one treatment volume throughout the course of therapy. Table 27-2 shows the partial brain volumes advocated by several cooperative groups for the successive phases of partial brain irradiation.

With the advent of functional imaging tools (e.g., functional MRI [fMRI]) it may be possible to specifically modify irradiation doses to functional brain areas. Figure 27-8 displays a treatment plan wherein the region governing motor control (e.g., finger tapping) is delineated to enable an accounting for dose deposition. In this case, this region in the right hemisphere (i.e., governing tapping by the left upper extremity) is included in the high-dose region but the contralateral side is well spared; a major caveat here is that the dose-response relationships for various functional subvolumes in the brain are largely unknown, and therefore, this

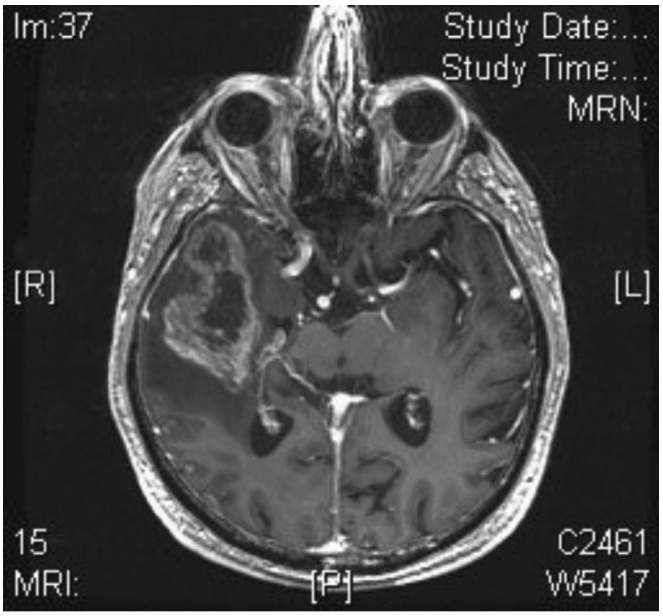


Figure 27-7 Lesion that could be treated without a full complement of margins because of anatomic barrier of the temporal bone.

information is of little practical dosimetric usefulness at this point in time.

In RTOG 08-25, it was noteworthy that approximately 80% of patients, irrespective of treatment arm, received IMRT. Lorentini et al[150] performed meticulous comparison of IMRT and three-dimensional (3D) conformal irradiation among patients treated for GBM. The IMRT plans consistently provided better target coverage than their 3D-conformal counterparts and yielded a statistically significant dose reduction to the healthy brain. The authors suggested that IMRT represents the superior technique when there are more than two regions of overlap between organs at risk (OAR) and the PTV.

Table 27-3 summarizes the tolerance of various OAR according to the new Quantitative Analysis of Normal Tissue Effects in the Clinic (QUANTEC) guidelines. Lawrence et al[151] postulated that the original estimates of Emami et al,[152] suggesting a 5% risk of chronic brain damage at 5 years when one third of the brain is irradiated to 60 Gy, were overly conservative. Instead, they hypothesized (Figure 27-9) that the dose correlated with a 5% risk of damage at 5 years following conventionally fractionated irradiation to the partial brain is 72 Gy, but data regarding subvolume and substructure sensitivity are not included in the QUANTEC assessment.

TABLE 27-2 Radiotherapy Volume Used in Current Clinical Trials

RT Dose	Block Edge Dosimetry Margin*	Source for RT Dose
46 Gy 14 Gy	T2 + 2 cm T1 + 2.5 cm	RTOG
60 Gy†	T1 + 2-3 cm	EORTC
50 Gy 10 Gy	T2 + 2 cm T1 + 2 cm	NCCTG

3D, *Three-dimensional;* EORTC, *European Organization for Research and Treatment of Cancer;* Gy, *Gray;* NCCTG, *North Central Cancer Treatment Group;* RT, *irradiation dose;* RTOG, *Radiation Therapy Oncology Group.*
**Both RTOG and EORTC prescribe dose to block edge (geometric) margin, whereas NCCTG prescribes dose to dosimetry (3D) margin.*
†CENTRIC studies: either RTOG or EORTC volumes and RT doses are used, at individual physician discretion.

There may sometimes be a tendency to overlook structures that, if damaged, would have led to noncatastrophic sequelae. For instance, although it is true that radiation-induced cataracts are easily repairable,[156] avoidance of entrance and exit dose to the eye may be a relatively simple means of preventing not only cataracts but also conjunctivitis and a dry eye, by sparing the lacrimal gland. Similarly, when one contours the ear canals, there is now a greater awareness of the risks of developing otitis externa as well as otitis media.

There are reports of cytopenias arising from cranial irradiation even among patients who have not received chemotherapy.[157] The hypothesized mechanism of this is either irradiation of circulating blood within the radiation portals, injury to marrow in the cranium, or the use of vertex beams that exit through the spinal axis. The latter mechanism has also been invoked to explain radiation-induced fatigue by some investigators.[158]

For tumors located in the temporal lobes, the exit dose to the parotid gland may cause xerostomia. Tumors in such locations may be best treated with IMRT because one of the success stories of the application of IMRT to the head and neck region is indeed the elimination of this bothersome side effect.

Overall, the aim is to achieve the treatment plan that most closely approximates the defined volumes and thereby produces the most conformal plans. Relatively low energy beams (e.g., 6 MV) are typically employed. In contrast to the irradiation of varying organs containing primary tumors, it is

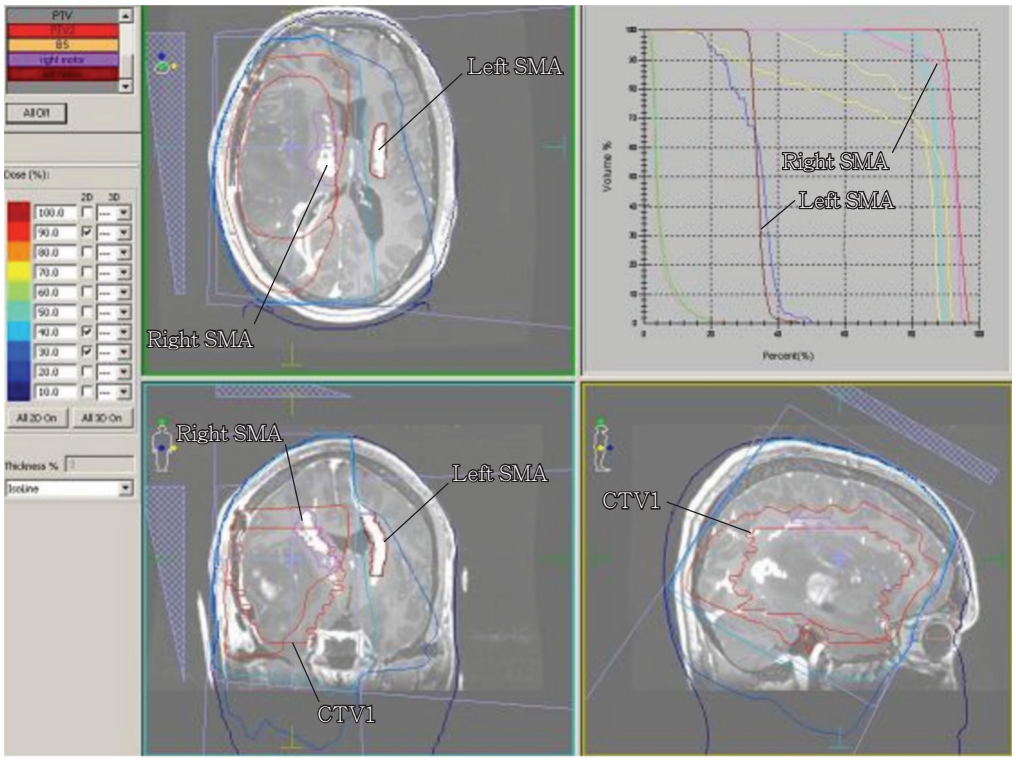


Figure 27-8 Treatment planning based on a functional MRI. Note delineation of the clinical target volume *(CTV)* as well as left and right somatomotor areas *(SMA)* controlling hand movements of the right and left upper extremities, respectively.

TABLE 27-3 Selected Organs at Risk for Treatment Planning of Malignant Glioma

Organ	Dose Limit	Comments
Brain parenchyma[151]	72 Gy	Brain appears to be more sensitive to fraction size > 2 Gy and to twice-daily radiation therapy
Optic apparatus[153]	60 Gy	12 Gy for single-fraction radiosurgery
Brainstem[154]	54 Gy	59 Gy if small volumes (i.e., 1-10 mL)
Parotid gland[155]	20 Gy 25 Gy	Severe xerostomia vis-à-vis sparing of one parotid gland Severe xerostomia vis-à-vis sparing of both parotid glands

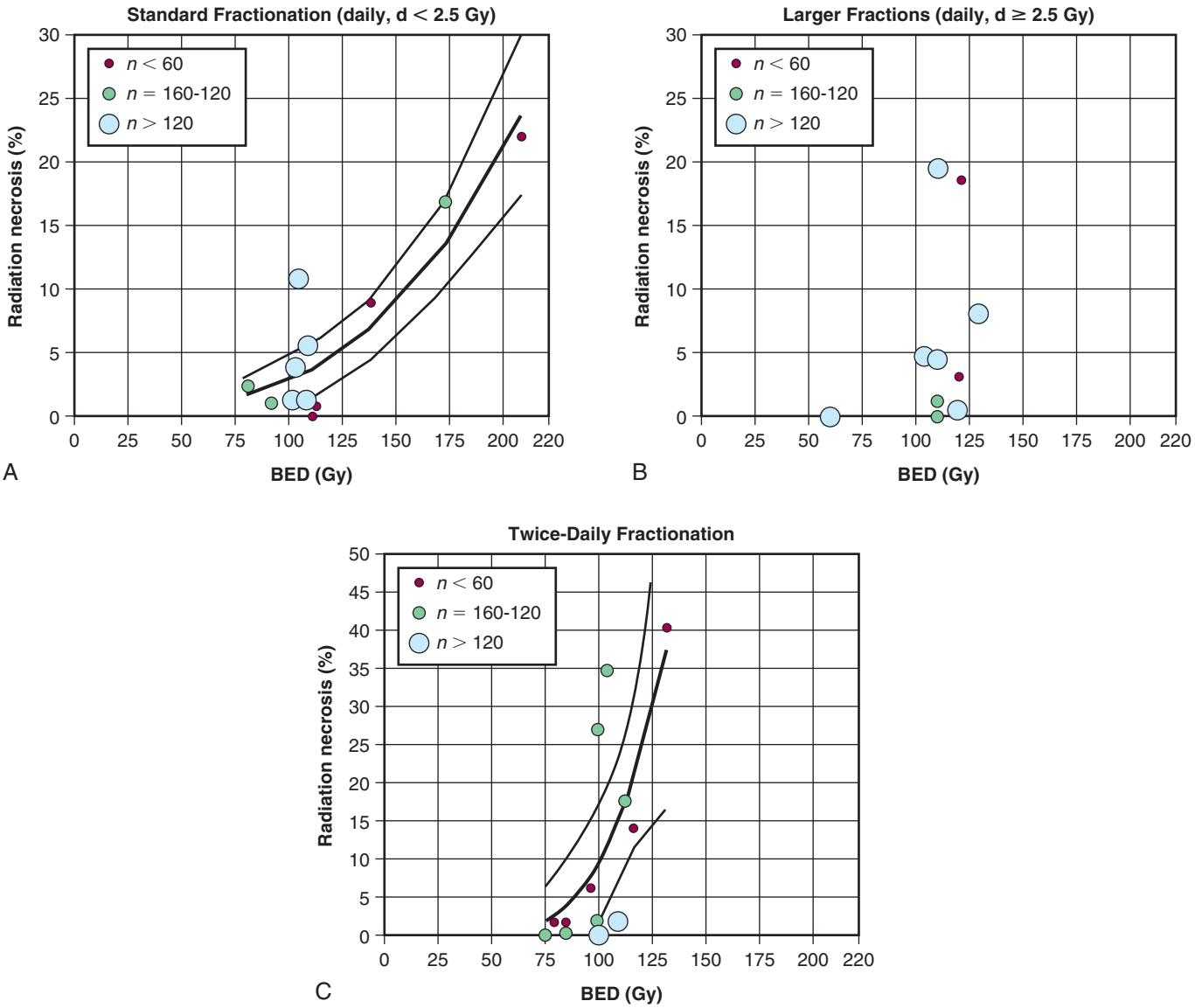


Figure 27-9 QUANTEC data for central nervous system tolerance based on the study in Lawrence et al. Relationship between biologically effective dose (BED) and radiation necrosis after fractionated radiotherapy. The Lawrence figure was done with a nonlinear least-squares algorithm using MatLab software (MathWorks, Natick, Mass.). The nonlinear function chosen was the probit model (similar functional form to the Lyman model). Dotted lines represent 95% confidence levels; each dot represents data from a specific study (Lawrence Table 2); *n* = patient numbers as shown. **A,** Fraction size less than 2.5 Gy. **B,** Fraction size 2.5 Gy or larger (data too scattered to allow plotting of "best-fit" line). **C,** Twice-daily radiotherapy. *Redrawn with permission from Lawrence YR, Li XA, Naqa I, et al: Radiation dose-volume effects in the brain. Int J Radiat Oncol Biol Phys 76:S20–S27, 2010.*

impossible to recommend a single idealized beam arrangement for high-grade gliomas. In this context, the role of proton therapy is being explored to further reduce dose to surrounding tissue distal to the tumor.

Miscellaneous Technique Issues

Despite the absence of level I evidence, IMRT is increasingly used, sometimes to escalate the dose and at other times to spare surrounding tissues or to explore the concomitant boost concept. However, clinical data supporting improved outcomes from IMRT in high-grade gliomas are essentially nonexistent.

Guidelines for tumor delineation and dose selection for WHO grade III gliomas are less well developed. In general, the FLAIR and T2 compartments are regarded as containing microscopic disease and therefore constitute the CTV. The typical dose is 59.4 Gy or 60 Gy in 1.8-Gy to 2-Gy fractions.

Toxicities of Radiation Therapy

Acute radiation morbidity includes fatigue, erythema, alopecia, headache, and rarely, nausea with or without vomiting; these are generally not severe and are usually self-limiting.[45] Some have cautioned that the combination of cranial RT and phenytoin as well as other anticonvulsants could give rise to the Stevens-Johnson syndrome,[159,160] but this dermatologic emergency is an exceedingly rare event, and the causal association between the two has not been established.

Late effects of radiation (e.g., somnolence and, especially, cognitive impairments) are more worrisome and may become manifest many years later.[161] The impact of partial brain irradiation on neurocognitive decline continues to be a hotly debated topic. The confounding factor is always the extent to which there is baseline cognitive impairment or decreased mentation secondary to tumor. Hippocampal sparing may emerge as a method to reduce the risks of neurocongnitive injury as it appears to do in the treatment of brain metastases with WBRT.[162]

Brain necrosis is a serious and uncommon late toxicity, and recently bevacizumab has been explored as a treatment.[146] In a small trial, all patients showed improvement of MRI abnormalities as well as a reduction in corticosteroid requirements following treatment with bevacizumab.[163]

We currently estimate the risk of normal tissue damage based on the most sensitive 5% of the population. Accordingly, we bias our recommendations in a manner that is not germane to most individuals, and preliminary efforts at predicting the likelihood of toxicities based on risk are ongoing.[164,165]

TREATMENT ALGORITHM, CONTROVERSIES, CHALLENGES, AND FUTURE POSSIBILITIES

Treatment Algorithm

For adults up to age 70 years with newly diagnosed GBM, the current standard of care is safe maximal surgical resection (with or without Gliadel wafer implantation) followed by concurrent EBRT (approximately 60 Gy in 30 fractions) with temozolomide and followed by at least 6 months of adjuvant temozolomide (Figure 27-4). For suspected progression that occurs within 3 months of completing RT, the possibility of pseudo-progression should be strongly considered.[166] Relapsed disease may be treated with re-resection, second-line chemotherapy, or experimental therapy in a clinical trial. Reirradiation is also a possibility but is used infrequently. Bevacizumab is approved for relapsed disease, as are carmustine wafers and Gliasite brachytherapy.

For newly diagnosed anaplastic gliomas, RT is typically administered as part of the initial therapy. Some advocate chemotherapy first, especially in 1p19q codeleted anaplastic oligodendroglial tumors.[12,13] Based on randomized trials, RT before and after PCV chemotherapy is clearly superior to RT alone for patients with 1p19q codeleted anaplastic oligodendroglial tumors.[98,99]

Controversies

Treatment for elderly patients (variably defined as older than 60, 65, or 70 years of age, depending on the study) remains controversial. Patients with a good performance status and few comorbidities are often treated according to the same algorithm used for younger patients. However, abbreviated radiotherapy courses appear to be noninferior[107] and are often employed. Temozolomide alone using standard rather than intensified dosing is a reasonable treatment strategy for elderly patients with *MGMT*-methylated tumors based on comparisons to RT alone, specifically in patients for whom combined-modality therapy is a significant challenge.[112,114] Definitive studies of combined RT and temozolomide restricted only to "elderly" patients have not been completed, and whether chemoradiation using a rapid course of RT is superior to RT or temozolomide alone is under investigation, but it must be borne in mind that the U.S. trials included patients even in their 80s when using combined-modality approaches.

Bevacizumab does not prolong survival when added to RT and temozolomide for newly diagnosed GBM.[90,91] Emerging data suggest that combining bevacizumab with nitrosourea therapy may be superior to bevacizumab or nitrosurea alone for recurrent GBM[136] and this is being further tested in Phase III study by the EORTC.

Treatment of anaplastic gliomas is an area of extreme controversy, with astrocytomas often treated as GBMs and a more variable approach used for oligodendrogliomas. Ongoing trials will attempt to define a standard algorithm based on the 1p/19q deletion status.

Challenges

Local control of high-grade gliomas remains a vexing problem. In addition, the increased recognition of pseudo-progression as an entity and the possibility of pseudo-response to antiangiogenic therapy such as bevacizumab[167] complicate matters further. A revised set of consensus criteria were recently developed in part to address some of these issues.[129,166] Certainly, correlative clinical follow-up to provide the proper perspective on the health status of the patient will never be abandoned, because imaging will always represent an imperfect surrogate for survival. Although new developments in diagnostic imaging continue to hold out promise for resolution of the diagnostic dilemmas faced by the neurooncology team, to date even the most sophisticated imaging studies (e.g., FDG PET, MRS) have not provided a consistently reliable solution to these and other vexing problems.

Future Possibilities

Prior dose-escalation trials for GBM, all conducted in the pre-temozolomide era, have been uniformly negative beyond 60 Gy. However, it is conceivable that the notion of dose escalation now needs to be revisited in the backdrop of control of microscopic disease by temozolomide enhancing the effect of focal dose-escalation, as well as the potential radioprotection offered by bevacizumab.[53]

The 5-year OS from the EORTC-NCIC study of patients with GBM treated with RT and temozolomide was approximately 10%, and for patients with favorable prognostic factors it approached 30%.[39] Moreover, a patient who lived more than 20 years following the diagnosis of GBM was described, perhaps the longest documented survivor.[168] He had been treated with surgery and partial brain irradiation with no concurrent or maintenance chemotherapy (59 Gy of 6-MV photons in conventional fractionation delivered via a shrinking-field technique). The authors speculated that the outcome may have stemmed from the fact that he had a favorable molecular profile (e.g., methylated *MGMT* promoter, *PTEN* wild-type, and *p53* positive, which the authors termed "triple positive," similar to the nomenclature of breast cancer). Whether this explained the long survival time is unclear. More importantly, these observations prove that one may strive to create and sustain hope for patients diagnosed with high-grade glioma.

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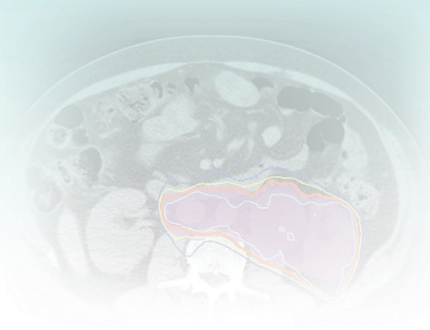
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CHAPTER

28 Benign Brain Tumors: Meningiomas and Vestibular Schwannomas



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Benign brain tumors are the most prevalent primary brain neoplasms. This chapter focuses on the two most common benign tumors, meningiomas and vestibular schwannomas.

MENINGIOMAS

INCIDENCE

Meningiomas comprise approximately 30% of all primary intracranial neoplasms, rendering them the most frequently reported primary intracranial tumor. The estimated prevalence is 97.5 per 100,000.

PATHOLOGY

The majority of meningiomas are benign (WHO grade I) and progress slowly, but despite this can produce considerable morbidity from local growth, edema, or progression to higher-grade histology. By current WHO standards, approximately 20% of meningiomas are atypical (WHO grade II) and can be difficult to manage long term. Less than 5% are anaplastic (WHO grade III), typically aggressive, malignant tumors.

STAGING EVALUATION

No formal tumor staging system has been adopted.

Meningiomas are optimally imaged by magnetic resonance imaging (MRI), which can be complemented, as needed, by computed tomography (CT) imaging to appraise bone involvement, hyperostosis, or intratumoral calcification. Biologic imaging for meningioma remains in its infancy.

PRIMARY THERAPY

The optimal primary therapy for meningiomas is surgery, which produces excellent results when gross total resection is safely accomplished.

Radiosurgery and fractionated external beam radiation therapy (EBRT) are used in selected patients, especially those with residual or recurrent disease, high-grade disease, or for whom the diagnosis is often based on imaging alone.

ADJUVANT THERAPY

Radiation therapy, either in single or multiple fractions, is often employed postoperatively following subtotal resection of a recurrent benign meningioma, a newly diagnosed or recurrent atypical meningioma, or an anaplastic meningioma.

There is less agreement on the adjuvant use of irradiation following subtotal resection of a newly diagnosed benign lesion, or following gross total resection of an atypical meningioma. In these settings, either immediate treatment or close surveillance are presently defensible.

LOCALLY ADVANCED DISEASE

Surgery, even if incomplete, is an important component of treatment for large, symptomatic meningiomas. Additionally, fractionated EBRT produces excellent long-term local control for large, unresectable or partially resectable, or complex meningiomas. With careful attention to tumor size and anatomy, single or multiple fraction radiotherapy may be used to target residual disease or, in selected cases, as primary therapy.

PALLIATION

Palliation can, on occasion, be the aim of treatment for patients, including those with advanced meningiomatosis, with refractory high-grade or multiply recurrent low-grade tumors that have failed standard treatments. There is a clear need for improved management options for such patients.

Harvey Cushing first used the term *meningioma* to describe tumors originating predominately from the meningeal coverings of the brain and spinal cord.[1] Although not disclosing a cell of origin, meningioma does aptly describe a range of clinically comparable histologic patterns and has endured. Though meningiomas are often approached as benign tumors, studies with long-term follow-up reveal that they are prone to infiltrate locally and to recur.[2] This chapter will consider the available data on intracranial meningiomas in a succinct fashion. For a more detailed review and lengthier bibliography, we refer you to the online version of this chapter.

ETIOLOGY AND EPIDEMIOLOGY

Based on surgical series, approximately 8000 meningiomas are diagnosed each year in the United States. Radiographic and autopsy studies suggest an even greater number of patients with clinically occult tumors.[3-5] A recent epidemiologic study revealed that meningiomas are the most frequently reported primary intracranial neoplasm, constituting about 30% of all brain primaries.[6,7]

The likelihood of developing a meningioma is proportional to age. Pediatric meningiomas are rare but are more likely to

exhibit an aggressive clinical course.[8-12] Meningiomas are most often diagnosed during the sixth to seventh decades of life.[13,14] However, the age-specific incidence continues to rise thereafter, even beyond 85 years of age.[6]

Although there are known associations with certain genetic, environmental, and hormonal risk factors, most meningiomas arise without discernible causation. Genetic factors will be discussed in the "Biologic Characteristics and Molecular Biology" section. Radiation exposure is a well-described environmental etiologic factor for meningiomas. These data stem largely from studies with long-term follow-up of atomic fallout or cranial and scalp irradiation for maladies such as tinea capitis.[15-19] Recent data suggests low-dose exposure, such as seen in dental x-rays, may also increase the risk of meningioma.[20] Indeed, radiation-induced meningiomas are among the most commonly reported secondary neoplasms.[16]

A hormonal role in meningioma induction, or growth promotion is supported by several findings. Meningiomas occur more frequently in females, at a ratio of 2 or 3:1. The incidence appears to increase with hormone replacement therapy, with long-acting oral contraceptives, and with obesity.[3,21-23] Moreover, tumor size or symptoms may progress during the luteal phase of menses or during pregnancy. Despite these observations, the precise role of hormones is unclear. In both sexes, more than 70% of meningiomas express progesterone receptors, up to 40% estrogen receptors, and nearly 40% androgen receptors as well.[3,24]

PREVENTION AND EARLY DETECTION

At this time, there are no known preventative interventions, and no evidence in favor of screening. For patients with small asymptomatic, incidentally detected meningiomas, surveillance, with the intent of ruling out aggressive clinical behavior, remains a judicious practice.

BIOLOGIC CHARACTERISTICS AND MOLECULAR BIOLOGY

Meningiomas occur more frequently in certain rare genetic conditions, such as type 2 neurofibromatosis (NF2).[8,25] Mutation in the *NF2* gene on chromosome 22q12 is the most common cytogenetic alteration. Nearly all NF2 meningiomas, most susceptible families, and about half of all meningiomas have alterations of the *NF2* locus.[26,27] Genetic losses of chromosomes 1p, 10, and 14q have been linked with malignant progression or recurrence, but have not yet been validated as independent prognostic markers.[3,26,27] Markers of tumor aggressiveness have been studied.[28-30] MIB-1 expression has been correlated with time to recurrence in some series,[31] but not in others.[32] Tumors lacking *NF2* disruptions but harboring oncogenic mutations in *AKT1* and *SMO* have been identified in therapeutically challenging meningiomas.[33]

PATHOLOGY AND PATHWAYS OF SPREAD

The World Health Organization (WHO) published its most recent grading criteria in 2007.[24] This system describes three grades and 13 histologic subtypes of meningioma (Table 28-1). This has simplified and further objectified the classification of meningioma, and strong associations between grade, relapse-free survival (RFS), and overall survival (OS) have been confirmed in subsequent studies,[24] but even with these improved criteria there remain disparities and interpretive license, particularly regarding the proportion of patients with grade II (atypical) histology. Classically, 5% of meningiomas were identified as atypical.[6] However, Perry et al, on whose work current grading criteria are largely based, found that more than 20% were WHO grade II.[24] Corroborating this proportion, Willis et al regraded patients using modern WHO guidelines and reported 20.4% as atypical.[34] Another recent analysis found that, whereas 4.4% of meningiomas were categorized as WHO grade II from 1994 to 1999, this steadily increased to 35.5% since 2004 (eFigure 28-1).[35]

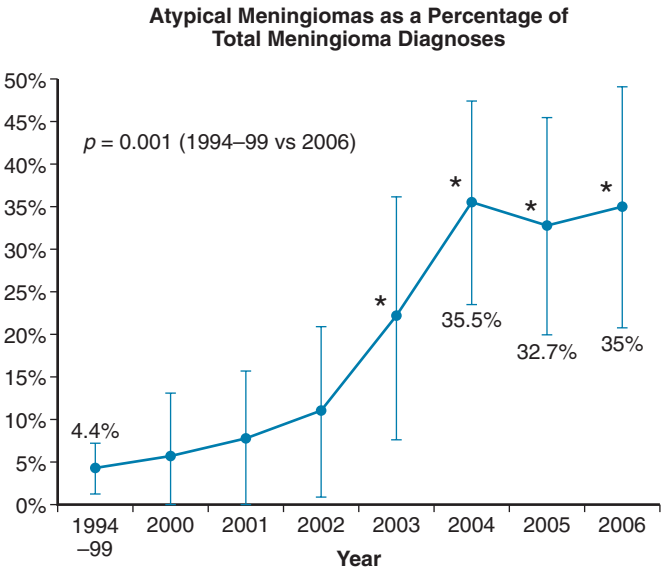
WHO grade is a dominant prognostic factor.[24,36,37] Compared to a grade I meningioma, a grade II tumor carries a seven- to eightfold increased recurrence risk at 3 to 5 years.[38] Grade III meningiomas are even more aggressive, with a high recurrence risk, and with 5-year OS of 32% to 64%.[3,9,23,39-43]

With reference to pathways of spread, meningiomas most commonly—although not exclusively—arise from dura and spread along dural planes. When located at the skull base, they often spread through skull foramina. Peritumoral vasogenic edema can develop from invasive tumor growth into surrounding brain, but more commonly there is no demonstrable brain invasion. In such cases it is widely accepted that edema results from vascular hyperpermeability, perhaps owing to disruption of the arachnoid membrane and pia mater, or to vasoactive substrates.[44] Regarding meningioma emanating from nondural sites, ventricular primaries are sporadically encountered, and rarely, meningiomas have been

TABLE 28-1 The 2007 World Health Organization (WHO) Criteria for Meningioma Grading

Grade I (Benign)	Grade II (Atypical)	Grade III (Anaplastic/Malignant)
Any major variant other than clear cell, chordoid, papillary, or rhabdoid Does not fulfill criteria for grades II or III	Frequent mitoses (≥4 per 10 hpf) **or** Three or more of the following: • Sheeting architecture • Hypercellularity (focal or diffuse) • Prominent nucleoli • Small cells with high nuclear cytoplasmic ratio • Foci of spontaneous necrosis **or** Additional subtypes/features • Chordoid meningioma • Clear cell meningioma • Brain invasion	Excessive mitotic index (>20 per 10 hpf) **or** Frank anaplasia defined as focal or diffuse loss of meningothelial differentiation resembling: • Sarcoma • Carcinoma • Or melanoma **or** Additional subtypes/features • Papillary meningioma • Rhabdoid meningioma

Modified from Perry A, Louis DN, Scheithauer BW, et al: Meningeal tumours. In Louis DN, Ohgaki H, Wiestler OD, et al, editors: WHO Classification of Tumours of the Central Nervous System, Lyon, 2007, IARC. Modified with the kind assistance of Arie Perry.
hpf, *High powered field.*



eFigure 28-1 Line graph depicting atypical meningiomas as a percentage of total meningiomas over time. Data points represent total percentage of WHO grade II meningiomas diagnosed in each calendar year (bars represent 95% CI).[35]

described originating from a variety of organ sites, including lung.[24,45,46]

CLINICAL MANIFESTATIONS, PATIENT EVALUATION, AND STAGING

Most data regarding the diagnosis and treatment of meningiomas are based on surgical series. As such, there is an inherent bias toward symptomatic tumors. Symptoms depend largely on the location of the lesion but can be influenced considerably by the presence of edema. Skull-base meningiomas can present with cranial nerve palsies or neuropathies.[47] Sphenoid wing meningiomas may present with seizures.[48]

With the increasing use of contrast-enhanced CT and MRI for head trauma, headaches, and such, the number of incidentally discovered meningiomas has risen. Incidentally discovered meningiomas are often smaller and may show little growth over time.[49-51] Although the clinical behavior of incidental meningiomas is not uniformly predictable, younger age (e.g., <60), larger size (e.g., >25 mm) at detection, male gender, and imaging findings (e.g., absence of tumor calcifications, presence of T2 hyperintensity, or pretreatment edema portend increased progression risk).[49]

Contrast-enhanced MRI is the imaging modality of choice for meningiomas. Tumors at the skull base may also be imaged with CT, to evaluate bony invasion, involvement of skull-base foramina, or hyperostosis. Additionally CT may identify calcifications, a finding predictive of more indolent growth.[3,7] MRI is generally superior for visualization of the contrast-enhanced lesion,[52-55] and MRI T2 signal hyperintensity may presage more aggressive behavior.[51,56,57]

PRIMARY THERAPY

Benign Histology (WHO Grade I)

Surgery

Surgery remains the mainstay, the treatment against which other management options are commonly judged, and the extent of surgical resection correlates with recurrence risk.[2,63,64] In 1957 Simpson reported a series of 265 patients treated surgically, giving rise to the system, still in widespread use, defining the extent of resection.[2] A description of the Simpson grades of resection and their associated crude recurrence rates is found in Table 28-2. Modern series employing current surgical and imaging techniques have generally validated this association.[14,23,65,66]

Surgery remains appropriate therapy for many meningiomas. Convexity meningiomas are often managed with surgery because these can typically be resected completely and without significant morbidity. However, even with convexity tumors, those surrounding or invading major draining veins or venous sinuses can pose considerable difficulty. Gross total resection of tumors involving the skull base is more challenging, but such may also be managed surgically. For meningiomas of the cavernous sinus and other select skull-base sites, close proximity to critical neurovascular structures renders radical resection potentially morbid. Optic nerve sheath meningiomas intricately involve the nerve's vasculature. Resection, which commonly leads to vision loss, is rarely advised, and primary radiation therapy has a favorable track record.

The major risk factors for postsurgical recurrence include tumor grade,[39] prior recurrence,[69] extent of resection,[2] and possibly presence of peritumoral edema.[70] These should be factored into decisions concerning postoperative surveillance versus irradiation.

TABLE 28-2 Simpson's Definitions of "Five Distinct Grades of Operation," With Respective Recurrence Risk*

Grade	Definition of Resection Extent	Recurrence
I	Macroscopically complete removal of tumor, with excision of its dural attachments and any abnormal bone	9%
II	Macroscopically complete removal of tumor, with coagulation of its dural attachments	19%
III	Macroscopically complete removal of tumor, without resection or coagulation of dural attachments, or of extradural extensions (e.g., invaded sinus or hyperostotic bone)	29%
IV	Partial removal, leaving tumor in situ	44%
V	Simple decompression or biopsy	N/A

Modified from Simpson D. J Neurol Neurosurg Psychiat 20:22–39, 1957.
N/A, *Not applicable.*
**Recurrences were identified "in a purely clinical sense to imply the reappearance of symptoms." Dr. Simpson calculated recurrence risk in a crude fashion, often excluding patients who had surgery within the prior 5 years.*

Postoperative Radiotherapy

Adjuvant radiotherapy is generally not recommended following gross total resection of a newly diagnosed grade I meningioma. Radiotherapy has often been used after subtotal resection, although considering the absence of randomized trials, differences in clinical practice are to be expected. Many patients are observed after subtotal resection.[71-73] However, a multitude of retrospective series has reported that radiotherapy improves local control after subtotal resection. Figure 28-1 illustrates long-term (typically 5 to 10 years) PFS outcomes from 35 series with 4389 patients following gross total resection alone, subtotal resection alone, subtotal resection with EBRT or, as will be discussed further, primary radiotherapy (RT).[3,74]

Goldsmith et al reported a series of 140 patients who received RT following subtotal resection and identified a dose-response.[39] Benign subtotally resected tumors had significantly improved PFS (93% versus 65% at 10 years) when a dose greater than 52 Gy was delivered. Moreover, Goldsmith[39,75] and Milosevic[76] found improved outcome with CT- or MRI-based treatment planning (Figure 28-2). A common approach following subtotal resection is 54 Gy in 27 to 30 fractions using CT- or MRI-based planning. It is informative to recognize that some studies evaluating RT after subtotal resection have found superior cause-specific survival (CSS) and possibly even OS compared to subtotal resection alone.[66,69,77]

Recurrent Meningioma

Recurrent meningiomas, including those that remain WHO grade I, display a considerably higher rate of recurrence after surgery alone than do newly diagnosed tumors.[23,66,69,78] Recurrent tumors often retain their original histopathologic grade,[79] nevertheless exhibiting more aggressive biologic behavior. In the setting of recurrence of a grade I meningioma, postoperative RT decreases the rate of tumor progression.[69,78] In a series by Taylor et al, the local control benefit of postoperative RT at time of first recurrence (88% versus 30% at 5 years) translated into an OS advantage (90% versus 45% at 5 years).[69] Miralbel et al reported 78% PFS at 8 years with surgery and postoperative RT after first recurrence compared with 11% with surgery alone.[78] A Phase II trial, which recently completed patient

Biologic imaging has been evaluated for meningioma, and although still considered experimental, may ultimately prove useful in determination of grade and tumor behavior,[58,59] in target delineation for radiation treatment planning,[60,61] and for differentiation of recurrence from treatment-related imaging findings.[62] Current limitations of biologic imaging include lack of specificity of compounds (for instance octreotide-labeled compounds, particularly when tumors are located in or around the sella) and lack of prospective data.

Sughrue et al have challenged the relevance of the Simpson grading scheme in the present era. They found no significant difference in 5-year progression-free survival (PFS) following Simpson grades I through IV resections, with respective 5-year PFS results of 95%, 85%, 88%, and 81% (p = ns).[67] Similar findings hade been reported by Condra and Oya.[57,66] These two studies, although identifying no difference in local control between Simpson grade I to grade III resections, did find shorter PFS with Simpson grade IV surgery.[57,66] In contrast, in a series of 391 convexity meningioma patients reported by Hasseleid et al, significant outcome differences were identified between Simpson grade 1, grades 2 + 3, and grades 4 + 5, supporting the continued applicability of Simpson's criteria.[68]

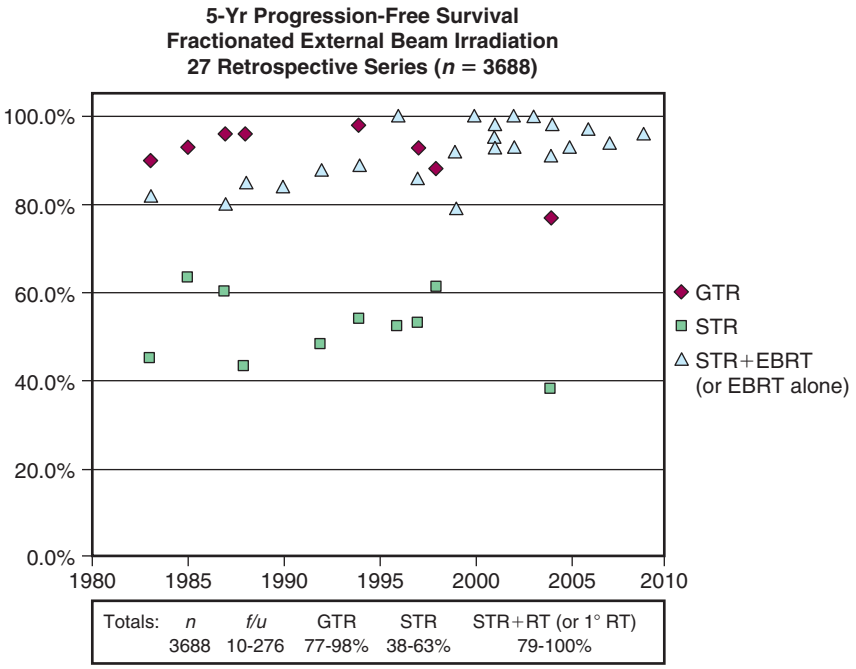


Figure 28-1 Scatterplot comparing 5-year progression-free survival following gross-total resection alone (GTR), subtotal resection alone (STR), and STR plus external beam radiation therapy (STR + EBRT) for patients with meningioma. The *x*-axis is the year of publication. Some of the patients plotted as STR + EBRT were treated with primary EBRT without surgery or histologic confirmation.

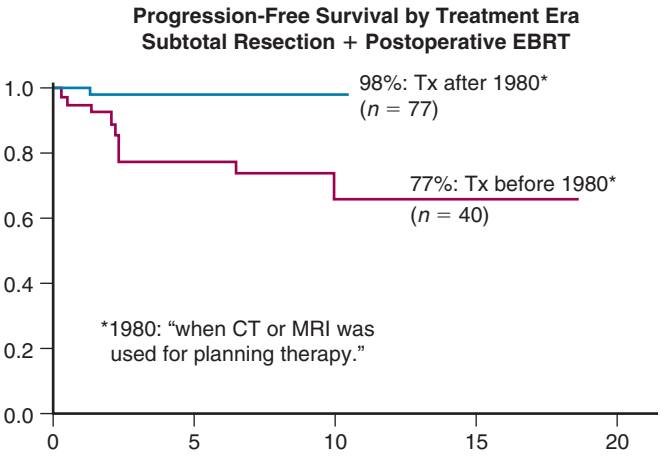


Figure 28-2 Progression free survival of patients with meningioma treated with external beam radiotherapy based on treatment era. Treatment planning techniques changed after 1980 with the advent of computed tomography (CT) and magnetic resonance imaging (MRI). Local control has likely improved secondary to better targeting of the tumor.[39]

accrual (Radiation Therapy Oncology Group [RTOG]-0539), categorized recurrent grade I tumors into an intermediate-risk cohort treated to 54 Gy in 30 fractions following either gross total or subtotal resection.

Definitive External Beam Radiation Therapy

Early reports of primary RT revealed inferior results, with local control rates on the order of 47%.[80] However, these included patients treated in the 1960s and 1970s, before the advent of current imaging and treatment planning paradigms. Many recent series using conformal techniques have corroborated excellent results from definitive radiotherapy with local control in excess of 90% at 5 to 10 years.[74,81-87] For biopsy-documented or suspected (image diagnosed) grade I meningioma, total doses have ranged from 45 Gy[74] to 57.6 Gy,[88] typically with 1.8 Gy to 2.0 Gy per fraction. The higher cumulative doses were predominately for larger or recurrent meningioma. For most patients doses in the range of 50 Gy to 54 Gy with standard fractionation have produced excellent results with modern imaging-based planning and treatment. Figure 28-3 depicts two examples of tumors appropriate for definitive EBRT. Recently, fractionated stereotactic series have been reported with excellent local control and functional outcome in such regions as the cavernous sinus.[74] eFigure 28-2 shows outcomes of definitive RT as compared with those of combined surgery with RT.

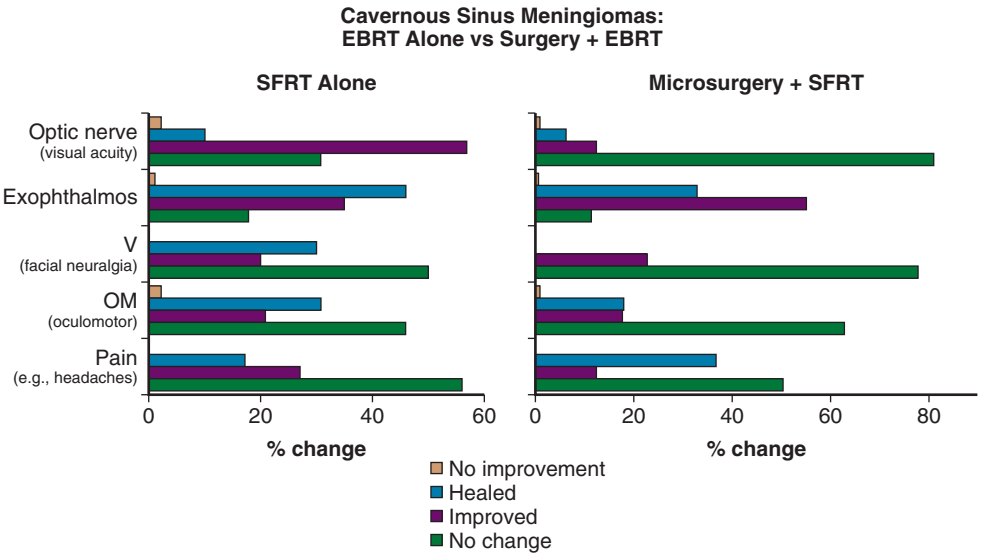
Optic Nerve Sheath Meningioma

Optic nerve sheath meningiomas represent only 1% to 2% of total meningiomas,[89-93] but they pose considerable clinical challenges because of their intimate association with the optic nerve and its vasculature. Historically, treatments included resection or observation, both leaving patients with poor functional outcomes. Accordingly, fractionated EBRT has been increasingly used.

Turbin et al reported 64 patients managed with surgery alone, surgery plus RT, RT alone, or observation. They found that RT alone resulted in excellent tumor control and was the only modality not leading to worsening of visual acuity.[94] Other series have confirmed excellent outcomes, with stabilization or improvement in visual acuity in up to 90%, and with local control exceeding 90%.[92,95-100] Doses of 40 Gy to 54 Gy with fractions of 1.6 Gy to 1.8 Gy have been standard and have produced results more favorable than observation, surgery alone, or surgery plus irradiation.[3,94,95,101] A recent single institution series by Brower et al reported 15 patients treated to a median of 50.4 Gy in 28 fractions and followed for a minimum of 5 years. RFS was 100%, and useful vision was retained in 86% of patients with useful vision prior to RT.[102]

Stereotactic Radiosurgery

Over the past two decades, stereotactic radiosurgery (SRS) has become an acceptable and frequently used modality and is generally considered suitable for meningiomas less than 3 cm to 4 cm in maximum diameter or less than 10 cc in volume, with distinct margins, with little or no surrounding edema, and at sufficient distance from critical normal tissues to permit



eFigure 28-2 Comparison of toxicity profiles of fractionated stereotactic radiotherapy (FSRT) alone versus combined microsurgery and FSRT.

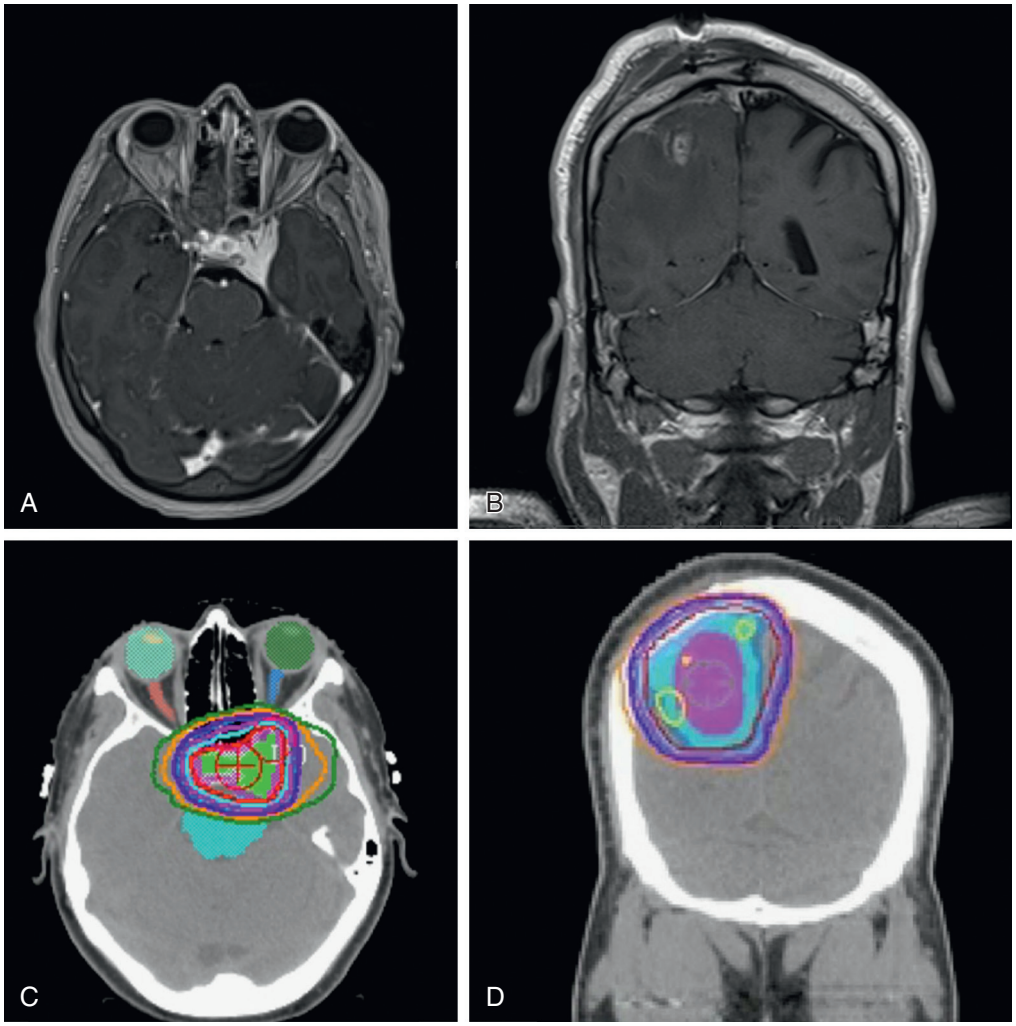


Figure 28-3 Examples of meningioma cases for which fractionated external beam radiotherapy (EBRT) would be indicated. **A,** shows an axial slice of a T1-weighted magnetic resonance imaging (MRI) of a patient with a cavernous sinus meningioma with optic nerve encasement. This patient was treated with fractionated EBRT and exhibited stable useful vision at last follow-up 1 year after therapy. **B,** shows an coronal slice of an T1-weighted MRI sequence of a patient with a resected grade II meningioma of the right frontal convexity with pathology demonstrating brain invasion. **C** and **D,** show the EBRT isodoses for these cases. The cavernous sinus meningioma was prescribed a dose of 52.2 Gy in 1.8 Gy fractions. The convexity grade II meningioma was treated to 55.8 Gy in 1.8 Gy fractions. The lesions remained controlled at 1 and 2 years, respectively.

TABLE 28-3 Comparative Analysis of Results with SRS and EBRT by Grade of Meningioma in Multiple Retrospective Series*

Grade/Treatment	*n*	Mean or Median Follow-up (mo.)	5-year PFS (%)	5-year OS (%)
Gr I—SRS	2281	19-103	75-100	82-100
—EBRT	3588	21-108	79-100	74-97
Gr II—SRS	119	27-48	26-72	40-83
—EBRT	345	32-66	20-68	28-91
Gr III—SRS	39	32-48	0-72	0-59
—EBRT	123	34-59	9-52	28-47

mo., *Months.*
**Five-year progression-free survival (PFS) and overall survival (OS) are compared for all series combined.*

appropriate dose restrictions.[65,103] Long-term local control has exceeded 85% in the majority of studies.[13,104-113] Table 28-3 compares the outcomes for SRS to those of definitive EBRT; this is not a direct comparison, but a compilation of retrospective series reported in the literature, and therefore inherently biased in terms of patient selection. Primary SRS appears to have equivalent local control outcomes to microsurgery with gross total resection for smaller meningiomas,[65,83,114-116] and in certain settings may produce superior results. A recent series by Kano et al demonstrated that there was no benefit from prior microsurgery for patients with cavernous sinus meningiomas.[117]

The University of Pittsburgh's initial publication of long-term outcomes used a median marginal dose of 16 Gy.[103] The rate of new neurologic toxicity was 5%. Since this report, it has become evident that lower single doses may be a sufficient. In the University of Pittsburgh's recent update of 972 patients, the median marginal dose was 14 Gy. Other reports have shown good local control with doses of 12 Gy or 13 Gy.[108,117-119]

Tumor volume has also been shown to predict for success with SRS. DiBiase has reported 5-year disease free intervals of 92% for patients with tumors ≤10 cc versus 68% for larger tumors.[120] Kondziolka et al similarly cited a decreased control rate with larger tumors.[103]

Patients at Higher Risk (WHO Grades II and III)

Atypical Histology (WHO Grade II)

Although there is general consensus on the need for an aggressive combined modality approach for anaplastic or malignant meningioma, considerable controversy exists regarding proper treatment paradigms for grade II meningiomas, particularly following gross total resection.[35,132] WHO grade II tumors carry considerably higher recurrence risk than their grade I counterparts.[3,13,43,66,133-135] Compared to grade I meningioma, recurrences of grade II tumors are seven- to eightfold more likely at 5 years, and there is an increased rate of mortality.[10] Although grade II tumors are often treated with combined surgery and postoperative irradiation, this has not been universally adopted.[40,136,137]

After incomplete resection, postoperative RT is typically recommended. This may be either fractionated EBRT or SRS. A relatively higher dose, as compared to grade I tumors, may be advisable. One study of EBRT demonstrated improved local control with doses exceeding 53 Gy.[39] Studies with proton therapy further inform the issue of total dose. Hug et al published results of 15 patients with atypical meningioma, some treated with combined photons and protons and others with photons alone, to total doses of 40 CGE (cobalt-Gray equivalent) to 72 CGE. Five-year local control was 90% with >60 CGE versus 0% <60 CGE. They noted improved outcome following combined photon and proton therapy, which was felt to be a reflection of higher doses with the use of protons.[42] Boskos et al published outcomes of 24 high-grade meningioma patients (79% WHO grade II), typically treated following incomplete resection. CSS at 5 years was 80% with >60 Gy versus 24% with <60 Gy, and there was a trend toward further improvement with >65 Gy.[138]

Aghi et al analyzed 108 patients following Simpson grade 1 resection of an atypical meningioma. One hundred patients were approached with initial surgery alone, and experienced a 5-year recurrence rate of 41% (eFigure 28-3). Recurrences led to reoperations (mean nearly three per recurrent tumor) and to worse survival. Eight patients received adjuvant fractionated EBRT, mean dose 60.2 Gy to the resection bed with a 1-cm margin. Among this small cohort there were no recurrences.[79] Although several series have demonstrated an advantage to adjuvant EBRT, not all series have shown such an advantage. In some series, survival appears to be worse in patients undergoing RT, possibly reflecting selection bias,[137,139] and results of prospective studies are eagerly anticipated. In the RTOG Phase II trial (RTOG-0539), patients with atypical histology were assigned to receive postoperative RT, 54 Gy in 30 fractions following gross total resection, or 60 Gy in 30 fractions after subtotal resection. The European Organisation for Research and Treatment of Cancer (EORTC) trial used higher doses of 60 Gy in 30 fractions after Simpson grade 1 to 3, or 60 Gy with a 10 Gy boost after Simpson grade 4 or grade 5 surgery.

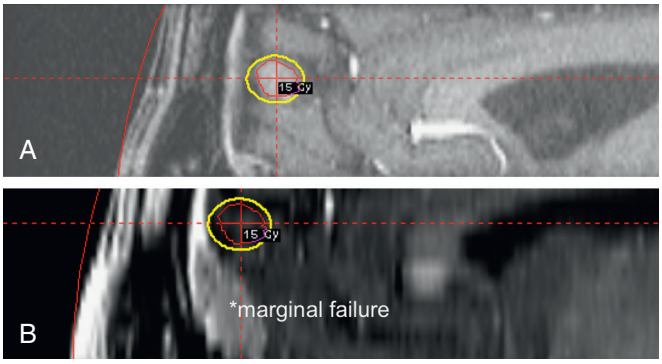


Figure 28-4 Example of a marginal failure after radiosurgery to a high-grade meningioma. **A,** Sagittal slice of T1-weighted magnetic resonance imaging (MRI) obtained during radiosurgical treatment planning; 15 Gy was delivered to the 50% isodose line which encompassed 100% of the meningioma *(red line)*. **B,** Sagittal slice of T1-weighted MRI obtained in follow-up demonstrating new enhancement along the dura adjacent to radiosurgical treatment volume.

Radiosurgery may also be considered for atypical tumors.[9,43,105,140-142] Stafford et al reported 14 WHO patients with grade II meningiomas treated with SRS, the majority of whom had recurrent tumors. With a median margin dose of 16 Gy, 5-year local control was 68%, compared to 93% for grade I lesions. The 5-year OS for grades I and II were, respectively, 92% and 76%.[13] Kano et al reported improved PFS with a single dose of 20 Gy compared to lower doses (2-year PFS 63.1% versus 29.4%) in a series of patients with recurrent tumors.[141] However, Hakim et al, using a median marginal dose of 15 Gy, achieved 4-year local control of 83%.[105] Moreover, with single fraction SRS, local control within the radiosurgical volume has been acceptable, but marginal failures remain problematic.[141,142] Figure 28-4 depicts an example of a marginal failure after SRS for an atypical meningioma.

Optimal dosing regimens, and choices among varying radiation modalities, are important matters for future study. Dose escalation may have a role for atypical meningioma, particularly following recurrence or subtotal resection, but caution with dose escalation is warranted. Using accelerated hyperfractionated EBRT with or without an SRS boost, Katz found a high rate of complications with no improvement in tumor control.[144] Future research will be strengthened by uniform adoption of WHO grading standards and by studies that clearly distinguish recurrent and de novo patients.

Malignant Histology (WHO Grade III)

Anaplastic meningiomas are rare, 2% to 3% of all meningiomas, with only about 300 newly diagnosed WHO grade III meningiomas in the United States annually.[145] They are aggressive and carry considerably higher recurrence risk and lower survival than their benign counterparts. Five-year recurrence rates in two large surgical series ranged from 72% to 78%.[41,135] Overall survival at 5 years ranged from 32% to 64%, and at 8 years 12%.[146] Failure of local control is often a cause of death.[40,42,76,147]

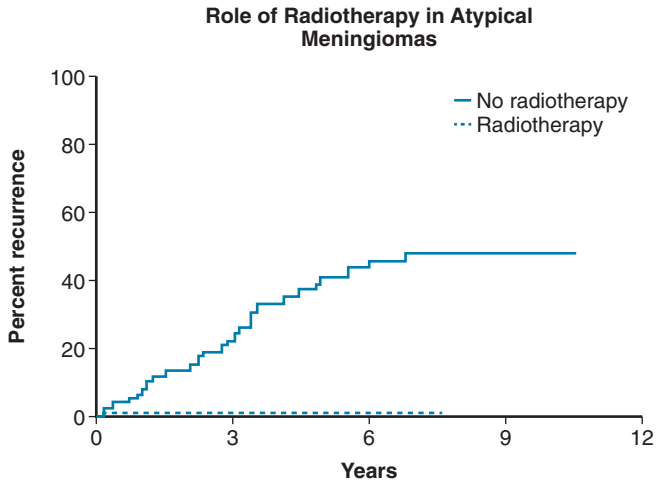
Patients with WHO grade III tumors are frequently treated with postoperative RT; however, given their relative rarity, this has not been tested in a clinical trial. A series from the Cleveland Clinic reported 13 patients over an interval of 23 years, 3 of whom received RT after initial surgery, and many more as salvage. They suggested that postoperative RT improved median survival (5.4 versus 3.4 years, $p = 0.13$) over surgery

Hypofractionated Stereotactic Radiotherapy

Hypofractionated stereotactic RT is a more recent development, consequential to technologies permitting accurate and repeated patient positioning with less rigid fixation. Recent data suggest that for larger volume tumors (e.g., >5 cc to 10 cc), the use of hypofractionation decreases the likelihood of posttreatment edema as compared to single fraction SRS.[121,122] Larger tumors, particularly those with pretreatment edema, may potentially be treated more safely with hypofractionated RT. Several series have now been reported and show equivalent local control to single fraction SRS or conventionally fractionated EBRT.[121,123-126] The most commonly reported fractionation scheme for treatment of benign meningioma has been 25 Gy in five fractions,[125,126] but more aggressive regimens, such as 24 Gy in three fractions have also been employed.[122]

Incidentally Detected Meningioma

With the increasing use of MRI, the number of incidentally discovered meningiomas has likewise risen. Most patients with incidental meningiomas can undergo a period of serial imaging follow-up and defer definitive therapy until tumor progression occurs. Several series document the natural history of incidental meningiomas.[56,57,127-130] The WHO grade and histologic features of an incidental meningioma are typically unknown, but the majority is likely WHO grade I because benign meningiomas are more common and more likely to be asymptomatic. Risk factors for tumor progression include younger patients, larger tumors at the time of discovery, and noncalcified tumors.[7,56] However, incidental meningiomas generally behave less aggressively and may be observed, withholding treatment until symptoms develop, sustained growth occurs, or concern about encroachment on sensitive structure arise.[131]



eFigure 28-3 Recurrence rates of atypical meningiomas after complete resection based on whether the patient received postoperative radiotherapy.

Huffmann et al treated 15 patients with SRS for atypical meningiomas, using a median prescription dose of 16 Gy.[140] Ten (67%) had recurrent tumors. At 18 to 36 months, 9 were progression-free, for a crude local control of 60%, similar to the 68% reported by Stafford et al.[13] However, in the Huffmann series, 6 of 15 patients (40%) progressed after SRS. Only 1 of the 6 failures was in field, and this occurred after a lower SRS dose of 15 Gy. However, all recurrences were central or marginal. Attia et al[142,143] assessed dose and conformality index (CI = treatment volume ÷ tumor volume) with SRS for residual or recurrent atypical meningioma. The median dose was 14 Gy (range 12 Gy to 18 Gy). Recurrence, defined as within 2 cm of the original tumor margin, developed in 48% of patients at 5 years, at a median of 25 months. CI was a significant predictor of recurrence ($p = 0.038$). Patients who recurred had a mean CI of 1.7 versus 4.6 for those who did not recur. When CI was considered, margin dose >14 Gy was not predictive of tumor control.[121,143] This raises the question whether the higher doses in some studies, for instance Kano et al,[141] might in part be a surrogate for a larger CI.

Skeie et al reported 100 patients with cavernous sinus meningioma, 7 of whom were categorized as grade II.[113] After SRS (mean 12.4 Gy), all seven atypical meningiomas progressed, five within 15 months, whereas only 9% of grade I meningiomas grew. Considering their entire group of 100 patients, larger meningioma volume, lower SRS dose, and suboptimal target coverage were predictive of recurrence. Emphasizing the dire implications of treatment failure, 6 of the 7 recurrent patients with atypical meningioma died of disease at a mean of 25 months after regrowth.[113]

A recent series from the Barrow Neurologic Institute reported no significant improvement in recurrence rate with RT (either SRS or fractionated EBRT) following "aggressive microsurgical resection" of atypical meningioma.[137] It is notable, however, that no patient in this study treated with a gross total resection and postoperative RT experienced recurrence, with actuarial data extending 7 to 9 years. Their median fractionated dose was 54 Gy with 1.8 Gy to 2.0 Gy per fraction, and the mean SRS dose was 14 Gy.[137]

alone.[146] Dziuk et al compared surgery alone to surgery plus RT in 38 patients with WHO grade III tumors. Nineteen (50%) received initial postoperative RT and experienced significant improvement in 5-year disease-free survival, 80% versus 15% for surgery alone ($p = 0.002$).[147] As with grade II tumors, there appears to be a dose-response with grade III meningiomas.[42,138,148,149] DeVries et al found an improvement in local control and survival with greater than 60 Gy.[148] Similarly, Boskos et al reported improved OS with doses exceeding 60 Gy and a trend toward further improvement beyond 65 Gy.[138] Nevertheless, as described previously with atypical meningioma, caution must be used with aggressive dose escalation. One report of accelerated hyperfractionation revealed a 55% rate of grade III to grade V toxicities.[144] The RTOG-0539 trial employed 60 Gy in 30 fractions for patients with malignant tumors (WHO grade III). The EORTC protocol used similar dose and fractionation following Simpson grade 1 to grade 3 resection, but added a 10 Gy in five fraction boost after Simpson grade 4 or grade 5 surgery.

Systemic Therapy

Systemic agents have not had a significant impact on the general management of meningioma to date. Several classes of agents have been evaluated, including hormonal therapy, chemotherapy, immune modulators, and targeted agents. Hydroxyurea has been used for several years, but radiographic responses are uncommon, and rates of progression for atypical and malignant histology have remained high.[158,159]

Because a majority of meningiomas express progesterone receptors, a randomized trial of the antiprogestin, mifepristone, versus placebo was conducted. Mifepristone resulted in increased toxicity but no improvement in response.[160] Several more recent trials employing novel growth factor agents have also been disappointing, with lack of a meaningful response rate or duration.[161,162] There has been recent interest in vascular endothelial growth factor (VEGF) inhibition for recurrent meningioma because of the high rate of VEGF expression and the fact that inhibitors such as bevacizumab may also treat peritumoral edema.[163] Somatostatin may have a measurable response rate in tumors that overexpress this receptor,[164] but more study is needed. There is a critical need for new approaches for patients who have anaplastic tumors, have failed multiple local therapies, or have diffuse and progressive meningiomatosis. It is likely that future investigation will incorporate biologic profiles to individualize and tailor treatment.

IRRADIATION TECHNIQUES AND TOLERANCE

Several methods of target delineation have been described, and there is controversy concerning the optimal method to account for microscopic spread along dura, bone, or into brain. With EBRT, margins as large as 2 cm beyond the gross tumor volume (GTV) have been described using modern imaging.[66] However, margins as small as 1 mm to 2 mm in fractionated stereotactic radiotherapy series have produced good long-term outcome, realizing that the follow-up in many such series is shorter, and the patients selected for such treatment may be inherently different.[81,82] Tight margins may be less applicable to meningiomas beyond grade I. Recent reports of radiosurgery for atypical meningiomas have found that increased conformality predicted for a higher rate of marginal failure.[141,143] In contemporary reports, a clinical target volume (CTV) margin of 1 cm to 2 cm for higher grade meningioma has been more common.

Dural Tail

A dural tail is a nonnodular, linear thickening of the enhancement that may extend from a meningioma on contrast-enhanced MRI. Targeting of the dural tail within the CTV is a subject of controversy. The dural tail was initially thought to result from direct tumor invasion into surrounding dura, though surgical series have found that the dural tail is composed almost entirely of hypervascular dura and is typically an imaging finding, not routinely visualized at surgery.[3,165-168] The Simpson resection grading scale predates MRI. Thus, it does not consider resection of the dural tail. Good results have been obtained from gross total resection alone, without specific attention to it. Furthermore, radiosurgical series have generally not targeted the dural tail.[3,13,103,106] In the recently completed RTOG and EORTC protocols, the dural tail was not targeted within the CTV. We will learn more about this topic from the reports of these trials.

Hyperostosis

Inclusion of hyperostotic bone within the GTV is also worthy of discussion. A Simpson grade 1 resection includes gross total resection of tumor, its dural attachments, and any abnormal bone.[2] Biopsy series have demonstrated a significant rate of bone involvement by meningioma in cases of hyperostosis,[169] and this is associated with a higher rate of recurrence.[170,171] This question needs to be addressed more thoroughly, but it is clearly justifiable to target hyperostotic bone within the treatment volume when this can be accomplished safely.

Toxicities of EBRT

The toxicities associated with EBRT are related to treatment volume and location. Many patients experience fatigue, and some have alopecia. Late toxicities include cataract formation, cranial nerve palsy or neuropathy, and panhypopituitarism can occur.[172,173] Rarely, patients experience symptomatic radionecrosis and may require long-term steroid therapy or surgical intervention.[39] Debus reported a series of 189 patients who received EBRT with modern fractionation schedules, treatment planning, and delivery techniques. The rate of grade 3 toxicities was 2.2%, even less in patients with no preexisting deficit.[81]

Cognitive decline remains a possible late effect, though this is controversial in the setting of partial brain irradiation and smaller treatment volumes.[174] Like most other sequelae, it has site-specific dose-volume relationships.[78,87,175] Temporal lobe dose predicts for cognitive decline,[176,177] and large treatment volumes are more likely to lead to symptomatic decline.[178] The likelihood of radiation-induced cognitive loss rises over time after brain radiotherapy. Cavernous sinus meningiomas, located just medial to the hippocampus, and sphenoid wing meningiomas, lateral to the hippocampus, may carry a higher risk of cognitive decline.[179]

Toxicities of Stereotactic Radiosurgery

The nature of the toxicities of SRS is also dependent on tumor size and location, and most toxicities are related to damage to nerves or to radiation-induced edema. Sensory nerves, such as the optic nerve, are more susceptible to injury than motor nerves. Fraction sizes of 10 Gy or less to the anterior visual pathway carry a 1% to 2% rate of optic neuropathy, but reported rates appear to rise with doses beyond 10 Gy.[13] However, a recent report from Japan suggests that point doses higher than 10 Gy may be acceptable when necessary.[180]

Radiation-Induced Meningioma

Radiation-induced meningiomas may be more clinically aggressive and multifocal.[16,18,150] Multifocal tumors have been reported to occur in 4.6% to 29% of patients with radiation-induced meningiomas,[16,18] compared with roughly 3% of patients with sporadic meningioma.[73] Reports have also suggested a higher incidence of atypia, with WHO grade II or grade III histology from 24% and 38%.[151] The latency between radiation exposure and the development of a secondary meningioma ranges from 2 years to 63 years, though exposure to radiotherapy at a young age,[151] larger radiation fields, and higher doses[152] tend to predict for a shorter latency.

The management of such tumors centers on surgical resection, if possible. Aggressive resection in the setting of previously irradiated tissue, however, poses a risk of wound breakdown and cerebrospinal fluid (CSF) leak. Full-dose re-irradiation has been reported in some cases of recurrent meningioma and can conceivably be accomplished, given the longer latency between treatment courses.[76,153-155] Radiosurgery has also been used.[156,157] Kondziolka described 19 patients with radiation-induced meningioma treated with radiosurgery and reported a control rate of 75% with acceptable toxicity. The advantage of the stereotactic approaches is that they can potentially deliver a curative dose of radiation while sparing the increased cumulative integral dose delivered by conventional EBRT. The disadvantage of a focal approach, however, is the high out-of-field failure caused by meningeal cancerization from the prior radiation,[157] or to microscopic tumor deposits outside the enhancing target.

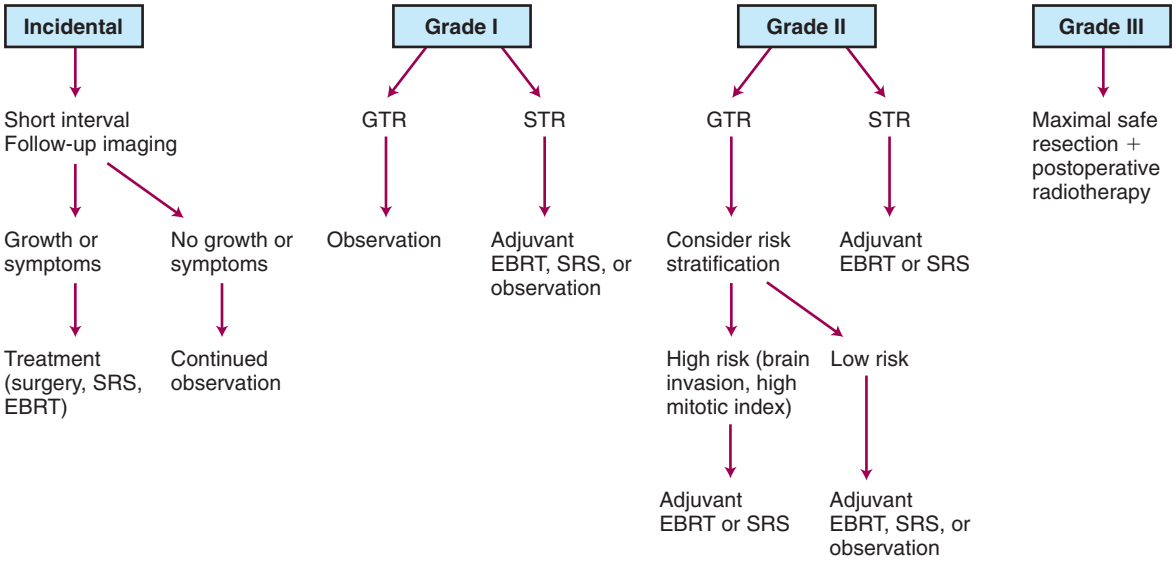


Figure 28-5 **Treatment algorithm for meningiomas** based on grade and operative status.

TABLE 28-4 Meningioma Radiotherapy Suggestions

	Modality	Dose	Fractions	GTV	CTV
Grade I	EBRT	50.4-54 Gy*	28-30	Enhancing tumor on postop MRI	Same as GTV
Grade II	EBRT	54-55.8 Gy	30-31	Enhancing tumor with tumor bed on postop MRI	1-cm expansion on CTV
Grade III	EBRT	59.4-63 Gy	33-35	Enhancing tumor with tumor bed on postop MRI	2 cm expansion on CTV (reduce to 1 cm at 54 Gy)
Grade I	SRS†	12-14 Gy	1	Enhancing tumor	Same as GTV
Grade II	SRS	14-18 Gy	1	Enhancing tumor	Same as GTV
Grade III	SRS	>14 Gy	1	Enhancing tumor	Same as GTV

CTV, *Clinical target volume;* EBRT, *external beam radiation therapy;* GTV, *gross tumor volume;* MRI, *magnetic resonance imaging;* postop, *postoperatively;* SRS, *stereotactic radiosurgery.*

**Good outcomes have been obtained with 45 Gy for optic nerve sheath meningiomas.*

†*SRS, for present purposes assumes single fraction radiosurgery. Good results have been reported with fractionated stereotactic treatments as well, for instance 5 Gy × 5.*[190]

Edema is a more common complication with single-fraction SRS than with standard fractionation EBRT.[3,96,119,181-185] Several risk factors have been identified for SRS-induced edema including higher marginal dose, tumor diameter greater than 4 cc, presence of pretreatment edema, and nonbasal location, including periventricular or parasagittal.[3,56,103,119,182,186,187] One report found that parasagittal meningiomas had a greater than fourfold increased risk of peritumoral edema after SRS.[188]

Response Assessment

No official response assessment criteria are yet available for meningioma, although Response Assessment in Neuro-Oncology (RANO) has formed a working group to address this issue. Because meningiomas are commonly slow growing, they are also commonly slow to respond to RT and will in most cases leave a residual imaging abnormality after treatment. With single-fraction SRS, the University of Pittsburgh reported that within the first four years, 58% of tumors had diminished in size, whereas by 10 years, 88% of tumors had decreased.[189] The University of Heidelberg reported a series of meningiomas treated with fractionated stereotactic radiotherapy in which 70% of patients experienced no change in tumor volume with a median follow-up of 5.7 years.[88]

The rates and time frames of response with nonbenign meningioma have not been thoroughly described. However, grade II tumors have a greater rate of both in-field and marginal failure, and this failure pattern is important in assessing response for grade II or grade III tumors after either fractionated EBRT or SRS.[142]

TREATMENT ALGORITHM, CONTROVERSIES, AND CLINICAL TRIALS

A treatment algorithm is presented in Figure 28-5. Corresponding dose and treatment volume guidelines are contained in Table 28-4. These depict a literature-based approach defined by risk strata. However, many controversies persist. There is substantial debate concerning which patients to observe, which to treat with primary fractionated EBRT or SRS immediately following surgery or indeed instead of surgery, and the selection of patients for postoperative RT. Gross total resection of a benign (WHO grade I) meningioma is considered definitive therapy, but there is less agreement following subtotal resection, or following gross total resection of a grade II meningioma. Subtotally resected grade II meningiomas are frequently managed with irradiation, and all grade III meningiomas demand aggressive treatment, irrespective of resection extent. Despite aggressive management, however, current approaches are insufficient for many high-risk patients. New systemic and biologic agents are needed.

Contemporary Trials

Two cooperative group trials have evaluated the role of RT in the management of meningioma. The EORTC phase II trial (22042-26042) evaluated PFS in patients with grade II and grade III meningioma. It stratified patients based on degree of resection and WHO grade. Patients with Simpson grade 1 to grade 3 resection receive standard postoperative EBRT (60 Gy in 30 fractions), whereas those with lesser resection receive an additional boost (10 Gy in 5 fractions).

The RTOG 0539 trial adopted a risk stratification approach to the postoperative management of meningiomas. Low-risk patients, including gross totally or subtotally resected WHO grade I tumors, were observed. Intermediate-risk patients, including recurrent WHO grade I, and gross totally resected WHO grade II tumors, received postoperative EBRT, 54 Gy in 30 fractions. High-risk patients, with WHO grade III, or subtotally resected or recurrent WHO grade II tumors, received 60 Gy in 30 fractions. Pending the reports from these cooperative groups, these may serve as reason approaches to patients with meningioma.

VESTIBULAR SCHWANNOMAS

INCIDENCE

Vestibular schwannomas occur with an estimated incidence of 0.6 to 0.8 per 100,000 person-years. This is a disease primarily of adults and represents approximately 8% of brain tumors and the vast majority of tumors of the cerebellopontine angle. The exception would be patients with NF2, in which pediatric presentations occur. Bilateral vestibular schwannoma is a pathognomonic feature of NF2.

BIOLOGIC CHARACTERISTICS

Both sporadic and NF2-associated tumors commonly have biallelic inactivating mutations of the tumor suppressor gene *NF2* (chromosome 22q12), which encodes the cytoskeletal protein merlin.

STAGING EVALUATION

The recommended workup includes neurologic examination with careful attention to cranial nerve function, contrast-enhanced MRI, formal audiometric testing, and other testing as clinically indicated.

PRIMARY THERAPY AND RESULTS

Tumors may be managed with microsurgical resection, SRS to 12 Gy to 13 Gy, or fractionated stereotactic radiation therapy (FSRT) using either a standard approach (i.e., 45 Gy at 1.8 Gy per fraction) or a hypofractionated approach (i.e., 20 Gy at 4 Gy per fraction). Local control is more than 90% with all treatment modalities.

Published reports of treatment-related toxicities such as hearing loss, facial neuropathy, and trigeminal neuropathy or neuralgia are generally less frequent with FSRT or expertly performed SRS in appropriately selected patients.

Surveillance MRI scans performed in the first few years after definitive RT may not accurately depict a tumor's ultimate response to treatment because there can be variability in the size and appearance of a schwannoma during this time.

There are no prospective randomized trials to guide treatment decisions, and multidisciplinary evaluation of each patient is an integral component of appropriate management.

INTRODUCTION

Vestibular schwannoma, previously erroneously referred to as acoustic neuroma, is a benign neoplasm originating from the epineural Schwann cells of the vestibular portion of the eighth cranial nerve. Most cases are unilateral and sporadic, although bilateral vestibular schwannoma is pathognomonic for NF2. Although these tumors are rarely fatal, symptoms such as hearing loss, tinnitus, imbalance, and cranial nerve deficits can significantly impair the quality of life. Management options include observation, resection, SRS, or FSRT.

ETIOLOGY AND EPIDEMIOLOGY

The incidence of vestibular schwannoma is increasing and has recently been estimated at 1.2 per 100,000 population per year.[191] More widespread use of intracranial imaging with CT and MRI has contributed to the increased incidence because vestibular schwannomas are identified on MRI in 0.2% of asymptomatic patients.[4] Roughly 85% to 90% of cerebellopontine angle tumors are vestibular schwannomas. Some cases can be attributed to genetic syndromes such as NF2, which pathognomonically presents with bilateral vestibular schwannomas. More than 90% of cases, however, are sporadic and unilateral. Risk factors for the development of sporadic vestibular schwannomas are poorly understood at present, with limited and highly controversial studies suggesting that risk may be increased with cell phone usage,[192] occupational exposure to loud noise (hours), and dental x-rays.[193] The median age of patients at diagnosis is 50 years; however, patients with NF2 typically manifest symptoms by 20 years to 30 years. In one report, it is suggested that in those with 20 or more years of occupational exposure, there is a 10-fold increase in the risk of developing vestibular schwannoma.[194]

BIOLOGIC CHARACTERISTICS

Biallelic inactivating mutations of the tumor suppressor gene *NF2*, located on chromosome 22q12, are commonly found in both sporadic and *NF2*-associated vestibular schwannomas.[195] *NF2* encodes the cytoskeletal protein merlin, which functions in embryonic development, cell adherence, maintenance of cell membrane stability, and cell proliferation. Recently, merlin has been hypothesized to suppress tumorigenesis by translocating to the nucleus to inhibit $CRL4^{DCAF1}$, an E3 ubiquitin ligase.[196] Merlin interacts with a wide variety of cell receptors and signaling pathways, such as EGFR, ERBB2, CD44, Rac, Ras/raf, and Wnt, providing opportunities for investigation of targeted therapies for vestibular schwannoma.[197] VEGF and VEGFR-1 have also been shown to be expressed at high levels in vestibular schwannoma.[198]

PATHOLOGY AND PATHWAYS OF SPREAD

Vestibular schwannomas are histologically similar to schwannomas arising from other cranial and peripheral nerves. Their histologic appearance is characterized by alternating zones of dense and sparse cellularity, known as Antoni A and B areas (Figure 28-6).

Most vestibular schwannomas arise from the superior and inferior branches of the vestibular portion of the eighth cranial nerve, within the internal auditory canal. It is rare for these tumors to originate along the cochlear nerve. Over time, progressive tumor growth may fill the internal auditory canal and extend into the cerebellopontine angle, causing compression of the brainstem and other nearby cranial nerves, most commonly the trigeminal and facial nerves.

The natural history of vestibular schwannoma is typically characterized by gradually progressive growth with gradual sensorineural hearing loss and potentially other cranial nerve deficits. A subset of patients can present with sudden hearing loss. Less than 5% of tumors may regress slightly with surveillance.[199] The average growth rate has been estimated at 1 mm to 2 mm per year for sporadic lesions[199,200] and 3 mm per year for patients with *NF2*-associated lesions.[201] Tumor size and growth rate do not consistently correlate with hearing loss, however. Cystic schwannoma is a well-recognized tumor subtype that tends to behave more aggressively, invading and splaying adjacent cranial nerves. It is rare for malignant degeneration to occur.

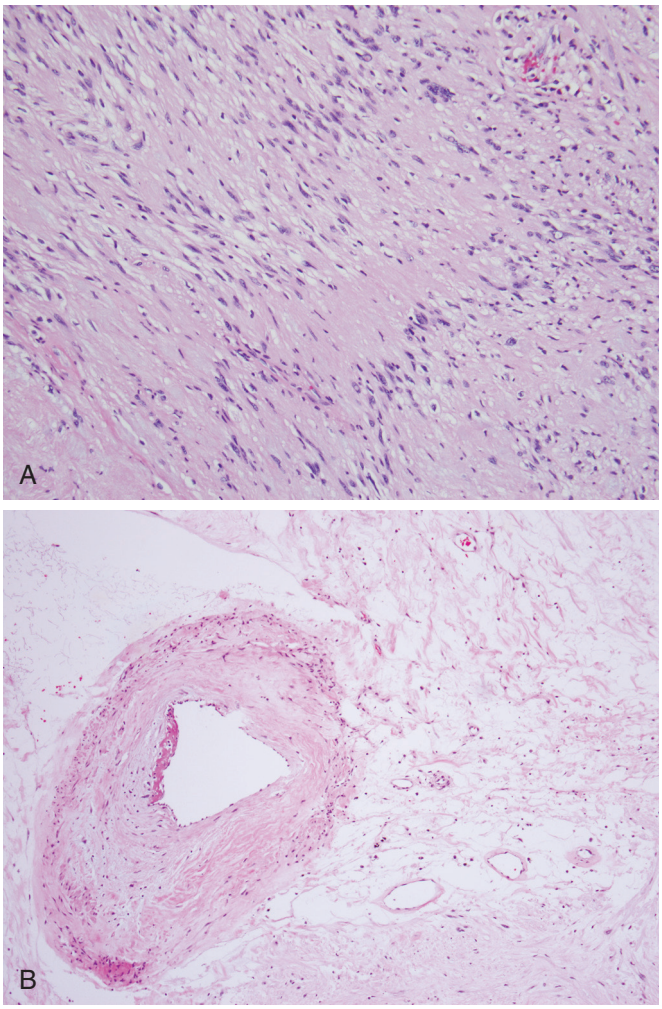


Figure 28-6 Histopathology of vestibular schwannoma. Tumors are well-circumscribed with areas of hyper- and hypocellularity (Antoni A and B areas) and contain thick-walled vessels. **A,** depicts hypercellularity (Antoni A area). **B,** depicts hypocellularity (Antoni B area) adjacent to a hypertrophic blood vessel.
Courtesy of Michael Castro, M.D.

CLINICAL MANIFESTATIONS, PATIENT EVALUATION, AND STAGING

Vestibular schwannoma is increasingly detected as an incidental finding on MRI or CT performed for other reasons. MRI is the imaging method of choice for visualizing vestibular schwannomas, which typically appear as contrast-enhancing lesions originating within the internal auditory canal on T1-weighted MRI images (see Figure 28-7, *A* and *B*). The extent of tumor may be described using the Koos grading system (Table 28-5).

Symptoms associated with vestibular schwannoma are related to the tumor's size and location with respect to nearby critical structures. When tumors are symptomatic, patients may complain of hearing loss (95% objective, 66% subjective), tinnitus (63%), imbalance or vertigo (61%), facial numbness or pain (17%), facial paresis or taste disturbance (6%), other cranial nerve deficits, or cerebellar dysfunction.[203] Involvement of the cochlear nerve is primarily responsible for hearing loss and tinnitus. Although involvement of the vestibular nerve results in unsteadiness, facial numbness is primarily the result of the trigeminal nerve being affected. In the rare instance of taste disturbance or facial paresthesias, facial nerve involvement is the culprit.

Sensorineural hearing loss classically affects high frequencies preferentially and may therefore be mistaken for noise- or age-related hearing loss. An example of a typical patient's audiogram is shown in Figure 28-8, along with the two mainstream classification systems for audiogram findings specific to patients with vestibular schwannoma, namely the Gardner-Robertson[204] and American Academy of Otolaryngology–Head and Neck Surgery (AAO–HNS)[205] methods. As a rule of thumb, patients whose speech discrimination score is 50% or less at 50 dB or more may not benefit from an approach focused on the preservation of hearing.[206] Each case must be considered individually, however, particularly in patients with bilateral vestibular schwannomas or other causes of contralateral hearing compromise.

Facial nerve function is characterized clinically by the House-Brackmann grading scale (Table 28-6). When clinically indicated, additional studies may be performed, such as facial nerve electromyography, caloric testing, or electronystagmography (Table 28-7).

TABLE 28-5 Koos Staging System for Vestibular Schwannoma

Stage I	Small intracanalicular tumor
Stage II	Small intracanalicular tumor with extension into cerebellopontine angle
Stage III	Larger tumor occupying cerebellopontine cistern without brainstem displacement
Stage IV	Extremely large tumor with marked displacement of brainstem and cranial nerves

Adapted from Koos W: [Microsurgery as a condition for progress in the treatment of acoustic nerve neurinoma]. Wien Med Wochenschr 127(8):246–249, 1977.[202]

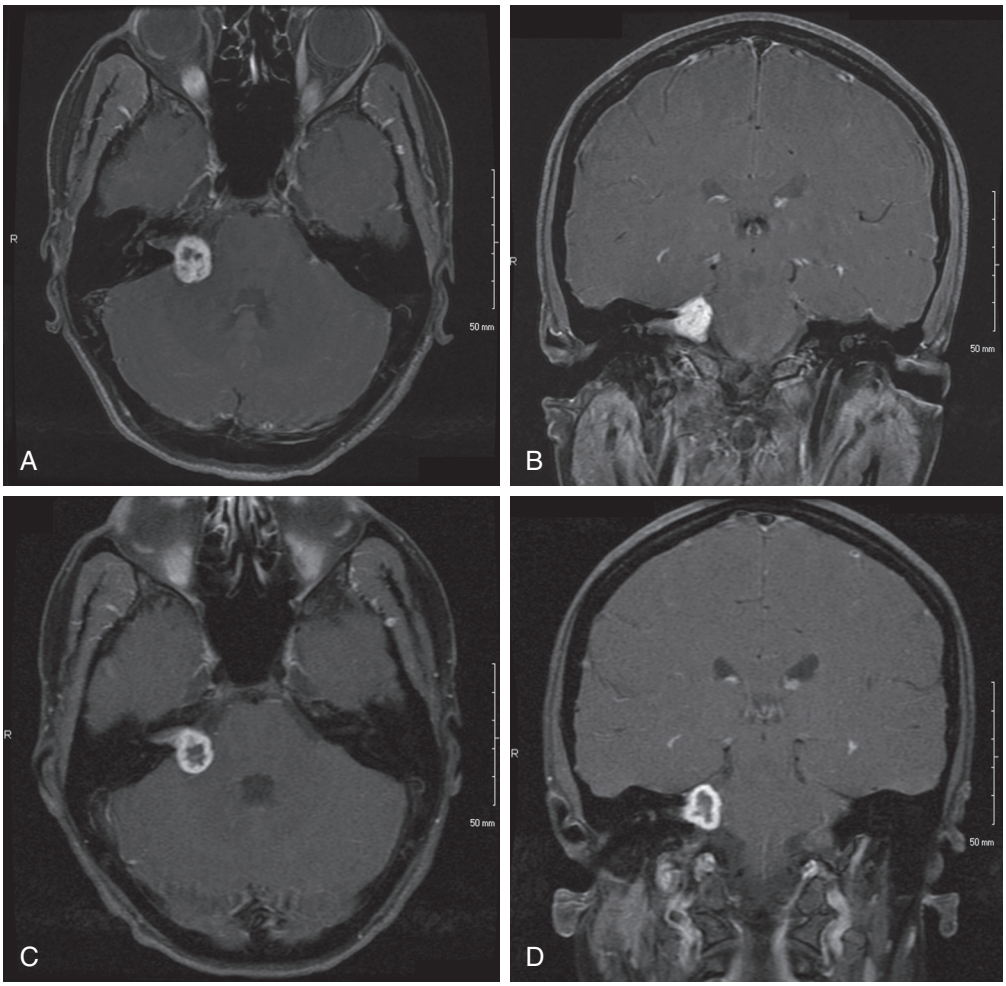
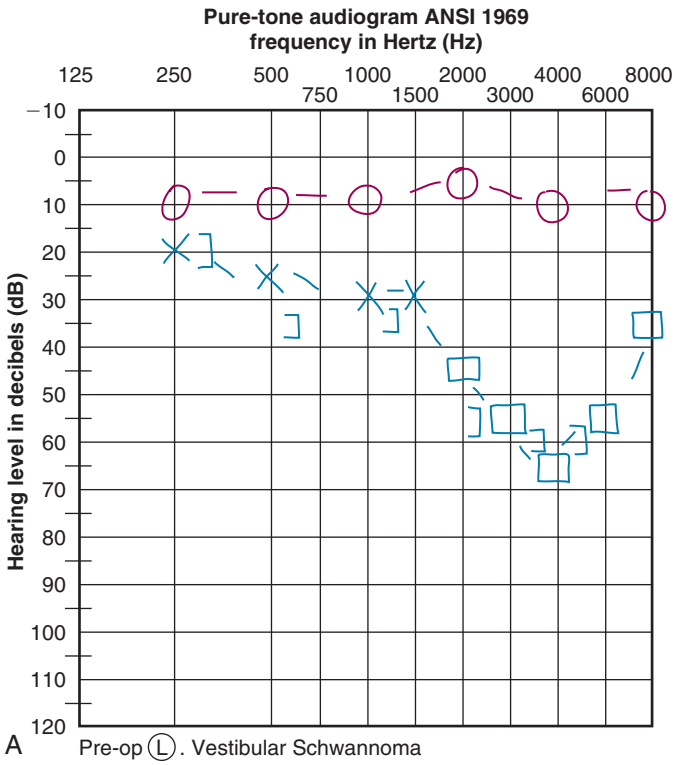


Figure 28-7 T1-weighted, contrast-enhanced magnetic resonance imaging (MRI) images from a 39-year-old woman with a right-sided vestibular schwannoma. She was treated with fractionated stereotactic radiotherapy (FSRT) to 50.4 Gy at 1.8 Gy/F. Shown are representative pretreatment axial **(A)** and coronal **(B)** images, and posttreatment axial **(C)** and coronal **(D)** images obtained 19 months after completing FSRT. Increased central necrosis is demonstrated in the posttreatment images.



Speech audiometry

	Right	Left	Sound field	Sound field aided	Test materials	LV REC
PTA (dBHL)	8	28				
SDT (dBHL) (SRT)	5	20			Spon	LV
WDS-quiet (% correct)	100	80			NU6	CD
WDS-noise (% correct)		M				
Pros. level / Noise level	50	60 / 40				
MCL	50	60				
UCL						

B

Audiogram symbols

		Air		Bone			
Ear	Color	Un-masked	Masked	Un-masked	Masked	No response	Sound field
Right	Red	o-o	Δ-Δ	<	⊏	↙	S
Left	Blue	x-x	□-□	>	⊐	↘	

C

Figure 28-8 Pretreatment audiogram of vestibular schwannoma patient showing typical high-frequency sensorineural hearing loss **(A).** Findings are used to classify hearing into varying grades of serviceable or nonserviceable hearing. The Gardner-Robertson[204] system assigned a grade of I to V, with grades I to II representing serviceable hearing **(B).** The American Academy of Otolaryngology–Head and Neck Surgery (AAO–HNS[205]) system assigns a class of A-D, with A-B representing serviceable hearing **(C).**

TABLE 28-6 House-Brackmann Facial Nerve Grading Scale[207]

Grade	Description	Characteristics
I	Normal	Normal facial function in all areas
II	Mild dysfunction	Gross: slight weakness noticeable on close inspection; may have very slight synkinesis At rest: normal symmetry and tone Motion: Forehead: moderate to good function Eye: complete closure with minimum effort Mouth: slight asymmetry
III	Moderate dysfunction	Gross: obvious but not disfiguring difference between two sides; noticeable but not severe synkinesis, contracture, or hemifacial spasm At rest: normal symmetry and tone Motion: Forehead: slight to moderate movement Eye: complete closure with effort Mouth: slightly weak with maximum effort
IV	Moderately severe dysfunction	Gross: obvious weakness or disfiguring asymmetry At rest: normal symmetry and tone Motion: Forehead: none Eye: incomplete closure Mouth: asymmetric with maximum effort
V	Severe dysfunction	Gross: only barely perceptible motion At rest: asymmetry Motion: Forehead: none Eye: incomplete closure Mouth: slight movement
VI	Total paralysis	No movement

TABLE 28-7 Diagnostic Algorithm and Surveillance of Vestibular Schwannoma

INITIAL EVALUATION
History and physical examination, with particular attention to cranial nerves and balance
MRI brain
Audiogram
Also consider: facial nerve electromyography, caloric testing, electronystagmography
FOLLOW-UP/SURVEILLANCE
MRI brain every 1 to 2 years
Audiogram as clinically indicated

MRI, Magnetic resonance imaging.

PRIMARY THERAPY

Because vestibular schwannoma is rarely a life-threatening diagnosis, the primary goals of therapy are local control and preservation of function. Options include surveillance, surgical resection, SRS, and FSRT.

There have been no true randomized, controlled trials published about patients with vestibular schwannoma, and interpretation of single-institution series is limited by differences in factors such as patient selection, treatment techniques, and methods of assessing and reporting tumor control and treatment or tumor-related neurologic deficits. For example, local control may be determined radiographically as a lack of tumor growth, a sign of progressive tumor growth, or a sign of need for further intervention. The natural history of vestibular schwannoma following RT may be characterized by a transient increase in size, often with a necrotic-appearing center (Figure 28-7, *C* and *D*), followed by stability or regression. This type of MRI finding may confound the results of some published SRS series, particularly in early years before this phenomenon was recognized. Hearing deficits are also analyzed in multiple different fashions, including subjectively (typically by querying patients about their ability to use the telephone with the affected ear) or using objective audiometric data. Facial function is typically scored using the House-Brackmann system (see Table 28-6), but investigators differ in their method of defining "significant" facial and other cranial nerve toxicity. Outcomes may also be reported as crude or actuarial rates, adding to the heterogeneity of published case series.

Currently, the choice of treatment modality is based on physician familiarity, bias and choice, patient characteristics (age, symptoms, location, and size of lesions), and the availability of different technologies. Analysis of the Surveillance, Epidemiology, and End Results (SEER) database from 2004 to 2009 revealed that 49% of patients underwent surgery alone, 24% RT alone, 2% both surgery and RT, and 24% did not receive treatment.[191] Observation was the most common management strategy for patients age younger than 10 years and older than 81 years, whereas surgery was most common for patients ages 11 to 70 years. Patients undergoing surgery had significantly larger tumors than those treated with RT (2 versus 1.5 cm, $p < 0.0001$).

Single-Modality Therapy

Surgery

Resection of vestibular schwannoma has been performed since 1894; it can be accomplished through a suboccipital

TABLE 28-8 Surgical Options for Vestibular Schwannoma

Surgical Approach	Indications	Advantages and Disadvantages
Suboccipital (retrosigmoid)	Tumor of any size with attempted hearing preservation	*Advantage:* lower risk of facial nerve injury *Disadvantages:* increased incidence of headache and CSF leak, risk of injury to cerebellum
Middle fossa	Small tumor (≤1.5 cm to 2 cm) involving lateral internal auditory canal with attempted hearing preservation	*Advantage:* hearing preservation rates may be highest *Disadvantages:* increased risk of injury to facial nerve and temporal lobe
Translabyrinthine	Nonserviceable hearing in affected ear	*Advantage:* complete visualization of internal auditory canal minimizes likelihood of incomplete resection *Disadvantage:* hearing sacrifice inevitable

(retrosigmoid or retromastoid), middle fossa, or translabyrinthine approach (Table 28-8). The suboccipital approach is feasible for tumors of any size but poses a risk for CSF leak and headache. The middle fossa approach is most suitable for tumors measuring less than 1.5 cm to 2 cm in size and has the risk for damage to the seventh cranial nerve. Hearing preservation can be attempted with either of these two approaches, although the fundus of the internal auditory canal is incompletely visualized, which can increase the likelihood for incomplete resection. The translabyrinthine approach can be performed for tumors of any size and eliminates this risk but results in inevitable sacrifice of hearing. Recurrence after gross total resection is uncommon.

With suboccipital and middle fossa approaches, published hearing preservation rates for vestibular schwannoma range from 20% to 71%.[208] Factors associated with increased preservation of functional hearing include better preoperative hearing, shorter intraaural and absolute wave V latency on preoperative auditory brainstem response testing, and superior vestibular nerve origin.[208] Better preoperative hearing measured by audiogram and smaller tumor size predict for hearing preservation in some studies but not in others.[208-210]

Other potential side effects of surgery include CSF leakage, facial nerve injury, headache, and meningitis.[206] Preservation of facial nerve function may be more likely for smaller tumors (i.e., <2 cm to 3 cm) and with increasing surgical experience.[211] Function-preserving surgical approaches have been described (i.e., near-total resection leaving a small tumor remnant adherent to structures such as the facial nerve).[212]

Stereotactic Radiosurgery

The first report of SRS for vestibular schwannoma was published by Leksell in 1971. Modern SRS can be performed with the Gamma Knife, linear accelerator, or proton beam techniques. Because of the minimally invasive nature and excellent clinical outcomes achieved with SRS, practice patterns at some institutions are shifting to favor SRS over resection. The ideal candidates have tumors less than 3 cm to 4 cm in size.

Several large, single-institution experiences with SRS for vestibular schwannoma have been reported. Using modern techniques and doses, as will be detailed, local control rates with SRS are generally greater than 90% and significant cranial nerve toxicity rates are less than 10% (Table 28-9).

Published hearing preservation rates are variable; 57% overall in a systemic review of patients treated with an average dose of 16 Gy.[223] Proposed mechanisms of hearing loss following SRS (in the absence of progressive tumor growth) include transient conductive hearing loss resulting from serous otitis media and delayed sensorineural hearing loss because of direct radiation injury to the vestibulocochlear nerve or cochlea, compression of the vestibulocochlear nerve or internal auditory artery from tumor edema, or thrombosis of the internal auditory artery. Patient-related factors that may correlate with increased likelihood of hearing preservation after SRS include age younger than 60 years, tumor volume less than 0.75 cm^3, intracanalicular tumor location, and better pretreatment hearing (class I Gardner-Robertson, speech discrimination score ≥80%, pure tone average <20 dB).[224]

Several retrospective reports have compared outcomes of patients treated with surgery versus SRS[225-228] (Table 28-10), demonstrating that both approaches achieve comparable local control rates of 91% to 100%,[226,228] but SRS produces equivalent or superior functional outcomes. A prospective analysis of 82 patients with small tumors (≤3 cm) eligible for either surgery or SRS at the Mayo Clinic found that patients who chose SRS subsequently had better preservation of normal facial movement and serviceable hearing.[226] A prospective analysis of 91 patients with small vestibular schwannomas (≤2.5 cm) treated with surgery ($n = 28$) or SRS ($n = 28$) at Haukeland University Hospital also showed better facial nerve function and hearing preservation in patients who underwent radiosurgery.[225] A comparison of patients treated with surgery ($n = 110$) or SRS ($n = 100$) published by Régis et al[227] found better preservation of serviceable hearing and facial and trigeminal function with SRS. Finally, a retrospective analysis of 96 patients performed by Karpinos et al[228] showed better preservation of measurable (but not serviceable) hearing and lower rates of facial and trigeminal neuropathy in patients treated with SRS. Tumor size was larger in the surgical group, however.

Fractionated Stereotactic Radiation Therapy

Vestibular schwannomas are slowly proliferating tumors with a low estimated α/β ratio of 2.5 to 4. The hypothesized radiobiologic advantage of FSRT, therefore, is based on reducing late toxicity to surrounding normal structures, such as the cranial nerves and brainstem. Stereotactic localization techniques also contribute to reduction of toxicity by allowing reduction of treatment volumes. Typical candidates are those with tumors too large for radiosurgery or rare patients with malignant schwannomas, although FSRT can certainly be performed for patients with smaller tumors.

Published single-institution outcomes of FSRT are comparable with those achieved with current, moderate-dose SRS, with local control rates greater than 90% and cranial nerve toxicity rates less than 10% (Table 28-11). Serviceable hearing preservation rates may be higher than those achieved with SRS. It will be important to monitor local control rates with increasing follow-up to ensure that they remain high. Combs et al have shown a serviceable hearing preservation rate of 68.6% at 10 years in 116 patients, most of whom were treated

TABLE 28-9 Single-Institution Outcomes of SRS for Vestibular Schwannoma

Series	No. pts	Dose	Local Control	Serviceable Hearing Preservation (%)	CN VII Toxicity (%)	CN V Toxicity (%)
Fukuoka et al, 2009[213]	152	12 Gy median (9 Gy-15 Gy)	92.4% at 8 years	71	0	2.6
Chopra et al, 2007[214]	216	13 Gy median (12 Gy-13 Gy)	98.3% at 10 years	44.5	0	5.1
Friedman et al, 2006[215]	390	12.5 Gy median (10 Gy-22.5 Gy)	90% at 10 years	NR	4.4	3.6
Lunsford et al, 2005[216]	829	13 Gy (10 Gy-20 Gy)	98%	78.6*	0*	4*
Chung et al, 2005[217]	195	13 Gy median (11 Gy-18.2 Gy)	96.8% at 10 years†	60	1.4 (transient)	1.1
Muacevic et al, 2004[218]	219	13 Gy median (10 Gy-15 Gy)	97% at 5 years	NR	0.5 (transient)	5.5
Flickinger et al, 2001[219]	190	13 Gy median (11 Gy-18 Gy)	97.1% at 5 years‡	73.5 at 5 years	1.1	2.6
Foote et al, 2001[220]	149	14 Gy mean (10 Gy-22.5 Gy)	87% at 5 years	NR	11.8 at 2 years	9.5 at 2 years
Prasad et al, 2000[221]	153	13 Gy median (9 Gy-20 Gy)	94%	40	3.3	2
Kondziolka et al, 1998[103]	162	16.6 Gy mean (12 Gy-20 Gy)	98%	47	21	27
Norén et al, 1993[222]	254	10 Gy-20 Gy	84% NF2 94% unilateral	77	17	19

NR, *Not reported, or results incompatible with table format.*
**In subset of patients treated to 12 Gy-13 Gy.*
†Intervention-free survival; radiologic control 93.6%.
‡Resection-free survival; radiologic control 91% at 5 years.

TABLE 28-10 Single-Institution Analyses Comparing Outcomes of Surgery, SRS, and FSRT for Vestibular Schwannomas

Series	Treatment (No. pts)	Serviceable Hearing Preservation	CN VII Toxicity	CN V Toxicity
SURGERY VS. SRS				
Myrseth et al, 2009[225]	SRS (63) Surgery (28)	68% 0%, $p < 0.001$	1.6% 46%, $p < 0.001$	NR
Pollock et al, 2006[226]	SRS (46) Surgery (36)	63% 5%, $p < 0.001$	2% 17%, $p = 0.04$	NR
Régis et al, 2002[227]	SRS (100) Surgery (110)	40% 5%, $p = 0.000001$	0% 47%, $p = 0.00005$	4% 29%, $p = 0.0009$
Karpinos et al, 2002[228]	SRS (75) Surgery (25)	44% 40%	6.1% 35.3%, $p = 0.008$	12.2% 22%, $p = 0.009$
SRS VS. FSRT				
Combs et al, 2009[229]	SRS (30) FSRT (172)	NR*	17% 2%	7% 3%
Anderson et al, 2007[230]	SRS (49) FSRT (20) or HypoFSRT (32)	33.3% 65.4%, $p = 0.087$	2.1% 2.0%	10.2% 0%, $p = 0.028$
Meijer et al, 2003[231]	SRS (49) HypoFSRT (80)	75% 61%	7% 3%	8% 2%, $p = 0.048$
Andrews et al, 2001[232]	SRS (69) FSRT (56)	33% 81%, $p = 0.0228$	2% 2%	5% 7%

FSRT, *Fractionated stereotactic radiation therapy,* HypoFSRT = *hypofractionated FSRT;* NR, *not reported;* SRS, *stereotactic radiosurgery.*
**Serviceable hearing preservation rates not compatible with table format.* p *Values included for statistically significant differences.*

with FSRT; patterns of hearing loss after 10 years were described as similar to those occurring in a healthy aging population.[233]

Four single-institution analyses (one prospective and three retrospective) have compared outcomes of SRS with those of FSRT (see Table 28-10), all of which show equal rates of local control.[229,230] Meijer et al[231] conducted a prospective study of 129 patients with vestibular schwannomas who were allocated to SRS (10 Gy to 12.5 Gy) versus hypofractionated FSRT (20 Gy to 25 Gy at 4 Gy/F to 5 Gy/F) on the basis of dentition, with edentulous patients ($n = 49$) receiving SRS and dentate patients ($n = 80$) receiving FSRT. Toxicity rates were low for both groups, but trigeminal nerve preservation was slightly higher in the FSRT group (98% vs. 92% at 5 years, $p = 0.048$). A review of 125 patients treated with SRS ($n = 69$) or conventional FSRT ($n = 56$) at Thomas Jefferson University also

TABLE 28-11 Larger Single-Institution Outcomes of FSRT for Vestibular Schwannoma

Series	No. pts	Dose	Local Control	Serviceable Hearing Preservation (%)	CN VII Toxicity (%)	CN V Toxicity (%)
Koh et al, 2007[234]	60	50 Gy at 2 Gy/F	96.2% at 5 years	77.3	0	0
Combs et al, 2005[235]	106	57.8 Gy at 1.8 Gy/F	93% at 5 years	94 at 5 years	2.3	3.4
Chan et al, 2005[236]	70	54 Gy at 1.8 Gy/F	98% at 5 years	84 at 5 years	1	4
Chang et al, 2005[237]	61	18-21 Gy at 6-7 Gy/F daily	98%	74	0	0
Williams et al, 2002[238]	125	25 Gy at 5 Gy/F for tumors <3 cm; 30 Gy at 3 Gy/F for tumors ≥3 cm	100%	83	0	1.6 (transient)
Fuss et al, 2000[239]	42	Mean 57.6 Gy at 1.8 Gy/F	97.7% at 5 years	85.2 at 5 years	0	4.8

NR, *Not reported, or results incompatible with table format.*

showed comparable outcomes, with the exception of functional hearing preservation, which was better for patients treated with FSRT.[232] An analysis of 202 vestibular schwannomas treated with SRS (n = 30) versus conventional FSRT (n = 172) at the University of Heidelberg found equivalent outcomes between the two groups, with the exception of patients treated with SRS doses of more than 13 Gy, who had lower rates of hearing preservation.[229] An analysis from the University of Wisconsin compared the outcomes achieved with SRS (n = 48), conventional FSRT (n = 19), and hypofractionated FSRT (n = 37) and found comparable outcomes, with nonsignificant trends toward increased cranial nerve V toxicity in patients treated with hypofractionated FSRT and inferior serviceable hearing preservation with conventional FSRT.[230]

Surveillance

Surveillance may be the best option for elderly patients or those with significant other medical comorbidities and can be considered for patients with small, asymptomatic tumors. Contraindications include brainstem compression, hydrocephalus, and arguably, the desire to preserve hearing.

A systematic review of 903 patients observed by MRI or CT over a mean period of 3.1 years found that 51% of tumors grew and 20% required intervention after a mean time of 2.1 years, primarily because of tumor growth with progressive symptoms.[199] Audiologic data from a subset of 60 patients with serviceable hearing at presentation revealed loss of serviceable hearing in 37%. Analysis of nearly 1000 patients managed expectantly demonstrated an overall hearing preservation rate of 54%.[240] Hearing preservation was more likely in tumors with average annual growth rates of 2.5 mm per year or less (75% versus 32% for faster-growing tumors). The facial nerve preservation rate was higher than 97%. Tinnitus has been shown to worsen with observation, however, while improving with treatment (either surgery or SRS).[241]

Targeted Therapy

Recent advances in our knowledge of the molecular biology of vestibular schwannoma have led to early clinical studies of targeted agents in patients with NF2 with progressive disease. Promising results have been seen with bevacizumab and lapatinib, including both radiographic responses and restored hearing. Other systemic agents currently under investigation include sorafenib, trastuzumab, protein kinase inhibitors, and p21-activated kinase inhibitors.[25]

Combined-Modality Therapy

Combined-modality therapy is rarely indicated in the initial management of vestibular schwannoma. Patients who fail surgical management commonly go on to receive radiation therapy, however, and the opposite is also true.

Management of Vestibular Schwannoma in the Patient with Neurofibromatosis 2

Bilateral vestibular schwannomas, as mentioned previously, occur commonly in patients with NF2, a disorder with an estimated prevalence of 1 in 100,000.[242] Patients with NF2 also have a predisposition to develop other tumors of the central nervous system (meningiomas, ependymomas, astrocytomas, neurofibromas), peripheral neuropathy, ocular findings (retinal hamartomas, epiretinal membranes, cataracts), and skin lesions (plaques and subcutaneous tumors), as recently reviewed by Asthagiri et al.[25] Pretreatment evaluation should therefore include MRI studies of the entire craniospinal axis.

In comparison with sporadic tumors, vestibular schwannomas in patients with NF2 tend to grow more quickly and to more aggressively surround or infiltrate the adjacent cochlear and facial nerves. Functional outcomes after treatment tend to be poorer in this population of patients. For example, in the experience of Combs et al,[235] a diagnosis of NF2 was associated with significantly reduced likelihood of serviceable hearing preservation in patients treated with FSRT (64% for NF2 versus 98% for sporadic tumors).

Mathieu et al[243] recently published the University of Pittsburgh's experience treating 74 vestibular schwannomas in 62 patients with NF2with SRS, with a mean marginal dose of 14 Gy (range, 11 Gy to 20 Gy). The actuarial local control rate was 81% at 10 years to 15 years. The margin dose was significantly related to serviceable hearing preservation on multivariate analysis, and the actuarial serviceable hearing preservation rate was 48% at 5 years in patients treated with a marginal dose of 14 Gy or less. Tumor volume of more than 5 cm^3 and maximum dose of more than 28 Gy predict for the development of other complications, such as facial weakness, trigeminal neuropathy or neuralgia, and vestibular dysfunction. The authors recommend offering treatment only for large symptomatic tumors or tumors manifesting with progressive growth or hearing loss to maximize preservation of function and quality of life.[243] One advantage of earlier intervention may be the potential for sparing function of the cochlear nerve, thereby allowing for future cochlear implantation.

Currently, the use of radiation in the management of vestibular schwannoma in patients with NF2 is controversial. The goal of therapy typically is to preserve function while maintaining quality of life. Many of these patients can simply have their tumors observed. However, patients with decreasing hearing, brainstem compression, or with nerve involvement causing symptoms should have treatment. Typically, surgery

is looked at as the first option. This is partly because of the fear of second malignancies from radiation, though the data on this is sparse.[242,244,245]

IRRADIATION TECHNIQUES AND TOLERANCE

Stereotactic Radiosurgery

Either linac-based or Gamma Knife radiosurgery may be employed to treat intracranial lesions with submillimeter precision. Examples of popular commercial linac radiosurgical systems include Novalis BrainLAB (BrainLAB AG, Feldkirchen, Germany), Radionics XKnife (Integra, Plainsboro, NJ), TomoTherapy (TomoTherapy, Inc., Madison, WI), TrueBeam STX or Edge (Varian Medical Systems, Palo Alto, CA), and CyberKnife (Accuray, Inc., Sunnyvale, CA). Radiosurgery technology is discussed elsewhere in more detail.

High-resolution MRI images should be used during treatment planning, either as the primary dataset or through fusion with a treatment planning CT scan. Care should be taken when relying solely on MRI, however, because spatial distortion may result in targeting errors with resulting compromise in local control.[246] The tumor is best visualized with contrast-enhanced T1 images, whereas the cochlea and semicircular canals are best seen with fast spin echo T2 sequences.

The ideal SRS prescription (marginal) dose is typically 12 Gy to 13 Gy; local control appears to be compromised with doses below this range[219,247] and cranial nerve toxicity increases with higher doses.[221,229,248,249] The incidence of cranial neuropathy may be greater with prescription doses of greater than 12.5 Gy. For example, a recent retrospective analysis by Foote et al[220] found the 2-year incidence of any cranial neuropathy to be 2% with prescription doses of 12.5 Gy or less versus 24% with doses of more than 12.5 Gy ($p < 0.0003$).

Facial, trigeminal, and auditory toxicities have also been shown to correlate with the length of nerve irradiated (represented by the transverse tumor diameter).[249] For example, in the early experience with higher-dose SRS, trigeminal and facial neuropathy rates were, respectively, higher in patients with an extracanalicular tumor dimension of more than 1 cm and a sum of extracanalicular and intracanalicular diameter of more than 2 cm.[250]

Other factors that correlate with increased facial nerve preservation rates include age of 60 years or less, tumor volume of 1.5 cm^3 or less, and marginal dose of 13 Gy or less.[251] Most cranial neuropathies develop within 2 years of SRS, but hearing loss can occur much later.

MRI treatment planning techniques have been found to correlate with reduced facial and trigeminal neuropathy[249] and increased hearing preservation,[247,249] although interera comparisons may be confounded by a tendency to prescribe lower marginal doses in more recent years. Other SRS parameters correlated with improved hearing preservation rates include prescribing a marginal dose of 13 Gy or less,[250] limiting the mean cochlear dose to less than 3 Gy,[252] and maximum dose to less than 4 Gy,[253] and limiting the dose to the cochlear nucleus to less than 10 Gy.[254]

The radiation dose to the brainstem must also be carefully monitored. In 1994, Kihlstrom et al recommended limiting the brainstem dose to 14 Gy or less with SRS, based on the development of adverse radiation imaging effects (ARIE) in 6 of 7 patients who received 14 Gy to 35 Gy for low-grade gliomas of the tectal midbrain.[255] In 2008, Sharma et al[256] demonstrated that ARIE and new neurologic deficits could develop after exposing 0.1 cm or more of brainstem to doses of more than 12 Gy. An example of an SRS treatment plan is shown in Figure 28-9.

Data is now emerging evaluating the use of fractionated proton therapy. Weber et al reported on 88 patients treated with fractionated proton therapy with a median dose of 12 CGE.[257] The 5-year local control rate was 94%. However, only 33% of patients were able to maintain serviceable hearing. As proton therapy utilization increases, it is expected that more literature will emerge to better delineate the benefits of proton therapy in this population.

Fractionated Stereotactic Radiation Therapy

The objective of FSRT is to combine the radiobiologic advantages of conventional EBRT with the reduced normal tissue exposure of SRS. Multiple localization systems have been developed, most of which achieve patient localization through cone-beam CT, megavoltage CT, or infrared light-emitting diodes and are accurate to within 1 mm to 3 mm.

At the University of Wisconsin, FSRT is typically delivered on a linear accelerator with the patient immobilized in an aquaplast head mask (Figure 28-10). To ensure treatment delivery accuracy, pre- and intratreatment continuous, real-time patient localization is carried out using optical guidance. For this purpose a patient specific maxillary bite block is manufactured before CT simulation, to which a fiducial array with passive optical markers is attached. Before the planning CT

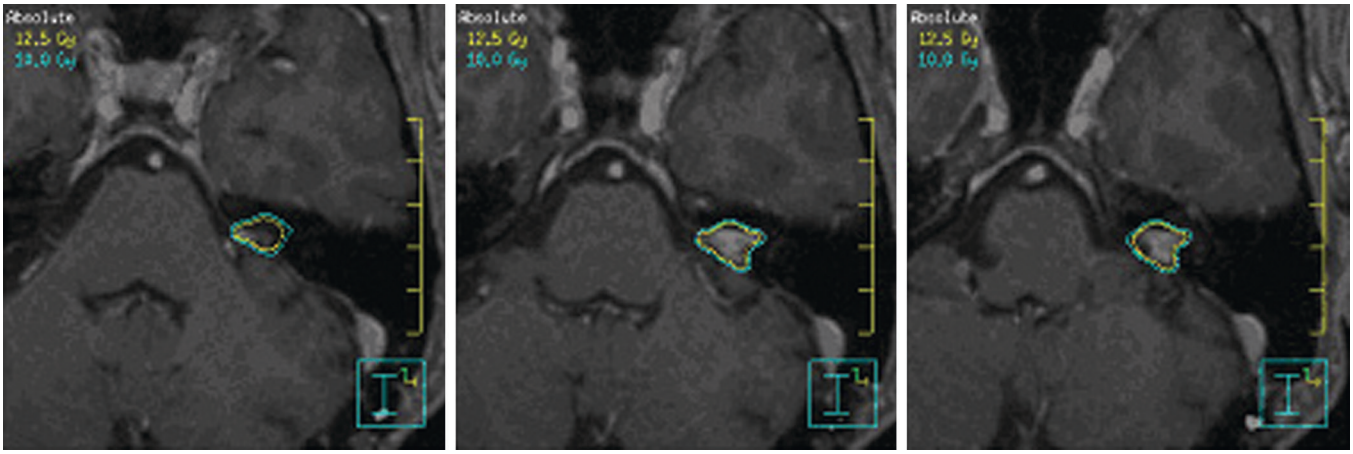


Figure 28-9 Linac stereotactic surgery (SRS) treatment plan delivering 12.5 Gy to a small left-sided vestibular schwannoma using four isocenters.

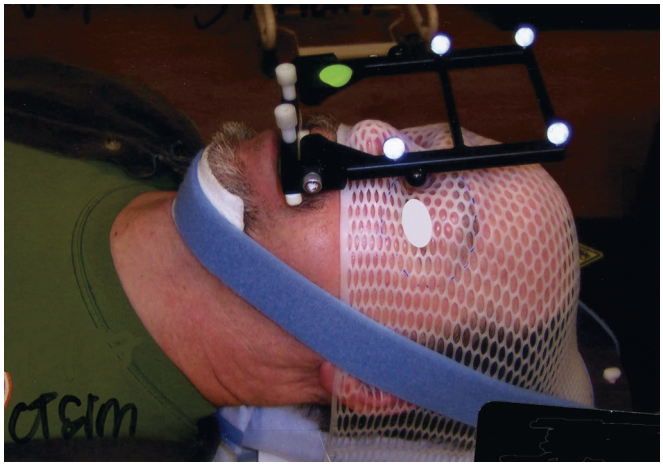


Figure 28-10 Patient immobilization and localization system for fractionated stereotactic radiotherapy (FSRT) at the University of Wisconsin.

and before each treatment fraction the fiducial array bite block complex is inserted, and setup is continuously monitored with optical guidance. If the patient moves out of the predetermined error tolerance band of 0.3 mm or 0.3 degrees of rotation, treatment is interrupted until realignment is achieved.

Common regimens prescribed are on the order of 45 Gy to 50 Gy at 1.8 Gy to 2 Gy per fraction, or 20 Gy to 25 Gy at 4 Gy to 5 Gy per fraction. Compared with untreated controls, 21 patients treated with 54 Gy in 27 fractions to 30 fractions had significantly lower rates of serviceable hearing preservation at 2 years (38% versus 67%).[258] A retrospective analysis of 89 patients treated with FSRT to 46.8 Gy versus 50.4 Gy at 1.8 Gy per fraction found that patients treated to 46.8 Gy were more likely to have preservation of serviceable hearing; however, there was no statistically significant relationship between cochlear dose and serviceable hearing preservation.[259] In contrast, a prospective analysis of 34 patients treated with FSRT to 45 Gy at 1.8 Gy per fraction prescribed to the 90% isodose line found that the dose to the cochlea was the only significant prognostic factor for hearing deterioration.[260] In their experience, the median hearing loss was 10 dB for patients with less than 73.3% of the cochlea exposed to 90% or more of the prescription dose (45 Gy), as opposed to 25 dB for patients with a volume getting 90% of the prescription dose (V_{90}) of 73.3% or more. An example of an FSRT plan is shown in Figure 28-11.

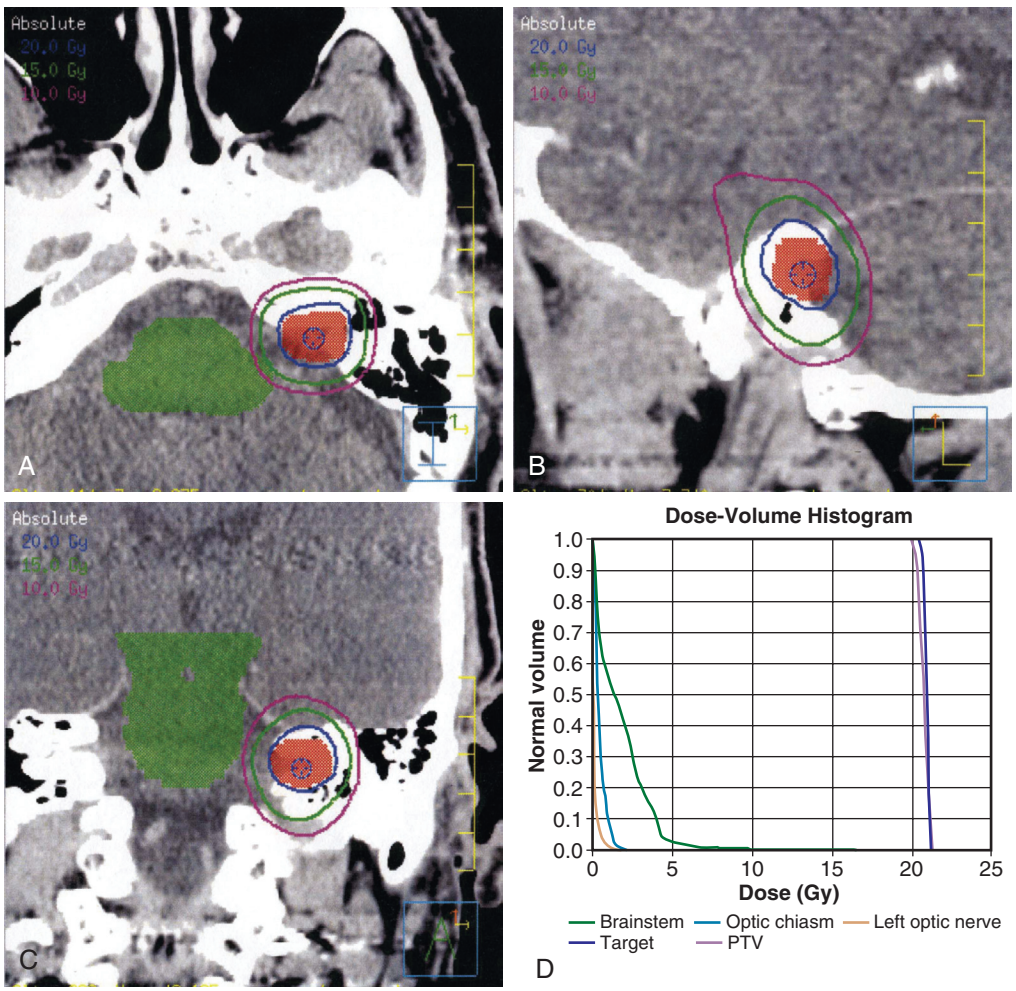


Figure 28-11 Fractionated stereotactic radiotherapy (FSRT) treatment plan delivering 20 Gy at 4 Gy/F weekly to a left-sided vestibular schwannoma. Representative axial (**A**), sagittal (**B**), and coronal (**C**) isodose lines are shown, along with the dose volume histogram (DVH) (**D**) demonstrating good coverage of the gross tumor volume (GTV) and planning target volume (PTV) with minimal dose to adjacent normal structures.

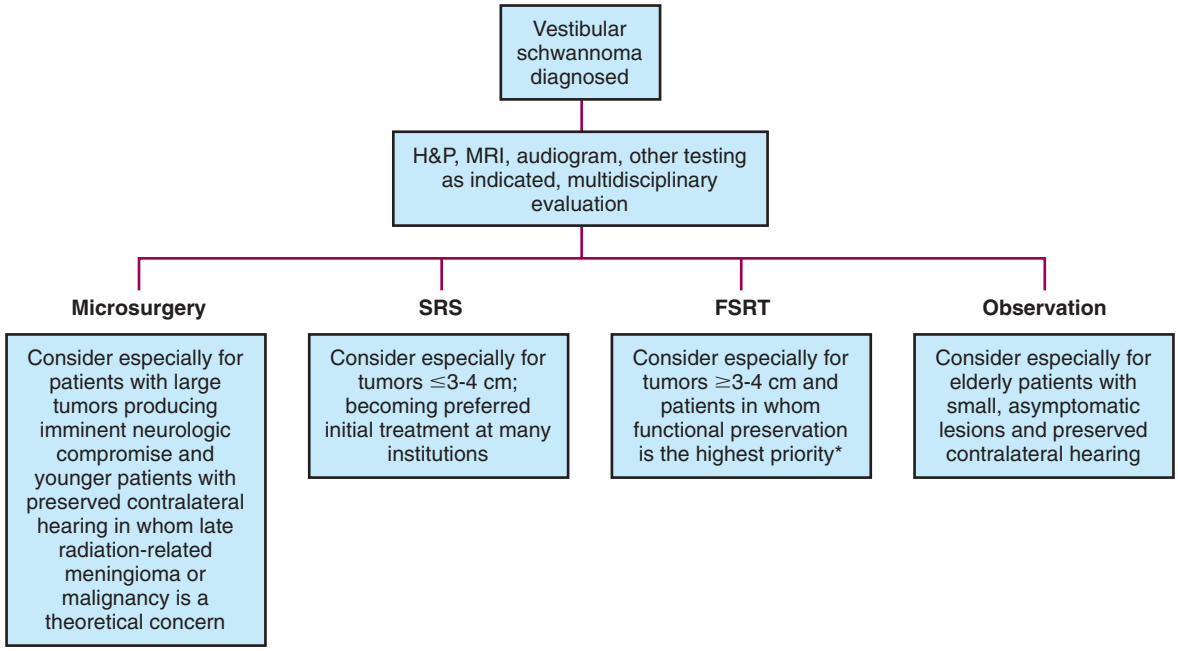


Figure 28-12 Treatment algorithm for vestibular schwannoma. Multidisciplinary evaluation is crucial to ensure that patient-specific factors and institutional strengths that may influence outcomes are taken into consideration.

TREATMENT ALGORITHMS, CHALLENGES, AND FUTURE DIRECTIONS

Patients with newly diagnosed vestibular schwannomas should be evaluated by a multidisciplinary team with expertise in neurosurgery, SRS, and FSRT for discussion of the risks and benefits of treatment, as well as observation (see the treatment algorithm in Figure 28-12). Resection may be performed for virtually any tumor and especially for large tumors causing brainstem compression or hydrocephalus that cannot effectively be managed nonsurgically. Hearing preservation rates may be lower with surgery than with radiation therapy; however, this has never been tested in a prospective randomized fashion. The ideal candidate for SRS is a patient with a small intracanalicular tumor not approaching the brainstem, with marginal doses of 12 Gy to 13 Gy. Conventional or hypofractionated FSRT may be a safer choice for tumors measuring 3 cm to 4 cm or larger and may result in higher hearing preservation rates. Radiation dose to the cochlea should be limited to maximize hearing preservation with either technique. Randomized, controlled trials comparing various treatment options would be valuable.

The cost-effectiveness of various forms of treatment is another important issue to consider. Banerjee et al[261] performed a comparative analysis of the costs incurred through microsurgery versus SRS for vestibular schwannoma. They determined that the mean cost of microsurgery is higher than the mean cost of SRS ($23,788 versus $16,143), but the follow-up costs after SRS tend to be higher because of factors such as increased use of MRI and audiograms, although this reflects practice patterns more than clinical necessity. The authors conclude that SRS is likely to be less expensive than microsurgery from a societal perspective, provided that recurrence rates remain low over prolonged follow-up times.[261]

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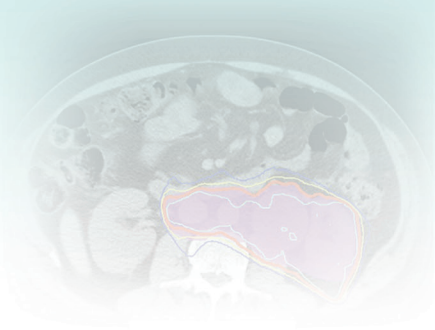
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CHAPTER

29 Pituitary Tumors and Craniopharyngiomas



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INCIDENCE

Pituitary tumors represent roughly 10% to 15% of primary intracranial tumors. Based on a meta-analysis, the overall estimated prevalence of pituitary adenoma is 16.7% (14.4% in autopsy series and 22.5% in radiographic series of all patients).

BIOLOGIC CHARACTERISTICS

Most pituitary tumors are benign. They may express or secrete excess hormones and are monoclonal in origin. MAPK and PI3K/Akt signaling pathways appear to have putative roles in pituitary tumorigenesis or continued growth. Genetic predisposition for the development of pituitary adenomas has been described in multiple endocrine neoplasia (MEN) syndromes, Carney syndrome, and isolated familial somatotropinomas. Pituitary carcinomas are extremely rare.

STAGING EVALUATION

Evaluation for patients with pituitary tumors includes a complete history and physical examination, neuroophthalmic assessment, laboratory tests with emphasis on the endocrine profile, and magnetic resonance imaging (MRI) of the brain with emphasis on the sellar and parasellar regions. Although no formal staging exists, these tumors are broadly classified by endocrine dysfunction, anatomic size, and secretory status.

PRIMARY THERAPY AND RESULTS

Primary therapy is optimized by a multidisciplinary approach, including endocrinology, neurosurgery, neuropathology, neuroradiology, neuroophthalmology, otorhinolaryngology, and radiation oncology. Depending on the endocrine abnormality, tumor size, location, and clinical presentation, management strategies can range from observation to surgery, medical management, radiation therapy, or a combination of these options. The primary goals of treatment include preservation or restoration of normal hormonal function, reversal of hypersecretory endocrine abnormalities, and improvement or stabilization of visual changes or neurologic symptoms. The standard surgical approach is transsphenoidal microsurgery.

ADJUVANT THERAPY

Adjuvant medical and radiation therapy options may be used to manage pituitary adenomas. Radiation options include fractionated radiation therapy and stereotactic radiosurgery (SRS), which are both generally used as adjuvant therapies rather than as primary therapies.

LOCALLY ADVANCED DISEASE

Large nonfunctional and some functional pituitary adenomas may require a combination of approaches, such as surgery, medical therapy, and radiation therapy to optimize long-term tumor control.

PALLIATION

Metastases to the pituitary are uncommon and occur most frequently from breast and lung cancer. The majority of metastases involve the posterior pituitary lobe. A short course of radiation therapy is usually effective in controlling these tumors.

CRANIOPHARYNGIOMAS

Craniopharyngiomas are uncommon tumors that are postulated to arise from the embryologic remnants of Rathke's pouch. They are typically slow growing and encapsulated. Although benign in nature, tumor growth and treatment can result in endocrinopathies and visual deficits. Gross total resection (GTR) results in excellent local control but can cause morbidity including hypothalamic dysfunction and visual deficits. Subtotal resection followed by external beam radiation therapy may yield equivalent control with less morbidity. Other options include SRS, intracystic bleomycin, and intracystic phosphorous 32. The 5-year progression free survival is approximately 85%.

INTRODUCTION

This chapter focuses on the etiology, epidemiology, detection, biology, anatomy, pathology, evaluation, and management (specifically the irradiation techniques and associated treatment side effects) of pituitary tumors. Given the diverse presentations of these tumors along with their complex anatomic location and proximity to critical structures such as the optic apparatus, cranial nerves, and internal carotid arteries, a multidisciplinary approach is needed for optimal patient care. Involvement of the endocrinologist, neurosurgeon, otorhinolaryngologist, radiation oncologist, neuroradiologist, neuroophthalmologist, and neuropathologist optimizes management of patients with pituitary tumors. At the end of this chapter, the evaluation and management of craniopharyngiomas will be briefly discussed.

ETIOLOGY AND EPIDEMIOLOGY

Etiology

The etiology of most pituitary tumors is not known. Based on rodent models, two primary modes of pituitary oncogenesis have been suggested.[1] The first model, known as the hyperplasia-adenoma sequence, suggests a hormone-dependent pathway. In this model, dysregulation of hormone or growth factor signaling leads to hyperplasia and tumor formation. For example, there is evidence that implicates overexpression of

transforming growth factor–alpha (TGF–α), fibroblast growth factor (FGF), and fibroblast growth factor receptors (FGFRs) in tumor formation.[2] In the second model, adenomas are believed to arise de novo, without the development of hyperplasia, likely as a result of one or a sequence of genetic alterations, a mechanism supported by some transgenic and knockout animal models.[2] In humans four genes known to be associated with familial pituitary tumor syndromes: multiple endocrine neoplasia (MEN) 1; cyclin dependent kinase inhibitor (CDKN) 1B; protein kinase, cAMP-dependent, regulatory (PRKAR) 1A; and aryl hydrocarbon receptor-interacting protein (AIP).[3]

For patients with MEN1, which is an autosomal dominant disease characterized by tumors of the pancreatic islet cells, parathyroid glands, and pituitary gland, 40% will develop pituitary adenomas, most commonly prolactinomas. Pituitary tumors associated with the MEN1 syndrome demonstrate loss of heterozygosity of chromosome 11q13 (location of the *MEN1* gene), which has also been implicated in malignant progression of some pituitary adenomas.[4] Alterations of *MEN1* do not appear to increase the risk for sporadic pituitary adenomas.[5]

In Carney's complex, a rare inherited condition characterized by endocrine overactivity, schwannomas, abnormal skin pigmentation, and myxomas, the implicated genetic defect is loss of function of PRKAR1A, whose gene is located on chromosome 17q23-24.[6] Additional genetic alterations are found in the McCune-Albright syndrome, a genetic disorder of bones, skin pigmentation, and hormones associated with premature puberty. Activating or gain-of-function *GNAS1* mutations (of the guanine nucleotide-binding protein [G protein], alpha-stimulating activity polypeptide 1 gene on chromosome 20q13.1) are seen in this condition. Patients with McCune-Albright syndrome demonstrate mosaicism, resulting from a postzygotic somatic mutation appearing early in the course of development that yields a monoclonal population of mutated cells within variously affected tissues.

In isolated familial somatotropinomas (i.e., the occurrence of two or more cases of acromegaly in a family without a history of MEN or Carney's complex), germline alterations in the aryl hydrocarbon receptor interacting gene (*AIP* gene) have been identified.[7,8] The syndrome of familial isolated pituitary adenomas (FIPA) accounts for 2% of pituitary adenomas and is associated with mutations in *AIP*, the gene that encodes aryl hydrocarbon receptor interacting protein.[9] The FIPA syndrome is also liked to mutations in *AIP* in 15% to 25% of families, and those affected are typically younger patients with more aggressive tumors[10] *AIP* mutations are usually associated with growth hormone secretion, but prolactinomas, nonfunctional adenomas, Cushing's disease, and other adenoma types can occur.

Finally, heterozygous mutations of *CDNK1B*, which encodes a 196 amino acid protein, the cyclin-dependent kinase CDK1 p27Kip1, can lead in humans to a multiple endocrine syndrome of familial pituitary adenomas and primary hyperparathyroidism, like MEN1, but also including testicular cancer and renal angiomyolipoma. The alterations in *CDNK1B*, located at 12p13, are rare, and lead to the multiple endocrine syndrome known as MEN4.[11]

Epidemiology

Although 10% of normal adults have a pituitary abnormality detectable on MRI, pituitary tumors account for only 10% to 15% of all primary intracranial tumors. The frequency of pituitary adenomas varies greatly, although recent community-based studies from Belgium and the United Kingdom suggest that the prevalence is higher than has been historically noted.[12,13]

Based on a meta-analysis, the overall estimated prevalence of pituitary adenomas was 16.7%, with 14.4% observed in autopsy series and 22.5% in radiographic series of volunteers or patients imaged for other diseases.[14] Over time, different criteria have been used for distinguishing hyperplasia from pituitary adenomas. The broader application of immunohistochemical staining for pituitary hormones and the differences in slice thicknesses for MRI may account for the wide variation in incidence reported in the literature.

The frequency of the various types of pituitary adenomas differs widely according to age and gender. Prolactinomas are the most common, followed by nonfunctioning adenomas, growth hormone (GH)–secreting adenomas, and adrenocorticotropic hormone (ACTH)–secreting adenomas. Nelson's syndrome (growth of an ACTH-secreting pituitary adenoma after bilateral adrenalectomy resulting from loss of adrenal suppression of pituitary inhibition) and thyroid-stimulating hormone (TSH)–secreting adenomas are rare.

PREVENTION AND EARLY DETECTION

No successful strategy has been described or is known to exist that prevents the development of these tumors. Given the prevalence of pituitary abnormalities on MRI scans in normal adult patients, the routine use of screening MRI or endocrine workup is not feasible and is not recommended. When imaging is performed not specifically for a pituitary lesion, an incidental finding of a pituitary lesion, the so-called "incidentaloma," may be diagnosed.[15] Most incidentalomas are <1 cm, nonfunctional, and may be associated with pituitary hormonal deficiencies, excess hormone secretion, or visual field defects.[16] The majority of incidentalomas in reality are pituitary adenomas with incomplete or limited biochemical work-up. Patients with macroincidentalomas (≥1 cm) should be evaluated for hypopituitarism and undergo visual field testing if the sellar mass abuts or compresses the optic chiasm. Based on autopsy series, pituitary incidentaloma occurs in 1.5% of children and adolescents.[17]

A patient with signs or symptoms suggestive of an endocrine abnormality should be referred to an endocrinologist for appropriate evaluation. Consultation with an endocrinologist and a medical geneticist is appropriate for patients if MEN1 or another familial syndrome associated with pituitary adenoma is suspected. For these patients, a baseline MRI of the pituitary can be considered, although routine imaging of the pituitary in a patient without clinical symptoms is not uniformly practiced. The management of inherited pituitary tumors is usually similar to that of sporadic adenomas.[18] Because pituitary tumors that arise as a part of MEN 1 and FIPA are more aggressive, occur at a younger age, and often respond poorly to treatment, earlier identification may be useful. To help identify carriers in whom regular clinical and biochemical monitoring would be useful, genetic screening for mutations in the relevant genes is recommended in patients with MEN 1 and Carney complex.

BIOLOGIC CHARACTERISTICS AND MOLECULAR BIOLOGY

Despite the screening of common oncogenes and tumor suppressor genes in pituitary adenomas, the molecular and cellular pathogenesis of pituitary tumors is largely unknown.[19] Based on *X* chromosome inactivation analysis, it appears that most pituitary adenomas derive from a monoclonal expansion, which suggests that general principles of tumorigenesis may apply to pituitary adenoma formation.[20] The MAPK (mainly Ras/extracellular signal-regulated protein kinase

[ERK]) and the PI3K/Akt signaling pathways appear to have putative roles in pituitary tumorigenesis or continued growth because the activity of these pathways are often activated in pituitary tumors. Because the Raf/MEK (mitogen-activated protein kinase/ERK kinase)/ERK signaling is a major pathway in the regulation of cell growth, proliferation and survival, it is likely that these genetic alterations could contribute to several aspects of pituitary tumor growth and survival.[21] Although its role is not fully understood, a docking protein in the endothelial growth factor receptor (EGFR) pathway, EGF pathway substrate number 8 (Eps8), is overexpressed (almost sixfold higher) in pituitary tumors compared with normal anterior pituitary tissue.[22] Because pituitary tumors are mostly benign, a protective mechanism to restrict uninhibited growth of tumor cells is probably active. The concept of oncogene-induced senescence is one possible mechanism. High pituitary $p21^{Cip1/WAF1}$ levels appear to promote senescence and restrict tumor growth.[23] One study proposed the possible presence of pituitary adenoma stemlike cells,[24] which has encouraged the investigative development of newer pharmacologic agents.[25] HMGA1B and HMGA2 overexpression in mice induces the development of GH and prolactin (PRL) pituitary adenomas mainly by increasing E2F1transcriptional activity.[26] Upregulation of PIT1, a transcriptional factor that regulates the gene expression of GH, Prl, Ghrhr, and Pit1 itself, also has a role in pituitary tumorigenesis.[27]

For somatotroph (growth hormone) adenomas, an activating mutation of the alpha subunit of the guanine nucleotide stimulatory protein (Gs-alpha) gene is found in about 40% of patients, which results in activation of adenylyl cyclase.[28] Overexpression of the pituitary tumor transforming gene (*PTTG*) is also seen in most human somatotroph adenomas.[29] Mutations of fibroblast growth factor-4 (FGF-4) have led to development of lactotroph adenomas in transgenic mice.[30]

ANATOMY, PATHWAYS OF SPREAD, AND PATHOLOGY

Anatomy and Pathways of Spread

The pituitary gland is a midline intracranial organ that measures approximately 8 mm in the anteroposterior axis, 10 mm in the transverse axis, and 6 to 8 mm in the supero-inferior axis. It occupies the cavity in the sphenoid bone known as the sella turcica. The pituitary gland is separated from the structures above it (i.e., the optic chiasm, hypothalamus, anterior cerebral arteries, and floor of the third ventricle) by the sellar diaphragm, which is formed by a circular fold of dura. Immediately anterosuperior to the diaphragm sella lies the optic chiasm. The pituitary stalk (infundibulum) crosses the sellar diaphragm and connects the hypothalamus to the pituitary gland. Anteriorly, the tuberculum sellae lies in the floor of the sella and extends supero-laterally to form the anterior clinoid processes. The posterior aspect of the sella forms the dorsum sellae and extends supero-laterally to form the posterior clinoid processes. Laterally, the cavernous sinuses contain cranial nerves III, IV, V_1 (ophthalmic nerve), V_2 (maxillary nerve), and VI and the internal carotid artery. Given the proximity of the pituitary to these various structures, parasellar tumors can affect cranial nerves III, IV, V, and VI, and suprasellar tumor extension can lead to bitemporal hemianopsia via compression of the optic chiasm. Figure 29-1 demonstrates the complex anatomy of the parasellar region.

The pituitary has two distinct embryologic origins; the first gives rise to the anterior and intermediate pituitary lobes, and the second gives rise to the posterior pituitary lobe. The anterior (adenohypophysis) and intermediate lobes are derived from Rathke's pouch, which is an evagination of ectodermal tissue from the primitive oral cavity (pharyngeal pouches). The

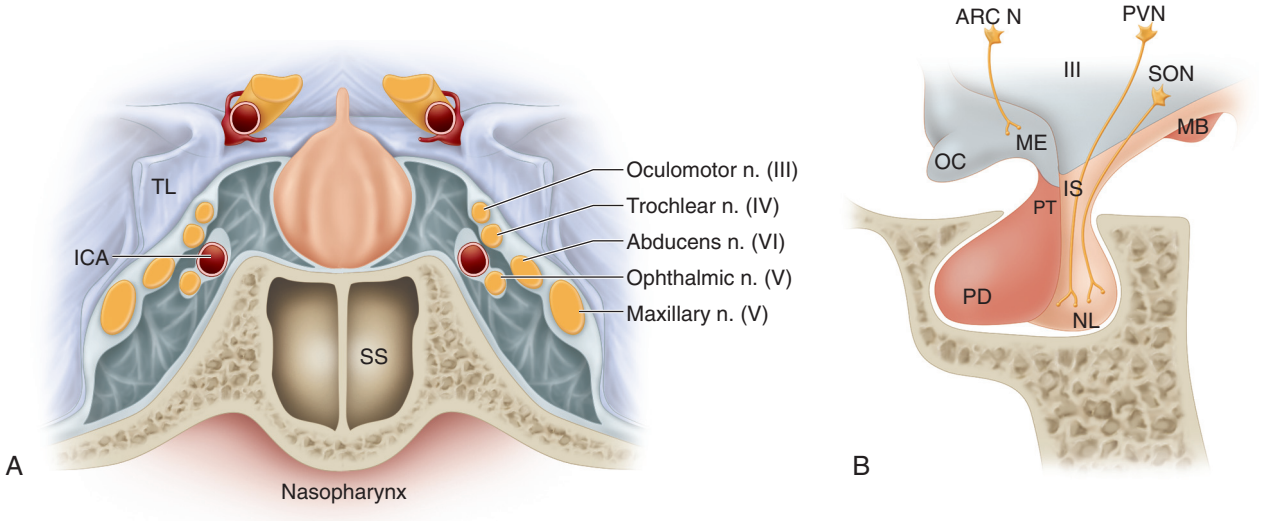


Figure 29-1 **A,** Anatomy of the sellar and parasellar regions. This coronal-view diagram illustrates the proximity of the pituitary gland to several important neural and vascular structures. The gland is laterally bordered by the cavernous sinuses *(black)*, which contain within their confines or their walls the carotid artery and the oculomotor, trochlear, maxillary, and abducens nerves and the first two divisions of the trigeminal nerves. The optic chiasm lies immediately superior to the gland. *ICA,* Internal carotid artery; *SS,* sphenoid sinus; *TL,* temporal lobe; *III,* third ventricle. **B,** Anatomy of the pituitary gland. This sagittal-view diagram of the pituitary gland shows the hypothalamus, pituitary stalk, and pituitary gland located in the sella turcica. The anterior gland, or adenohypophysis, is composed of the pars distalis (PD), rudimentary pars intermedia, and pars tuberalis (PT). The posterior gland, or neurohypophysis, is composed of the median eminence (ME), located in the hypothalamus, the infundibular stem (IS), and the neural lobe (NL). The large neurons located in the supraoptic (SON) and paraventricular (PVN) nuclei project to the neural lobe, where they store and release oxytocin and vasopressin into the systemic circulation under the appropriate stimulus. *ARC N,* Arcuate nucleus; *MB,* mammillary bodies; *OC,* optic chiasm.
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posterior lobe (neurohypophysis) and stalk are derived from the diencephalon and, therefore, have a neuroectodermal origin. The anterior pituitary lobe accounts for most of the pituitary gland and produces at least six hormones: prolactin (PRL), adrenocorticotropic hormone (ACTH), follicle-stimulating hormone (FSH), luteinizing hormone (LH), growth hormone (GH), and thyroid-stimulating hormone (TSH). The intermediate lobe produces melanocyte-stimulating hormone (MSH). The posterior lobe stores and releases two hormones, vasopressin (antidiuretic hormone [ADH]) and oxytocin, which are produced by the hypothalamus.

The hypothalamic-hypophyseal portal system, a vascular network that surrounds the infundibulum and connects the anterior lobe of the pituitary with the hypothalamus, has an important role in the regulation of the anterior pituitary hormones mediated by stimulating or inhibiting hormones derived from the hypothalamus. These hormones include GH-releasing hormone, GH-inhibiting hormone (somatostatin), prolactin-secreting hormone, prolactin-inhibiting hormone, corticotrophin-releasing hormone, thyrotropin-releasing hormone, FSH-releasing hormone, and LH-releasing hormone. The anterior pituitary hormones are also regulated by a hormonal feedback mechanism from the target glands such as the adrenals.

Pituitary tumors are generally classified as microadenomas or macroadenomas depending on the diameter of the tumor as described by Hardy.[31] A microadenoma is less than 1 cm in diameter, whereas a macroadenoma has a diameter of 1 cm or greater. Incidental microadenomas have been observed with a frequency of 3% to 25% in large, unselected autopsy series.[32] Microadenomas are more frequently seen in females, whereas macroadenomas occur with equal frequency in males and females. Macroadenomas are more common than microadenomas. For lesions less than 3 mm in diameter, the term *pico-adenoma* has been used.[33]

Pathology

Before the introduction of electron microscopy, modern immunohistochemical procedures, and modern staining and fixation techniques, pituitary tumors were classified according to Mallory's trichrome histologic staining technique as chromophobic, acidophilic (or eosinophilic), or basophilic tumors. Based on classic fixation and staining, Cushing's disease was associated with basophilic adenoma, acromegaly with eosinophilic adenoma, and nonfunctioning adenoma with chromophobic adenoma. With newer methods of immunostaining, it has become possible to identify cells as prolactin, ACTH, GH, LH FSH, alpha subunit, or TSH. It is important to note that the functional status of a pituitary adenoma is defined by clinical symptoms and not by immunohistochemical staining patterns.[34]

According to the World Health Organization (WHO) classification of pituitary tumors, they are defined as neoplasms located in the sella turcica. This classification is based on structural similarities of the normal parenchymal cells and the immunohistochemical demonstration of hormone secretion. Based on this definition, pituitary adenomas may express more than one or two hormones, based on immunohistochemical patterns. The classification includes a new entity designating a borderline adenoma or adenoma of uncertain behavior.[35] The atypical adenoma is defined as an invasive tumor with an elevated mitotic index (MIB-1-labeling index greater than 3%) and extensive nuclear immunostaining for TP53.[35] The German Registry of Pituitary Tumors reported the frequency of atypical pituitary adenomas as 2.7%.[36]

Most lesions are easily identified on routine histopathologic testing, but metastatic well-differentiated neuroendocrine carcinoma can present a diagnostic challenge.[37] For patients with acromegaly or Cushing's disease, hyperplasia may be clinically indistinguishable from an adenoma. Differentiation of hyperplasia from adenoma can be made using a reticulin stain. Normal pituitary tissue is composed of small acini of pituitary cells surrounded by an intact reticulin network. In hyperplasia, the architecture of the acini is maintained, but the acini are increased in size, and the reticulin stain demonstrates an intact network. Pituitary adenomas are characterized by a complete disruption of the reticulin fiber network.

The pathologic hallmark of pituitary adenomas is the monotonous and monomorphous proliferation of neoplastic cells that replaces the normal acinar pattern in the pituitary lobe. GH-producing cells are seen with greater frequency anteriorly in the lateral aspects of the pituitary. Prolactin-producing cells are distributed throughout the pituitary but have a greater density in the posterior lateral aspect of the gland. ACTH-producing cells are present in the median wedge. TSH-producing cells are seen in the anterior aspect of the median wedge. Gonadotropin-producing cells are distributed throughout the anterior pituitary. Nonfunctioning adenomas typically have solid sheets, nests, and sinusoidal patterns and are interrupted by pseudo-papillae and striking pseudo-rosettes around vascular channels. Overlap of the distribution of these functional hormonal secretory cells does exist, and they do not reside in well-demarcated zones of the pituitary. Mitoses are seen in 3.9% of noninvasive adenomas, 21.4% of invasive adenomas, and 66.7% of carcinomas.[38]

The usefulness of labeling-index and TP53 immunostaining is not clear because these assessments may not correlate with tumor behavior. Invasive pituitary adenomas usually exhibit a higher Ki-67 proliferation index.[39] Markers such as proliferating cell nuclear antigen (PCNA), Ki-67/MIB-1, and antiapoptotic Bcl-2 have not demonstrated consistent correlation with tumor invasiveness or recurrence.[40] Galectin-3, a β-galactoside-binding protein, may play a role in pituitary tumor progression, and immunostaining for this is also available.[41]

The pituitary is composed of at least six distinct cell types, which are responsible for the production of at least one hormone. Advances in molecular biology have identified three major pathways of cytodifferentiation of adenohypophyseal cells, T pit; Pit-1; and SF-1, GATA-2, ER.[42,43] These pathways are determined by a complex pattern of transcription expression, which help classify various adenomas.[44] In situations in which histologic and immunohistochemical profiles are atypical, electron microscopy can be helpful in achieving accurate classification.

CLINICAL MANIFESTATIONS, PATIENT EVALUATION, AND STAGING

Clinical Manifestations

Patients with pituitary tumors can have a number of different symptoms and presentations, depending on the size and mass effect of the tumor and hormonal abnormalities. Headaches can occur with a lesion of any size. When the tumor extends superiorly into the suprasellar region, visual loss can occur, including bitemporal or homonymous hemianopsia, superior or inferior field cut deficits, and central scotoma. Extension into the cavernous sinus can lead to cranial nerve dysfunction (commonly III and IV cranial nerve palsies). Cranial nerves V and VI are less commonly affected. Lateral extension into the temporal lobe may cause seizures. The clinical presentations and endocrine abnormalities can vary, depending on the age and sex of the patient. Patients with large adenomas may have compromised pituitary function, which can lead to

hypogonadism, secondary hypothyroidism, and adrenal insufficiency.[45] Diabetes insipidus is extremely rare and most commonly is a manifestation of an invasive and infiltrative tumor (such as a metastasis), an inflammatory condition (such as neurosarcoidosis), or a lesion that arises from or is attached to the infundibulum or hypothalamus (such as a craniopharyngioma).[46] If the gland acutely infarcts or hemorrhages, pituitary apoplexy may result, which may require urgent surgical decompression.

Patient Evaluation

General Approach

For all patients, a detailed history should be obtained and a thorough physical examination performed. This will allow assessment of the possible manifestations of the underlying endocrine disorder and any neurologic deficits, such as bitemporal hemianopsia from superior compression of the optic apparatus by the tumor. Neurologic sequelae may include headache from pressure effects on the dura, cranial nerve (III, IV, V, and VI) abnormalities from extension into the cavernous sinus, visual symptoms from suprasellar extension to the optic chiasm or nerves, and behavioral changes.

Ophthalmologic evaluation with formal visual field testing should be done in patients with visual symptoms and those with extension of the tumor outside the sella. Bitemporal hemianopsia is classically associated with suprasellar extension of the pituitary tumor, causing compression of the anterior aspect of the optic chiasm. Other visual field deficits can also occur. Changes in ophthalmologic assessment can be used to monitor the response to therapy.

Laboratory Assessment

Initial tests help determine if a pituitary deficiency exists and diagnose the secretory status of the adenoma. Screening studies should include TSH, free thyroxine (T_4), ACTH, cortisol, prolactin, somatomedin C (insulin-like growth factor-1 [IGF-1]; this is the primary molecule mediating the effects of growth hormone at the cellular level, and its secretion, primarily from the liver, is directly regulated by growth hormone), LH, FSH, alpha subunit, and, in men, testosterone. The alpha subunit is common among the three glycoprotein pituitary hormones, FSH, LH, and TSH and is also found in placental chorionic gonadotropin; rarely pure alpha-subunit secreting tumors are identified, and these are generally otherwise "nonsecreting chromophobe adenomas." These patients often have visual field abnormalities and partial hypopituitarism. The elevated serum alpha subunit shows a variable response to stimulation by thyrotropin-releasing hormone and is generally not suppressed by thyroid hormone administration. Tumor immunocytochemical studies demonstrate the presence of only the alpha subunit. Following resection or radiotherapy, serum alpha level subunit levels decrease. These patients therefore represent a new subset of functioning pituitary tumors. Determination of alpha subunit concentration is useful in managing some patients with pituitary tumors previously thought to have nonfunctioning chromophobe adenomas.

In addition to endocrine evaluation, a complete blood count, blood chemistry assessment, and urinalysis should be obtained. Because physiologic hormonal variations in the blood and urine levels can occur, the interpretation of these results should be considered based on diurnal variations, age and gender of the patient, and pregnancy and menopausal status. The conditions and timing under which these samples are obtained also influence interpretations of the results. Because the diagnosis of Cushing's disease can be difficult, multiple tests are performed over time and at different times during the day to help make a conclusive diagnosis.[47]

For patients with suspected Cushing's disease, 24-hour urinary free cortisol (UFC), midnight salivary cortisol, and 1-mg overnight dexamethasone suppression tests have similar sensitivity and specificity. The most precise method of measurement for 24-hour urinary free cortisol is tandem mass spectrometry. Salivary cortisol levels can have a wide range of normal nighttime values, which can raise questions about accuracy. The overnight dexamethasone suppression test may be influenced by several medications and requires specific time constraints (i.e., the tablet needs to be taken at 11 pm and blood test performed at 8 am the next day). As a result, this test should not be used as the sole test for diagnosing Cushing's syndrome. The definitive test for Cushing's disease and exclusion of ectopic ACTH syndrome is inferior petrosal sinus sampling, which requires measurement of ACTH from the right and left petrosal sinuses and peripheral site before and after corticotropin-releasing hormone (CRH) administration.

For patients with prolactinoma who also have macroadenoma, the prolactin level is usually greater than 200 ng/mL. Other common conditions that have been associated with hyperprolactinemia include end-stage renal disease, renal insufficiency, depression, primary hypothyroidism, acquired immunodeficiency syndrome, sarcoidosis, and nonalcoholic cirrhosis.[48] On the other hand, pituitary stalk compression from tumor may also cause elevated prolactin levels in the range of 150 ng/mL or less. Because antidepressants, protease inhibitors, verapamil, and phenothiazines may elevate prolactin levels, careful review of the medications that the patient is taking is necessary. A pregnancy test is mandatory for women with amenorrhea or hyperprolactinemia. Elevated serum prolactin levels greater than 300 ng/mL are usually diagnostic of pituitary adenoma, and levels greater than 100 ng/mL in nonpregnant patients often are associated with pituitary adenoma.

For patients with acromegaly, most cases result from excess secretion of growth hormone by a pituitary tumor.[49] The definitive test is measurement of growth hormone response to 75 g or 100 g of oral glucose (oral glucose tolerance test). This glucose load should normally cause marked suppression of the GH release to a level under 2 ng/mL. To ensure accuracy, these measurements of serum glucose and GH must be performed every 30 minutes for 2 hours. IGF-1 is also elevated after adjusting for gender and age variation. IGF-1 levels provide the best intermittent method for monitoring response to treatment, although dynamic testing of GH kinetics with the oral glucose tolerance test (OGTT) is also frequently used.

Mild hyperprolactinemia (<200 ng/mL) may be seen in some patients with nonfunctional adenomas as this is a common finding when any sellar mass causes stalk compression, interrupts blood flow and leads to interference with the prolactin-inhibiting dopamine transport.[50,51] Because these patients do not have hormone-related symptoms, nonfunctioning adenomas can be quite large at the time of diagnosis.

Imaging

Dynamic MRI of the brain with gadolinium is the imaging test of choice[52] given its superior resolution compared with computed tomography (CT), which evaluates calcifications and bony changes better than MRI (Figure 29-2). Dynamic coronal imaging techniques after contrast administration enhance normal pituitary tissue earlier and more intensely and help delineate adenoma tissue, which tends to enhance later. Because pituitary adenomas are less vascular than the normal pituitary gland, they usually appear hypointense following gadolinium administration, in the early, or immediate postgadolinium phase, and later may either remain hypointense, hyperintense, or isointense to the rest of the gland, emphasizing the need for dynamic MR imaging. On noncontrast T1-weighted MR images

Regardless of the presentation, accurate diagnosis and implementation of appropriate therapy or therapies is desired. A multidisciplinary approach optimizes patient care.



Figure 29-2 Axial T1-weighted, contrast-enhanced MRI of a pituitary adenoma demonstrating a large macroadenoma extending beyond the sella.

they may appear hypointense or isointense to the normal pituitary gland.[53] The posterior lobe of the pituitary has a high signal intensity on T1-weighted images (posterior pituitary bright spot) that distinguishes it from the anterior lobe, which has signal intensity similar to that of white matter. Thin slices (at 2-mm to 3-mm intervals) obtained before and after gadolinium contrast administration with images in the coronal, axial, and sagittal planes provide detailed information for the initial diagnosis and allow detection of small lesions. For patients who have undergone previous surgery, fat suppression techniques can help differentiate surgical fat grafts from tumor tissue. For patients undergoing SRS, thin-slice (1-mm) imaging with contrast medium is obtained to define the tumor and optic apparatus. For hypersecretory adenomas, positron emission tomography (PET) imaging with coregistration may be valuable.[54]

For patients with suspected Cushing's disease, thin-slice images of 1-mm thickness have greater sensitivity; even so, the tumor may not be detected in about 50% of patients.[55] Spoiled gradient recalled acquisition sequences may have superior sensitivity (80%) compared with conventional spin echo images following contrast enhancement.[56] The degree of contrast enhancement does not differentiate one sellar mass from another. A clear distinction between an intrasellar mass and normal pituitary tissue is not consistent with a pituitary adenoma.

Macroadenomas can compress the adjacent pituitary and may distort the pituitary stalk. When larger lesions demonstrate extrasellar extension, MRI scans can help delineate the relationship of the cavernous sinus laterally and the optic chiasm superiorly. If a plane of normal pituitary tissue can be observed on coronal-view, T1-enhanced images, the likelihood of cavernous sinus involvement is extraordinarily low. When there is significant suprasellar extension, the optic chiasm can be difficult to identify and may be best seen on coronal-view, fast spin-echo T2-weighted images. Pituitary apoplexy is caused by intratumoral hemorrhage and can be seen on T1-weighted images as an area of high signal intensity.

Imaging studies other than MRI may be needed. High-resolution CT may be used when MRI is contraindicated (i.e., because the patient has a pacemaker). CT scans can be useful when planning for transsphenoidal surgery. Pneumatization of the sphenoid sinus and cortical thinning of the sellar floor can be determined by bone windows. Angiograms are useful when aneurysms are considered within the radiographic differential diagnosis.

Differential diagnosis for a sellar lesion includes pituitary adenoma, congenital lesions (craniopharyngioma and Rathke's cleft cyst), infiltrative disease (granuloma, lymphocytic hypophysitis, and tuberculosis), primary lymphoma, chordoma, germ cell tumor, metastases, arachnoid cysts, aneurysm, inflammatory lesions, and meningiomas.

Serial MRI should be performed on a regular basis to detect tumor recurrence. Following SRS or radiation therapy, the initial scan should be obtained 6 months after treatment and then yearly.

Staging

Classification of detectable or symptomatic pituitary tumors can be based on endocrine dysfunction, clinical presentation, and anatomic extent of disease. These tumors can also be broadly classified as functional or nonfunctional based on their secretory activity. As adenomas enlarge, they can extend into suprasellar, parasellar, or infrasellar structures. To aid with surgical and imaging assessment, Hardy and Verzina[57] developed a classification system. Wilson's[58] modification of this classification system incorporates imaging and intraoperative findings of sellar destruction (grade) and extrasellar extension (stage). Others have defined giant adenoma as a lesion with extension beyond the sella and suprasellar space or size greater than 4 cm.[59,60] No universally accepted staging system exists for pituitary tumors.

PRIMARY THERAPY

General Strategies

The primary objectives of therapy include preservation or restoration of normal hormonal function, reversal of endocrine dysfunction, removal or control of the tumor mass effect, and reversal of neurologic symptoms while minimizing potential morbidity such as hypopituitarism. Modern surgical approaches, medical management, and innovative radiation techniques have improved the likelihood of accomplishing these goals.

Surgery

Advances in transsphenoidal approaches with microsurgical techniques have made this procedure the initial treatment of choice for patients with nonfunctioning pituitary adenomas, acromegaly, Cushing's disease, and TSH-secreting adenomas. Surgery provides immediate decompression for patients with progressive visual loss, symptomatic pituitary hemorrhage (apoplexy), or other signs or symptoms of neurological mass effect such as cranial neuropathy or hydrocephalus. For patients with prolactinoma who do not tolerate or respond to medical therapy, surgery can be considered. Surgery has also been useful in reducing the tumor bulk for combined management with radiation therapy or medical therapy. For patients undergoing SRS, surgery may play an important role because

a distance of 2 mm to 5 mm is needed between the tumor and the optic apparatus to deliver a sufficient dose to the tumor and to minimize the risk for optic neuropathy. Reoperation results in lower rates of success compared with the initial surgery.[61]

Four different transsphenoidal approaches (transnasal, sublabial/transseptal, transethmoidal, or transantral) can be considered. The transsphenoidal technique is the preferred approach for microadenomas, for pituitary tumors with extension toward the sphenoid sinus, and for some macroadenomas with suprasellar extension. This technique provides decompression of the optic chiasm and removal of intrasellar and suprasellar tumor tissue.

Transcranial surgery is generally reserved for large intracranial extensions and for cases in which transsphenoidal surgery has technical limitations (e.g., small sella and inadequate pneumatization of the sphenoid sinus).

A wholly endoscopic approach, for which nasal septal or oral incisions are not needed, may be used, and appears to have results that are similar to minimally invasive transnasal or sublabial approaches, although no true randomized, head-to-head comparisons have been conducted to determine whether complications or length of hospitalization are altered.[62,63] For patients undergoing endoscopic endonasal approaches, nasal crusting (98%) and discharge (46%) were the most common postoperative symptoms based on a prospective cohort study.[64] It may also be used to complement microsurgical approaches.

Finally, a supraorbital approach (the Lynch or modified Lynch procedure) has also been used for recurrent and residual suprasellar tumors. This approach allows one to avoid scar tissue from previous approaches and provides access for optic apparatus decompression.[65]

The various approaches for giant pituitary tumors (>4 cm) have recently been compared in a systematic review by Komotar et al.[66] Endoscopic endonasal approach resulted in a higher rate of gross total resection (GTR) (47.2% versus 9.6%; $p < 0.003$) and improved visual outcomes (91.1% versus 45.7%; $p < 0.003$) than either the microscopic transsphenoidal or the open transcranial approach for these tumors. It is important to note that the open transcranial approach may remain the treatment of choice for certain tumors and factors such as suprasellar extension (particularly lateral extension) and the location of the optic chiasm should be accounted for during selection of the operative technique. Berkmann[67] described the use of intraoperative MRI in 32 patients with tumors exhibiting suprasellar extension and causing visual impairment. The authors used a 0.15 T MRI to perform intraoperative pituitary imaging after safe resection was thought to be complete. Following the intraoperative MRI, additional tumor was removed in 8 patients (25% of cases).

Based on a questionnaire study of 958 neurosurgeons reporting on their own experience with transsphenoidal surgery, the risk for complications was inversely proportional to the surgeon's level of experience.[68] Reported complication rates among experienced surgeons include perioperative mortality (<1%), central diabetes insipidus (2%), cerebrospinal fluid (CSF) rhinorrhea (2%), and meningitis (2%). Transient central diabetes insipidus is reported to occur in up to 22% of patients at an active pituitary surgery center.[69] These complications are more common in patients with macroadenomas. The experience of the surgeon may influence the rate of this and other complications.[63,70]

The incidence of postoperative CSF rhinorrhea after transsphenoidal surgery ranges from 0.5% to 15% with the majority reporting 0.5% to 6%.[71] Use of a synthetic collagen fleece may decrease CSF leak and can help avoid the use of a lumbar drain.[71]

Medical Therapy

Because management of hormonal dysfunction as a result of oversecretion or undersecretion can have significant effects on quality of life and longevity, medical therapies play an important role in the management of patients with pituitary tumors as either primary or adjuvant therapy. Primary goals include correction of hormonal dysfunction and reduction of the mass effect from a secretory adenoma.

The initial treatment of choice for most prolactinomas includes dopamine agonists such as bromocriptine or cabergoline because they are highly effective in controlling hyperprolactinemia. Dopamine is the primary neuroendocrine inhibitor for the secretion of prolactin from the anterior pituitary gland. Dopamine produced by neurons in the arcuate nucleus is secreted into the hypothalamo-hypophyseal blood vessels of the median eminence, which supply the pituitary gland. The lactotrope cells that produce prolactin secrete prolactin continuously in the absence of dopamine; dopamine inhibits this secretion. Thus, in the context of regulating prolactin secretion, dopamine was historically referred to as prolactin-inhibiting factor and is sometimes still referred to as prolactin-inhibiting hormone, or prolactostatin. Therefore, dopamine-agonists would be expected to and have been shown to be clinically effective at reducing prolactin secretion. In addition, partial tumor regression and improvement in mass effect from an enlarged adenoma are frequently observed with medical treatment alone. Long-term maintenance treatment is generally necessary to control hyperprolactinemia and growth of a prolactinoma.

Medical therapy can be used in several situations for patients with GH-secreting tumors as well. Somatostatin analogs such as octreotide or lanreotide can be used to lower elevated GH levels before surgery, for patients with persistent GH and IGF-1 elevation after surgery and for patients who continue to receive medical therapy until radiation therapy or radiosurgery has taken full effect. Pegvisomant is a modified version of human GH designed to bind to and block the GH receptor. It blocks the action of GH at the GH receptor level, especially in the liver, to reduce the production of IGF-1, which is responsible for most of the symptoms of acromegaly, thus normalizing its levels is effective in controlling the symptoms of acromegaly.[72] A number of concerns remain regarding its use, including high cost, a number of side effects such as reactions at the injection site, swelling of the limbs, chest pain, hypoglycemia, nausea, and hepatitis, but more importantly the fact that blocking of the GH receptor reduces feedback control of the GH regulation leading to increase in GH levels, the long-term effects of which remain ill-defined.

Medical management of Cushing's disease is generally reserved for patients who have failed surgery or radiation therapy, although this is controversial. Agents that modulate pituitary ACTH release (cyproheptadine), glucocorticoid antagonists (RU486), or agents that inhibit steroidogenesis (ketoconazole) must be taken for the rest of the patient's life and are associated with a number of side effects.

Medical treatment of hormonal deficiencies resulting from the pituitary tumor may be optimally managed by an endocrinologist, at least at those times when rapid or significant replacement or medication adjustment is needed. Hypopituitarism can have variable clinical manifestations, and management should be individualized to minimize the impact of this condition. Depending on the deficiency, glucocorticoids, gonadal steroids, and thyroid hormones may be needed. Commonly used medicines include hydrocortisone and cortisone acetate for glucocorticoid replacement and L-thyroxine for hypothyroidism. Gonadal steroids used include estrogen and progestin for women and testosterone for men. Careful

optimization of medication supplementation, especially to avoid supraphysiologic doses of steroids, appears to be important in minimizing the effect of hypopituitarism.[73]

Radiation Therapy and Stereotactic Radiosurgery

Radiation therapy and SRS are important and useful treatment options for select patients with pituitary tumors. They can be considered as postoperative treatment after subtotal removal of a pituitary adenoma, as treatment for recurrent or progressive tumors after surgical or medical treatment, and as primary treatment when surgery or medical therapy is contraindicated or ineffective. Unlike medical therapy, radiation options offer the potential for definitive control of the tumor and permanent reduction of hormone hypersecretion. Radiographic control of the tumor occurs in the vast majority of patients. Normalization of excess hormone production is, however, relatively slow, and quite variable, and depends on a number of factors. Because the effect of radiation on tumor control or hormone suppression may take years, the use of radiation therapy and SRS is variable among institutions. The type of radiation used depends on a number of factors, including tumor size, proximity of the tumor to the optic apparatus, technology availability and expertise, and physician preference.

The lack of prospective, randomized data comparing different radiation delivery methods has resulted in strong proponents for fractionated versus radiosurgical approaches.[74-76] Most of the literature is based on single-institutional results. Fractionated radiation therapy has the benefit of limiting radiation damage to nearby radiation-sensitive structures such as the optic apparatus, whereas SRS can be conveniently performed in a single session and results in more rapid biochemical remission.[77]

Advances in radiation therapy have led to techniques that allow more focused delivery of radiation to the tumor and decreased dose to the normal brain. Sophisticated treatment planning systems, incorporation of CT and MRI studies, stereotactic guidance, radiation therapy approaches such as intensity-modulated radiation therapy (IMRT) and image-guided radiation therapy (IGRT), micro-multileaf collimators, and relocatable frames or masks have improved precision.[76,78,79] Results with radiation therapy, including specifics regarding dose and margin selection, will be discussed in greater detail later in the chapter.

SRS delivers a highly focused, single, large fraction of ionizing radiation to a small intracranial target volume (Figure 29-3). Frame-based systems (e.g., proton beam, helium ion, Gamma Knife, and linear accelerator SRS techniques) and frameless systems (e.g., CyberKnife and linear accelerator-based units) have been used to treat pituitary tumors. Given the sharper dose gradient of SRS versus fractionated approaches, the potential for radiation injury to normal brain and vessels and secondary tumor formation may be less with SRS.

Because the results with SRS vary widely, the comparison of SRS with other treatments is difficult. Many of the published studies have used a wide range of tumor delineation approaches, doses, different prescription isodose line selection, different definitions for response or cure, and short follow-up times, and of course there is selection bias because larger tumors are often not selected for SRS. A wide spectrum of peripheral doses, ranging from 12 Gy to 35 Gy prescribed to the 30% to 100% isodose line have been used, although higher doses are typically reserved for secretory tumors. It is generally believed that lower doses (14 Gy to 18 Gy) are sufficient for nonfunctioning adenomas where the primary goal is radiographic tumor control, whereas higher doses (18 Gy to 35 Gy) are needed for functioning pituitary tumors, where the primary goal is ablation of endocrine oversecretion. Because the efficacy of SRS for functioning pituitary adenomas may be compromised by the concomitant use of cytostatic hormone-suppressing medical therapies, these drugs are typically stopped 6 to 8 weeks before and after SRS.

Given the proximity of the pituitary tumor to adjacent critical structures, particularly the optic nerves and chiasm, appropriate selection of patients for SRS is needed. The optic apparatus (optic chiasm and nerves) is the major dose-limiting critical structure in SRS and fractionated treatment planning. A single-fraction dose to the optic chiasm should be limited to 8 Gy to 9 Gy to minimize damage to the visual pathways. A retrospective review to evaluate the risk of clinically significant radiation optic neuropathy (RON) for patients having undergone SRS for tumors adjacent to the optic apparatus showed that 1.9% developed RON with a median maximum radiation dose to the optic nerve of 10 Gy.[80] RON developed at a median of 48 months after SRS. The authors suggested a clinically significant risk of RON of 1.1% for those who receive 12 Gy or less to a small segment of the optic apparatus. Accurate localization of the target volume and the optic chiasm using MRI is essential. For patients undergoing fractionated treatment, the dose to the chiasm should not exceed 54 Gy and the dose per fraction should be

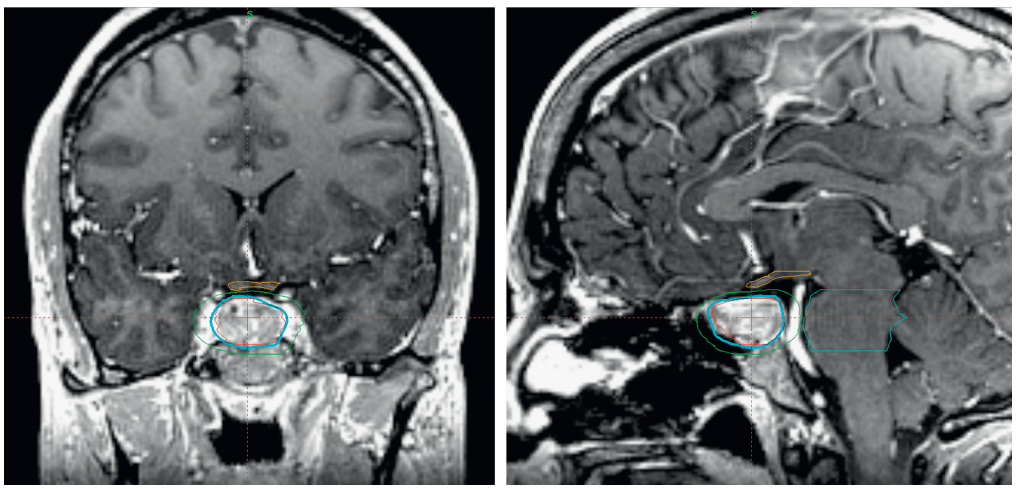


Figure 29-3 Stereotactic radiosurgery plan (coronal and sagittal) for a patient with a nonsecretory pituitary adenoma. A dose of 16 Gy was prescribed to the 50% isodose line *(blue)*. The 8-Gy isodose line is shown in green. The maximum dose to the optic chiasm *(outlined in orange)* was 6.4 Gy.

1.8 Gy/day. It is important to minimize the hot spot around the optic nerves and chiasm.

Unlike the optic nerves, the cranial nerves in the cavernous sinus are more resistant to radiation effects.[81] This may be a result of the increased sensitivity of sensory nerves such as the optic and acoustic nerves compared with the nonsensory nerves of the parasellar region. After repeat SRS, nonsensory cranial neuropathy, however, has been reported.[82]

TREATMENT STRATEGIES FOR SPECIFIC TUMORS

Nonfunctioning Adenoma

Nonfunctioning adenomas are the most frequent type of macroadenoma and typically present with decrease in visual acuity and constriction of the visual field defects, and in some cases, varying degrees of hypopituitarism.[83,84] Nonfunctioning adenomas account for approximately 30% of all pituitary adenomas and often extend beyond the sella turcica. Other presenting symptoms may include headaches from local mass effect or obstruction of the third ventricle causing hydrocephalus, cranial nerve deficits from cavernous sinus involvement, and hypopituitarism resulting from compression of the pituitary gland. Evaluation should include visual field testing, MRI scanning, and an endocrine workup. Generalized, schematic treatment algorithms for a nonfunctioning pituitary microadenoma and macroadenoma are outlined in Figures 29-4 and 29-5, respectively.

Surgery

Management of a nonfunctioning pituitary adenoma is influenced by the size of the tumor, symptoms, physical examination findings, and associated endocrine disorders. For a microadenoma or asymptomatic nonfunctioning adenoma, observation is generally recommended. For a symptomatic tumor or one with mass effect causing progressive symptoms or measurable visual impairment, surgery is the best option because it provides pathologic tissue confirmation, immediate debulking of the tumor, and amelioration of the mass effect, especially relative to the optic chiasm, in 90% to 95% of patients. The results with surgery are variable and depend on the extent of resection possible because of location of invasion (within the subarachnoid spaces intracranially, the cavernous sinuses, or the nose/paranasal sinuses). Recurrence rates range from 10% to 18% at 5 to 6 years and 20% to 80% at 10 years.[85-87]

Medical Therapy

No medical treatment has consistently reduced the size of nonfunctional pituitary adenomas. The use of a dopamine agonist is not recommended because response is uncommon.

Radiation Therapy Options

If the tumor cannot be completely removed, surgical decompression followed by radiation therapy or SRS can provide excellent results. For patients with recurrent tumors or those who are not good surgical candidates, fractionated radiation therapy or SRS can be considered, depending on the proximity of the tumor to the optic apparatus, as well as growth rate on

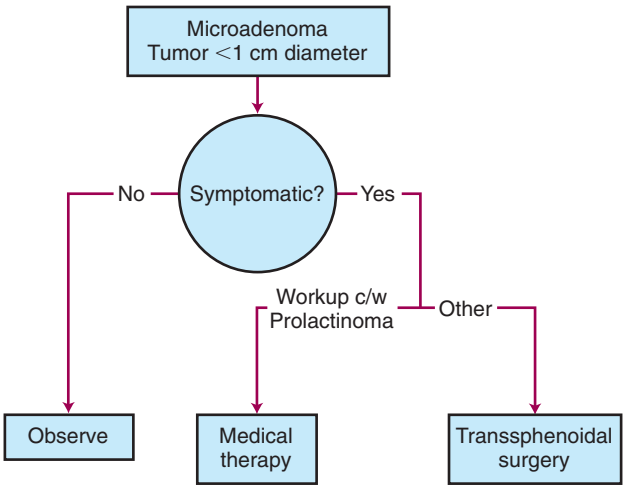


Figure 29-4 Generalized treatment algorithm for pituitary microadenoma.

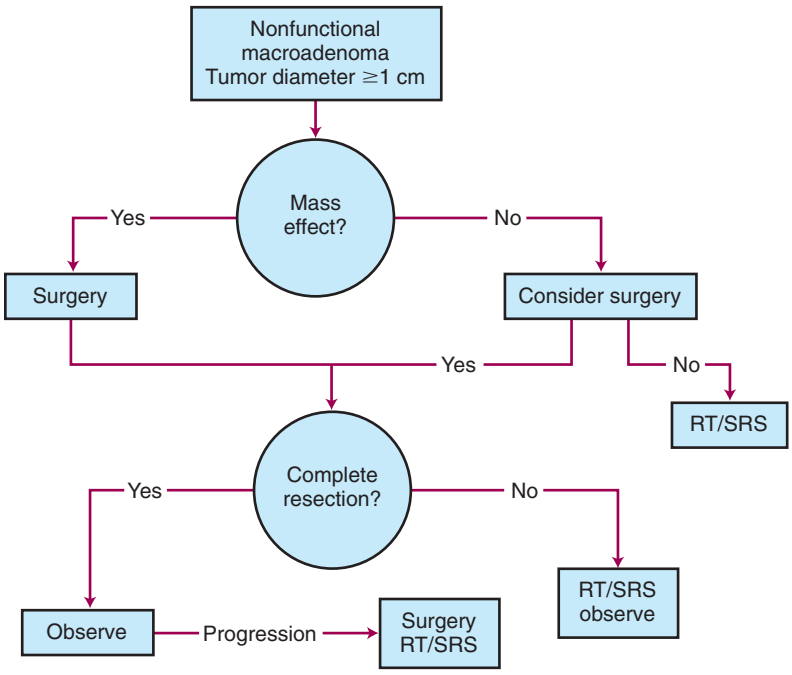


Figure 29-5 Generalized treatment algorithm for nonfunctional pituitary macroadenoma. *RT*, Radiation therapy; *SRS*, stereotactic radiosurgery.

sequential MRI scans. Table 29-1 summarizes some of the recent larger studies of SRS using doses ranging from 13 Gy to 20 Gy.[88-95] Using these doses, the local radiographic control rates are excellent (90% to 100%). The tumor volume in more than half of these patients decreases on follow-up MRIs. Hypopituitarism occurs in up to 39% of patients. More recent series have not reported visual complications, especially when the maximum dose to the optic apparatus is kept below 8 Gy to 9 Gy.

Numerous retrospective studies have demonstrated excellent local control rates with conventional fractionated radiation therapy (45 Gy in 25 fractions). The largest series from Brada et al[96] of 252 patients reported local control rates of 97% and 92% at 10 and 20 years, respectively. Another large study from Sasaki et al[97] demonstrated a 98% local control rate at 10 years. No prospective trials have compared fractionated radiation therapy to SRS.

Prolactinoma

Prolactinomas are the most common functioning pituitary tumors, with the vast majority occurring as microadenomas in women. Symptoms may include amenorrhea, galactorrhea, and infertility in women and decrease in libido, infertility, and visual disturbances in men. Diagnosis is typically made from sustained elevation of serum prolactin levels above the normal range. MRI of the brain can help confirm the diagnosis, although a negative MRI can be seen in women with microadenomas.[98]

Goals of treatment include restoration of sexual and reproductive function, normalization of prolactin levels, control of galactorrhea, and improvement of neurologic symptoms. It is important that other causes of increased prolactin levels such as effects of medicines, pregnancy, and renal insufficiency are considered in the differential diagnosis. Treatment options include observation, medical therapy, surgery, and irradiation.[48] A generalized schematic treatment algorithm for a prolactinoma is outlined in Figure 29-6.

Surgery

Surgery is standard second-line therapy and is reserved for patients who cannot tolerate medical therapy or are not responsive to maximally tolerated dose of dopamine agonists,[99] have rapid progressive vision loss, or women who wish

TABLE 29-1 Summary of Recently Published Larger Studies of SRS for Nonfunctioning Pituitary Adenomas

Author	Year	No. Pts	Follow-up (mo)	Peripheral Dose (Gy)	Local Control Rate (%)	Visual Complication Rate (%)	Hypopituitarism Rate (%)
Mingione[88]	2006	100	46.4*	18.5	92.2	0	25
Liscak[89]	2007	140	60	20	100	0	1.4
Pollock[90]	2008	62	64	16	96.8	0	27
Park[91]	2011	125	62	13	90	0.8	24
Gopalan[92]	2011	48	95	18.4	83	0	39
Iwata[93]	2011	100	33	21/3 fractions 25/5 fractions	98	1.7	4
Starke[94]	2012	140	50.4	18	90	0†	30.3
Sheehan[95]	2013	512	36	16	93	NA	21

Gy, *Gray;* mo, *months; NA, not available; SRS, stereotactic radiosurgery.*
**Mean follow-up.*
†15 patients (12.8%) had visual decline secondary to tumor progression.

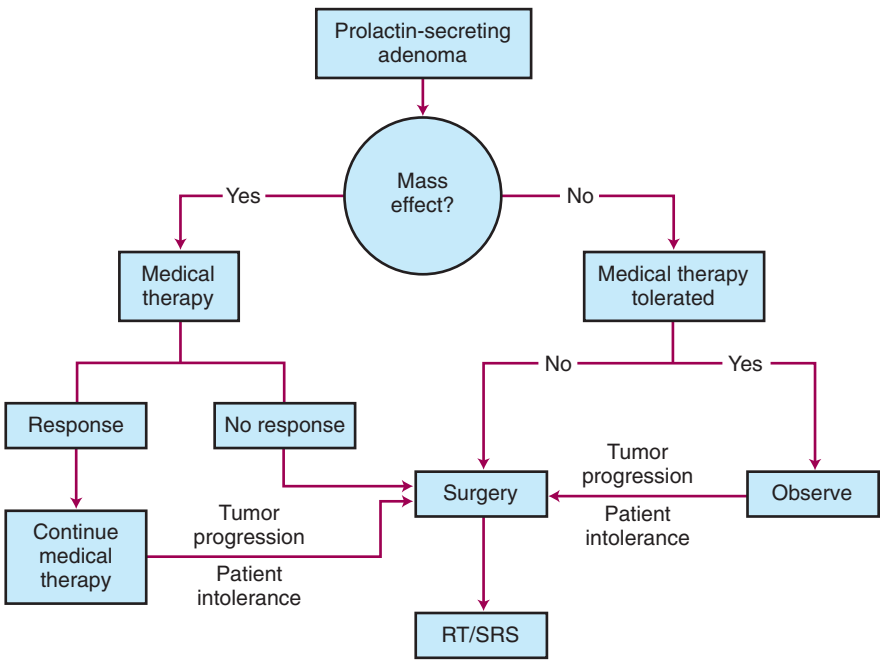


Figure 29-6 **Generalized treatment algorithm for prolactin-secreting adenoma. Note: some patients may elect to have surgery as definitive therapy.** *RT,* Radiation therapy; *SRS,* stereotactic radiosurgery.

to conceive. Based on a review of 50 surgical series of more than 4000 patients, the curative surgical resection rates for microprolactinomas and macroprolactinomas was 74.7% and 33.9%, respectively, using a normalization of prolactin levels before 12-week follow-up as the definition of remission.[100] Biochemical recurrence, however, occurs in 20% of patients within the first year. The best predictor for persistent cure is a prolactin level less than or equal to 5 ng/mL on postoperative day 1. The long-term surgical cure rates for microprolactinomas and macroprolactinomas are 50% to 60% and 25%, respectively, where a cure is considered normal prolactin levels. Surgery is also sometimes used in women with a large adenoma who want to become pregnant.

Medical Therapy

The initial treatment of choice for patients with prolactinoma is medical therapy with a dopamine agonist such as bromocriptine or cabergoline because these drugs decrease secretion and tumor size in most patients. Medical therapy can rapidly normalize prolactin levels and reduce tumor size in 80% to 90% of patients.[100] Bromocriptine, which is taken two or three times per day with meals, is associated with a greater number of side effects (e.g., nausea, vomiting, fatigue, and orthostatic hypotension) compared with cabergoline, which is taken once or twice a week. In a double-blinded study of 459 female patients comparing bromocriptine with cabergoline over 8 weeks, normal prolactin levels were achieved in 59% and 83% of patients, respectively.[101] Cabergoline was better tolerated, with 3% discontinuing its use versus 12% who stopped taking bromocriptine. Because cabergoline has been associated with an increased risk for cardiac valve thickening in patients with Parkinson's disease, who take much higher doses compared with patients with prolactinoma, this potential risk needs to be reviewed and carefully monitored.[102] For some patients, medical therapy may be gradually withdrawn every 2 years to 3 years to assess remission. This strategy is most effective for patients with low prolactin levels and small tumors. Approximately 8% of patients with prolactinoma are intolerant to or unresponsive to medical treatment.

Because the risk of symptomatic tumor enlargement during pregnancy is low for microprolactinomas (3% to 5%), it is recommended to stop medical treatment as soon as diagnosis of pregnancy is established[103,104]

Radiation Therapy Options

Based on the success of dopamine agonists and because of the risk for hypopituitarism in young female patients, radiation therapy or SRS is usually reserved as third-line therapy. For patients who do not respond to or are intolerant of medical therapy and are not candidates for surgical salvage, radiation options may be considered.

The results with conventional radiotherapy from the late 1970s to the early 1990s have been modest. One of the earliest studies from Sheline et al[105] of 28 patients demonstrated a prolactin normalization rate of 29%. Littley et al[106] found a decrease in serum prolactin levels in all 58 patients treated with external beam radiation therapy (EBRT) and a 50% probability of prolactin level reduction to 500 mU/L in 10 years. Patients more likely to achieve normalization of serum prolactin levels after EBRT had smaller tumors, pretreatment prolactin levels higher than 6000 mU/L, and tumors with positive immunostaining for prolactin. Tsagarakis[107] reported normal serum prolactin levels at a mean of 8.5 years after EBRT in 18 of 36 patients. Pituitary irradiation can lead to hypothalamic dysfunction and impairment of dopamine secretion, which causes hyperprolactinemia. This may explain the mildly elevated prolactin levels (usually, <50 mU/L) in some patients after radiotherapy of pituitary adenomas.

SRS has also been used after failure of medical therapy or surgical treatment. Table 29-2 summarizes recent larger publications on the results of SRS for prolactinomas with normalization rates for prolactin ranging from 17% to 43.5%.[108-113] A multidisciplinary approach is important to optimize treatment.[114]

Because it may take some time for normalization of prolactin levels to occur after EBRT or SRS, the use of dopamine agonists may be required. Landolt[115] reported worse outcomes for patients receiving dopamine agonists at the time of SRS. Pouratian[116] also reported worse outcomes in patients receiving antisecretory medication at the time of SRS. Antisecretory medications may alter the cell cycle, which makes the tumor cells less radiosensitive. As a result, a 2-month break between medical therapy and SRS has been suggested.[115]

Acromegaly

Acromegaly is a rare condition, with a prevalence of approximately 60 per million. GH hypersecretion leads to metabolic and functional disturbances of multiple organs (i.e., cardiovascular, musculoskeletal, and respiratory dysfunction) and an increased incidence of colonic polyps, although whether this increases the incidence of colorectal cancer is not fully determined.[49] The overall life span of patients with acromegaly is shorter than their normal counterparts, implying a significant risk of disease-associated mortality in the long term. In addition, characteristic bony and soft-tissue enlargement occurs in the frontal bones, hands, feet, spine, nose, and mandible. As a result, early diagnosis and treatment are essential to minimize the impact on life expectancy and morbidity. Unfortunately, the gradual onset of symptoms and changes as a result of excessive GH secretion delays diagnosis in many patients.

Although surgery is the initial treatment of choice for most patients, a multidisciplinary approach is often needed given

TABLE 29-2 Summary of Recently Published Larger Studies of SRS for Prolactinomas

Author	Year	No. Pts	FU (mo)	Peripheral Dose (Gy)	Hormone Remission Rate (%)	Local control rate (%)	Visual complication rate (%)	Hypopituitarism Rate (%)
Wan[108]	2009	176	67.3	35	23.3	90.3	0	1.7*
Kobayashi[109]	2009	27	37.4	18.4	17.4	100	0	0
Jezkova[110]	2009	35	75.5	49	37.1	97.1	0	14.3
Tanaka[111]	2010	22	60	25	17	100	0	42
Sheehan[112]	2011	32	31	24	26	93†	NA	38
Liu[113]	2013	22	36	15	27.3	86.4	0	4.5

FU, *Follow-up;* Gy, *Gray;* mo, *months;* NA, *not available;* No. Pts, *number of patients; SRS, stereotactic radiosurgery.*
**Included all 347 secretory adenomas treated with SRS.*
†*Included patients with acromegaly treated with SRS.*

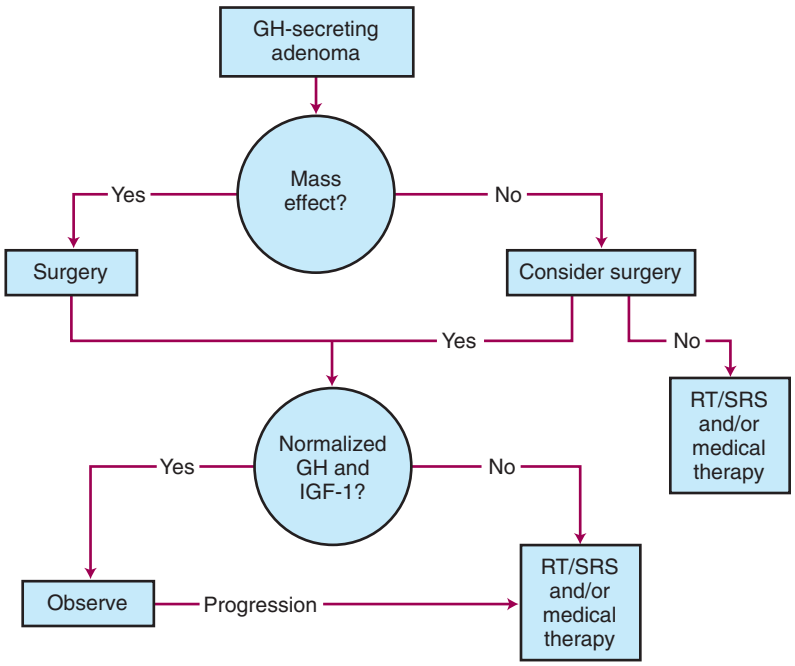


Figure 29-7 Generalized treatment algorithm for growth hormone–secreting adenoma. *GH*, Growth hormone; *RT*, radiation therapy; *SRS*, stereotactic radiosurgery.

the complexity of this disease.[117] Because liver-derived IGF-1 mediates the effects of GH at the tissue level, the primary goal of therapy is to normalize IGF-1 levels to within the reference range for the patient's age and gender; additional therapeutic goals are to preserve pituitary function and to prevent tumor growth. Normalization of age- and sex-matched IGF-1 levels and the suppression of serum GH levels to less than 0.4 mg/L in response to a 75-g oral glucose load are generally used to define biochemical cure for acromegaly.[118] Normalization of IGF-1 levels is a better criterion for cure than GH levels because some patients with acromegaly can have normal GH levels.[118,119] Untreated or incompletely treated acromegaly is associated with significant morbidity and excess mortality, which may be as high as three times that of the general population.[73,117] The treatment options for acromegaly include surgery, irradiation, medical therapy, or a combination of treatment approaches. A generalized treatment algorithm for acromegaly is outlined in Figure 29-7.

Surgery

The initial treatment of choice for acromegaly is surgery.[117,120] Goals of surgery include alleviation of mass effect from suprasellar extension and complete removal of the GH-secreting adenoma. Because the criteria used for biochemical cure have changed with time and the duration of follow-up varies, surgical series are not directly comparable. When surgery is performed by experienced pituitary neurosurgeons, the GH levels fall to normal in 80% to 90% of patients with microadenomas.[121,122] The success rate is lower in patients with higher preoperative GH concentrations or macroadenomas (<50%).[123] Recurrence rates after surgery are estimated to be approximately 20%.[124] Using modern criteria for cure (i.e., normal serum IGF-1 and glucose-suppressed GH concentrations of less than 1 ng/mL), the surgical remission rates are 70% and 61%, respectively.[125] The largest series evaluated 506 patients who underwent transsphenoidal surgery. Overall remission was 57.3% as defined by normalization of IGF-1 levels.[126] The normalization results for microadenomas and macroadenomas were 75% and 50%, respectively. A recent retrospective study of 46 patients with acromegaly with no residual tumor on postoperative MRI and nadir GH of less than 0.4 mg/L on a postoperative oral glucose tolerance test reported that the mean duration from surgery to IGF-1 normalization was 10 months (range, 3 days to 57 months).[127] Longer remission times were required for patients with higher postoperative IGF-1 levels.

Medical Therapy

Three different types of medicines (somatostatin analogs, dopamine agonists, and a GH receptor antagonist) are used to treat patients with acromegaly who have failed surgery, are not surgical candidates, or are refractory to radiation options. Given the latency for normalization of IGF-1 and GH levels after irradiation, medical therapy is also used as an adjunct after radiation treatments. The most commonly used medicines are the somatostatin analogs (octreotide and lanreotide) rather than somatostatin, given the much higher potency and half-life of the analogs. These analogs bind to somatostatin receptors subtypes 2 and 5, reduce IGF-1 levels in 38% to 66% of patients and lead to tumor shrinkage in 30% to 45% of patients.[128-130] Response is best predicted by determining whether the subtype of somatotroph adenoma is sparsely or densely granulated.[131] The most common side effects of somatostatin analogs include nausea, abdominal cramping, diarrhea, and gallstones. A disadvantage of these agents is the lifelong dependence. Dopamine agonists such as cabergoline are generally not effective and are not used frequently unless a patient is unable to tolerate somatostatin analogs.

Pegvisomant, a GH receptor antagonist that is administered daily via the subcutaneous route, has been tested in a placebo-controlled randomized trial and shown to normalize IGF-1 levels in 90% to 97% of patients.[132-134] Side effects include flu-like symptoms, nausea, diarrhea, and abnormal liver function tests. Because pegvisomant does not inhibit GH secretion or tumor growth, it is not used as first-line therapy. Pegvisomant requires lifelong treatment, may cause elevated aminotransaminases in 20% of patients, and may carry a small risk for increase in tumor size. In addition, pegvisomant is extraordinarily expensive compared with other medical therapies.

Radiation Therapy Options

Irradiation can be used in the definitive or adjuvant setting for patients with acromegaly. Given the relatively long lag time for normalization of the IGF-1 and GH levels after radiation treatment, it is important that these patients be followed closely with blood work every 3 to 6 months and yearly MRIs. If patients are taking a short-acting (daily) somatostatin analog (SSA), they may need to be off medication for about 1 month, or longer, to assess the efficacy of radiation; the interval for a patient on a long-active SSA, given once monthly, may need to be on a medication holiday up to 3 months, which means that perhaps only once yearly IGF-1 level will be measured. The published reports on radiation therapy and SRS have typically used varying definitions of cure relative to GH levels. Earlier publications, which defined remission as growth hormone levels below 5 ng/mL to 10 ng/mL, reported remission rates of 80% to 100%.[135,136] Using modern definitions for normalization of both GH levels (<2 ng/mL) and IGF-1 levels, the results for radiation therapy and SRS are less impressive. Table 29-3 summarizes the recent radiation therapy results.[137-141]

The rate of hormone remission and hypopituitarism at 10 years is approximately 50% to 60% and 60% to 80%, respectively. The largest study, a retrospective review of 884 patients with acromegaly undergoing radiotherapy, demonstrated that 63% of patients had normalization of IGF-1 levels by 10 years.[139] In this series, new hormone deficiencies included 18% for LH and FSH, 15% for ACTH, and 27% for TSH. Variability in the success rates in normalization of IGF-1 levels for patients undergoing radiation therapy may be a result of differences in pretreatment serum GH concentrations. Within the first 2 years mean GH values drop to 50% to 70% of their maximal values, followed by a slow decrease over years.[142] Higher doses of EBRT may be considered when treating patients with acromegaly (50.4 Gy to 54 Gy versus 45 Gy for nonfunctional tumors).

Table 29-4 summarizes the recent SRS results that have used IGF-1 level normalization as the definition for cure.[108,112,143-147] Using peripheral doses of 20 Gy to 26.5 Gy, IGF-1 level normalization rates range from 17% to 60%. The local control rates are excellent, suggesting that SRS could possibly also have a definitive role in this condition. Mean time to remission ranges from 24 to 36 months for patients undergoing SRS. Although the time to remission appears to be faster with SRS compared with radiation therapy, the ideal SRS candidate should have a well-defined target volume that is far enough away from the optic chiasm, and this limits the use of SRS.[146]

It is important to note that the latency period to achieve the hormonal control is directly related to hormone level and therefore the tumor volume before treatment.[148] Medication may be used as an adjuvant treatment after radiation therapy to help lower the growth hormone and IGF-1 levels. Given the concern for the potential suppressive effects of somatostatin analogs, which may compromise the effectiveness of radiation therapy, some centers do not recommend using these medications for, typically, 6 to 8 weeks before and after radiation.[143,149]

TABLE 29-3 Summary of Recently Published Studies of Radiation Therapy for Acromegaly

Author	Year	No. Pts	Follow-up (yr)	Hormone Remission Rate (%)
Barrande[137]	2000	128	2	7
			5	35
			10	53
			15	66
Minniti[138]	2005	74	2	9
			5	29
			10	52
			15	77
Jenkins[139]	2006	884	2	22
			10	63
			20	77
Jallad[140]	2007	89	5.9	54
Mullan[141]	2009	63	5	66
			10	71

FU, *Follow-up;* No. Pts, *number of patients;* yr, *years.*

Cushing's Disease

Cushing's disease results from an ACTH-secreting adenoma of the anterior pituitary, which is responsible for 70% to 80% of ACTH-dependent Cushing's syndrome cases in adults. Given the many nonspecific symptoms and signs, the diagnosis is often delayed. This syndrome, which is associated with increased morbidity and age-corrected mortality, occurs more commonly in women and is a heterogeneous disorder. Clinical findings include truncal obesity, hirsutism, acne, easy bruisability, muscle weakness, and moon facies. These patients can have menstrual irregularities, gonadal dysfunction, hypertension, diabetes mellitus, and osteoporosis. Tests used to diagnose Cushing's disease include a 24-hour urine collection to

TABLE 29-4 Summary of Recently Published Larger Studies of Stereotactic Radiosurgery for Acromegaly

Author	Year	No. Pts	FU (mo)	Peripheral Dose (Gy)	IGF-1 Normalization Rate (%)	Local Control Rate (%)	Visual Complication Rate (%)	Hypopituitarism Rate (%)
Pollock[143]	2007	46	63	20	50	100†	0	33
Vik-Mo[144]	2007	53	66	26.5	17	100	4	13.1
Losa[145]	2008	83	69	21.5	60	97.6	0*	8.5
Castinetti[146]	2009	43	102	24	42	NA	NA	21
Wan[108]	2009	103	67.3	21.4	36.9	95.1	NA	1.7
Sheehan[112]	2011	130	31	24	53	93‡	0	34.0
Franzin[147]	2012	103	71	22.5	60.7	97.3	0	7.8

FU, *Follow-up;* Gy, *Gray;* mo, *months;* NA, *not available;* No. Pts, *number of patients.*

**Included other types of adenomas.*

†Six patients did not have measurement on follow-up scans.

‡Included patients with prolactinomas.

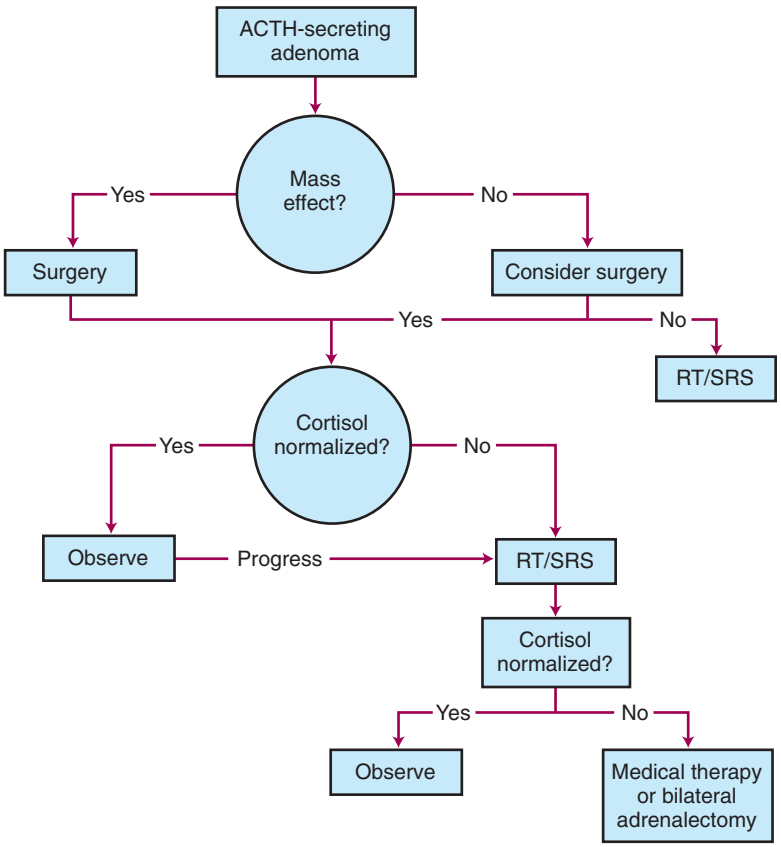


Figure 29-8 Generalized treatment algorithm for adrenocorticotropic hormone–secreting adenoma. *RT*, Radiation therapy; *SRS*, stereotactic radiosurgery.

measure urinary-free cortisol levels, midnight testing of ACTH levels, and dexamethasone suppression test among others.[47] Untreated or incompletely treated hypercortisolism is associated with significant morbidity and excess mortality, which may be as high as two to three times, or more, the rates of the general population.[73]

The treatment options for Cushing's disease include surgery, irradiation, medical therapy, total bilateral adrenalectomy, or a combination of treatment approaches.[150,151] Most centers define remission as urinary-free cortisol levels in the normal range with resolution of clinical findings or a series of normal serum cortisol levels obtained throughout the day.[152] A generalized, schematic treatment algorithm for Cushing's disease is outlined in Figure 29-8.

Surgery

Surgical removal of the pituitary adenoma is the best initial treatment for Cushing's disease because it can rapidly correct the hypersecretion of ACTH. Most patients have a microadenoma; 25% to 50% of patients with Cushing's disease will have no discernible lesion on MRI of the brain. Although a tumor is identified in 70% to 90% of cases, it is more likely that no tumor may be identified at the time of surgical exploration in patients with MRI-negative Cushing's disease.[153,154] For patients with no discernible lesion in whom surgery is being contemplated, bilateral inferior petrosal sinus sampling (BIPSS) may help improve the outcome, through better localization and lateralization. The inferior petrosal sinuses receive drainage from the pituitary without blood from other sources. Therefore, if the patient has pituitary Cushing's, the ACTH levels in the IPS are high compared to an ACTH level drawn in the periphery. In contrast, in ectopic Cushing's, the ACTH in the IPS and the periphery should be equivalent because the tumor is located elsewhere.

Ideally, an experienced neurosurgeon should remove the tumor in its entirety, leaving the normal pituitary intact. Although an abnormality may not always be seen on MRI of the brain, surgery leads to hormonal control in 80% to 90% of patients with microadenomas and in up to 50% with macroadenomas.[122] If a microadenoma cannot be identified in an adult patient in whom fertility is not an issue, one may perform either a hemihypophysectomy related to the potential side of localization suggested by BIPSS, although there remains concern about the localization capability of BIPSS. Total hypophysectomy is usually reserved for patients who undergo reoperation without visual identification at the second (or later) surgery of an adenoma, with remission rates of 50% to 70% even with this strategy.[155-158] Because dural invasion by ACTH-producing adenomas usually occurs laterally into the wall of the cavernous sinus, identification and removal of the invaded dura including the medial cavernous sinus wall allows for better biochemical cure.[159]

For most patients, the surgical approach is transsphenoidal. A series from Cavagnini of 300 patients with a follow-up time of 10 years demonstrated a remission rate of 70% and a recurrence rate of 15%.[160] In another study, low ACTH levels (<10 ng/mL) during the early postoperative period correlated with remission in 97.9% of cases, whereas an ACTH level of more than 30 ng/mL correlated with a remission rate of only 18%.[161] A more recent series from Patil et al[162] noted a 25% recurrence rate at 5 years for patients who achieved initial remission after transsphenoidal surgery. Given the varied results, experience with transsphenoidal surgery for Cushing's disease appears to be an important factor in terms of remission and recurrence.

If a patient does not achieve remission after surgery, a bilateral adrenalectomy can be considered. Patients undergoing bilateral adrenalectomy can develop Nelson's syndrome with

Under local anesthesia, femoral catheters are advanced bilaterally up to the IPS. After fluoroscopic confirmation of catheter position, multiple blood samples are drawn simultaneously from the right and left IPS and from a peripheral vein for ACTH level assessment, and the pituitary-to-peripheral ACTH ratios are calculated. If the ratio is greater than 2 the patient has Cushing's disease. If the pituitary-to-peripheral ratio is less than 1.5 to 1 the patient has ectopic Cushing's, and pituitary surgery should not be performed. Because each half of the pituitary drains into the ipsilateral IPS, BIPSS may also help lateralize the tumor.

a risk of 8% to 43% in adults[163] and 25% to 66% in children.[164,165] Bilateral adrenalectomy removes the peripheral source of cortisol, and hence the negative feedback suppression of ACTH production at the level of the pituitary is impaired; this can result in oversecretion of both ACTH and MSH (which is structurally similar to ACTH, and the loss of negative feedback results in oversynthesis of proopiomelanocortin, a precursor for both ACTH and MSH synthesis). This results in skin and mucosal hyperpigmentation, muscle weakness, and growth of the pituitary adenoma. For some patients, the growth of the adenoma can be quite rapid, leading to visual complications. Invasion of the cavernous sinus may cause cranial nerve palsies. In addition, the adenoma may be less responsive to radiation options, which is used in 20% to 30% of patients. Given its rarity and complexity and the controversies regarding diagnosis and treatment, it is one of the most challenging endocrine conditions.[166]

Medical Therapy

Medical management is reserved for patients who do not respond to surgery or irradiation options; lifelong therapy is needed. Medicines used to inhibit steroidogenesis include ketoconazole, aminoglutethimide, metyrapone, mitotane, and etomidate.[167] Ketoconazole is the best tolerated drug and is effective as monotherapy in up to 70% of patients. Because this drug can be hepatotoxic, it is important to monitor liver function tests. Metyrapone, an 11 alpha-hydroxylase inhibitor, is often used as an adjuvant to ketoconazole or radiation therapy.

Pasireotide, approved by the Food and Drug Administration (FDA) in December 2012, is a multireceptor-targeted somatostatin analog with high binding affinity to four of the five known somatostatin receptor subtypes (sst1, sst2, sst3, sst5)[168] and regulates anterior pituitary hormone secretion. Unlike other somatostatin analogs, pasireotide binds with the highest affinity to sst5, with 40-fold increased affinity to sst5 compared to other somatostatin analogs. Sst5 is the most prevalent somatostatin receptor expressed on ACTH-secreting pituitary adenomas.[169] In a double-blind Phase III, randomized, multicenter study (PASSPORT-CUSHINGS B2305) in 162 patients with de novo (if not surgical candidates), persistent or recurrent Cushing's disease, pasireotide demonstrated a rapid (approximately 50% decrease by 2 months) and sustained reduction in urinary-free cortisol levels, with significantly improved clinical signs and symptoms of Cushing's disease. Among those with a measurable pituitary tumor on MRI at baseline and month 12, mean percentage decrease in tumor volume was 43.8% in patients receiving pasireotide 900 µg bid.[170]

Radiation Therapy Options

Irradiation is typically used as an adjuvant for patients who are not cured after surgery. It can also be used definitively for patients unable to undergo surgery. For children, some consider this as the initial therapy because the cure rates are similar to those of surgery.[171,172] Both fractionated radiation therapy and SRS have been used to treat patients with Cushing's disease. For patients who are treated with EBRT, doses of 50 Gy to 54 Gy may be considered. One study from Estrada used postoperative irradiation (mean dose, 50 Gy) and reported an 83% remission rate at 5 years.[173] Minniti et al[174] reported on 40 patients with Cushing's disease who received 45 Gy of EBRT. The normalization rate of cortisol levels was 78% at 5 years and 84% at 10 years. Other EBRT series have yielded remission rates ranging from 46% to 56%.[175,176]

Most of the SRS series are small and report endocrine cure rates that are similar to the EBRT results. Recent series have reported remission rates of 28% to 53%,[82,108,109,112,177] which are listed in Table 29-5. As with other secretory tumors, the peripheral dose used is higher (>20 Gy). The largest series from Jagannathan[82] reported on 90 patients with a median follow-up of 45 months. In this series, a 54% remission rate was achieved. The timing of hormone normalization can be quite variable (2 months to 8 years), although most patients will achieve remission within the first 2 years. Patients with persistent disease should be considered for adrenalectomy or repeat SRS, which has been associated with higher rates of cranial nerve damage.[82] No trials have compared SRS with fractionated EBRT.

Nelson's Syndrome

Some Cushing's disease patients do not achieve remission after surgery or irradiation and may require bilateral adrenalectomy as salvage treatment. As a result, some patients may develop Nelson's syndrome, which is characterized by hyperpigmentation, rapid growth of the adenoma, and invasion of the tumor into the parasellar regions.[178] The few reports of SRS for Nelson's syndrome have resulted in endocrine remission rates of 36% or less.[179,180]

Thyroid-Stimulating Hormone–Secreting Adenomas

TSH-secreting adenomas are rare (0.5% to 1.5% of all pituitary tumors) and typically present as macroadenomas with mass effect and features of thyrotoxicosis.[181] Surgical removal of the TSH-secreting adenoma is the best treatment option after the hyperthyroidism has been controlled with medications. Because these tumors are usually large at diagnosis and can invade the sella or extend beyond it, complete removal can be difficult; for this reason, remission rates may be only 50% after surgery.[182] When the tumor cannot be completely removed or the patient is not a surgical candidate, irradiation can be considered. Somatostatin analogs or dopamine agonists have been used to decrease TSH hypersecretion. The use of octreotide results in normalization of TSH levels in 79% of patients.[183]

TABLE 29-5 Summary of Recently Published Larger Studies of Stereotactic Radiosurgery for Cushing's Disease

Author	Year	No. Pts	FU (mo)	Peripheral Dose (Gy)	Cortisol Normalization (%)†	Local Control Rate (%)	Visual Complication Rate (%)	Hypopituitarism Rate (%)
Jagannathan[82]	2007	90	45	25	53	95	5.6*	22
Petit[177]	2008	33	62	20	52	NA	0	52
Wan[108]	2009	68	67.3	23	27.9	NA	0	1.7
Kobayashi[109]	2009	30	64.1	28.7	35	100	NA*	NA
Sheehan[112]	2011	82	31	24	54	NA	NA	22

FU, *Follow-up;* Gy, *Gray;* mo, *months;* NA, *not available*; No. Pts, *number of patients.*

**Several patients had undergone previous stereotactic radiosurgery.*

†24-hour urinary-free normalization rate.

Etomidate can reduce cortisol levels within hours and is used for acute control of elevated cortisol levels. Etomidate, developed as an anesthetic induction agent, suppresses corticosteroid synthesis in the adrenal cortex by reversibly inhibiting 11-beta-hydroxylase; it leads to primary adrenal suppression and is associated with increased risk of pneumonia, sepsis, and death. In a retrospective review of almost 32,000 patients, etomidate, when used for the induction of anesthesia, was associated with a 2.5-fold increase in the risk of dying than those given propofol. Patients given etomidate also had significantly greater odds of having cardiovascular morbidity and significantly longer hospital stay. These results strongly suggest that clinicians should use etomidate judiciously.

Mitotane causes adrenal suppression of cortisol secretion and is cytotoxic to adrenocortical cells. It is typically used for patients who have failed multiple medical therapies. Until the effects of irradiation have normalized ACTH levels, hypercortisolism can be decreased by use of the aforementioned medications.

Gonadotropin-Secreting Adenomas

Gonadotropin-secreting adenomas usually present as macroadenomas with mass effect and hypogonadism. They secrete LH or FSH, alpha subunit, or a combination of these hormones. The results with irradiation are limited.

Pituitary Carcinomas and Aggressive Pituitary Tumors

Pituitary carcinomas are very rare (0.2% of all pituitary tumors).[184] They have clinical features of pituitary adenomas, with most secreting prolactin or ACTH. Because the malignant nature of these tumors cannot be clearly determined by pathologic testing, the diagnosis is a clinical one based on findings of subarachnoid spread, brain involvement, or systemic metastases from a pituitary tumor.[141] The overall prognosis for these tumors is poor despite aggressive treatments that have included radiation therapy with mean survival of 1.9 years.[185] Rare examples of persistent response to chemotherapy (temozolomide) have been reported.[186]

For patients with aggressive pituitary tumors, a significant number of the published cases have demonstrated a response to temozolomide. Overall, 24/40 (60%) of the published cases demonstrated a response to temozolomide. The highest response rates were seen among prolactinomas (73%) and ACTH-secreting tumors (60%), whereas nonfunctioning pituitary tumors exhibited lower response rates (40%). Responsivity became typically evident in the first 3 months of therapy and low MGMT expression, as determined by immunohistochemistry, was associated with a high response rate (76%), whereas high MGMT expression was not associated with responses. MGMT promoter methylation, however did not correlate with temozolomide response. Temozolomide is therefore the first chemotherapeutic agent to show substantial response rates in aggressive pituitary tumors. MGMT immunohistochemistry, but not MGMT methylation analysis, shows promise as a predictive tool.[187]

LOCALLY ADVANCED DISEASE AND PALLIATION

Repeated Course of Irradiation

If tumors recur after fractionated radiation therapy, a repeat course of fractionated treatments may be considered after careful consideration of alternative treatment options, the interval that has elapsed since the first course of radiation therapy, and the details of the prior radiation treatment (e.g., technique used, dose given, and fractionation schedule used). Schoenthaler reported on 15 patients who were reirradiated with a median dose of 42 Gy in 1.8-Gy to 2-Gy fractions.[188] Local control was achieved in 12 patients. All patients developed hypopituitarism from the initial or repeat course of radiation therapy. Two patients later developed pituitary carcinoma and temporal lobe radionecrosis. Flickinger et al[189] reported on 10 patients with suprasellar or pituitary tumors who were reirradiated with doses ranging from 35 Gy to 49.6 Gy in 1.8-Gy to 2-Gy fractions. Six patients had pituitary tumors. One patient developed optic neuropathy a little more than 1 year after completing the therapy. The study authors suggest that a 40% estimation of the original radiation dose effect is a reasonable guideline to account for prior radiation therapy.

Palliation of Metastases

Metastases to the pituitary occur infrequently and most commonly arise from breast and lung cancers.[190] The reported rates of breast cancer metastasizing to the pituitary range from 6% to 8%. The most commonly reported symptoms include diabetes insipidus, anterior pituitary dysfunction, visual field defects, and headaches. Most metastases occur in the neurohypophyseal region, although breast cancer metastases have a predilection for the adenohypophyseal region. Because these are invasive tumors, surgery is difficult. SRS (median dose, 13 Gy) has been used for select patients with a progression-free survival (PFS) rate of 66.7%, a 12-month survival rate of 18%, and a median survival time of 5.2 months.[191]

IRRADIATION TECHNIQUES AND TOLERANCE

Techniques of Irradiation

Before the advent of sophisticated radiation delivery techniques, imaging techniques, and treatment planning efforts, the field arrangement for pituitary tumors included a two-field, opposed lateral field technique, a three-field technique of two opposed lateral, and an anterior vertex field. Bilateral 110-degree coronal arcs with a 30-degree wedge and 330-degree rotational arcs were also used. Comparison of these various techniques demonstrated that the three-field technique delivered less dose to the temporal lobes than the two-field technique, the rotational techniques were superior to the stationary field techniques in terms of sparing the temporal lobes, and the four-field noncoplanar arc technique delivered less dose to the frontal lobe.[192] When comparing the three-field coplanar technique to the four-field noncoplanar arrangement, the mean volume of normal brain receiving dose was higher with the coplanar techniques.[193]

Modern techniques of fractionated radiation therapy and SRS have capitalized on improvements in immobilization, imaging, planning, and treatment delivery. Using a fixed head frame, SRS is delivered in one fraction using a linear accelerator (see Figure 29-3), cobalt unit (Gamma Knife), or protons. The use of SRS is limited to smaller tumors (<4 cm in diameter) that are 2 mm to 5 mm away from the optic apparatus.

Given the success of SRS in treating pituitary tumors, fractionated irradiation with highly conformal fields is being used more frequently for patients who are not ideal candidates for SRS or in centers that do not have access to SRS. The use of relocatable frames and precision thermoplastic masks and the daily verification of proper positioning before treatment have replaced conventional fractionated approaches at most centers. This precision allows for sparing of more normal brain tissue. As a result, the treatment margin around the tumor can be decreased to 3 mm to 5 mm. Minniti et al[76] reviewed the results of eight studies with 490 patients with functioning or nonfunctioning pituitary adenomas treated with stereotactic conformal radiotherapy. With a median follow-up of 39 months, tumor control was 98%. More recently, Kim reported 7-year PFS and disease-specific survivals (DSS) of 97.1% and 100%, respectively, for patients undergoing fractionated stereotactic radiation therapy.[194] The preliminary results suggest that conformal radiation techniques are equivalent to those of conventional radiation therapy, with significantly smaller brain volumes being irradiated, and in particular, with much lower doses to the temporal lobes. The potential difference in biologic effectiveness of SRS versus fractionated courses has not been tested in a prospective manner.

Treatment Morbidity

Both SRS and fractionated radiation therapy are well tolerated during and shortly following the course of treatment. Some patients undergoing fractionated irradiation may experience

temporary alopecia, fatigue, skin erythema, and headaches. Worsening of vision or other cranial nerve deficits during radiation therapy is uncommon. Patients undergoing frame-based SRS may notice headache, temporary tenderness and numbness of the pin sites, and fatigue. Because the treatment volumes with SRS are generally smaller compared with those of EBRT, the side effects are generally less for patients undergoing SRS. Unfortunately, no prospective trials have compared SRS with radiation therapy with regard to acute and long-term side effects. Unlike patients with some brain tumors, patients with pituitary tumors need to be followed for long periods of time because these tumors can recur 20 years or longer after primary treatment has been completed.

The most commonly reported long-term side effect from SRS and fractionated EBRT is hypopituitarism, and in particular hypothyroidism, which occurs in 30% to 80% of patients within 10 years after treatment. The cause for hypopituitarism (damage to the hypothalamus versus damage to the pituitary) is an area of debate.[195] Dosimetric data suggest that minimizing radiation dose to the pituitary and to the hypothalamus may reduce the incidence of radiation-associated hypopituitarism.[196] The risk of developing hypopituitarism following radiosurgery is lowered when the mean radiation dose to pituitary is kept below 15 Gy and the dose to the distal infundibulum is kept below 17 Gy.[197]

For patients undergoing conventional EBRT with older irradiation techniques, the incidence of optic neuropathy is 1% to 3% and the risk of radiation necrosis is 0% to 2%.[198,199] Fractionated radiation is associated with a low risk for optic pathway injury with estimate incidence of 0.8% to 1.3% at 10 years and 1.5% at 20 years.[96,200] A review of 34 studies of SRS for pituitary adenomas reported a 1% risk of decrease in visual acuity and a 1.3% risk for other cranial nerve neuropathies (trigeminal, oculomotor, trochlear, or abducens nerve) after SRS.[75] The Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC) report recommends optic chiasm dose tolerance ranges from 8 Gy to 10 Gy for single fraction and 55 Gy to 60 Gy for conventional fractionation.[201] If radiation-induced optic neuropathy occurs, it usually presents as painless vision loss within the first 3 years of treatment. Using modern radiation approaches and MRI-based planning, the risk for radiation necrosis and optic neuropathy should be 1% or less when using doses of 45 Gy in 25 fractions.

Vascular complications can also occur following EBRT and SRS although the risk of stroke is an area of debate. An increased incidence for cerebrovascular accidents has been reported for patients undergoing radiation therapy, although the relative contribution from irradiation remained to be determined.[202,203] The risk of injury to the cavernous portion of the carotid artery is low, with only a few case reports published.[204] Recently, 462 pituitary adenoma patients (236 of whom received radiotherapy) treated with surgery as primary therapy between 1959 and 2008 at the University Medical Center Groningen in The Netherlands were studied regarding the incidence of stroke.[205] The comparison of events was therefore between the two groups of patients with pituitary adenoma, treated with or without radiotherapy. Postoperative radiotherapy, mostly 45 Gy in 25 fractions, was not associated with an increased incidence of stroke (5.5% versus 5.3%, $p = 0.23$) or differences in causative mechanism or anatomic localization of stroke compared with surgery alone even though the follow-up was more than twice as long for the patients who had been irradiated. Preexisting coronary or peripheral artery disease was the primary stroke risk factors.

The effect of irradiation on neurocognitive status is not clear given the effects of other therapies, such as medications and surgery, and of the tumor.[206] It appears that patients who underwent surgery before radiation therapy may be at a higher risk for cognitive deficits.[207,208] A large study investigating radiotherapy effects on cognition,[209] noted a significant worsening in anterograde memory performance when comparing healthy controls to those with pituitary tumors treated with surgery or radiotherapy. This study showed that although treated pituitary tumors in general were associated with worsening memory, there was no significant difference when comparing the surgery and radiotherapy treatment groups.

Patients undergoing radiation therapy or SRS are at higher risk for secondary brain tumors. Brada reported that the cumulative risk for developing meningiomas and gliomas after the treatment of pituitary adenoma at 20 years is 2%.[210] An update from the Royal Marsden Hospital reviewed 426 pituitary adenoma patients treated with radiotherapy after resection and found a cumulative risk of second brain tumors of 2% at 10 years and 2.4% at 20 years with 12 years median follow-up.[211] Because the risk of second brain tumors may also be higher in patients with pituitary adenomas than the general population, estimating the relative risk of second brain tumors compared to general population may be flawed. Loeffler et al[212] reported on two patients with pituitary adenomas who developed new tumors following SRS. He concluded that the risk for new tumors after SRS appears to be significantly less than that after fractionated EBRT. Another study of 5000 Gamma Knife SRS patients followed for more than 10 years reported no increased risk of malignant disease.[213]

TREATMENT ALGORITHMS, CHALLENGES, CONTROVERSIES, FUTURE POSSIBILITIES, AND CLINICAL TRIALS

The optimal management of pituitary neoplasms requires a multidisciplinary and individualized approach because these tumors are diverse, are associated with morbidity and mortality, and present a challenge regarding the best treatment approach. Because the treatment management strategy varies depending on a number of factors, including the type of tumor (secreting tumor versus nonsecreting tumor), the imaging characteristics, and the clinical presentation and symptoms, a multidisciplinary approach ensures that the most effective therapy is being considered for each patient (see treatment algorithm by the five specific tumor types within prior section). Because surgical treatment, medical therapy, and radiation treatment options can be effective options, choosing the optimal treatment for an individual patient may be controversial and challenging. The patient's age, medical condition, compliance with medicine, treatment tolerance, and preference should also influence the decision, as should an assessment of the potential long-term effects of hypopituitarism on excess morbidity and mortality.[50] Close collaboration among the various disciplines is necessary for comprehensive long-term care. Clinical findings, endocrine evaluation, and MRI findings can establish the diagnosis of pituitary tumors in most patients and help define the initial treatment decisions.

Laboratory investigations and pituitary imaging provide detailed information concerning endocrine dysfunctions and anatomic relationships of pituitary tumors. Sophisticated surgical approaches and irradiation techniques provide safe and successful treatment of patients with pituitary adenomas. Pathobiologic assessments of pituitary tumors are yielding new insights into the genetic and molecular biologic makeup of these tumors and may help to predict which tumors are at higher risk for recurrence.

Because proponents exist for both SRS and fractionated EBRT, prospective, randomized controlled trials are needed to help answer questions. In the future, radiation sensitizers or combinations of medicines with radiation therapy may help

to improve the therapeutic ratio and decrease the latency of response, which would allow irradiation to become a more valuable treatment option.

CRANIOPHARYNGIOMA

Craniopharyngiomas are histologically benign neuroepithelial tumors that are postulated to arise from the hypophyseal duct or Rathke's pouch, or its remnants in the adult. They comprise 5% to 10% of pediatric and 1% to 4% of adult brain tumors and have a bimodal distribution with peak rates at childhood (5 year to 14 years) and older adulthood (50 year to 74 years).[214] Although these tumors are generally slow growing, circumscribed, and encapsulated, the frequent involvement of structures such as the pituitary stalk, hypothalamus, adjacent basal vasculature, and optic apparatus complicates their management.[215]

A large number of treatment modalities are used including GTR, limited surgery followed by radiation therapy, SRS, and intracystic radiotherapy and chemotherapy. In 1997, the 5-year survival rate was estimated at 80% and decreased with older age at diagnosis.[216] From more modern series, for adults treated with surgery and radiotherapy, the 5- and 10-year PFS rates were 85% and 69%, and cause-specific survival (CSS) rates were 88 and 88%, respectively.[217] In the pediatric population, a review of modern studies demonstrates a 5-year disease control of at least 90%.[218]

Treatment

Typical upfront management consists of either GTR or limited surgery followed by adjuvant radiotherapy. The timing of radiotherapy remains controversial and some series have demonstrated good salvage with radiotherapy at the time of progression.[227,228] Aggressive surgical resection can result in excellent long-term control and survival but can also be associated with significant morbidity including hypothalamic dysfunction, optic pathway damage, frontal lobe executive function damage, and rarely, mortality.[217] Surgical series demonstrate 10-year overall survival (OS) ranging from 85% to 92% and 10-year local control ranging from 42% to 81% depending on extent of tumor removed and whether radiotherapy was given.[227,228]

Radiotherapy

The group at Princess Margaret Hospital (PMH) reported their long-term follow-up results in 53 adult patients treated with surgery and radiotherapy (median dose 50 Gy in 25 fractions).[217] The 5- and 10-year PFS rates were 85% and 69%, OS rates were 76% and 70%, and CSS rates were 88% and 88%, respectively.

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The long-term morbidity associated with this disease and its treatments includes hypopituitarism, increased cardiovascular risk, hypothalamic damage, visual and neurological deficits, reduction in quality of life, cognitive and behavioral function, vasculopathies, and secondary malignancies.

Biologic Characteristics and Pathology

The two major histopathologic subtypes of craniopharyngioma are adamantinomatous and papillary. The papillary subtype is also referred to as squamous papillary and comprises 11% to 14% of all craniopharyngiomas and is only seen in adults.[219,220] Papillary craniopharyngiomas appear similar to Rathke cleft cysts that have undergone squamous differentiation and consist of mature squamous epithelium and pseudopapillae.[221] Macroscopically, they can have a combination of solid and cystic components. The cysts tend to contain a yellowish fluid. There is no evidence for a distinct mutation in this subtype.[222]

Adamantinomatous tumors are a more frequently observed subtype and are most commonly associated with childhood disease, although they can be seen across the age spectrum.[223] These tumors likely arise from the transformation of embryonic rests during the development and involution of the Rathke's pouch.[222] They also have solid and cystic components. A distinct feature includes dark brown to black fluid within the cysts related to cholesterol crystal deposition; it is often described as having an appearance and consistency similar to motor oil (or "crank-case oil"). More often than the papillary subtype, these tumors also contain calcification and tend to be more adherent to neighboring structures. Microscopically, they demonstrate Rosenthal fiber formation, nodules of wet keratin, a palisading basal layer of cells and intense surrounding gliosis.[223] Animal models have demonstrated a distinct relationship between aberrant Wnt/β-catenin pathway signaling in the pathogenesis of adamantinomatous craniopharyngioma.[224] In humans, some patients with adamantinomatous craniopharyngiomas also present with alterations of the β-catenin gene, CTNNB1, which alters intracellular levels of β-catenin, leading to accumulation of its unphosphorylated form, which is subsequently translocated to the nucleus, where it binds with transcription factors such as c-myc and cyclin D1, leading to oncogenesis.[222] This knowledge may lead to targeted therapies for adamantinomatous histology.

Anatomy and Pathways of Spread

Craniopharyngiomas are typically suprasellar in location although other rare presentations have been documented. They can be divided into prechiasmal and retrochiasmal because these locations may dictate the presenting symptoms. They can appear well encapsulated on gross examination but can be locally aggressive causing an intense glial reaction on adjacent brain. As these tumor grow they can compress adjacent structures including the pituitary and hypothalamic region, chiasm, and third ventricle, and if large the surrounding cerebral hemispheres and posterior fossa. The formation of multiple cysts is characteristic of these tumors.

Clinical Manifestations, Patient Evaluation, and Staging

Patients present with symptoms related to the surrounding structures mentioned previously. These include headaches, visual field cuts, decline in visual acuity, and hormonal abnormalities (including antidiuretic and GH insufficiency, amenorrhea, impotence, and galactorrhea).

Imaging

Craniopharyngiomas are common tumors located in the suprasellar region. Contrast enhancement, cyst formation, and calcification are the three characteristic features of craniopharyngiomas on CT. More than 90% of suprasellar craniopharyngiomas exhibit at least two of these three features, thus providing easy radiologic detection.[225] Of note the squamous papillary subtype is less likely to demonstrate calcifications on imaging. MRI typically demonstrates a hyperintense abnormality on T1-weighted images, which differentiates craniopharyngioma from Rathke's cleft and tumor cysts. Upon contrast administration, both the solid and cystic components typically enhance. CT and MRI have complementary roles in achieving the diagnosis and understanding the extent of the craniopharyngioma.[226] In addition to obtaining baseline CT and MRI with and without contrast, patients should also undergo baseline endocrine and ophthalmologic evaluations.

In the PMH series, age (<53 or ≥53) was found to be prognostic factor for OS and CSS and multiple surgeries were associated with worse PFS. The timing of radiotherapy had no prognostic significance. New endocrinopathies and visual dysfunction were observed in 53% and 17% of patients after surgery, and in 11% and 6% after radiotherapy, respectively. Unfortunately, no prospective data evaluating the role of radiotherapy in adult patients with craniopharyngioma exists.

Prospective data from 28 pediatric patients treated with three-dimensional (3D) conformal radiotherapy using a 1-cm clinical tumor volume (CTV) margin at St Jude demonstrated a 3-year PFS rate of 90.3%.[229] Review of the available outcomes for pediatric patients treated with surgery and radiotherapy demonstrates poorer cognitive outcome for patients younger than 7.4 years, long duration of prediagnosis symptoms, more extensive surgery, multiple surgical procedures, and diabetes insipidus. The percentage of total brain, supratentorial brain, or left temporal lobe volumes receiving a dose in excess of 45 Gy had a significant impact on longitudinal IQ.

Irradiation Techniques and Tolerance

Surgical decompression should be considered before radiotherapy. Fractionated radiotherapy typically consists of doses of 54 Gy given at 1.8 Gy per fraction. Conformal radiotherapy including 3D-CRT or IMRT should be considered given the proximity of these tumors to critical normal structures. A range of CTV margins from 2 cm down to 5 mm have been used. Cyst expansion can occur during radiotherapy, and therefore the smaller CTV margin should be used in the setting of surveillance MRIs throughout therapy to ensure target coverage.[230]

SRS can be considered for these tumors. A retrospective report from Pakistan used SRS to treat 35 patients (17 children and 18 adults) with craniopharyngioma.[231] The prescription dose ranged from 8 Gy to 14 Gy resulting in 88.5% tumor control rate at a mean follow-up of 22 months. A multimodality treatment approach including stereotactic drainage and intracystic bleomycin followed by SRS with a mean dose of 10.8 Gy ± 8.7 Gy demonstrated good response for patients with monocystic and small tumors, but progression occurred in most patients with large multicystic targets.[232] A retrospective review of 222 benign skull-based tumors (including 7 with craniopharyngioma) treated with Gamma Knife SRS estimated the long-term risk (mean clinical follow-up of 83 months) of radiation-induced optic neuropathy (RION): the chance of RION according to the maximum radiation dose received by the anterior visual pathway was 0% for patients receiving ≤8 Gy, 8.1 Gy to 10.0 Gy, 10.1 Gy to 12.0 Gy, and 10% for those receiving >12 Gy.[233]

Proton therapy has been used for these tumors both as the only treatment and as an adjunct to photon therapy.[234-237] Dosimetric comparative studies demonstrate the possibility of reduced whole-brain and whole-body radiotherapy doses when compared to modern photon-IMRT.[238] When considering proton therapy, monitoring for changes in tumor, and especially cyst anatomy during treatment remains important with one report describing intervention needed in 6 out of 17 children because of changes in the tumor.[235] A retrospective evaluation of quality of life and executive function following surgery and proton therapy demonstrates a high incidence of depression and decline in executive function in this population.[234]

Cystic craniopharyngiomas may be treated with intracystic phosphorus-32 (^{32}P), which has been used for many decades.[239-241] To deliver ^{32}P, the cyst volume is estimated to determine the amount of P32 necessary to deliver 200 Gy to 250 Gy to the cyst wall. A cannula is placed into the cyst stereotactically and 1 cc of fluid is removed. ^{32}P is instilled thorough the cannula with 0.2 cc of saline to flush the cannula. Patients are typically admitted overnight for observation. This technique results in good control of the treated cyst with a reported 5-year freedom from progression of 86%.[242] However, the 5-year freedom from progression outside of the treated cyst was only 54.5%. Overall freedom from progression was 45.6% at 5 years. Ten percent of these patients developed permanent deterioration of vision, attributed to tumor progression. Hasegawa et al reported that 23% patients experienced worsened visual function after intracystic ^{32}P. Although some vision loss was felt to be as a result of tumor progression, a few of these patients were felt to be related to radiation.[241] Because ^{32}P only treats the cyst and not the entire tumor, the use of ^{32}P has been described in combination with EBRT and SRS.[243,244]

Conclusions

Craniopharyngioma, although histologically benign, can be difficult to treat because of location, which makes a GTR difficult without morbidities. Radiation can help control disease that is not completely resected, with outcomes that may be favorable to a GTR by limiting the toxicities of treatment. These toxicities have implications on vision, growth, and cognitive development and need to be factored when choosing primary treatment. SRS can be considered in select cases when there is good separation of the optic pathway and the tumor. Recurrence is difficult to treat because many of these patients have already received radiation. SRS, intracystic bleomycin, and intracystic ^{32}P may be considered for recurrence. Future directions include targeted therapies, particularly for lesions where specific targetable alterations can be identified.

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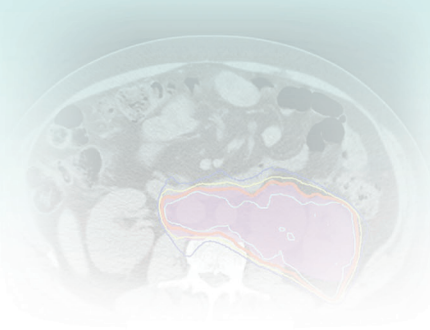
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CHAPTER

30 Spinal Cord Tumors



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INCIDENCE

The incidence of spinal cord tumors in the United States is approximately 0.63 per 100,000 population. Tumor origin is grouped by location: extradural or intradural and extramedullary or intramedullary.

BIOLOGIC CHARACTERISTICS

The tumor histologic type is an important prognostic factor in spinal cord tumors. Most intramedullary spinal tumors are tumors of glial origin such as astrocytoma and ependymoma. Most intradural, extramedullary tumors are either meningioma or schwannoma; chordoma and chondrosarcoma, as well as vascular lesions, account for most primary extradural tumors. For glial tumors, histology and grade predict outcome. Patients with ependymoma have longer survival than those with astrocytoma. Within the astrocytoma grouping, low-grade (versus high-grade) and pilocytic (versus diffuse fibrillary) subtypes have a more favorable prognosis.

STAGING EVALUATION

There is no Joint Committee on Cancer staging system for spinal cord tumors.

The clinical workup should include a full history and physical examination, with special attention given to a thorough neurologic assessment. Radiographic imaging of the tumor should be done by magnetic resonance imaging (MRI). Depending on the histology and clinical situation, laboratory tests may include a cerebrospinal fluid (CSF) evaluation, which should be performed after a complete neuraxis imaging study (preferably MRI) with and without contrast. A tissue diagnosis should be obtained, whenever feasible and safe.

PRIMARY THERAPY

If technically safe and achievable, complete surgical resection should be considered for all tumors, excluding spinal lymphomas. In general, if the tumor is completely resected, and is low-grade, postoperative adjuvant treatment may not be necessary. Definitive radiation therapy is considered in patients who cannot undergo resection. Radiation treatment is also recommended for patients with spinal lymphomas, who typically undergo biopsy only, followed by both chemotherapy and irradiation.

ADJUVANT THERAPY

Radiation therapy is frequently employed for tumors that are incompletely resected, for those with nerve root seeding, for high-grade tumors irrespective of the extent of resection, or for most recurrent tumors.

In adults, if there is a subtotal resection (STR) or the tumor is recurrent, postoperative irradiation is indicated for most histologic diagnoses. In pediatric patients, observation with close imaging follow-up after STR is an alternative option, which allows maximal opportunity for spinal growth to be completed. In these situations close observation is necessary and radiotherapy might have to be used if progression is noted. There is a limited role for chemotherapy.

LOCALLY ADVANCED DISEASE AND PALLIATION

Surgical resection may be indicated for symptoms because of spinal cord compromise in these settings. Noninvasive approaches such as radiation therapy may be preferred for palliation, particularly if there is no immediate cord compromise or if surgery is not feasible. For radiotherapeutic palliation, fractionation regimens are similar to those used for spinal column metastases.

Spinal cord tumors are a rare heterogeneous group of tumors with diverse clinical and biologic characteristics. These tumors are challenging to treat because of the functional morbidity associated with their location, which also imposes significant limitations on definitive treatment. The majority of these tumors are approached primarily with surgery, whereas irradiation is used for a significant proportion of tumors that are incompletely resected, recurrent, or located in areas in which surgery would result in unacceptable functional morbidity. Chemotherapy has a limited role.

EPIDEMIOLOGY AND ETIOLOGY

Primary spinal cord tumors comprise 3% of all primary central nervous system (CNS) tumors in adults.[1] Age-adjusted incidence rates are slightly higher for men than women, 0.67 compared with 0.59 per 100,000 population, respectively, and in non-Hispanic whites as compared to Hispanics or non-Hispanic blacks, 0.79 compared with 0.61 compared with 0.45 per 100,000 population, respectively.[1,2] Most of these tumors present as extramedullary masses (70%); intramedullary tumors are less common. Approximately 15% to 25% of spinal tumors involve the cervical spine, including the foramen magnum; 50% to 55% involve the thoracic spinal canal; and 25% to 30% involve the lumbosacral spine. The most common histologic subtypes in adults include meningeal tumors, nerve sheath tumors, and ependymal tumors as shown in Table 30-1.[1]

In the pediatric population, spinal cord tumors are slightly more common, representing 4% to 5% of all primary CNS tumors.[1] Ependymal tumors, gliomas, and nerve sheath tumors are the most common histologic subtypes in children.

TABLE 30-1 Distribution of Primary Spinal Cord Tumors by Histologic Type[1]

Histologic Type	Adult Distribution (%)	Pediatric Distribution (%)
Meningeal tumor	41	8.8
Glial origin		
Ependymoma	21.7	24.6
Pilocytic astrocytoma	0.8	12.6
Other glioma	2.3	11.6
Nerve sheath tumor	22.6	13.9
Hemangioma	3.2	1.9

Pilocytic astrocytomas, which are much more common in the pediatric population, comprise the majority of gliomas as listed in Tables 30-1.[1]

The etiology of spinal cord tumors is largely unknown. Prior exposure to radiation therapy may increase risk of developing secondary malignancies such as sarcomas and gliomas as well as benign tumors such as meningiomas, although the exact magnitude of risk has not been quantified. Depending on the histologic type, tumors may be associated with genetic syndromes such as neurofibromatosis (NF) 1 and 2 as well as von Hippel-Lindau (VHL) disease. Tumors of the spine can be detected in 40% of patients with NF1 on imaging, but they often have a long indolent natural history, causing neurologic symptoms in only 2% of patients.[3] However, in patients with NF2, spinal tumors can be found in 60% to 80% of patients, are more aggressive in terms of their growth, and often require resection with or without adjuvant radiotherapy.[4] Patients with VHL are at high risk for developing hemangioblastomas (60% to 80%), which arise in the spine half of the time.[5,6]

PREVENTION AND EARLY DETECTION

There is no known method for prevention of spinal cord tumors. Early detection relies on careful neurologic examination and consideration of the possibility of a spinal cord tumor in the differential diagnosis. Because of the rarity of these tumors, there are no recommendations for routine screening for the general public. Although routine screening with MRI of the spine has not been recommended by the Academy of Pediatrics for patients with NF1, there may be a role for surveillance of the spine with MRI for patients with NF2 and VHL.[4,5,7]

BIOLOGIC CHARACTERISTICS AND MOLECULAR BIOLOGY

Like their intracranial counterparts, the diversity of primary spinal axis tumors partly results from the large spectrum of phenotypically distinct cells in the axis, which are capable of neoplastic transformation.[8] The genetic and molecular bases of spinal cord tumors are not yet well understood and vary depending on histologic findings and age at diagnosis.[9] Data regarding molecular characteristics of spinal cord tumors are limited both by the rarity of the diseases and the limited amount of tissue available for analysis. Even so, there have been studies describing various genetic aberrations and some evidence suggesting differential origins of spinal cord and intracranial tumors.

Specific genetic alterations that lead to the development of spinal cord tumors are suggested by the occurrence of these tumors in several genetic syndromes. For example, NF1 leads to the development of intramedullary astrocytomas, suggesting a role of the *NF1* gene. Similarly, NF2 is associated with the development of ependymomas and meningiomas and VHL predisposes to hemangioblastoma. In addition to specific genetic syndromes, it might be expected that spinal cord tumors share genetic and biologic characteristics with their related intracranial tumors, given their histopathologic similarities. Examples of this are *BRAF* aberrations, *CDKN2A* loss, and *PTEN* loss in low-grade spinal astrocytomas and losses on chromosome 22q in both spinal cord and intracranial meningioma.[10,11] In this manner, molecular data from studies of the more common intracranial tumors may still have value when applied to primary spinal cord tumors.

Conversely, there are molecular data suggesting some types of spinal tumors may be distinct from their intracranial counterparts. For example, gene expression clustering suggests a distinct pattern that is specific for extracranial ependymomas and genetic lesions involving *NF2* seem to be limited to spinal ependymomas.[12-14] This is certainly consistent with the spine-specific location for ependymoma development in patients with NF2. Further study of the potential molecular differences between spinal and intracranial variants of various tumors may be important to elucidate the mechanisms underlying tumor formation.

Most tumors are histologically benign but can cause significant morbidity by direct compression of important neural structures. Not surprisingly, histologic typing and grade are important prognostic factors in spinal cord tumors. Patients with ependymoma have a longer median survival time than those with astrocytoma. Additionally, low-grade (versus high-grade) and pilocytic (versus diffuse fibrillary) astrocytomas have more favorable prognoses.

ANATOMY, PATHOLOGY, AND PATHWAYS OF SPREAD

Anatomy

Enclosed in the bony vertebral column, the spinal cord extends from the *medulla oblongata* of the brainstem to approximately the level of L1or L2 at the *conus medullaris*. It measures approximately 43 cm to 45 cm. The periphery of the cord is composed of white matter, which contains sensory and motor tracts, and the central region contains the butterfly-shaped gray matter, which houses nerve cell bodies. Three layers of meninges, the innermost pia mater, arachnoid mater, and outer dura mater, cover the elliptically shaped spinal cord and are continuous with the brainstem and brain. The delicate pia mater envelops the spinal cord and blood vessels. From this layer extends the denticulate ligaments, which connect with the dense, protective dura mater to stabilize the cord within the spinal canal. The dura mater terminates beyond the conus medullaris at the *filum terminale*, which is a strand of fibrous tissue that attaches to the coccyx, providing longitudinal support to the cord. Between these two layers lies the arachnoid, which is filled with CSF.

The spinal cord is responsible for transmitting motor and sensory neural signals between the peripheral nervous system and the brain and contains its own independent pathways for coordinating certain reflexes (Figure 30-1). Functionally, the cord is divided into 31 segments. At each level, a pair of spinal nerves exits: 8 cervical, 12 thoracic, 5 lumbar, 5 sacral pairs, and 1 coccygeal pair. In the cervical region, the spinal nerves exit above the corresponding vertebrae, whereas from the thoracic region and downward, the spinal nerves exit below the equivalent named vertebrae. Although the vertebral column continues to lengthen until adulthood, the canal and the cord are actually much shorter than the column because both

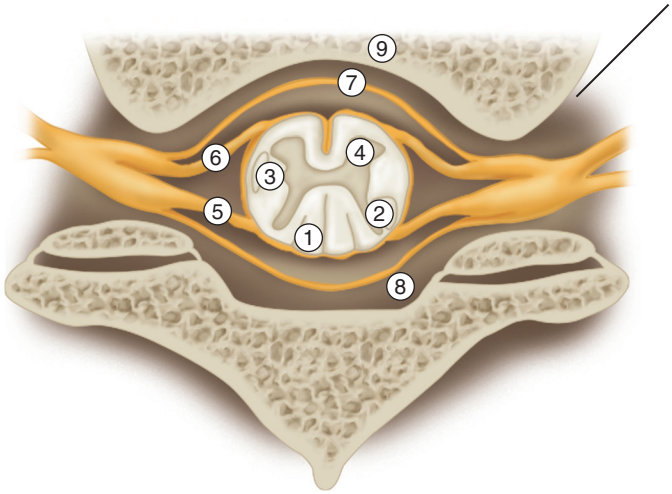


Figure 30-1 Spinal cord anatomy *(1)* Posterior column. *(2)* Lateral spinothalamic tract. *(3)* Lateral corticospinal tract. *(4)* Anterior horn cells. *(5)* Dorsal root. *(6)* Ventral root. *(7)* Dura. *(8)* Epidural space. *(9)* Vertebral body.

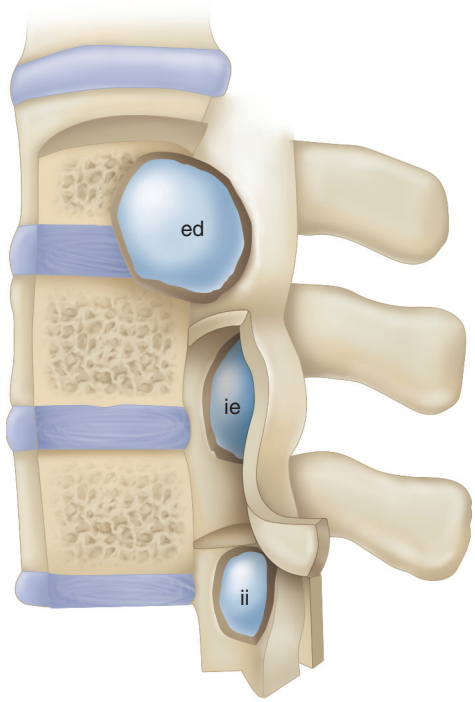


Figure 30-2 Location within the spinal column. *ed*, extradural; *ie*, intradural extramedullary; *ii*, intradural intramedullary.

stop lengthening at approximately 4 years of age. This growth differential is responsible for the formation of the *cauda equina*, a collection of the lower lumbar, sacral, and coccygeal nerves that fills the lower spinal column beyond the conus medullaris.

Within the spinal canal, there exists a well-defined extradural space containing epidural fat and blood vessels. The extradural space communicates with adjacent extraspinal compartments via the intervertebral foramina. The blood supply comes from a single anterior spinal artery (75%) and two smaller posterior arteries (25%). The cervical region relies on the vertebral and inferior cerebellar arteries, whereas the thoracic and lumbar regions depend on the radicular arteries. Venous drainage occurs through a vast network of plexuses.

Tumors are classified based on their location (Figure 30-2). Intradural tumors include both intramedullary and extramedullary tumors. Intramedullary tumors develop from the cells that make up the spinal cord and cauda equina, and extramedullary tumors arise from the supportive tissues that lie outside the spinal cord and cauda equina, such as the meninges, vascular supply, and connective tissue. Extradural tumors arise from the vertebral canal itself or supportive tissues surrounding the dura.

Pathology and Pathways of Spread

The overall and anatomic distributions of histologic types are listed in Tables 30-1 and 30-2. Intradural extramedullary schwannoma (neurilemmoma) and meningioma are the most common intradural tumors, although occasionally they may present as extradural tumors. Other intradural extramedullary tumors include epidermoid and drop metastases of intracranial primary tumors such as medulloblastoma. The most common intramedullary tumors are those derived from glial precursors, most frequently, ependymomas and astrocytomas of low- to intermediate-grade. Nonneoplastic conditions may mimic spinal cord tumors (Figure 30-3), including acute transverse myelitis, *Angiostrongylus cantonensis* infection, infectious meningitis, intradural disc hernia, pseudotumor, sarcoidosis, and tuberculosis.[15-19]

The predominant mode of spread of primary tumors is by direct extension. Spread along the subarachnoid space with spinal or cranial involvement of the meninges may also occur. One should not always assume that a spinal cord tumor found on imaging is the primary lesion because the primary tumor could be intracranial in location. Although CSF seeding is uncommon, primary intracranial tumors that show a tendency toward leptomeningeal metastases include medulloblastoma and ependymoma, and rarely glioblastomas and anaplastic gliomas.[20-22] There is a paucity of lymphatics in the spinal cord and therefore nodal spread is rare. Hematogenous spread is also quite rare, and when encountered, is more often a consequence of metastatic disease from an extraneous source spreading through Batson's venous plexus (<1%).[23]

TABLE 30-2 Anatomic Distribution of Spinal Tumors by Histologic Type

Extradural	Intradural Extramedullary	Intradural Intramedullary
Chondroblastoma	Ependymoma, myxopapillary type	Astrocytoma
Chordoma	Epidermoid	Ependymoma
Chondrosarcoma	Lipoma	Ganglioglioma
Hemangioma	Meningioma	Hemangioblastoma
Lipoma	Neurofibroma	Hemangioma
Lymphoma	Paraganglioma	Lipoma
Meningioma	Schwannoma	Medulloblastoma
Metastasis		Neuroblastoma
Neuroblastoma		Neurofibroma
Neurofibroma		Oligodendroglioma
Osteoblastoma		Teratoma (mature)
Osteochondroma		
Osteosarcoma		
Sarcoma		
Vertebral hemangioma		

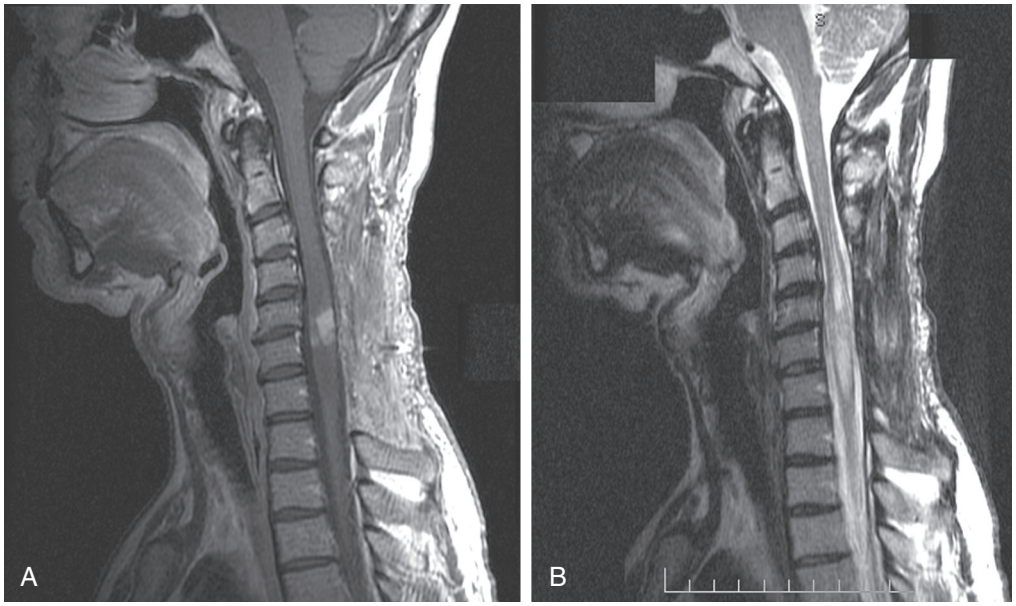


Figure 30-3 A pseudotumor, mimicking a neoplastic lesion, is shown in a sagittal-view, T1-weighted MR image with contrast **(A)** and in a T2-weighted image **(B)**.

CLINICAL MANIFESTATIONS, PATIENT EVALUATION, AND STAGING

The clinical presentation of tumors of the spinal axis is a function of the local anatomy (Figure 30-1). A spinal cord tumor produces local and distal symptoms and signs; the latter reflect involvement of motor and sensory long tracts within the spinal cord. These allow localization of the level of the lesion based on clinical findings. Localized pain from compression or stretching of the dura and bony periosteum can occur, as well as radicular pain from nerve root compression or involvement.

Clinical Workup

The diagnostic approach to primary spinal cord tumors is shown in Figure 30-4. In addition to focusing on neurologic symptoms, the history should include an evaluation of the patient's functional status and associated symptoms, which may suggest metastatic disease or nonmalignant causes of spinal cord tumors. It is also important to assess for family history and a detailed review of systems to investigate genetic disorders associated with spinal cord tumors.

Physical examination should involve an extensive neurologic assessment. Flaccid weakness, atrophy, fasciculations, and reduced deep tendon reflexes are seen in corresponding myotomes with involvement of the anterior horn cells and the ventral roots (lower motor neuron lesions). A tumor involving the lateral corticospinal tracts can cause weakness, spasticity, extensor plantar response (Babinski sign), and hyperreflexia (upper motor neuron lesion). Motor weakness and spasticity are seen with tumors above the conus medullaris. Weakness and flaccidity are seen with tumors below the conus because they compress the peripheral nerve roots of the cauda equina. A tumor restricted to the conus should not cause weakness, although one also involving the cauda equina or the lumbar enlargement of the spinal cord will do so.

Sensory impairment often helps to localize the level of the tumor based on loss of dermatomal function, although the upper level of impaired long-tract function may be several segments below the actual tumor (Figure 30-5). A lesion involving the lateral spinothalamic tract causes numbness, paresthesias, and decreased temperature sensation over the contralateral limb or trunk below the lesion. This produces the classic finding of a sensory level, which is best demonstrated with a pin or a large metal or cold object to test temperature sensation and with observation for absence of perspiration. A lesion in the posterior column causes an ataxic or tabetic gait. Standing posture is affected with the eyes closed (Romberg's sign). Paresthesias can occur below the level of the lesion.

Because pain and temperature pathways cross over in the spinal cord and proprioceptive and motor pathways do not, a unilateral spinal cord lesion can result in ipsilateral paralysis

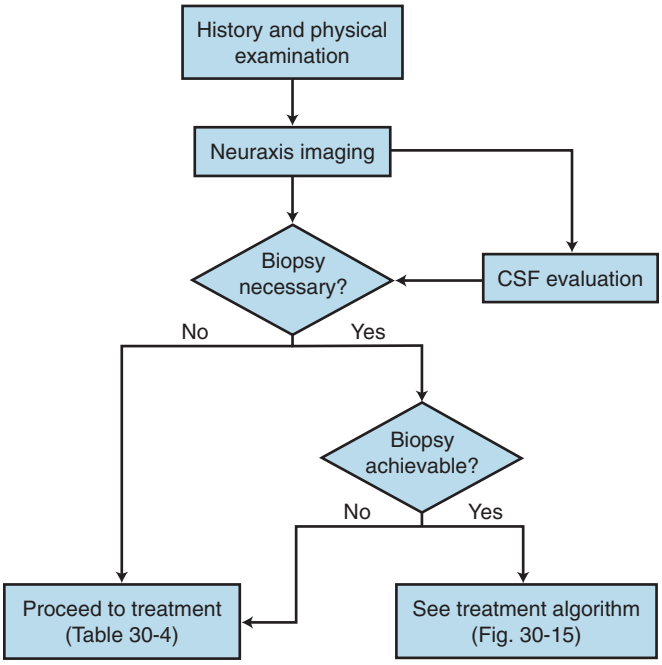


Figure 30-4 **Diagnostic algorithm for primary spinal cord tumors.** *CSF*, Cerebrospinal fluid.

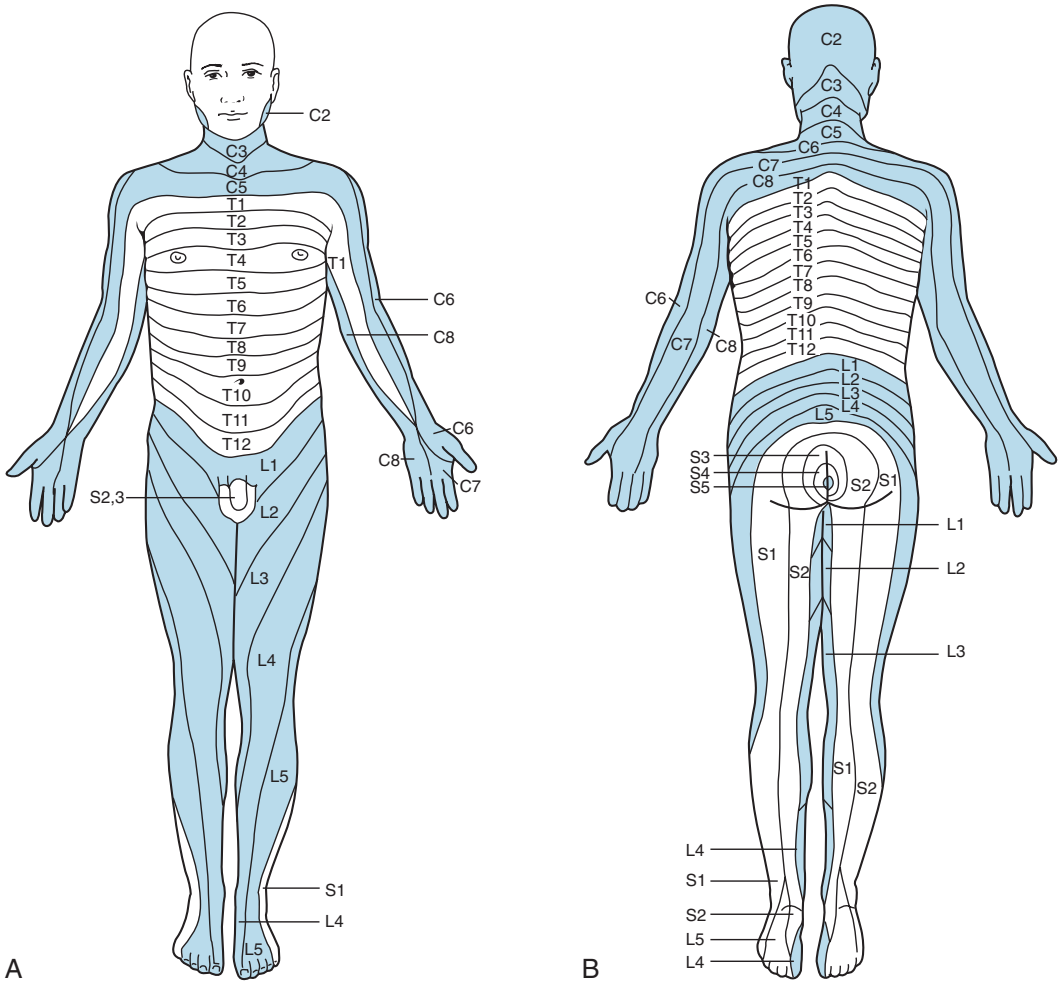


Figure 30-5 Anterior **(A)** and posterior **(B)** views of the dermatomes. *C*, Cervical; *L*, lumbar; *S*, sacral; *T*, thoracic.
(Adapted from Netter FH, Freidberg SR, Baker RA: Disorders of spinal cord, nerve root, and plexus. In Netter FH, Jones HR, Jr, Dingle RV, editors: The Ciba Collection of Medical Illustrations, Vol 1. Nervous System, Part II. West Caldwell, NJ, Ciba-Geigy, 1986, pp 181–189; Keegan JJ, Garrett FD: The segmental distribution of cutaneous nerves in the limbs of man. Anat Rec 102:409, 1948.)

and proprioceptive loss as well as contralateral pain and temperature loss below the level of the lesion. Because light touch travels in two pathways, one that crosses in the spinal cord (spinothalamic tract) and one that does not (posterior columns), it is usually spared in unilateral lesions. This combination of findings is known as the Brown-Séquard syndrome.

Both genitourinary and bowel symptoms can result from a spinal cord tumor. Bladder symptoms include hesitancy, dribbling, incontinence, urgency, or acute retention. Loss of bladder control is seen early in the presentation of tumors at or below the conus and later in tumors above the conus. Lesions above L1 can lead to impotence or reflex priapism. Lesions involving S2 to S4 may produce loss of erection and ejaculation ability. Decreased genital sensation can occur from lesions affecting the S2 nerve roots. If bowel control is affected, constipation occurs more frequently than incontinence.

The most common presenting symptom from spinal canal tumors is pain, caused by nerve root compression, bony destruction, or more subtly, pressure on the dura or deafferentation. The pain may be radicular, midline, or centrally located. Radicular pain is secondary to involvement of the posterior roots and is typically described as shooting pain in the dermatomal distribution. The nerve can be compressed inside of or outside of the dura. Midline spinal pain presents as discomfort localized to the area of the tumor and is thought to arise from pain-sensitive structures in the dura and extradural tissues. Characteristically, pain is more severe with extradural lesions. With spinal cord compression, a dull or burning pain, more widespread than segmental spinal or radicular pain, sometimes occurs. This type of pain, although relatively rare, has numerous designations, including central pain, causalgia, and deafferentation pain. It involves a limb or trunk below the lesion. Pain is the most common presenting symptom in patients with sacrococcygeal tumors. Headache may be caused by elevated intracranial pressure, which is unusual in patients with primary spinal cord tumors, with the exception of large tumors involving the foramen magnum. It can be caused by upward seeding of the tumor or by the development of carcinomatous meningitis from malignant tumors.

The clinical presentation of a spinal tumor rarely indicates whether it is extradural or intradural. However, intramedullary tumors can cause a characteristic neurologic syndrome. Early on, decreased temperature and pain sensation occurs in the dermatomes of the spinal segments occupied by the tumor and two or three segments caudal to the lesion. Other sensory modalities are not diminished while the tumor is confined to the central cord. This "dissociated" sensory loss is rarely seen with extramedullary tumors. Additionally, weakness and atrophy are early findings in the myotomes of the corresponding cord segments involved by tumor. As the tumor grows

transversely, reflexes produced at the level of the tumor disappear and spastic paralysis with hyperreflexia develops below the lesion. Eventually, all sensory modalities are affected. Cervical tumors can produce Horner's syndrome by interrupting unilateral autonomic pathways.

Lesions in the conus medullaris can produce several symptoms, including saddle anesthesia, acute urinary retention, incontinence of bowel and bladder, and impotence. If the lesion remains confined to the conus, it will not cause paralysis of the lower limbs and the ankle reflexes are preserved. More commonly, tumors originating in the conus are diagnosed when they have enlarged enough to cause signs characteristic of intramedullary tumors. These findings can also be mixed with those caused by growth of the tumor in the direction of the cauda equina, such as radicular pain.

Lesions of the cauda equina can cause radicular pain in the thigh, weakness, and atrophy of muscles, including the gluteus, hamstring, gastrocnemius, and anterior tibialis muscles. Saddle anesthesia, absent ankle reflexes, impotence, urinary urgency or acute retention, and constipation are also commonly seen. Depending on the location of the lesion, other reflexes may be affected.

Neuroimaging

Certain tumors may display characteristics on plain films such as the calcifications seen in meningiomas. Increased intracranial pressure can cause enlargement of the bony spinal canal, erosion of the pedicles, and scalloping of the posterior wall of the spinal canal. Computed tomography (CT) can be useful for evaluating the vertebral column in extradural tumors. Myelography has been replaced by more-advanced, less-invasive imaging but can be useful in patients who cannot tolerate MRI.

MRI with gadolinium contrast is the diagnostic study of choice in the evaluation of intramedullary and extramedullary spinal cord lesions. Advantages of MRI include the high soft-tissue contrast between the spinal cord and associated anatomic structures and tumor, ability to display the spine in multiple views, availability of multiple pulse sequences, lack of bony artifact, and capacity for three-dimensional (3D) visualization. Most spinal cord tumors enhance with contrast, the most common exception being World Health Organization (WHO) grade II gliomas. Edema appears as an area of low-signal intensity on T1-weighted MRI images and high-signal intensity on T2-weighted MRI images. Tumor infiltration may be differentiated from edema by suppression of CSF signal using fluid-attenuated inversion recovery (FLAIR) sequences. MR spectroscopy may help to differentiate tumor from spinal cord necrosis. MRI of the entire neuraxis is strongly recommended in the initial workup.

Cerebrospinal Fluid Examination

Examination of CSF may be indicated for diagnostic and staging purposes as well as for monitoring of therapeutic response in certain tumors. Because of the risk of herniation caused by increased intracranial pressure, neuroimaging studies should precede lumbar puncture. When obstruction of CSF flow occurs because of tumor expansion, patients can develop hydrocephalus. A lumbar puncture in a patient with a spinal cord tumor who presents with a headache should therefore be performed cautiously.

CSF examination is especially useful in the assessment of tumors that may seed the subarachnoid space and spread via the CSF. As such, CSF examination is routinely done at the time of diagnosis of ependymoma and primitive neuroectodermal tumors. The appearance of xanthochromic CSF, resulting from high protein content with an absence of erythrocytes, is characteristic of spinal cord tumors obstructing the subarachnoid space. CSF evaluation should include cytology for malignant cells, protein, and glucose. A high protein concentration with normal glucose levels and normal cytologic findings is seen in spinal cord tumors. However, if the tumor has seeded the meninges, the glucose level may be low and cytologic testing may reveal a malignant tumor.

Histologic Confirmation of Disease

The approach for histologic confirmation depends on the clinical presentation and suspected histologic type. The morbidity of potential biopsy should be weighed against the benefits of confirming the histologic type and whether it would change management. Image guidance can be used to improve safety and efficacy of biopsy. In patients presenting with acute spinal cord compression, surgical decompression should be considered to relieve progression of neurologic symptoms and establish a diagnosis.

Staging

There are no routine staging systems for the classification of spinal tumors.

PRIMARY THERAPY

General Principles of Surgery

Maximal surgical resection remains the primary treatment of choice for the majority of tumors.[24] As modern diagnostic and therapeutic techniques such as MRI, the operating microscope, microsurgical tools, and intraoperative neurophysiologic assessment have become available, more aggressive surgical intervention has become a more prevalent treatment strategy. This section will discuss general principles of surgery for CNS lesions, depending on anatomic location within the spinal cord. The outcome of surgery and its role in multidisciplinary management are described in the sections for each individual type of tumor. Table 30-3 shows an overview of the outcomes of the most common spinal cord tumors by treatment modality.

Surgical Planning

Neuroimaging is the basis for preoperative planning of the surgical approach. MRI obtained both before and after the administration of intravenous gadolinium-based contrast is the most sensitive modality for detecting tumor and delineating tumor from reactive changes such as a syrinx. CT scans are most useful for delineating the bony anatomy, acute blood and intratumoral calcifications. Spinal angiography is occasionally necessary to distinguish spinal cord tumors from vascular malformations such as dural arteriovenous malformations.

Surgical Techniques, Postoperative Management, and Complications

The use of the operating microscope is essential for spinal cord tumor surgery. The availability of other surgical adjuncts, including image-guided navigation systems, intraoperative ultrasound assessment, the carbon dioxide (CO_2) laser, and the ultrasonic aspirator (CUSA), are of value for selected tumors.[25] In addition, the use of 5-aminolevulinic acid fluorescence–guided surgery has been used to aid in the resection of spinal tumors; however, the benefits in spinal surgery have not been proven at this time.[26,27]

Multiple modalities are available for intraoperative monitoring of physiologic function. The most commonly used

TABLE 30-3 Outcomes of the Most Common Spinal Cord Tumors by Treatment Modality

Treatment	OS_3 (%)	OS_5 (%)	OS_{10} (%)	CSS_5 (%)	CSS_{10} (%)	CSS_{15} (%)	DFS_5 (%)	DFS_{10} (%)	DFS_{15} (%)	LC_3 (%)	LC_5 (%)	LC_{10} (%)	Overall LC (%)
Low-Grade Glioma													
GTR or STR + XRT	—	57-88	52-83	—	—	—	38-44	10-26	—	—	—	—	31-100
Ependymoma													
Surgery	—	67-100	68-100	69-96	62-93	—	—	—	—	—	—	—	95-100
Surgery + XRT	—	67-100	67-100	69-97	62	46	59	59	—	—	—	—	88-100
Meningioma													
GTR or STR + XRT	—	—	—	—	—	—	93	80	68	—	—	—	94-99
STR alone	—	—	—	—	—	—	63	45	9	—	—	—	—
Chordoma													
Surgery + XRT	88-97	75-80	54	—	—	—	—	—	—	67-71	40-75	54	—
Chondrosarcoma													
GTR or STR + XRT	—	—	90	—	—	—	36-72	84	—	—	—	—	97

CSS, *Cause-specific survival;* DFS, *disease-free survival;* GTR, *gross total resection;* LC, *local control;* OS, *overall survival;* STR, *subtotal resection;* XRT, *radiation therapy.*
The numbers in subscript denote the number of years. References are found in the text.

techniques are somatosensory evoked potential (SSEP) and monitoring and electromyography (EMG). Motor-evoked potential (MEP) monitoring is more difficult to use reliably because it is more sensitive to the paralytic agents used in anesthesia. EMG is of particular use for cauda equina and foramen magnum tumors, where monitoring of the extremity musculature, the anal sphincter, and sometimes, the urinary sphincter can reduce the risk of postoperative deficits.[28]

Surgery for Intradural Extramedullary Tumors

Meningiomas and schwannomas (neurilemmomas) occur in the intradural extramedullary spinal compartment. Most of these tumors can be completely resected with curative intent because the normal spinal cord is not invaded by tumor.

Surgery for Intramedullary Tumors

The most common intramedullary tumors are ependymomas and astrocytomas. Modern series advocate maximum safe resection of intramedullary spinal tumors. The ability to resect these tumors completely varies widely, from less than 10% to as much as 86%, depending on the histologic type.[29-36] Complete resection is achieved more frequently for WHO grade I tumors; gliomas of higher grade tend to be infiltrative, and therefore are less often resected completely.[33,37-41] The gross total resection (GTR) rates for ependymomas range from 19% to 100%, whereas significantly less than 50% of astrocytomas are totally resectable.[42-45] For infiltrative astrocytomas, the role of surgery is most frequently limited to biopsy for diagnosis. Laminectomy offers limited functional benefit by decompressing the spinal cord in the case of bulky infiltrative tumors. Functional postoperative outcomes may be excellent in selected cases, with the majority of patients (more than 70%) experiencing either improvement or stabilization of their preoperative presenting symptoms, often after transient postsurgical worsening.[29,36,46,47] The incidence of total, permanent postoperative paralysis is reported at 1%.[48] Paralysis is often the result of unpredictable vascular events.

Intramedullary tumors are almost always approached through a laminectomy exposure with the patient in the prone position.[48] After the dura is opened, a longitudinal myelotomy is made over the widened region of the spinal cord, where imaging demonstrates the closest approximation of the tumor to the surface and the incision is deepened several millimeters until the tumor surface is reached. Infiltrative tumors with poorly defined dissection planes cannot be removed completely and, therefore, biopsy for diagnosis is often the safest course of action. When there is an exophytic component to the tumor, maximum safe debulking is typically performed.

Both intramedullary and extramedullary tumors can be associated with a CSF-filled syrinx dilating the central canal. The preferred treatment is tumor removal. If this is not possible, even modest shrinkage of the tumor by means of irradiation can stabilize or even reduce the size of a syrinx. Postoperatively, a syrinx can form from scarring in the central canal. A syrinx drainage procedure may not result in a significant improvement in neurologic function.

Postoperative Management

Corticosteroids are routinely administered before, during, and after surgery to minimize edema of the spinal cord. Intravenous or oral dexamethasone or high-dose intravenous methylprednisolone is most often the agent of choice. Once maximum symptom resolution has occurred, usually within a week of initiation of high-dose glucocorticoids, steroids should be tapered as rapidly as possible to minimize steroid-related side effects, as long as there is not associated worsening of symptoms.

Complications of Surgery

In patients who are neurologically intact before surgery, the incidence of significant acute morbidity is generally low, usually 5% or less.[48] Spinal deformities, including scoliosis and kyphosis, as well as infection and CSF leakage, can occur.[49,50] The development of postlaminectomy spinal deformities is a serious postoperative complication, occurring in up to 40% of pediatric and adolescent patients and may be observed as soon as 8 months postoperatively.[51]

General Principles of Radiation Therapy

The intent of radiation therapy in the treatment of spinal cord tumors is to improve local control and neurologic function while potentially increasing survival times. Radiation therapy is frequently used for tumors that are incompletely resected, at high risk of recurrence, located in areas where surgery would result in unacceptable functional morbidity, as well as for recurrent tumors. Outcomes of radiation therapy and its role in multidisciplinary management are described in a subsequent section for each individual type of tumor.

Because of the potential for growth and developmental side effects, the use of irradiation in children and infants with spinal cord tumors is controversial. Some authors do not recommend postoperative radiation therapy and suggest that observation with close follow-up and re-resection at the time of relapse is a safer approach, particularly for benign tumors or low-grade gliomas.[29] With this strategy, radiation therapy may be avoided, delayed or used only for children with multiply recurrent tumors.

General Principles of Chemotherapy

The efficacy of chemotherapy may be limited by the intact blood–nervous system barrier. Regional drug delivery may be in the form of intracerebrospinal fluid therapy, intraarterial infusion, and intratumoral therapy. Extramedullary spinal tumors gain their blood supply from meningeal blood vessels that are significantly more permeable than those of the brain, and chemotherapy may be of more use for these tumors. Drugs that have some efficacy in treating primary CNS malignant tumors and that are thought to cross the blood-brain barrier have been used in the treatment of malignant glial tumors of the spinal cord; however, no clear benefit from the use of chemotherapy has been demonstrated thus far.[40,52-55]

LOCALLY ADVANCED DISEASE AND PALLIATION

The principles of treatment are the same for patients with more locally advanced disease and palliation as for definitive treatment. Because of the severity of symptoms related to lack of control of spinal cord tumors, in most cases irradiation dose should not be substantially decreased, although this may be a consideration with large fields. Patients with end-stage disease requiring palliation of pain are typically treated based on the general principles of palliative management.

IRRADIATION TECHNIQUES AND TOLERANCE

Definition of Treatment Volumes

3D or intensity-modulated treatment planning based on International Commission on Radiation Units (ICRU) volume definitions is the norm.[56,57] The gross target volume (GTV)

TABLE 30-4 Suggested Definitions of ICRU Volumes Based on MRI and Dose Ranges Delivered to Volumes

	Initial Treatment Field			Final Treatment Field			
Diagnosis	**GTV1**	**Margin to CTV1**	**Dose (Gy)**	**GTV2**	**Margin to CTV2**	**Dose (Gy)**	**Dose to Craniospinal Axis (If Indicated)**
WHO grade I glioma	NA	NA	NA	Enhancing tumor (T1 + C)	1 cm	45-50.4	NA
WHO grade II glioma	Enhancing tumor (T1 + C) + Edema (T2/FLAIR)	2 cm	45	Enhancing tumor (T1 + C)	2 cm	50.4-54	NA
WHO grade III-IV glioma	Enhancing tumor (T1 + C) + Edema (T2/FLAIR)	2 cm	45-50.4	Enhancing tumor (T1 + C)	2 cm	55.8-61.2	Leptomeningeal spread on MRI: 30-39.6 Bulky disease: 55.8-61.2
Ependymoma	Enhancing tumor (T1 + C) + edema (T2/FLAIR)	2 cm	45	Enhancing tumor (T1 + C)	2 cm	50.4-55.8	Positive CSF: 36 Leptomeningeal spread on MRI: 39.6
Meningioma, benign/atypical	NA		NA	Enhancing tumor (T1 + C)	1 cm	45-55.8	NA
Meningioma, malignant	Enhancing tumor (T1 + C) + edema (T2/FLAIR)	2 cm	45-50.4	Enhancing tumor (T1 + C)	2 cm	54-61.2	NA
Chordoma	Enhancing tumor (T1 + C) + tumor bed	2 cm	50	Enhancing tumor (T1 + C)	2 cm	60-70	NA
Chondrosarcoma	Enhancing tumor (T1 + C) + tumor bed	2 cm	50	Enhancing tumor (T1 + C)	2 cm	60-70	NA
Sarcoma	Enhancing tumor (T1 + C) + tumor bed + surgical track, including scar	2 cm	50	Enhancing tumor (T1 + C)	2 cm	60-70	NA
Vertebral hemangioma	Enhancing vascular lesion + entire involved vertebral body	≥1 cm	NA	NA	NA	36-45	NA

C, *Contrast;* CSF, *cerebrospinal fluid;* CTV, *clinical target volume;* FLAIR, *fluid-attenuated inversion recovery;* GTV, *gross tumor volume;* Gy, *Gray;* MRI, *magnetic resonance imaging;* NA, *not available.*

represents the grossly visible disease burden. Typically, this is the T1-enhancing abnormality on MRI or the nonenhancing tumor seen on T2 or FLAIR images. If there is no residual abnormality after a surgical resection, the tumor resection cavity is defined to be the GTV. The clinical target volume (CTV) incorporates the GTV plus a margin for microscopic disease extension and includes areas at high suspicion for disease recurrence. Suggested definitions and doses to be delivered to the GTV and CTV are listed by histologic diagnosis in Table 30-4. The planning target volume (PTV) adds a dosimetric margin that takes into account uncertainties in daily treatment setup and physiologic variations that are difficult or impossible to control, such as (potential) fluctuations in the mass effect from cord edema that may occur over the course of treatment. Organs at risk typically include the thyroid, salivary glands, esophagus, lungs, heart, stomach, small bowel, liver, kidneys, bladders, ovaries, testicles, and uninvolved portions of the spinal cord itself.

Treatment Techniques

The most common approaches include a single posteroanterior (PA) field, opposed lateral fields, a PA field with opposed laterals, and oblique wedge-pair fields, which are typically designed to treat the PTV. For tumors in the cervicothoracic region, a split-beam approach is sometimes used. The central axis is placed just above the shoulders. Opposed lateral fields are used to treat the upper spine, whereas a PA field is used for the area of the spine below. Tumors in the thoracic region are often treated with a three-field approach using a PA field and opposed lateral beams. In the lumbar region, care must be taken to minimize the dose to the kidneys; a four-field approach using anteroposterior (AP)/PA and opposed lateral beams with the AP/PA beams preferentially weighted may be useful. In all sites, 3D conformal approaches are preferable, when feasible (Figure 30-6).

The advent of intensity-modulated radiation therapy (IMRT) techniques now allows for the development of sophisticated treatment plans, using several beam directions and treatment fields that may allow the dose to critical structures to be minimized.[58,59] The use of image guidance may also allow for reduced PTV margins. It is therefore important to compare different treatment field setups and techniques using dose-volume histograms to select the most appropriate option. In select centers, proton beam therapy is being used to decrease dose to organs at risk.

Certain neoplasms require treatment of the entire craniospinal axis. Several modifications of this approach are used in clinical practice (Figure 30-7). Patients may be treated either in the supine or prone position, often in an immobilization cast to ensure daily positional reproducibility.[60,61] The intracranial contents, including the upper segments of the cervical cord, are treated through opposed lateral fields. Customized blocks protect the normal head and neck tissues from the primary radiation beam. The spine is treated through one or two posterior fields, depending on the size of the patient. In one method, the collimator for the lateral cranial fields is angled to match the divergence of the upper border of the adjacent

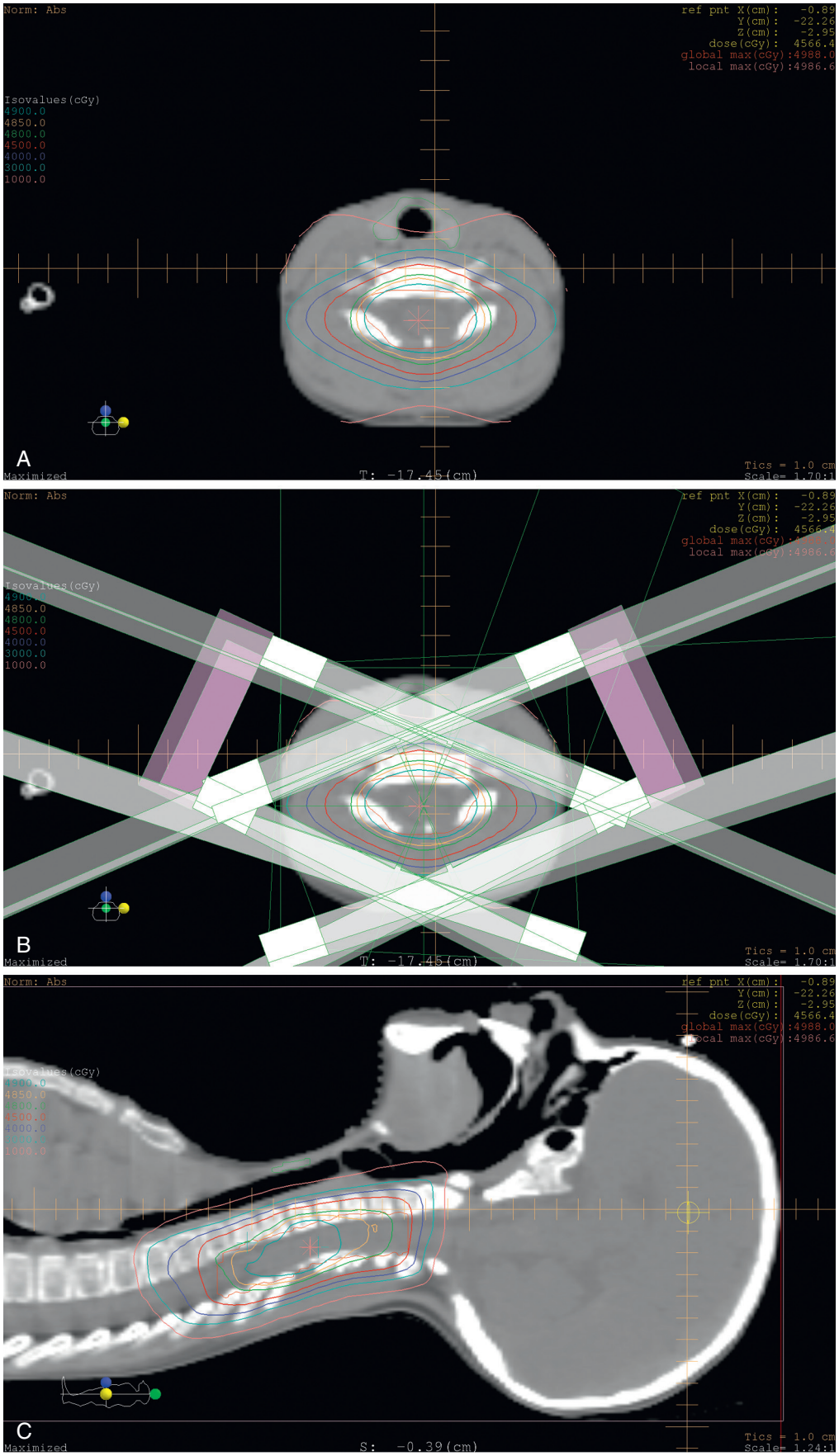


Figure 30-6 Patient is a 6 year-old boy with an atypical neurocytoma of the cervical and upper thoracic cord who underwent subtotal resection and was subsequently found to have radiographic evidence of disease progression. He received salvage radiation therapy with three-dimensional conformal technique to 48.5 Gy in 28 fractions. Images **A** and **B** represent the isodose distribution with and without beams respectively, whereas image **C** depicts a sagittal image with isodose distribution.

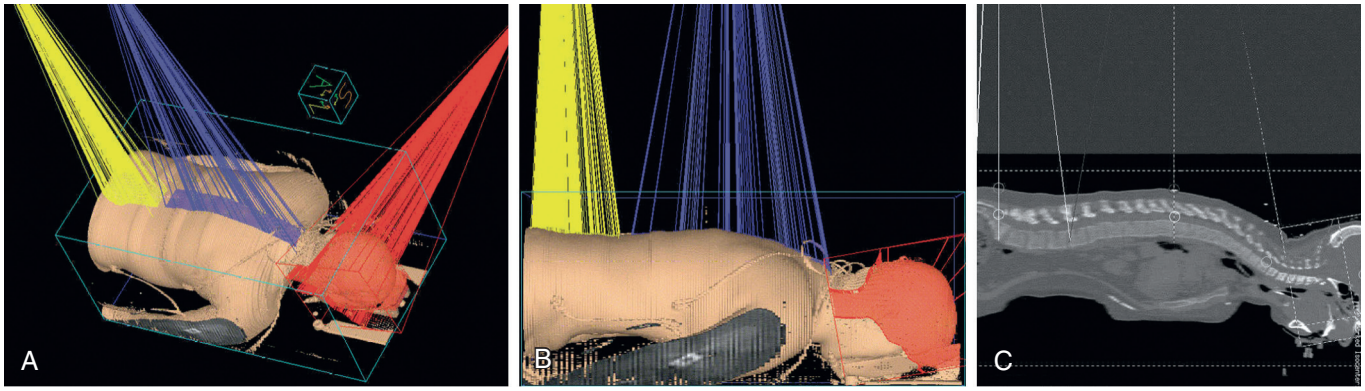


Figure 30-7 Two- and three-dimensional treatment planning images of craniospinal axis radiation therapy. Patients are treated in the supine or prone position, and an immobilization cast often is used to ensure positional reproducibility. Intracranial contents and the upper one or two segments of the cervical cord are treated through opposed lateral fields. Customized blocks protect the normal head and neck tissues from the primary radiation beam. The spine is treated through one or two posterior fields.

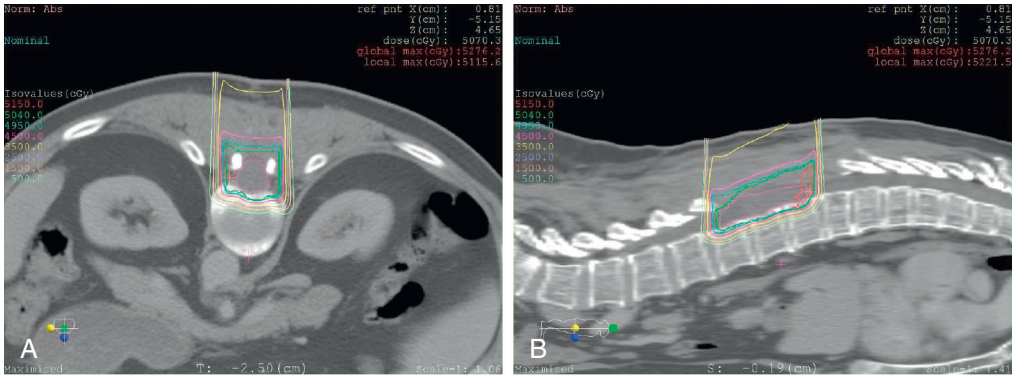


Figure 30-8 Axial **(A)** and sagittal **(B)** views of the isodose distributions from a proton plan for a patient with low-grade astrocytoma prescribed to 50.4 CGE.
Courtesy Massachusetts General Hospital.

spinal field, and the treatment couch is angled so that the inferior border of the cranial field is parallel to the superior edge of the spinal field. Alternatively, one may dispense with collimator and couch angles by calculating appropriate gaps. The gap is calculated so that the 50% isodose lines meet at the level of the anterior spinal cord. All junction lines are moved 0.5 cm to 1 cm every 8 Gy to 10 Gy to avoid overdosing or underdosing segments of the cord. This is accomplished by shortening the inferior margin of the lateral cranial fields, symmetrically lengthening the superior and inferior margins of the posterior spinal field, and shortening the cranial margin of the caudal spinal field; a fixed block is placed at the inferior margin of the caudal spinal field to keep the lower margin of the irradiated volume at the same location. IMRT, volumetric modulated arc therapy (VMAT), or proton radiotherapy has been used to treat the craniospinal axis, especially in children, to better conform the target dose and allow improved sparing of critical structures.[62-67]

Proton radiation therapy may be considered in certain clinical situations (Figure 30-8). In patients with chordoma and chondrosarcoma, there is a well-defined role for proton therapy that allows for dose escalation with improved sparing of critical organs.[68-75] Proton therapy is also considered in pediatric patients to limit exposure to normal structures, and also in young adults, in which heart and breast sparing may reduce delayed second malignancies and cardiac complications.

Both single fraction and multifraction stereotactic radiosurgery (SRS) or stereotactic body radiotherapy (SBRT) deliver a highly conformal high dose of radiotherapy with stereotactic guidance (Figure 30-9). Advantages include patient convenience with a shorter treatment course and the steep dose gradient at the edge of the field, which may allow for greater tissue sparing. The use of image guidance before treatments is critical given the large doses and high conformality delivered with this technique. SRS has been used with clinical effectiveness for benign, malignant, and metastatic lesions in the spine and spinal cord, but its role remains limited, mainly because of technical and dosimetric considerations.[76-92]

Tolerance of the Spinal Cord and Lumbosacral Nerve Roots

A dose of 45 Gy to 50.4 Gy in 25 to 28 fractions over 5 to 5.5 weeks is usually considered to be safe. The risk of myelopathy is less than 1%, well below the steep portion of the dose-response curve.[93,94] It is estimated that with conventionally fractionated irradiation (1.8 Gy to 2 Gy per fraction in 5 fractions per week), the 5-year incidence of myelopathy is 5% for doses in the range of 57 Gy to 61 Gy (tolerance dose $TD_{5/5}$) and 50% for doses of 68 Gy to 73 Gy ($TD_{50/5}$).[94] There is no convincing evidence that the cervical and thoracic cord differ in their radiosensitivity, and there appears to be little change in tolerance with variations in the length of cord irradiated.[94] Table 30-5 shows a range of isomorbid fractionation schemes, all of which carry a 5% risk of radiation myelopathy. The use of chemotherapy may decrease the tolerance of the spinal cord.[95,96]

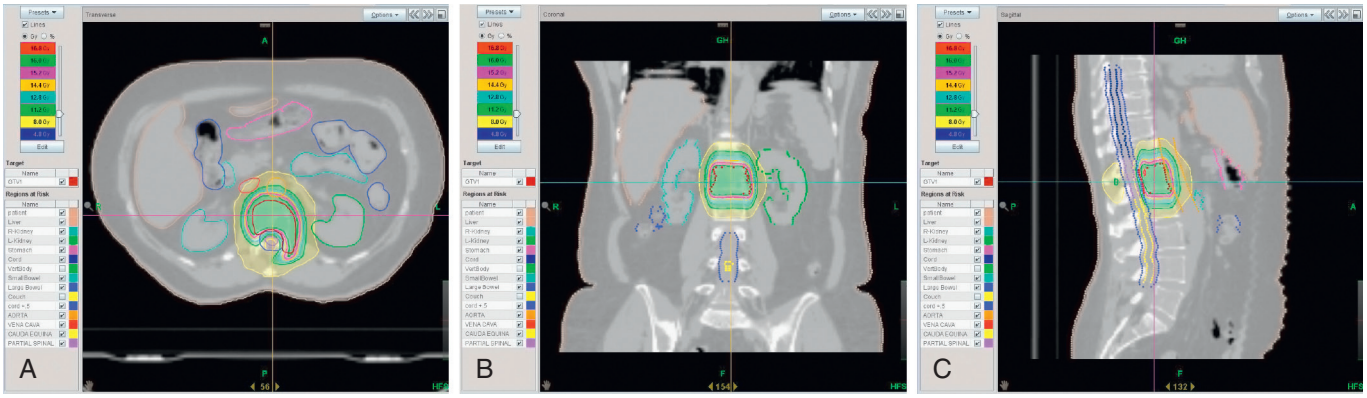


Figure 30-9 Patient is a 62-year-old woman with a biopsy-proven spine metastasis from a lung primary. She was treated with a single fraction of radiotherapy to 16 Gy prescribed to the 95% isodose line. Pain resolved within 24 hours. At 1 year, there was no progression of the spine disease.

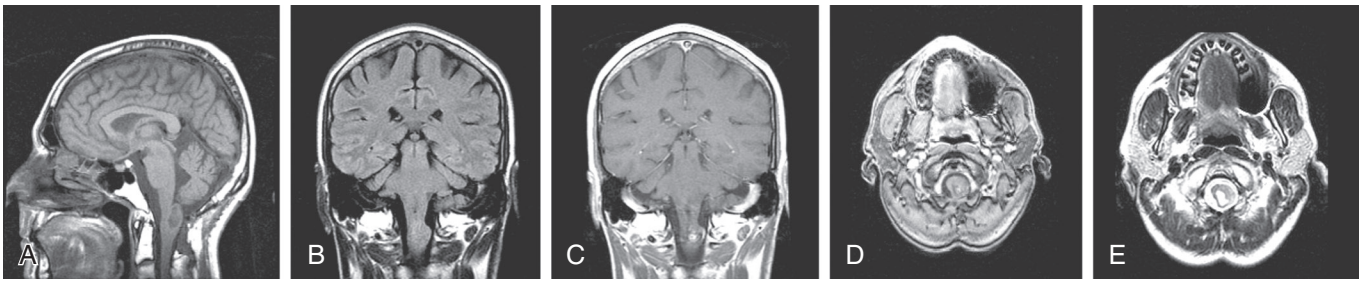


Figure 30-10 MRI of an upper cervical spine pilocytic (WHO grade I) astrocytoma. Shown are **(A)** sagittal-view, T1-weighted; **(B)** coronal-view, fluid-attenuated inversion recovery (FLAIR); **(C)** coronal-view, T1-weighted view with contrast; **(D)** axial-view, T1-weighted, spoiled gradient-recalled (SPGR) with contrast; and **(E)** axial-view, T2-weighted image.

TABLE 30-5 Fractionation Schemes with a 5% Risk of Radiation-Induced Spinal Cord Myelopathy

Dose per Fraction (Gy)	No. Fractions	Total Dose (Gy)
2	29	58
3	13	39
3.3	11	33
4	7	28
5	5	25
10	1	10

Data from references 93, 97-105.

The tolerance of the lumbosacral nerve roots appears to be somewhat higher than that of the spinal cord. Most series report a 0% complication rate if patients are treated to doses of 70 Gy (or equivalent) as long as fraction sizes are kept at or below 2 Gy.[106,107]

The Quantitative Analysis of Normal Tissue Effects in the Clinic (QUANTEC) workgroup reviewed data from preclinical, conventional, reirradiation, and SBRT studies to refine normal tissue dose and volume tolerance guidelines.[108] Based on this, a total dose of 54 Gy, 60 Gy, or 69 Gy with conventional 2-Gy once-daily fractionation was associated with a myelopathy rate of less than 1%, 6%, and 50%, with a calculated strong dependence on dose/fraction ($\alpha/\beta = 0.87$ Gy). For partial cord irradiation as part of spinal SRS/SBRT, a maximum cord dose of 13 Gy in a single fraction or 20 Gy in three fractions appeared to have a minimal (<1%) risk of injury.[109] However, emerging data from Stanford University suggest that spinal cord tolerance may be higher.[110]

PRIMARY THERAPY BY TUMOR TYPE

Astrocytoma

Astrocytomas represent 3% of adult and 24% of pediatric spinal canal tumors.[1] They are one of the most common intramedullary spinal cord tumors and comprise 35% to 45% of all reported cases of intramedullary tumors in adults. In children, 75% to 90% of intramedullary spinal cord tumors are astrocytomas, the majority of which are low-grade or juvenile pilocytic astrocytomas (Figure 30-10). Fewer than 20% of pediatric and 25% of adult spinal cord astrocytomas are malignant.[111-115]

Back pain and motor deficits are the most common presenting symptom in astrocytomas, occurring in up to 87% of patients. The median time from onset of symptoms to diagnosis ranges from 6 months to 2 years. In general, high-grade astrocytomas tend to have a shorter prodrome (median duration, 1.6 months to 7 months) than low-grade tumors (median duration, 2 years). Tumor dissemination by spread along the subarachnoid space is reported in up to 58% of patients with high-grade astrocytomas. Approximately 1% of WHO grades III to IV spinal cord astrocytomas have multifocal disease at presentation.[115]

Prognostic Factors

The most significant prognostic factors in patients with primary spinal cord astrocytoma are tumor histology, tumor grade, age, and performance status. High histopathologic grade is typically associated with a high risk of mortality and short median survival time.[112-114,116-119] In a Mayo Clinic review, median survival of patients with pilocytic tumors was significantly longer than those with infiltrative astrocytomas (39.9 years versus 1.85 years, $p < 0.001$).[114] Similar findings were reported from another retrospective review from M. D.

Anderson Cancer Center (MDACC) where the 5-year overall survival (OS) for pilocytic tumors was 85% compared to 36% for infiltrative tumors. When looking more specifically at grade of infiltrative tumors in this study, higher grade conferred worse median survival which was 7.6, 2.8, and 1.4 years for WHO grades II, III, and IV, respectively.[112] According to a Surveillance, Epidemiology, and End Results (SEER) database review, 5-year OS for grades I, II, III, and IV was 82%, 70%, 28%, and 14% respectively.[113] Because of the rare nature of this disease, almost all data are based on retrospective reviews fraught with selection bias. Therefore, neither the extent of resection nor treatment with adjuvant irradiation appears to be prognostic, although this is controversial.[112-117,120-124]

Treatment and Outcomes

The treatment of choice for intramedullary astrocytomas is complete excision of the tumor, when it can be safely accomplished without neurologic compromise.[122] Otherwise, an incomplete excision is typically performed for grade I lesions, and biopsy alone is the surgical strategy for the nonexophytic component of an infiltrative glioma.[114,116,118,120-124] GTR is typically extremely difficult to achieve because of the infiltrative nature of all but the pilocytic lesions, with most authors reporting a 0% to 50% likelihood of GTR for spinal cord astrocytoma.[34,41,114,116,118,122,124,125] A series from Japan suggests that complete excision with favorable outcomes was achieved in 50% of patients with low-grade tumors, suggesting that complete excision should be attempted in this population, whereas total excision was difficult and functional outcomes were poor among patients with high-grade tumors.[116] In patients with favorable prognostic factors (low-grade histologic findings, good performance status, and young age), observation with serial imaging studies, reserving irradiation for local recurrence, is an appropriate management option, particularly for young children.[48,111-114,125-127] In the remainder of patients, adjuvant irradiation (RT) is usually recommended because progression of tumor in the spinal cord may lead to significant neurologic impairment.[29,34,111-114,117,121,126,128] Doses have traditionally been based on the experience with cerebral tumors, with lower grade tumors typically receiving 45 Gy to 54 Gy and high-grade tumors receiving higher doses.[111,114,117,121,125,126,129,130]

The overall outcomes are similar for patients with low-grade gliomas of the spinal cord treated either by GTR or STR or biopsy followed by external beam irradiation (EBRT), with most series reporting OS at 5 and 10 years in the ranges of 55% to 100% and 39% to 83%, respectively, and disease-free survival (DFS) of 38% to 93% and 26% to 80% at 5 and 10 years, respectively. Overall long-term local control rates for gliomas range from 31% to 100%, with grade being the strongest predictor.[111-114,116-119,121,126,127,131] A retrospective review from the Mayo Clinic suggests that postoperative EBRT may improve OS in infiltrative gliomas but not with pilocytic tumors, while a mulitiinstitutional retrospective review shows postoperative EBRT prolongs progression-free survival (PFS).[114,117] However, there are multiple series showing that the use of postoperative EBRT does not influence outcome.[112,113,126] A comparison of survival and local control rates is shown in Table 30-3.

With high-grade tumors in adults and children, the median survival time is quite poor (4 months to 10 months) despite surgery and EBRT. Almost all patients die of local or disseminated disease.[38,41,111-114,116,120,123-125,128] In regard to treatment, multiple retrospective series have failed to consistently improvements in outcome with the administration of radiation therapy, although the Mayo Clinic series described previously did show a survival benefit with the addition of postoperative EBRT for infiltrative tumors.[112-114,116,119,120,123-125,128] Nevertheless, radiation therapy remains the standard of care for these patients.

Data specific to adjuvant chemotherapy (after surgery or radiation therapy) for spinal cord astrocytomas are scant and composed mostly of small retrospective series.[52,54,111,112,132-139] In a retrospective series from MDACC, the use of chemotherapy at diagnosis was associated significantly with improved PFS but not OS in patients with infiltrative astrocytomas.[112] In two small trials, children with high-grade spinal astrocytoma had a 5-year PFS of 46% to 50% and a 5-year OS of 54% to 88% when chemotherapy was given either in the adjuvant setting or at the time of relapse.[54,132] Extrapolating from the results of Stupp et al for intracranial glioblastoma, temozolomide has emerged as a treatment strategy in high-grade tumors in upfront treatment as well as recurrent disease.[133,137,140,141] Overall, although there is no clear evidence of a difference in outcomes with or without chemotherapy for spinal cord tumors, chemotherapy is usually given for patients with malignant astrocytoma.[133-135,140]

Ependymoma

Ependymomas, which are glial tumors, are approximately equal in incidence to astrocytomas, although some studies suggest that they are more common.[118,122,142,143] The mean age at presentation is 30 years to 39 years. These tumors are more common in adults than in children and in males than in females.[144,145] The median duration of symptoms before presentation is 2 years to 4 years and pain is the most common presenting symptom.[144,146-148] Two thirds occur in the lumbosacral region and 40% arise from the filum terminale (Figure 30-11).[45,149] Because of the propensity of these tumors for seeding the craniospinal axis, CSF evaluation and craniospinal MRI are strongly recommended. It is also important to note that 11% of patients with intracranial ependymomas have documented spinal metastases, so imaging of the brain may be indicated to rule out a primary brain tumor (Figure 30-12).[150]

Pathology

Ependymomas arise from ependymal cells and typically occur in the central canal of the spinal cord, the filum terminale, and the white matter adjacent to a ventricular surface. They are either low-grade tumors or anaplastic tumors, the latter being more likely to disseminate via the CSF. The majority of tumors are low grade. Myxopapillary ependymomas are low-grade tumors that typically occur in the lumbosacral region (filum terminale), are well-differentiated, and are often encapsulated but can seed the CSF, typically with "drop metastases" at the thecal sac. Myxopapillary ependymomas often progress slowly and cause milder-than-expected neurologic deficits for their size. Some published series have included ependymoblastomas; however, these are primitive neuroectodermal tumors (PNETs), which have a high propensity to disseminate throughout the CNS and therefore should be considered in the medulloblastoma-PNET family of tumors.

Prognostic Factors

Multiple factors have been reviewed in the literature as being prognostic for local recurrence and survival. Factors prognostic for a favorable outcome include patient age younger than 40 years; tumors with a lumbosacral location, myxopapillary histologic findings, or a grade of WHO grade I; tumors amenable to GTR or STR; and good preoperative function of the patient.[43,116-118,122,144,149,151,152] Some authors believe that the volume of residual disease appears to correlate with a worse outcome after EBRT, whereas other authors have found no differences in outcomes when comparing complete excision with STR followed by EBRT.[44,117,149,153-155]

Myxopapillary subtypes appear to be associated with a favorable prognosis, potentially because of ease of resection

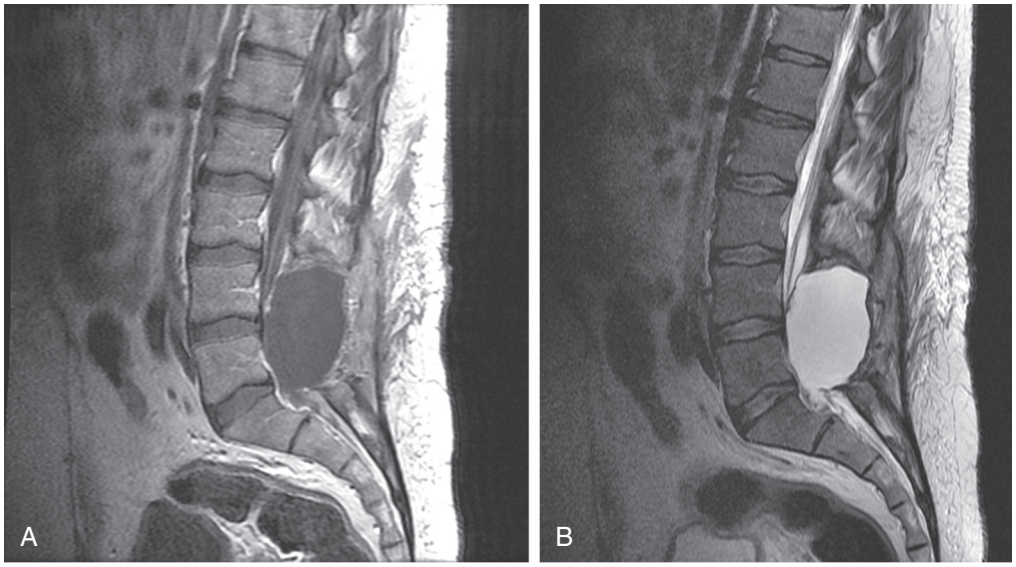


Figure 30-11 MRI of a sacral ependymoma. Shown are T1-weighted image with contrast medium **(A)** and T2-weighted sagittal image **(B)**.

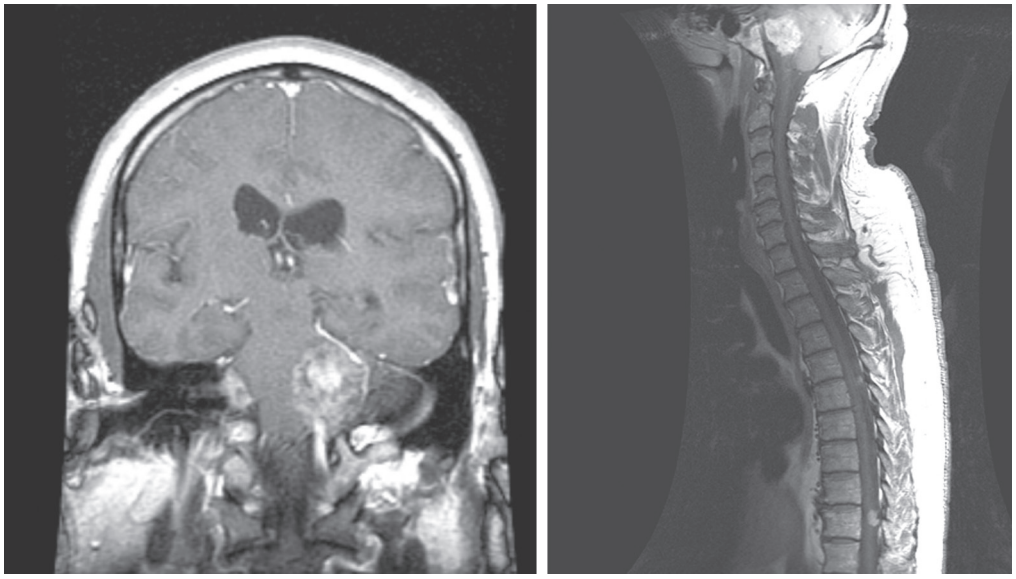


Figure 30-12 MRI of a myxopapillary ependymoma with drop metastases. Shown are T1-weighted, coronal-view image **(A)** and sagittal-view image **(B)**, both with contrast enhancement.

because of their anatomic location. Five-year OS for the myxopapillary subtype and for WHO grade I tumors are 97% to 100%, respectively, and the 5-year disease-specific survival (DSS) is 97%.[153,156] Patients who are able to achieve GTR have improved outcomes and the upfront addition of radiation therapy is of questionable benefit.[146,152,157-159] However, one study suggests that pediatric patients with this tumor had higher recurrence rates, even in the setting of GTR, and appeared to benefit from postoperative irradiation.[157] A retrospective review from the Rare Cancer Network suggests that higher postoperative radiation dose (>50.4 Gy) for the myxopapillary subtype may be associated with improved PFS.[158]

Treatment and Outcomes

Most intradural extramedullary ependymomas are myxopapillary and are often amenable to complete surgical resection if they are not multifocal.[26,148,159] The goal of surgery is GTR. Every attempt should be made to remove tumors as a whole as opposed to piecemeal removal, because of the risk of seeding, including upward seeding to the cranial nerves. The potential for cure may increase the severity of a hopefully transient deficit that surgeon and patient may be willing to incur and illustrates the importance of prospective multidisciplinary management of these tumors. Typically, complete resection is achievable in 79% to 100% of modern series.[36,37,42,43,116,118,143,148,159] Five- and 10-year OS for all spinal cord ependymomas is 67% to 100% and 68% to 100%, respectively.[43,44,116-118,122,143,148,149,153] DSS at 5 and 10 years is 69% to 96% and 62% to 93%, respectively.[33,117,122,160] Local control rates after GTR are 95% to 100%.[31,43,116,118,146,157,161] Late failures may occur more than 4 years after curative surgery, particularly with the myxopapillary subtype, warranting long-term follow-up.[159]

Postoperative EBRT appears to improve local control in patients with STR ependymomas and also for patients with high-grade lesions and those with neuraxis dissemination.[117,144,149,157-160,162,163] In most but not all series, the outcome

for STR followed by EBRT appears to be similar to that of complete resection. Typically, the dose given to the tumor bed is 49 Gy to 56 Gy, whereas the craniospinal axis (if indicated) receives 30 Gy to 36 Gy, and in selected instances, up to 45 Gy.[44,121,146,152,156,158,161,164] Low-grade lesions with a low risk of seeding are typically treated with limited fields to 50.4 Gy to 55.8 Gy in 1.8-Gy daily fractions. In patients with tumors at high risk of seeding, when pretreatment CSF cytologic studies reveal malignant cells, or if the spinal MRI scan shows evidence of leptomeningeal disease, the craniospinal axis should be treated to 36 Gy in 1.5-Gy to 1.8-Gy daily fractions. Subsequently, the primary tumor site is boosted to a total dose of 50.4 Gy to 55.8 Gy. If gross leptomeningeal spread is evident, the craniospinal axis dose should be 39.6 Gy (1.8 Gy/fraction) or 40.5 Gy (1.5 Gy/fraction), with the same boost dose to the primary tumor as previously discussed. For patients with anaplastic ependymoma, if neuraxis radiation is to be employed, some have advocated total doses as high as 45 Gy.

In patients undergoing EBRT following incomplete resection, OS at 5 years, 10 years, and 15 years is 67% to 100%, 67% to 100%, and 75%, respectively.[43,44,117,153,156,159] Cause-specific survival (CSS) at 5 years, 10 years, and 15 years for all tumors is 74% to 93%, 50% to 93%, and 35% to 46%, respectively.[117,160,165] CSS at 5 years is 87% to 97% for myxopapillary and low-grade lesions and 27% to 71% for high-grade tumors.[153,156] DFS at 5 years and 10 years is 59 and 59%, respectively.[160] Local control rates are 72% to 100%.[44,118,153,157,159,161,166]

There is no strong body of evidence thus far demonstrating that the addition of chemotherapy to EBRT improves the outcome.[53,55,167] A single trial of etoposide for recurrent spinal ependymoma has shown a median response duration of 15 months, with a median survival time of 16 months.[55] Responders had a median survival time of 20 months, whereas those who did not respond lived only 4 months; the results approached statistical significance. Pediatric patients with anaplastic ependymoma or ependymoblastoma are routinely given chemotherapy.[168-170] Further trials are ongoing evaluating the use of chemotherapy following surgery and radiotherapy in newly diagnosed ependymoma.

Meningioma

Spinal meningiomas make up only 8% of all meningiomas but account for 25% to 46% of all spinal neoplasms.[171-173] They tend to occur in females three to seven times more commonly than in males.[49,171-175] Most patients are older than the age of 40 years, with a mean age at diagnosis of 49 years to 63 years.[174,175] The incidence appears to be bimodal, the first peak being in the third decade of life, with a second larger peak seen after age 50.[174,175] In younger patients, 13% have NF2.[175] Younger patients (younger than 50 years of age) have a recurrence rate of 23% compared with 5% in older patients, though not all authors agree that young age in and of itself carries a worse prognosis.[171,175]

The most common site is the thoracic region, where 55% to 80% of meningiomas of the spine occur, whereas cervical lesions make up approximately one third of all lesions.[171,172,174-176] The incidence by location varies with age: younger than age 50 years, 39%, 56%, and 5% of lesions occur in the cervical, thoracic, or lumbar spine, respectively; in patients older than age 50 years, the distribution is 16%, 80%, and 5% in the cervical, thoracic, or lumbar spine, respectively.[175]

Treatment and Outcomes

The mainstay of treatment of spinal meningiomas is surgical resection.[142,177] Meningiomas in most patients can be removed through a posterior (laminectomy) approach because they are commonly situated in a lateral or anterolateral location, and even the more anteriorly placed tumors cause enough lateral displacement of the spinal cord to allow access for resection without traction on the spinal cord. If the tumor is located anterior to the spinal cord, it may require an anterior approach, including corpectomy with arthrodesis. Anteriorly situated meningiomas are sometimes unresectable because of their encasement of the anterior spinal cord or because they lie at the foramen magnum encasing a vertebral artery.

Functional improvement of neurologic deficits is seen in 66% to 100% of patients.[49,142,174,176,177] Complete resection is achievable in 82% to 100% of cases, with a 1% to 6% late local failure rate.[142,172,176,177] With STR, late local recurrence rates range from 17% to 100%.[49,142,172,177] Because local failures can take place even decades after surgery, the actual late failure rate may be even higher, similar to that seen in patients with intracranial meningiomas. In one large series, after complete resection, relapse-free rates at 5 years, 10 years, and 15 years were 93%, 80%, and 68%, respectively, and after STR, relapse-free rates at 5 years, 10 years, and 15 years were 63%, 45%, and 9%, respectively.[171] Because local failure rates in the spine are higher with STR, some authors recommend radiation therapy.

The role of irradiation is not well understood because of the small number of cases reported in the literature; most clinicians extrapolate from the data on irradiation of intracranial meningiomas.[171,174,176,178] The expected outcome of radiation therapy is long-term stabilization of disease.[179] Patients who undergo complete resection should be observed. When patients are irradiated, the dose delivered is typically 50.4 Gy to 54 Gy, based on the data from the treatment of intracranial meningioma.[179]

The use of SRS in the treatment of spinal meningioma has been reported.[81,89,91,180] After a mean follow up of 33 months, 91% of meningiomas had shown a treatment response with only one patient developing a transient myelopathy 9 months after treatment. The mean prescription dose was 19.4 Gy (range 14 Gy to 30 Gy) delivered in one to five sessions (median, two).[91]

Chemotherapy has a limited role in this disease. It is sometimes considered for patients who cannot receive further surgery or radiation therapy or for those with diffuse multifocal disease. Hydroxyurea and somatostatin have been used.[181,182]

Chordoma

Chordomas are slow-growing neoplasms thought to arise from remnants of the embryonic notochord that are present in the vertebral bodies and axial skeleton. Expression of the transcription factor *brachyury*, a gene important in notochord development, is characteristic of these tumors and helpful in diagnosis. Chordomas make up approximately 4% of spinal tumors and primarily involve the skull base and sacrococcygeal regions.[68,183,184] A SEER-based analysis suggests, however, that chordomas may be more equally distributed between cranial sites (mostly skull base), the mobile spine, and the sacrum and coccyx.[185] Most chordomas occur during the fourth decade of life, with a male to female ratio of 2 to 1, though sacrococcygeal chordomas tend to arise in the fifth and sixth decades.[186-191]

Prognostic Factors

Several prognostic factors have been identified. Location is prognostic for survival, with a 5-year OS of 66% for sacrococcygeal tumors and 50% for vertebral lesions.[69] Overall, 14% to 39% of patients develop metastases at a median of 5 years, most commonly to the lungs.[98,183,184,186,192,193] The incidence of metastases varies by location of the primary tumor: 26% to 44% of patients with sacrococcygeal lesions develop metastatic disease (usually to the thecal sac), whereas 61% of those

with vertebral primaries can metastasize, typically in a caudal direction. In some series, skull-base lesions have rarely been reported to metastasize.[186,189] Gender may also be prognostic: 5-year and 8-year local control rates are 81% and 75% for men and 65% and 17% for women, respectively.[194,195] The prognostic importance of age is controversial; in some series, children have a higher incidence of metastases, but in other series, patients older than the age of 52 years have a worse local control rate.[68,196,197] Finally, residual microscopic disease after resection (either tumor spillage or positive margins) increases the risk of local relapse to 60% to 64% from 25% to 28% after GTR.[191,198] Primary tumor size less than 8 cm has also been suggested as a good prognostic factor.[197]

Treatment and Outcomes

Although en bloc GTR has traditionally been advocated for these lesions, it is rarely possible. As such, most patients undergo STR or biopsy followed by EBRT. However, surgery is an important component of treatment despite potential morbidity; a recent large database review showed that patients who had undergone more radical resection had significantly prolonged survival times.[197] In most series, patients have been treated with conventional photon radiotherapy, typically to doses of 55 Gy to 70 Gy in 2-Gy fractions, with 5-year OS of 38% to 58%.[184,186,187,189,199-201] Although EBRT prolongs the disease-free interval, most tumors recur unless they have been completely resected; local progression is the most common cause of death.[187] In one older series, the local control rate of sacrococcygeal tumors was 0% with either surgery or EBRT as monotherapy but was 40% when the two were combined.[184]

Some treatment series using conventional photon irradiation suggest that local control rates improve with increasing radiation dose. With doses of less than 40 Gy, more than 48 Gy, more than 50 Gy, and more than 55 Gy, 5-year DFS is approximately 0%, 13%, 31%, and 41%, respectively.[186,200] However, not all authors have found that increased dose improves outcome.[202]

Most experts now advocate charged particle therapy, typically with protons, as the modality of choice, alone or in combination with photons.[68-75,203,204] When patients are treated either immediately after maximum resection or at the time of recurrence, with median doses of 65 Gy to 76 Gy equivalent using charged particle radiation therapy, local control rates at 3 years, 5 years, and 10 years are 67% to 71%, 40% to 75%, and 54%, respectively, with OS at 3 years, 5 years, and 10 years of 88% to 97%, 75% to 80%, and 54%, respectively.[68,71,72,107,205] There is some suggestion that radiation is more effective in controlling chordomas after initial resection rather than at recurrence.[70,206]

SRS/SBRT has also been used in the treatment of residual and recurrent cervical spine chordoma. A mean dose of 19 Gy in a single fraction prescribed at the tumor margin resulted in a 4-year local control rate of 80% without neurologic sequelae in one series.[207]

The experience with interstitial irradiation is minimal. This modality has fallen out of favor with the advent of charged particle therapy and SRS.[208-210]

Chondrosarcoma

Primary chondrosarcoma of the spine is a rare, slowly growing tumor thought to originate from primitive mesenchymal cells or from the embryonal rests of the cranial cartilaginous matrix. Spinal chondrosarcomas are slightly more common in men than in women and the median age of presentation is 51.[211-213] Of the axial skeleton chondrosarcomas, 33% occur in the mobile spine, most often in the thoracic region, whereas another 33% arise in the sacrum.[212-214]

Patients with spinal chondrosarcomas typically have a long-term OS of 25% to 54%.[211-213,215] Adverse prognostic factors include positive surgical margins, high tumor grade, and older patient age.[214,215] Twelve percent to 19% of lesions are grade 4 tumors, which carry a poor prognosis (3-year OS of only 14%; median survival time of 2.7 years; 75% to 86% incidence of metastases).[214,215]

Treatment and Outcomes

Surgical resection is the mainstay of treatment of these lesions with en bloc resection consistently showing significantly better local control and survival rates.[216] OS after any degree of resection is 55% to 72%, 67%, and 63% at 5 years, 10 years, and 15 years, respectively.[213,214] The median survival time is typically 6 years, with local control rates ranging from 36% to 72%.[212,214,215] Patients with GTR have a better outcome than those with STR. After complete resection, the local control rate is 97%, with a 90% 10-year OS and an 84% DFS.[214] Many chondrosarcomas have indolent courses, but others behave more aggressively. Radiation therapy after incomplete resection has been shown to lengthen the disease-free interval from 16 months to 44 months in one series.[212] The use of adjuvant radiation with doses exceeding 60 Gy to 65 Gy is associated with a high rate of local control, although the quality of the supporting evidence is low.[216] Chemotherapy has not been shown to improve outcomes.[212]

Miscellaneous Primary Spinal Tumors

Chloroma

Spinal canal chloroma (also known as granulocytic sarcoma) is defined as an extramedullary localized tumor mass of blasts of granulocytic lineage. This tumor can arise during the course of acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS), either at the same time as the initial tumor or at relapse, but also as an isolated tumor without any signs of medullary involvement. Spinal chloromas occasionally precede the development of systemic disease by weeks to years.

Spinal complications of chloromas, such as cord compression secondary to epidural tumor or cauda equina syndrome, have been described but are uncommon. The median age at presentation is 22 years, with a 7.8:1 male-to-female ratio. The thoracic spine is most commonly involved (73%), followed by the lumbar region (34%), sacral region (23%), and cervical region (5%). Multiple noncontiguous areas of involvement are found in 18% of patients.

The most effective treatment appears to be multimodality therapy coupled with early diagnosis. Options include surgical decompression, intravenous or intrathecal chemotherapy, radiation therapy at doses of 20 Gy to 30 Gy, or any combination of these treatments. Patient survival times range from 18 days to 9.5 years after diagnosis. In a review of the literature, no clear relationship could be found between the specific treatment modality used and the length of survival. Those receiving systemic therapy soon after diagnosis experienced the longest disease-free episodes, however.[217]

Epidermoid Tumor

Epidermoid tumors are benign congenital lesions derived from ectodermal tissue thought to arise because of errors in neural tube closure. These tumors account for approximately 1% of all intracranial tumors but are even rarer in the spine.

Given their benign nature and indolent drown pattern, complete surgical excision is usually curative though many asymptomatic tumors may be observed. Incompletely excised tumors may recur, but because of their slow growth, this may take several years. Radiation does not have a role in the management of these benign lesions but has been used as adjuvant

Epidermoid tumors have male preponderance and are most commonly found in the lumbosacral region. They can be differentiated from arachnoid cysts using diffusion-weighted or FLAIR images given the high degree of restricted diffusion in epidermoids.

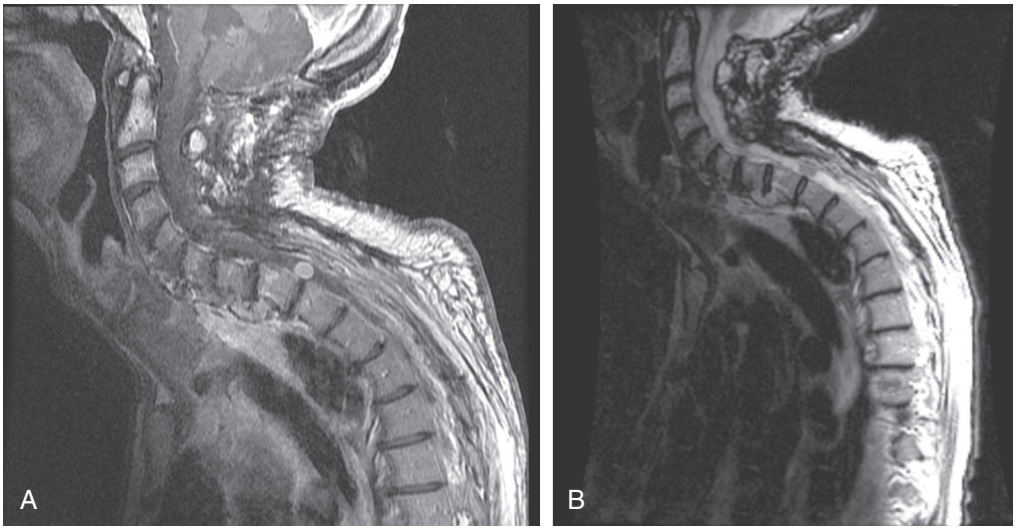


Figure 30-13 MRI of a spinal hemangioblastoma with an associated syrinx in the setting of von Hippel-Lindau syndrome. Shown are a T1-weighted image with contrast enhancement **(A)** and a T2-weighted sagittal-view image **(B)**.

therapy for intracranial epidermoids that have exhibited malignant transformation.[218]

Hemangioblastoma

Intramedullary hemangioblastomas are slowly growing vascular tumors composed of endothelial and stromal components and account for 3% to 13% of intramedullary spinal tumors.

Multiple CNS hemangioblastomas are diagnostic of VHL. Multiply recurrent hemangioblastoma may also raise the suspicion of VHL. Patients with isolated spinal hemangioblastoma should be screened for other manifestations of VHL by ophthalmologic evaluation, brain MRI, and abdominal CT scanning to rule out retinal and cranial hemangioblastoma and renal tumors, respectively. In patients with VHL, 51% of neuraxis lesions are located in the spinal cord and only 29% are completely intramedullary, with the remainder having an extramedullary component (Figure 30-13).[220]

Factors prognostic for favorable outcome (defined as improvement or stabilization of neurologic function) are minimal or no preoperative neurologic deficits, lesions smaller than 0.5 cm^2, dorsally located lesions, and total surgical removal of the lesion.[220,221] Progressive syringomyelia is a negative prognostic factor with respect to preservation of neurologic function and is often recalcitrant to treatment attempts.

Surgical resection is the mainstay of treatment for symptomatic lesions. Hemangioblastomas are extremely vascular tumors occurring in the spinal intramedullary compartment. The dorsal location of most of these lesions and the commonly associated cyst help to simplify the removal somewhat because the cyst provides a safe route for approaching the tumor. Removal of the enhancing tumor is satisfactory to prevent reaccumulation of the cyst, and the remainder of the cyst wall may, therefore, be left intact. Tumor margins are addressed first and feeding arteries are coagulated. Then the tumor is dissected and removed en bloc. After surgical resection, 41% to 68% of patients experience improvement of neurologic function and another 32% to 84% have stabilization of their preoperative function.[219,220,222]

Although SRS is an option for cerebellar hemangioblastoma, it has not been properly evaluated for spinal hemangioblastoma because of concerns regarding the radiation tolerance of the spinal cord.[131] A few small series suggest safety and efficacy.[80,110,223]

Lipoma

Primary spinal lipomas are benign, congenital, intradural-extramedullary lesions located in the cervicothoracic region. These tumors account for approximately 1% of spinal cord tumors. The classic presentation is that of a slow ascending spastic monoparesis or paraparesis with rapid late deterioration.

Early surgical decompression is mandatory for preservation of existing neurologic function, but complete surgical debulking is almost impossible due to the infiltrative nature of the tumors.[224-226] There is no known role for radiation therapy or chemotherapy.

Lymphoma

Primary spinal cord lymphomas are uncommon lesions. Only 4% of lymphomas are primary epidural tumors of which 90% are of B-cell origin (Figure 30-14).[227-229] Typically, lymphomas involving the spinal cord are seen in the context of primary CNS non-Hodgkin's lymphoma, with 27% having positive CSF findings and 16% eventually developing leptomeningeal disease involving the spine.[228]

If the initial presentation is one of spinal cord compression, management is similar to that of other metastatic tumors described, although rapid responses may be seen with steroids, chemotherapy, and irradiation to a median dose of 38 Gy.[227] Lengthy administration of preoperative steroids may result in disappearance of the tumor by the time of surgery (ghost-tumor effect). Otherwise, management is similar to that of cerebral non-Hodgkin's lymphoma. After decompressive laminectomy, STR, and spinal irradiation, the local control rate is 60%, with a median duration of survival of 42 months.[227]

Neurocytoma

Central neurocytoma has been reported to arise in the spine.[230,231] Staining for synaptophysin and neurospecific enolase allows these tumors to be reliably distinguished. As in the brain, their behavior is variable. Because this tumor arises centrally in the spinal cord, observation or irradiation may be the primary management strategy, with resection reserved for tumors with progressive neurologic deficits.

Sarcoma

Primary soft-tissue sarcomas of the spinal cord are exceedingly rare, accounting for 0.7% of CNS malignant tumors of

The male-to-female ratio is 1.8 to 1.[219] The median age at presentation is 36 years for sporadic lesions, whereas patients with VHL typically present a decade earlier and have multiple tumors.



Figure 30-14 MRI of a lymphoma involving the bone and spinal cord. Shown is a sagittal-view, T1-weighted image with contrast enhancement.

which 5.6% of these are found in the spinal canal.[232] Malignant fibrous histiocytoma represents the most common histologic diagnosis and may display a more aggressive biology that frequently recurs locally and distantly.[233] Tumors arise from the nerve roots of the cauda equina, the spinal cord, or the spinal blood vessels.[232,234] Surgical debulking and postoperative EBRT to approximately 60 Gy in 1.8-Gy to 2-Gy fractions represents the typical treatment approach described in the literature.[232,234] The 5-year OS of patients with high-grade lesions is significantly worse at 28% than the 83% reported with low-grade lesions. The role of chemotherapy is not known. Other sarcomas that may arise in the spine include Ewing sarcoma, rhabdomyosarcoma, and osteosarcoma.

Schwannoma

Spinal schwannoma may present simultaneously in both the spinal canal and the thoracic cavity. These dumbbell-shaped tumors are typically benign and may involve the spinal cord and spinal nerves via the neural foramina. Surgical resection is the treatment of choice.[50,235,236] Schwannomas arise from spinal rootlets (most often, the dorsal rootlets) and may grow along the nerve root in a dumbbell fashion through a neural foramen. Therefore, resection requires removal of sections of the involved rootlets. Only 3% of these tumors are malignant; adjuvant EBRT has been used in such cases with mixed outcomes.[235,236] Although surgery is the mainstay of treatment for spinal schwannomas, SRS and hypofractionated SBRT have also been used.[81,91,237]

Teratoma

True intramedullary teratoma is an extremely rare tumor, with only nine cases reported in the literature.[238] Early surgical resection is recommended to preserve neurologic status. Because teratomas may adhere to the functional neural tissue of the spinal cord in such a way that no dissection plane is available, complete resection is often not possible. A low-grade histopathologic status predominates, so the symptomatic recurrence of incompletely resected mature teratomas is often slow and may eventually require a second surgical procedure.[239] Radiation therapy is generally reserved for multiply recurrent, subtotally resected disease.

Vertebral Hemangioma

Vertebral hemangiomas are benign growths of endothelial origin typically located in the thoracic and upper lumbar spine. They are the most common benign spinal column tumors, with an incidence of approximately 11%. Because vertebral body hemangiomas are most frequently stable over long periods of time, some authors consider them to be nonneoplastic. Growth causing progressive symptoms has been documented. Only 1% to 2% of patients develop clinically significant pain. New onset of back pain followed by subacute progression of a thoracic myelopathy, typically over a period of 4 months to 5 months, is the most common presentation for patients with neurologic deficit.[240] These tumors also occasionally cause root and cord compression syndromes. A preoperative diagnosis of compressive vertebral hemangioma can often be made on imaging studies.[241]

Treatment is initiated only when progressive symptoms, including focal pain or progressive neurologic deficit, develop. Historically, standard treatment consisted of surgical removal of the lesion. Endovascular embolization of these vascular growths with or without surgical decompression may also provide pain control.[242] Vertebroplasty has high reported rates of success. More extensive resections are used for aggressive lesions.[243] The local control rate at 3 years is 70%. Of lesions that regrow, 90% recur within the first 2 years.[244]

Irradiation is an effective treatment alternative. A meta-analysis demonstrated that a total dose of 30 Gy given in 2-Gy fractions resulted in a 57% complete amelioration of pain in 57% of patients and 32% experienced partial improvement of pain.[245] A second, smaller analysis showed an apparent dose-response effect. Patients treated with the biologic equivalent of 36 Gy to 44 Gy in 2-Gy fractions had significantly better complete pain relief than those treated with 20 Gy to 34 Gy (82 versus 39%, respectively).[246]

Treatment-Related Complications

Radiation myelopathy may present as a transient early delayed or late delayed reaction. Transient radiation myelopathy is clinically manifested by momentary, electrical shock-like paresthesias or numbness radiating from the neck to the extremities, precipitated by neck flexion (Lhermitte's sign).[247] The syndrome typically develops 3 months to 4 months after treatment and spontaneously resolves over the following 3 months to 6 months without therapy. It is attributed to transient demyelination caused by radiation-induced inhibition of myelin-producing oligodendroglial cells in the irradiated spinal cord segment.[247-249]

Irreversible radiation myelopathy usually is not seen earlier than 6 months to 12 months after completion of treatment. Typically, half of the patients who develop radiation-induced myelopathy in the cervical or thoracic cord region will do so within 20 months of treatment and 75% of cases will occur within 30 months.[250] The signs and symptoms are typically progressive over several months, but acute onset of plegia over several hours or a few days is possible. It is thought to be multifactorial in origin, involving demyelination and white matter necrosis ultimately resulting from oligodendroglial cell depletion and microvascular injury. The diagnosis of radiation myelopathy is one of exclusion with the following characteristics: (1) a history of radiation therapy in doses sufficient to result in injury must be present; (2) the region of the irradiated cord must lie slightly above the dermatome level of expression of the lesion; (3) the latent period from the completion of

treatment to the onset of injury must be consistent with that observed in radiation myelopathy; and (4) local tumor progression must be ruled out.

There are no pathognomonic laboratory tests or imaging studies that conclusively diagnose radiation myelopathy. MRI findings include swelling of the spinal cord with hyperintensity on the T2-weighted images with or without areas of contrast enhancement.[248-251] There is no known consistently effective treatment for radiation myelitis.[252,253] The probability of dying from radiation myelopathy is approximately 70% with cervical lesions and 30% with thoracic spinal cord injury.[254]

Radiation side effects in children include growth abnormalities such as decreased vertebral height, kyphosis, and scoliosis.[255] Secondary malignant disease, including bone or soft-tissue sarcomas and glioblastoma, has been reported after irradiation of spinal cord tumors.[256-258]

TREATMENT ALGORITHM, CHALLENGES, AND FUTURE POSSIBILITIES

Treatment Algorithm

Primary tumors of the spinal cord are uncommon. Much of the literature groups these tumors together by location (intramedullary vs. extramedullary) when reporting outcomes. However, spinal cord tumors clearly behave differently depending on the histologic type, and this needs to be taken into account when making management decisions. The primary treatment for most spinal cord tumors continues to be surgical resection, with irradiation recommended for patients in whom a complete resection cannot be achieved, for those at high risk of recurrence, and for those with tumors involved in areas where resection would cause unacceptable functional morbidity. The role of chemotherapy in the management of spinal cord tumors remains unclear. A general simplified treatment algorithm is shown in Figure 30-15.

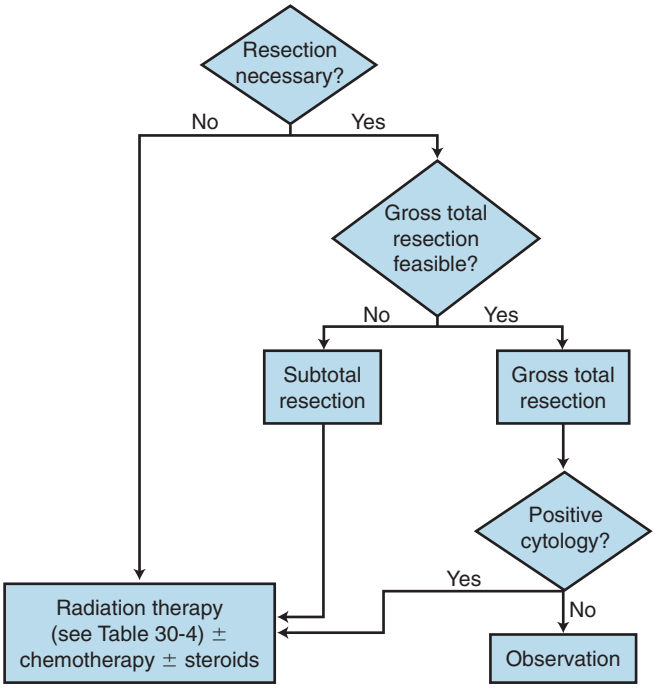


Figure 30-15 Treatment algorithm for the general management of primary spinal tumors. Details about the histologic diagnosis and radiation therapy are provided in the text and Table 30-4.

Challenges and Future Possibilities

Future directions in the management of spinal cord tumors include continued evolution in how these diseases are diagnosed and treated. Advances in imaging may ultimately assist in noninvasively obtaining an accurate tissue diagnosis of a suspicious spinal cord lesion and accurately measuring treatment response. To this extent, novel MRI contrast agents could serve as biochemical reporters of various cellular functions.[259] These newer contrast agents could be tailored to report on the physiologic status or metabolic activity of biologic systems. For example, enzyme-activated agents may correlate developmental biologic events with gene expression. Calcium-activated agents can measure intracellular signal transduction, whereas pH-activated agents provide a blood oxygen level-dependent (BOLD) signal that might be used for noninvasive mapping of human nervous system function. Furthermore, T2-activated agents can detect specific oligonucleotide sequences. Graded functional diffusion map imaging and apparent diffusion coefficient characteristics have shown promise as a potential imaging biomarker in glioblastoma.[260] Relative cerebral blood volume imaging may also be useful in diagnosing tumors and assessing response.[261-263] These areas of interest are currently under investigation in the setting of primary brain tumor treatment, and it remains to be seen how the results will be applied to spinal cord therapy.

Intraoperative fluorescence-guided resection with 5-aminolevulinic acid–induced porphyrins has been suggested to improve outcomes in patients with brain tumors. This method potentially enhances diagnostic accuracy and extent of tumor resection as compared to neuro navigation-guided approaches.[264] This technique has been found to be feasible in the spine and additional studies are needed to better define its role in the management of CNS tumors.[27]

Continued advances in radiation therapy will allow for improved treatment accuracy and precision. The validation and incorporation of functional imaging may improve our ability to define our targets.[265] Fractionated EBRT techniques with photons such as IMRT, VMAT, and helical tomotherapy provide much improved conformality over 3D approaches, which enables increased dose to targeted tissues while minimizing dose to organs at risk. Because most spinal cord tumors typically recur locally, IMRT should allow the exploration of anatomic/biologic treatment planning and delivery to optimize different doses to different cell populations within heterogeneous volumes. To better understand and predict toxicity, better refinements in dose and volume tolerance are necessary, with improvements presented in the recent QUANTEC study.[108,109]

Additional useful radiation therapy techniques include charged particle therapy and hypofractionated regimens/SBRT. Although the role of charged particle therapy with protons has been defined for chordoma and chondrosarcoma, the use of protons is being explored in other histologies of spinal cord tumors.[164] As our experience with patients treated hypofractionated regimens and SBRT grows, long-term data are needed to best assess efficacy and safety.[265]

As we maximize our capacity to conform high doses of radiation therapy to our target, we must also rely on image-guidance to ensure optimal delivery. CT-based image-guided radiation therapy has permitted improved treatment precision. Moreover, further advances are under way with the development of MR-guided linear accelerators. This technology may deliver even better daily targeting for spinal tumors, given the high soft tissue contrast afforded by MRI.

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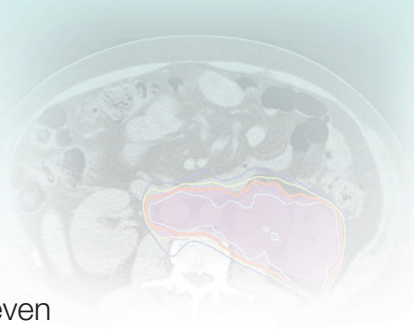
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CHAPTER

31 Orbital, Ocular, and Optic Nerve Tumors



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INCIDENCE
There are 2800 estimated cases of primary ocular tumors annually. The most frequent intraocular primary tumor is ocular melanoma; the second most frequent primary tumor is retinoblastoma seen primarily in children.

BIOLOGIC CHARACTERISTICS
Clinical behavior varies with specific histological and genetic subtype.

STAGING EVALUATION
For melanoma, Collaborative Ocular Melanoma Study (COMS) size criteria are used, and for orbital lymphoma, Ann Arbor staging criteria are used. Ocular rhabdomyosarcomas are discussed in Chapter 68 and retinoblastomas in Chapter 71.

PRIMARY THERAPY
Primary therapy differs by lesion site and histology. For melanoma, iodine-125 (^{125}I) plaque irradiation is used for small and intermediate-size lesions, and enucleation is used for large lesions or eyes with poor vision. Proton beam therapy is also effective for ocular melanoma. For lymphoma, orbital irradiation is used for low-grade lesions and chemotherapy with or without irradiation is used for high-grade lesions. For optic nerve sheath meningioma, orbital irradiation allows for vision preservation and reduction of cranial nerve deficits. For optic pathway gliomas, chemotherapy can be used to delay radiotherapy in children, whereas radiotherapy offers high rates of progression-free survival.

ADJUVANT THERAPY
Adjuvant therapy and outcomes vary with tumor type and extension.

LOCALLY ADVANCED DISEASE
Treatment approach and outcomes vary with specific tumor type.

PALLIATION
Irradiation is effective treatment for advanced primary or metastatic disease and offers symptomatic relief and vision preservation in patients with choroidal metastases. Chemotherapy or hormonal treatment is used for some metastatic tumors.

Based on the incidence rates from the Surveillance, Epidemiology, and End Results Program of the National Cancer Institute, the American Cancer Society estimated that approximately 2800 new cases of all types of primary ocular and orbital malignant tumors were diagnosed in the United States in 2013.[1] Uveal melanoma is the single-most common malignant tumor of the eye and orbit and makes up nearly 70% of all cancers of these tissues.[1] Irradiation is used in the management of many ocular and orbital cancers, as well as in the management of several benign ocular processes. Understanding the pathophysiologic processes of ocular cancers and the results of radiation treatment can guide treatment recommendations.

Complicating the assessment of ocular cancer treatment is the real possibility that therapy itself may result in loss of vision or loss of the treated eye. A thorough understanding of radiation tolerances and treatment sequelae is vital for maximizing overall and vision-related quality of life following treatment.

ETIOLOGY AND EPIDEMIOLOGY

Eyelid Skin Cancers

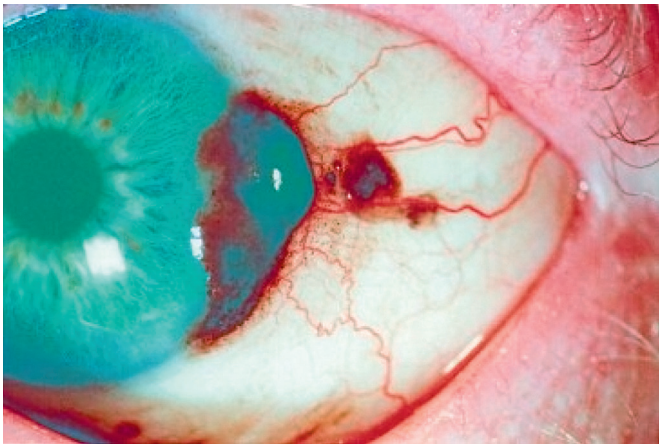
Basal cell cancers make up 90% of eyelid skin cancers; the other 10% is composed of squamous cell cancers. Basal and squamous cell carcinomas of the periorbital skin (nasal bridge, medial canthus, and eyelid) most frequently occur on the lower eyelid and medial canthus. Patients with sun exposure and those who are immunosuppressed have an increased incidence of these cancers.[2,3]

Uveal Melanoma

Uveal melanoma is the most common primary malignant intraocular neoplasm.[1] It is thought to arise from melanocytes of the uveal tract. The incidence in the United States has remained relatively unchanged and is estimated to be 5.1 per million patients per year.[1,4] Uveal melanomas are more common in lightly pigmented persons and are infrequent in nonwhite races[4]; the average age at diagnosis is 62 years.[4-6] Although the disease occurs with equal frequency among men and women, there is significant variation in age-adjusted incidence between sexes (male = 5.58, 95% CI, 5.5-6.2; female = 4.4, 95% CI, 4.2-4.7 per million).[4,7] The tumors are *rarely* bilateral.[4] Factors proposed as increasing the risk for the development of uveal melanoma are prolonged sustained sunlight exposure[7] and lighter-colored irises.[8] Certain diseases may predispose to melanoma, including xeroderma pigmentosum,[9] which is an inherited disorder of DNA repair; oculodermal melanocytosis,[10] in which the ocular surface and the uveal tract are hyperpigmented; and dysplastic nevus syndrome.[11] There are some reports implying a possible rare genetic predisposition, although most melanomas occur as sporadic tumors.

Conjunctival Melanoma

Conjunctival melanomas are rare (5% of ocular melanomas), although the incidence is believed to be increasing.[12] Lesions most commonly arise from primary acquired melanosis (60%) or conjunctival nevus (eFigure 31-1). The lack of atypia on biopsy of the nevus connotes a low likelihood of transformation



eFigure 31-1 Primary conjunctival melanoma. Conjunctival melanoma including a small, additional lesion peripheral to the main juxtalimbal tumor.
Courtesy Seregard S: Conjunctival melanoma. Surv Ophthalmol 42(4):321–350, 1998. Review.[16]

to melanoma.[13] Similar to uveal melanoma, conjunctival melanoma has no particular gender predilection and occurs almost exclusively in Caucasians. Its incidence increases with age and seems to plateau at ages older than 60 years.[14-16]

Retinal Tumors

Retinoblastomas are discussed in Chapter 71.

Optic Nerve Tumors

Meningioma

Optic nerve sheath meningiomas arise from the meningothelial cap cells of arachnoid villi and can develop anywhere along the optic nerve, from the globe to the prechiasmal intracisternal optic nerve. They may be unilateral, bilateral, or multifocal. Patients with type 2 neurofibromatosis are predisposed to bilateral or multifocal lesions.[17] Meningiomas from other locations can also extend to involve the optic nerve. Optic nerve sheath meningiomas are more common in women (61% versus 39%) and present commonly at age 40.[18] Bilateral cases appear to have an earlier age of onset.

Glioma

Optic pathway gliomas account for 1% to 5% of intracranial gliomas and 4% of orbital tumors. They occur most frequently in children, with 75% in the first decade and 90% in the first two decades of life.[19] In pediatric patients with optic pathway glioma, 10% to 38% have type 1 neurofibromatosis, and 15% to 40% of children with neurofibromatosis 1 have an optic glioma.[20] When bilateral, the lesions are pathognomonic for neurofibromatosis 1.

These tumors are increasingly being seen as markers of enhanced risk in patients and their families for the subsequent development of central nervous system (CNS) tumors. Up to 30% to 40% of such patients have a second primary CNS tumor.[21,22]

Orbital Tumors

In a recent report of 1264 consecutive patients with orbital masses, 33% of patients had malignant lesions. Rhabdomyosarcoma was the most common malignant tumor in children, representing 3% of all orbital masses, and lymphoma was the most common malignant tumor in older patients, representing 10% of cases.[23] In one large series, metastatic breast cancer comprised 4% of these lesions.

Rhabdomyosarcoma

Rhabdomyosarcomas are discussed in Chapter 68.

Lacrimal Gland Tumors

Lacrimal gland tumors are rare. The gender distributions are equal and patient age ranges from 10 years to 73 years (mean of 46 years). Most of these lesions are malignant and are typically either adenoid cystic carcinoma or mucoepidermoid carcinoma histology.[23,24] Benign pleomorphic adenomas represent the majority of benign lacrimal masses, although the overall incidence is exceedingly low.

Orbital Lymphoma

Primary orbital lymphomas are rare and account for less than 1% of all lymphomas. The incidence of these tumors has tripled in the United States over the last two decades, as a result of the increase in the primary intraocular lymphoma associated with primary CNS lymphoma. Lymphomas in the orbit can occur anteriorly in the conjunctival tissues or in the retrobulbar region. Patients who are immunocompetent tend to present in the late 50s to 60s, whereas patients who are immunodeficient present at an earlier age, similar to primary CNS lymphoma. Primary orbital lymphoma is slightly more common in men than in women.

Primary adnexal lymphoma (conjunctival, lacrimal gland, orbit, and eyelids) is a distinct clinical and biological disease entity relative to the primary uveal (intraocular)/primary CNS manifestation and has a different natural history. Adnexal lymphomas are most commonly the low-grade subtype of non-Hodgkin's lymphoma (NHL) known as mucosa-associated lymphoid tissue (MALT)-type lymphoma. The median age at diagnosis is about 65 years[25] and unlike all other subtypes of NHL, the male-to-female ratio favors females.[26] Unlike its CNS counterpart, primary adnexal lymphoma is not associated with HIV infection[27] but does have a strong etiological association with *Chlamydia psittaci* infection, similar to the association of *Helicobacter pylori* with primary gastric MALT lymphoma.

Primary intraocular lymphoma may present with malignant lymphoid cells involving the retina, vitreous, or optic nerve head with or without concomitant CNS involvement; it represents a variant of primary CNS lymphoma. The age distribution is bimodal and exhibits two peaks at approximately 31 years and 60 years. The rise in incidence in this subtype is thought to be linked to the greater numbers of patients who are pharmacologically and virally immunosuppressed.[28]

Metastatic Tumors

The most common primary tumor to metastasize to the orbit is breast cancer followed in incidence by lung cancer.[29] Other orbital metastases have been reported to occur from neuroblastoma, renal cell cancer, and prostate cancer. Similarly, choroidal metastases are most frequently of breast cancer origin, followed by lung cancer.[30] In one report of 420 patients, uveal metastasis arose from a primary cancer of the breast in 196 patients (47%), the lung in 90 patients (21%), the gastrointestinal tract in 18 patients (4%), the kidney in 9 patients (2%), the skin in 9 patients (2%), the prostate in 9 patients (2%), and other cancers in 16 patients (4%).

Benign Ocular Conditions

Pterygium

A pterygium is a benign growth of fibrovascular tissue on the cornea. These lesions may become red and inflamed, ultimately encroaching on the visual axis. In addition to functional impairment, these may be viewed as cosmetic nuisances for patients.

Most pterygia are located nasally and occur in patients aged 20 years to 50 years; men and women are equally affected.[31] They are more commonly encountered in warm, dry climates or in patients who are chronically exposed to outdoor elements or smoky and dusty environments. Ultraviolet light exposure appears to be the most significant factor in the development of pterygia,[32] whereas hereditary contributions are considered rare.

Orbital Inflammatory Syndrome or Pseudotumor

Orbital pseudotumor, or idiopathic orbital inflammatory syndrome, is a nonspecific inflammatory process of unknown etiology that may mimic orbital lymphoma and comprises some 10% of all orbital mass lesions.[23] The diagnosis of pseudotumor is vague and remains one of exclusion.[33] Because the disease mimics infectious or neoplastic processes, these must be ruled out. Autoimmune disease, endocrinopathies, and granulomatous processes also must be excluded, as well as local infection with secondary involvement of the orbit, such as sinusitis and subperiosteal abscess.

Secondary lymphomatous involvement of the orbit is also not infrequent and patients with lymphoma at other sites can also present with eye involvement at any point in the course of their disease.

The term *pseudolymphoma* has been advocated to describe a diagnosis of reactive lymphoid hyperplasia. In general, lymphoid hyperplasia arises in the anterior ocular structures, and pseudotumor arises more posteriorly in the bony orbit. However, the literature includes reports of patients with biopsied and unbiopsied lesions, as well as reactive lymphoid hyperplasia and the more nonspecific inflammatory lesions. For this reason, the term *pseudotumor* refers to any idiopathic inflammatory lesion of the orbit.

Although the precise etiology is unknown, several theories have been proposed.[34] The response to steroids and immunosuppressive drugs suggests an autoimmune disorder.[35] Similarly, a fibroproliferative disorder and aberrant wound healing provoked by infection or autoimmune disease have also been postulated as causes of reactive lymphoid hyperplasia.

Graves's Ophthalmopathy

The pathogenesis of Graves's ophthalmopathy is thought to be autoimmune, triggered by an autoantigen which, once encountered, triggers T lymphocytes to invade the orbit and stimulate glycosaminoglycan production in fibroblasts, which undergo a phenotypic change as a result of surrounding cytokine influences, resulting in tissue edema, lymphocyte infiltration, and marked enlargement of the extraocular muscles.[36] The ophthalmopathy typically goes through three phases: progression, followed by stabilization, and perhaps some improvement. Because lymphocytes and fibroblasts are sensitive to radiation, retrobulbar irradiation has been advocated as a treatment. Residual signs of ophthalmopathy after the disease has reached a plateau are thought likely to be the result of fibrosis and other tissue changes rather than persistent inflammation.

Macular Degeneration

Age-related macular degeneration (AMD) is the leading cause of blindness in patients older than 65 years.[37] The progressive loss of central vision is usually consequential to an atrophic process involving the retinal epithelium and choriocapillaris in the macula, which is classified as dry AMD.[38] The wet form of AMD is an exudative process with subretinal neovascularization. Wet AMD generally progresses to destructive disciform scarring of the macula, with fibrovascular scars involving the choroid and sensory retina. Poor visual acuity is the result.

PREVENTION AND EARLY DETECTION

Because of the rarity of all ocular tumors, no prevention or early detection methods have been developed for most tumor types. However, in children born into a family with known retinoblastoma, early and careful ophthalmologic evaluation is warranted. Genetic counseling and evaluation of the siblings of patients with retinoblastoma is important, given the high hereditary likelihood.[39] After the diagnosis of unilateral retinoblastoma, routine evaluation of the uninvolved eye is indicated because of the increased risk of contralateral disease (see Chapter 71). Similarly, physicians caring for patients with neurofibromatosis 1 and optic pathway gliomas should be wary of additional intracranial lesions because a second primary CNS tumor will develop in approximately 30% to 40% of those patients.[22] Early detection may provide the best opportunity for interventions that optimize patients' quality of life.

MOLECULAR BIOLOGY AND BIOLOGIC CHARACTERISTICS

Ocular Melanoma

Ocular melanoma is a biologically distinct malignancy relative to its cutaneous counterpart. Recent data suggest that specific chromosomal aberrations within the tumor may be associated with clinical outcomes. Kilic et al conducted a cytogenetic analysis of 74 primary uveal melanomas, which led to the identification of common cytogenetic chromosomal losses, including 1p (24%), 3p (41%), and 3q (42%), and 6q (28%). Common chromosomal gains include 6p (18%) and 8q (53%). The degree to which each chromosomal aberration impacted disease-free survival varied, although monosomy of chromosome 3 seemed to have the largest impact when correcting for other confounding factors. It is detected in more than 70% of metastasizing and 20% of nonmetastasizing uveal melanomas; by contrast, the loss of 1p occurred only in the metastasized uveal melanomas.[40,41] Concomitant loss of 1p and monosomy of chromosome 3 were strongly predictive of decreased survival.[42] Recent efforts to classify uveal melanomas with biomarker-based assays to predict distant disease-free survival have focused on gene expression profiling and have resulted in the classification of tumors into two classes: class 1 or low-grade tumors (with a reduced propensity for distant spread) and class 2 or high-grade tumors, which have a higher level of aneuploidy, proliferation rate, and much reduced survival relative to class 1 tumors (95% in class 1 versus 31% in class 2 at 7 years).[43-46] Such information can be gleaned from fine-needle aspiration biopsy in patients likely to be treated with local, conservative modalities such as proton therapy or episcleral plaque radiotherapy.[47]

Orbital Lymphoma

The biology and natural history of these tumors varies with the histological classification within the Revised European-American Lymphoma system or the Working Formulation.[61,62] Stage and histological type play the most significant roles in outcome for orbital lesions.

Primary adnexal/conjunctival lymphoma is predominantly comprised of MALT type lymphoma and thus is dissimilar to the CNS manifestation, which is most frequently the diffuse large B-cell subtype of NHL. Clonality is easily demonstrated in the vast majority of cases because heavy chain immunoglobulin (IgH) rearrangement occurs in 80% of patients.[63] Despite multiple cytogenetic, mutation, and comparative genomic hybridization studies, a keystone mutation found in more than 50% of cases has not been identified. Although chromosomal losses and gains are relatively common, the frequencies are nonuniformly distributed between reports. At present, the most frequent translocation identified (15% to 40% of patients) includes t(11:18)(q21:q21) and results in the juxtaposition of the API2 (apoptosis inhibitor 2) gene and the MALT1 gene.[64-66] The translated fusion product of the aforementioned translocation leads to the constitutive activation of IK protein kinase, which degrades I-kB, and the subsequent translocation of the NF-kB complex to the nucleus, which in turn affects genes involved in inflammation, apoptosis, and immunity.[67,68]

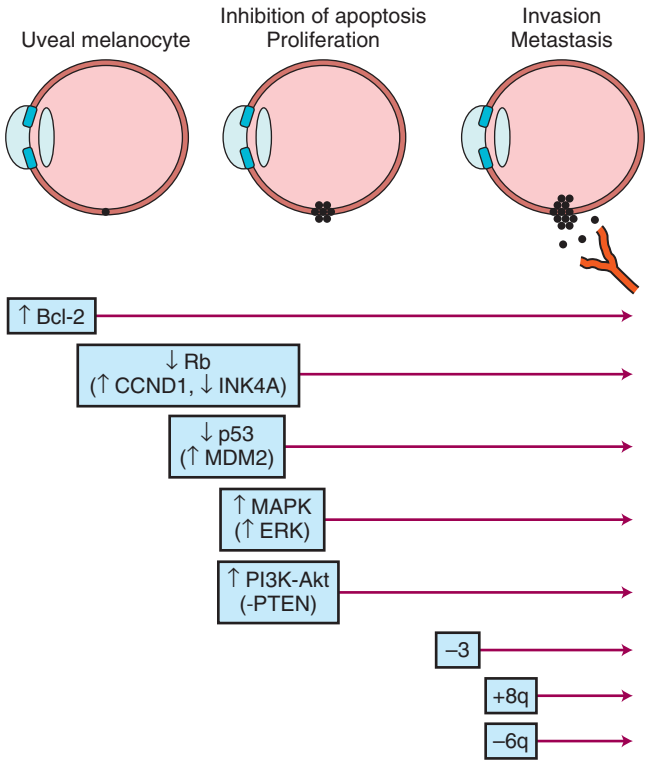
Primary intraocular lymphoma is believed to be a subset of primary central nervous system lymphoma. Roughly 90% of cases are of the diffuse large B-cell NHL subtype, and roughly 10% are either Burkitt's or T-cell lymphoma. Because pathologic diagnosis can be difficult, flow cytometry is often done to document the presence of monoclonal populations of B lymphocytes derived from immunoblasts or centroblasts. These probably arise from late germinal center or postgerminal center lymphoid cells with a predilection for clustering around cerebral blood vessels secondary to an incompletely understood neurotropism. Expression profiling has resulted in the description of three characteristic transcriptomic profiles, known as germinal center B cell, activated B-cell, and type 3 B-cell lymphoma.[69] Further gene expression profiling studies

Although the genetic mutations characteristic to cutaneous melanomas have been better characterized (i.e., BRAF, NRAS), the mutations characteristic to choroidal melanomas are only now being appreciated (eTable 31-1). For instance, BRAF, which is among the more common mutations in cutaneous melanoma, occurs at a low frequency in uveal melanomas; however, its incidence in iris (~50%) and conjunctival (22.7%) melanomas is much higher.[48,49] The most common genetic mutations in uveal melanomas are uncommon in cutaneous melanoma (eFigure 31-2). Those mutations more common in the posterior uvea are distinct from iris and conjunctival melanomas, and include GNAQ, GNA11, and BAP1.[50,51] Eighty percent of all uveal lesions harbor mutations in either GNAQ (~50%) or GNA11 (~30%). These are heterotrimeric GTP-binding protein alpha-subunits that couple G-protein signaling to MAPK activation. MAPK is commonly activated in cutaneous melanomas under the direction of BRAF or NRAS.[52-55] The high incidence of these mutations in nearly all uveal lesions and some blue nevi have led some to believe that these mutations are early oncogenic events in the development of melanoma.[56] Late oncogenic mutations include decreased PTEN and BAP1 mutations, or their complete absence. Somatic mutations in BAP1 (BRCA1 associated protein-1) are common among class 2 uveal melanomas (84%), but not class 1 melanomas.[51] This protein facilitates the transformation to a class 2 melanoma by unknown means and results in a highly metastatic phenotype.[57] The sequential mutation of BAP1 in uveal melanoma is thought to be a late oncogenic event relative to other insults like GNAQ mutations.[51] PTEN loss, similar to BAP1 mutations, occurs in a high proportion of class 2 uveal melanomas and results in unfettered PI3K-Akt signaling, leading to resistance to apoptosis, increased growth potential, and reduced disease-free survival.[58,59]

eTABLE 31-1 Genotypic Differences between Cutaneous and Uveal Melanoma

Gene	Cutaneous	Uveal
BRAF	50%-70% (mut)	<5%
NRAS	15%-30% (mut)	<5%
AKT3	40%-67% (amp)	—
GNAQ	83% (blue nevi)	45% (mut)
GNA11	—	32% (mut)
BAP1	5%	47% (mut)
KIT	11%-21%	<5%
CDKN2A	30%-70% (del/mut/silenced)	<5%
PTEN	5%-20% (del/mut)	15%-58.7%
APAF1	(40% silenced)	—
TP53	(10% loss/mut)	<5% (mut)
CCND1	6%-44% (amp)	65% (amp)
MITF	10%-16% (amp)	>75% (amp)

Amp, *Amplification;* AKT3, *v-Akt murine thymoma viral oncogene homolog 3;* APAF1, *apoptotic protease activating factor 1;* BAP1, *BRCA1 associated protein-1 (ubiquitin carboxy-terminal hydrolase);* BRAF, *sarcoma viral oncogene homolog B1;* CCND1, *cyclin D1;* CDKN2A, *cyclin-dependent kinase inhibitor 2A;* GNAQ, *guanine nucleotide-binding protein G(q) subunit alpha;* GNA11, *guanine nucleotide binding protein (G protein), Alpha 11 (Gq Class);* KIT, *stem cell factor receptor;* MITF, *microphthalmia-associated transcription factor;* Mut, *mutation;* NRAS, *neuroblastoma RAS viral oncogene homolog;* PTEN, *phosphatase and tensin homolog;* TP53, *tumor protein 53.*



eFigure 31-2 Molecular pathogenesis of uveal melanoma. Molecular alterations implicated in the development and progression of uveal melanoma.
Courtesy Triozzi PL, Eng C, Singh AD: Targeted therapy for uveal melanoma. Cancer Treat Rev 34(3):247–258, 2008.[60]

have been heterogeneous and have drawn limited conclusions (largely because of tissue availability and small numbers). Several key translocations are being investigated further: TTF (70%), PAX5 (60%), CMYC (60%), PIM1 (50%), IG loci (38%), BCL6 (23%), CD95 (20%), and PRDM1 (19%).[70-72]

Orbital Pseudotumor

The histopathologic types of orbital pseudotumor vary, and attempts to refine and subdivide them have been advocated. The histopathologic spectrum of idiopathic orbital inflammation is typically nondiagnostic and diverse, ranging from the typical diffuse polymorphous infiltrate to the atypical granulomatous inflammation, tissue eosinophilia, and infiltrative sclerosis. One report suggested dividing this condition into three principal types: lymphoid, granulomatous, and sclerosing types.[73] Several authors have endorsed the exclusion of reactive lymphoid hyperplasia and defined pseudotumor as a mixed inflammatory infiltrate with fibrosis of varying degrees.[74]

Pterygium

Pterygia represent a degeneration of the conjunctival stroma with replacement by thickened, tortuous elastotic fibers.[75] Activated fibroblasts in the leading edge of the pterygium invade and fragment Bowman's layer. Pterygium development resembles actinic degeneration of the skin.

PATHOLOGY AND PATHWAYS OF SPREAD

Skin Cancers

Squamous cell cancers have regional lymph node involvement in 5% to 24% of patients, whereas nodal involvement in basal cell carcinoma is rare.[76-78] Lymph node involvement is more common for larger tumors, recurrent tumors, and those with perineural invasion.[79] Patients with recurrent lesions or perineural invasion may have tumor cells spread more peripherally than is clinically apparent, and advanced imaging approaches may be needed to adequately describe the extent of spread.[80,81] Standard hematoxylin and eosin staining detects approximately half of cases with perineural invasion; the addition of $p75^{NGFR}$ and S-100 may enhance the detection rate, although the prognostic significance is unclear.[82] Tumors located in the embryologic fusion planes of the face are more deeply infiltrating.[81] The area around the medial canthus may affect the depth of treatment necessary for a successful outcome.[83]

Ocular Melanoma

Uveal melanomas arise from melanocytes of neuroectodermal origin and have a large nuclear to cytoplasmic ratio, prominent or multiple nucleoli, and frequent mitotic figures. Tumors are generally classified as composed of either spindle cells or epithelioid cells.[84] Spindle cells have a fusiform shape and less pronounced atypia, whereas epithelioid cells are larger and more ovoid in shape and have more anaplastic characteristics. Uveal melanomas are classified as spindle cell melanomas if they are composed of only spindle cells, mixed cell melanomas if they contain both spindle cells and epithelioid cells, and epithelioid cell melanomas if they contain predominantly or exclusively epithelioid cells. Occasionally, the cells within the melanoma undergo necrosis, and these tumors are classified as necrotic melanomas. Melanomas tend to be slow-growing tumors, but the rate of growth can be quite variable and more rapidly growing tumors tend to be anaplastic and composed of epithelioid cells.

At the time of diagnosis, most posterior uveal melanomas are confined inside the sclera of the eye. Extraocular extension of the melanoma can occur through emissary canals, through which normal ocular structures such as vessels and nerves enter and exit the sclera, and generally not by atrophy or thinning of the sclera. Extraocular extension is classified as microscopic or gross (visible on gross inspection), occurs in 8% to 14% of eyes harboring a melanoma, and is associated with a worse prognosis[85,86] as reflected by the seventh edition AJCC staging system.

Despite the relatively small size and location, ocular melanoma has a high rate of distant failure, which drives patient mortality, although identifiable metastatic disease occurs in less than 3% of patients at the time of initial diagnosis. In the COMS report, sites of metastasis from melanoma included liver (91%), lung (28%), and bone (18%) (eFigure 31-3). Melanomas of the iris rarely metastasize. More unusual sites of spread include skin and subcutaneous tissue, brain, and spinal cord tissue. The brain is an infrequent site of metastasis; in the COMS report, brain metastases were discovered in only 4% of patients at the time of death.[87] Lymph node involvement was noted in 10% of patients who died from metastatic disease within the COMS.[87]

Choroidal Metastasis

The most common pathologic type is adenocarcinoma from the breast or non–small cell lung cancer. Most patients have other sites of metastatic disease. Disease extent can be localized to the choroid or infiltrative. The average number of lesions seen in the choroid in one large series was two and in about 25% of cases, multiple or bilateral tumors are present.[30,88,89] Orbital metastases can also occur but are typically less common and are unilateral; however, patients with breast cancer may have an increased incidence of bilateral globe involvement.[90]

Orbital and Ocular Lymphoma

A wide range of NHLs have been described involving the orbit and globe. In patients with orbital lymphomas, most of the lesions are of B-cell origin and classified as low or intermediate grade according to the World Health Organization (WHO) classification.[91] The most common subtype of ocular adnexal lymphoma which is generally referred to as "extranodal marginal zone B-cell lymphomas (EMZL)" is a MALT type lymphoma.[92] Primary uveal lymphomas involving the iris or choroid are usually of the aggressive, diffuse, large B-cell type.[25,93,94]

The pattern of spread in low-grade lymphomas associated with lacrimal and conjunctival sites is similar to that of its counterparts in the rest of the body. Risk of involvement of distant sites ranges from 15% to 20% at 5 years, although there is some suggestion that lacrimal and soft-tissue lesions may have rates of distant relapse as high as 50%.[95] Primary uveal lymphomas tend to disseminate into or be a component of disease within the CNS, with 60% to 80% of these ultimately being diagnosed as intracranial primary CNS lymphoma.[96]

Optic Nerve Sheath Meningioma

Meningiomas spread along the path of least resistance, remaining confined to the subarachnoid or intradural space of the intraorbital optic nerve. The tumor may invade the dura, adjacent orbital tissue, muscle, bone, and globe. These tumors may traverse the optic canal and affect the intracranial segment of the optic nerve or adjacent structures. Optic nerve sheath meningiomas have histological features similar to those of

Immunologic cytochemical staining, polymerase chain reaction testing, and flow cytometry are all helpful for demonstrating surface membrane or cytoplasmic markers that correspond to a lymphoma. Polyclonal distributions are associated with pseudolymphoma.



eFigure 31-3 Natural history of ocular melanoma. Massive distant failure in the liver three years from a patient treated for ocular melanoma.

intracranial meningiomas and are graded according to WHO criteria on the basis of sheeting, number of mitoses, cellularity, nucleoli, nuclear-to-cytoplasmic ratio, necrosis, frank anaplasia, subtype, and brain invasion.[97] Most lesions demonstrate concentric formations of spindle cells or ovoid meningothelial cells, with sheets of polygonal cells separated by vascular trabeculae, and are of the meningothelial or transitional subtypes.[98,99]

Lacrimal Gland Tumors

Pathologic findings are typically those of adenoid cystic cancer, followed by mucoepidermoid cancer and adenocarcinoma. Outcome seems to be related to the presence of necrosis, hemorrhage, perineural invasion, and high mitotic count.[100,101]

Optic Pathway Glioma

In the pediatric form of the disease, the cell of origin for optic nerve gliomas is unknown. Optic nerve gliomas are classified as grade-1 astrocytomas and are frequently either of the pilocytic or fibrillary subtype in the WHO classification of gliomas. Optic nerve gliomas develop in stages, from generalized hyperplasia of glial cells in the nerve to complete disorganization with loss of neural landmarks within the nerve and nerve sheath. A reactive meningeal hyperplasia may be incited, making it difficult to distinguish a glioma from a perioptic meningioma. Histologically, the WHO grade-1 variant consists of a population of cells that are biphasic and have compacted bipolar cells and less dense multipolar cells. The biphasic component often consists of spindle-shaped cells with elongated or ovoid nuclei and is frequently associated with "Rosenthal fibers." These fibers are representative of degenerating astrocytes and contain eosinophilic, spherical, cylindrical granular aggregates composed of degenerated glial filaments.[102] These lesions may appear cystic.[103]

Similar to intracranial low-grade gliomas, these lesions grow slowly, and bony constraints determine the route of extension.[104] Intracranial extension is common for more advanced lesions, which may result in enlargement of the optic canal. In the diffuse type, the optic nerve appears enlarged and thickened, and it effaces the arachnoid space; whereas in the extrinsic/peripheral subtype, the tumor fills the subarachnoid space and minimally enlarges the diameter of the optic nerve. Except for the neurofibromatosis 1 variety, optic nerve gliomas are nearly always unilateral. Chiasmal involvement and extension beyond the optic pathways are less common, and cystic enlargement is more common (10%) in patients with neurofibromatosis 1.[105] Resultant hydrocephalus is uncommon in patients with neurofibromatosis 1.

In the adult form of the disease, optic nerve gliomas are more likely to be diffusely infiltrative, including astrocytoma (WHO grade II), anaplastic astrocytoma (WHO grade III), or glioblastoma (WHO grade IV).[106] Spread beyond the original site may occur anywhere along the optic tracts as far back as the lateral geniculate bodies in the optic radiations, although this is rare. Histologically, adult lesions may display more nuclear atypia, mitoses, endothelial proliferation, and necrosis because the lower-grade subtypes are less common.

Orbital Pseudotumors

Pseudotumors are rarely infiltrative. One review documented infiltration of the retrobulbar fat in 76% of patients, enlargement of the extraocular muscles in 57%, thickening of the optic nerve/sheath complex in 38%, contrast enhancement in 95%, and proptosis in 71%.[107] Intracranial extension is unusual but has been documented in up to 8.8% of patients.[108]

CLINICAL MANIFESTATIONS, PATIENT EVALUATION, AND STAGING

The diagnostic algorithm for ocular, orbital, and lid tumors is given in Figure 31-1.

Skin Cancers

Patients should be evaluated for lymph node involvement with physical examination of the parotid, facial, and neck node areas. Symptoms of pain, formication, or other sensory changes may indicate perineural invasion.[109,110] The role of sentinel lymph node biopsy is unclear and should not be considered standard practice.[111] In some cases, it may be necessary to biopsy the distal branch of the suspected involved cranial nerve, although this approach confers morbidity and is prone to false-negative determinations because perineural invasion perineural invasion (PNI) may skip locations along the nerve.[112] Magnetic resonance imaging (MRI) of the face and orbits is the most sensitive modality for determining the clinical extent of perineural invasion because it may detect enlargement of the affected nerves[113] and should be considered in cases in which either clinical symptoms or documented histological features are suggestion of PNI.

Ocular Melanoma

At the time of presentation, 30% of patients with ocular melanomas may be asymptomatic. Symptomatic patients often complain of visual symptoms such as flashes of light, floaters, decreased visual acuity, or scotoma. Those who have visual symptoms typically have a more posteriorly located tumor, a large tumor, or an associated retinal detachment leading to a visual field deficit (Figure 31-2). Rarely, pain and redness are presenting symptoms, occurring in large or necrotic tumors

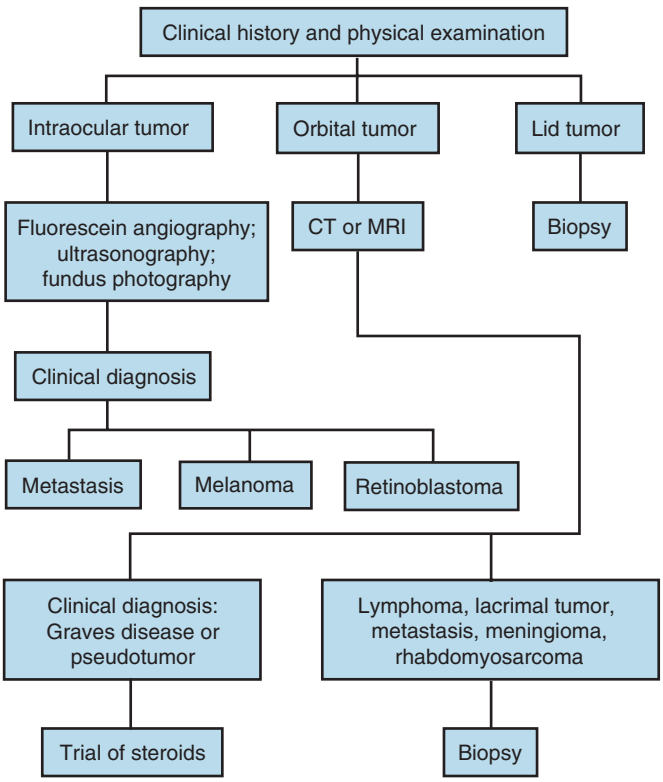


Figure 31-1 Diagnostic algorithm for orbital tumors.

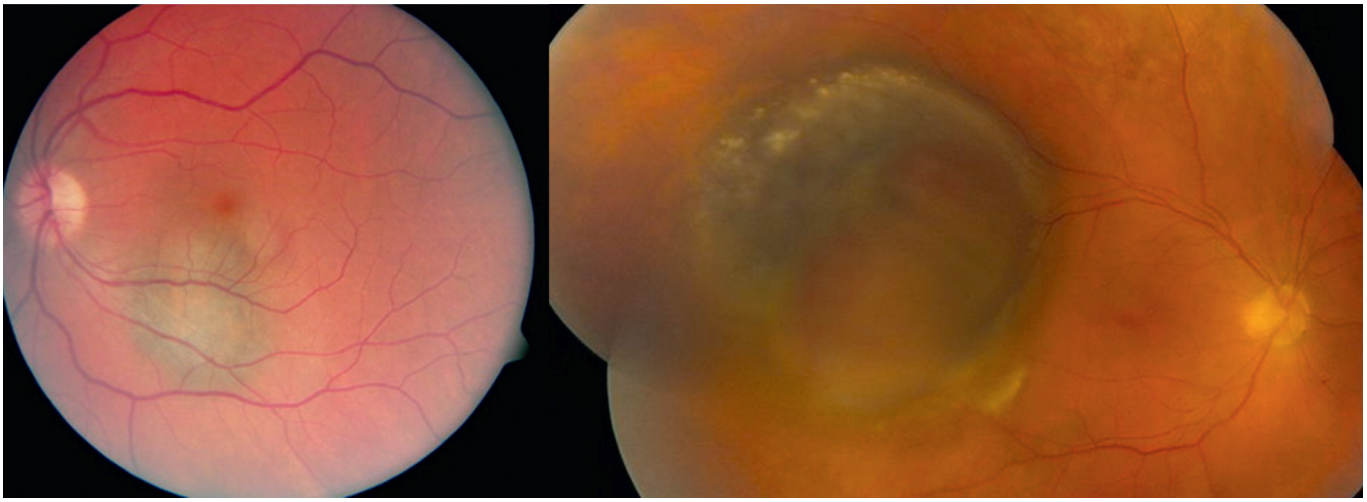


Figure 31-2 Primary choroidal melanoma. *Page right:* Infero-nasal macular choroidal melanoma, 1.8 mm in height, not amenable to transscleral fine-needle aspiration biopsy and *page left:* COMS large, not amenable to plaque radiotherapy.
Courtesy Young TA, Burgess BL, Rao NP, et al: Transscleral fine-needle aspiration biopsy of macular choroidal melanoma. Am J Ophthalmol 145(2):297–302, 2008.[114]

that have associated inflammation. Tumors of the ciliary body often appear silhouetted against the red reflex and are detected late because of the lack of direct impact on vision until there is significant mass effect. Iris melanomas are typically detected early and are often visible on standard ophthalmologic examination.

The diagnosis of melanoma is based primarily on ophthalmoscopic appearance and ancillary testing. The tumor typically appears as a unilateral, solitary, elevated, dark brown or gray, variably pigmented, dome-shaped mass (Figure 31-2). Orange pigment (lipofuscin) is often found on the surface of the tumor and is thought to represent increased metabolic activity.[115] The presence of lipofuscin can help differentiate these lesions from uveal nevi. Retinal detachment may be present and is more likely in larger tumors.

The initial ophthalmologic workup includes fundus photography, fluorescein angiography, and ultrasonography of the globe (Figure 31-3). These tests facilitate making a correct diagnosis and are also useful in following the lesions for growth or regression after treatment. Ocular melanoma exhibits a central hypoechoic area referred to as the acoustic quiet zone; metastases often have higher internal reflectivity. Ocular melanomas display a double circulation pattern and fluorescein leakage on fluorescein angiography. Standard indirect ophthalmoscopy and MRI may be useful in determining ciliary body involvement and extrascleral extension. In a large prospective trial, 645 of 647 patients who underwent enucleation for melanoma had that diagnosis confirmed at pathologic evaluation. Two of the patients had adenocarcinoma.[116] In eyes with opaque media secondary to cataract or vitreous hemorrhage, ultrasonography of the globe and MRI of the orbits can allow an accurate diagnosis. Optical coherence tomography is useful for estimating macular edema and determining whether there is retinal detachment overlying the tumor.[117] Biopsy of a lesion suspicious for an ocular melanoma is used in cases of diagnostic uncertainty and to determine cytogenetic characteristics for prognostic information. In patients requiring biopsy, histopathologic and immunohistochemical assessments can be useful in confirming the diagnosis and determining the presence of druggable mutations. Although this additional information may be useful at the time of presentation with metastatic disease, its role is still poorly defined when the disease is clinically localized. Fine-needle aspiration may result in vitreous hemorrhage and so in the setting where a characteristic gross appearance is present, biopsy may be avoided.

To assess disease extent, care providers should obtain a general history and perform a physical examination with attention directed to skin lesions, weight loss, the lungs, and the liver. History of a prior cancer would indicate the possibility of a metastatic lesion in the eye rather than a primary melanoma. Because the most frequent site of metastasis is the liver, the workup generally includes liver enzyme levels, which often prompt radiographic imaging. This approach was recently reported to have low sensitivity but high specificity and predictive value.[119] MRI has the highest sensitivity for detecting liver metastases, but its role in the initial evaluation is poorly defined. A recent prospective study of patients at high risk for uveal melanoma based on stage, histologic grade, and genetic subtype used serial MRIs for surveillance. They identified hepatic metastases in 48% of patients with a median of 18 months following treatment; most patients (92%) were asymptomatic, and 49% had less than five lesions, all less than 2 cm in diameter.[120] Other sites of metastatic disease include the lung. In such cases, imaging with chest computed tomography (CT) scanning is most accurate for early detection of disease.

Negative prognostic indicators include largest basal diameter, tumor thickness, ciliary body involvement, extraocular extension, and location of the anterior tumor margin. For each millimeter increase in tumor diameter, risk of cancer-related death increases (HR 1.08, $p = 0.0012$).[121] In a retrospective review of 289 patients in Finland, extraocular growth (HR 2.27, $p = 0.0076$) and ciliary body involvement (HR 1.89, $p = 0.0011$) conferred a similar hazard for cancer-related death (after accounting for competing risks). The 7th edition of the AJCC staging manual has been revised to reflect this and has been subsequently evaluated and validated by the European Ophthalmic Oncology Group (Table 31-1).[122]

Prognosis and duration of vision preservation and patient's quality of life outcomes after local therapies (not including enucleation) are affected by tumor-related factors such as tumor cell type, tumor size, tumor location relative to other intraocular structures, extension of the tumor outside the sclera[123,124] and the location of the anterior tumor margin. Tumors located anterior to the equator of the eye in the anterior choroid or ciliary body have a worse prognosis than those

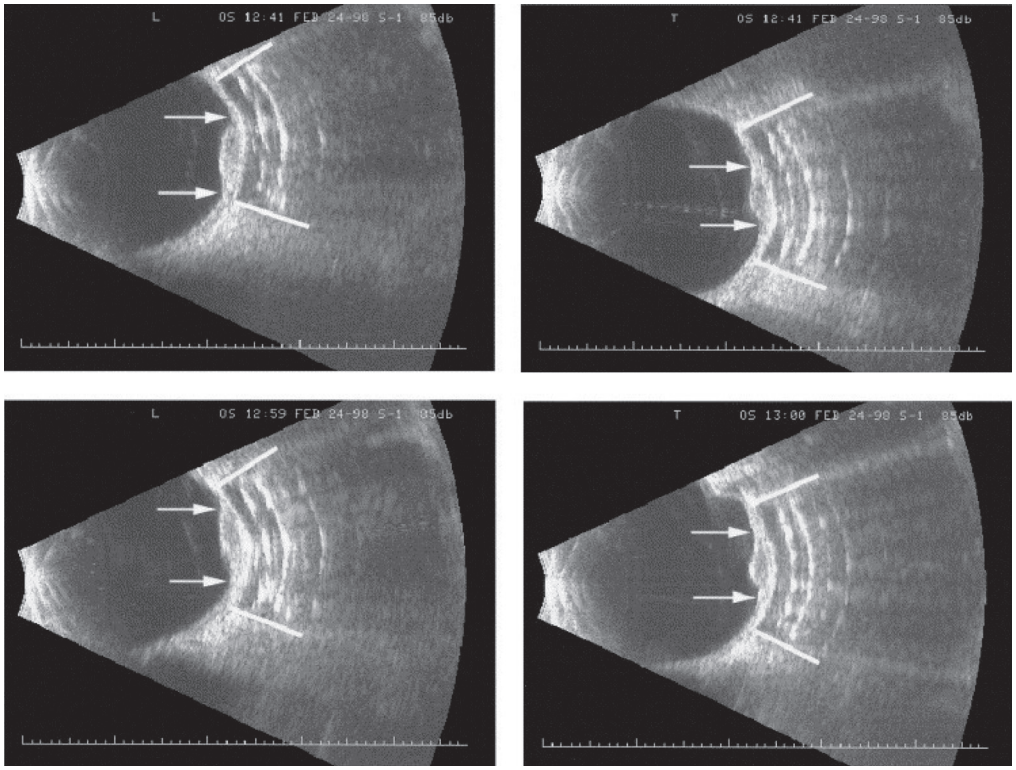


Figure 31-3 Ultrasound localization of plaque insertion. Intraoperative B-scan echograms of an episcleral plaque localized over a posterior choroidal melanoma. *(Top left)* Longitudinal section of an initially malpositioned plaque showing inadequate coverage of the posterior tumor margin *(arrows)*. *(Top right)* Transverse section of the same patient's eye showing good coverage of the lateral tumor margins *(arrows)*. *(Bottom left)* Longitudinal section of the same patient's eye after repositioning of the plaque, showing good coverage of the anterior and posterior tumor margins *(arrows)*. *(Bottom right)* Transverse section of the same patient's eye after repositioning of the plaque, documenting maintenance of good coverage of the lateral tumor margins *(arrows)*.
Courtesy Tabandeh H, Chaudhry NA, Murray TG, et al: Intraoperative echographic localization of iodine-125 episcleral plaque for brachytherapy of choroidal melanoma. Am J Ophthalmol 129(2):199–204, 2000.[118]

TABLE 31-1 COMS and AJCC 7th Edition Staging of Choroidal Melanoma

Thickness (mm)	**AJCC 7th edition T Staging**						
>15					4	4	4
12.1-15				3	3	4	4
9.1-12.0		3	3	3	3	3	4
6.1-9.0	2	2	2	2	3	3	4
3.1-6.0	1	1	1	2	2	3	4
≤3.0	1	1	1	1	2	2	4
	≤3.0	3.1-6	6.1-9.0	9.1-12.0	12.1-15.0	15.1-18.0	>18

	Largest Basal Diameter (mm)		
Thickness (mm)	**COMS Staging**		
>10	L	L	L
2.5-10	M	M	L
1.5-2.4	S	M	L
	5-16	<16	>16

	Largest Basal Diameter (mm)
	Stage Grouping
Stage I	T1a N0 M0
Stage IIa	T1b-d or T2a N0 M0
Stage IIb	T2b or T3a N0 M0
Stage IIIa	T2c-d or T3b-c or T4a N0 M0
Stage IIIb	T3d or T4b-c N0 M0
Stage IIIc	T4d-e N0 M0
Stage IV	any-T N1 M0 or any-T Any-N M1a-c

a: No ciliary body involvement/extraocular extension. b: Ciliary body involvement. c: No ciliary body with or without extraocular extension ≤5 mm. d: +ciliary body with or without extraocular extension ≤5 mm. e: +extraocular extension ≥5 mm.

located more posteriorly.[124] Conversely, lesions more posterior, which approximate the macula, have a higher probability of developing visual acuity loss at 1 and 3 years.[125] Patients with spindle cell tumors having a better survival rate than those with epithelioid cell tumors.[126,127] The prognosis is more favorable in spindle cell melanoma, intermediate in mixed cell tumors, and poorest in epithelioid or necrotic melanoma. Survival rates are adversely affected by increased size of the uveal melanoma. Although the previous literature had various size classifications, the COMS has established a standard size classification.[85,128,129] Small melanomas are 1 mm to 3 mm thick and less than 16 mm in largest dimension. Medium-sized melanomas are 2.5 mm to 10 mm thick (8 if close to optic disc) and less than 16 mm in basal diameter, and large melanomas are more than 10 mm thick or more than 16 mm in largest dimension (Table 31-1).

Ocular Metastasis

In 93% of cases, patients with uveal metastasis from breast cancer presented to ophthalmologists with visual symptoms. Of 264 patients with uveal metastasis, 225 (85%) had choroidal metastasis, 8 (3%) had iris metastasis, 2 (<1%) had ciliary body metastasis, and 29 (11%) had metastasis in multiple uveal sites. Asymptomatic metastases were detected in 56% of patients in the opposite eye.[130] CT and MRI often demonstrate a space filling enhancing mass which is hyperintense on T1 and hypointense on T2 (eFigure 31-4).

Patients with orbital tumors more often present with diplopia, ocular motility disorder, and proptosis. Lesions are usually unilateral.[131] Metastatic disease may be detected in a high proportion of the patients who present with this entity.

Orbital Lymphoma

Orbital lymphoma can involve the soft tissues and present as a palpable mass. The most common ocular complaints are floaters and blurred vision, although proptosis, diplopia, and inflammation can also be present.[132-134] Conjunctival lymphomas are erythematous and present as a visible and palpable mass that is sometimes referred to as salmon colored. Patients should be evaluated for systemic disease with routine staging for a lymphoma workup, including complete blood count, liver function tests, chemistries, lactic dehydrogenase, bone marrow biopsy, and imaging of the chest, abdomen, and pelvis. Full nodal examination with assessment of symptoms, including weight loss, fevers, and night sweats should be included. Bone marrow examination should be performed for stages 3 to 4 disease or any patient with bulky disease. CT or MRI scans of the orbit can be used to delineate the extent of retrobulbar and soft-tissue involvement (eFigure 31-5).

Primary intraocular lymphoma is one of the most challenging intraocular tumors to diagnose. Cytologic examination of vitreal aspirates remains the gold standard for exclusion of neoplastic disease in patients with chronic idiopathic uveitis.[135-137] Patients with primary vitreous involvement should also have cerebrospinal fluid (CSF) examination and MRI of the brain and meninges.[138] Sixty percent to 80% of patients with primary vitreous involvement have bilateral involvement.[139-141]

Staging and prognosis is determined by the Ann Arbor staging system and International Prognostic Index.[142,143] A localized orbital lymphoma would be stage IeA.

Optic Nerve Sheath Meningioma

Patients typically have painless progressive visual acuity loss or visual field defect.[144] Afferent papillary defect, dyschromatopsia, scotomas, altitudinal defects, and spontaneous or gaze-evoked transient visual obscurations usually associated with edema and swelling of the optic disc may also be present. Proptosis, lid edema, chemosis, and limited motion of extraocular muscles are often secondary to mass effect. Approximately 45% of patients present with vision of 20/40 or better; about 25% have poor vision (minimal light perception, count fingers).[145] Ophthalmoscopic examination may reveal optic nerve head or disc swelling, macular edema, nerve pallor, or choroidal folds.

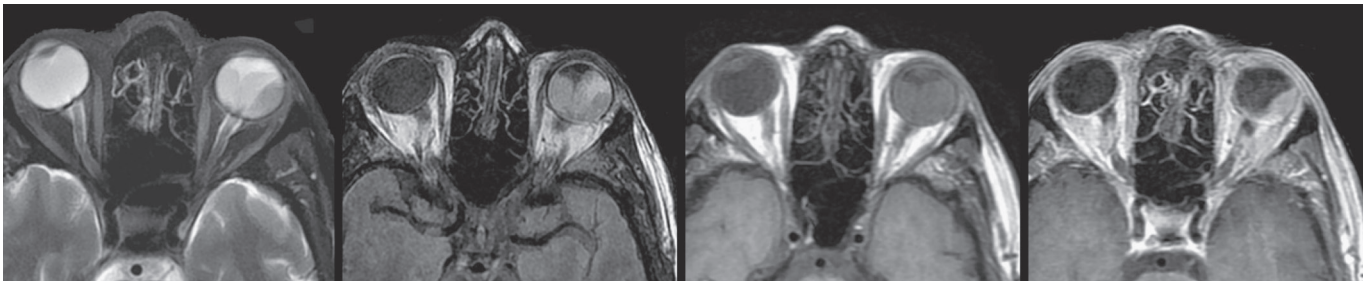
MRI is the procedure of choice for diagnosis of these lesions.[146] Lesions appear slightly hypointense to brain and optic nerve tissue on T1-weighted images and may be either diffuse, tubular enlargements, or localized eccentric expansion of the optic nerve (eFigure 31-6). They are homogenously enhanced following administration of gadolinium. Modern techniques may illustrate vascular changes and differentiate between alternative causes of optic neuropathy.[147] Thin CT scans may reveal regular or irregular thickening of the nerve sheath meninges. The nerve may appear normal in size or smaller as the result of circumferential compression or atrophy. Calcification has been described in 30% of patients and is associated with slower growth.[148] Differential diagnosis includes sarcoid, demyelinating optic neuritis, orbital inflammatory disease, schwannoma, lymphoma, hemangiopericytoma, and optic nerve metastasis.

Visual loss will generally occur in untreated eyes over 5 to 10 years.[149,150] Rapid growth has been observed during pregnancy, which may be mediated by hormone receptors.[151,152] Other tumors have demonstrated rapid visual loss even without radiographic enlargement, possibly as a result of microvasculature changes. Similar to other meningiomas, many will remain stable over a lifetime, but those that present with unilateral visual decline will likely continue to adversely impact vision.[153]

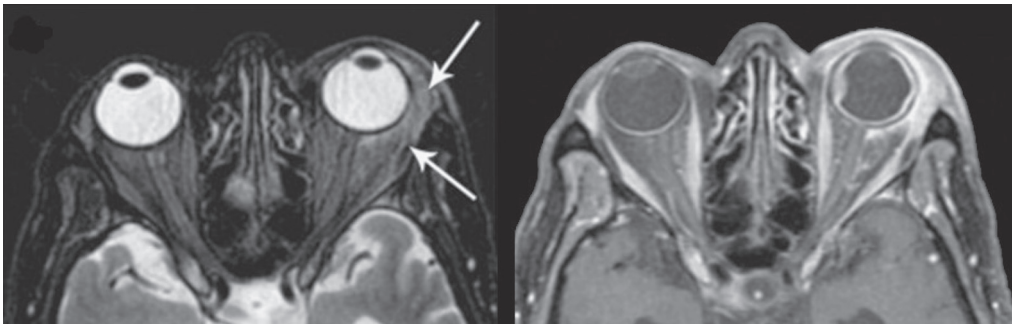
Optic Pathway Gliomas

Patients may be asymptomatic depending on the location of the mass. Typically, lesions within the orbit present with proptosis, visual loss, and strabismus, whereas individuals with extraorbital/intracranial lesions exhibit visual loss, spasmus nutans, obstructive hydrocephalus, and endocrine/hypothalamic disturbances. Patients with neurofibromatosis 1 are more likely to present with hydrocephalus, nystagmus, and proptosis.

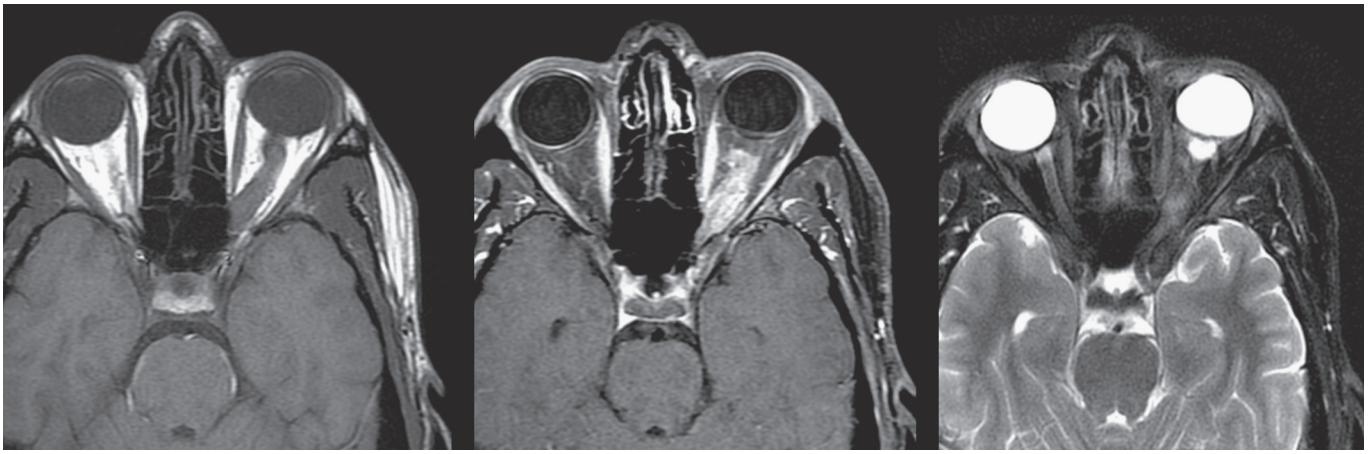
Between 10% and 20% of optic pathway gliomas are confined to the orbit, with the remainder involving the intracranial compartment.[154,155] Children with isolated optic nerve tumors have a better prognosis than those whose lesions involve the chiasm or that extend along the visual pathway.[156-159] Children with neurofibromatosis type 1 also have a better prognosis, especially when the tumor is found in asymptomatic patients at the time of screening.[157,160] MRI is the preferred method for evaluation of optic pathway glioma[161] because both the intraorbital and intracranial component can be effectively characterized with this modality. In the intracranial region, MRI provides superior evaluation of the optic nerve, chiasm, tracts, and geniculate body and of optic irradiation compared with CT scanning. When evaluating the orbit, gadolinium-enhanced T1-weighted images with fat saturation are effective at defining the extent of adult optic glioma. Typically these lesions are hypo- to isointense on T1-weighted images, hyperintense on T2-weighted sequences, and enhanced with gadolinium administration (eFigure 31-7). Patients with neurofibromatosis 1 have characteristic features including the double intensity/pseudo-CSF signal and extension to the lateral geniculate ganglia and temporal lobes.[162]



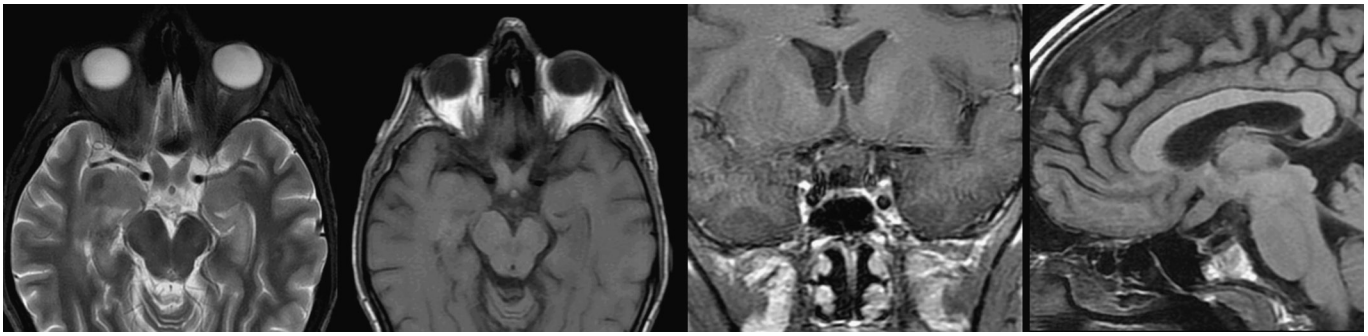
eFigure 31-4 Axial MRI images—Orbital metastasis. Axial T2, T2 FLAIR, T1 FLAIR, T1 FLAIR with contrast and T2 Flair of a patient with an untreated orbital metastasis from breast cancer with complete vision loss and orbital pain.



eFigure 31-5 Axial MRI images—Orbital lymphoma. Systemic lymphoma involving the orbit. Axial fat-saturated T2-weighted image and contrast axial T1-weighted image show enhancing tumor in the anterior left orbit centered at the lacrimal fossa *(arrows)* with circumferential involvement of the globe, which reveals abnormal scleral, choroid, and retinal enhancement. There is also infiltration of the conjunctiva and eyelids.



eFigure 31-6 Axial MRI images—Optic nerve sheath meningioma. Axial T1, T1 with contrast, and T2 Flair of a patient with an untreated optic nerve sheath meningioma with progressive vision loss and cranial nerve deficits.



eFigure 31-7 Axial, coronal, and sagittal MRI images—Optic pathway glioma. Axial T2, T1 noncontrast, coronal T1 with contrast, sagittal T1 FLAIR without contrast of a chiasmal low grade glioma.

Orbital Pseudotumors

Patients have proptosis, decreased ocular motility, soft-tissue edema, decreased visual acuity, or pain. Typical presentations include unilateral or bilateral anterior pseudotumor or unilateral or bilateral retrobulbar disease.[34] Orbital imaging is important to verify the extent of involvement. CT scanning may reveal a unilateral focal or more diffuse mass. Biopsy is recommended whenever possible to ensure accuracy of diagnosis.[34] Lymphoma, metastatic carcinoma, and sarcomas may be ruled out by a biopsy.

Lacrimal Gland Tumors

Most patients have an orbital mass that is frequently appreciated on examination and pain. Fine-needle aspiration is preferred for obtaining histologic diagnosis. CT scanning of the orbit should be performed to determine the extent of the mass.

Graves's Ophthalmopathy

Signs and symptoms of Graves's ophthalmopathy vary widely and range from mild periorbital soft-tissue fullness with no significant functional impairment to diplopia and visual loss. Visual loss is usually secondary to dysthyroid optic neuropathy and keratopathy. Other prominent symptoms include bilateral exophthalmia, extraocular muscle dysfunction, diplopia, blurred vision, eyelid and periorbital edema, chemosis, lid lag and retraction, and compressive optic neuropathy. Imaging with MRI may distinguish between acute inflammatory active and fibrotic, inactive end-stage disease.[163] CT scanning of the orbit will demonstrate changes consistent with enlargement of extraocular muscles, which are usually symmetric.[164]

PRIMARY AND ADJUVANT THERAPY

Periocular Skin Cancers

In general, surgical excision is the preferred treatment. In a large group of patients treated with Mohs's surgery for basal cell cancer, there was a 0% recurrence rate following treatment for a newly diagnosed basal cell cancer, but a 7% recurrence rate for those treated for recurrent basal cell cancer.[165] Incomplete excision rates can be high (25.4%) and are more common in morpheaform-type basal cell carcinoma and medial canthus lesions.[166] Incomplete excision results in increased recurrence rates relative to complete excisions (8.4% versus 4.6%). Another report of patients with squamous cell cancer demonstrated a recurrence rate of 3% at 5 years following Mohs's surgery.[167]

If surgery is not feasible because of associated functional and cosmetic problems, treatment with radiation has been successful for patients with either histologic type.[168-170] In more than 1000 patients with eyelid tumors treated with radiation, Fitzpatrick et al[171] noted a 5-year local control rate of 95% and 93% in basal cell and squamous cell carcinoma primary cancers, respectively. Similar results have been observed in more recent series using high-dose-rate brachytherapy and surface molds (99% local control among primary tumors and 87% for recurrent lesions).[172] The presence of pathologic or clinical perineural invasion may require wider radiation fields.[80,173,174] Clinically apparent perineural invasion or grossly involved nerves may prompt consideration of coverage of the infraorbital nerve as well as the trigeminal ganglion.[80,173,174]

Ocular Melanoma

The primary therapy of posterior uveal melanomas depends on many factors. Ocular factors involved in the selection of the treatment modality include tumor size, location, the presence or absence of extraocular extension, and visual function in the involved and uninvolved eye. Systemic factors important in management decisions include patient age, presence or absence of metastatic disease, and general health of the patient. The treatment algorithm is shown in Figure 31-4. Observation without treatment is used for asymptomatic small melanomas with dormant characteristics or elderly patients with severe systemic health problems or with short life expectancy. In these situations, the treating physician and patient must weigh the risks of treatment (loss of vision and possible tumor dissemination) against the risks of withholding treatment with growth of the tumor and subsequent increased risk of metastatic disease. The COMS group reported that at 2 and 5 years, 21% and 31%, respectively, of small melanomas managed initially by observation had grown.[129] Factors associated with growth after observation in COMS report No. 4 included orange pigmentation, the absence of drusen, thickness of greater than 2 mm, basal diameter of greater than 12 mm at diagnosis, and lack of adjacent retinal pigment changes.

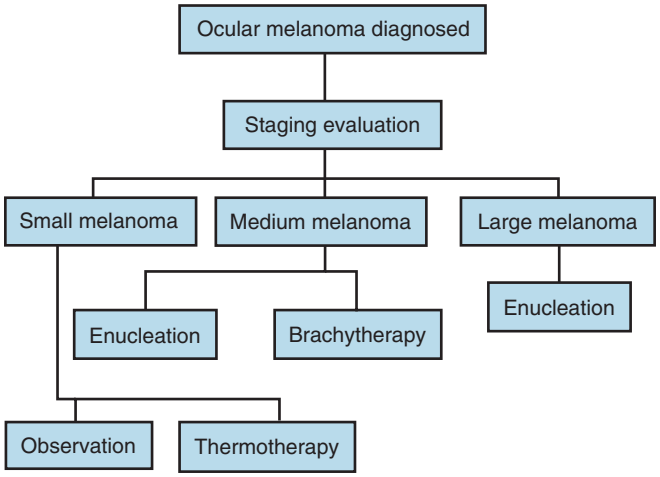


Figure 31-4 Treatment algorithm—Choroidal melanoma.

Enucleation has been the standard of care for the treatment of choroidal melanoma since the 19th century. Enucleation requires disinsertion of the extraocular muscles from the sclera, with removal of the entire globe with a long segment of optic nerve. It is the treatment of choice for large tumors, when the eye is blind, when there is pain from mass effect or invasion, or where the tumor has invaded or is contiguous with the optic nerve. An increase in the death rate at 2 years following enucleation has been reported; putatively supporting the hypothesis that enucleation may induce dissemination of tumor cells (Zimmerman-McLean hypothesis). However, this hypothesis remains controversial, with no strong evidence to support it.[175] Although all eyes with uveal melanoma can be treated by enucleation, the obvious morbidity of immediate and permanent loss of the eye and vision prompted the development of other techniques to treat these neoplasms.

Photocoagulation, transpupillary thermotherapy, and local resection have been used for treating selected patients. Transpupillary thermotherapy is probably the most common management for small melanomas and has produced excellent control (81% local control at 5 years) in selected patients.[176,177] Local resection has a high morbidity and is thus used rarely. It may be considered for anterior tumors involving the ciliary body or iris. Appropriate use of these techniques in the treatment of choroidal melanomas remains investigational.

TABLE 31-2 Eye Plaque Prescription Dose by Local Control and Vision Preservation

Dose	5-yr LC	>20/200	Loss >6 lines	Inst./Org/Au.
85 Gy	90%	3 yr 57%	49%	COMS[85,87,123,180,181]
75 Gy	97.3%	5 yr 57.8%	—	Fontanesi et al[182]
70 Gy	82%	5 yr 58%	—	Quivey et al[183]
63 Gy	90%	5 yr 78%	10%	WFU[184]

Radiotherapy Options

Radiation therapy in the management of uveal melanomas has revolutionized the treatment of this ocular cancer. The principal advantage of irradiation in the management of these tumors is that the globe is spared, salvaging the eye and useful vision in many patients. Two main modalities of treatment are used: episcleral plaque radiotherapy and charged particle therapy (Video 31-1). In episcleral plaque therapy, tumors up to 18 mm in diameter and 8 mm to 10 mm thick may be treated, whereas with charged particle therapy tumors up to 24.4 mm in diameter and 14 mm in height have been treated.[178,179]

A randomized multicenter trial (COMS) enrolled 1317 patients with medium-size melanomas to treatment with enucleation or with brachytherapy with ^{125}I plaques. This study demonstrated equivalent 5-year overall survival rates of 81% in both arms[85] (eFigure 31-8). Visual acuity decreased over time in a proportion of patients treated with brachytherapy, with a 5-year cumulative rate of visual acuity of 20/200 or worse in the study eye at two consecutive examinations of 63% (95% CI, 59% to 68%).[116] The risk of vision loss was associated with a history of diabetes, thick tumors, tumors close to or beneath the macula, tumors with secondary retinal detachments, and tumors that were not dome-shaped.[180] Five years after plaque therapy, enucleation was necessary in 10% of patients because of tumor growth and in 3% of patients secondary to complications such as radiation-induced ischemia, pain, or loss of visual acuity[85] (Table 31-2).[181] Risk factors for treatment failure were older age, greater tumor thickness, and proximity of the tumor to the foveal avascular zone.[116]

Charged particle radiotherapy, primarily proton beam therapy, is a less common technique for treating uveal melanoma largely because of patient access. With this technique, tantalum rings are sutured to the external sclera at the margins of the tumor for localization, and charged particles (either protons or helium ions) are delivered in four or five fractions over a 7-day period. The standard target dose is 50 Gy to 70 Gy.[179,185,186] An advantage of charged particle therapy is the relatively uniform dose of radiation delivered to the entire tumor and the sharp reduction in dose outside the treated area.[187] Visual acuity following charged particle therapy is less thoroughly characterized relative to episcleral plaque therapy. However, a report from the Curie Institut-Orsay Proton Therapy Center of patients with ≥20/40 vision before treatment showed acuity at 5 years was stable in 19.6%, reduced to 20/200 to <20/40 in 10.9%, and significantly declined to < 20/200 in 18.6% after treatment.[179]

Ocular Metastasis

Choroidal metastases are sensitive to radiation, but overall survival rates are poor. In one study, external beam radiotherapy (EBRT) was used in 137 patients with uveal metastasis (52%), providing tumor control in 116 patients (85%) at a mean follow-up of 21 months. Using Kaplan-Meier estimates, the overall survival of all patients with uveal metastasis from breast cancer was 65% at 1-year, 34% at 3-year, and 24% at 5-year follow-ups.[130]

Ocular Lymphoma

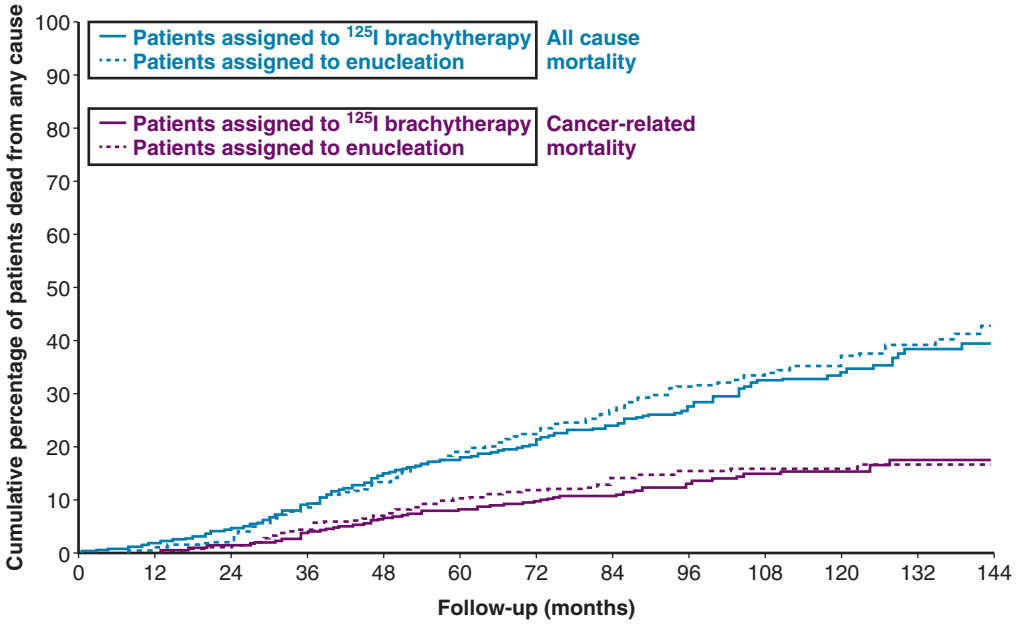
With systemic disease, chemotherapy is the preferred definitive therapy; radiotherapy should be reserved for palliation. Patients with solitary low-grade lymphoma can be successfully treated with local irradiation to the orbit with doses greater than 25 Gy.[199] Patients who have intermediate-grade lymphoma may be treated with a combination of systemic chemotherapy and irradiation. Radiation therapy should be considered if a less than complete response in the orbit is observed following chemotherapy.[200-202] Doses to the orbit or conjunctiva range from 20 Gy to 36 Gy (1.8 Gy to 2 Gy per fraction in most series) and result in 89% to 100% local control rates. Follicular lymphomas are controlled with doses in the mid 20-Gy range, whereas data suggest that MALT lymphoma should receive 30 Gy to 36 Gy with 1.8 Gy/fraction to 2 Gy/fraction.[203,204] A trial of antibiotics before radiotherapy may be appropriate in a selected subset of patients with an indolent history of biopsy-proven primary conjunctival MALT lymphoma.[205] Complication rates are acceptably low with doses in the range of 20 Gy to 30 Gy.[203,206-209] Cataract formation is common without lens shielding although with extended times, even low doses (<5 Gy) may result in cataracts.[210-212] A recent publication suggested inferior results when only partial orbital irradiation was given compared with entire orbital irradiation, with control rates of 66% and 100%, respectively.[213]

Primary Intraocular Lymphoma

Currently, most primary intraocular lymphomas are treated with systemic high-dose methotrexate-based chemotherapy.[214] Ferrari advocates for upfront chemotherapy in patients with primary intraocular lymphoma followed by whole brain radiotherapy with fields that encompass both orbits. However, treatment-related factors such as cumulative dose of methotrexate, response to chemotherapy, and age at presentation should be considered.[215-217] Orbit directed radiotherapy should always include both globes and whole brain because from 60% to80% of cases may have bilateral ocular involvement and as many as 70% to 80% will go on to develop primary CNS lymphoma. Complications of EBRT are common and patients older than 60 are at increased risk for severe delayed neurotoxicity following combined methotrexate and whole brain radiotherapy.[216] Additional toxicities can include cataracts (50%), dry eyes (40%), punctate keratopathy (20%), radiation retinopathy (20%), and optic atrophy (10%). Doses for primary CNS and intraocular lymphoma are controversial and range from 23.4 Gy in the consolidation setting following systemic methotrexate to 45 Gy.[216] Ocular recurrences are often treated with EBRT and increasingly with intraocular methotrexate.

Optic Nerve Sheath Meningiomas

For most patients, stereotactic fractionated EBRT is preferred as the definitive therapy because it offers both excellent local control and long-term preservation of visual function.[218-225] Turbin et al[219] studied 59 patients with visual loss at presentation. These patients were divided into four groups: observation, surgery, radiation therapy, or surgery and radiation therapy. Only the group treated with radiation alone did not have significant visual loss at the last follow-up. Other series with shorter durations of follow-up have reported stable or improved vision in most patients treated with more modern radiation therapy delivery techniques.[220-224] More precise delivery of EBRT to smaller volumes reduces the amount of



eFigure 31-8 **All-cause and cancer-related mortality.**
Courtesy Diener-West M, Earle JD, Fine SL, et al: Collaborative Ocular Melanoma Study Group: The COMS randomized trial of iodine 125 brachytherapy for choroidal melanoma, III: Initial mortality findings. COMS Report No. 18. Arch Ophthalmol 119(7):969–982, 2001.[85]

A systematic review found that as of 2012, three randomized controlled trials and 16 uncontrolled and 9 controlled cohort studies had reported using charged particle therapy for ocular melanoma. One randomized trial compared helium ions to ^{125}I plaque radiotherapy and found similar local control rates across radiotherapy modalities, although there were more anterior segment complications in the helium ion group.[183] An additional study from the Curie Institute found that the combination of transpupillary thermotherapy and proton beam irradiation (60 GyE) resulted in a higher response rate (greater reduction of tumor thickness), less retinal detachment, and a lower secondary enucleation rate, although the former two findings were not statistically significant.[188] The other two trials compared proton beam therapy (50 GyE). The final randomized study was a dose-seeking trial, which found no significant difference between complication rates between 50 Gy and 70 Gy.[189] The case series suggested favorable survival rates, but with significant complication rates including (but not limited to) optic neuropathy, compromised visual acuity, and anterior segment complications. Although the aforementioned systematic review by Wang suggested that local control rates may be more favorable with charged particle therapy relative to brachytherapy, there have been no randomized controlled studies designed to answer this question.[190] Trials focused on delineating appropriate patient selection for either technique are needed to elucidate the role of charged particle therapy.

Newer techniques such as stereotactic radiosurgery are being used at some centers.[191] However, no long-term data are available on efficacy or complication rates. Early 3- and 5-year local control rates have been reported to be 88.8% and 81.9%, respectively. Visual acuity is short-lived; in one series, many patients had near-complete loss as assessed with a Snellen eye chart.[192]

In 1994, the German Cancer Society began a prospective study to examine the results of standardized EBRT for choroidal metastases with 40 Gy in 20 fractions.[193] With a median follow-up of 5.8 months (range 1 months to 44 months), 41 of 50 patients were dead. The median survival time of all patients was 7 months, and for patients with breast cancer, 10 months. Of the 50 symptomatic eyes, visual acuity increased greater than or equal to two lines in 36% (18 of 50 eyes), was stabilized in 50% (25 of 50 eyes), and decreased in 14% (7 of 50 eyes). No patient with asymptomatic metastasis ($n = 15$ eyes) developed ocular symptoms during follow-up. No patient with unilateral tumor and unilateral irradiation developed contralateral metastasis. Severe side effects, possibly related to tumor progression, occurred in three eyes (5%). More recent series are limited, although improvements in systemic therapy in subsets of patients with breast cancer (Her 2/Neu positive) may favor more prolonged fractionation to preserve optic structures.[194-197]

Nonbreast cancer metastases to the orbit also carry a poor prognostic outcome, with metastatic lung cancer demonstrating a shorter survival rate than metastatic breast cancer. Patients should be assessed for systemic extent of disease, confirmation of histology, and determination of available salvage systemic therapy options to decide on fractionation pattern and shielding. Patients with limited extraorbital disease may have improved prognoses and potential quality of life gains relative to those with widely progressive systemic disease. If the primary tumor is chemosensitive, the use of systemic therapy and localized EBRT may be indicated. Doses of radiation are typically 30 Gy to 40 Gy in 2-Gy to 2.5-Gy fractions. Consideration should be given to sparing the cornea or lens if possible.[198]

normal tissue exposed to radiation. These techniques require better immobilization for reproducibility of treatment, CT treatment planning for better tumor localization, image guidance, and conformal beam arrangements for optimizing treatment planning.[225]

Treatment is usually initiated as soon as a decline in visual acuity or fields is documented (20/40 vision) or with progressive tumor enlargement without loss of vision. It is advisable to treat these lesions with tight margins. Dose per fraction should be no more than 1.8 Gy to 2 Gy, with total doses of 50 Gy to 54 Gy. The risk of radiation-related toxicity to the optic structures rises from 2% at doses of 45 Gy to 50 Gy to about 5% at doses of 54 Gy.[226-228] Similarly, at fraction sizes of more than 2 Gy per fraction and total doses higher than 60 Gy radiation optic neuropathy occurs in about 47% of patients, whereas at doses of 1.9 Gy per fraction to a similar total dose, the risk is 11%.[229,230] Complications can include radiation retinopathy, optic neuropathy, cataract formation, or dry eye, depending on the volume of normal tissue and dose gradients. Some authors have expressed concerns when treating a patient with diabetes because of potential vascular complications associated with irradiation.[231]

Optic Pathway Glioma

The goals of treatment include improvement in progression-free survival (PFS) and stabilization of visual function. Optimal management should weigh the age at diagnosis, visual function, and the presence of progression. Observation is an option for young patients with neurofibromatosis as these tumors rarely progress before age 6.[232] Spontaneous regressions have been reported in low-grade gliomas in children (although uncommon) but may be related to telomere length.[233-235] For children with isolated optic nerve lesions and progressive symptoms, local radiation therapy is preferred and may result in prolonged progression-free survival.[236-238] Surgical resection is usually not preferred as the first-line approach because the rate of vision deficits postoperatively is high.[239]

One report detailed outcomes of 24 patients treated with radiation therapy only if there was evidence of visual deterioration or other clinical or radiographic evidence of disease progression. Radiation doses ranged from 45 Gy to 56.6 Gy (median, 54 Gy) in 1.8 Gy/fraction with up to a 17-year follow-up period (median, 6 years). The 6-year actuarial rates of freedom from disease progression and overall survival were 88% and 100%, respectively. Visual improvement or stabilization was seen in 21 patients (91%) after radiation therapy. A high incidence of endocrine abnormalities was reported, and 15 of 18 patients evaluated after treatment had growth hormone deficiency.[236]

In young patients who are still at risk for neurocognitive sequelae from radiotherapy, chemotherapy may be a viable option. Response rates approximating 50% to 75% have been noted in multiple studies; typical drugs include carboplatin and vincristine or temozolomide.[240-242] One study treated 50 patients with progressive gliomas with carboplatin on a phase II Pediatric Oncology Group (POG) study. Objective responses were found in 30% of patients.[243] Durable responses may be seen in adults with 1p19q codeletion; however, this mutation is uncommon in children relative to adults.[244,245] Similarly, the changing landscape of mutation analysis has shown a high incidence of BRAF-KIAA1549 fusion gene aberrations (61%) among patients with non-NF1 optic pathway gliomas, suggesting a potential therapeutic target that has not been explored.[246] There is a slight predominance of the BRAF-KIAA1549 fusion gene aberration in children relative to adults (64% versus 56%).[246] The implications of the changing understanding of the genetics of the disease are unknown.

Orbital Pseudotumor

Treatment for orbital pseudotumor is usually recommended in the setting of progression symptoms or declining visual function, although the condition can occasionally resolve without treatment. An oral dose of prednisone (80 mg/day for 1 week followed by a taper) is generally considered the first-line treatment.[247] Additional options may include nonsteroidal antiinflammatory steroids, although reports demonstrate improved responses with steroids. Immunosuppressive drugs such as cyclosporine and chemotherapy (cyclophosphamide, azathioprine, or methotrexate) have been employed with modest efficacy and should be limited to aggressive or refractory lesions.[248]

Local therapy is generally reserved for patients who fail the preceding and can either consist of radiation therapy at doses between 20 Gy and 30 Gy at conventional fractionation or surgery.[249-251] Surgery is typically only indicated when the lesion is burned out and the patient requires decompression. These lesions are radioresponsive. Irradiation is typically used for patients who fail to respond to medical management, patients who are intolerant of steroids, or those who have a rapidly aggressive course. Patients with the focal persistent sclerotic subtype of pseudotumor may benefit, especially when orbital decompression is required.[252]

The EBRT treatment technique varies based on the anatomic extent of the lesion (Figure 31-5). Patients with anterior lesions may be treated with an anterior direct electron beam that includes the lesion with a margin that is determined by the beam penumbra. Central lens shielding may be accomplished with either a lead-mounted contact lens or a hanging lens block. Low-energy electrons have significant skin sparing, and a bolus may be necessary to increase the surface dose. When pursuing this technique, particular attention must be paid to the scleral dose, and the recognition that if bolus material is used, the eyelids should be closed, to reduce trauma and irritation to the scleral surface. Even with closed eyelids, it is useful to instruct the patients to "look straight up" at a constant imaginary point, to minimize ocular motion and positional variability.

Total EBRT doses are typically 20 Gy delivered in 2-Gy fractions. One report of nine patients treated with initial total doses of 3 Gy noted that five of these patients required further irradiation for durable control of orbital disease.[251] Local control rates range from 74% to 100% for doses of 3.8 Gy to 36 Gy.[34,250,251,253]

Lacrimal Gland Tumors

Primary therapy is surgical resection with adjuvant EBRT as needed for close surgical margins, perineural invasion, or adenoid cystic histology.[254] Even with aggressive treatment, local recurrence rates were high following surgery and EBRT for adenoid cystic histologic types.[101,255] Eye-sparing surgery may be possible in limited cases with small tumors and favorable features although adjuvant radiotherapy is uniformly recommended regardless of resection extent.[256]

Graves's Disease

Peterson and others reported results in 311 patients treated with orbital irradiation, with 80% showing improvement of soft-tissue symptoms, 75% showing improvement in corneal signs, 61% and 52% having improved extraocular dysfunction and proptosis, and 41% to 71% having improved visual acuity.[257] After irradiation, 76% were able to discontinue corticosteroid therapy.

An older randomized controlled double-blinded trial treated 42 patients with EBRT to one eye and sham therapy to the other eye.[258] Six months later, the therapies were reversed.

Patients with unilateral retrobulbar lesions are usually treated with a photon wedged-pair technique. Donaldson et al suggested treatment with a central eye bar to shield the lens in each field.[253] However, low-dose regions in the retrobulbar area do result from this technique. Bilateral retrobulbar lesions are treated with opposed lateral fields with a half-beam block used to spare the anterior segment of the eye if it is uninvolved (see Figure 31-5).

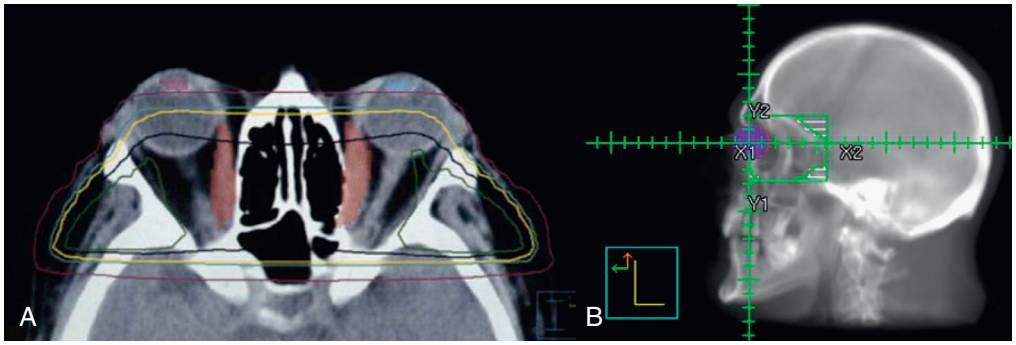


Figure 31-5 Treatment planning—Graves's ophthalmopathy. (A) Axial slice of a non contrasted CT from a patient with Graves's ophthalmopathy with corresponding isodose lines and **(B)** representative Digitally Reconstructed Radiograph with isocenter position just posterior to the lens to facilitate half-beam blocking to limit lens dose.

TABLE 31-3 Outcomes and Dose per Fraction for Adjuvant Therapy for Pterygia

Author	Year	# pts	Recurrence (%)	Dose/# Fx
Monteiro-Grillo et al[269]	2000	94 Primary 63 Rec.	5.4 19	30 Gy/3 or 60 Gy/6 —
Nishimura et al[270]	2000	490	11.8	50 Gy/4-5
Paryani et al[271]	1994	149 Rec. 500 New	— 1.7	— 60 Gy/6
Wilder et al[272]	1992	258	12	24 Gy/3
Dusenbery et al[273]	1992	36	29	24 Gy/2-4
Jurgenliemk-Schulz et al[274]	2004	86	7	25 Gy/1

Rec., *Recurrent.*

There was no apparent benefit for the orbit that received initial irradiation. This study has been criticized because it included patients whose onset of symptoms ranged from 0.2 to 16 years and may have included patients who had a more fibrotic reaction (i.e., more stable) compared with an active inflammatory process. A more recent controlled trial randomized 44 patients to orbital EBRT and 44 to sham irradiation. After 12 months, 52% of the patients who were irradiated had improvement compared with 27% of the patients who were sham-irradiated ($p = 0.02$).[259] Similarly, a meta-analysis of the use of multiple modalities for Graves's disease-related ophthalmopathy found a significant benefit of combined steroids and irradiation over corticosteroids alone, although the benefit of radiotherapy as monotherapy was limited.[260] In light of the controversy, the American Society of Ophthalmic Plastic and Reconstructive Surgery recommend a trial of steroids and radiation for patients with progressive symptoms.

Long-term follow-up suggests that orbital irradiation is safe, with a similar incidence of cataract formation to the corticosteroid group but with a possibly increased risk of retinopathy for patients with diabetes.[261] Thus, orbital irradiation is typically used in the setting of symptomatic Graves's ophthalmopathy that is difficult to control with steroids, for patients with poor tolerance to steroids, or for patients for whom surgical orbital decompression has failed.

Pterygia

Treatment for pterygia involves surgical excision with removal of the fibrous tissue down to the level of Tenon's capsule. Free conjunctival flaps may be grafted over the bare sclera; autografting has markedly reduced recurrence rates with the adoption of this technique. Recurrence rates have varied, with rates of 20% to 68% with surgery alone, although more recent series have rates of recurrence of 12% for primary, 21.4% for recurrent lesions.[262-265] Topical Mitomycin-C was found to be equivalent to conjunctival autografts.[266] Postoperative adjuvant therapy with irradiation, topical thiotepa, mitomycin, or other antimetabolic agents may diminish the chance of recurrence and have been used in multiple institutional series (see Table 31-3).[267,268]

A randomized trial treated 96 patients with a single dose of 25 Gy using a strontium-90 (^{90}Sr) ophthalmic applicator or sham irradiation within 24 hours of surgery showed crude local control rates of 93 versus 33% in the treated and sham group, respectively, with no serious complications being observed in either group ($p = 0.004$).[274]

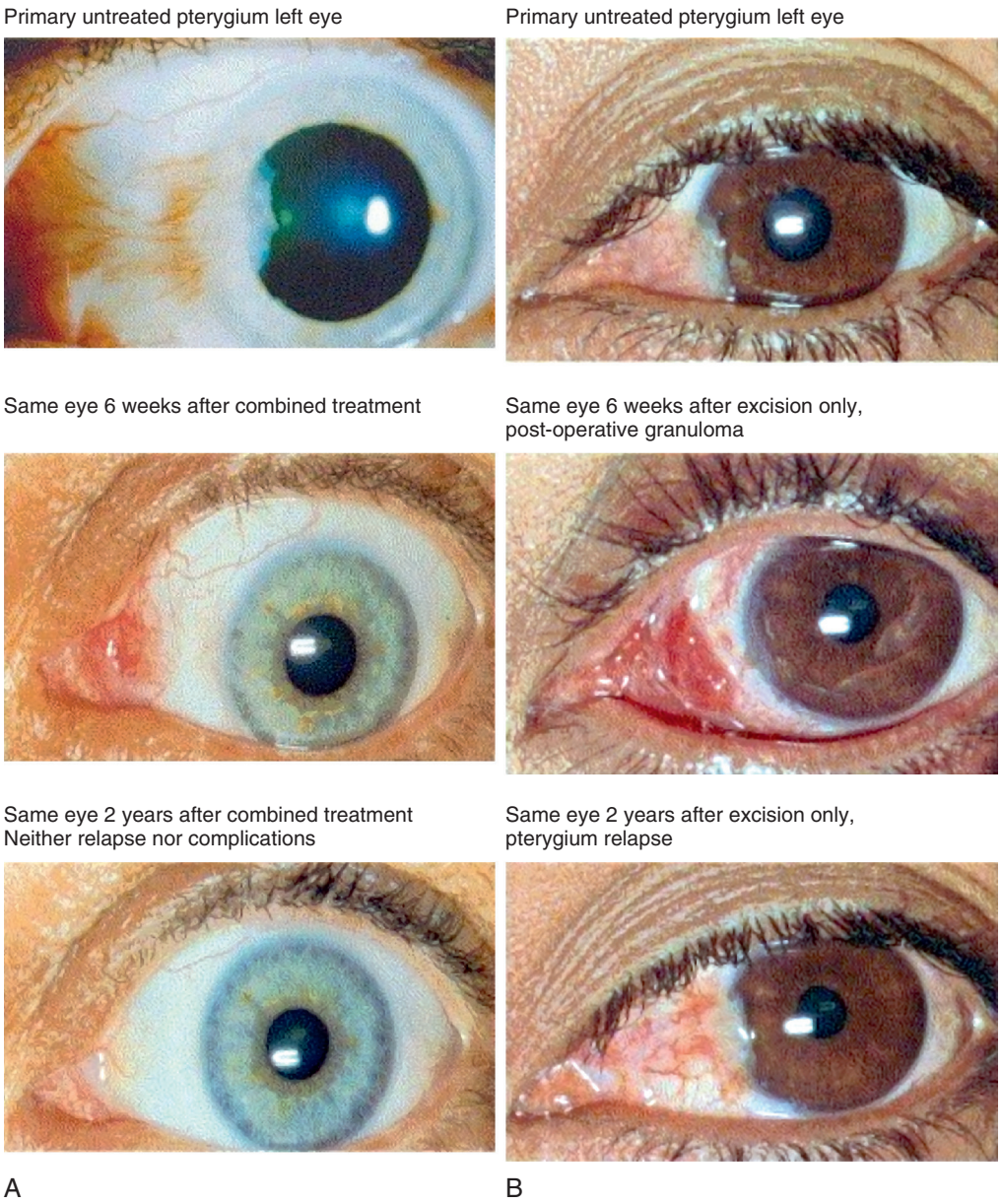
Macular Degeneration

The advent over the past 5 years of intravitreal injection of vascular endothelial growth factor (VEGF) blockers for management of exudative macular degeneration has greatly improved the visual prognosis of patients with macular degeneration.

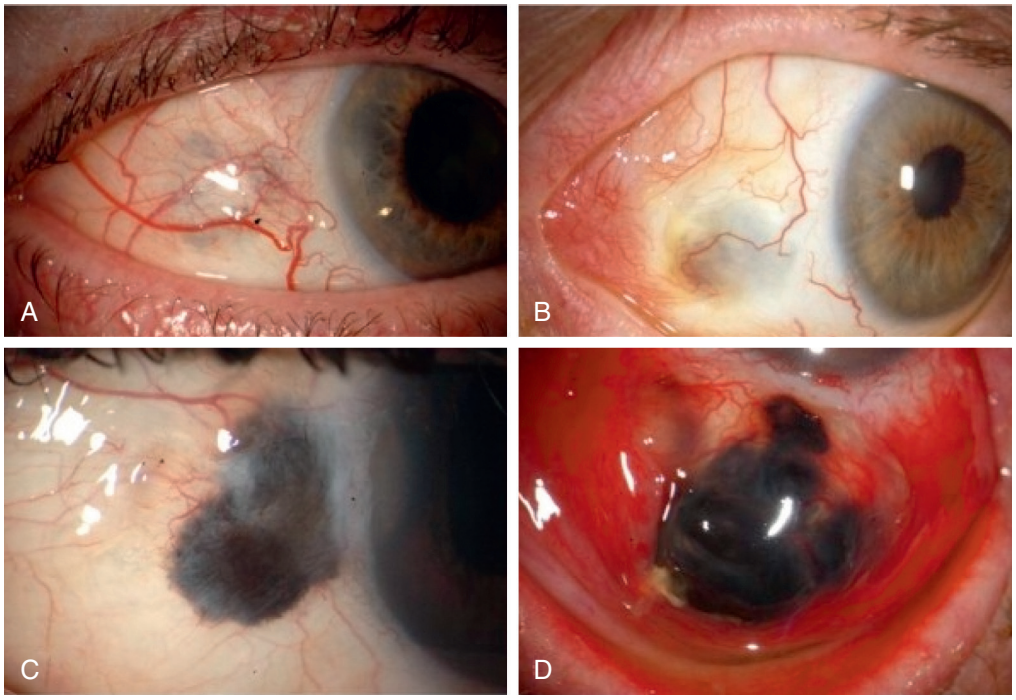
In the 1990s there was interest in using ionizing irradiation as a treatment for macular degeneration, because it can destroy vascular tissue and prevent neovascularization. The rationale for using local irradiation for choroidal neovascular membrane is based on the radiosensitivity of proliferating endothelial cells, reduction in the inflammatory response, and possible occlusion of aberrant vessels. Various dose schedules and techniques have been used; 3DCRT (10 Gy to 24 Gy, in 2-Gy to 4-Gy fractions), proton radiotherapy (8 CGE to 24 CGE, single fraction), stereotactic low-voltage radiotherapy (16 Gy to 24 Gy in one fraction or 20 Gy to 40 Gy in 2-Gy fractions), and macular brachytherapy (12.5 Gy to 32.4 Gy in one application ^{90}Sr or ^{103}Pd).[276]

Early studies with three-dimensional conformal radiotherapy suggested stabilization of vision and even improvement

Multiple retrospective studies have used irradiation with beta emitters started within 24 hours of surgery (Table 31-3 and eFigure 31-9). Doses range from 10 Gy to 60 Gy and are given in one to six fractions.[269-274] There does not appear to be a dose-response relationship. Recurrence rates are more common for pterygia that are recurrent after initial surgery. Complication rates are low, but instances of scleral necrosis (eFigure 31-10), cataract induction, corneal thinning, symblepharon, cataract, and corneal ulceration have been described. These are much more common in patients who have been reirradiated.[273] Treatment with multiple fields with possible dose overlap may be responsible for some of these complications.



eFigure 31-9 Pterygia before and after therapy. (A) Anterior segment slides before and after combined treatment. **(B)** Anterior segment slides before and after surgery alone.
Courtesy Jürgenliemk-Schulz IM, Hartman LJ, Roesink JM, et al: Prevention of pterygium recurrence by postoperative single-dose beta-irradiation: a prospective randomized clinical double-blind trial. Int J Radiat Oncol Biol Phys 59(4):1138–1147, 2004.[274]



eFigure 31-10 Scleral necrosis following plaque brachytherapy. Scleral necrosis after plaque radiotherapy of uveal melanoma in 4 cases. **A,** Mild scleral necrosis involving <50% of scleral thickness. **B,** Mild to moderate scleral necrosis involving <50% of scleral thickness seen as an avascular area. **C,** Severe scleral necrosis involving >50% of scleral thickness with invasion of overlying Tenon's fascia and conjunctiva. **D,** Severe scleral necrosis with scleral perforation, globe hypotony, and vitreous hemorrhage.
Courtesy Kaliki S, Shields CL, Rojanaporn D, et al: Scleral necrosis after plaque radiotherapy of uveal melanoma: A case-control study. Ophthalmology 120(5):1004–1011, 2013.[275]

in vision.[277,278] A randomized controlled trial from the Netherlands treated 34 patients with 24 Gy in four fractions compared with a control group. The time until vision decreased by at least three lines was prolonged.[279] However, the results from other studies have been mixed.[280-284] The rise of anti-VEGF therapeutics has limited further application of conventional EBRT and directed development to more targeted techniques such as epimacular brachytherapy, stereotactic radiation, and proton radiotherapy.[285] The therapeutic ratio and utility of conventional EBRT has largely been limited by adjacent normal tissue tolerance.

More recent techniques such as epimacular brachytherapy (EMB) have been attractive because the lens is essentially spared and little to no radiation retinopathy events have been observed. Angiography and optical coherence tomography in several studies have shown a marked reduction in choroidal neovascularization at 12, 24, and 36 months.[286] This technique however requires a pars plana vitrectomy with subsequent placement of the ^{90}Sr source adjacent the fovea. Prospective evaluations of the safety and efficacy showed stable visual acuity and suggested potential reduction in the frequency of anti-VEGF injections. The recently reported CABERNET study, which assessed vision outcomes and frequency of anti-VEGF injections over time in patients receiving anti-VEGF monotherapy with or without EMB showed that patients in the monotherapy arm required 1.5 times more anti-VEGF injections over 12-months.[287] There was a high rate of cataracts secondary to vitrectomy.[288] Although the efficacy did not meet the prespecified 10% noninferiority margin (primary endpoint of the trial) for occult lesions, it did result in the reduced visual acuity loss of fewer than 15 letters in classic and minimally classic lesions. The benefit of anti-VEGF monotherapy versus anti-VEGF therapy plus EMB in patients pretreated with anti-VEGF therapy is being evaluated in the MERLOT trial, which is ongoing.

Altogether newer treatment delivery methods with stereotactic therapy show promise in that the low energy photons are less likely to cause damage to deep adjacent ocular structures, is less invasive than EMB, and sharper penumbra (less low dose spillage) can facilitate dose escalation.[289] This technique requires eye immobilization with a suction-enabled contact lens for an approximate 5-minute exposure to deliver the required single fraction dose. Estimated dosimetry suggests minimal dose to adjacent organs at risk (lens, optic nerve) on the order of 199 mGy to 1200 mGy.[290] The accuracy and precision of the delivered dose is estimated to be submillimeter at 0.4 mm to 0.6 mm.[291] The results of the recently reported INTREPID study demonstrated reduced ranibizumab retreatment relative to the sham arm (mean 3.74 versus mean 2.64) with only modest improvement in acuity at 52 weeks in the loss of fewer than 15 letters.[292] Further studies examining the utility of newer radiotherapy techniques in addition to anti-VEGF therapeutics are ongoing.

LOCALLY ADVANCED DISEASE AND PALLIATION

Ocular Melanoma

Patients with large choroidal melanoma are usually treated with enucleation, although proton beam radiotherapy and plaque brachytherapy have been used in selected circumstances. Plaque brachytherapy is often avoided in large tumors because of increased complication rates associated with treatment, higher incidence of transcleral extension (contraindication), lower vision preservation rates, and technical considerations, which limit adequate dosimetric coverage.[293] Certain situations may favor an approach that preserves vision with plaque brachytherapy even in large tumors. Such situations include poor vision in the contralateral eye, or individuals not felt to be able to tolerate the psychological effects of loss of their eye as a result of poor mental health. In the largest reported experience with large tumors treated with plaque radiotherapy, the enucleation rate following treatment was 34% at 10 years.[294] Factors that resulted in a short time to enucleation following plaque brachytherapy include >50% ciliary body involvement, thickness greater than 8 mm and tumor proximity to the fovea.[294]

The COMS enrolled 1003 patients to a study that randomized them to either enucleation or enucleation preceded by EBRT (20 Gy).[128] Patients receiving preoperative radiotherapy had no significant difference in 5-year overall survival. The 5-year all-cause mortality rate for large melanomas was 40%. There was no difference in local control between the two groups.

More recent single-institution series such as the one from the French Ocular Oncology Center demonstrated clinically equivalent survival estimates for patients with large choroidal melanoma following either enucleation or proton beam therapy, although the enucleation group had a slight predominance of tumors with greater thickness (12.0 ± 2.8 versus 9.8 ± 1.6).[295] Eye retention and best-corrected visual acuity of 0.1 (20/200) or better was 74% at 1 year and 32% at 5 years in the proton therapy group. Despite the former, early reports on the application of proton beam radiotherapy should still be considered investigational for COMS large choroidal melanoma.

Orbital Lymphoma

Irradiation to the orbit can provide effective palliation for patients with widespread systemic disease or locally advanced disease. Even in patients who have received prior radiation therapy, reirradiation for local disease progression that is resulting in progressive visual loss or symptoms can be considered.[296,297]

IRRADIATION TECHNIQUES AND TOLERANCE

Plaque Irradiation

Multiple different isotopes have been used for plaque therapy, including cesium-131 (^{131}Cs), cobalt-60 (^{60}Co), gold-198 (^{198}Au), palladium-103 (^{103}Pd), ruthenium-106 (^{106}Ru), iodine-125 (^{125}I), and iridium-192 (^{192}Ir).[298-301] The most commonly used isotope is ^{125}I as it was mandated by the COMS medium study. This isotope carries the advantage of low-energy gamma rays and therefore decreased shielding and dose to distant structures. Ruthenium-106 is a beta emitter that has few shielding concerns, but it has a penetration of only a short distance, which may limit its application.

A variety of plaque applicators have been used for ocular melanomas, but the most commonly used ones are those developed for the COMS (Figure 31-6). These plaques allow shielding of the posterior and lateral structures with a 0.5-mm thick gold alloy shield (77% gold, 14% silver, 8% copper, and 1% palladium). The overall design includes a circumferential collimating lip and incorporates a 1-mm Silastic carrier for seeds, which allows for different prescription depths. However, not all plaque designs incorporate Silastic carriers, and this should be taken into account with the use of other plaques and isotopes.[302] Originally, COMS dosimetry ignored the contributions of source anisotropy, and backscatter from the gold allowed plaque and Silastic attenuation (density is actually greater than assumed water equivalent sclera (eFigure 31-11). Recent studies that have studied the incorporation of these

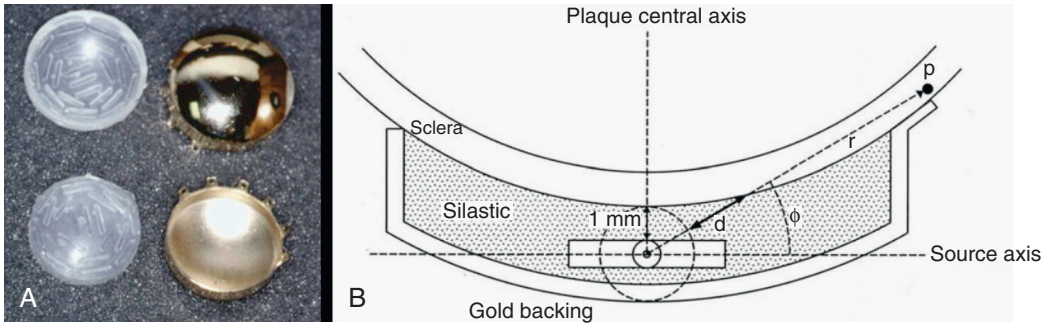


Figure 31-6 COMS plaque and corresponding diagram of construction. A, View of the convex and concave surface of the unassembled Silastic insert and gold backing comprising the classic COMS Eye Plaque. **B,** Cross-sectional diagram depicting the seed centrally resting in the Silastic just superficial to the gold backing in relation to the sclera that the entire eye plaque rests on.
Courtesy Astrahan MA: Improved treatment planning for COMS eye plaques. Int J Radiat Oncol Biol Phys 61(4):1227–1242, 2005.[302]

factors into treatment planning have shown that these adjustments may result in reduction of the calculated doses to critical structures within the globe such as the macula, sclera, optic disc, lens, and opposite retina.[303] Although hypothesized to be significant, this has yet to be demonstrated in a patient data set.

Plaque selection should incorporate the largest basal tumor diameter plus an additional 2-mm margin circumferentially around the tumor. Placement of the seeds within the applicator varies, depending on the height of the tumor. The prescription point should be the apex of the tumor or 5 mm, whichever is greater, as prescribing to heights of 3 mm or less can result in dosimetric uncertainty.[302] The prescription point is calculated by taking into account the tumor height in mm based on ultrasound plus 1 mm to account for scleral thickness and 1.4 mm to take into account the thickness of the Silastic carrier.

In the COMS, a total dose of 85 Gy was used and delivered to the apex of the tumor at a dose rate between 0.5 Gy/hour and 1.25 Gy/hour. The optimal dose of radiation therapy for treatment of choroidal melanoma is controversial. Equivalent local control, survival, and disease-free survival rates with less ocular morbidity and vision loss have been reported with lower radiation therapy doses.[184]

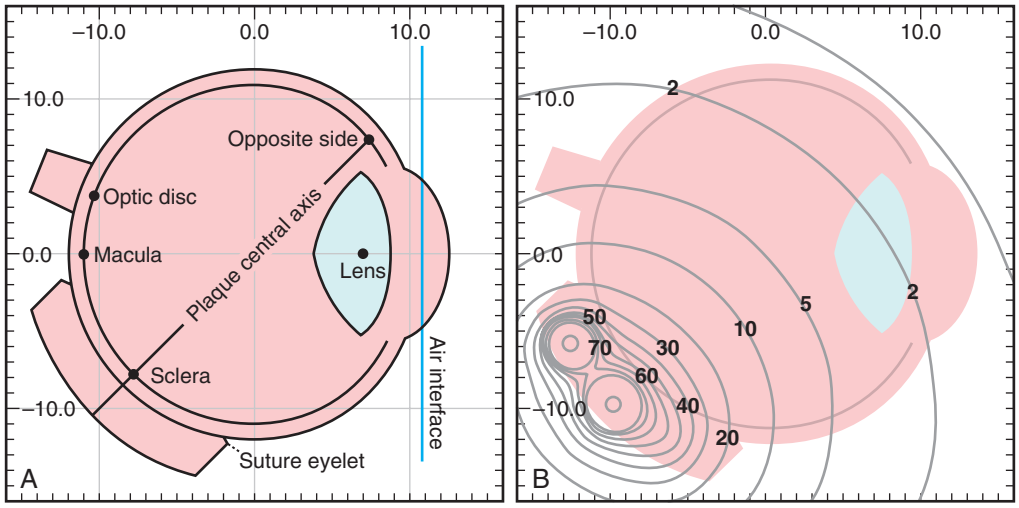
Principal complications of radiotherapy to the eye include cataract formation, radiation retinopathy, macular edema, and optic neuropathy.[305] Anti-angiogenic therapeutics such as intravitreal bevacizumab may be useful in treating radiation retinopathy (eFigure 31-13). Radiation effects on the retina and optic nerve may be potentiated by the presence of systemic vascular diseases such as hypertension and diabetes mellitus and often result in loss of useful vision. The proximity of the tumor to critical visual structures such as the optic nerve and macula is predictive of the long-term visual prognosis. Although no radiation tolerance has been ascribed to the macula itself, at doses of 50.5 Gy (IQR 18.6 to 97.3) delivered using plaque brachytherapy, the median visual acuity at 3 years was less than 20/50, whereas vision was a median of less than 20/200 at a median dose of 61.5 Gy (IQR 25.7 to 110.9).[306] Previous estimates of optic nerve tolerance were likely overly conservative as subsequent series have observed that a radiation dose per fraction threshold for radiation induced optic neuropathy approximates zero at fractions less than 2 Gy per fraction, whereas doses greater than or equal to 2 Gy per fraction increases the risk of radiation-induced optic neuropathy from 3% to 7%, from a total dose of 55 Gy to 60 Gy and then escalates at doses greater than 60 Gy to a risk of greater than 7% to 20%.[211,307]

Skin Lesions

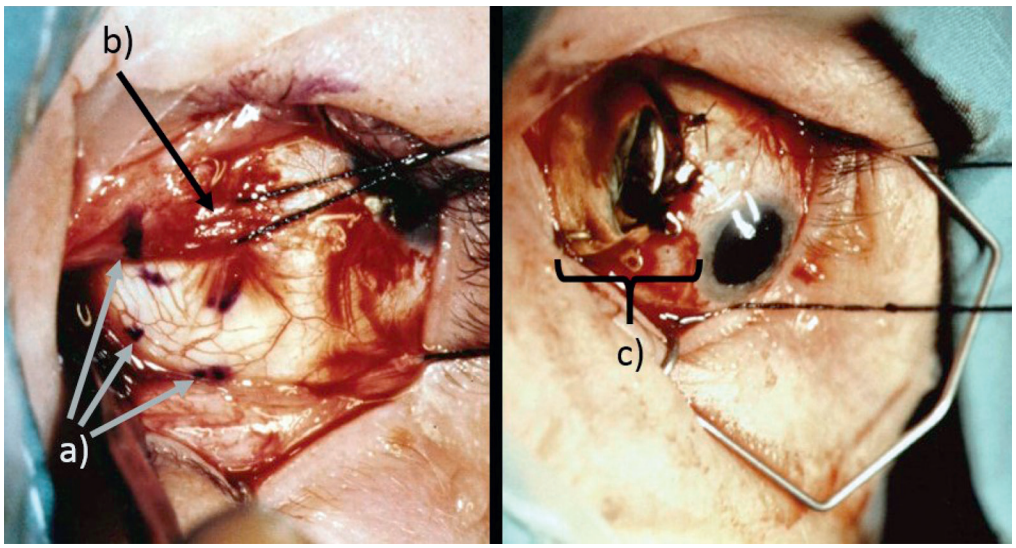
Treatment of skin lesions close to the eye can be difficult. The close proximity of normal structures must be balanced with the dosimetric constraints that are present with electrons. Most of the data supporting the use of radiation therapy came from series using kilovoltage x-ray beams. However, this type of x-ray equipment is no longer widely available. Electrons have a larger penumbra and area of beam constriction laterally, necessitating larger treatment fields than kilovoltage beams. One report demonstrated higher corneal doses with electrons compared with kilovoltage beams (doses were two to four times higher). Also, the 95% isodose area was 32% wider with kilovoltage beams than with 6-MeV electrons.[83] A minimum recommended field size of 4×4 cm is required for reliable electron dosimetry. Treatment fields may be made smaller with the use of skin surface lead shielding for collimation of the beam to the clinically relevant volume. Lower energy electrons are skin sparing at superficial depths. Institutional data tables should be referenced regarding optimal bolus thickness if the dose at the superficial skin is to be therapeutic. Verification of the superficial skin dose with solid state dosimeters (such as thermoluminescent dosimeters), silicon diodes, or film is recommended in each instance.[309-311]

Unilateral Eye Lesions

Treatment of one eye may be necessary for patients with choroidal or orbital metastasis or orbital lymphomas. Pretreatment imaging is essential in deciding on the need for the extent of the orbit and orbital contents to be included in the field. Typically, a wedged-pair technique is used if the entire orbit needs to be treated. This field arrangement is designed to limit the irradiation to the opposite eye. Reduced exit dose to the temporal lobe and brainstem can be minimized by placing the isocenter just deep to the apex and half beam blocking each of the wedged fields to minimize divergence beyond the treatment field and limiting the total volume of normal brain treated. CT planning can assist with location of the normal optic structures and the tumor volume that is to be included in the field (Figure 31-7). Three-dimensional treatment planning may enable more treatment conformity around the structure to be treated and decrease normal tissue sequelae. A single anteroposterior photon field can be considered that permits the use of a hanging block to spare the lens dose (Figures 31-8 and 31-9). Eye drops (such as 5% proparacaine hydrochloride) may be required in the case of lens shielding as repeated shield insertions can cause eye irritation. Patients

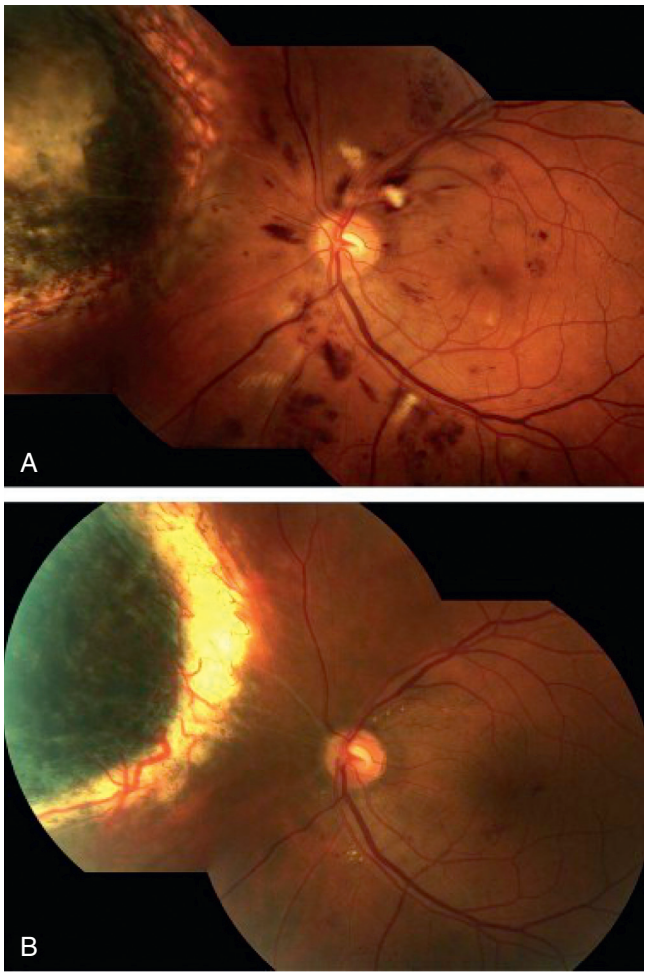


eFigure 31-11 COMS plaque dosimetry. Diagrammatic representation of plaque dosimetry. **(A)** Schematic representation of relation of COMS plaque to dosimetry of eight 1-mCi ^{125}I seeds based on COMS calculations **(B)**.
Courtesy Astrahan MA: Improved treatment planning for COMS eye plaques. Int J Radiat Oncol Biol Phys 61(4):1227–1242, 2005.[302]



eFigure 31-12 Episcleral plaque insertion. A, Sites of transilluminated tumor markings over the surface of the sclera on the immobilized globe. **B,** Insertion of the rectus muscle with corresponding suture for immobilization. **C,** Inserted plaque against the lateral portion of the globe once sewn into place with three to four eyelets.

The plaque is placed by the ophthalmologist by marking the boundary of the tumor base with a surgical marking pencil or light cautery that can be seen when the tumor is transilluminated intraoperatively after mobilization of the globe (see Video 31-1). The plaque is then centered over the marks. Appropriate plaque placement and/or transillumination may require detachment of the ocular rectus muscles. The plaque is then sutured to the sclera (eFigure 31-12). Good placement can be confirmed with ultrasonic evaluation of the eye. Occasionally, the melanoma is located adjacent to the optic nerve (peripapillary tumors), in which case the use of a notched plaque may allow better dosimetry and coverage of the tumor in this situation.[304]



eFigure 31-13 Bevacizumab for radiation retinopathy. Bevacizumab for radiation retinopathy. **A,** A composite color photograph reveals a darkened and flattened choroidal melanoma. Before bevacizumab there is intraretinal microangiopathy (microaneurysms, vascular sheathing), intraretinal hemorrhages, cotton-wool spots, and macular edema (visual acuity 20/32). **B,** One year and after four injections a composite color photograph reveals marked resolution of the retinal hemorrhages and edema (visual acuity 20/20). Note persistent intraretinal microangiopathy, ghost vessel formation, and dots of intraretinal exudates.
Courtesy Finger PT: Radiation retinopathy is treatable with anti-vascular endothelial growth factor bevacizumab (Avastin). Int J Radiat Oncol Biol Phys 70(4):974–977, 2008.[308]

After the patient is immobilized, the tumor volume should be outlined, followed by design of the treatment field based on the margin felt necessary to encompass the tumor, beam penumbra, and setup uncertainties. The distance of microscopic tumor beyond the gross clinical volume is a mean of 5 mm, but this distance may vary with extent of perineural invasion and grade.[312] At least an additional 0.5 cm should be provided beyond that which would be used for orthovoltage equipment. For instance, for a tumor less than 2 cm in size, the penumbra would include a horizontal margin of 0.5 cm to 1 cm for an orthovoltage field, whereas electrons require an additional 0.5 cm—a total of 1 cm to 1.5 cm for a tumor ~2 cm in size. Depth of treatment should be determined with attention to perineural invasion, location near an embryologic fusion plane, and size of the lesion, but in general should include a bolus of varying thickness depending on beam energy if superficial dose is intended. If perineural invasion is present, reviewing the relevant path of the involved nerve and additional imaging is often required.[313-318] Tungsten eye shields may provide better shielding of anterior eye structures than lead for 9-MeV electrons.[319,320]

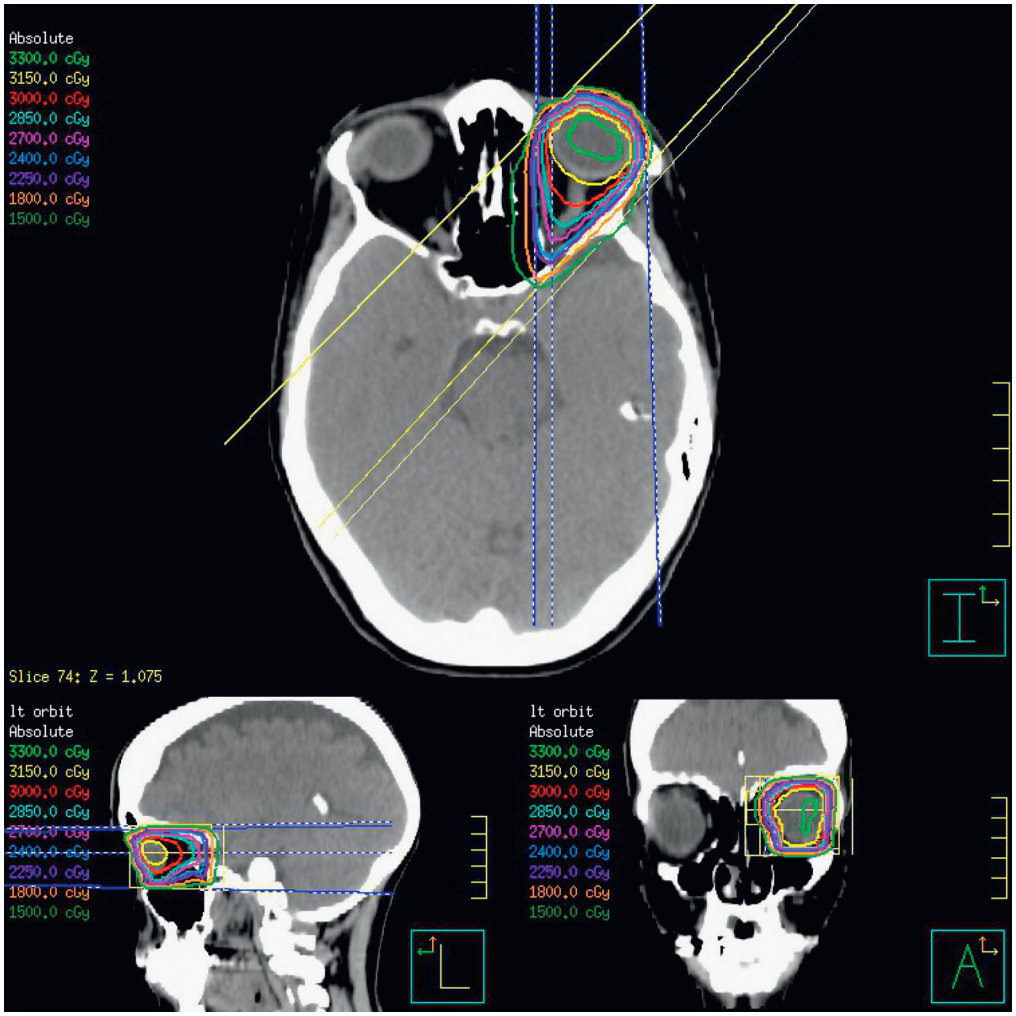


Figure 31-7 Treatment planning—Orbital metastasis. Axial, sagittal, and coronal noncontrasted CT slices of a three-dimensional conformal radiotherapy plan for a patient with a metastasis of the globe treated to a total dose of 30 Gy in three Gy fractions.

should be discouraged from using numbing medications outside of daily shield insertion because it may numb them to self-induced trauma during the excessive tearing often seen following and at later time points during therapy.[321]

Bilateral Eye Lesions

Treatment of both eyes is usually done with opposed lateral fields. If it is possible to spare the lens (i.e., Graves's ophthalmopathy), then the central axis of the beam should be placed just posterior to the lens (5 mm behind the most anterior aspect of the globe). A split-beam technique is used to block the anterior structures if possible. Graves's disease, bilateral choroidal metastasis, and bilateral lymphomas are treated in this manner. Some have proposed a mixed photon electron field technique for the treatment of bilateral orbital disease to maximize homogeneity of the periorbital and retro-orbital tissues while minimizing the dose to the lens, although this technique requires the use of a wax compensator and a sunken lead alloy eye block to prevent dose to the anterior segment of the eye.[323]

Anterior Lesions

Involvement of the conjunctiva may require treatment of the anterior structures alone. This can be accomplished with electron fields directed en face to the globe. Central lens shielding can be accomplished with a hanging block at which the patient is instructed to look (see Figure 31-8). En face electrons can be used with a lead contact lens if electrons of not more than 6 MeV and tungsten if 9-MeV electrons are used.[319] In the case of a unilateral superficial conjunctival orbital lymphoma, the aforementioned technique can be considered, although caution should be employed as any involvement of the retrobulbar tissues will receive less than a therapeutic dose and treatment of the partial relative to the complete orbit has resulted in treatment failures.[213]

Intensity-Modulated Radiation Therapy

Techniques using three-dimensional treatment planning and intensity-modulated radiation therapy may be advantageous for treating optic nerve meningiomas or gliomas (Figures 31-10 and 31-11). All critical structures of the eye should be identified at the time of CT simulation and volume delineation and appropriate planning dose constraints applied. Patient immobilization is crucial, and the use of a stereotactic setup should be considered.[324]

Tolerance Issues

Sequelae from radiation exposure to the eye vary by type of radiation therapy (photon, electron, or brachytherapy), total

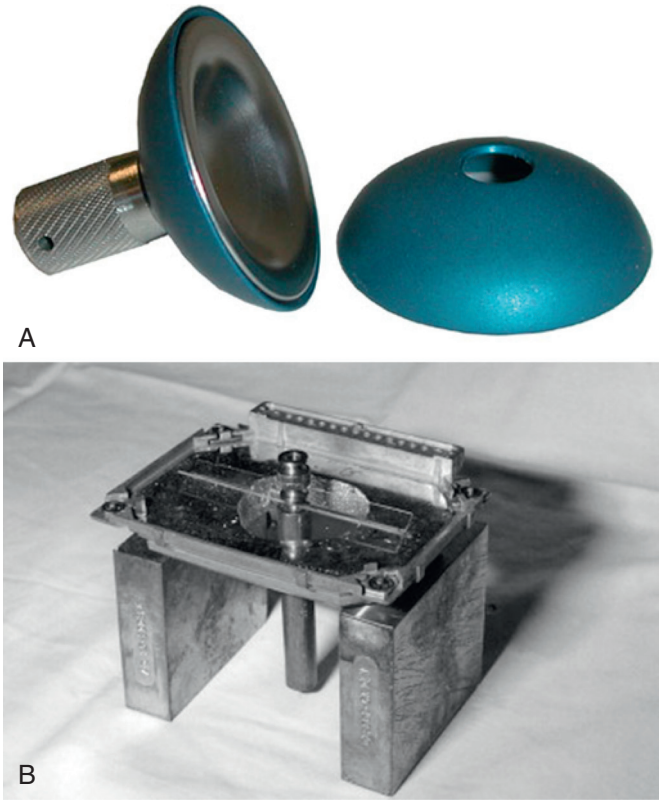


Figure 31-8 **Treatment setup. (A)** Representative tungsten lens shields used for reducing anterior radiotherapy dose to the lens. **(B)** Hanging block apparatus.

dose, radiotherapeutic fraction size, and part of the eye included in the radiation exposure. Unrelated medical conditions such as diabetes, hypertension, and collagen vascular diseases can affect the radiation tolerance of structures in the eye. Systemic chemotherapy or steroids can enhance radiation toxicity or contribute to additional symptoms.

The most sensitive structure in the eye is the lens, which is located directly behind the pupil. The germinal layer of the lens located at the equator is the layer most sensitive to radiation. These cells undergo mitotic division, elongate, lose their nuclei, and migrate posteriorly to the center of the lens. This posterior migration and proliferation of the lens's epithelial cells reduce lens clarity, causing a cataract, and often some degree of visual loss. A radiation cataract usually presents first as a posterior, central subcapsular opacification. The latency and frequency of lens opacities are a function of radiation therapy dose and fractionation.

In most human studies, total fractionated doses under 5 Gy have not produced visually significant lens opacities. Merriam and Focht[325] reported cataract formation with EBRT fractions of 1.5 Gy to 2 Gy, to a total dose of 12 Gy. When single-dose, total body irradiation was used, cataracts developed in 80% of survivors; the incidence decreased to 20% when fractionated EBRT was given to a total dose of 13 Gy.[325] Reduction of dose to the lens may be possible with customized lens shields, pencil-beam lead blocks, or more complex treatment planning with IMRT. Lens extraction for cataract development can correct the vision in an otherwise functioning eye following irradiation.

Other anterior structures in the globe include the cornea and conjunctiva. The conjunctiva is a mucous membrane of nonkeratinized squamous epithelium with goblet cells overlying a thin substantia propria.[326] It covers the inner surface of the eyelid and outer surface of the eye, extending to the peripheral cornea. The cornea is composed of nonkeratinized stratified squamous epithelium. Its outermost surface is composed of irregular microvilli made optically smooth by the precorneal tear film. The basal cells are attached to Bowman's layer, which is made up of randomly dispersed collagen fibrils that may become opacified by scar tissue. The stroma, which makes up 90% of the total corneal thickness, is composed of fibroblasts and collagen lamellae.

Acute effects of fractionated radiotherapy include injection and erythema of the conjunctiva with irritation that is usually self-limited. Fractionated doses of radiation to a total dose above 40 Gy to 50 Gy to the cornea can produce edema with punctate keratitis.[327] Management consists of aggressive lubrication, patching, and antibiotic drops. Recurrent corneal erosions may progress to ulceration and infection leading, to either opacification or perforation. Ulcerations of the cornea have been reported with fractionated radiation therapy to doses above 40 Gy.[207,328] Similarly, ulceration, telangiectasias, and keratinization can develop in the conjunctiva.

The eyelid skin is the thinnest in the body. The lids contain sebaceous, serous, and apocrine glands, which contribute to the tear film. There are puncta on the medial lid margins that form the opening to the nasolacrimal drainage system. Transient effects of eyelash loss and erythema occur at 30 Gy to 40 Gy with conventional fractionation, whereas permanent lash loss occurs at doses above 50 Gy.[167,171] Scarring and fibrosis can develop at doses above 50 Gy, which can result in ectropion or entropion of the lid as well as stenosis of the eyelid puncta.

There are several structures necessary for adequate tear film production, which include the lacrimal gland, goblet cells, meibomian glands, and accessory lacrimal glands. Dry eye syndrome can result from injury to any component of the tear film. Symptoms include burning, decreased vision, excessive tearing, and a foreign body sensation. Examination reveals corneal changes ranging from keratitis to corneal scarring and opacification. One report described 19% of patients who received doses less than or equal to 45 Gy in 25 fractions developing a dry eye syndrome compared with 100% for doses above or equal to 57 Gy in 30 fractions.[230] Severe keratitis sicca can lead to corneal ulceration and perforation of the globe. Prevention of lacrimal damage requires consideration of the location of the lacrimal gland when designing fields for radiation therapy delivery.[329]

The sclera covers the posterior 80% of the globe. It is largely avascular and consists of collagen fibrils, fibroblast, and ground substance. It is resistant to radiation and can withstand doses of more than 150 Gy that are delivered with plaque radiotherapy used to treat choroidal melanomas. Scleral thinning, necrosis, and ulceration are unusual complications of high doses of radiation therapy.[275,330]

The retina consists of an extensive network of neural, glial, and vascular elements. The blood supply to the outer layers of the retina is via the choriocapillaris. The inner retinal layers are supplied by the branches of the central retinal artery, of which the largest branches are the temporal and nasal arcades. Pathology involving the region within the temporal arcades is more visually significant than that occurring elsewhere. Radiation retinopathy is caused by occlusive microangiopathy manifest by cotton wool spots, microaneurysms, telangiectasias, hemorrhages, macular edema, exudates, neovascularization, vitreous hemorrhage, and pigment changes. Visual symptoms

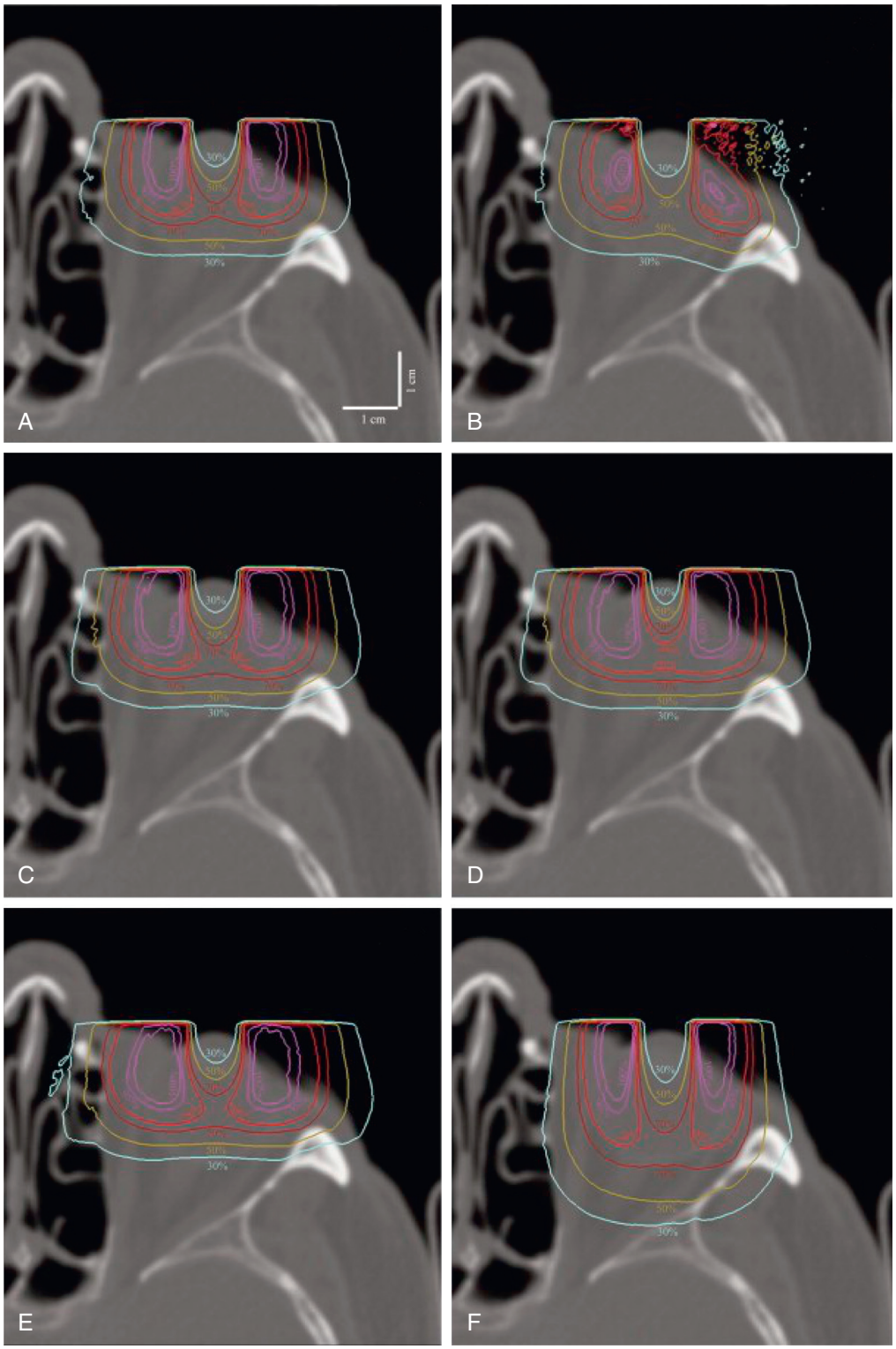


Figure 31-9 Hanging block dosimetry. Isodose lines at the isocenter slice for the following treatment setups: **A,** 6-MeV, hole diameter *(h)* = 3.0 cm, rod diameter *(r)* = 1.0 cm, with bolus; **B,** 6 MeV, *h* = 3.0 cm, *r* = 1.0 cm, no bolus; **C,** 6 MeV, *h* = 3.5 cm, *r* = 1.0 cm, with bolus; **D,** 6 MeV, *h* = 3.5 cm, *r* = 0.8 cm, with bolus; **E,** 6 MeV, *h* = 4.0 cm, *r* = 1.0 cm, with bolus; and **F,** 9 MeV, *h* = 3.0 cm, *r* = 1.0 cm, with bolus. All plotted cases have used the 15 × 15 cm^2 electron applicator. Inner to outer relative isodose lines correspond to 100%, 95%, 80%, 70%, 50%, and 30% of the maximum absorbed dose of each case.
Contribution from: Brualla L: Int J Radiat Oncol Biol Phys 83(4), 2012.[322]

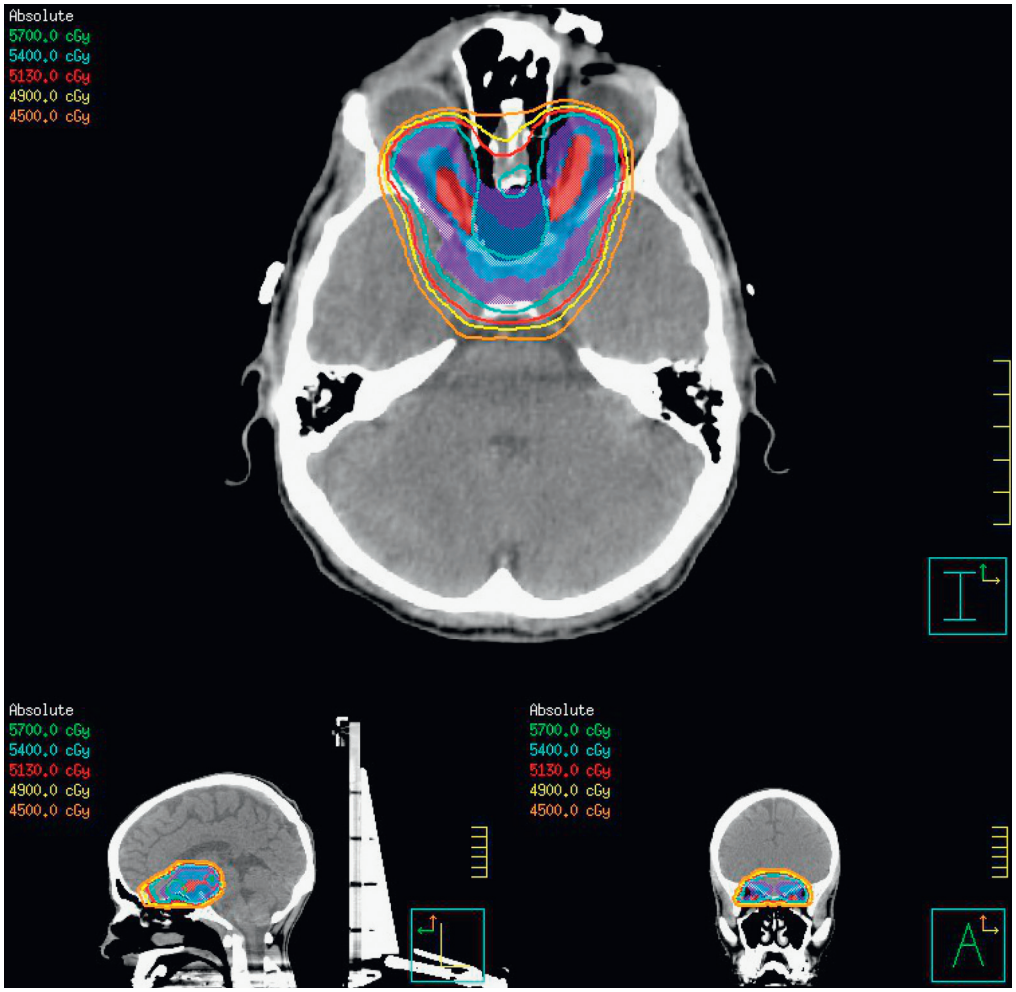


Figure 31-10 Treatment planning—Optic pathway glioma. Axial, sagittal and coronal noncontrasted CT slices of an IMRT radiotherapy plan for a patient with a chiasmal low grade glioma treated to a total dose of 54 Gy in two Gy fractions.

secondary to radiation retinopathy depend on the area of the retina that is affected. A history of diabetes, collagen vascular disease, hypertension, and treatment with chemotherapy predisposes patients to radiation-induced injury.[230] In one report, radiation retinopathy was not observed at doses below 45 Gy in 25 fractions but increased steadily above this dose.[230] Patients also seemed to be at increased risk if they were treated with doses per fraction greater than or equal to 1.9 Gy.[230] Although the estimated tolerance dose with a 5% risk at 5 years ($TD_{5/5}$) is 45 Gy and the $TD_{50/5}$ is 65 Gy, the threshold dose for the retina is thought to be between 30 Gy and 35 Gy.[211] A meta-analysis of radiotherapy as it relates to retinopathy in macular degeneration found no damage in patients treated up to 24 Gy although it appears this risk rises sharply after 45 Gy to 50 Gy.[331]

Optic nerve injury is secondary to ischemia and generally presents with painless monocular loss of vision. Damage begins with perivascular lymphocyte cuffing, loss of endothelial cells, and hyalinization, with fibrosis, thrombosis, and infarction of neural tissue. Fractionation plays a key role in modulating the development of optic nerve injury. Of patients who were treated to a total dose of 45 Gy to 50 Gy and received a daily fraction size of more than 2.5 Gy, 18% developed visually significant changes, whereas those patients who received fractions below 2.5 Gy did not develop optic neuropathy.[332] Stereotactic radiosurgery that delivers large fraction sizes can cause optic neuropathy with single doses of 8 Gy, although tiny volumes to high doses have been given without toxicity.[333] With conventional fractionation, the $TD_{5/5}$ of the optic nerve is considered to be 60 Gy.[230]

CONCLUSIONS AND FUTURE POSSIBILITIES

The COMS has made a significant contribution to the understanding of and treatment of choroidal melanoma, which is the most common primary intraocular malignant tumor. Future investigations may shed light on the role of charged particle therapy and optimize patient selection for additional therapy. By understanding and incorporating ocular anatomy and physiology with more directed treatment techniques, a better therapeutic ratio may be expected with the use of irradiation for patients with ocular pathology. Finally, advances in molecular biology and immunohistochemistry may lead to better insight into disease processes and patient selection for treatment.

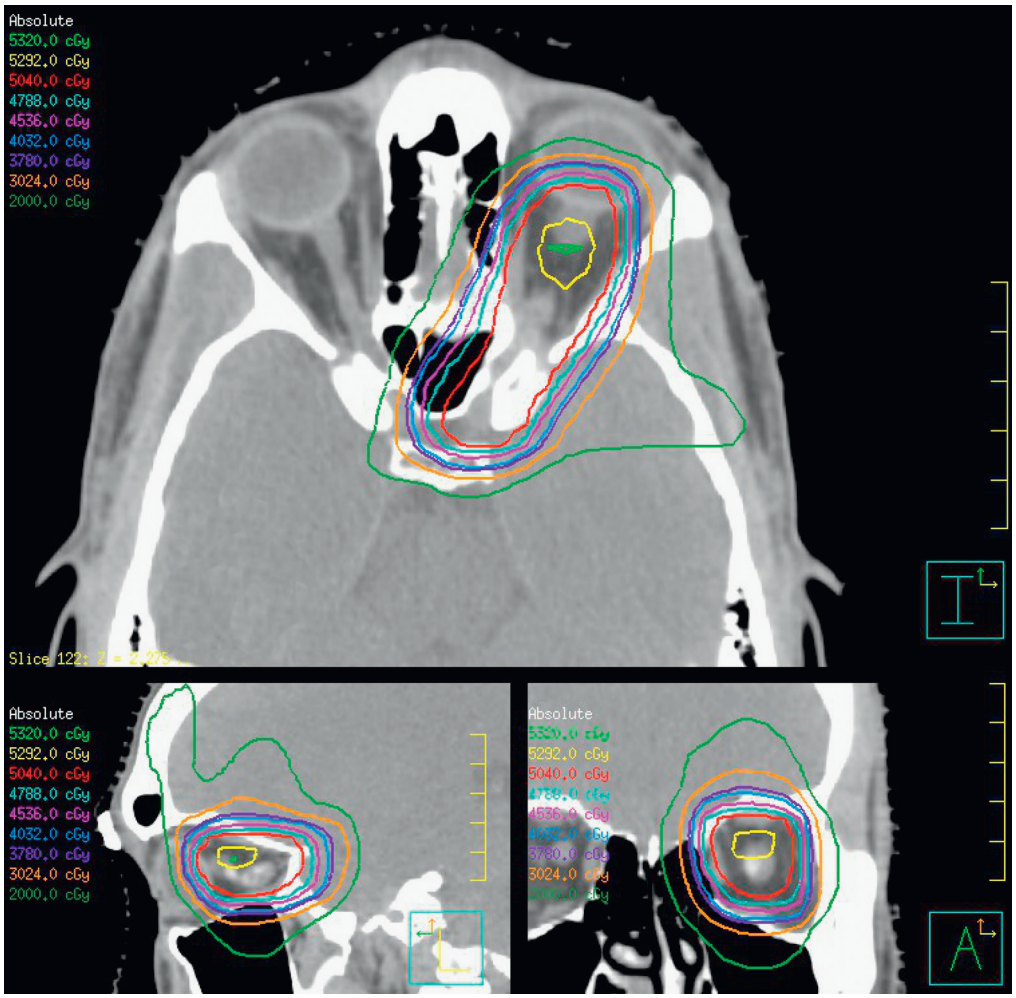


Figure 31-11 Treatment planning—optic nerve sheath meningioma. Axial, sagittal and coronal noncontrasted CT slices of a three-dimensional conformal radiotherapy plan treated with a fractionated stereotactic setup with reduced margins to a total dose of 50.4 Gy in 1.8 Gy fractions.

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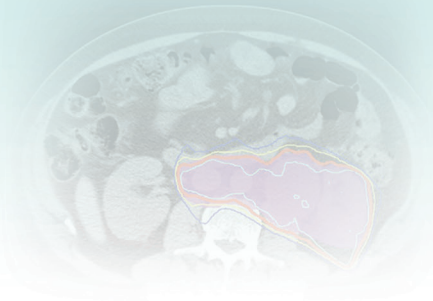
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Overview



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Although representing about 4% of cancers, a variety of neoplasms with diverging natural histories arise in the relatively small body region of the head and neck. Essential basic physiologic functions that are critical for one's expression, respiration, nutrition, and social interactions are all located within the head and neck region, including one's personal appearance. Depending on the site, size, and pattern of spread, head and neck cancers can cause various degrees of structural deformities and functional handicaps, compromising comfort and social integration. Treatments used in the management of head and neck tumors can induce additional mutilations and malfunctions, worsening the quality of life. Consequently, optimizing outcomes in terms of survival, tumor control, function, and quality of life is challenging.

Knowledge of the basic principles of oncology and expertise in patient assessment and in individual specialties are essential for the optimal staging workup of patients and for appropriate treatment selection. Integrated interdisciplinary collaborations among surgical, radiation, medical, and dental oncologists as well as interactions among oncologists and pathologists, radiologists, reconstructive surgeons, physical medicine and rehabilitation physicians, psychiatrists, nurses, speech and swallowing therapists, dieticians, social workers, chaplains, and other health and spiritual care personnel are essential for optimal management and rehabilitation of patients with head and neck cancer. Well-functioning, integrated, and coordinated care is essential to yield the highest complication-free cure rate with maximal functional and cosmetic outcome. Close collaborations among radiation oncologists, dosimetrists, medical physicists, radiotherapists, and oncology nurses are important to deliver quality radiotherapy.

Long-term investment in cancer research has come to fruition for certain cancers. The mortality rate for most cancers in the United States increased for decades, but since 1975 the rate has decreased.[1] Many advances have been achieved in the understanding of the biology, natural history, and treatment of head and neck cancers.

This summary highlights a few interesting and evolving concepts and recent findings of clinical interest in the carcinogenesis, biology, and treatment of head and neck cancers. Site-specific issues are discussed in the subsequent chapters.

MOLECULAR BIOLOGY AND ECOGENETICS

The molecular tumor progression model was initially proposed by Fearon and Vogelstein.[2] This model states that tumors progress by activation of oncogenes and inactivation of tumor suppressor genes (TSGs), with each process producing a growth advantage for a clonal population of cells, and that specific genetic events usually occur in a distinct order (i.e., multistep carcinogenesis) that is not necessarily the same for each tumor.

For head and neck carcinomas, Califano et al[3] described a preliminary tumor progression model using allelic loss or imbalance as a molecular marker for oncogene amplification TSG inactivation. They identified *CDKN2A* (formerly designated *p16*; 9p21), *TP53* (17p), and *RB1* (13q) as candidate TSGs, and *CCND1* (cyclin D1 gene; 11q13) as a candidate proto-oncogene. The results of this work support the initial observations of the colorectal molecular progression model in that clonal genetic changes occur early in the histopathologic continuum of tumor progression. About one third of histopathologically benign squamous hyperplasias contain a clonal population of cells with shared genetic anomalies characterizing head and neck cancers. Identification of such early events facilitates discovery of genetic alterations associated with further transformation and aggressive clinical behavior. Genetic mutations of the PI3K/Akt/mTOR pathway have been reported in most head and neck squamous cell carcinomas (HNSCCs).[4] Mutation rates are low in human papillomavirus (HPV)-positive squamous cell carcinomas of the head and neck when compared to HPV-negative cancers. PIK3CA is the most commonly mutated oncogene pathway in HPV-positive cancers.[5] With further validation, this knowledge will contribute greatly to the development of screening strategies, focusing on previous steps of the estimated 10 or more genetic alterations required to generate an invasive tumor phenotype and to the conception of early pharmacologic or genetic therapy approaches.

Tobacco and alcohol exposure has long been recognized as the dominant risk factor in head and neck carcinogenesis. Although the use of these substances was estimated to account for approximately three fourths of oral and pharyngeal carcinomas,[6] neoplasms develop in only a small fraction of exposed individuals. This intriguing information raised the notion of the contribution of genetic susceptibility or predisposition and other cofactors (e.g., viral infection) to carcinogenesis. The potential pathways are thought to include genetic polymorphism influencing environmental carcinogen absorption and detoxification, individual sensitivity to carcinogen-induced genotypic alterations, and so on. These ideas can now be tested properly because of progress in molecular biology concepts and assay methodology. The ability to identify smokers at high risk for the development of cancer, for example, has important practical clinical implications, such as in selecting individuals for more aggressive screening programs or for enrollment in intensive chemoprevention trials (discussed later).

RECEPTOR TYROSINE KINASES

Intensive research efforts sparked by the characterization of epidermal growth factor receptor (EGFR, also known as HER1 or ERBB1) in the late 1970s generated insights into the structures and functions of receptor tyrosine kinases (RTKs) and their roles in the ligand-mediated signaling pathways governing proliferation, differentiation, survival, and other key cellular processes.

More than two decades after the initial characterization of the EGFR, it is known that receptor tyrosine kinases are highly related in structure and domain arrangements despite their unique biologic roles. This class of receptors comprises 58 members distributed among 20 subfamilies (reviewed by Gschwind et al[7]). EGFR-mediated signaling and its deregulation in pathogenesis and as the target of therapeutic intervention of human tumors have also been reviewed.[8,9] Its value as a prognostic-predictive biomarker and as a target of therapeutic intervention in head and neck carcinoma is addressed in the section on "Biomarkers and Molecular Targeting."

Deregulation of the *RET* gene-encoded transmembrane receptor tyrosine kinase plays an important role in the pathogenesis of papillary and medullary thyroid cancer (reviewed by Santoro et al[10]). The *RET* gene is located in the pericentromeric region of the short arm of chromosome 10. Alternative splicing of the RET product results in two protein isoforms: RET9 and RET51. RET shows that a single gene can induce different types of cancer, depending on the mutation. The genetic characteristics of papillary thyroid carcinoma (PTC), the most common thyroid neoplasm, are chromosomal inversions or translocations leading to several types of combinations of intracellular kinase-coding RET domain with heterologous genes, producing the *RET*/PTC chimeric oncogenes. In vitro and in vivo irradiation was found to induce the formation of a RET/PTC1 rearrangement,[11] and RET/PTC rearrangements have been found in more than 60% of post-Chernobyl accident papillary thyroid carcinomas.[12] These findings contribute to the understanding of the pathogenesis of radiation-induced thyroid carcinoma.

In contrast to the rearrangement observed in papillary thyroid carcinoma, germline point mutations in *RET* cause three types of related dominantly inherited cancer syndromes: multiple endocrine neoplasia type 2A (MEN2A), MEN2B, and familial medullary thyroid carcinoma (FMTC).[13-15] Most RET mutations in MEN2A and FMTC affect cysteine in the extracellular cysteine-rich domain (i.e., codon 634 [particularly, C634R] in MEN2A) or are evenly distributed among various cysteines in FMTC. Mutations in the kinase domain have also been observed. The most common mutation in MEN2B is M918T in the kinase domain. Somatic mutations of V804, M918, and E768 occur in about one half of sporadic medullary thyroid carcinomas (MTCs).[13-16] Functionally, RET cysteine mutants form covalent dimers leading to constitutive kinase activity, whereas the M918T mutation causes a change in the substrate specificity.[17]

VIRAL CAUSES

Nasopharyngeal carcinoma (NPC) has been an excellent model for studying viral causes of human cancer. Although the association between Epstein-Barr virus (EBV) and NPC has been recognized for about four decades, significant progress in this field has been made only more recently. For example, the EBV genome was characterized (reviewed by Liebowitz[18]) and found to consist of a linear, 172-kb, double-stranded DNA having five unique sequences, separated by four internal repeats along with two terminal repeats. The DNA circularizes by homologous recombination at random locations within terminal repeats in the nucleus of infected cells. The length of terminal repeat is therefore specific for each infected cell, and this is the basis for clonality assay, which may be useful in determining the putative primary tumor in patients presenting with nodal metastasis from an unknown source. The genome encodes several families of proteins, such as early antigens (EAs), EB nuclear antigens (EBNAs), and latency membrane proteins (LMPs). Many of these proteins control viral behavior and affect cell proliferation regulatory mechanisms, and they are thought to play a role in transformation and carcinogenesis and to influence the tumor response to therapy. EBNA-1 regulates viral genome replication during cell division and was found to induce growth and dedifferentiation of an EBV(–) NPC cell line.[19] LMP-1 seems to alter growth of epithelial cells, induce well-differentiated squamous carcinomas from human epithelial cell-line transfectants, and is associated with BCL2 expression in tumors.[20,21]

More work has been done on the molecular genetics of NPC. Many NPCs were found to have deletions of the short arm or some regions of the short arm of chromosomes 3 and 9, suggesting the possibility of the existence of TSGs in these regions.[22,23] For example, some studies[24,25] revealed that the combined frequency for chromosome 3p and 9p (bearing *CDKN2A* and *RASSF1A*) losses in the normal nasopharyngeal epithelium among southern Chinese individuals in Hong Kong, a population at high risk for NPC, was 82.6%, compared with 20% in the low-risk populations. In contrast, latent EBV infection was detected only in high-grade nasopharyngeal dysplasia or NPC. Consequently, it was postulated that the abnormal genetic changes in chromosomes 3p and 9p predispose nasopharyngeal cells to sustain latent EBV infection, and this combination promotes a cascade of events leading to malignancy. One study revealed that in patients with nonmetastatic NPC, the plasma level of EBV DNA, particularly when assayed after completion of therapy, is a robust prognostic biomarker (see section "Biomarkers and Molecular Targeting").

The causal relationship between HPVs and some human neoplasms has been established, particularly for carcinoma of the uterine cervix. Most cervical cancers contain integrated HPV DNA, most commonly of high-risk types HPV-16 and HPV-18.[26] Cell culture studies clearly demonstrated that the high-risk HPVs can transform and immortalize epithelial cells from the cervix, foreskin, and oral cavity.[27-29] In contrast, HPV-6 and HPV-11, associated more often with benign lesions, do not possess this capability.[30,31] Expression of E6 and E7 open reading frames of the HPV-16 or HPV-18 genome is sufficient for immortalization.[32,33]

The potential role of HPV in head and neck carcinogenesis has attracted attention (reviewed by Blitzer[34]). Carcinomas of the tonsil, oral tongue, and floor of the mouth were found to have a relatively high prevalence of HPV DNA.[35-37] A high proportion of verrucous carcinomas, rare locally invasive carcinomas with papillomatous morphology, are associated with HPV.[38,39] Verrucous carcinomas of the larynx predominantly contain HPV-6, HPV-11, HPV-16, or related DNA.[40] The evidence for the role of HPVs in carcinogenesis of tonsillar carcinomas is increasing because these tumors contain HPV DNA in most of the cells and express readily detectable levels of HPV RNA.[41] In a series of 253 patients, Gillison et al[42] detected HPV in 25% of tumors, with HPV-16 present in 90% of the positive neoplasms. HPV presence was most common in oropharyngeal carcinoma, occurring in individuals with no history of smoking and alcohol consumption, and having a basaloid subtype without *TP53* mutation. Laboratory data showing that transcriptionally active, integrated HPV-16 DNA persisted in an oral carcinoma cell line having features indistinguishable from those of the primary tumor[43] provide strong evidence for an active role of HPV in carcinogenesis.

Ang et al[44] reported that tumor HPV status is a strong and independent prognostic factor for survival among patients with oropharyngeal cancer. They performed a retrospective analysis of the association between tumor HPV status and survival among patients with stage III or IV oropharyngeal squamous cell carcinoma who were enrolled in a randomized trial comparing accelerated fractionation radiotherapy with standard fractionation radiotherapy, each combined with cisplatin (Radiation Therapy Oncology Group [RTOG] 0129). Proportional hazards models were used to compare the risk of death among patients with HPV-positive cancer and those with HPV-negative cancer. With a median follow-up of 4.8 years, patients with HPV-positive tumors had significantly better 3-year rates of overall survival (OS). After adjustment for age, race, tumor and nodal stage, tobacco exposure, and treatment assignment, patients with HPV-positive tumors had a 58% reduction in the risk of death. These results have been confirmed by others.[45]

Understanding HPV infection and the mechanisms of HPV-induced malignant conversion is essential for developing strategies for preventing HPV infection and virus-associated carcinogenesis, such as blocking expression of its E6 and E7 proteins.

TREATMENT OF RELATIVELY LOCALLY ADVANCED CANCERS

Refinement in surgical resection and reconstructive techniques and advances in radiotherapy planning and delivery technology have produced good outcomes for most patients with early-stage head and neck cancers. Unfortunately, for more locally advanced cancers, the current standard therapy consisting of surgical resection and preoperative or postoperative irradiation achieves poor results in terms of disease control, preservation of organ function, or both. Consequently, there has been a continuous search for better treatment approaches. This quest plus the simplicity of clinical evaluation and a well-characterized pattern of relapse make head and neck carcinomas ideal models for testing the relative efficacy of novel therapy concepts and modalities. For example, most clinical radiobiologic investigations have been conducted in patients with head and neck cancers.

Clinical Radiobiology: Fractionation Schedules

Radiobiologic concepts derived from more than two decades of integrated laboratory and clinical investigations led to the conception of two classes of new fractionation schedules for the treatment of head and neck cancers. These altered fractionation regimens are referred to as *hyperfractionation* and *accelerated fractionation schedules*. Hyperfractionation exploits the difference in fractionation sensitivity between tumors and normal tissues manifesting late morbidity. In contrast, accelerated fractionation attempts to reduce tumor proliferation as a major cause of radiotherapy failure. Although there are many permutations in accelerating radiation treatment, the existing schedules can be conceptually grouped into two categories: pure and hybrid accelerated fractionation regimens, depicting the absence and presence of concurrent changes in other fractionation parameters, respectively.

These radiobiologically sound fractionation regimens have been extensively tested in patients with intermediate and more locally advanced head and neck carcinomas, mainly of the oropharynx. This line of clinical research has concluded. Results of the completed phase III clinical trials have been reviewed,[46,47] and the results and conclusions are briefly reviewed here.

Hyperfractionation

The clinical trial results, most notably those of the European Organization for Research on Treatment of Cancer (EORTC), show a moderate (10% to 15%) but consistent improvement in the local control of T2 to T3, N0 to N1 oropharyngeal carcinomas.[48] The incidence of late toxicity with a 10% to 15% total dose increment delivered twice daily in smaller than standard fraction sizes was within the range observed with conventional fractionation schedules, although none of the studies was designed to test the equivalency of late morbidity.

Accelerated Fractionation

The trial results indicate that mucosal toxicity limits the magnitude of overall time reduction to at most 2 weeks without decreasing the total dose. With *pure accelerated fractionation* (no or minimal change in the total dose and fraction size relative to a conventional schedule), delivery of 10 fractions per week (Vancouver trial[49]) induced severe acute mucositis. Administration of continuous daily irradiation without a weekend break (CAIR trial[50]) caused severe late effects, which were thought to be consequential.

With *hybrid accelerated fractionation*, delivery of three fractions of 1.6 Gy per day, separated by an interval of approximately 6 hours, without reduction of the total dose (EORTC trial[51]) increased late complications such as soft-tissue fibrosis, peripheral neuropathy, and myelopathy. Based on the repair kinetic data obtained from experimental spinal cord and skin models and from human skin, these late morbidities can be ascribed in part to the occurrence of compounding incomplete cellular repair of sublethal injury. A 12-Gy total dose reduction (as in continuous hyperfractionated accelerated radiation therapy [CHART][52]) seemed more than sufficient to offset the compounding incomplete repair associated with the delivery of three fractions per day and thereby resulted in lesser severity of a number of late complications, including skin telangiectasia, mucosal ulceration, and laryngeal edema. However, CHART did not improve tumor control in patients with a variety of locally advanced head and neck carcinomas. This study showed that it is possible to substitute radiation dose by overall time reduction and thereby provide indirect evidence for the importance of tumor clonogenic proliferation in determining local cure by irradiation. Theoretically, this regimen should benefit a subset of patients with rapidly proliferating tumors. Based on subset analyses, the investigators postulated that this subgroup might be those with T3 to T4, well-differentiated carcinomas of the larynx. This study warrants further analysis.

A pure accelerated fractionation regimen delivering six fractions per week (Danish trial[53]) and a hybrid variant by concomitant boost (RTOG trial[54]) yielded improved local control rates for locally advanced head and neck cancers without increasing the morbidity. The Danish trial (DAHANCA 7) randomized a total of 1485 patients eligible for primary irradiation alone to receive 66 Gy to 68 Gy in 33 to 34 fractions given in 5 or 6 fractions per week. The compliance rate to both regimens was high. The incidence of acute severe mucositis and dysphagia was higher in patients receiving 6 fractions per week, but there was no difference in the incidence of late edema or fibrosis. The 5-year actuarial locoregional control rates in 1476 evaluable patients were 70% and 60% for accelerated and conventional regimens, respectively ($p = 0.0005$). The benefit for acceleration resulted primarily from improvement in primary tumor control.

The RTOG randomized trial 90-03 compared the relative efficacy of three altered fractionation regimens with the standard dose of 70 Gy in 35 fractions over 7 weeks.[54] The test

radiation schedules were hyperfractionation (81.6 Gy in 68 fractions over 7 weeks, with 1.2 Gy given twice daily), split-course accelerated fractionation (67.2 Gy in 42 fractions of 1.6 Gy twice daily over 6 weeks, including a 2-week break), and a concomitant boost regimen (72 Gy in 42 fractions over 6 weeks, with 1.8 Gy daily for the first 3.6 weeks and 1.8 Gy [large field] plus 1.5 Gy [boost field], 6 hours apart, for the last 2.4 weeks). Analysis of results for the 1073 patients enrolled showed that the concomitant boost and hyperfractionation regimens yielded significantly higher locoregional control than standard fractionation. The split-course accelerated regimen did not improve locoregional control rates over the standard fractionation regimen. The acute mucosal reactions were more severe in patients receiving altered fractionation regimens, but there was no difference in the complication rates at 6, 12, 18, and 24 months after therapy. With long-term follow up (5 years), only patients treated with hyperfractionation had improved locoregional tumor control and improved OS, without an increase in late toxicity, when compared to standard fractionation.[55]

Conclusions

More than two decades of intensive clinical investigations of altered fractionation schedules have produced conceptually interesting and clinically important findings. Trials addressing hyperfractionation show that this biologically sound regimen yields a moderate but consistent improvement in locoregional control and OS of moderate or more locally advanced HNSCC, with no observed increase in late toxicity.

The results of accelerated fractionation indicate that acute mucosal toxicity limits the magnitude of overall time reduction to at most 2 weeks and that late complications resulting from compounding incomplete repair compromise delivery of three fractions of 1.6 Gy per day without a reduction in total dose. Acceleration by concomitant boost also appears to be associated with a higher rate of late complications. However, acceleration of radiotherapy by delivering six fractions per week yielded significantly improved local tumor control rates relative to standard fractionation without increasing the morbidity in the treatment of predominantly locally advanced carcinomas.

All in all, well-organized clinical trials enrolling more than 6000 patients to test the relative efficacy of various altered fractionation regimens have generated important data. In terms of radiobiological findings, the trial results demonstrated the existence of differential fractionation sensitivity between head and neck carcinomas and late-responding normal tissues and firm evidence that tumor clonogenic proliferation is a major obstacle to curing advanced head and neck cancers with fractionated radiotherapy. Clinically, the results of these trials call for changing radiotherapy practice for the treatment of moderate or advanced head and neck carcinomas. Because of the magnitude of therapeutic gain achieved with six fractions per week, economic and logistic considerations determine the choice of the new standard treatment. For reasons of cost, resource utilization, and patient convenience, many centers have adopted the relatively simple six-fractions-per-week regimen as the standard radiotherapy for patients with intermediate-stage head and neck carcinomas and those with locally advanced cancers either not eligible for protocol studies (having contraindications to chemotherapy or biologically targeted agents) or choosing to receive irradiation alone.

The data open the challenge for conceiving creative approaches to integrate altered fractionation regimens with cytotoxic or biologic agents to further improve the therapeutic outcome. Several concepts have been tested or are undergoing preclinical and clinical testing.

Combination of Radiation with Chemotherapy

Sequential versus Concurrent Radiation and Chemotherapy

Most combined irradiation-chemotherapy regimens tested have evolved empirically by administering drugs found to have some activity against tumors of interest in a dose and time sequence known to be tolerated in a single-modality therapy setting. Meta-analyses of available data of randomized trials in head and neck cancer undertaken a few years ago showed that despite a high initial response rate, multiagent chemotherapy given before radiation treatment (neoadjuvant setting) has a small impact on the locoregional control and survival rates.[56] Concurrent irradiation and chemotherapy yielded an almost 10% higher survival rate relative to irradiation alone.[57] Unfortunately, the complication rates of combined regimens are also higher than those of radiotherapy only.[57]

The Meta-Analysis of Chemotherapy in Head and Neck Cancer (MACH-NC) Collaborative Group undertook an extensive meta-analysis. The project investigators obtained updated patient data of 93 randomized trials enrolling a total of 17,346 patients. This study revealed tremendous heterogeneity in eligibility criteria and results between studies exploring chemotherapy for patients with nonmetastatic head and neck carcinoma, which made a simple conclusion on the role of chemotherapy difficult. Nonetheless, the analysis revealed a small statistically significant benefit with the addition of chemotherapy to locoregional therapy, which consists of a 4.5% improvement in survival at 5 years. The benefit primarily reflected the favorable effect of concurrent irradiation and chemotherapy, resulting in a 6.5% overall improvement in the survival rate. The study authors conclude that the benefit of concomitant chemotherapy is confirmed and is greater than the benefit of induction chemotherapy. They suggest that future clinical trials should compare concurrent chemotherapy with induction and concurrent chemotherapy to see if the reduction in distant metastasis seen with induction chemotherapy will further improve survival and to determine if induction chemotherapy adversely affects the compliance to concomitant chemoradiation, the most important component of sequential therapy.[58] Unfortunately, to date, in the patient populations studied and with the cytotoxic agents administered in three Phase III clinical trials, there has been no improvement in survival when induction chemotherapy was added to concurrent chemoradiotherapy.[59-61]

Results of many published Phase III trials[62-68] confirm the finding of meta-analyses that chemotherapy given concurrently with irradiation yields better locoregional control and survival rates than irradiation alone in patients with locally advanced HNSCC. Two trials have also shown the benefit of concurrent irradiation and chemotherapy given in the postoperative adjuvant setting.[69,70]

The combined irradiation-chemotherapy regimen most extensively tested is the combination of conventionally fractionated irradiation (70 Gy in 35 fractions over 7 weeks) with cisplatin. In previous trials, cisplatin was given in a dose of 100 mg/m^2, administered during weeks 1, 4, and 7 of radiotherapy (approximately one third of patients were not able to tolerate the last dose). The systemic and mucosal toxicities of such a high-dose, intermittent cisplatin regimen are rather severe. There are four trials showing locoregional control or survival benefit of alternative cisplatin regimens, such as five doses of 20 mg/m^2 over 5 consecutive days or four doses of 25 mg/m^2 over 4 sequential days during weeks 1, 4, and 7[71,72]; weekly fixed doses of 50 mg during the 7- to 9-week course of postoperative radiotherapy[73]; or 6 mg/m^2/day for 5 days each week during the 7-week course of radiotherapy.[68]

Unfortunately, recording and reporting of the late morbidity of combined irradiation and chemotherapy have not been sufficiently consistent and systematic.[74] A thorough report of the long-term results of a French cooperative group (GORTEC) trial reveals that the late complication rate of the combination of irradiation with concurrent carboplatin and fluorouracil was significantly higher than that of irradiation alone.[65] Because of the lack of adequate reporting, controversy still exists about whether the late toxicity of the combination of standard irradiation with 100 mg/m^2 of cisplatin given every 3 weeks may be higher than irradiation alone. It is hoped that longer and more complete follow-up data on late morbidities will be reported in the future. Despite this uncertainty, many oncologists consider 100 mg/m^2 of cisplatin given during weeks 1, 4, and 7 of conventionally fractionated irradiation as the standard of care for patients with locally advanced head and neck carcinomas who are found to be medically fit to receive chemotherapy. The majority of current ECOG and RTOG clinical trials are using 40 mg/m^2 cisplatin given weekly during radiotherapy.

Principles for Optimizing Combined Radiotherapy and Systemic Therapy

A clear understanding of the therapy objective is essential for designing a logical combined-therapy regimen. The purpose of combining irradiation and systemic therapy in the treatment of neoplastic diseases can be to eliminate hematogenous micrometastases that have occurred before initiation of locoregional therapy or to improve the probability of eradicating primary tumors and involved regional nodes. Depending on the pattern of failure, one or both objectives may be desirable in given clinical settings. The primary objective determines the choice of the agents and the timing of drug administration relative to irradiation. If the main aim is to reduce the probability of metastatic relapse, it is logical to select the least toxic agents with proven antitumor activity and administer irradiation and systemic therapy sequentially, rather than concurrently, to minimize direct drug-irradiation interactions that may increase normal tissue toxicity within the radiation treatment volumes. If the major purpose is to increase local tumor control, it is logical to select drugs based on mechanisms of action and administer systemic therapy concurrently with irradiation to maximize drug-radiation interactions. In the latter scenario, therapeutic benefit occurs only when the combined therapy enhances tumor response more than it increases normal-tissue toxicity.

Analysis of the data from the randomized trial RTOG 90-03 on altered fractionations for locally advanced head and neck carcinomas enrolling more than 1000 patients, 60% of whom had stage IV disease, revealed that locoregional relapse is the predominant pattern of failure. Overall, the actuarial locoregional tumor recurrence rate was close to 50%, compared with less than 20% for distant metastasis.[54] Consequently, for the time being, effort should preferentially focus on developing combined therapy aiming at improving locoregional control for patients with locally advanced HNSCC, especially in patients with a more than a 10-pack a year smoking history, HPV-negative cancer, or an oral cavity, hypopharynx, or larynx primary cancer. The finding that concurrent irradiation and systemic therapy improved outcome but that sequential combined therapy did not improve outcome is consistent with this first principle. Such confirmation should be taken into account in the design of future trials.

Despite three decades of clinical research, many scientific questions related to combinations of irradiation and chemotherapy are still not answered. Newer cytotoxic agents with higher efficacy are needed. Factors to be taken into account in selecting agents for combination with irradiation include mechanisms of drug-radiation interaction, pharmacodynamic characteristics, and clinical activity in inducing tumor response in a single-modality therapy setting. A large number of laboratory studies have been undertaken to optimize the combination of irradiation with chemotherapy, particularly using newer cytotoxic and biologic agents such as taxanes, inhibitors of growth factor receptor signaling pathways, and so on.

HIGH-PRECISION RADIOTHERAPY

Advances in computerized radiotherapy planning and delivery technology offered the possibility of conforming irradiation to an irregular tumor target volume (i.e., conformal radiotherapy).[75] It is feasible to reduce the radiation dose to more of the critical normal tissues surrounding the tumor without compromising dose delivery to the intended target volume, resulting in a reduction in morbidity. Reduced toxicity permits escalation of the radiation dose or combining of irradiation with intensive chemotherapy, each of which has the prospect of improving HNSCC control. Basic expertise in anatomy, imaging, and patterns of tumor spread are vital for clinical application of precision radiotherapy.

Precision radiotherapy can be accomplished by the use of an array of x-ray beams individually shaped to conform to the projection of the target, which is referred to as three-dimensional conformal radiation therapy (3DCRT). Technology is also available to modify the intensity of the beams across the irradiated field as an added degree of freedom to enhance the capability of conforming dose distributions in three dimensions. This irradiation technique is called *intensity-modulated radiation therapy* (IMRT). Proton beams offer an even higher magnitude of normal tissue sparing, which is desirable for the treatment of head and neck tumors. Carbon ion beams may offer enhanced normal tissue sparing compared to proton beams, with the added benefit of being biologically more effective, particularly for malignant tumors considered to be resistant to photon and proton irradiation (i.e., hypoxic tumors, inoperable melanoma and salivary gland cancers).

The roles of 3DCRT and, particularly, IMRT in reducing morbidity and perhaps improving the control of squamous cell carcinoma through radiation dose escalation are being tested in a number of medical centers. Results already reveal that these modalities are effective in sparing the parotid glands from receiving a high radiation dose and, thereby, they diminish radiation-induced permanent xerostomia in selected patients.[76-79] Improved OS has also been reported with the use of IMRT.[80]

Single-institution studies testing the role of IMRT in the management of NPC and oropharyngeal cancers have yielded exciting results. In patients with NPC, IMRT was given alone or, for locally advanced stages, in combination with chemotherapy consisting of concurrent cisplatin and adjuvant cisplatin plus 5-fluorouracil.[81] In a series of 67 patients with a median follow-up of 31 months, the 4-year estimates of local progression-free, locoregional progression-free, distant metastasis-free, and OS rates were 98%, 97%, 66%, and 88%, respectively. The worst acute toxicity was grades 1 to 2 in 51 patients (76%), grade 3 in 15 patients (22%), and grade 4 in 1 patient (2%). The worst late morbidity was grade 1 in 20 patients (30%), grade 2 in 15 patients (22%), grade 3 in 7 patients (10%), and grade 4 in 1 patient (2%). Xerostomia was less pronounced than after 3DCRT and decreased with time. At 3 months after IMRT, 8% of patients had no dry mouth, 28% had grade 1 xerostomia, and 64% had grade 2 xerostomia. Of the 41 patients evaluated at 2 years, 66% had no dry mouth and 32% had grade 1 xerostomia, and only 1 patient had grade 2 xerostomia.

In a series of 74 patients with oropharyngeal carcinoma reported by Chao et al,[82] 14 received IMRT alone, 17 had IMRT combined with cisplatin-based chemotherapy, and 43 underwent surgery followed by postoperative IMRT. With a median follow-up of 33 months, the 4-year estimates of locoregional control, distant metastasis-free, disease-free survival (DFS), and OS rates were 87%, 90%, 81%, and 87%, respectively. Grades 1 and 2 cases of late xerostomia were reported for 32 and 9 patients, respectively. Late skin toxicity occurred in three patients (two had grade 1 toxicity, and one had grade 2 toxicity), mucositis in three patients (all had grade 1 toxicity), and trismus in three patients.

Inspired by encouraging single-institution data, a number of prospective multiinstitutional trials addressing the role of IMRT in the treatment of head and neck carcinomas were completed. RTOG 0022 evaluated the efficacy of IMRT in the treatment of 69 patients with T1 to T2, N0 to N1, M0 oropharyngeal cancer. The patients underwent bilateral neck irradiation without concurrent chemotherapy. A dose of 66 Gy in 30 fractions of 2.2 Gy each was administered to the gross tumor planning target volume (PTV), 60 Gy in 30 fractions of 2 Gy each to the intermediate-risk PTV, and 54 Gy in 30 fractions of 1.8 Gy each to the low-risk elective lymph node region PTVs. With a median follow up of 2.8 years, the 2-year estimated locoregional failure rate was 9% (and only 6% in the 49 patients without a major underdose deviation). The maximal late grade 2 or greater toxicity was skin 12%, mucosa 24%, salivary 67%, esophagus 19%, and osteoradionecrosis 6%. The incidence of grade 2 or higher xerostomia was 55% at 6 months, 25% at 12 months, and 16% at 24 months. The authors concluded that IMRT for early-stage oropharyngeal cancer results in high local and regional tumor control rates with lower salivary toxicity when compared with patients treated in previous RTOG clinical trials.[83]

RTOG 0225 evaluated IMRT in the treatment of 68 patients with stage I to IVB NPC (94% were World Health Organization [WHO] type 2 or 3). The PTV for the gross tumor at the primary tumor site and within involved lymph nodes received 70 Gy in 33 fractions of 2.12 Gy each. Regions at risk for subclinical disease and electively treated lymph nodes received 59.4 Gy in 33 fractions of 1.8 Gy each to the PTV. Patients with T2 to T4 primary tumors or with nodal disease beyond N1 category received concurrent cisplatin chemotherapy and adjuvant cisplatin and 5-fluorouracil chemotherapy. The estimated 2-year local progression-free survival (PFS) was 92.6%, regional PFS was 90.8%, local and regional PFS was 89.3%, and the distant metastasis-free survival was 84.7%. The estimated 2-year PFS was 72.7%, and 2-yr OS was 80.2%. Late grade 3 toxicity included esophageal toxicity in 4.7% of patients, mucous membrane toxicity in 3.1%, and xerostomia in 3.1%. The incidence of grade 2 xerostomia at 1 year was 13.5%. Only two patients developed grade 3 xerostomia. No patient developed grade 4 xerostomia. The authors concluded that it is feasible to administer IMRT with or without chemotherapy to patients with NPC and that such treatment is effective with 90% locoregional PFS and minimal grade 3 xerostomia.[84]

Proton beam therapy is being evaluated for patients with locally advanced head and neck cancers.[85-104] Liebsch et al[105] at Massachusetts General Hospital have used proton beam therapy with or without chemotherapy in the treatment of 17 patients with NPC. They escalated the dose to 73.6 Gy by taking advantage of the Bragg peak physical characteristics of the proton beam. With a median follow-up of 43 months, they reported a 3-year relapse-free and OS rate of 91%, which is quite encouraging. Slater et al[106] from Loma Linda University Medical Center treated 29 patients with oropharyngeal carcinoma with proton beam therapy. They were able to escalate the dose to 75.9 Gy in 45 fractions over 5.5 weeks (concomitant boost). With a median follow-up of 28 months, they reported a 2-year locoregional control rate of 92%, DFS rate of 81%, and grade 3 or higher late toxicity of 11%. Proton beam therapy has also been shown to be safe and effective in the treatment of a variety of head and neck malignant tumors located in the region of the skull base adjacent to critical normal tissues, including the eyes, optic nerves, brainstem, and brain. Promising reports are emerging for neuroendocrine tumors of the sinonasal tract, skull base adenoid cystic carcinoma, olfactory neuroblastoma, and sphenoid sinus malignant disease.[107-110] Prospective studies in well-defined patient cohorts are ongoing to determine the outcomes, cost, and value of proton therapy.

Carbon ion therapy holds promise in the treatment of selected head and neck malignant disease. Potential advantages of carbon ion therapy include improved tumor control resulting from even more conformal and precise tumor targeting than photons and protons, thus allowing for dose escalation to the tumor, reduction of dose to normal tissues, and greater radiobiologic effectiveness because of high linear energy transfer (LET), and completion of therapy with at least 50% fewer treatments. Examples include the treatment of inoperable salivary gland malignant tumors and mucosal melanomas. Mizoe et al[111] from the National Institute of Radiological Sciences (NIRS) in Chiba, Japan, treated 8 patients with advanced inoperable salivary gland cancers with carbon ion therapy (64 GyE to 70.2 GyE in 16 to 18 fractions over 4 to 6 weeks). With a median follow-up of 90 months, they report 100% tumor control and no grade 3 or higher late morbidity. Similarly, Castro et al[112] from Lawrence Berkeley Laboratory treated 9 patients with inoperable salivary gland tumors with neon ions (8 patients) or helium ions (1 patient) (52 GyE to 70 GyE, 2 GyE per fraction, four fractions per week). With a median follow-up of 17 months, they reported a 78% tumor control rate, with no grade 3 or higher late effects. These results appear to be better when compared with the RTOG/MRC randomized trial comparing photons with neutrons,[113] but the series are small. Finally, Yanagi et al[114] from NIRS have treated 72 patients with mucosal malignant melanoma of the head and neck with carbon ions (52.8 GyE to 64 GyE in 16 fractions over 4 weeks). With a median follow-up of 49.2 months, they reported no grade 3 or higher late effects and a 5-year local control rate of 84.1%. The 5-year OS and cause-specific survival rates were 27% and 39.6%, respectively.

More developments are needed to fully benefit from these new sophisticated technologies. Challenges to treating the head and neck region with charged particle therapy include the presence of air cavities and dental restorations. Current treatment planning is limited by field size and the need to patch and match scattered proton or carbon ion beams. Full development of intensity-modulated proton and carbon ion pencil beam scanning is well under way, has been found to be feasible, and has been instituted in the clinic. Prospective clinical trials evaluating larger numbers of patients with long-term follow-up are needed to compare the outcomes of photons, protons, and carbon ions. Areas needing improvement to refine margins of coverage include immobilization devices, topographic and biologic tumor imaging to better define target volumes, and quantification of day-to-day anatomic variations occurring during the course of radiotherapy as a result of motion and changes in tumor and normal tissue volume.

Although results of IMRT and proton beam therapy are encouraging, the observation that most recurrences originate from the high-dose region indicates that radiation dose escalation with low LET irradiation alone will improve the tumor control outcome only for a subset of patients. Further advances in the treatment of solid tumors will likely come through application of newer knowledge about tumor biology, as

exemplified by translational research addressing the role of EGFR in tumor progression and as a target for therapeutic intervention and high LET irradiation.

BIOMARKERS AND MOLECULAR TARGETING

Progress in searching for useful markers for early detection of tumor, estimation of tumor burden, prediction of response to therapy, and monitoring of disease progression has been slow. However, some studies of head and neck carcinomas have generated optimism.

A review of the literature data up to a few years ago identified TP53, EGFR and one of its ligands, transforming growth factor-alpha (TGF-α), and cyclin D1 as promising prognostic biomarkers for HNSCC.[115-117] A few studies[118-120] corroborated the prognostic value of EGFR. A study using HNSCC specimens of patients enrolled in a Phase III trial of the RTOG[54] and randomized to receive standard irradiation,[120] for example, revealed no correlation between EGFR expression and T category, N category, American Joint Committee on Cancer (AJCC) stage grouping, and recursive partitioning analysis (RPA) classes[121] (r = –0.07 to 0.17). However, patients with more than median EGFR-expressing tumors, as measured using an image analysis-based immunohistochemical (IA-IHC) assay, were found to have significantly lower OS and PFS rates because of a significantly higher locoregional relapse rate. Multivariate analysis showed that EGFR expression was a strong, independent predictor of survival and of locoregional relapse.

A completed follow-up study, using a validation set of patients enrolled in the same trial, revealed high reproducibility of the IA-IHC assay and confirmed the absence of correlation between EGFR expression and tumor stage and other clinical prognostic variables (r = –0.20 to 0.18). The results validated previous findings that higher tumor EGFR expression predicted worse rates of OS, PFS, and locoregional relapse, with hazard ratios of 1.97, 2.15, and 3.12, respectively. However, the questions of whether EGFR predicts for the risk for metastasis and whether EGFR is a marker for tumor clonogen proliferation have not been resolved.

Recognition of the importance of the ERBB family of tyrosine kinase receptors in coregulating cell proliferation, death, and angiogenesis led to development of several strategies targeting the EGFR signaling pathway for cancer treatment. Two of these strategies, a monoclonal antibody (e.g., cetuximab) and small-molecule kinase inhibitors (e.g., gefitinib, erlotinib) have gone through various stages of preclinical and clinical development for several types of cancers. Several reviews summarize the status of these clinical investigations.[8,9,120,122] Randomized trials of treatment for colorectal adenocarcinoma[123] and HNSCC[124] showed that cetuximab given in combination with irinotecan or cisplatin yielded higher objective response rates (23% and 26%, respectively) than chemotherapy alone. However, the higher response rates for combined therapies have not translated into improved OS rates relative to monotherapy. Two Phase III trials enrolling patients with non–small cell lung cancer showed that gefitinib did not improve the response rate or survival rate when it was added to cisplatin-gemcitabine or carboplatin-paclitaxel doublets.[125,126]

In contrast to the results of combinations of EGFR antagonists with chemotherapy, data regarding the combination of cetuximab with radiotherapy in patients with locally advanced HNSCC are impressive. A completed international Phase III trial (IMCL CP02-9815) revealed that compared with irradiation alone, adding cetuximab to irradiation resulted in a significant improvement in OS and locoregional control rates without increasing mucositis or dysphagia.[127] These findings validate the notion that selective enhancement of the tumor response leading to durable locoregional control can be achieved by "designer drugs" targeting a specific molecular pathway.

Progress has been made in identifying prognostic markers in patients with NPC. The study of Chan et al[128] showed in a series of 170 patients that the posttreatment plasma level of Epstein-Barr virus (EBV) DNA was strongly correlated with PFS and OS rates, more so than the pretreatment titer. For example, the relative risk for NPC recurrence was 11.9% (95% CI, 5.53 to 25.43) for patients with a posttreatment EBV DNA titer, compared with 2.5% (95% CI, 1.14 to 5.7) for patients with higher pretreatment titers of EBV DNA. The positive and negative predictive values for recurrence for higher posttherapy EBV DNA were 83% (58% to 98%) and 98% (76% to 89%), respectively. NRG Oncology (NRG HN001) is evaluating this marker to see if it is useful in identifying high-risk patients for testing more aggressive therapy and monitoring their response to treatment. Eligible patients include those with detectable plasma EBV DNA before treatment. All patients will be treated with 69.96 Gy in 33 fractions with 6 weekly doses of cisplatin 40 mg/m^2. Plasma EBV DNA will be determined again 1 week after completion of treatment. Patients with undetectable plasma EBV DNA will undergo Phase III randomization to either observation or three cycles of cisplatin (80 mg/m^2) and 5-FU (1000 mg/m^2/d) for 4 days by intravenous continuous infusion every 28 days starting 4 weeks after completion of radiation therapy. Patients with detectable plasma EBV DNA will undergo Phase II randomization to either three cycles of cisplatin (80 mg/m^2) and 5-FU (1000 mg/m^2/d) for 4 days by intravenous continuous infusion or four cycles of gemcitabine (1000 mg/m^2) days 1 and 8 and paclitaxel (80 mg/m^2) days 1 and 8 every 21 days starting 4 weeks after completion of radiation therapy.

Tumor HPV status (HPV DNA and p16 expression) as a strong and independent prognostic factor for survival among patients with oropharyngeal cancer has been discussed.[44,45] This appears to be independent of treatment by radiotherapy alone or combined with concurrent chemotherapy.[129] It is possible that patients with HPV-positive tumors are being overtreated with concurrent irradiation and chemotherapy and are experiencing excessive toxicity despite an excellent prognosis. Current studies are evaluating dose de-escalation by reducing the radiotherapy dose, decreasing the cisplatin dose, or replacing cisplatin with cetuximab or some other biologically targeted agent. In the RTOG 1016 clinical trial, patients with HPV-related oropharynx cancer are randomly assigned to either accelerated RT to 70 Gy administered over 6 weeks with concurrent high dose cisplatin (100 mg/m^2) days 1 and 22 or the same IMRT with cetuximab (400 mg/m^2 loading dose pre-IMRT, then 250 mg/m^2 weekly during IMRT and for 1 week after IMRT). In the ECOG 3311 clinical trial, patients with HPV-related oropharynx cancer undergo transoral resection and neck dissection for T1-T2, N0-N2 disease. Low-risk patients (T1-T2, N0-N1, 0-1 positive nodes, negative margins) then undergo observation. Intermediate-risk patients (close margins [<3 mm], <1 mm extracapsular extension, and two to four positive nodes) are randomly assigned to receive either IMRT to 50 Gy in 25 treatments or IMRT to 60 Gy in 30 treatments. High-risk patients (positive margins, >1 mm extracapsular extension, or 5 or more positive nodes) receive IMRT to 66 Gy in 33 treatments with concurrent weekly cisplatin (40 mg/m^2). In the ADEPT clinical trial, coordinated by Washington University School of Medicine, patients with HPV-related oropharynx cancer undergo complete resection with negative margins by transoral surgery and neck dissection. Patients with positive nodes with extracapsular extension are

randomized to 60 Gy in 30 fractions either alone or with concurrent weekly cisplatin 40 mg/m^2.

PREVENTION OF HEAD AND NECK CANCERS

The concept of *field cancerization* was first described by Slaughter et al[130] in 1953 and has long been validated by clinical data. This evolving notion describes diffuse subcellular injury to the epithelium, resulting from interactions between prolonged carcinogen exposure and individuals' genetic profiles, rendering the whole anatomic field at risk for developing invasive cancers through stepwise, progressive accumulation of genetic alterations. It follows that an individual who develops and survives an upper aerodigestive cancer is at a higher risk (i.e., susceptible) for forming a second primary tumor in the same anatomic field during the ensuing years. The field cancerization and multistep carcinogenesis concepts form the basis for research on cancer chemoprevention.

Results of relatively large series revealed that patients cured of their first head and neck cancer had a more than 20% projected lifetime risk of development of a secondary primary tumor. The estimated annual secondary primary tumor development rate ranged from 4% to 6% for at least 8 years after the diagnosis of the first cancer.[131,132] A secondary primary tumor is the leading cause of death in patients with early head and neck cancers.[133]

This patient population has served as a model for addressing the efficacy of *adjuvant chemoprevention* regimens. An initial trial testing the role of *cis*-retinoic acid in preventing secondary primary tumors had yielded encouraging results.[134] Unfortunately, two large, multiinstitutional, randomized trials did not confirm its benefit.[135,136]

Leukoplakia and erythroplakia carry increased risk for transformation into squamous carcinomas. This patient subset has been used as a model to test *chemoprevention of malignant transformation*. The weaknesses of this model are that the natural history of leukoplakia is rather variable, with spontaneous improvement occurring in many cases, and that the malignant transformation rate at 8 years may vary from 18% to 36%, depending on the degree of dysplasia observed histologically.[137] Consequently, large series and prolonged follow-up studies are required to properly test the efficacy of a given primary chemoprevention strategy.

Identification of key genetic changes resulting in development of malignant clones and markers of multistep carcinogenesis will aid in selecting patients with the highest risk for enrollment into chemoprevention trials and thereby in reducing the required sample size. Markers can also serve as intermediate, surrogate endpoints for assessing the efficacy of chemoprevention regimens, and thereby, shorten the length of the required follow-up. Physicians can counsel their patients regarding healthy lifestyle choices, such as abstaining from using tobacco products and alcohol or from engaging in early-age sexual activity with multiple partners (including oral sex practices) and receiving the HPV vaccine. They can also advise them to practice good oral hygiene and eat a diet rich in fresh fruits and vegetables.

SUMMARY

The past two decades have been an exciting era for participation in clinical trials and laboratory research that have produced gratifying progress in understanding and treating head and neck cancer. Advances in molecular biology techniques opened new research avenues yielding new concepts and knowledge, such as the multistep tumor progression model, genetic susceptibility to environmental carcinogen-induced tumorigenesis, processes of virus-induced changes in cellular behavior, and factors and mechanisms governing the radiation response of cells and tissues. Some of the wisdom gained has already found applications in developing novel therapy strategies that have completed or are undergoing preclinical and clinical testing. Examples include altered photon fractionation regimens, charged particle therapy, mechanism- or molecular-oriented combined-therapy modalities, and conformal radiotherapy with photons and charged particles. The basic and translational research efforts have paid off in that the head and neck cancer mortality rate in the United States has declined since the inception of record keeping. For example, the annual death rate for men because of oral cavity and pharyngeal cancers in the United States decreased by an average of 1.9%, 3%, and 1.2% between 1975 and 1993, between 1993 and 2001, and between 2001 and 2010, respectively.[1]

It is likely that the pace of discovery will increase in the coming years. Sensitive methods for detecting occult tumor foci for screening and staging purposes will be developed, and new approaches in characterizing the genetic profile of cancers will accurately depict their individual virulence, predict the therapy response, and guide treatment selection. Optimism about developing rational novel therapy strategies aimed at specific molecular targets to prevent malignant transformation or reverse malignant phenotyping is also increasing. The insights and new technologies gained from further research should have a sizable impact in reducing the mortality rate caused by head and neck cancers.

The accelerated pace of new discoveries and the large number of research directions make it increasingly complex to determine what constitutes the standard therapy for a variety of patient subsets. When several treatment options can yield approximately the same locoregional tumor control rate, other determinants to be taken into account in selecting the treatment of choice include cosmetic and functional outcome, acute and long-term morbidity (quality of life), resource utilization (cost), physician expertise, patient convenience, out-of-pocket costs (transportation, time off work for the patient, family members, and friends, indirect medical costs), and patient preference.

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CHAPTER

32 Oral Cavity



William M. Mendenhall, Robert L. Foote, Pamela L. Sandow, and Rui P. Fernandes

INCIDENCE

For 2015, there were 30,260 estimated new cases and 5990 estimated deaths.

BIOLOGIC CHARACTERISTICS

The natural history of oral cavity carcinoma depends on its anatomical site, histologic type, and stage of the tumor.

STAGING EVALUATION

A physical examination should be performed to determine the location and extent of the primary tumor and to assess for presence and extent of nodal involvement.

Computed tomography (CT) scanning will help to determine the extent of the tumor (particularly, deep invasion), detect bone invasion (CT plus panoramic x-ray film [Panorex] view) and to assess regional lymph nodes; for retromolar trigone lesions, magnetic resonance imaging (MRI) is useful to assess muscle invasion; and chest radiograph to detect pulmonary metastases. The routine use of positron emission tomography (PET) is not recommended.

PRIMARY THERAPY

For early disease (T1 to early T2 lesions), single modality surgery or radiotherapy (RT) can achieve excellent local control and survival in most oral cavity sites (85% to 90%). The treatment choice is predicated on function and treatment side effects.

Moderately advanced (large T2-early T3) lesions are treated with RT alone or surgery plus irradiation with moderate local control (60% to 80%).

LOCALLY ADVANCED DISEASE

Locally advanced disease (large T3 to T4 lesions), combined RT plus surgery is indicated in most sites because single modality disease control is poor (≤30%). RT alone or combined with concomitant chemotherapy likely results in a lower probability of cure.

For locally recurrent cancers seen after the primary tumor has been treated with surgery alone, salvage with surgery is appropriate, followed by postoperative RT, RT with or without chemotherapy, or palliative RT. Reirradiation may be considered if a recurrence is low volume, unifocal, or as a result of low dose or a marginal miss. It may also be considered for a T1-T2N0 metachronous second primary that is not amenable to surgery.

Locally recurrent cancers that occur after definitive RT alone or combined with chemotherapy can be managed with surgical salvage, palliative chemotherapy, or supportive care.

PALLIATION

Moderate dose palliative RT can be given as 30 Gy in 10 fractions over 2 weeks or 20 Gy in 2 fractions with a 1 week interfraction interval.

The estimated number of newly diagnosed oral cancers in 2015 is 30,260.[1] The estimated number of deaths is 5990.

The oral cavity consists of the lip, floor of mouth, oral tongue (the anterior two thirds of the tongue), buccal mucosa, upper and lower gingiva, hard palate, and retromolar trigone. The frequency of involvement of various locations is shown in Table 32-1.[2] After a general discussion of etiology and epidemiology, issues relative to the various subsites will be presented separately. A discussion of preradiotherapy and postradiotherapy dental care is included.

ETIOLOGY AND EPIDEMIOLOGY

Oral cavity cancer is predominately a disease of middle-aged men who use tobacco and alcohol. Approximately 95% of carcinomas appear after age 45 with an average age of 60 years.[2] The use of tobacco in any form is associated with an increased risk of oral cancer.[3-5] Some evidence suggests that patients with oral cavity cancer who continue to smoke during RT have poorer outcomes.[6] The risk of tobacco-related cancers of the upper aerodigestive tracts declines among former smokers after 5 years and after 10 years of abstention the risk may approach that of nonsmokers.[7] Although the effects of alcohol and tobacco in inducing cancers of the upper aerodigestive tract seem to be additive, the risk of alcohol consumption without tobacco use is unclear. Some studies indicate a slightly increased risk with alcohol use in the absence of tobacco, whereas others show no apparent increased risk.[8,9]

Human papillomavirus (HPV) infection, marijuana smoking, betel quid use, and drinking the beverage "mate" have also been implicated as causative agents in the formation of squamous cell carcinomas of the upper aerodigestive tract.[10-13] In recent years, oral cancers have increased among relatively young females who have never consumed alcohol or smoked. The reason for this is unclear.[14]

Smokeless tobacco (snuff) can promote carcinomas of the buccal gingival sulcus, which are diagnosed most often in older, white women living in the southeastern United States. Carcinoma of the buccal mucosa is also associated with chewing tobacco. It is commonly seen in the southeastern United States, with a male to female ratio of 3 or 4 to 1.[15] Leukoplakia is seen with oral carcinoma in approximately 15% of cases.[16]

Persons with a "Scotch-Irish" complexion (red hair and blue eyes) or prolonged exposure to sunlight are most susceptible to lip carcinoma.[17] In one series, 82% were previous or present tobacco smokers.[18] Pipe smoking is an alleged risk factor, but this has not been substantiated by most studies. Lip cancer is often associated with poor dental hygiene or edentulous patients.[18,19] Lip trauma and a history of alcohol abuse

TABLE 32-1 Distribution of Oral Cavity Cancer: 14,253 Cases

Site	Percentage
Lower lip	38
Tongue	22
Floor of mouth	17
Gingiva	6
Palate	6
Retromolar trigone	5
Upper lip	4
Buccal mucosa	2

Reprinted from Krolls SO, Hoffman S: Squamous cell carcinoma of the oral soft tissues: A statistical analysis of 14,253 cases by age, sex, and race of patients. J Am Dent Assoc 92:571, 1976.

are also related factors.[18] Most cases appear after age 40 years, but approximately 10% occur before age 40 and a few before age 30 years. This disease is uncommon in blacks.

PREVENTION AND EARLY DETECTION

This information on prevention and early detection is of major importance for patients with oral cavity cancers. It is covered in the Part B Overview, "Head and Neck Tumors," by Robert L Foote and K. Kian Ang; it will not be reiterated here.

ORAL CARE

A complete dental examination should be performed on all patients, whether dentate or edentulous, before irradiating any portion of the mandible or maxilla. The radiation oncologist should inform the patient's dentist of the anticipated RT treatment plan, including dose and location of the RT fields. To make appropriate pretherapy recommendations, the dentist should be familiar with possible post-RT complications, such as caries and osteoradionecrosis. There is a lifelong risk of impaired healing that can lead to osteoradionecrosis, especially when teeth are extracted from hypovascularized and hypocellular bone.[20] Therefore, one objective of the pretherapy oral evaluation is to determine whether teeth in the proposed irradiated area can be reasonably maintained in a healthy state for the remainder of the patient's life.

Medical, dental, and psychosocial issues that affect a person's future dental health should be assessed at the pretherapy evaluation. The patient's compliance, motivation for daily oral hygiene procedures, dental awareness, and access to dental care are predictors of dental health. A panoramic radiograph, intraoral radiographs, and hard and soft-tissue examinations should be performed to identify high-risk dental factors such as deep caries, nonrestorable teeth, root tips, bony pathology, endodontically treated teeth, periapical and pulpal pathology, and nonfunctional teeth. Teeth exhibiting periodontal disease should be evaluated to determine their long-term prognosis. Some prognostic factors for poor periodontal health include probing depths more than 6 mm, gingival recession, furcation involvement, or mobility.[21,22] Because of the numerous reported cases of progression of gingival recession and periodontal disease after RT, it may be difficult to assess the longevity of each tooth.

To reduce the future risk of osteoradionecrosis, teeth with high-risk dental factors should be removed before the patient receives doses of more than 55 Gy.[21] Whether extraction of teeth with moderate disease is indicated remains controversial. If the patient has poor resistance to dental disease or an unwillingness to perform routine dental care or fluoride applications, pretherapy extraction of moderately diseased teeth may be justified. A healing time of 14 to 21 days is recommended after extraction, before initiating of RT.[20] Extraction should be accomplished as atraumatically as possible, with alveoloplasty to remove sharp, bony projections. The dentist should coordinate dental appointments with the radiation oncologist to minimize the delay in cancer therapy. However, extraction of healthy teeth does not reduce the risk of osteradionecrosis and should be avoided.[23]

Denture adjustments, smoothing edges of sharp teeth, dental cleaning, and oral hygiene instruction can be accomplished at the pretherapy dental visit. Ill-fitting dentures that irritate mucosal surfaces should be worn with caution during RT. Daily disinfection of dental prostheses is recommended.

Impressions for custom fluoride trays can be made before or within the first 2 weeks of RT. Patients who receive RT to major salivary glands are at lifelong risk for rampant caries. Daily use of 0.4% stannous fluoride or 1.1% sodium fluoride gel for 5 minutes each evening before sleep, in custom trays, is imperative as long as natural teeth remain. Patients should be advised to refrain from rinsing, eating, or drinking for 30 minutes after fluoride application. The dentist and radiation oncologist should consistently promote proper oral hygiene and use of fluoride throughout the posttreatment years.

Clinical practice guidelines for the treatment of cancer therapy-induced oral mucositis have been published.[24] RT-induced mucositis cannot be prevented; however, excellent oral hygiene can reduce the risk of oral infections. Supersoft toothbrushes and mild toothpastes are available for patients to facilitate proper oral hygiene during and after RT.

Consultation with the radiation oncologist is required before postirradiation extraction of teeth or invasive procedures that involve the exposure of irradiated bone. Preextraction and postextraction hyperbaric oxygen therapy may be indicated to promote healing of extraction or surgical sites.

Patients should be closely monitored for possible late effects of RT to oropharyngeal regions. Trismus, xerostomia, caries, and oral candidiasis can persist or occur at any time after treatment is completed.

MOLECULAR BIOLOGY

A discussion of the molecular biology of head and neck cancers is found in the Part B Overview, "Head and Neck Tumors" preceding this chapter.

LIP CANCER

Anatomy

The lips are composed of the orbicularis oris muscle that surrounds the mouth and is covered externally by skin and internally by mucous membrane. The upper and lower lips are attached to the gingiva by raised folds of mucous membrane called the *labial frenula*. The vascular supply is from the superior and inferior labial branches of the facial arteries. The sensory nerve of the upper lip is the infraorbital nerve; the mental nerve provides sensory innervation for the lower lip.

Lymph vessels from both lips drain into the submandibular lymph nodes (level Ib). In addition, lymph from the central part of the lower lip drains into the submental lymph nodes (level Ia). The submental nodes (level Ia) drain either to the submandibular lymph nodes (level Ib) or to the jugulo-omohyoid node (level II). The submandibular lymph nodes drain to the deep cervical chain of lymph nodes (levels II to IV).[25]

Pathology and Patterns of Spread

The most common neoplasms are moderately to well differentiated squamous cell carcinomas; approximately 5% are poorly differentiated.[26] Basal cell carcinomas usually arise on the skin above or below the lip and invade the vermilion border but rarely arise from the vermilion border. Squamous cell carcinomas start on the vermilion of the lower lip and less commonly on the upper lip. The commissure is rarely the site of origin. Leukoplakia is a common problem on the lower lip and may precede carcinoma by many years.[16]

Early lesions can initially invade adjacent skin and the orbicularis oris muscle. Advanced lesions can invade the adjacent commissures of the lip and buccal mucosa, the skin and wet mucosa of the lip, the adjacent mandible, and eventually the mental nerve. The incidence of perineural invasion is approximately 2%.[27] Lymph node involvement at presentation occurs in approximately 5% to 10% of patients. An additional 5% to 10% of patients with a clinically negative neck subsequently develop lymph node metastases. The risk of lymph node involvement increases with depth of invasion, poor differentiation, larger lesions, invasion of the commissure, and recurrence after prior treatment.[19]

Hendricks et al[28] from the Mayo Clinic reported the following incidence of positive cervical lymph nodes by T stage: T1, 2%; T2, 9%; and T3, 30%. The overall incidence of adenopathy was 19% when the commissure was involved.[26] De Visscher et al[29] reported a nodal recurrence rate of 5.4% after primary surgical resection in 184 patients with squamous cell carcinoma of the lower lip. Ninety-three percent of lesions were stage I at presentation.

Clinical Manifestations and Staging

Carcinoma of the lip usually presents as a slowly enlarging exophytic lesion with an elevated border. Occasionally there is minor bleeding. Erythema of the adjacent skin may suggest dermal lymphatic invasion. Anesthesia or paresthesia of the skin indicates perineural invasion.[30]

The American Joint Committee on Cancer (AJCC) staging for lip cancer applies to lesions arising from the vermilion surface (Table 32-2).[31]

TABLE 32-2 American Joint Committee on Cancer: Oral Cavity Primary Tumor Staging

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Tumor 2 cm or less in greatest dimension
T2	Tumor more than 2 cm but not more than 4 cm in greatest dimension
T3	Tumor more than 4 cm in greatest dimension
T4 (lip)	Tumor invades through cortical bone, inferior alveolar nerve, floor of mouth, or skin of face (i.e., chin or nose)
T4 (oral cavity)	Tumor invades through cortical bone into deep (extrinsic) muscle of tongue (genioglossus, hyoglossus, palatoglossus, and styloglossus), maxillary sinus, or skin of face
T4b	Tumor involves masticator space, pterygoid plate, or skull base or encases internal carotid artery

Reprinted from the American Joint Committee on Cancer: Lip and oral cavity. In Edge SB, Byrd D, Compton CC, et al, editors: AJCC cancer staging handbook, ed 7, Chicago, 2010, Springer, pp 49–61.

Early lip cancers rarely require diagnostic imaging. Locally advanced, deeply infiltrating, or recurrent carcinomas may benefit from a CT scan or panoramic x-ray film to evaluate possible bony invasion and regional nodal spread.

Treatment

Early Lesions (<2 cm)

The majority of these lesions can be surgically excised with primary closure as an outpatient procedure. Surgery is satisfactory if the lip commissure does not need to be resected, and if the resulting aperture of the oral cavity permits the insertion of dentures. Postoperative RT is recommended for positive margins or perineural invasion.[27,33,34]

Tumors that should be treated with RT include those involving a commissure to obtain better cosmesis and improved local control.[35] The uncommon, poorly differentiated lesions are also preferably treated by RT to cover a more generous treatment volume and the first echelon lymph nodes. An algorithm for treatment planning is shown in Figure 32-1.

Moderately Advanced Lesions (2 cm to 4 cm)

The length of the lower lip is approximately 7 cm. Removal of more than half of the lower lip with simple closure produces a poor cosmetic and functional result so that a reconstructive procedure is usually necessary. In these cases, RT has the advantage of a better functional and cosmetic result. Traditionally, the reconstructed lip may look normal in a photograph, but it may lack sensory and motor innervation as well as elasticity. However, there have been recent improvements in the functional and cosmetic results of various reconstructive surgical procedures.[36-38]

Stranc et al[35] studied lip function in 37 patients after surgery (19 cases) or RT (18 cases) and compared them to normal controls. Compared with surgery, RT produced better preservation of lip sensation, intercommissural distance, and elasticity. Inadequate lip seal was observed in 2 of 18 patients (11%) after RT compared with 8 of 19 patients (42%) treated surgically.

Teichgraeber and Larson reviewed the M. D. Anderson Hospital experience for patients with lip cancer involving the commissure.[39] Of the 22 patients with T2 lesions who were treated with surgery, 10 patients (45%) had recurrence. There are no data for commissure involvement treated with RT, but the relative ease of RT and the cosmetic and functional results lead us to recommend RT for lesions exhibiting this pattern of spread.

Locally Advanced Lesions (>4 cm)

Large lesions are managed by resection and postoperative RT.[34] Erythema of the skin adjacent to the lesion may indicate dermal lymphatic involvement; wide-field irradiation is recommended followed by consideration of surgical resection depending on the response to RT. Management by definitive radiotherapy and concomitant chemotherapy is generally preferred in patients who are not surgical candidates.

Management of the Neck

Regional lymphatics are not electively treated for T1 and T2 lesions unless perineural invasion or commissure involvement is present. Patients with advanced (>4 cm), poorly differentiated, or recurrent tumors often require elective neck treatment. Other factors associated with an increased risk of nodal spread include perineural invasion, maximal thickness more than 6 mm, or low p27Kip1 protein expression.[40] The decision to employ elective neck irradiation or elective neck dissection depends on the modality selected for treatment of the primary tumor.

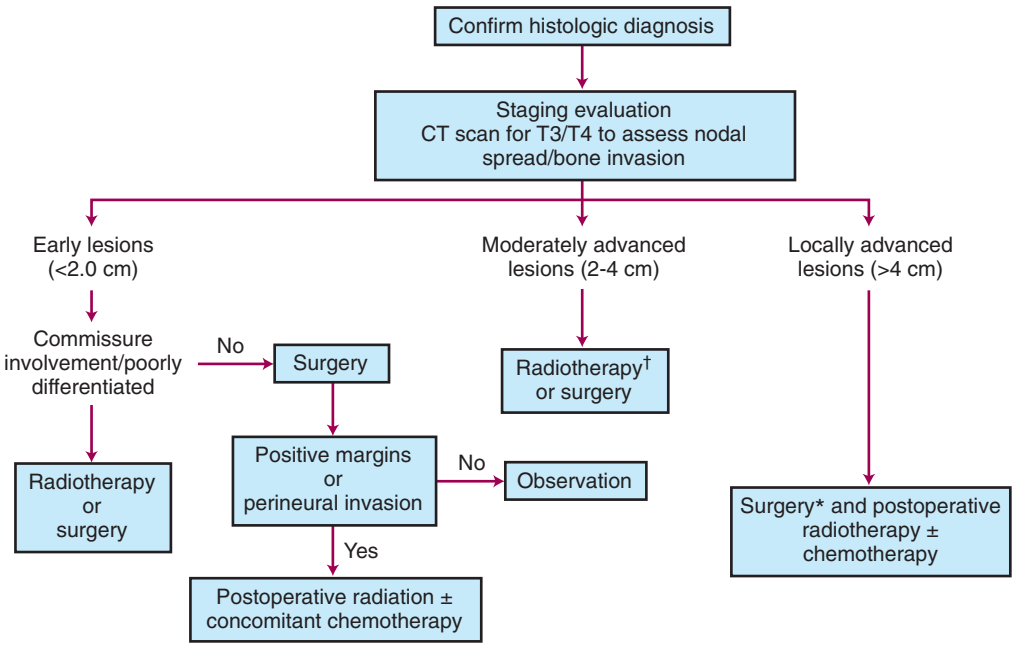


Figure 32-1 Treatment algorithm for de novo lip cancer. *Treat neck (neck dissection or radiotherapy).[28] †If poorly differentiated, dermal or commissure involvement.[26]

TABLE 32-3 Lip Carcinoma Treated with Interstitial Radiotherapy (N = 869 Patients)

Category	Local Recurrence Rate (5-year, %)	Survival Rate (5-year, %)
T1	7.4	99.5
T2	12.7	97.4
T3	26.4	81.4

Data from Jorgensen K, Elbrond O, Andersen AP: Carcinoma of the lip. A series of 869 patients. Acta Otolaryngol (Stockh) 75:312–313, 1973.

Results

T1 to T3 Lesions

Interstitial Irradiation with or without External Beam Irradiation (EBRT)

Jorgensen et al[41] reviewed 869 patients with squamous cell carcinoma who were treated with an interstitial radium implant alone; 90% of the lesions were less than 2 cm in size. The local recurrence and survival rates are shown in Table 32-3; 99% of the primary tumors were ultimately controlled with RT alone or combined with salvage surgery. Thirty-eight percent of patients with T3 tumors who developed a local recurrence developed lymph node metastases. Only 4% of patients died of lip cancer. Twenty-nine complications arose, of which two were bone necrosis.

Pierquin et al[42] reported on 50 patients with carcinoma of the lower lip treated with brachytherapy. Only one local recurrence (2%) was observed.

McKay and Sellers[26] reviewed 2854 patients; 92% of whom were initially treated with brachytherapy and EBRT. The primary lesion was controlled in 84% of the cases; 8% were salvaged later for an overall local control rate of 92%. Regional control was achieved in 58% of patients who presented with positive nodes. However, the ultimate rate of neck control was only 35% when neck nodes appeared at a later date. The cause-specific and absolute 5-year survival rates were 89% and 65%, respectively.

Tombolini et al[43] reported on 57 patients with squamous cell carcinoma of the lower lip treated with low-dose rate brachytherapy alone. Patients with clinically positive neck nodes received EBRT to the involved side of the neck. International Union Against Cancer (UICC) T stages were T1 in 27 cases (47%), T2 in 20 cases (35%), and T3 in 10 cases (18%). The 5-year local control rate was 90%.

Orrechia et al[44] treated 47 patients with T1 (n = 21) and T2 (n = 26) lip cancers with iridium-192 (^{192}Ir) brachytherapy. The 5-year and 10-year disease-free survival (DFS) rates were 92% and 85%, respectively.

Guinot et al[45] treated 39 patients with lip carcinoma using high dose rate brachytherapy twice daily to total doses ranging from 40.5 Gy to 45 Gy and observed a 3-year local control rate of 88%. Acute and chronic reactions were similar to those observed after low-dose rate brachytherapy.

Petrovich et al[46] reported on 250 patients with lip cancer treated with RT; half were treated with brachytherapy and the remainder with EBRT. Two hundred forty-seven patients (99%) had squamous cell carcinomas and 240 patients (96%) had lower lip carcinomas. The incidence of lymph node metastasis was 9%. Eleven percent experienced recurrences after RT and half were salvaged; 18 patients (7%) died of lip cancer. Moderately advanced tumors and tumors near the commissures were best treated with EBRT.

EBRT or Surgery

Babington et al[34] reported on 130 patients with lip carcinoma; 75% had T1 tumors. Initial treatment consisted of surgery (39%), RT (48%), or both (13%). Close (≤2 mm) or positive margins were observed in 27% of those treated surgically. The 2-year relapse-free survival rates were 82% and 54% after RT and surgery, respectively ($p < 0.001$). The recurrence rate after surgery was significantly higher for those with close or positive margins.

Baker and Krause[18] reported on 279 patients treated with either RT (47%) or surgery (53%) at the University of Michigan

TABLE 32-4 Carcinoma of the Lip—University of Michigan (*N* = 279 Patients)*

Extent of Primary Lesion	Patients	Local Recurrence (%)	5-Year Survival (%)	
			Cause-Specific	Absolute
<1 cm	85	10.6	100	76
1 to 3 cm	154	9.1	92	71
>3 cm	29	20.7	71	52
Bone invasion	11	90.9	50	45

Modified from Baker SR, Krause CJ: Carcinoma of the lip. Laryngoscope 90:19–27, 1980.
**Treated by radiotherapy, 47%; treated by surgery, 53%.*

(Table 32-4). There was no difference in the 5-year cause-specific survival (CSS) rates between the two groups. Patients with positive regional nodal metastases had a 5-year CSS of 29%. Regional lymph node metastases developed in 31% of those treated for locally recurrent lesions, indicating the need for elective neck treatment for this subset of patients.

De Visscher et al[29] treated 184 patients with squamous cell carcinoma of the lower lip surgically; 93% had stage I cancers. The local and regional recurrence rates were 4.9% and 5.4%, respectively.

Mohs's Surgery

Mohs and Snow[47] reported on 1148 patients with squamous cell carcinomas of the lower lip treated with microscopically controlled surgery. The 5-year local control rates were 94.2% for those with T1 lesions and 59.6% for patients operated on for T2 lesions. The 5-year local control rates were 96.3% for well to moderately differentiated tumors compared with 66.7% for those with poorly differentiated cancers.

Holmkvist and Roenigk[48] reported on 50 consecutive patients with of squamous cell carcinoma of the lip treated with Mohs micrographic surgery (MMS). Four patients (8%) experienced a recurrence; all were successfully salvaged with additional MMS. The average time to recurrence after the initial MMS was 2.5 years. Hruza[49] also reported a relatively long interval between MMS and initial recurrence, with 20% of recurrences developing after 5 years.

T4 Lesions

Cancers that present with bone or nerve involvement are usually treated with a combination of surgery and EBRT. There are limited data pertaining to the local control rates after RT or surgery alone, ranging from 0% to 74%[26,45]; therefore, combined treatment is usually recommended. Byers et al[27] observed that 80% of patients with histologically proven perineural invasion developed cervical node metastases. Eight of 25 patients (32%) in their series who presented with either perineural invasion, tumors larger than 3 cm, or regional metastases died of disease.

The postoperative EBRT portals should include the primary site as well as the regional lymphatics (levels IA, IB, and II). The low neck is usually treated to doses sufficient for subclinical disease, and doses are frequently higher in patients with positive nodes. The total dose ranges from 60 Gy to 70 Gy, at 2.0 Gy per once-daily fraction to the primary site, depending on the pathologic findings. Higher doses with altered fractionation schemes (e.g., 74.4 Gy at 1.2 Gy per fraction twice daily), as well as concomitant chemotherapy should be considered in patients with positive margins or other high-risk factors such as extracapsular extension.[50-55]

Recurrent Lesions

Cross et al[19] reported on 563 patients treated with surgery for recurrent lip cancer. The prognosis was particularly poor for those with high-grade tumors of whom 16.7% were salvaged compared with 31.8% and 42.9% for those with well and moderately differentiated cancers, respectively. Holmkvist and Roenigk[48] reported on four patients treated with MMS; all four were salvaged.

Techniques of Irradiation

EBRT is usually delivered with either orthovoltage x-rays or electron beam. The electron beam energy depends on the tumor thickness. Lead shields are placed behind the lip to limit the dose to the oral cavity and mandible. Orthovoltage fractionation schedules range from 40 Gy to 45 Gy in 3 to 4 weeks for smaller lesions, and 50 Gy to 63 Gy in 4 to 7 weeks for moderately advanced lesions. The dose is increased 10% to 15% for electron beam RT to account for differences in the relative biological effectiveness. Orthovoltage x-rays are preferred, if available, because the maximum dose is at the surface and there is less beam constriction compared with electron beam.

An appositional field with a margin of 1 to 1.5 cm is sufficient for most small to moderately advanced lesions if orthovoltage irradiation is used. The field borders are determined by bimanual palpation. Because of beam constriction, 2.0-cm to 2.5-cm margins are necessary if an electron beam is employed. A lead shield is used to collimate the beam at the skin/lip surface.

Brachytherapy may be used as the sole treatment or in conjunction with EBRT. Implantation is usually performed under local anesthesia using ^{192}Ir sources and a single-plane plastic tube technique. The sources are arranged horizontally 10 mm to 12 mm apart with crossing sources on the lateral aspects of the implant. Three to five horizontal sources are used depending on the size of the lesion. The advantage of the plastic tube technique is that the volume of the implant is more easily adapted to the extent of the tumor and the commissure is readily included, if necessary. A gauze roll is placed between the lip and gum to increase the distance between the radioactive sources and the alveolar ridge. The recommended dose is 60 Gy to 70 Gy at a dose rate of 0.4 Gy to 0.5 Gy per hour for an implant alone. Large infiltrative lesions may be first treated with EBRT, 30 Gy at 2.5 Gy per fraction to shrink the tumor, followed by interstitial brachytherapy boost to deliver an additional 35 Gy to 40 Gy. Treatment of lip cancer with high-dose rate (HDR) interstitial needles is advocated by some.[45]

T3 and T4

Low-volume T3 cancers may be treated with primary RT, preferably combining EBRT to the primary lesion and neck followed by a brachytherapy boost. EBRT is administered with parallel-opposed fields, including the lip lesion and the level I and II lymph nodes (Figure 32-2).[56] A cork is placed in the mouth to displace the maxilla and upper lip and reduce the volume of normal tissues included in the fields. A separate anterior field is used to treat the levels III and IV lymph nodes with a tapered midline block over the larynx. The supraclavicular lymph nodes are at low risk and are not included in

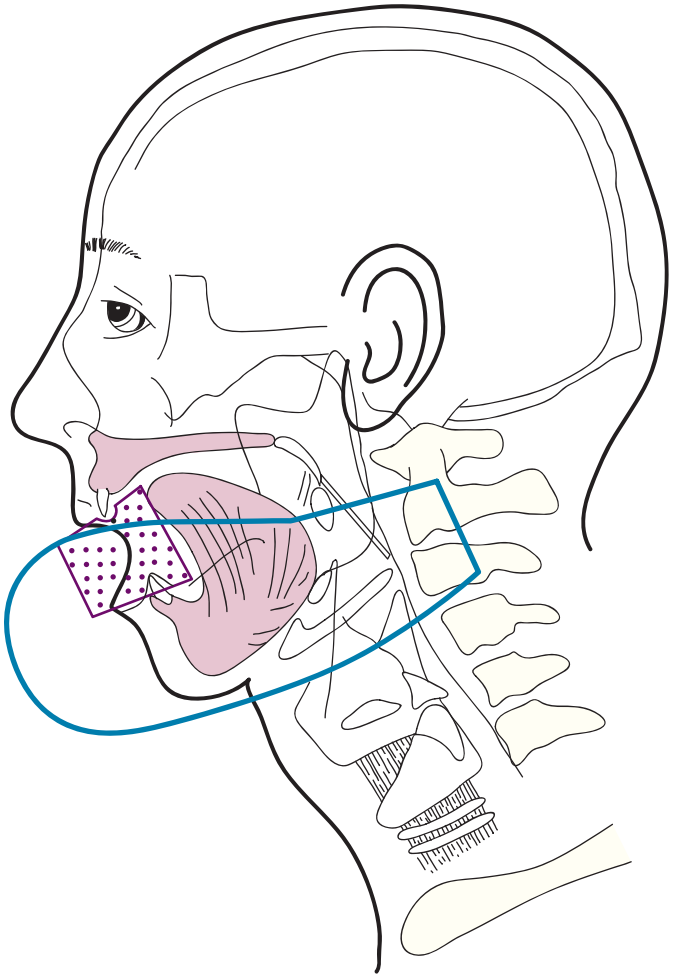


Figure 32-2 Parallel-opposed fields used to treat a carcinoma of the lower lip in conjunction with the levels I and II lymph nodes. *(From Mendenhall WM: Radiotherapy for cancer of the lip: treatment technique. In Werning JW, editor: Oral cancer, New York, 2005, Thieme Medical Publishers Inc.)*

the fields. Both sides of the neck are treated with RT because it is unlikely that T3 and T4 primary lesions would be well lateralized.

The junction between the parallel-opposed fields and the low-neck field is at the thyroid notch. The dose fractionation schedule used varies from 38.4 Gy at 1.6 Gy twice daily to 50 Gy at 2 Gy per fraction once daily, followed by a brachytherapy boost. Low-energy photons such as 4 MV or 6 MV beams are recommended.

High-volume T3 and T4 cancers are unlikely to be cured with RT alone and are better treated with surgery and postoperative RT. RT fields are similar to those used to treat patients with RT alone. A petroleum jelly gauze bolus is placed over incisions to ensure the surface dose is adequate. The fields are extended to the skull base along the course of the third division of the fifth cranial nerve if perineural invasion is present. The dose depends on the surgical margins: negative (R0), 60 Gy; microscopically positive (R1), 66 Gy; and gross residual disease (R2), 70 Gy. Patients are treated once daily at 2 Gy per fraction, 5 days a week, in a continuous course. Intensity modulated radiotherapy (IMRT) may be employed to limit the dose to one or both parotid glands to a mean dose of ≤26 Gy to reduce long-term xerostomia if this can be done without jeopardizing target coverage.

Complications

After RT, there is gradual atrophy of the irradiated tissues. The irradiated lip must be protected from sun exposure by use of hats and ultraviolet protectants. Because the anterior teeth and gingiva are protected by lead shields when radiation is given by EBRT, radiation caries, bone exposure, and osteoradionecrosis are uncommon.

Fitzpatrick[57] reported a 3.3% incidence of late complications that required surgical intervention. Orrechia et al[44] observed a 10.6% incidence of mucosal necrosis after RT for 47 T1 and T2 lip cancers treated with ^{192}Ir brachytherapy. The risk of late complications increased with dose, dose per fraction, and volume.

FLOOR OF MOUTH

Anatomy

The floor of the mouth is a semilunar space overlying the mylohyoid and hyoglossus muscles, extending from the inner surfaces of the mandibular alveolar ridge to the ventral surface of the oral tongue. Its posterior boundary is the base of the anterior tonsillar pillar; it is bisected anteriorly by the frenulum of the tongue. The mylohyoid muscle arises from the mylohyoid ridge of the mandible and is the muscular floor of the oral cavity. The posterior insertion is at the level of the third molars.

The submandibular glands lie along the body of the mandible. The inferior aspect of the gland extends below the inferior edge of the mandibular arch; part of the gland is superficial to the mylohyoid muscle. The submandibular gland is palpable as a soft mass over the posterior portion of the mylohyoid muscle when the muscle is tensed by forcing the tip of the tongue against the maxillary incisor teeth.

The submandibular duct (Wharton's duct) is approximately 5 cm long and arises from the portion of the gland that lies between the mylohyoid and hyoglossus muscles. The duct passes deep and then superficial to the lingual nerve and exits in the anterior floor of the mouth near the midline.

The sublingual glands are the smallest of the major salivary glands and are the most deeply situated. Each lies in the floor of the mouth between the mandible and the genioglossus muscle.

The first echelon nodes for the floor of mouth are the submandibular lymph nodes (level IB), which may be stratified into preglandular, intraglandular, and postglandular groups. Lymph may also drain into the submental (level IA) nodes. These lymph nodes eventually drain to the jugulo-omohyoid (level II) nodes.[25]

The lingual nerve is a branch of the mandibular nerve and provides the sensory innervation to the floor of the mouth. It enters the mouth between the medial pterygoid muscle and the ramus of the mandible and passes anteriorly under the oral mucosa medial to the third mandibular molar.

The hypoglossal nerve (cranial nerve XII) is the motor nerve of the tongue. It passes anterior to the inferior aspect of the hyoglossus muscle and then to the lateral aspect of the genioglossus muscle. Injury to the hypoglossal nerve results in paralysis and atrophy of the ipsilateral oral tongue. The tongue deviates to the paralyzed side on protrusion because of the unopposed contralateral genioglossus muscle.

Pathology and Patterns of Spread

Most floor-of-mouth neoplasms are squamous cell carcinomas; most are moderately differentiated. Adenoid cystic and mucoepidermoid carcinomas arise from the minor

salivary glands and account for 2% to 3% of floor-of-mouth tumors.

Most floor-of-mouth carcinomas are located in the anterior midline adjacent to Wharton's ducts. Extension toward the gingiva and periosteum occurs early and frequently.

Small to moderate size (stage T1 and T2) lesions are associated with metastases to the ipsilateral regional lymph nodes in 15% to 38% of cases, depending on the size and depth of invasion of the primary tumor.[58-60]

Mohit-Tabatabai et al[61] reviewed 84 patients with squamous cell carcinoma of the floor of the mouth and concluded that lesion thickness was related to the probability of subclinical cervical metastases in clinically node negative (N0) patients (Table 32-5). Patients with a primary lesion more than 1.5 mm thick had a 20% or higher risk of lymph node metastases.[61] Histologic grade and configuration of the primary lesion did not have a statistically significant correlation with subsequent development of neck node metastases. O'Brien et al analyzed the impact of tumor thickness on the incidence of regional lymph node metastases and found that the risk increased significantly for lesions 4 mm or more in thickness.[59] The reported incidence of recurrence in the untreated clinically negative neck varies from 20% to 35%.[60,62] Histologic grade and extent of vascular and perineural invasion have been implicated as predictors of lymph node spread.[63]

The distribution of clinically positive neck nodes at diagnosis is shown in Figure 32-3,[64] and the distribution of pathologically positive nodes after elective neck dissection in 62 patients with carcinoma of the floor of the mouth is shown in Figure 32-4.[65] The incidence of positive lymph nodes was 19% for those with T1 or T2 lesions and 26% for patients with T3 or T4 cancers.

TABLE 32-5 Floor-of-Mouth Carcinomas: Correlation of Primary Tumor Thickness with Neck Failure*

Thickness (mm)	T1N0	T2N0
0.1 to 1.5	1/38 (3%)	0/19
1.6 to 3.5	1/5 (20%)	3/7 (43%)
≥3.6	7/11 (64%)	2/4 (50%)

Reprinted from Mohit-Tabatabai MA, Sobel HJ, Rush BF, et al: Relation of thickness of floor of mouth stage I and II cancers to regional metastasis. Am J Surg 152:351–353, 1986.
**Number of treatment failures/total number of patients.*

Clinical Manifestations, Patient Evaluation, and Staging

Floor-of-mouth carcinomas usually present as slightly elevated mucosal lesions with well-defined borders. A background of leukoplakia may be present. The lesions are often diagnosed by a dentist or physician during a routine physical examination.

T1 and T2 tumors may be noted initially when the patient feels a lump in the floor of the mouth with the tip of the tongue. Advanced lesions tend to produce pain, bleeding, foul breath, loose teeth, and change in speech due to fixation of the tongue.

Bimanual palpation is necessary to accurately determine the extent of induration and degree of fixation to the periosteum. Extensive lesions may exhibit invasion into the soft tissues of the neck or skin.

The AJCC staging system[32] (Table 32-2) is based on tumor size and invasion of adjacent structures such as bone or soft

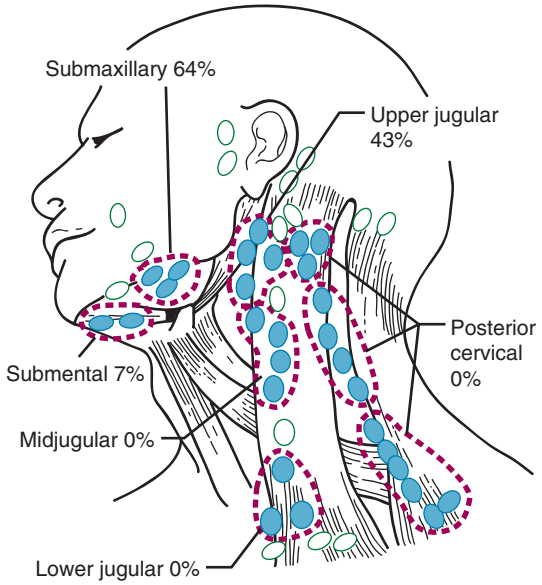
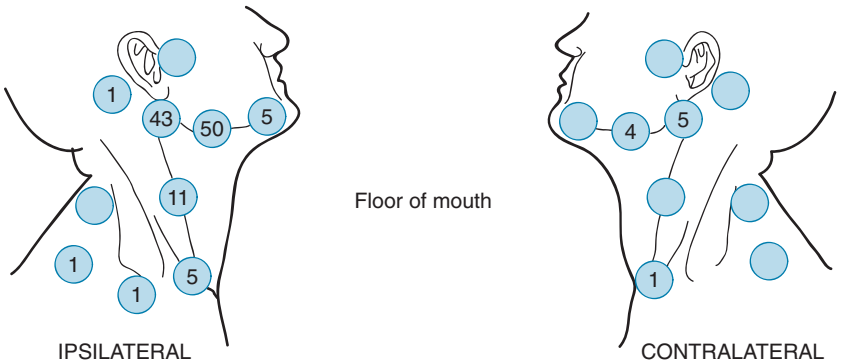


Figure 32-4 The distribution of involved neck nodes in the N0 neck when elective dissection in 62 patients with carcinoma of the floor of the mouth.
(From Byers RM, Wolf PF, Ballantyne AJ: Rationale for elective modified neck dissection. Head Neck Surg 10:162, 1988.)



N_0	N_1	N_{2A}	N_{2B}	N_{3A}	N_{3B}	N_1–N_3 / Total
179	38	4	17	9	11	79 / 258 = 30.5%

Figure 32-3 Carcinoma of the floor of the mouth: nodal distribution on admission, M. D. Anderson Hospital, 1948-1965.
(From Lindberg RD: Distribution of cervical lymph node metastases from squamous cell carcinoma of the upper respiratory and digestive tracts. Cancer 29:1448, 1972.)

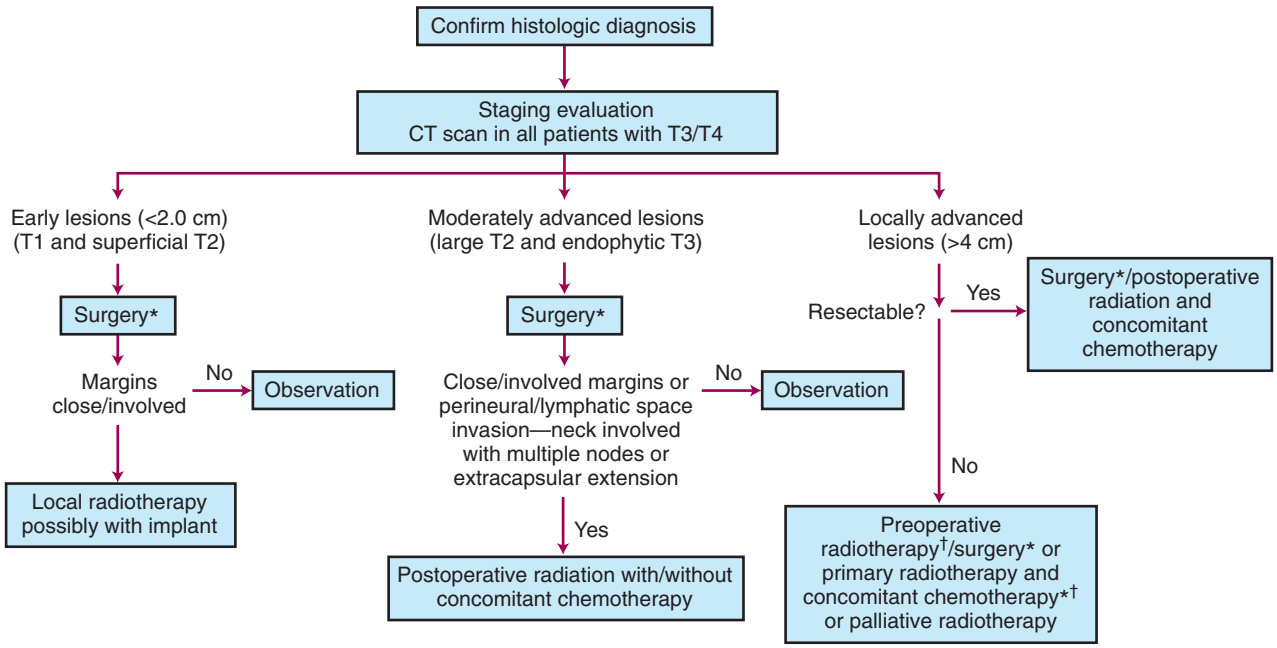


Figure 32-5 Treatment algorithm for de novo floor of mouth cancer. *Treat neck (neck dissection or radiotherapy) in any patient with a primary lesion >1.5 mm thick.[61] †May use concomitant chemotherapy.[72]

tissue of the neck. Radiographic studies may facilitate staging with reference to (1) the status of the mandible and teeth, (2) the deep extent of the tumor, and (3) the evaluation of the regional lymph nodes. CT scans should be obtained in essentially all patients. The mandible may be evaluated by panoramic x-ray films, dental films, and CT scanning. MRI is useful to evaluate marrow space and muscle invasion and perineural involvement.[66]

The role of PET scanning as part of the initial staging workup for oral cavity cancers has not gained widespread acceptance. It may, however, be useful in early detection of recurrences and in prediction of which patients may benefit from elective neck dissection after chemoradiation.[67-69]

Treatment

Early Lesions (T1 and Superficial T2)

Surgery and RT produce equal cure rates for T1 and superficial T2 lesions. The risk of RT induced bone and soft-tissue necrosis is significant. Therefore, surgery is usually the treatment of choice. The neck is also treated with an elective neck dissection,[70] although some advocate observation of the neck in select patients with clinically negative nodes (cN0).[71] A treatment algorithm is shown in Figure 32-5.

Sentinel lymph node biopsy is being investigated for possible use in oral cavity cancers.[73,74] However, a recent study showed that this procedure was less sensitive for floor-of-mouth cancers (80%) compared with other oral sites (100%).[75]

Some patients present after excisional biopsy of the primary tumor. If the margins are either close or involved and there is no evidence of visible or palpable residual tumor, an interstitial implant alone to the primary site is a good alternative provided that the depth of invasion is less than 1.5 mm. Reexcision may not be feasible because the surgeon does not know exactly what to remove. An additional advantage of RT is the ability to treat a larger area. Six patients were treated in this manner at M.D. Anderson Hospital[76] and seven patients at the University of Florida.[77] All had disease locally controlled and none of the patients developed regional lymph node metastases. Conversely, Sessions et al[71] have recommended reexcision rather than RT if close or positive margins are found on permanent sections.

Moderately Advanced Lesions (Large T2 and Exophytic T3 Lesions)

Infiltrative lesions with fixation or tethering to inner tables of the mandible are best treated by excision with resection of the periosteum with or without a rim of mandible. Postoperative RT is indicated for patients with close (≤5 mm) or positive margins, perineural invasion, or lymphatic space invasion.

One common indication for adjuvant RT is the inability of the surgeon to obtain adequate margins of resection, because this often leads to local recurrence,[78] even if immediate reexcision is performed.[79] Jacobs et al[80] and Laramore et al[81] reported a large intergroup study where adjuvant postoperative EBRT (60 Gy) was administered for locally advanced cancers. They found that the relapse rate was 11% in patients with satisfactory margins and 26% in those with unsatisfactory margins. Unsatisfactory margins tend to reflect a higher residual tumor burden; therefore, it may be prudent to deliver a higher dose of postoperative RT. At the University of Florida, patients with involved margins receive hyperfractionated RT to increase the dose given to the primary site while minimizing the potential late morbidity.[53] An alternative is 70 Gy in 35 fractions over 6 weeks treating once-daily, 4 days weekly and twice daily, one day per week during the last 5 weeks of irradiation.

Lapeyre et al[82] reported on 36 patients with oral tongue or floor-of-mouth carcinomas treated with brachytherapy after resection with close or positive margins. The local control was 88.5% at 2 years. Grades 2 to 3 chronic sequelae were seen in 3 of 19 patients (16%) with floor of mouth cancers.

The neck should be electively dissected if it is clinically negative. If there are multiple positive nodes or extracapsular extension, postoperative RT is indicated.[33,53] Based on the latest results of the European Organization for Research and Treatment of Cancer (EORTC) and Radiation Therapy

Oncology Group (RTOG) trials, concomitant chemotherapy is generally recommended as well in high-risk postoperative settings such as positive margins or extracapsular extension.[50,52]

Locally Advanced Lesions (Endophytic T3 and T4)

Patients with locally advanced floor-of-mouth cancers are treated with surgery followed by postoperative RT. In some cases, preoperative RT can be used for unresectable tumors. Patients with extensive tongue invasion with fixation or extension into the soft tissues of the neck, as well as those with massive neck disease can be treated with palliative RT (30 Gy in 10 fractions or 20 Gy in 2 fractions with a 1 week interfraction interval).

Concomitant Postoperative Chemoradiation

The issue of whether concomitant chemotherapy is beneficial when administered with postoperative RT for head and neck cancer was recently addressed by two randomized trials (RTOG 9501 and EORTC 22931).[50,52] Each of these showed an improvement in local regional control and DFS when cisplatin (100 mg/m^2) was given on days 1, 22, and 43 of the RT regimen.[50,52] Severe acute effects are seen more frequently with chemoradiation compared with postoperative RT alone.

Results

Outcomes after RT alone vary with the stage of disease and treatment technique. The RT schedules used at the University of Florida are shown in Table 32-6.[83] EBRT alone results in lower local control rates compared with brachytherapy alone or combined with EBRT.[84] The M. D. Anderson experience with RT alone is depicted in Table 32-7.[85] The failure rates range from 2% for T1 lesions to 23% and 79% for T3 and T4 lesions, respectively. For T2 and T3 lesions, brachytherapy with or without EBRT appears to result in better local control than EBRT alone.

Sessions et al[71] reported on 280 patients who were treated with surgery alone, RT alone, or combined surgery and RT. Tumor categories were: T1, 106 patients; T2, 107 patients; T3, 40 patients; and T4, 27 patients. The local recurrence rate was 41%. The 5-year CSS rates by treatment modality are shown in Table 32-8.

One hundred sixty patients with T1 (79 patients) and T2 (81 patients) floor-of-mouth cancers were treated at the Institute Gustave-Roussy with low-dose rate ^{192}Ir brachytherapy.[86] One hundred twenty-seven patients had a clinically negative neck and 33 patients (21%) had N1 neck disease. Patients with T2 and/or N1 lesions underwent a neck dissection. With a minimum follow-up of 9 years, local control rates were 93% for T1 cancers and 88% for T2 tumors.

Pernot et al[87] reported 207 patients with floor-of-mouth carcinomas treated with EBRT and ^{192}Ir brachytherapy (105 patients) or brachytherapy alone (102 patients). Tumor categories were 41%, Tl; 48%, T2; 8%, T3; 2%, T4; and 1% TX. Neck categories were 83%, N0; 12%, Nl; 3%, N2; 2%, N3. The 5-year local control rates were 97%, 72%, and 51% for Tl, T2, and T3 tumors, respectively. The 5-year CSS were: T1, 88%; T2, 47%; and T3, 36%.

Rodgers et al[88] reviewed 194 patients treated at the University of Florida. Patients with advanced lesions (T3, T4) had lower control rates when treated with RT or surgery alone compared with those treated with combined surgery and RT (Table 32-9). The 5-year CSS were: stage I, 96%; stage II, 70%; stage III, 67%; and stage IVA, 44%.

Techniques of Irradiation

Because of the proximity of the gingival ridge, which is vulnerable to high-dose RT-induced soft-tissue injury or osteoradionecrosis, the floor of the mouth has a lower RT tolerance than other portions of the oral cavity. Therefore, preirradiation and postirradiation oral care is critical.

TABLE 32-6 Carcinoma of the Floor of Mouth: RT Schedules Currently Prescribed at the University of Florida

	Interstitial Only (Gy)	Intraoral Cone Only (Gy)	EBRT ± Interstitial (Gy)	Intraoral Cone Plus EBRT (Gy)
TX—No visible or palpable tumor	55	45 over 3 wk	Not recommended	Not recommended
TX—Palpable induration or positive margins	65	55 over 4 wk	45 plus 25	15 to 18 in 10 fractions plus 50
Early superficial	60 to 65	45 over 3 wk	Not recommended	Not recommended
Early, 1 to 3 cm, induration	Not recommended	Not recommended	45 plus 25 to 30	15 to 24 in 10 fractions plus 45
Locally advanced	Not recommended	Not recommended	74.4 to 76.8 (1.2 twice a day) EBRT plus cisplatin	Not recommended

Modified from Million RR, Cassisi NJ, Clark JR: Cancer of the head and neck. In DeVita VT, Jr, Hellman S, Rosenberg SA, editors: Cancer: principles and practice of oncology, ed 3, Philadelphia, 1989, J. B. Lippincott Company, pp 488–590.
EBRT, *External beam irradiation;* TX, *status postexcisional biopsy.*

TABLE 32-7 Floor-of-Mouth Cancer: Failure to Control the Primary Lesion versus RT Technique—M. D. Anderson Hospital; January 1948 through December 1968

Category	Failure Rate (No. Failures/Total Patients)	EBRT Alone	Interstitial Alone	EBRT and Interstitial
T1	1/49 (2%)	0/10	1/31 (3%)	0/8
T2	9/77 (11.5%)	5/23 (22%)	3/34 (9%)	1/20 (5%)
T3	14/60 (23%)	9/25 (36%)	3/17 (18%)	2/18 (11%)
T4	19/24 (79%)	13/16 (81%)	2/4	4/4

Reprinted from Chu A, Fletcher GH: Incidence and causes of failures to control by irradiation the primary lesions in squamous cell carcinomas of the anterior two-thirds of the tongue and floor of mouth. Am J Roentgenol Radium Ther Nucl Med 117:502–508, 1973.
EBRT, *External beam irradiation.*

TABLE 32-8 Floor-of-Mouth Carcinoma: 5-Year Cause-Specific Survival Rates versus Treatment Modality and CTNM Stages: Washington University (*N* = 227)

Treatment	All Stages (*N* = 227)	Stage I (*N* = 58)	Stage II (*N* = 51)	Stage III (*N* = 54)	Stage IV (*N* = 64)
Local resection	76.2%	81.2%	50.0%	100%	0.0%
Composite resection	62.5%	25.0%*	100%	100%	53.9%
RT	43.2%	41.7%*	33.3%	33.3%*	53.9%
Local resection and RT	60.9%	75.0%	41.7%	100%	100%
Composite resection/RT	54.9%	94.4%	75.9%	35.0%*	40.0%
Significance level	$p = 0.158$	$p = 0.0032$	$p = 0.059$	$p = 0.0045$	$p = 0.401$

Reprinted from Sessions DG, Spector GJ, Lenox J, et al: Analysis of treatment results for floor-of-mouth cancer. Laryngoscope. 110(10 Pt 1):1764–1772, 2000 [table 5].
RT, *Radiotherapy.*
**Significant* p < 0.05 by X^2/Fisher's exact test.*

TABLE 32-9 Floor-of-Mouth Carcinoma: Initial and Ultimate Local Control Rates* University of Florida (*N* = 194 Patients)

T Category	Radiation Alone	Surgery Alone	Surgery and Radiation
T1			
Initial	32/37 (86%)	9/10 (90%)	1/1 (100%)
Ultimate	35/37 (94%)	9/10 (90%)	1/1 (100%)
T2			
Initial	25/36 (69%)	9/12 (75%)	7/7 (100%)
Ultimate	31/36 (86%)	10/12 (83%)	7/7 (100%)
T3			
Initial	11/20 (55%)	†	9/9 (100%)
Ultimate	13/20 (65%)	†	9/9 (100%)
T4			
Initial	2/5 (40%)	1/2 (50%)	5/8 (63%)
Ultimate	2/5 (40%)	1/2 (50%)	5/8 (63%)

Reprinted from Rodgers LW, Jr, Stringer SP, Mendenhall WM, et al: Management of squamous cell carcinoma of the floor of mouth. Head Neck 15:16–19, 1993 [table 2].
**Grouped by initial treatment to the primary site. Forty-seven patients were excluded from local control analysis because they died within 2 years of treatment with the primary site continuously disease free.*
†*No patients in category.*

T1 and T2 Cancers

Patients with superficial (≤4 mm thick), well-differentiated squamous cell carcinoma of the floor of mouth may be treated either with brachytherapy alone or, when accessible, with intraoral cone RT. Brachytherapy is not feasible if the tumor abuts or extends onto the mandibular alveolar ridge because of the risk of bone exposure. Brachytherapy may be performed with iridium using the plastic tube technique.

Intraoral cone RT is administered with either orthovoltage x-rays or electrons. Orthovoltage x-rays are preferred because there is less beam constriction and the surface dose is higher. Before each treatment, it is necessary for the radiation oncologist to verify the position of the tumor relative to the intraoral cone. Because a small volume of tissue is included in the intraoral cone field, the dose per fraction may be increased to 2.5 Gy to 3.0 Gy once daily.

Cancers thicker than 4 mm and those that are poorly differentiated have an increased risk of subclinical disease in the regional nodes. The first echelon nodes for the floor of mouth are the level I and II nodes. EBRT is delivered with either 4-MV or 6-MV x-rays using parallel-opposed fields that encompass the primary tumor as well as the first echelon nodes. An intraoral stent is placed in the mouth to displace the maxilla and upper lip out of the fields (Figure 32-6).[56] The EBRT fields are treated to 46 Gy in 23 fractions once daily or 38.4 Gy at 1.6 Gy per fraction twice daily. Brachytherapy follows the EBRT if that is the technique selected to boost the tumor. If intraoral cone RT is selected to boost the tumor, it precedes the EBRT so the extent of the tumor can be optimally defined and because it may be difficult to place the cone after EBRT because of patient discomfort. The total dose ranges from 65 Gy to 70 Gy.

The low neck (levels III and IV nodes) is irradiated with an anterior field, using 4-MV or 6-MV x-rays to 50 Gy in 25 fractions or 40.5 Gy in 15 fractions specified a D-max. The latter schedule is preferred if treatment to the upper neck will be completed in less than 25 fractions. A tapered midline block is used to shield the larynx. The junction between the parallel-opposed fields and the low neck field is at the thyroid notch (Figure 32-7).[89]

T3 and T4 Cancers

The likelihood of cure without a major complication after primary RT is low. Therefore, if patients are treated with curative intent, postoperative RT is combined with resection of the primary tumor and a neck dissection. The fields are similar to those described for patients treated with RT alone. The superior border of the field is extended to the skull base if there are multiple positive nodes or extracapsular extension. The portals are reduced off of the spinal cord at 44 Gy to 46 Gy and, if necessary, the neck posterior to the reduced fields may be irradiated with 8-MeV to 10-MeV electrons. Patients with ipsilateral positive nodes may be treated with IMRT to reduce the dose to the contralateral parotid gland and, thus, the risk of long-term xerostomia.[90,91] Patients with bilateral positive nodes are treated with parallel opposed field because parotid-sparing IMRT may result in an increased risk of a marginal recurrence. Those with negative nodes may be treated with parallel opposed fields excluding most of the parotid glands. A petroleum jelly gauze bolus is placed on the incision to ensure an adequate surface dose. Patients with negative margins generally receive 60 Gy at 2 Gy per fraction. Altered fractionation should be considered for patients with positive margins and for those with an interval of more than 6 weeks between surgery and initiation of postoperative RT. The preferred schedule at the University of Florida is 74.4 Gy at 1.2 Gy per fraction administered twice daily in a continuous course over 6.5 weeks, usually with concomitant cisplatin.

An occasional patient may present with an incompletely resectable tumor, usually because of fixed neck disease. In this event, RT precedes surgery in an effort to render the tumor

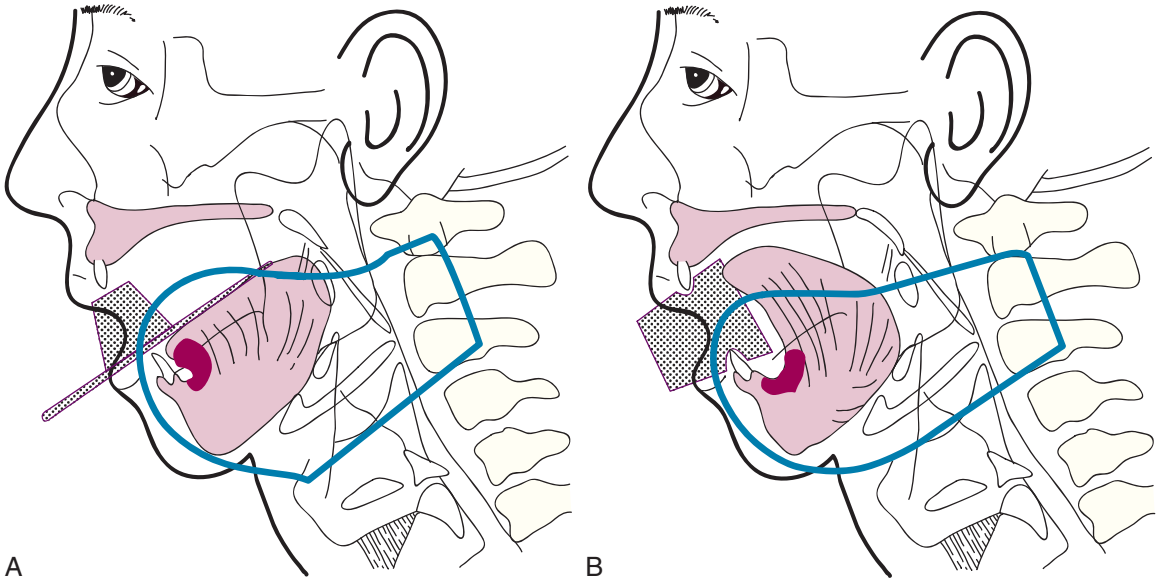


Figure 32-6 **A,** Portal for treatment of carcinoma of the floor of the mouth with tongue invasion; the tongue is depressed into the floor of the mouth with a tongue blade and cork. **B,** Portal for irradiation of limited anterior floor of mouth carcinoma without tongue invasion. Two notches are cut on a cork so it can be held in the same position between the patient's upper and lower incisors during every treatment session; the tip of the tongue is displaced from the treatment field. The anterior border of the field covers the full thickness of the mandibular arch. The lower field edge is at the thyroid cartilage, ensuring adequate coverage of the submandibular lymph nodes. The superior border is shaped so that much of the oral cavity, oropharynx, and parotid glands are out of the portal. The minimum tumor dose to the planning target volume (PTV) is specified at the primary site (i.e., not along the central axis of the portal) with the aid of computer dosimetry.
(From Parsons JT, Mendenhall WM, Moore GJ, et al: Radiotherapy of tumors of the oral cavity. In Thawley SE, Panje WR, Batsakis JG, et al, editors: Comprehensive management of head and neck tumors, ed 2, Philadelphia, 1999, W.B. Saunders Company, pp 695–719). [Figures 35-8 and 35-9, p 704].

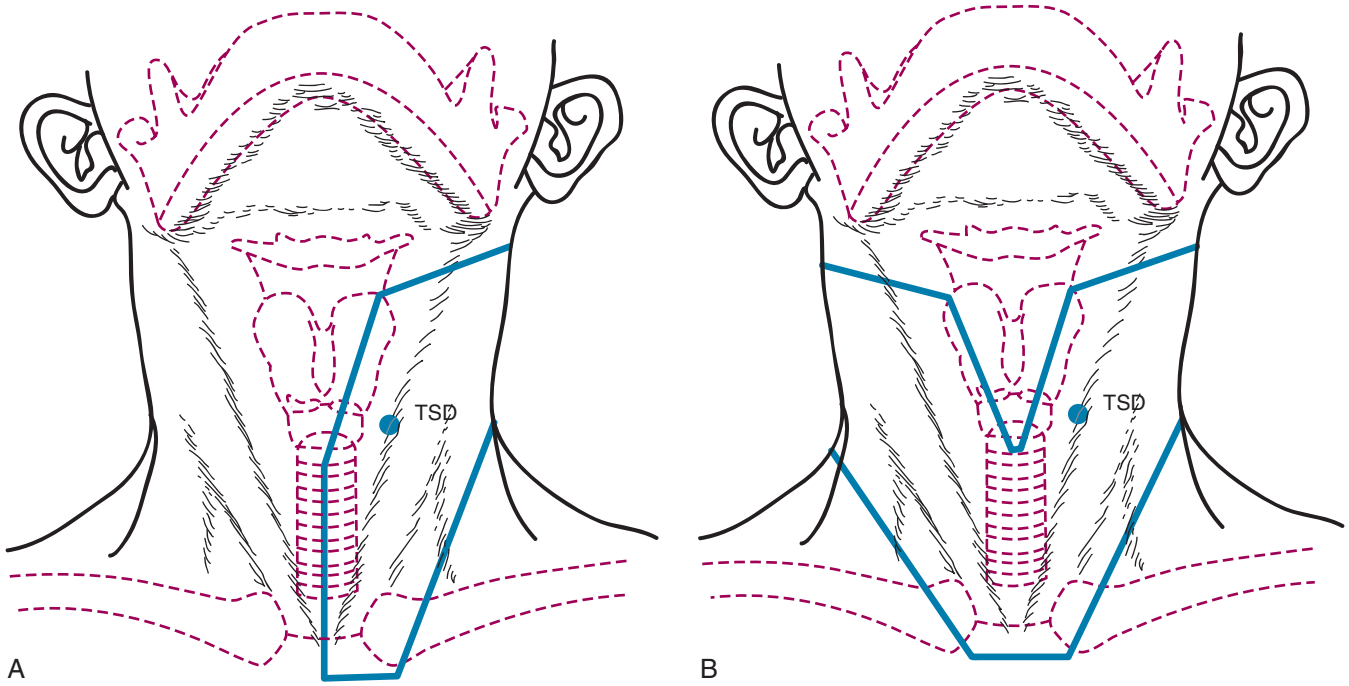


Figure 32-7 **A,** Portal used to irradiate the ipsilateral neck. In patients with N0 disease, the nodes in the lateral supraclavicular fossa are at low risk and are not irradiated electively. **B,** Fields for bilateral lower neck RT of the N0 neck. The larynx shield should be carefully designed. Because the internal jugular vein lymph nodes lie adjacent to the posterolateral margin of the thyroid cartilage, the shield cannot cover the entire cartilage without producing a low-dose area in these nodes. A common error in the treatment of the lower neck is to extend the low neck portal laterally out to the shoulders encompassing lateral supraclavicular lymph nodes that are at negligible risk while partially shielding the high-risk midjugular lymph nodes with a large rectangular laryngeal block. The inferior extent of the shield is at the cricoid cartilage or first or second tracheal ring; the shield must be tapered because the nodes tend to lie closer to the midline as the lower neck is approached.
(From Parsons JT, Mendenhall WM, Million RR: Radiotherapy of tumors of the oropharynx. In Thawley SE, Panje WR, Batsakis JG, et al, editors: Comprehensive management of head and neck tumors, ed 2, 1999, W.B. Saunders Company, pp 861–875). [Figure 10, A *is* Figure 42-2, B*,* p 867*]. [Figure 10,* B *is Figure 42-7,* A*, p 872].*

TABLE 32-10 Carcinoma of the Floor of the Mouth: Treatment Complications (N = 194 Patients)

Initial Treatment	Patients With Severe* Complications	Patients with Mild to Moderate† Complications
Radiotherapy alone	6/117 (5%)	49/117 (42%)
Surgery alone	6/36 (17%)	3/36 (8%)
Surgery and radiotherapy‡	6/41 (15%)	8/41 (20%)

Reprinted from Rodgers LW, Jr, Stringer SP, Mendenhall WM, et al: Management of squamous cell carcinoma of the floor of mouth. Head Neck 15:16–19, 1993 [table 3].

**Postoperative complications (myocardial infarction, pulmonary embolism, etc.), wound infection or dehiscence, fistula formation, or osteoradionecrosis requiring hospitalization or surgical intervention.*

†Small bone exposure, soft-tissue necrosis, or minor infection. Osteoradionecrosis or surgical wound complication requiring outpatient therapy only.

‡Preoperative or postoperative radiotherapy.

resectable. Approximately 46 Gy to 50 Gy is delivered to the primary tumor and both sides of the neck followed by a reduction and a boost to the area limiting resection to 60 Gy to 70 Gy.

Patients with advanced disease and a remote chance of cure are treated with palliative intent. The dose fractionation schedules employed at the University of Florida are 20 Gy in 2 fractions with a 1-week interfraction interval or 30 Gy in 10 fractions over 2 weeks.

Complications

A limited soft-tissue necrosis may develop in the floor of the mouth, usually at the site of the original lesion. These ulcers are painful and usually respond to local anesthetic measures (viscous lidocaine or tetracaine lollipops), antibiotics, and time. If the ulceration develops on the gingiva, the underlying mandible may be exposed. It is recommended to discontinue wearing of dentures, apply a local anesthetic and administer antibiotics. Recent data suggests that pentoxifylline, 400 mg three or four times daily, may be beneficial in this setting, and may also reduce late RT-induced fibrosis.[92] If the soft-tissue or bone necrosis progresses, hyperbaric oxygen and surgical debridement may be necessary.[93,94] Eighteen of 194 patients (9%) treated at the University of Florida developed severe complications (Table 32-10).[88]

Sessions et al[71] reported on 280 patients treated with surgery alone or RT. They observed late RT complications in 41% of patients treated by EBRT and brachytherapy, most of which appeared within 1 year of treatment. Surgical complications included infection (5%), wound slough (9.6%), orocutaneous fistula (6.1%), carotid artery exposure/blowout (1.1%), and delayed fatality (1.4%). Fifty-eight percent of these complications were related to the use of combined surgery and external RT.

Bone necrosis was seen in 18% of patients treated with brachytherapy for T1-T2 floor-of-mouth cancers at the Institut Gustave-Roussy; 2.5% were severe.[86]

ORAL TONGUE CANCERS

Anatomy

The tongue is located in the floor of the mouth, and at rest, fills most of the oral cavity. It is involved with mastication, taste, and oral cleansing; but its main functions are propelling food into the pharynx when swallowing, and forming words when speaking.

The sulcus terminalis divides the tongue into the oral and pharyngeal portions; the oral portion consists of the anterior two thirds of the tongue. The tongue is attached to the floor of the mouth by the frenulum. The circumvallate papillae are the largest taste buds; they are 1 mm to 2 mm in diameter and lie anterior to the sulcus terminalis.

The oral tongue consists of four muscles: the genioglossus, hyoglossus, styloglossus, and palatoglossus. They all originate outside the tongue and insert into it and their function is to move the tongue. There are four intrinsic muscles of the tongue that alter the shape of the tongue.

The muscles and mucous membranes of the tongue have separate nerve supplies. The hypoglossal nerve (cranial nerve XII) is the motor nerve of the tongue. It descends from the medulla and exits through the hypoglossal canal from whence it passes laterally between the internal jugular vein and internal and external carotid arteries to curve anteriorly and enter the tongue. It passes anteriorly on the inferior aspect of the hyoglossus muscle and then to the lateral aspect of the genioglossus muscle. Injury of the hypoglossal nerve results in paralysis and eventual atrophy of the ipsilateral tongue.

The lingual nerve, which is a branch of the mandibular division of cranial nerve V, is the sensory nerve for the oral tongue. For special sensation such as taste, the anterior two thirds of the tongue is supplied by the chorda tympani branch of the facial nerve (cranial nerve VII). The chorda tympani joins the lingual nerve and runs anteriorly in its sheath. The blood supply to the tongue is from the lingual artery; two lingual veins accompany the lingual artery. The deep lingual vein begins at the tip of the tongue and runs posteriorly in the median plane.

The tongue has a submucosal plexus of lymph vessels. There are three routes of lymphatic drainage from the oral tongue: the tip of the tongue drains to the submental lymph nodes (level Ia); lymph from the lateral aspects of the tongue drains to the submandibular lymph nodes (level Ib) and from there into the deep cervical lymph nodes (level II-IV); and lymph from the medial tongue drains directly to the inferior deep cervical lymph nodes (levels III and IV). Approximately 15% of patients have lymphatic metastases that bypass level II and present in levels III and IV.[95] Lymphatic drainage is unilateral; drainage to the contralateral lymphatics is unlikely.

Pathology and Patterns of Spread

Ninety-five percent of oral tongue cancers are squamous cell carcinomas. Leukoplakia is also common.[96] Verrucous carcinoma and minor salivary gland tumors occur infrequently.

Nearly all squamous cell carcinomas occur on the lateral and ventral surfaces of the tongue. Anterior-third (tip) lesions are usually diagnosed early. Middle-third lesions often invade the musculature of the tongue and subsequently extend into the lateral floor of mouth. Posterior-third lesions grow into the musculature of tongue, floor of mouth, anterior tonsillar pillar, base of tongue, glossotonsillar sulcus, and the mandible.

The distribution of clinically positive neck node metastases on presentation is shown in Figure 32-8.[64] Forty-five percent of patients with cancers of the oral tongue have clinically positive nodes at diagnosis; 5% are bilateral. Byers et al[65] reported a 19% incidence of subclinical disease for T1N0 and T2N0 lesions, and 32% for T3N0 to T4N0 cancers after elective neck dissection. Ozeki et al[97] have reported three cases with metastases to the lingual lymph nodes.

Clinical Manifestations, Patient Evaluation, and Staging

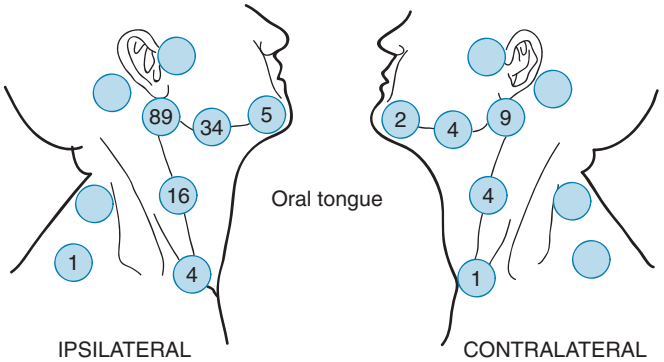
Patients with oral tongue carcinomas usually present with a sense of tongue irritation or of a mass in the tongue. Deep

infiltration may affect speech and swallowing. Advanced ulcerative lesions are often associated with a foul odor and pain.

Palpation of the tongue and floor of mouth, visual examination, and assessment of tongue mobility will help define the extent of the primary tumor. CT and, to a lesser extent MRI, is useful for defining the deep extent of larger primary tumors and to assess the neck. The staging system is depicted in Table 32-2.[31]

Treatment

A treatment algorithm is shown in Figure 32-9.



N_0	N_1	N_{2A}	N_{2B}	N_{3A}	N_{3B}	N_1–N_3 / Total
197	40	9	32	8	16	105 / 302 = 35%

Figure 32-8 Carcinoma of the oral tongue: nodal distribution on admission, M. D. Anderson Hospital 1948 to 1965. *(From Lindberg RD: Distribution of cervical lymph node metastases from squamous cell carcinoma of the upper respiratory and digestive tracts. Cancer 29:1448, 1972.)*

Early Lesions (T1 and Superficial T2)

Surgery and RT are equally effective in controlling small oral tongue cancers. Superficial well-defined lesions can be cured using resection alone with good functional results.[98,99] Postoperative RT is recommended for close or positive margins,[78,100] extensive nodal disease (large or multiple positive neck nodes), vascular space invasion, extracapsular extension, or perineural invasion.[33,53] Although the risk of a significant RT complication is low, surgery is the preferred treatment in the authors' institution because of a lower risk of bone exposure or soft-tissue necrosis that may persist for months or years after RT.

Patients are treated with definitive RT if they decline surgery or are at high risk for operative complications.[101] RT for early stage oral tongue carcinoma can be given with EBRT combined with an interstitial implant or an intraoral cone boost, or with an interstitial implant alone.[85,102] The results of EBRT alone are suboptimal.

Moderately Advanced Lesions (Large T2 and T3)

Moderately advanced primary cancers are managed by partial glossectomy followed by postoperative RT. Preoperative RT is rarely used because it is easier for the surgeon to define the extent of the tumor in the patient who is unirradiated and because the risk of postoperative complications is higher.

Advanced Lesions (T4)

The likelihood of cure for T4 tongue cancers is low. Early T4 cancer may be suitable for partial glossectomy and adjuvant RT. More advanced lesions require a total glossectomy either with or without a total laryngectomy (to prevent aspiration) and reconstruction. Preoperative RT alone or plus concurrent chemotherapy can be given to patients with unresectable tumors, giving at least 50 Gy in 25 fractions to attempt to render the tumor operable or allow the surgeon to perform a more complete resection. Patients who are in poor health or

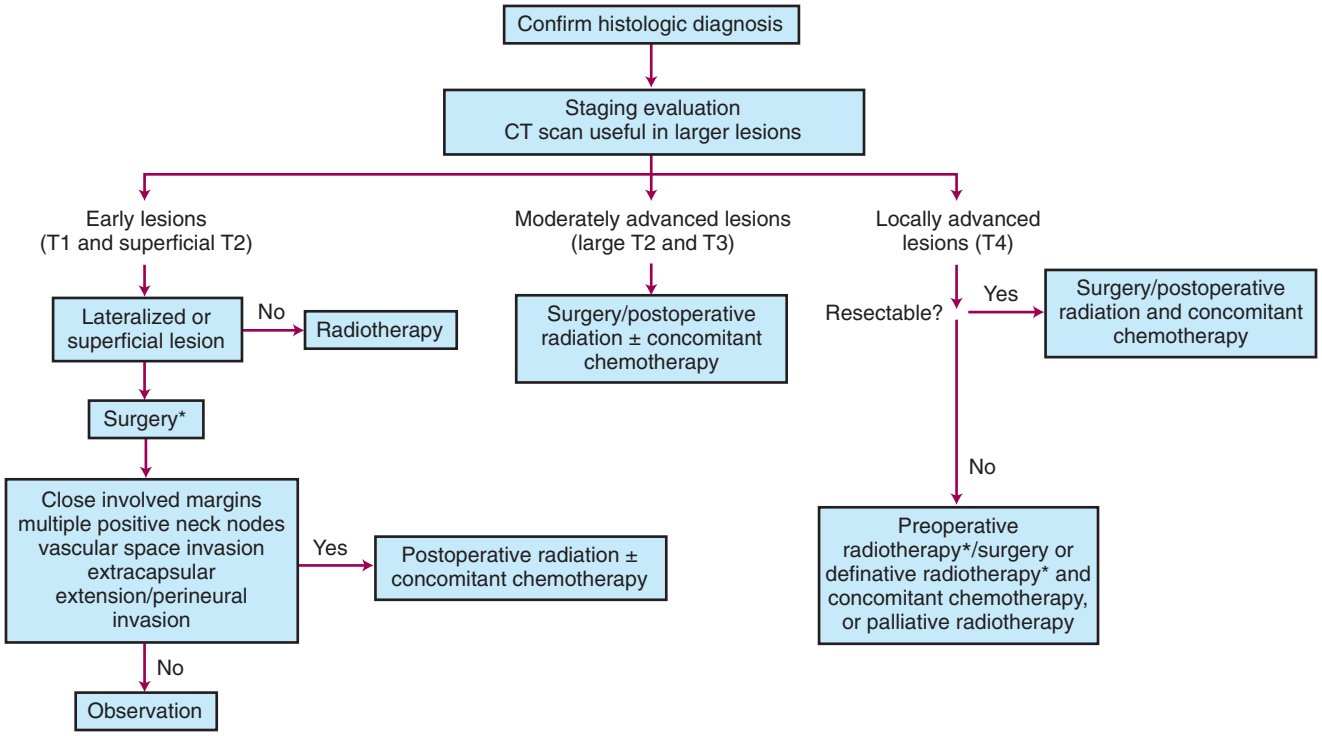


Figure 32-9 Treatment algorithm for de novo oral tongue cancer. *Treat neck (neck dissection or radiotherapy) for primary tumors >2 mm thick.[98] †May use concomitant chemotherapy.[72]

who also have advanced neck disease are treated with palliative RT.

Results

Wang et al[103] evaluated results of various boost techniques combined with EBRT for patients with T1 and T2 oral tongue lesions and observed a 5-year actuarial local control rate of 54% after an interstitial implant, 50% after intraoral cone orthovoltage RT, and 86% after intraoral cone electron beam therapy. The reason that local control was better after electron beam intraoral cone boost compared with orthovoltage intraoral cone is unclear. Compared with interstitial implantation, intraoral cone RT is associated with a lower dose to the mandible and does not require anesthesia or hospitalization. It may also be associated with fewer complications. Wang et al at Massachusetts General Hospital gave 3.0 Gy per fraction for eight to nine daily fractions with intraoral electron beam RT (five fractions per week) followed immediately by EBRT with 1.6 Gy twice daily for 12 days.[103] The patient was given a 1.5 to 2 week split and resumed RT to a total EBRT dose of 51.4 Gy; the total dose is approximately 75 Gy.

Intraoral cone RT with orthovoltage x-rays is preferred at the University of Florida.[104] Patients usually receive 3.0 Gy per fraction with intraoral cone treatment for 7 to 9 days for a total of 21 Gy to 27 Gy followed by EBRT to 30 Gy in 10 once-daily fractions or 32 Gy at 1.6 per fraction twice daily over 2 weeks to the primary site and neck.

Brachytherapy may also be combined with EBRT to treat oral tongue cancer.[99,102,105] Patients treated at the University of Florida with EBRT followed by an interstitial implant had a local control rate of 83%.[101] Wendt et al[105] reported on the M. D. Anderson experience with T1N0 and T2N0 oral tongue carcinomas in which patients underwent either brachytherapy alone or combined with EBRT. Of 8 patients who were treated with EBRT alone, 5 (63%) developed a local recurrence. Six of 18 patients (33%) treated with interstitial therapy failed at the primary site. In those patients treated with a combination of EBRT and brachytherapy, the 2-year local control rate was 92% for those treated with EBRT doses less than 40 Gy combined with a moderately high brachytherapy dose, compared with 65% for patients who received EBRT doses of 40 Gy or more with a lower brachytherapy dose.[105] A review of the pertinent literature supports the efficacy of brachytherapy (Table 32-11).[84]

TABLE 32-11 Local Control of Oral Tongue Carcinoma as a Function of Radiation Modality Employed

	E + I vs E	I vs E	E + I vs I
Chu and Fletcher[85]	E + I > E	I > E	No difference
Fu et al[102]	E + I > E	I > E	E + I < I*
Horiuchi and Adachi[106]	E + I > E	I > E	E + I > I†
Lees[107]	E + I > E	I > E	No difference
Mendenhall et al[84]	—	—	E + I < I‡

Adapted from Mendenhall WM, Van Cise WS, Bova FJ, et al: Analysis of time-dose factors in squamous cell carcinoma of the oral tongue and floor of mouth treated with radiation therapy alone. Int J Radiat Oncol Biol Phys 7:1005–1011, 1981.

E, *External beam irradiation;* I, *interstitial irradiation.*

External beam plus more than 40 Gy radium produced significantly better results than external beam plus less than 40 Gy radium.

**Local control alone not reported by T stage.*

†*Difference noted primarily in T3 and T4 lesions.*

‡*T2 lesions.*

Subclinical disease in the neck nodes is common in patients with oral tongue cancer. Matsuura et al stressed the importance of elective treatment to the neck, especially as tumor thickness increases.[108] In their experience, patients with tumor thickness 8 mm or more were at an increased risk of nodal failure in the clinically negative neck. Wendt et al[105] also showed the importance of elective therapy to the clinically negative neck. Failure in the neck occurred in 44% of patients receiving no elective neck RT; 27% of the failures were in patients receiving less than 40 Gy compared to an 11% failure rate for those who received 40 Gy or more. Byers et al[109] recommended elective treatment to the clinically negative neck in patients with T2 to T4 primary tumors. Haddadin et al[110] observed that patients with T2 tongue carcinomas had a significantly better outcome after an elective neck dissection compared with those who were followed with salvage reserved until development of a regional failure (75% versus 39% 5-year survival rates, respectively). Based on a review of the Memorial Sloan-Kettering Cancer Center (MSKCC) experience, Spiro et al[98] recommended that elective neck therapy be given for primary tumors exceeding 2 mm in thickness because the risk of cervical metastasis approached 40% in this cohort of patients. O-Charoenrat et al[111] found that increasing tumor thickness predicted for occult cervical node metastasis and poor outcomes in patients with stages I and II oral tongue squamous cell carcinoma treated at the Royal Marsden Hospital. Univariate analysis of DFS showed poorer outcomes for patients older than 60 years ($p = 0.0423$) and with tumors thicker than 5 mm ($p = 0.0067$). The impact of tumor thickness on outcome ($p = 0.005$) was also appreciated in a multivariate analysis. They recommended elective neck treatment for tumors more than 5 mm thick.

The use of sentinel lymph node biopsy and PET scanning may alter the treatment paradigm as more experience is gained in their use for oral cavity cancers.[112]

Bourgier et al reported on 279 patients treated with exclusive low-dose rate brachytherapy with or without an elective neck dissection for T2N0 squamous cell carcinoma of the oral tongue.[113] The incidence of subclinical cervical node metastases was 45%. The 2-year local and regional control rates were 79% and 76%, respectively. The incidence of grade 3 complications was 3%.

Fein et al[101] compared the results and complications of treatment with RT or surgery for squamous cell carcinoma of the oral tongue. The control rates for RT alone or surgery alone or in combination with RT were the same for stage T1 and T2 lesions; combined modality treatment resulted in higher cure rates for T3 and T4 tumors (Table 32-12). In an analysis of patients with T1 and T2 lesions, those receiving less than 30 Gy of EBRT plus an interstitial implant had a better outcome than those receiving surgery plus or minus postoperative RT.[101] Currently, for patients receiving RT alone, a dose of 1.6 Gy per fraction is given twice daily to 32 Gy followed immediately by an interstitial implant for an additional 35 Gy to 40 Gy. This technique decreases the overall treatment time and avoids the large dose per fraction associated with 30 Gy in 10 fractions over 2 weeks.[101]

Chao et al[100] reported on 55 patients with stage T1 and T2 lesions treated with surgery and postoperative RT. Thirty-nine patients received EBRT alone and 16 patients had an interstitial implant as part of the treatment. By adding an interstitial implant for patients with positive margins, the local control was equivalent to that observed for patients with negative margins treated with EBRT alone.

Sessions et al[99] reported on 332 patients with oral tongue cancer treated with surgery or RT at Washington University. Tumor stages at presentation were T1 116 patients; T2, 128 patients; T3, 71 patients; and T4, 17 patients. Local recurrences

occurred in 34% and 31% suffered a neck recurrence. The 5-year CSS versus treatment group for 279 of the 332 patients are shown in Table 32-13.

Techniques of Irradiation

T1 and T2 Cancers

Reduction of overall treatment time is vital to the successful treatment of oral tongue carcinomas with RT alone. Patients with well-differentiated carcinomas that are 4 mm or less are optimally treated with brachytherapy alone. Interstitial implantation may be accomplished with iridium using the plastic tube technique. The total dose varies from 65 Gy to 70 Gy over 5 to 7 days.

Although intraoral cone RT has been used successfully to treat oral tongue cancers, it is often difficult to immobilize the lesion so that setup reproducibility may be problematic. If treatment with an intraoral cone is chosen, then the cone is positioned so that the tumor is treated with a 1-cm margin. The intraoral cone therapy should be done before EBRT because of better tolerance and because the lesion can be clearly defined. Orthovoltage x-rays or electron beam may be used. If electrons are used, a beam spoiler or bolus is necessary to ensure an adequate surface dose. Additionally, a larger margin is necessary because of beam constriction compared with orthovoltage RT.

Patients who have poorly differentiated carcinomas, as well as those with 5 mm or more depth of invasion, should be treated with a combination of EBRT and brachytherapy. Parallel-opposed fields include the primary tumor as well as the levels I and II lymph nodes. A cork-and-tongue block displaces the tongue inferiorly and the maxilla superiorly to minimize the amount of normal tissue included in the treatment volume (Figure 32-10). The fields are weighted 3:2 to the side of the tumor and either 30 Gy in 10 fractions once daily or 32 to 38.4 Gy at 1.6 Gy per fraction twice daily is delivered over 2 to 2.5 weeks with 4-MV or 6-MV x-rays. Although ^{60}Co is an ideal beam for treatment of patients with oral cavity

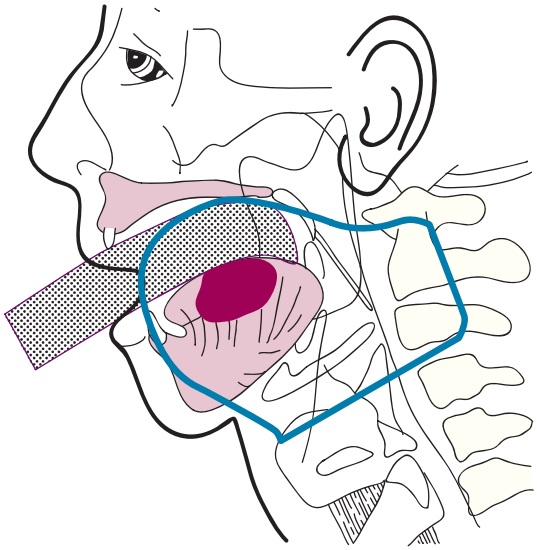


Figure 32-10 Well lateralized squamous cell carcinoma of the oral tongue (neck stage N0). A single ipsilateral field is used. The field encompasses the submaxillary (level Ib) and subdigastric (level II) lymph nodes; the entire width of the vertebral body is included to ensure adequate posterior coverage of the subdigastric lymph nodes (level II). Stainless steel pins are usually inserted into the anterior most and posterior most aspects of the lesion to the aid in localizing the cancer on the treatment planning (simulation) roentgenogram or CT scan and to confirm coverage by the interstitial implant. For lesions smaller than 2.0 cm in diameter, the low neck is not irradiated (unless the histology is poorly differentiated squamous cell carcinoma). The larynx is excluded from the radiation field. The anterior submental skin and subcutaneous tissues are shielded, when possible, to reduce submental edema and late development of fibrosis. The upper border is shaped to exclude most of the parotid gland. An intraoral lead block (stippled area) shields the contralateral mucosa. The block is coated with beeswax to prevent a high-dose effect on the adjacent mucosa resulting from scattered low-energy electrons from the metal surface. The usual preinterstitial tumor dose is 32 Gy using 1.6 Gy per fraction, twice-a-day fractionation. For larger lesions, which extend near the midline, treatment is applied by means of parallel opposed portals with no intraoral lead block.
(From Parsons JT, Mendenhall WM, Million RR: Radiotherapy of tumors of the oral cavity. In Thawley SE, Panje WR, Batsakis JG, et al, editor: Comprehensive management of head and neck tumors, vol 1, ed 2, Philadelphia, 1999, W. B. Saunders Company, pp 695–719. Copyright 1999, with permission from Elsevier). [Figures 35-17, A, B, *p 714].*

TABLE 32-12 Oral Tongue Carcinoma: Probability of Local Control at 2 Years According to T Category and Treatment Method at the University of Florida

	Local Control Percent (No. Patients)		
T Category	Radiation Alone*	Surgery Alone or Plus Radiation	*p* Value
T1	79% (18)	76% (17)	0.76
T2	72% (48)	76% (19)	0.86
T3	45% (29)	82% (24)	0.03
T4	0% (10)	67% (5)	0.08

Adapted from Reprinted from Fein DA, Mendenhall WM, Parsons JT, et al: Carcinoma of the oral tongue: A comparison of results and complications of treatment with radiotherapy and/or surgery. Head Neck 16(4):358–365, 1994 [table 1, page 360].
Note: Numbers in parentheses indicate number of patients in each subset.
**Radiation alone or followed by a neck dissection.*

TABLE 32-13 Oral Tongue Carcinoma: 5-Year Cause-Specific Survival versus Treatment and Stage Grouping (*N* = 279)

Treatment	All Stages (*N* = 279)	Stage I (*N* = 95)	Stage II (*N* = 85)	Stage III (*N* = 65)	Stage IV (*N* = 34)
Local resection	73%*	71.4%	86.7%	33.3%	—
Composite resection	60.9%	100%	62.5%	57.1%	40%
Radiation	46%	75%	58.8%	25.0%	11.1%
Local resection and radiation	65.4%	81.0%	50.0%	71.4%	—
Composite resection and radiation	43.8%	100%	66.7%	33.3%	30.0%
Significance level	$p = 0.002$	$p = 0.770$	$p = 0.230$	$p = 0.225$	$p = 0.559$

Reprinted from Sessions DG, Spector GJ, Lenox J, et al: Analysis of treatment results for oral tongue cancer. Laryngoscope 112(4):616–625, 2002 [table 7].
**Significant at $p < 0.05$ by chi-squared/Fisher's exact test.*

cancers, it is not available in most clinics. The levels III and IV nodes are included in an anterior field as previously described. After EBRT, 35 Gy to 40 Gy is added with an interstitial implant.

T3 and T4 Cancers

Patients with T3 and T4 oral tongue carcinomas are difficult to cure with RT alone. The ability to adequately encompass the primary tumor with an interstitial implant is difficult for all but the occasional patient with a favorable low volume T3 cancer. The risk of a major complication, such as a soft-tissue necrosis or bone necrosis, is high after successful RT. Therefore, most patients are treated with surgery and postoperative RT. As for other sites, dose depends on margin status: Patients with negative margins generally receive 60 Gy at 2 Gy per fraction. Altered fractionation should be considered for patients with positive margins or for those with multiple risk factors or an interval of more than 6 weeks between surgery and initiation of postoperative RT. At our institution, the preferred schedule is 74.4 Gy at 1.2 Gy per fraction administered twice daily in a continuous course over 6.5 weeks. Concomitant cisplatin is also recommended for high-risk situations (close or positive margins or extracapsular nodal extension).[53]

Radiotherapy portals are designed to include the primary tumor and both sides of the neck (levels I to IV). The initial fields extend to the skull base to include the retropharyngeal nodes if the cervical nodes are involved. A petroleum jelly gauze bolus is placed on the incisions to ensure an adequate surface dose. IMRT may be employed to spare the contralateral parotid gland unless bilateral positive nodes are present.

Patients with incompletely resected T3 and T4 carcinomas have a poor prognosis and are treated with EBRT from 74.4 Gy to 76.8 Gy at 1.2 Gy per fraction twice daily over 6.5 weeks with concomitant chemotherapy. Thereafter, patients are evaluated for resection of residual primary tumor (nidusectomy) versus an interstitial implant. Nidusectomy is preferred because of the high risk of necrosis associated with the addition of brachytherapy. Patients who have advanced, unfavorable oral tongue cancers and who are unsuitable for aggressive treatment are treated with palliative RT consisting of either 30 Gy in 10 fractions over 2 weeks or 20 Gy in 2 fractions with a 1-week interfraction interval.

Complications

After RT, patients may complain of a sensitive tongue, even after the mucosa appears to have healed. Taste tends to reappear from 1 to 3 months after treatment; however, because of xerostomia, post-RT taste perception is less sensitive.

Small, self-limited soft-tissue necroses are fairly common. If these occur, recurrent cancer must be ruled out. If the lesion is thought to be necrotic, conservative treatment is instituted. The patient is examined frequently and broad-spectrum antibiotics such as tetracycline are initiated as well as pentoxifylline.[92] Viscous lidocaine or a tetracaine lollipop can be applied to the ulcer for local analgesia. Hyperbaric oxygen treatment is indicated for larger progressive necroses that do not respond to conservative management. Surgery is employed as a last resort for large persistent necroses that are often associated with bone necrosis.

Osteoradionecrosis occurs infrequently; the onset varies from one month to many years after RT.[114] It is more common in patients receiving higher doses per fraction or with tumor invading the bone.[115] If a patient has dentures, the dentures must be removed or altered by the dentist to avoid trauma to areas of exposed bone; healing may require many months. Management is similar to that for soft-tissue necroses.

TABLE 32-14 Oral Tongue Carcinoma: Severe Complications (N = 170 Patients)

T Category	Radiation Alone*	Surgery Alone or with Radiation	p Value
T1	1/18 (6%)	1/17 (6%)	0.74
T2	6/48 (13%)	3/19 (16%)	0.50
T3	1/29 (3%)	7/24 (29%)	0.01
T4	1/10 (10%)	2/5 (40%)	0.24
Overall	9/105 (9%)	13/65 (20%)	0.03

Reprinted from Fein DA, Mendenhall WM, Parsons JT, et al: Carcinoma of the oral tongue: A comparison of results and complications of treatment with radiotherapy and/or surgery. Head Neck 16(4):358–365, 1994 [table 6, page 363].

**Radiation alone or followed by planned neck dissection.*

RT-induced xerostomia is common and is related to the volume of salivary tissue irradiated and the radiation dose. Patients who are treated with brachytherapy or intraoral cone RT without EBRT usually retain salivary function.

Oral pilocarpine has been advocated by some for xerostomia. Pilocarpine exercises a broad spectrum of pharmacologic effects, including increasing the secretions of exocrine glands, most notably the salivary glands. In a multicenter, randomized, double-blind, placebo-controlled trial published in 1993, pilocarpine produced a clinically significant benefit.[116] However, its efficacy has been questioned by the outcomes of recent randomized trials.[117,118] The recommended dose is 5 mg, three to four times a day. The time interval necessary to achieve optimal results is 8 to 12 weeks.

Amifostine has been used more recently in an effort to lessen the untoward effects of RT. It can be administered either intravenously or subcutaneously.[119,120] The latter is generally felt to be more convenient and associated with less toxicity.[121] A full course of treatment with amifostine is quite expensive. This fact, coupled with its potential to cause nausea and skin reactions, has limited its acceptance in some centers.

At the University of Florida, the severe complication rate for 170 patients treated with surgery alone or in combination with RT for oral tongue cancer was compared with the severe complication rate for patients treated with RT alone; the findings are presented in Table 32-14.[101]

Sessions et al[99] reported major treatment complications in 21 of 270 patients (12.8%), most of which occurred in those receiving composite resection and RT. Complications associated with RT included orocutaneous fistula (6/224 [2.7%]), flap necrosis (1/224 [0.4%]), carotid hemorrhage (1/224 [0.4%]), xerostomia (7/224 [3.1%]), trismus (5/224 [2.2%]), radiation caries (3.1%), soft-tissue ulcer (22/224 [9.8%]), bone necrosis (14/224 [6.2%]), and dysphagia (3/224 [1.3%]).[99]

BUCCAL MUCOSA

Anatomy

The lateral walls of the oral cavity are formed by the cheeks. The buccal mucosa is composed of the inner lining of the cheeks. It is contiguous with the lips and has the same structure.

The muscle of the cheek is the buccinator. The buccal fat pad is superficial to the fascia covering the buccinator muscle and gives the cheeks a rounded contour.

Branches of the maxillary and mandibular nerves (cranial nerves V2 and V3) provide sensory innervation to the skin, cheek, and the mucous membranes lining the cheeks. The

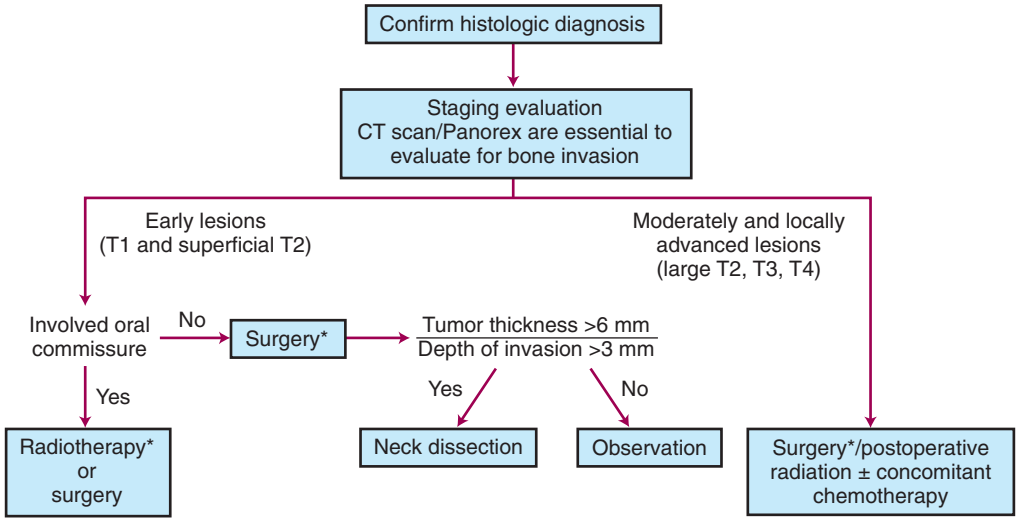


Figure 32-11 Treatment algorithm for de novo buccal mucosa cancer. *Treat neck (radiotherapy or neck dissection) for T2 to T4 tumors.[122,123]

facial nerve (cranial nerve VII) provides motor innervation to the muscles of the cheeks and lips. The lips and cheeks function together as an oral sphincter propelling food into the oral cavity. If the facial nerve is paralyzed, food tends to accumulate within the cheek along the affected side so that saliva and food dribble out of the corner of the mouth.

Pathology and Patterns of Spread

The majority of tumors originating from the buccal mucosa are low-grade squamous cell carcinomas that are frequently associated with leukoplakia. Verrucous carcinomas are observed more frequently in the buccal mucosa than in other parts of the oral cavity.[122]

Early lesions tend to be discrete, exophytic, mucosal growths. Advanced tumors tend to be ulcerated and are often associated with muscle invasion. Lesions that involve the lower gum may invade the mandible. Advanced lesions may extend to the soft tissues of the cheek.

The first echelon lymphatics are the submandibular (level Ib) and subdigastric (level II) lymph nodes. The incidence of positive nodes at diagnosis ranges from 9% to 31%; the risk of subclinical disease is 16%.[123] Bilateral cervical node metastases are unusual. Advanced cancers have a higher propensity (60%) for lymph node metastases.[122]

Clinical Manifestations and Staging

Although pain tends to be minimal, even when the lesion is large, posterior extension may result in involvement of the lingual or dental nerves which may cause ear pain. Extension behind the pterygomandibular raphe into the pterygoid muscles or into the buccinator and masseter muscles may cause trismus. Intermittent bleeding may occur when the lesions are irritated by chewing.

CT imaging can be used to evaluate the deep extension of the lesion, to detect bone invasion, and to assess the parotid and facial nodes.[66] The AJCC staging system is depicted in Table 32-2.[31]

Treatment

Early Lesions (T1 and Superficial T2 Lesions)

The preferred treatment for patients with carcinoma of the buccal mucosa is surgery. RT alone is used to treat patients by default in the uncommon situation where surgery is not feasible. Patients with T1 and T2 cancers may be treated with a combination of EBRT and an interstitial implant.[122] A treatment algorithm is shown in Figure 32-11.

Moderate to Locally Advanced Cancers (Large T2, T3, and T4)

Superficial T2 and T3 cancers may be treated with RT; however, if there is deep muscle invasion, the cure rates after RT are poor.[124,125] The preferred treatment for patients with large T3 and T4 cancers is resection of the primary tumor in conjunction with a neck dissection followed by postoperative RT. Patients who are not surgical candidates are treated with EBRT and concomitant chemotherapy. Although it would be desirable to include brachytherapy as part of the treatment, the likelihood of adequately encompassing an advanced tumor with an interstitial implant is remote, and so these patients are treated with EBRT to 76.8 Gy in 64 twice-daily fractions over 6.5 weeks. The concurrent chemotherapy regimen that is used most often at our institution is once-weekly cisplatin, 30 mg/m^2.

The management of verrucous carcinomas is controversial because of the perceived risk that the tumor may become more aggressive if it recurs after RT. However, there is little evidence in the literature to support this theory.[126] Many tumors that recur after treatment (surgery, RT, or chemotherapy) are biologically more aggressive. Therefore, it is reasonable to treat these lesions with RT if surgery is not feasible.[127] The dose is essentially the same as that prescribed for other squamous cell carcinomas. Wang[128] reported a series of patients with verrucous carcinoma treated with RT; the results were comparable to those for patients treated for squamous cell carcinoma.

Results

Five-year DFS rates after RT range from 50% to 60%, depending on the stage of the primary lesion and the presence or absence of lymph node metastases.[62,128] Ash[62] reviewed the outcomes of 374 patients; 97% were initially treated with RT. The primary lesion was controlled in 52% of the patients; however only 25% of advanced lesions were controlled. Nair et al[129] evaluated the role of RT in the management of carcinomas of the buccal mucosa; RT was either administered with an interstitial implant consisting of 65 Gy over 6 days (45 patients), continuous course EBRT consisting of 52.5 Gy in

TABLE 32-15 Results of Radiotherapy in Cancer of the Buccal Mucosa: Site of Failure versus TN Category

UICC TN Category	Primary Failure No. (%)	Nodal Failure No. (%)	Total Failure No. (%)
T1N0	0/13 (0)	0/13 (0)	0/13 (0)
T2N0	13/49 (27)	7/49 (14)	18/49 (37)
T3N0	15/49 (31)	1/49 (2)	15/49 (31)
T4N0	6/12 (50)	1/12 (8)	7/12 (58)
Any T and N1	51/94 (54)	48/94 (51)	55/94 (59)
Any T and N3	12/17 (71)	15/17 (88)	14/17 (82)

Reprinted from Nair MK, Sankaranarayanan R, Padmanabhan TK, et al: Oral verrucous carcinoma. Treatment with radiotherapy. Cancer 61(3):458–461, 1988.

TABLE 32-16 Carcinoma of the Buccal Mucosa Treated Surgically: Primary Tumor Parameters versus Outcome

Clinical Factors	Patients	Recurrence
TUMOR CATEGORY		
T1	23	5 (22%)
T2	32	11 (34%)
T3	20	6 (30%)
T4	14	6 (43%)
THICKNESS		
<3 mm	18	4 (22%)
3 to 5.9 mm	26	6 (23%)
≥6 mm	26	14 (54%)
DEPTH OF INVASION		
<1 mm	13	2 (15%)
1 to 2.9 mm	18	6 (33%)
≥3 mm	22	12 (54%)
Total cases	89	28 (31%)

Reprinted from Urist MM, O'Brien CJ, Soong SJ, et al: Squamous cell carcinoma of the buccal mucosa: Analysis of prognostic factors. Am J Surg 154:411–414, 1987.

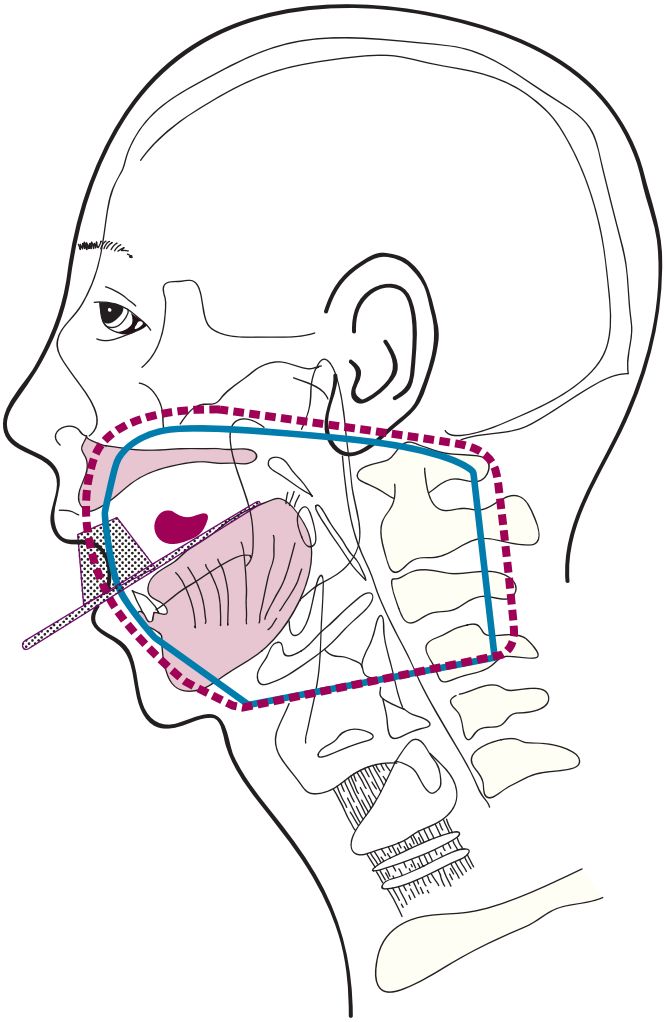


Figure 32-12 Buccal mucosa. Mixed ipsilateral en face 6-MV x-rays *(solid line)* and electrons *(dotted line)*. The electron field is 1 cm larger in all dimensions, as a result of beam constriction, except where it matches the anterior low neck field at the thyroid notch. *(Figure 1 from Mendenhall WM: Radiotherapy treatment technique. Cancer of the buccal mucosa. In Werning JW, editor: Oral cancer, New York, 2005, Thieme Medical Publishers Inc.).*

15 fractions over 19 days or 60 Gy in 25 fractions over 33 days (139 patients), or as planned split-course EBRT consisting of 35 Gy in 15 fractions over 19 days—3-week split—25 Gy in 10 fractions over 12 days (46 patients). The split-course technique tended to be used in elderly patients or for those with massive tumors. The results are shown in Table 32-15. Relapse at the primary site increased with T stage.

Urist et al[130] reviewed results of 105 patients with squamous cell carcinomas of the buccal mucosa treated by resection of the primary tumor and neck dissection (Table 32-16). In a multivariate analysis, tumor thickness greater than 6 mm was the only significant prognostic factor. Depth of invasion greater than 3 mm was also highly significant but only in the univariate analysis.

Diaz et al[125] reported on 119 patients with buccal mucosal carcinomas treated at the M. D. Anderson Cancer Center (MDACC). Eighty-four were treated with surgery alone (71%), whereas 22 received postoperative RT and 13 received preoperative RT. None were treated with RT alone. Thirty-eight patients (32%) experienced local recurrences. Five-year OS by T category were T1, 79%; T2, 65%; T3, 56%; and T4, 69%. Muscle invasion, Stensen's duct involvement, and extracapsular spread of involved nodes were significantly associated with decreased survival.[125]

Techniques of Irradiation

T1 and T2

The patient is immobilized in the supine position with an aquaplast face mask. EBRT is administered with an ipsilateral field arrangement that includes the primary lesion and the levels I and II lymph nodes. The anterior and superior borders of the field should be at least 2 cm from the borders of the primary tumor. The posterior border should be at the posterior aspect of the spinous processes if the nodes are to be irradiated; the inferior border is at the thyroid notch. The oral commissures and lips are shielded if possible to reduce the acute effects. Patients may be treated with either a "wedge pair" of 6-MV x-ray beams or an en face "mixed beam" of 6-MV x-rays and electrons (Figure 32-12). The electron energy used in the mixed beam technique varies depending on the depth of

the tumor. Because of the steep falloff of the electron beam at depth, it is preferable to risk overshooting rather than underdosing the deep extent of the tumor, and to use higher electron beam energies such as 15-MeV or 20-MeV beams. The EBRT dose fractionation schedule is 38.4 Gy at 1.6 Gy per fraction, twice daily. The ipsilateral low neck is treated with en face 6-MV x-ray field matched at the level of the thyroid notch.

If possible, a portion of the treatment should be given with intraoral cone irradiation or an interstitial implant to minimize the high dose volume and reduce the overall treatment time. Interstitial implantation is accomplished using ^{192}Ir via the plastic tube technique. The implant consists of a single plane of three to five horizontal tubes spaced 10 mm to 12 mm apart with crossing tubes at either end of the horizontal tubes. Ribbons containing ^{192}Ir seeds are afterloaded into the tubes to deliver approximately 30 Gy to 35 Gy at 10 Gy to 12 Gy per day specified at 5 mm from the plane of the sources after EBRT.

T3 and T4 Lesions

Well-lateralized tumors may be treated with the ipsilateral field arrangement as previously described. Patients with significant tumor extension toward the midline are treated with parallel-opposed fields weighted 3:2 toward the side of the lesion. Field reductions occur at 40.8 Gy to 45.6 Gy and at 60 Gy. The clinically negative low neck is treated with an anterior field with a 6-MV x-ray beam to 50 Gy in 25 fractions once daily. Thereafter, part or all of the low neck may be boosted depending on the presence and location of clinically positive neck nodes. IMRT may be considered, depending on the extent of the lesion, to optimize tumor coverage while limiting the dose to adjacent critical structures such as the cerebellum and temporal lobe.

For postoperative RT, the target volume includes the primary tumor bed and ipsilateral submandibular (level I) and subdigastric (level II) nodes. Patients with extensive positive ipsilateral nodes should be considered for RT to both sides of the neck. Patients with a tumor category of T2 or higher, tumor thickness more than 6 mm, or depth of invasion more than 3 mm have a greater than 30% risk of local recurrence, and should be treated with postoperative RT.[130]

Patients with advanced cancers unsuitable for aggressive therapy are treated with palliative RT. The fractionation scheme is either 20 Gy in 2 fractions with a 1-week interfraction interval, or 30 Gy in 10 fractions over 2 weeks.

Complications

The buccal mucosa tolerates high-dose RT with a low risk of late complications. Trismus may develop if the muscles of mastication receive high doses of RT.

GINGIVA

Anatomy

The gingiva is composed of fibrous tissue covered by mucous membrane that is firmly attached to the periosteum of the alveolar processes of the mandible and maxilla. The lower gingiva includes the mucosa covering the mandible from the gingival-buccal gutter to the origins of the mobile mucosa on the floor of the mouth. There are no minor salivary glands in the mucous membranes of the alveolar ridges.

The gingiva receives sensory innervation from the nerves supplying the teeth that are branches of cranial nerves V2 and V3 (buccal, infraorbital, greater palatine, and mental nerves).

Pathology and Patterns of Spread

Squamous cell carcinomas are most common, usually arise from the posterior portion of the mandibular gingiva, and are often associated with leukoplakia. Verrucous carcinomas may also occur, usually on the lower gingiva.

Squamous cell carcinomas of the mandibular gingiva may invade the underlying bone, retromolar trigone, adjacent buccal mucosa, and floor of the mouth. Byers et al[131] reported that 22% had associated leukoplakia, 36% had mandibular invasion, and 5% had perineural involvement. Bone invasion usually starts because there is no complete bony barrier in the edentulous portion of the mandible. The lingual and buccal plates are relatively resistant to tumor penetration. Tumor entry through the mental, mandibular, and other small foramina tend to occur in less than 10% of patients.[132]

Metastatic spread occurs first to the submandibular (level I) and upper internal jugular (level II) lymph nodes. Byers et al[131] reported 16% clinically positive nodes at diagnosis; contralateral lymph node involvement was found in only 3% of cases. Subclinical lymph node disease has been reported in 17% to 19% of cases.[131] The incidence of involved lymph nodes was 12% for T1 and T2 lesions, and 13% for T3 and T4 stage cancers.[65] The distribution of positive lymph nodes after elective neck dissection is shown in Figure 32-13.[65]

Clinical Manifestations and Staging

The patient with squamous cell carcinoma of the gingiva may first present to the dentist with ill-fitting dentures, pain, loose teeth, or a sore that will not heal. Intermittent bleeding and pain may occur when the lesion is traumatized. Invasion of the inferior dental nerve may produce paresthesia or anesthesia of the lower lip.

Because bone invasion compromises the results of RT, careful radiographic examination of the mandible with panoramic x-ray films, dental radiographs, and CT scan is essential. The AJCC staging system is shown in Table 32-2.[31]

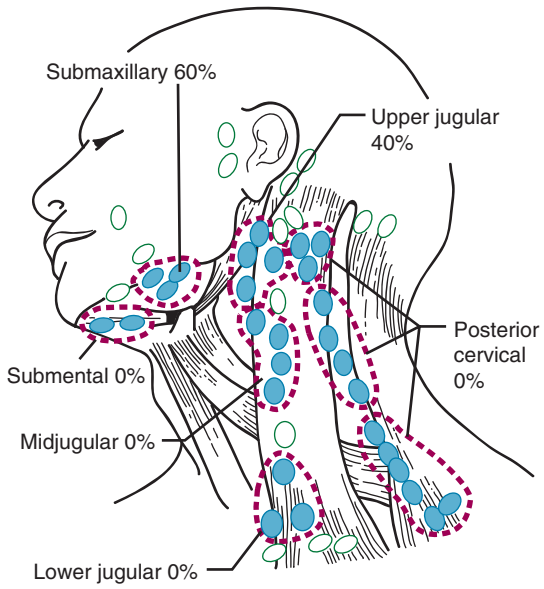


Figure 32-13 Carcinoma of the gingiva. The distribution of involved lymph nodes after elective modified neck dissection for patients with a clinically negative neck.
(From Byers RM, Wolff PF, Ballantyne AJ: Rationale for elective modified neck dissection. Head Neck Surg 10:163, 1988).

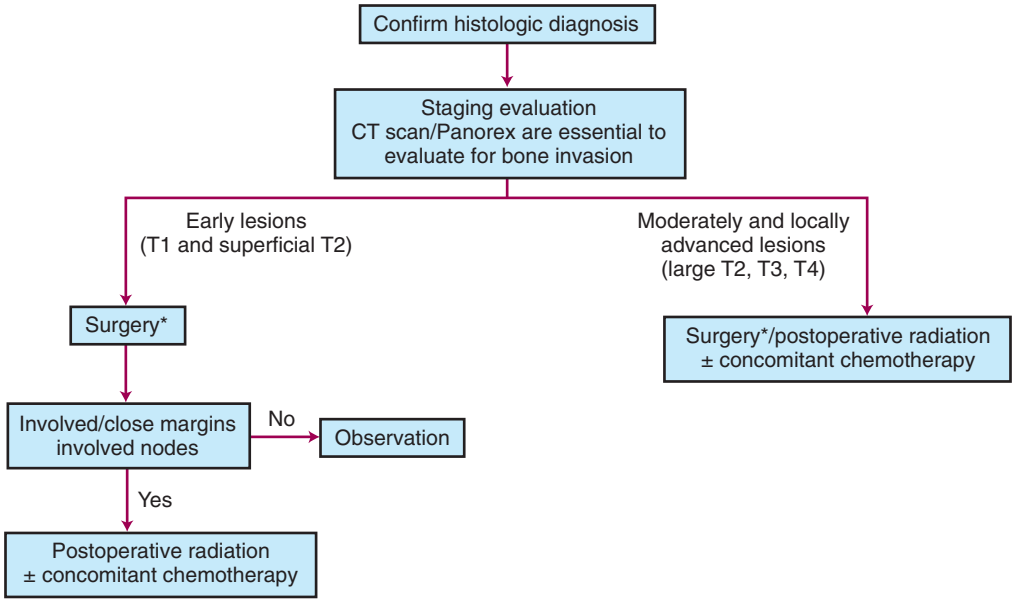


Figure 32-14 Treatment algorithm for de novo gingival cancer. *Treat neck (neck dissection).[65,131]

Treatment

Early Lesions (T1 and Superficial T2 Lesions)

The majority of these lesions are managed by surgery. Small lesions may be removed by transoral resection; however, rim resection is necessary in most cases. When direct bone invasion is present, removal of a segment of the mandible (segmental mandibulectomy) or maxilla is required. A treatment algorithm is shown in Figure 32-14.

Moderate to Locally Advanced Lesions (Large T2, T3, and T4 Lesions)

Large lesions may require a segmental mandibulectomy or partial maxillectomy.[133] Because of the likelihood of local invasion through or along the subperiosteal lymphatics, RT is often indicated after resection to eradicate microscopic disease at the margins, to sterilize subclinical disease in the cervical lymph nodes, and thus improve the likelihood of cure.[33] Postoperative RT is also indicated in the presence of perineural invasion and extensive nodal disease (large node(s) or multiple positive nodes or extranodal extension).[53] Concomitant chemotherapy during EBRT is also recommended in the postoperative setting, as outlined elsewhere in this chapter.

Results

Cady and Catlin[133] reviewed 606 patients with squamous cell carcinoma of the gingiva treated by surgery. The survival rate was 43% for patients with mandibular gingival lesions and 40% for those with maxillary alveolar ridge cancers. Soo et al[134] reviewed a 20-year experience with squamous carcinoma of the gums in 347 patients treated at the MSKCC. Sixty-four percent of patients presented with a clinically negative necks (N0). Ninety-seven percent of patients were treated surgically. The 5-year CSS was 54%. Advanced clinical stage (stages III and IV), prior dental extractions, bone invasion, and involvement of surgical margins were predictive of a lower survival rate on univariate analysis. Clinical stage was the only significant predictor of survival on multivariate analysis.

Byers et al[131] reported a 5-year OS of 43% for patients with squamous cell carcinoma of the mandibular gingiva. Fifty-one of these patients were treated with surgery that included resection of bone in 28 patients with early lesions. Only 1 of 28 patients developed a recurrence. Segmental mandibulectomy and neck dissection were used for 23 patients with advanced disease; there were no local failures. Postoperative RT was given for close margins, nerve invasion, or extensive nodal metastases (large nodes, multiple nodes, or extracapsular extension). For those treated with surgery and postoperative RT, control above the clavicles was achieved in 95% of patients.

Overholt et al[135] retrospectively reviewed results of 155 patients treated surgically for carcinoma of the mandibular gingiva. Decreased local control was observed for primary lesions larger than 3 cm ($p = 0.021$) and persistently positive surgical margins ($p = 0.027$). Survival was adversely affected by advanced T category ($p = 0.001$), positive initial and final surgical margins ($p = 0.004$), mandibular invasion ($p = 0.014$), and cervical metastases ($p < 0.001$). Local control and survival were not affected by extent of mandibular resection, tumor extension beyond the mandibular gingiva, recent dental extractions in the region of the primary tumor, perineural invasion, or histologic grade.

Patients treated with RT alone for T3 and T4 lesions have 5-year OS ranging from 30% to 40%.[123,131] Wang[128] reported a 78% control rate for patients with T1 lesions and 27% for those with T2 cancers after treatment with RT alone. Fayos[136] reported a 50% local control rate after RT alone for lesions with early bone invasion and a 25% local control rate after RT alone for those with extensive invasion.

Techniques of Irradiation

T1 and T2 Lesions

Patients who are not deemed to be surgical candidates are treated with RT. Small lesions may be treated by intraoral cone RT combined with EBRT. Interstitial implant has no place in the management of this disease because of the proximity of the bone and the high risk of osteoradionecrosis.

EBRT may be administered with either an ipsilateral en face combination of 4-MV or 6-MV x-rays and electrons, or with two 4-MV or 6-MV x-ray beams arranged in a wedge pair (Figure 32-15). The latter technique is preferred because it is possible to vary the depth of the target volume more precisely,



Figure 32-15 Patient with an early-stage carcinoma of the retromolar trigone. Radiotherapy is delivered with two 6-MV x-ray beams via a "wedge-pair" arrangement.
(Figure 1 from Mendenhall WM: Radiotherapy treatment technique. Cancer of the maxillary alveolar ridge and retromolar trigone. In Werning JW, editor: Oral cancer, New York, 2005, Thieme Publishing.)

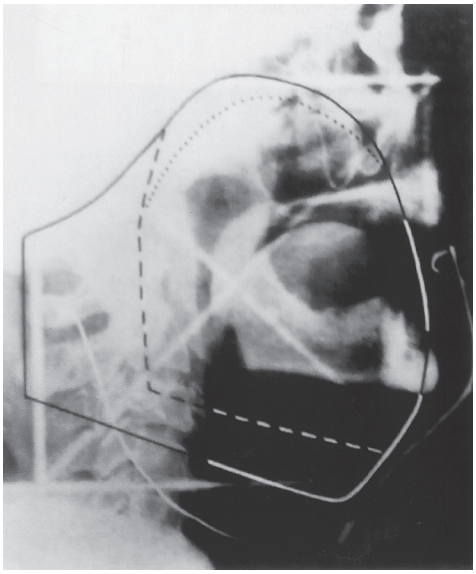


Figure 32-16 Typical portal for irradiation after hemimandibulectomy, partial maxillectomy, and radical neck dissection for pathologic T4N0 retromolar trigone lesion. **(A)** Field reductions made at 45 Gy *(dashed line)* and 60 Gy *(dotted line)*.
(Figure 2 from Amdur RJ1, Parsons JT, Mendenhall WM, et al: Postoperative irradiation for squamous cell carcinoma of the head and neck: an analysis of treatment results and complications. Int J Radiat Oncol Biol Phys 16(1):25-36, 1989.)

and underdosing the medial extent of the tumor is less likely. Lesions that exhibit significant extension onto the soft palate, or into the tongue (unusual for a T1 or T2 tumor) would be treated with parallel-opposed fields weighted 3:2 to the side of the tumor. Alternatively, IMRT may be employed to spare the contralateral parotid. The doses used are from 60 to 65 Gy over 6 to 6½ weeks for T1 tumors, and 70 Gy over 7 weeks or 74.4 Gy in 62 fractions twice daily for T2 tumors. The low neck (levels III and IV) is treated with an anterior 4-MV or 6-MV x-ray field matched at the thyroid notch and receives 50 Gy in 25 fractions.

T3 and T4 Lesions

Patients with T3 and T4 carcinomas have a relatively low chance of cure with RT alone and are optimally treated with surgery and postoperative RT. The postoperative dose varies with the margins. Patients with negative margins generally receive 60 Gy at 2 Gy per fraction. Altered fractionation is considered for patients with positive margins and for those with multiple risk factors or a prolonged interval between surgery and radiation therapy. At our institution, the preferred schedule is 74.4 Gy at 1.2 Gy per fraction administered twice daily in a continuous course over 6.5 weeks. As with other sites, concomitant cisplatin is also recommended for high-risk situations.

Patients are treated with parallel-opposed portals that include the primary tumor and upper neck nodes (levels I and II) (Figure 32-16). The fields are weighted 3:2 toward the side of the tumor. The anterior low neck (levels III and IV) is treated with an en face 6-MV x-ray field matched at the level of the thyroid notch. A petroleum jelly gauze bolus is placed on the incisions to ensure an adequate surface dose. Fields are reduced off of the spinal cord at approximately 45 Gy. An electron beam may be used to irradiate the posterior neck (level V) if additional RT to these sites is indicated after off-cord reduction.

Patients who are not suitable for surgery are treated with twice-daily EBRT to 76.8 Gy in 64 fractions over 6.5 weeks combined with concomitant chemotherapy. The field arrangements are similar to those previously described. We routinely exclude the spinal cord at 40 Gy if chemotherapy is used concomitantly. IMRT may be used to reduce the dose to the contralateral parotid unless bilateral positive nodes are present. Patients who are unsuitable for aggressive treatment receive moderate dose palliative RT; 30 Gy in 10 fractions over 2 weeks or 20 Gy in 2 fractions with a 1 week interfraction interval.

For postoperative cases, radiation volumes include the adjacent segment of the mandible or maxilla. The entire hemimandible or hemimaxilla from the distal neural foramen to the pterygopalatine ganglion must be treated when perineural invasion is present. The low neck must be irradiated if involved nodes are present or if the primary tumor is advanced. Postoperative EBRT doses range from 60 Gy to 75 Gy at 1.8 Gy to 2.0 Gy per day. If the resection margins are positive, 74.4 Gy at 1.2 Gy per fraction, twice daily with a minimum 6-hour interfraction interval is currently used at our institution. Cisplatin is administered concomitantly, based on the results of recently published randomized data from the RTOG and EORTC.[50,52]

Complications

Surgical complications include orocutaneous fistulae and bone exposure. The complications of RT include dental caries, soft-tissue necrosis, and osteoradionecrosis. The risk is greatest for more advanced lesions.

RETROMOLAR TRIGONE

Anatomy

The small triangular surface posterior to the third mandibular molar, overlying the ascending ramus is called the

retromolar trigone. Beneath the mucosa of the retromolar trigone is the pterygomandibular raphe, which is attached to the pterygoid hamulus on the posterior mylohyoid ridge of the mandible. It serves as the insertion of the buccinator and superior constrictor muscles. Behind the pterygomandibular raphe (between the medial pterygoid muscle and the ascending ramus of the mandible) is the pterygomandibular space, which contains the lingual and dental nerves. There is a small fat pad between the pterygoid muscle group and the mandibular foramen through which the mandibular nerve passes before it enters the alveolar canal. The subdigastric lymph (level II) nodes are the first echelon nodes for the retromolar trigone.

Pathology and Patterns of Spread

The vast majority of these tumors are squamous cell carcinomas. The primary tumor may spread to the adjacent buccal mucosa, anterior tonsillar pillar, mandibular gingiva, and mandible. Posterior spread to the pterygomandibular space and medial pterygoid muscle may occur. Invasion of the periosteum may occur early. Byers et al[137] reported a 25% incidence of bone invasion at diagnosis.

The incidence of clinically positive ipsilateral nodes on presentation is 39% and the risk of subclinical disease in the cervical lymph nodes is approximately 25%.[137] The distribution of positive nodes after an elective neck dissection is shown in Figure 32-17.[65]

Clinical Manifestations and Staging

Retromolar trigone cancers tend to produce pain that may be referred to the external auditory canal and preauricular area. Invasion of the pterygoid muscles can produce trismus and is better demonstrated by MRI than by CT.[66] CT scan of the head and neck (and MRI in selected cases) is useful for determining the deep extent of the primary tumor, bone invasion, and presence of positive neck nodes. The staging system is depicted in Table 32-2.

Treatment

Early Lesions (T1 and T2 Lesions)

Local control rates for T1 and T2 lesions are similar following surgery or RT.[137] If the tumor extends to the tonsillar pillar, soft palate, or buccal mucosa, and an extensive resection is required, RT is selected. If possible, intraoral cone irradiation should be used for a portion of the treatment. Small lesions without detectable bone invasion can be resected with removal of the periosteum or a rim resection of the mandible. A treatment algorithm is shown in Figure 32-18.

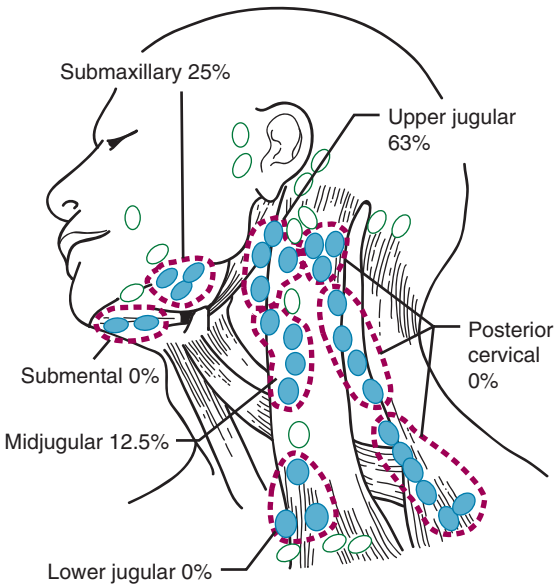


Figure 32-17 Carcinoma of the retromolar trigone. The distribution of involved lymph nodes after elective modified neck dissection for patients with a clinically negative neck.
(From Byers RM, Wolf PF, Ballantyne AJ: Rationale for elective modified neck dissection. Head Neck Surg 10:163, 1988.)

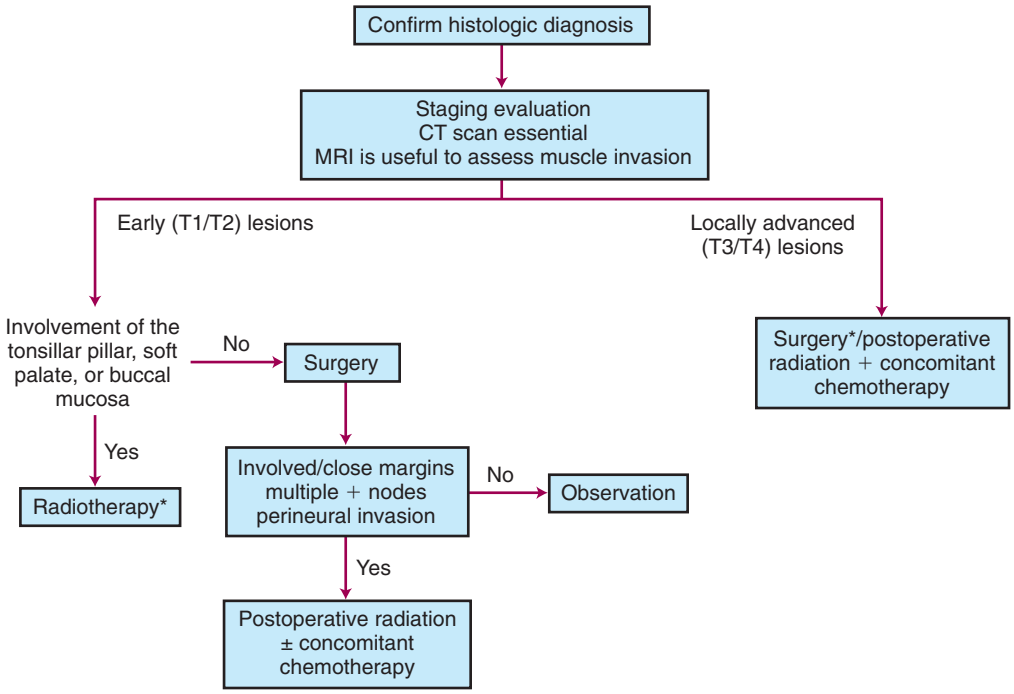


Figure 32-18 **Treatment algorithm for de novo retromolar trigone cancer.** *Treat neck (radiotherapy or neck dissection).

Locally Advanced Lesions (T3 and T4)

Superficial T3 lesions can be treated by RT. Locally advanced cancers (especially those with evidence of bony invasion) require a segmental mandibulectomy followed, in almost all cases by postoperative RT.

Results

Lo et al[138] reported on a series of patients treated with RT at the MDACC (Table 32-17). Patients with retromolar trigone cancers were grouped with those having anterior tonsillar pillar lesions. Local control varied from 70% to 76% after RT for those with T1, T2, and T3 cancers. Salvage surgery resulted in ultimate local control rates varying from 92% to 100%.

Mendenhall et al reported on 99 patients treated with RT alone or combined with surgery at the University of Florida.[139] The likelihood of cure was influenced by extent of disease and treatment; those treated with surgery and RT had a better chance of cure than those treated with RT alone (Table 32-18).

Kowalski et al[140] reported on 114 patients who underwent an extended "commando" operation between 1960 and 1991 for carcinoma of the retromolar trigone. Sixty-six patients received postoperative RT (median 50 Gy). Tumor categories were: T1, 5 patients; T2, 44 patients; T3, 24 patients; T4, 28 patients; and TX, 13 patients. Forty-one patients (36%) experienced a recurrence at one or more sites: local 31 (27%); dissected neck, 9(22%); contralateral neck, 3 (7%); and distant, 7 (17%). The 5-year overall survival rates by T stage were: T1, 80.0%; T2, 57.8%; T3, 46.5%; T4, 65.2%, and overall, 55.3%.

Byers et al[137] reported on 110 patients with squamous carcinoma of the retromolar trigone who were treated at the MDACC from 1965 to 1977 and followed for ≥5 years. Seventy patients had T1 and T2 tumors, and 77 patients had a clinically negative neck. Sixty patients received either surgery alone (n = 46) or combined with preoperative or postoperative RT (n = 14). Fifty patients were treated with RT alone. Failure at the primary site occurred in 7 of 60 patients (12%) treated surgically, and in 8 of 50 patients (16%) of patients treated with RT alone.

Techniques of Irradiation

Treatment techniques for retromolar trigone cancers are similar to those discussed in the preceding section on gingival cancers.

Complications

Thirty percent of the patients reported by Lo et al[138] developed some degree of bone exposure but only 9 patients (5.6%) required a segmental mandibulectomy. The probability of bone exposure was not found to be dose related. Huang et al[141] reported on 65 patients treated for retromolar trigone cancer and observed complications that included bone necrosis, soft-tissue necrosis, and severe trismus, occurring in 12% after surgery and postoperative RT, 11% after RT alone, and none after preoperative RT and surgery.

Kowalski et al[140] observed complications in 51.8% of 114 patients who underwent an extended commando operation between 1960 to 1991; 21 patients (18.4%) had a wound infection.

HARD PALATE

Squamous cell carcinoma of the hard palate is relatively rare. In a series of about 5000 patients with oral cavity cancers, only 25 patients (0.5%) had squamous cell carcinoma of the hard

TABLE 32-17 Local Control Rates after Radiotherapy: Anterior Faucial Pillar-Retromolar Trigone—M. D. Anderson Hospital

Category	Local Control	Treatment of Primary Failure	No. Patients Salvaged	Ultimate Control Rate
T1	12/17 (71%)	Surgery (5)*	5/5	17/17 (100%)
T2	57/81 (70%)	No treatment (2) Surgery (21) Surgery + RT (1)	19/24†	76/81 (94%)
T3	19/25 (76%)	Surgery (5) Surgery + Chemo (1)	4/6†	23/25 (92%)
T4	3/5	Surgery (1) Chemo (1)	1/2†	4/5

Reprinted from Lo K, Fletcher GH, Byers RM, et al: Results of irradiation in the squamous cell carcinomas of the anterior faucial pillar-retromolar trigone. Int J Radiat Oncol Biol Phys 13:969–974, 1987.

Chemo, *Chemotherapy;* RT, *radiotherapy.*

**Numbers in parentheses indicate number of patients.*

†Five T2 patients, one T3 patient, and one T4 patient died in less than 2 years with no evidence of local disease.

TABLE 32-18 Local Control of Squamous Cell Carcinoma of the Retromolar Trigone Treated at the University of Florida

	Definitive Radiation			Surgery + Radiation			Total		
T Category	No. Pts.	No. Local Recurrences	5-Year LC	No. Pts.	No. Local Recurrences	5-Year LC	No. Pts.	No. Local Recurrences	5-Year LC
T1-T3	26	13	49%	31	6	78%	57	19	65%
T4	9	6	44%	33	11	65%	42	17	61%
Total	35	19	48%	64	17	71%	99	36	63%

Reprinted from Mendenhall MW, Morris CG, Werning JW, et al: Retromolar trigone squamous cell carcinoma treated with radiotherapy alone or combined with surgery. Cancer 103(11):2320–2325, 2005.

LC, *Local control.*

palate.[142] In a similar study, carcinoma of the hard palate represented 3% of all oral cavity carcinomas.[143]

The male-to-female ratio is approximately 1:1. For both males and females, the peak incidence tends to occur in the seventh decade, with more than 98% of patients older than the age of 40.[144]

Anatomy

The palate forms the roof of the oral cavity and the floor of the nasal cavity. The anterior two thirds, or bony part of the palate, is called the hard palate and is formed by the palatine processes of the maxilla and the horizontal plates of the palatine bones. Anteriorly and laterally, the hard palate is bounded by the maxillary alveolar ridge and gingiva. Posteriorly, the hard palate is contiguous with the soft palate. The hard palate is covered by a mucous membrane overlying the periosteum. Deep to the mucosa are the secreting palatine glands. The incisive foramen is posterior to the maxillary central incisors; the nasopalatine nerves pass through this foramen.

The greater palatine foramina are medial to the third maxillary molars; the greater palatine vessels and nerves emerge from this foramen. The greater palatine nerve innervates the gingiva, mucous membrane, and glands of the hard palate. The nasopalatine nerve innervates the mucous membrane of the anterior part of the hard palate. Because of the rich blood supply from the greater palatine artery, the incidence of osteoradionecrosis and soft-tissue necrosis is lower than that reported for the mandible.[145]

Pathology and Patterns of Spread

Malignant tumors of the hard palate are most often adenoid cystic carcinomas and mucoepidermoid carcinomas arising from minor salivary glands. Squamous cell carcinoma is relatively uncommon. Kaposi's sarcoma and melanomas may also originate from the mucosa of the hard palate.[144]

Most squamous cell carcinomas originate on the gingiva and spread secondarily to the hard palate. Perineural invasion occurs via the greater palatine foramen. The risk of positive lymph nodes is 13% to 24% at diagnosis.[146,147] The incidence of subclinical disease in the cervical lymphatics is 22%.[62]

Clinical Manifestations, Patient Evaluation, and Staging

Patients with squamous cell carcinomas of the hard palate may first present to the dentist with ill-fitting dentures, pain, loose teeth, or a sore that will not heal. Intermittent bleeding and paresthesias may also occur.

Imaging of the hard palate is primarily with CT scanning and is occasionally supplemented with MRI. Imaging of the neck nodes must include the facial and retrozygomatic nodes.[66] Facial nodes are best assessed by bimanual examination, particularly in patients with dental fillings. If the lesion is an adenoid cystic carcinoma, it is essential to search for perineural spread. The AJCC staging system is shown in Table 32-2.[31]

Treatment

Surgery is the usual initial treatment for most lesions; postoperative RT is indicated for patients with more extensive cancers. The role of primary RT in the management of hard palate carcinomas is ill defined. If the lesion has a large surface area and is superficial, RT can be used as initial treatment. However, most patients are treated with surgery because the underlying bone is often involved and, in that scenario, RT is unlikely to be effective.[148] Postoperative RT is indicated for close or involved margins, perineural or vascular invasion, multiple involved nodes, extracapsular extension, or bone invasion.[53] Dose and fractionation recommendations are similar to those given for other sites. A treatment algorithm is shown in Figure 32-19.

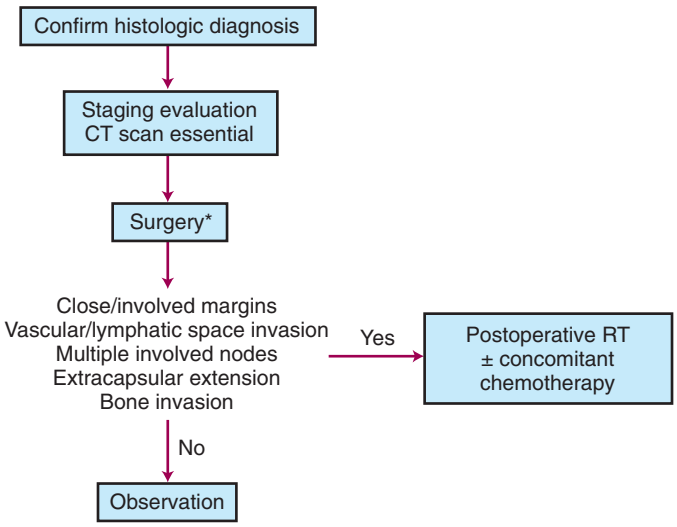


Figure 32-19 Treatment algorithm for de novo hard palate cancer.
*Treat neck (neck dissection).

Malignant salivary gland tumors of the hard palate are often treated by a combination of surgery and postoperative RT, particularly if they are high-grade tumors (adenocarcinoma, salivary duct carcinoma, high-grade mucoepidermoid, myoepithelial carcinoma, others?). Low-grade (acinic cell carcinoma, adenoid cystic carcinoma, low-grade mucoepidermoid) minor salivary gland carcinomas can be treated by surgery alone if negative margins can be achieved. Some malignant minor salivary gland tumors have been successfully controlled by high-dose RT alone.[149]

Results

Shibuya et al[150] reported the RT results for malignant lesions of the hard palate; the 5-year OS for those with squamous cell carcinomas was approximately 45%. For patients with minimal bone invasion and clinically negative neck, the 5-year OS was 75%. Data from the University of Virginia are presented in Table 32-19 for 41 patients treated with surgery, RT or both.[151]

Yorozu et al[152] reported on 31 patients treated with EBRT at the Christie Hospital between 1990 and 1997. Twenty-six received RT alone and five were treated postoperatively for positive surgical margins. The 5-year local and ultimate local control rates after salvage surgery were 53% and 69%, respectively. Survival rates were 48% for patients with squamous carcinomas and 63% for those with minor salivary gland carcinomas. T category was the only significant predictor of 5-year local control rates, which were 80% for T1 and T2 lesions and 24% for T3 and T4 lesions, respectively. The only significant predictor for survival was N category.

Tran et al[153] reported on 38 patients treated for salivary gland tumors of the palate at University of California at Los Angeles. Twenty-three of 38 tumors were on the hard palate; adenoid cystic carcinoma was the most common histologic type. Twenty-five patients received surgery alone; 13 were treated with surgery and postoperative RT. The local control rates were comparable for the two groups of patients (88% and 85%, respectively).

TABLE 32-19 Hard Palate Malignancies Treated by Surgery, Radiotherapy, or Both: 5- and 10-Year Survival Rates

	5-Year		10-Year	
Histology	**Absolute**	**Cause-Specific**	**Absolute**	**Cause-Specific**
Squamous cell carcinoma	10/26 (38%)	10/17 (59%)	8/25 (32%)	8/15 (53%)
Salivary gland tumors				
Adenocarcinoma	5/7 (71%)	5/7 (71%)	3/6 (50%)	3/5 (60%)
Adenoid cystic carcinoma	3/3	3/3	1/2	1/1
Malignant mixed tumor	5/5	5/5	1/4	1/1

Reprinted from Chung CK, Johns ME, Cantrell RW, et al: Radiotherapy in the management of primary malignancies of the hard palate. Laryngoscope 90:576–584, 1980.

Kovalic et al[154] reported on 13 patients with carcinoma of the hard palate treated at Washington University. Histologic types included adenoid cystic carcinoma, 9 patients; squamous cell carcinoma, 3 patients; and mucoepidermoid carcinoma, 1 patient. T-stages were T1, 1 patient; T2, 5 patients; T3, 3 patients; and T4, 4 patients. All had a clinically negative neck. Ten patients received excision and postoperative RT; 3 patients were treated with RT alone. The 10-year DFS and local control rates were 77% and 92%, respectively.

A group of 50 patients was treated surgically at the University of Cincinnati and included 25 patients with squamous cell carcinomas, 11 with adenoid cystic carcinomas, 6 with adenocarcinomas and 8 with miscellaneous histologies.[155] The 5-year OS by histology were squamous carcinoma, 76%; adenoid cystic carcinoma, 90%; and overall, 85%. The 10-year OS for adenoid cystic carcinomas fell to 75%, consistent with their tendency to develop late recurrences, including distant metastases.

Most relapses are found at the primary site. Evans and Shah reported a 53% incidence of isolated primary site failure.[144] The incidence of recurrence in the cervical nodes was 30%; failure involving both the primary site as well as the cervical lymph nodes was 10%. No patient treatment failed with results of distant metastases only. Seven percent of the patients experienced treatment failure in both distant and local regional sites.[144]

The risk of developing metachronous carcinomas is high. In the University of Virginia's experience, 28% of the patients developed a metachronous primary carcinoma during their lifetime and 13% developed a third, fourth, or fifth carcinoma. The oral cavity was the most common site for metachronous cancers.[146]

Techniques of Irradiation: Hard Palate and Maxillary Alveolar Ridge

T1 and T2 Lesions

The preferred initial treatment for patients with T1 and T2 carcinomas of the hard palate is surgery. RT is used by default to treat the occasional patient who is not a surgical candidate. Most of these lesions are not well lateralized, consequently, RT is administered with parallel-opposed fields encompassing the primary tumor with a margin of 2 cm or less. A cork-and-tongue block is placed in the mouth to displace the tongue, mandible, and lower lip inferiorly and to reduce the amount of normal tissue included in the fields (Figure 32-20, *A*). These lesions are not amenable to brachytherapy and so patients are treated with EBRT alone. The likelihood of cure with RT alone, even for early-stage lesions, is relatively low so that an altered fractionation technique should be employed. We prefer hyperfractionated RT and use 74.4 Gy to 76.8 Gy at 1.2 Gy per fraction, twice daily, over 6 to 6.5 weeks. The volumes are extended to include the regional lymph nodes (levels I and II) for patients with aggressive, poorly differentiated cancers (see Figure 32-20, *B*). The disadvantage of irradiating the regional lymph nodes is that the acute toxicity of the treatment is significantly increased. Fields are reduced at 45.6 Gy in 38 fractions to limited portals that adequately encompass the primary cancer. The low neck (levels III and IV) is irradiated with an anterior field that abuts the primary fields at the level of the thyroid notch and receives 50 Gy in 25 fractions over 5 weeks.

T3 and T4 Lesions

Patients with T3 and T4 cancers are optimally treated with surgery and postoperative RT using fields encompassing the primary tumor and regional lymph nodes as previously described. Postoperative RT is initiated within 6 weeks of surgery. Patients with negative margins generally receive 60 Gy at 2 Gy per fraction. Reduction off of the spinal cord is performed at 44 Gy to 46 Gy and the posterior strips are treated with 8 MeV to 10 MeV elections if it is necessary to irradiate these areas to a higher dose. An altered fractionation technique should be considered for those who have positive margins, multiple risk factors, or a prolonged surgery-RT interval.[53] Systemic cisplatin chemotherapy is usually administered concomitantly with RT in the postoperative setting.[50,52]

Patients with T3 and T4 cancers who are not surgical candidates have a low chance of cure with RT. Patients are treated to 76.8 Gy at 1.2 Gy per fraction twice daily over 6.5 weeks combined with concomitant chemotherapy such as weekly cisplatin 30 mg/m^2. Patients who are not candidates for aggressive therapy are treated with moderate dose palliative RT over 1 to 2 weeks.

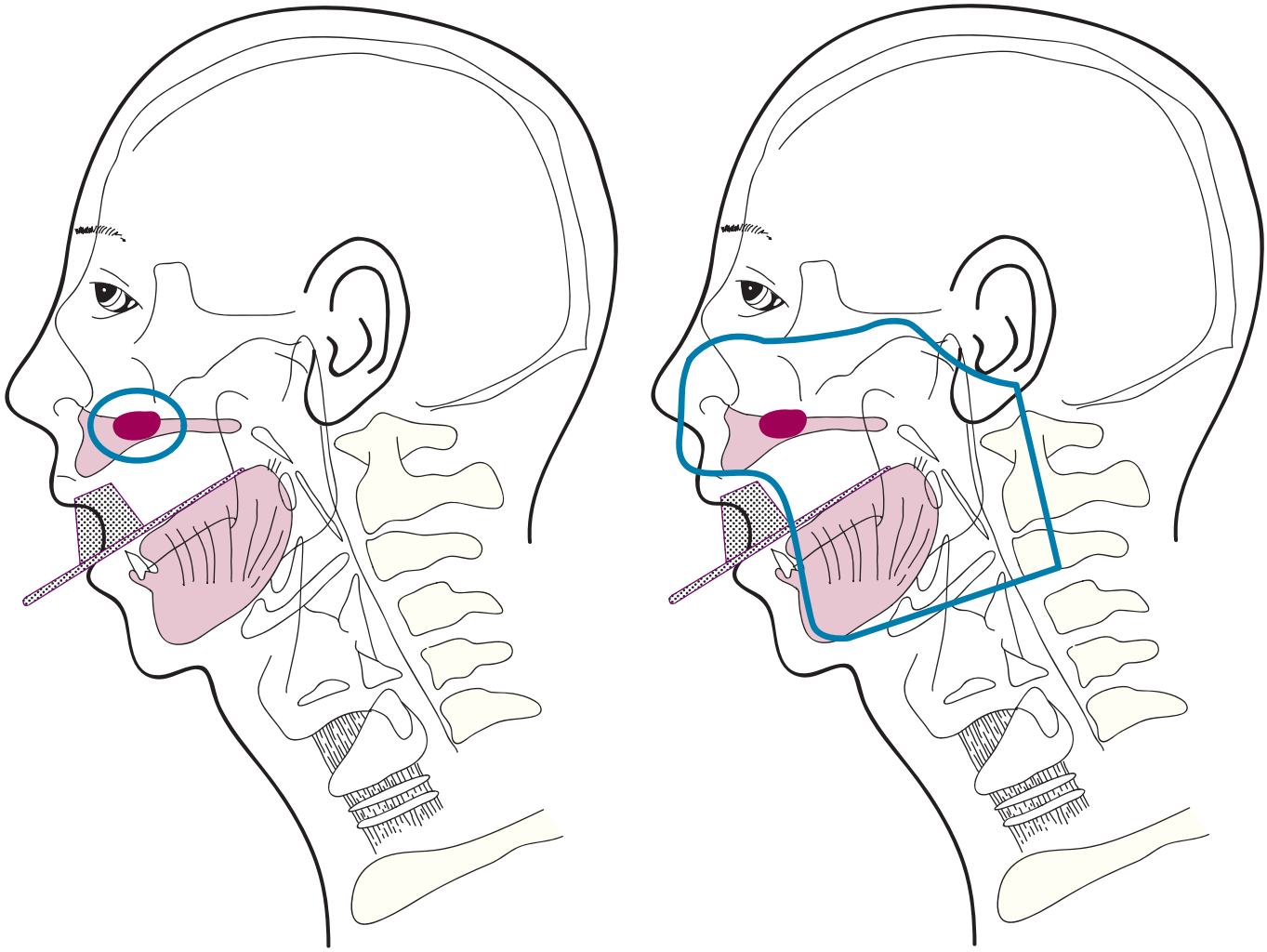
Complications

No severe complications occurred in the patients who received RT (60 Gy in 5 to 6 weeks) at the University of Virginia.[151] Most patients developed xerostomia and temporary loss of taste.[146]

Yorozu et al[152] reported results for 31 patients treated with EBRT at the Christie Hospital between 1990 and 1997. Twenty-six patients received RT alone and five were treated postoperatively for positive surgical margins; necrosis occurred in 1 patient.

CONCLUSIONS AND FUTURE POSSIBILITIES

Treatment algorithms by site within the oral cavity are covered in the separate site presentations and discussions within this chapter. In general, early lesions at any site in the oral cavity can be treated by single modality treatment with excellent results. As lesions become more extensive, the need for combined modality treatment increases (i.e., surgery plus RT with or without chemotherapy, RT plus concomitant chemotherapy, or all three modalities). Future trials should address issues of sequencing when combined modality treatment is indicated,



A B

Figure 32-20 **A,** Early-stage hard palate carcinomas. Parallel-opposed 6-MV x-ray fields include the tumor with a 2-cm margin. Cork-and-tongue block displace the tongue and mandible inferiorly to minimize the amount of normal tissue included in the fields. **B,** Advanced hard palate carcinoma. Portals include the primary tumor and upper neck nodes (levels I and II). The superior margin of the portals is extended to include V_2 to the skull base.
(Figure 2 from Mendenhall WM: Radiotherapy treatment technique. Cancer of the maxillary alveolar and hard palate. In Werning JW, editor: Oral cancer, New York, 2005, Thieme Publishing; Cancer of the maxillary alveolar and hard palate. In Werning JW, editor: Oral cancer, New York, 2005, Thieme Publishing, Figures 1 and 2.)

as well as the need for concomitant chemotherapy when altered fractionation RT is employed and the optimal chemotherapy agents and regimen (cisplatin, cetuximab, docetaxel alone, or combined).

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CHAPTER

33 Oropharyngeal Cancer



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INCIDENCE

The estimated annual incidence of oropharyngeal cancer in the United States is slightly more than 10,000 patients. The incidence of oropharyngeal cancer has gradually increased over the past several decades, particularly in younger patients.

BIOLOGIC CHARACTERISTICS

Squamous cell carcinomas (SCCs) represent more than 95% of all tumors arising within the oropharynx. Approximately 70% of patients present with nodal involvement, and 10% to 15% of these have distant metastases. Human papillomavirus (HPV) has been associated with an increasing proportion of oropharyngeal carcinomas, particularly those arising from the tonsillar fossa and base of tongue in patients without significant tobacco or alcohol exposure. Patients with HPV-positive tumors have notably better clinical outcomes than those with HPV-negative tumors and are more responsive to conventional therapies.

STAGING EVALUATION

Staging entails a detailed history and physical evaluation, cross-sectional imaging with computed tomography (CT) or magnetic resonance imaging (MRI), chest imaging, routine blood cell counts, and serum chemistry studies. A chest CT scan should be obtained if the risk of pulmonary metastases is elevated; this occurs in patients with advanced nodal involvement, a locally advanced primary tumor (stages T3 and T4), low cervical lymph nodes, or recurrent disease. 18F-fluorodeoxyglucose positron emission tomography (FDG PET) has assumed increased importance in the initial staging, treatment planning, and postradiation nodal evaluation of these patients.

PRIMARY THERAPY

Traditionally, the preferred treatment for patients with small (stages T1 and T2) oropharyngeal SCCs has been radiation therapy. Historical data show equivalent outcomes between radiation and surgery for early-stage oropharyngeal cancers, but less functional compromise has conventionally been seen with radiation therapy. Newer transoral surgical techniques have diminished morbidity and improved recovery times associated with surgery, making this a viable alternative to radiation alone in early stage oropharyngeal cancers. For those undergoing radiation, long-term toxicities have been reduced by intensity-modulated radiation (IMRT) techniques that diminish the dose to the salivary glands and other critical structures or by unilateral radiation techniques when appropriate.

LOCALLY ADVANCED DISEASE

Multiple Phase III trials and a comprehensive meta-analysis demonstrate that concurrent chemotherapy enhances the radiation response in locoregionally advanced head and neck cancers, leading to improved locoregional control and survival. Given the functional compromise often induced by surgical resection, even with free-flap reconstruction, concurrent chemoradiation has emerged as a standard of care for the majority of locally advanced oropharyngeal cancers provided the patient can tolerate the rigors of combined modality treatment. Molecular targeting agents, specifically cetuximab, can improve overall survival (OS) rates if the patient is not a suitable candidate for cytotoxic chemotherapy.

Contraindications to an "organ-sparing" approach include bone invasion or the anticipation of severe functional deficits following treatment. Patients with these contraindications should be treated with surgery and postoperative radiation. The addition of concurrent chemotherapy to postoperative radiation has demonstrated benefit for patients with high-risk pathologic features including positive surgical margins and extracapsular nodal spread.

For patients with advanced nodal disease who undergo definitive radiation with or without chemotherapy but have an incomplete nodal response to treatment, a neck dissection is warranted.

The recent recognition of the excellent prognosis of patients with HPV-associated oropharynx cancer, coupled with the significant incidence of long-term toxicity and functional disability in some patients after definitive chemoradiation, has increased interest and clinical investigation of transoral surgical techniques. These surgical approaches have less morbidity that traditional open surgical procedures and may allow for a reduction in the need for, or the intensity of, postoperative radiation and chemotherapy.

The oropharynx consists of the base of the tongue, tonsillar region, soft palate, and lateral and posterior oropharyngeal walls (Figure 33-1). Determining the precise annual incidence for new cancers of the oropharynx is difficult because there is overlap with other head and neck sites within various reporting classifications. The cumulative incidence of cancers of the "oral cavity and pharynx," comprised of the tongue, mouth, pharynx, and oral cavity, was estimated at 42,440 in the United States in 2014, with 30,220 male and 12,220 female patients.[1] Malignant tumors within the oropharynx, defined as tumors arising from the base of tongue, tonsillar complex, soft palate, or lateral and posterior pharyngeal walls by the American Joint Committee on Cancer (AJCC) staging definition,[2] are generally thought to represent approximately 25% of the total. This places the estimated total at slightly more than 10,000 new oropharyngeal carcinomas per year in the United States, although some believe the rate is lower.[2]

The incidence of head and neck cancers has increased during the twentieth century, particularly in persons born after 1920. The higher cancer incidence over this time period is associated with the rise in alcohol and tobacco consumption in the United States and other westernized countries over the

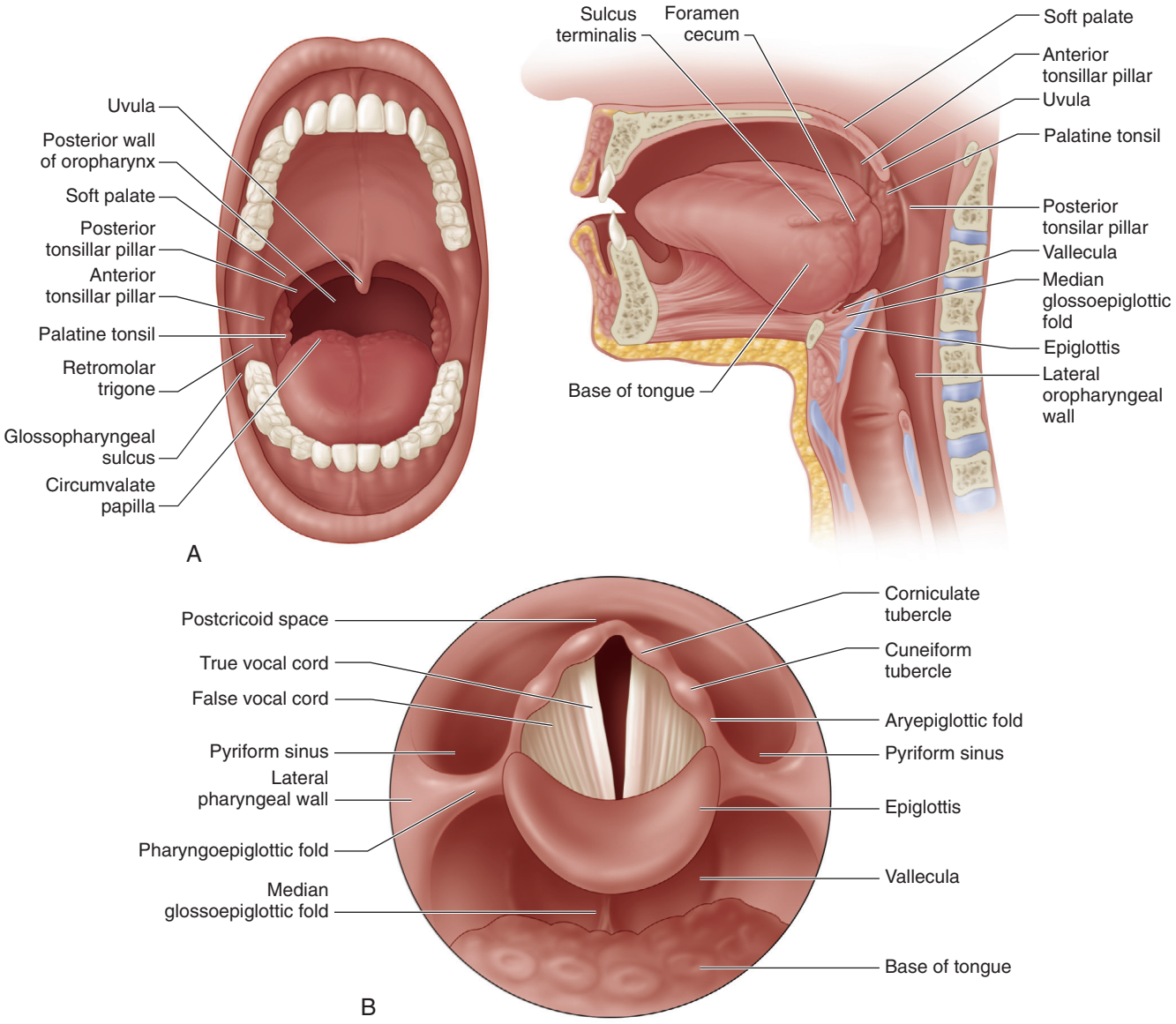


Figure 33-1 Normal anatomy of the oropharynx. **A,** Anterior view and lateral view of the oropharynx with left lateral structures removed. **B,** Oropharynx as viewed through a fiberoptic endoscope.

same era.[3,4] This trend has reversed over the past two decades in the United States, with a small decline in SCCs of the head and neck, likely secondary to a reduction in tobacco use. Despite this general reduction in head and neck cancers and the diminished incidence rate seen for the neighboring oral cavity, the incidence of oropharyngeal carcinomas has continued to increase since the early 1980s, predominantly in men younger than age 60 years.[5-7] The increase in oropharyngeal cancers is not thought to be attributable to the reduction in tonsillectomy frequency between the 1970s and the 1990s because this trend would not be expected to alter the incidence of base of tongue primary tumors.[8]

The worldwide estimated annual incidence of tumors defined as arising either from the oral cavity or the pharynx excluding the nasopharynx, including oropharyngeal site tumors, was 404,585 in 2002. Over two thirds of the patients were male, and the mortality rate on average was less than half of the incidence rate.[9] Such an analysis comes with the typical challenges in documenting such malignant diseases, particularly among the medically underserved internationally. Geographic variations in global rates reflect the prevalence of known risk factors, such as tobacco and alcohol use, within specific populations.

ETIOLOGY AND EPIDEMIOLOGY

Tobacco and Alcohol Use

SCC of the oropharynx most commonly affects patients older than 50 years, and men more than women. Despite this generalization, over the past 30 years oropharyngeal cancer rates have been on the rise in both men and women under the age of 45 years.[6] Both alcohol and tobacco use are long-known, well-defined risk factors for SCCs of the head and neck, including those arising within the oropharynx. Again, separating data regarding oral cavity tumors and oropharyngeal tumors within published series can be challenging given reporting methods, and results may overstate the role of tobacco and alcohol use in oropharyngeal malignant diseases. The two substances individually and together contribute to a

field cancerization effect within the upper aerodigestive tract. The effect of alcohol consumption and cigarette smoking on oropharyngeal cancer risk is reported to be dependent on both the intensity and duration of use and was traditionally responsible for approximately 80% of oropharyngeal cancers, with a higher proportion in men than in women in one series.[10]

A population-based study in Sweden compared 605 patients with head and neck cancer with 756 controls. A hazard ratio (HR) of 8.4 was seen with current smokers; this figure was increased by an earlier starting age, longer duration of smoking, greater lifetime total consumption, and increased intensity of daily tobacco use.[11] Increasing alcohol intake, particularly more than 50 g per day, was also associated with an increased relative risk of head and neck cancers. A compilation of case-control studies places the tobacco-associated odds ratio at 2.13 for tobacco users when compared with never users, with the ratio doubling in persons who smoke more than 30 cigarettes per day or those who have smoked for more than 30 pack-years.[12] Involuntary or secondhand tobacco exposure may also be a risk factor, particularly when the person has been exposed for more than 15 years either at home or at work.[13] Alcohol use increases the rate of oropharyngeal carcinomas in never smokers, prior smokers, and current smokers, and the risk decreases with cessation of alcohol use.[14] Although use of either alcohol or tobacco elevates the risk of oral cavity and oropharyngeal cancer, there is a synergistic effect from the use of both simultaneously. The risk is calculated to be 13-fold the expected risk of each used independently, creating an approximately 50-fold greater risk for oral cavity and oropharyngeal cancer compared with that of nonsmokers and nondrinkers.[14,15] Tobacco cessation decreased the risk of head and neck cancer by 40% in years 1 through 4, although the risk of head and neck cancers did not return to baseline until 20 years had elapsed after either tobacco or alcohol cessation.[16]

Human Papillomavirus Infection

Additional behavioral risk factors have been described besides classic tobacco and alcohol abuse, and they appear to correlate with an elevated risk of oral HPV infection. The role of HPV corresponds to the identified increase in head and neck cancer incidences seen in younger nonsmokers and nondrinkers. The increased incidence has been seen both in the United States and in European countries, despite the general trend of fewer head and neck cancers. This rise has been most marked among young patients in sites associated with HPV.[6] HPV is a sexually transmitted disease recently recognized as a risk factor for SCC of the head and neck, particularly in the oropharyngeal subsite, although the connection was initially suggested in 1983.[17] HPV has been implicated in approximately 25% of head and neck cancers based on polymerase chain reaction (PCR) detection of HPV DNA. This prevalence is site specific, with a significantly higher percentage of HPV-associated cancers in the oropharynx compared with the oral cavity or larynx.[18] A recent meta-analysis found the overall prevalence of HPV in oropharyngeal cancers to have increased over time. Before 2000, the rate of positivity was 40.5%, increasing to 64.3% from 2000 to 2004 and 72.2% between 2005 and 2009.[19] Evaluation of more distant time periods demonstrates an even lower rate of HPV involvement, with a 16.3% detection rate from 1984 to 1989, increasing to 71.7% from 2001 to 2004.[20] These trends constitute a population-based HPV-positive increase of 225% over this time period, whereas the HPV-negative incidence dropped by 50%.

The link between HPV and oropharyngeal cancers is several-fold and mimics the lines of evidence associating HPV and cervical cancer. First, HPV has been identified in tumor cells of head and neck SCCs.[17,21] HPV status is most commonly assessed by either immunohistochemistry for p16 or in situ hybridization for high-risk HPV subtypes. Both methods have demonstrated prognostic significance despite some studies suggesting a 15% to 20% false-positive and false-negative rates for p16 immunohistochemistry testing as a surrogate for HPV.[22,23] Identified prevalence rates have varied, depending on the tumor subsite, sensitivity of the HPV detection method, and geographic location, with associated ethnic variance.[24] HPV-16 is the most common HPV subtype associated with oropharyngeal SCCs, seen in 85% to 90% of HPV-associated cancers.[18,21] The remainder are associated with HPV subtypes 18, 31, 33, and 35, which also play a role in the development of cervical cancer. Second, HPV-positive SCCs of the head and neck have viral characteristics concordant with HPV-associated carcinogenesis, including a high viral load and viral oncoprotein expression.[24] The oncogenic function of these HPV-associated oncoproteins ultimately accounts for the different molecular alterations found in HPV-positive tumors compared with HPV-negative tumors.

Additional evidence for an HPV association includes significant links in case-control studies between HPV seropositivity and SCCs of the head and neck. A case-control study comparing 100 patients diagnosed with oropharyngeal cancer and 200 controls found oropharyngeal cancer to be closely associated with oral HPV-16 infection (odds ratio, 14.6), oral infection with any of the HPV types (odds ratio, 12.3), and seropositivity for the HPV-16 L1 capsid protein (odds ratio, 32.2), strongly associating oral HPV with oropharyngeal cancer.[25] Behavioral risk factors associated with oral HPV infection have also been correlated with an increased risk of oropharyngeal cancer. They include a high lifetime number of vaginal sex partners and oral sex partners.[25] This correlation between HPV DNA in tumor specimens and lifetime sex partners has also been identified by others,[26] as has age at first intercourse and genital warts.[27] Patients with HPV-associated head and neck cancers also have an increased risk of anogenital cancers, of which cervical and anal cancers have been strongly associated with HPV infection, and vice versa.[28] Again, this supports the influence of sexual behavior and HPV infection on oropharyngeal cancer risk.

Patients with HPV-associated oropharyngeal cancers tend to have distinct clinical and pathologic features compared with those with HPV-negative cancers (Table 33-1). Besides the history of high-risk sexual behavior described earlier, patients with HPV-associated oropharyngeal cancers are more likely to be light users or nonusers of alcohol and tobacco,[29,30] although this lack of connection has not been universally identified.[27]

TABLE 33-1 Distinctive Clinicopathologic Characteristics for HPV-Positive and HPV-Negative Head and Neck SCC

	HPV-Positive	HPV-Negative
Anatomic site	Tonsil, base of tongue	All sites
Histology	Basaloid	Keratinized
Age	Younger	Older
Social economic status	Trend higher	Trend lower
Risk factors	Sexual behavior	Alcohol and tobacco
Survival	Improved	Worse
Incidence	Increasing	Decreasing
EGFR expression	Commonly negative	Commonly positive

Adapted from Vidal L, Gillison ML: Human papillomavirus in HNSCC: Recognition of a distinct disease type. Hematol Oncol Clin North Am 22(6):1125–1142, vii, 2008.

Despite the apparent lack of association between HPV-associated oropharyngeal cancers and tobacco use, there is a correlation with marijuana use and its intensity and duration.[5] Individuals with HPV-positive SCC of the head and neck tend to be younger by approximately 5 years compared with patients who are HPV negative.[24] Pathologically, HPV-positive cancers are more likely to be poorly differentiated with basaloid features.[31]

A meta-analysis of the prognostic impact of HPV in head and neck SCCs demonstrated that patients who are HPV positive were likely to have improvements in rates of OS (HR, 0.85) and disease-free survival (DFS) (HR, 0.62). Similar improvements in OS and DFS were identified specifically within the oropharyngeal subsite.[32] Improved outcomes with HPV positivity were confirmed in an Eastern Cooperative Oncology Group (ECOG) Phase II multicenter trial in which higher response rates were seen after induction chemotherapy and after chemoradiation treatment. This led to a statistically improved OS and a lower risk of progression.[31] Analysis of the subset of patients with stage III or IV oropharyngeal cancer in Radiation Therapy Oncology Group (RTOG) study 0129 found HPV status to be the major determinant of OS, followed by duration of tobacco use and tumor stage.[33] Locoregional recurrences were reduced at 3 years (13.6% versus 35.1%) in HPV-positive tumors, and OS was 82.4% versus 57.1%. Although the bulk of the survival difference was attributable to HPV positivity, favorable prognostic features associated with the HPV-positive subgroup accounted for approximately 10% of the outcome difference.

Patients who are HPV positive also have a lower risk of second malignant tumors because such patients lack the field cancerization effect produced by alcohol and tobacco exposure.[29,30] Given the different clinical, pathologic, and molecular characteristics, as well as the improved prognosis and treatment response, it has been proposed that HPV-positive and HPV-negative SCCs of the oropharynx should be considered distinct disease entities with different goals and expectations from treatment.[34]

PREVENTION AND EARLY DETECTION

Classic prevention for SCC of the oropharynx, and head and neck cancers in general, has revolved around tobacco cessation and bringing alcohol use to more moderate levels. With the impact of HPV now better understood, ongoing HPV vaccination campaigns to lower the incidence of cervical cancer may simultaneously reduce HPV-related head and neck cancers. Two vaccines are currently available for HPV: one against HPV types 16 and 18, Cervarix (GlaxoSmithKline), and a quadrivalent vaccine against HPV types 16, 18, 6, and 11, Gardasil (Merck). Both vaccines have been advised for women between the ages of 13 and 26 years because they lead to a reduction in precancerous cervical lesions and cancer incidence related to HPV.[37] The vaccine is also now recommended for young men between the ages of 13 and 26 because of its ability to reduce the incidence of genital warts, and, in the population of men who have sex with men, the incidence of anal intraepithelial neoplasia.[38,39]

Routine examinations of the oral cavity and proximal oropharynx should be part of a standard medical history and physical and dental examination. Routine oral examinations in high-risk patients have the potential to reduce cancer-related deaths through the discovery of premalignant and early-stage malignant changes. Unfortunately, the same substance abuse conditions that predispose individuals to head and neck cancers correlate with underuse of health and dental services,[36] often leading to late detection and diagnosis of head and neck cancers. Radiation oncologists can play a role in the early detection of secondary oral cavity and oropharyngeal cancers attributable to field cancerization in patients who have been treated for primary head and neck cancers and are undergoing follow-up in the radiation oncology clinic.

Potentially malignant lesions include erythroplakia, leukoplakia, erythroleukoplakia, oral submucous fibrosis, and lichen planus.[40-44] *Leukoplakia* and *erythroplakia* are Greek terms translated as "white plaque" and "red plaque," respectively. Leukoplakia is an exclusionary diagnosis and is currently defined as "a white plaque of questionable risk having excluded (other) known diseases or disorders that carry no increased risk for cancer."[40] The worldwide prevalence of leukoplakia is estimated at approximately 2% of the general population,[41] with the highest incidence in men from the fifth through the seventh decades; histologic findings show hyperplasia of the squamous epithelium. Most leukoplakia lesions do not progress to SCC; the annual transformation rate is estimated at 1%.[42] This rate is strongly dependent on the presence and severity of dysplasia.[43] Dysplasia, carcinoma in situ, or carcinoma is frequently present within erythroplakia, which has only one sixth of the prevalence of leukoplakia. Of the premalignant lesions, transformation to malignancy is highest in erythroplakia, particularly when dysplastic changes are present, with an annual transformation rate of at least 2.9%.[44] Others have predicted that the vast majority of erythroplakias will ultimately undergo malignant transformation.[42]

Multiple chemopreventive regimens have been evaluated to prevent progression of dysplasia within the upper aerodigestive tract. At least one randomized study demonstrated a decreased rate of biopsy-proven dysplasia after the administration of isotretinoin.[45] However, the toxicity was significant, with almost half of patients requiring dose reduction. In addition, most responders relapsed within the first 3 months after treatment. Larger randomized trials found no reduction in the rate of second primary tumors with isotretinoin.[46-48]

Currently, no chemopreventive strategies have been validated or are widely in use for high-risk patients, including those with known dysplasia. Clinical trials continue to search for effective treatment approaches. Close follow-up with biopsy and surgical excision or laser therapy as indicated remains mandatory for patients with premalignant lesions.

BIOLOGIC CHARACTERISTICS AND MOLECULAR BIOLOGY

Significant research is ongoing to determine the genetic and molecular impact of HPV on associated oropharyngeal SCCs. Molecular profiles of HPV-positive tumors are distinct from those of HPV-negative tumors. The oncogenic function of viral E6 and E7 from HPV appears to propel the molecular abnormalities present in HPV-positive tumors. Inactivation of TP53 and PRB is seen with both types but are the result of separate mechanisms. E6 inactivates TP53 function in HPV-positive tumors, whereas disruptive mutations of TP53 are more common in HPV-negative tumors. Besides TP53, disparate effects on 14-3-3σ, RASSF1A, cyclin D, PRB, and P16 have been identified between HPV-positive and HPV-negative tumors. Disruption of TP53 by alcohol- and tobacco-mediated damage seems to be a critical genetic alteration in HPV-negative tumors. A molecular impact of tobacco exposure has also been identified in cells with HPV present. Normal oral keratinocytes transfected with HPV and subsequently exposed to tobacco carcinogens are found to have enhanced E6 and E7, increased resistance to apoptosis, impaired DNA repair, and activated telomerase.[49]

Epidermal growth factor receptor (EGFR) expression in oropharyngeal cancers correlates inversely with HPV status.[50,51]

Other Risk Factors

Numerous other potential risk factors have been described for oropharyngeal cancer and head and neck cancers in general. A family history of head and neck cancers produces an odds ratio risk increase of 1.7, although this is only seen in subjects exposed to tobacco, suggesting that this factor may represent an environmental as much as a genetic influence.[35] Diets low in raw vegetables and citrus and noncitrus fruits have increased the oral cancer risk in a majority of studies.[8] These results seem to hold true even when studies have been controlled for alcohol and tobacco usage, although the effect on diet and nutritional deficiencies from heavy alcohol and tobacco abuse is substantial and such factors can be difficult to account for in case-control studies.

Nutritional deficiencies, as signified by a body mass index decline before diagnosis, have also been associated with oral cancer risk. This was again seen primarily among individuals with active or prior alcohol and tobacco use. Poor oral hygiene, as measured by surrogates such as tooth loss and infrequent dental visits, also correlates with an elevated rate of oral and oropharyngeal carcinomas.[36] In short, the family history, diet, nutritional status, and oral hygiene may all play a role in oropharyngeal carcinoma predisposition, but defining the impact of each of these in the setting of the more dominant risk factors of alcohol and tobacco use is challenging, particularly given the potential interplay between such factors.

Not surprisingly, given its association with HPV-negative tumors, EGFR expression predicts for a lower rate of response to induction chemotherapy and inferior OS and disease-specific survival rates. A similar effect was seen in an analysis of the conventional arm of RTOG 90-03, in which 155 patients with adequate pathologic specimens were evaluated for expression of EGFR by immunohistochemical testing.[52] EGFR expression did not correlate with T category, N category, or category grouping, but high EGFR-expressing tumors had higher local recurrence rates and worse DFS and OS. Distant metastases did not differ between the two groups.

PATHOLOGY AND PATHWAYS OF SPREAD

Pathologic Findings

Primary oropharyngeal tumors are almost exclusively SCC (≈95% of tumors). Alternative pathologic types include melanoma (eFigure 33-1), primary lymphoid malignant tumors (eFigure 33-2), minor salivary gland tumors, sarcomas, and other oddities. Given the preponderance of SCC in this site, this chapter will refer to the evaluation and treatment of SCC unless another type is specifically indicated.

A substantial literature has been generated evaluating the histologic subtypes of SCC of the head and neck, the appropriate nomenclature for these tumors, and their clinical impact. Specific subtypes include the spindle cell variant characterized by noncohesive spindle cells, which closely resembles sarcoma microscopically. The basaloid squamous variant is a distinct subtype traditionally correlated with aggressive behavior and poor patient outcomes.[53] However, the recent correlation of HPV-associated malignant disease with the basaloid subtype has shown that the basaloid group is a mixture of both HPV-16-positive and HPV-16-negative carcinomas. Because the HPV status imparts a substantially favorable influence on outcome, the implication is that the basaloid phenotype alone does not confer a worse clinical outcome.[54] Angiolymphatic invasion and perineural invasion are both associated with increased rates of cervical nodal metastases and a worse prognosis.[55]

The prototypical SCC of the head and neck, including the oropharynx, is moderately differentiated, with approximately 60% moderately differentiated, 20% well differentiated, and 20% poorly differentiated. Some studies have found tumor grade to be predictive of regional nodal metastasis and, subsequently, clinical outcome. The determination of tumor grade based on traditional cytologic and histologic features of differentiation is challenging to reproduce because of interobserver variability. As a result, the tumor grade seems to have limited prognostic value, particularly when compared with the clinical staging parameters.[55] Undifferentiated carcinomas with a lymphoid stroma arising from the tonsil have biologic behavioral characteristics and an increased radiosensitivity that are more similar to undifferentiated nonkeratinizing nasopharyngeal carcinomas rather than conventional types of SCC.[56] Again, this subtype seems to serve as a surrogate for HPV positivity.

Pathways of Spread

The oropharynx makes up the central portion of the upper aerodigestive tract, encompassing the tongue base, palatine (faucial) tonsils, inferior aspect of the soft palate, and posterior and lateral oropharyngeal walls[57] (Figures 33-1, 33-2, and 33-3). The anterior margins are the anterior tonsillar pillars, the hard-soft palate junction, and the circumvallate papillae of the tongue, placing the posterior third of the tongue within the oropharynx. Superiorly, the oropharynx is bounded by the inferior aspect of the soft palate, posteroinferiorly by the pharyngoepiglottic folds that lie approximately at the level of the hyoid bone, and inferiorly by the glossoepiglottic fold and vallecula. The lateral and posterior borders of the oropharynx are defined by the pharyngeal constrictor muscles and their overlying mucosa. Understanding the anatomy of the oropharynx is necessary when identifying the typical pathways of spread by oropharyngeal neoplasms.[58-60]

Soft Palate

The soft palate is a mobile flap of soft tissue with a central aponeurosis that serves as the attachment point for several palatine muscles. Five muscles form the bulk of the posterior and lateral portions of the soft palate. These muscles (levator veli palatini and tensor veli palatini muscles, muscle of the uvula, palatoglossus muscle, and palatopharyngeal muscle) insert on the palatine aponeurosis but have important attachments to the tongue base, posterolateral pharyngeal wall, and torus tubarius. The palatoglossus muscle and overlying mucosa form the anterior tonsillar pillar, which is the anteriormost part of the lateral oropharynx. The palatopharyngeal muscle, with its overlying mucosa, forms the posterior

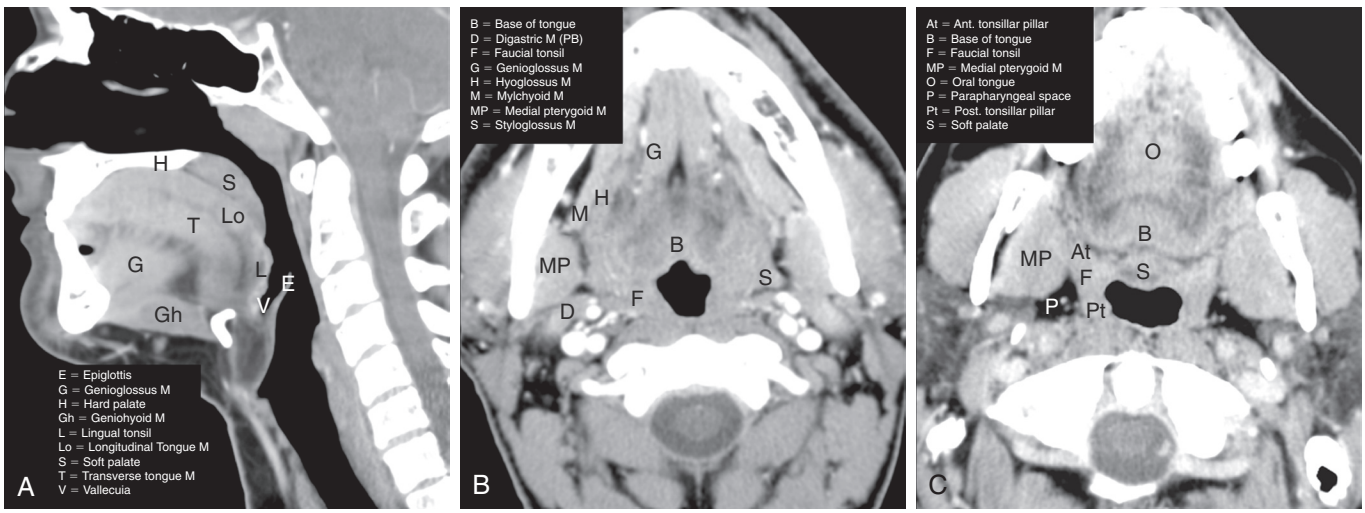
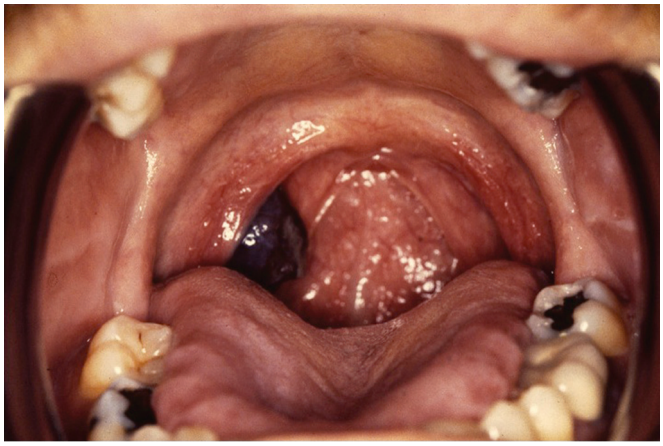
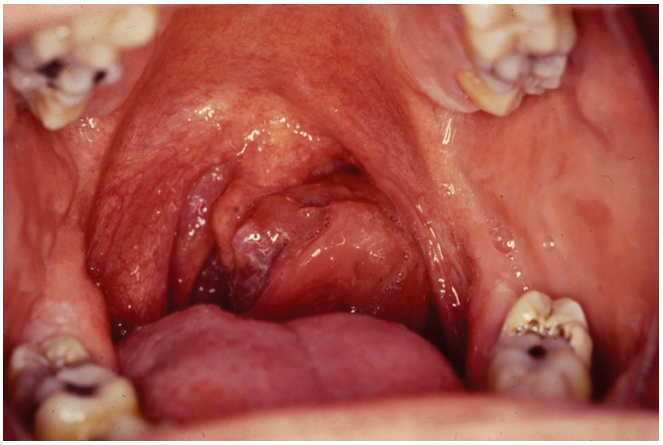


Figure 33-2 Normal CT scans of the oropharynx: sagittal **(A)** and axial **(B** and **C)** scans.



eFigure 33-1 Hyperpigmented mass arising from the right tonsillar fossa pathologically confirmed as a mucosal melanoma.



eFigure 33-2 Large, protuberant, lobulated mass arising from the left tonsillar fossa displacing the uvula contralaterally and occupying the majority of the oropharyngeal lumen, identified as a diffuse large B-cell lymphoma. The tumor was treated with three cycles of CHOP followed by 36 Gy of involved-field radiation. The patient remains disease free 15 years from the time of treatment.

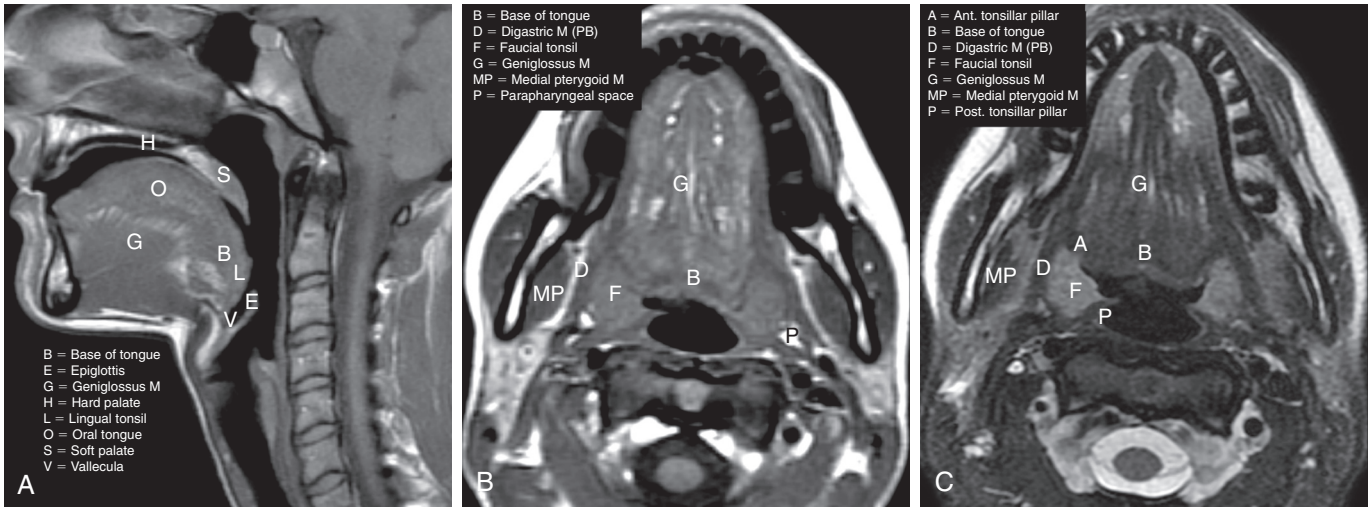


Figure 33-3 Normal MRI of the oropharynx: sagittal T1-weighted **(A)**, axial T1-weighted **(B)**, and axial T2-weighted **(C)** scans.

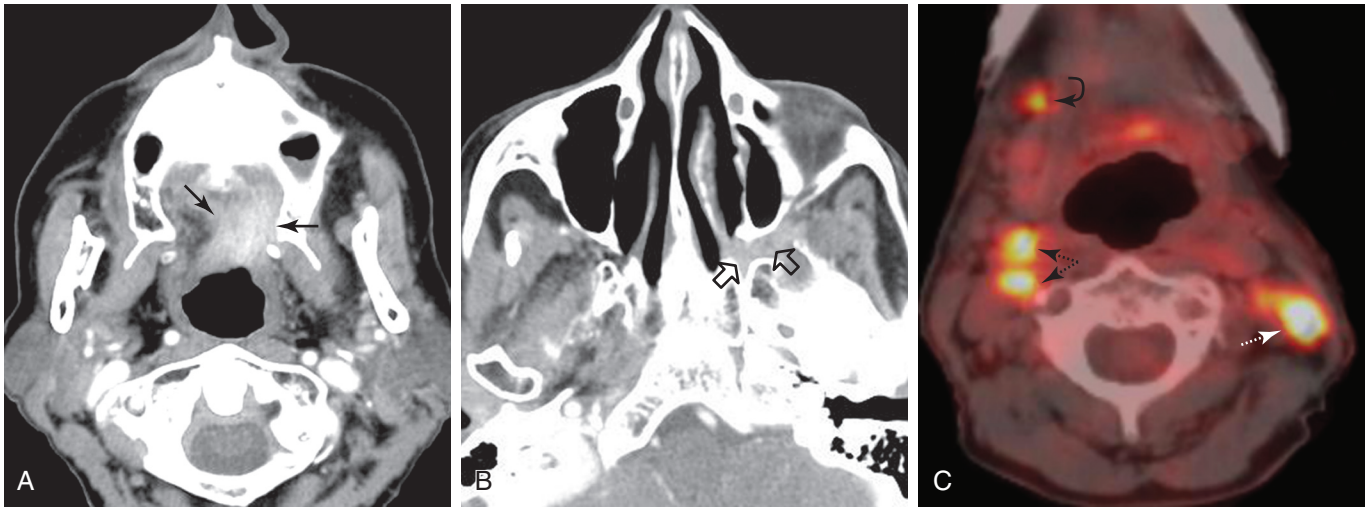


Figure 33-4 T4bN2c soft palate SCC: Axial **(A** and **B)** contrast-enhanced CT scans demonstrate a large enhancing mass of the soft palate *(black arrows)* with erosion of the hard palate. There is upward spread of mass along the lateral nasopharynx wall as well as upward perineural tumor spread via the greater palatine foramen into the pterygopalatine fossa *(open arrows).* The CT and PET/CT **(C)** images demonstrate N2c nodal metastasis involving levels Ia, Ib *(curved black arrow)*, IIa *(dashed black arrows)*, and IIb *(dashed white arrow).*

tonsillar pillar. The two pillars connect laterally and inferiorly with the lateral oropharyngeal wall.

The inferior aspect of the soft palate, which forms the upper portion of the oropharynx, is the site of the majority of soft palate tumors. The superior surface of the soft palate, part of the nasopharynx, is seldom a primary site of neoplasm. The soft palate also contains a substantial number of minor salivary glands. These glands are the site of origin for nonsquamous neoplasms of the soft palate.

A soft palate tumor can spread anteriorly to involve the hard palate. There is also potential for perineural spread along the greater and lesser palatine branches of the maxillary nerve superiorly into the pterygopalatine fossa[61] (Figure 33-4). Further perineural spread from the pterygopalatine fossa can result in extension along branches of the maxillary division of the trigeminal nerve into the orbit via the inferior orbital fissure, into the central skull base via the foramen rotundum, and into the facial nerve and temporal bone via the nerve of the pterygoid canal (vidian nerve). This perineural spread can result in palsies of both the trigeminal and facial nerves. Patients with advanced disease and perineural spread may present with trismus resulting from involvement of the pterygoid muscles or branches of the trigeminal nerve.

Tonsillar Region

The palatine (faucial) tonsils consist of lymphoid tissue constrained within a fibrous capsule that projects into the oropharynx between the triangle formed by the anterior and posterior tonsillar pillars. The tonsillar fossa is bounded laterally by the superior pharyngeal constrictor muscle. The anterior and posterior tonsillar pillars consist of the mucosa overlying the palatoglossus and palatopharyngeal muscles, respectively. SCC is the most frequent neoplasm of the palatine tonsils, followed distantly by non-Hodgkin's lymphoma. Tumors within the tonsillar region can spread superiorly to the soft palate along the vertically oriented palatoglossus and palatopharyngeal muscles, as well as inferiorly to the tongue base and posterolaterally to the oropharyngeal wall[62] (Figures 33-4 and 33-5).

The superior pharyngeal constrictor muscle, in addition to forming the posterior and lateral borders of the oropharynx, courses deep to the palatine tonsils as it extends anteriorly to

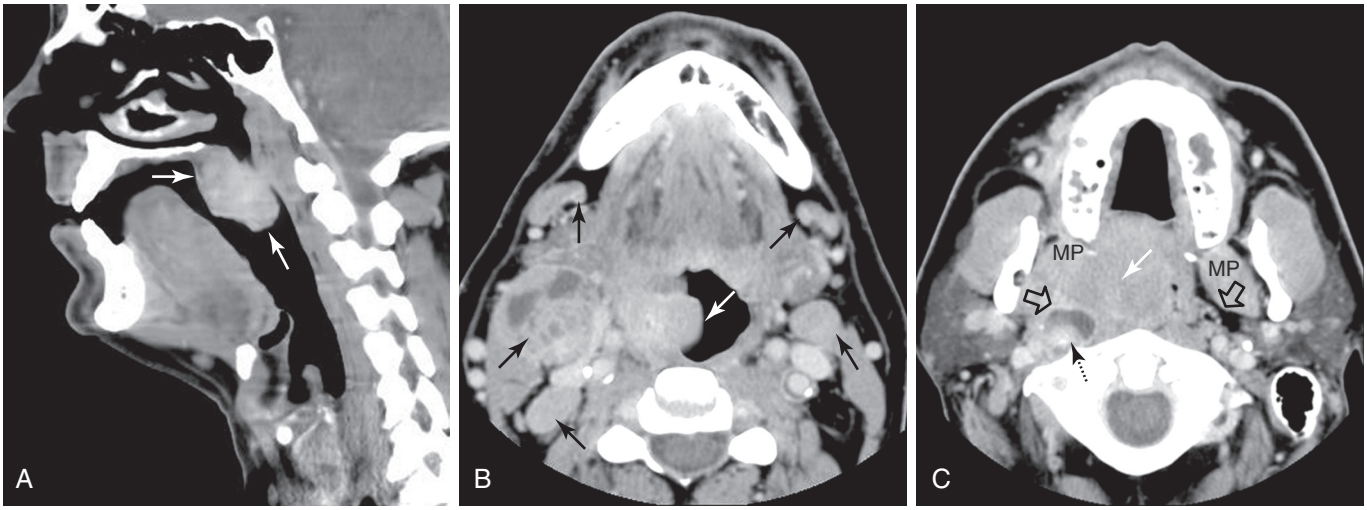


Figure 33-5 T4aN2c SCC of tonsil and soft palate: Sagittal **(A)**, and axial **(B** and **C)** contrast-enhanced CT scans demonstrate a large enhancing mass of the palatine tonsil and soft palate *(white arrows).* There is invasion of the medial pterygoid (MP) muscle indicating a T4a lesion. There are bilateral enlarged and abnormally enhancing level Ib and IIa lymph nodes *(black arrows)* as well as an abnormal right level IIb node consistent with N2c nodal spread. An abnormal heterogeneously enhancing right lateral retropharyngeal lymph node is identified *(dashed black arrow)* with extracapsular spread into the parapharyngeal space *(open arrows).*

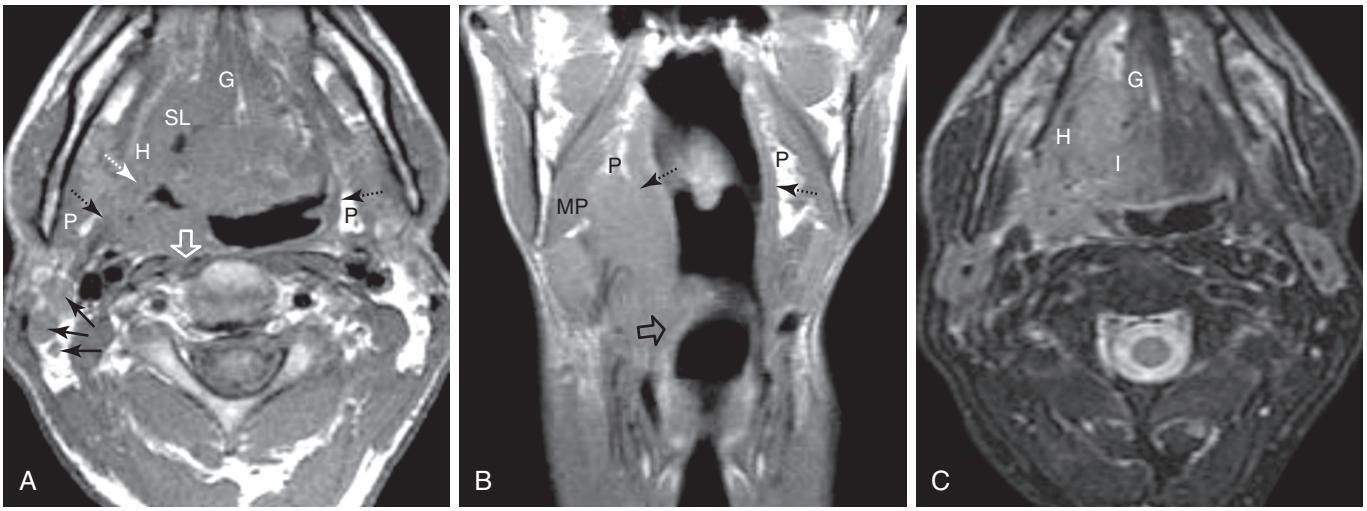


Figure 33-6 T4bN2b tonsillar SCC: Axial T1-weighted **(A)**, coronal T1-weighted **(B)**, and axial T2-weighted **(C)** noncontrast-enhanced MRI images demonstrate an extensive right tonsillar and posterior oropharyngeal wall neoplasm. The lesion extends across the glossotonsillar sulcus *(dashed white arrow)* into the oral tongue and sublingual space (SL). There is invasion of the intrinsic tongue musculature (I) as well as the hyoglossus (H) and genioglossus (G) muscles. The lesion infiltrates the superior pharyngeal constrictor muscle *(dashed black arrows)* to involve the parapharyngeal space (P) and MP muscle. The lesion invades the prevertebral space *(open white arrow).* There is inferior spread into the supraglottic larynx *(open black arrow).* Several enlarged right level IIb lymph nodes are seen *(black arrows).* These findings are consistent with a stage of T4bN2b.

insert on the pterygomandibular raphe.[57] This fibrous raphe is a shared insertion site with the buccinator muscle, with the raphe extending to the medial pterygoid plates superiorly and the lingual cortex of the mandible inferiorly just posterior to the mylohyoid line. Tonsillar neoplasms that invade the superior pharyngeal constrictor muscle and involve the pterygomandibular raphe, therefore, can spread anteriorly to the buccinator muscle and space, superiorly to the medial pterygoid plate and masticator space, and inferiorly to the lingual cortex of the mandible. Lateral extension of tumor allows its entry into the parapharyngeal space (Figure 33-6). Involvement of the parapharyngeal space by tonsillar neoplasms may result in spread to and along the styloglossus and stylopharyngeal muscles, which extend superiorly toward the skull base and attach to the styloid process. Lateral extension into the medial pterygoid muscle is often associated with involvement of the mandibular division (V3) of the trigeminal nerve. Involvement of V3 can allow perineural tumor spread inferiorly into the mandible along the inferior alveolar nerve and superiorly along the main trunk of V3 to the foramen ovale and cavernous sinus.[61]

Oropharyngeal Wall

The posterior and lateral walls of the oropharynx are formed by the superior pharyngeal constrictor muscle and overlying mucosa. The deep aspect of the superior constrictor muscle is separated from the prevertebral fascia by a thin layer of retropharyngeal fat. Tumors within the posterior aspect of the oropharynx can extend through this layer of fat and fascia and into the prevertebral space[63,64] (see Figure 33-6). Advanced

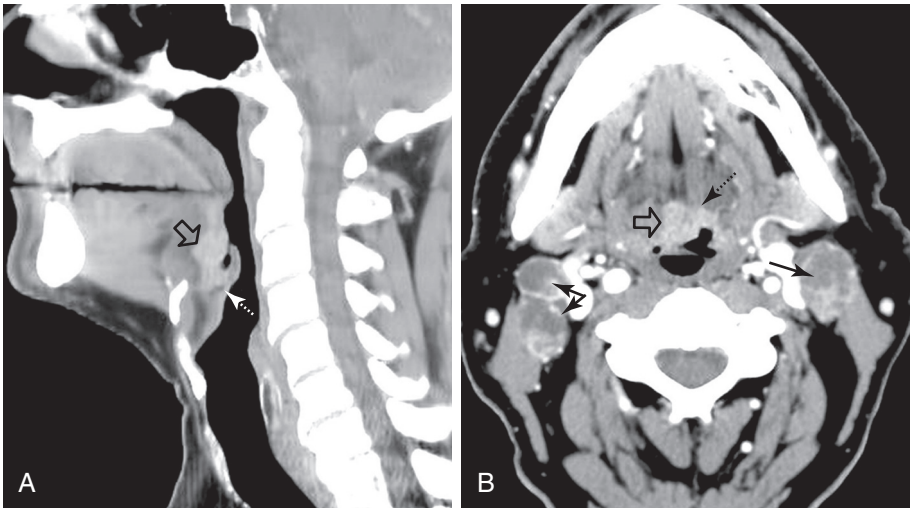


Figure 33-7 T2N2c base-of-tongue SCC: Sagittal **(A)** and axial **(B)** views. A 2.2-cm enhancing neoplasm of the tongue base *(open arrows)* indicating a T2 primary. The lesion extends into the vallecula *(dashed white arrow)* but does not invade the adjacent genioglossus muscle *(dashed black arrow).* There are abnormal heterogeneously enhancing bilateral level IIa and right level IIb lymph nodes *(black arrows)* consistent with N2c nodal spread.

tumors can ultimately involve the vertebral column, although such spread is typically inhibited by the multiple intervening fascial planes and the longus colli and longus capitis muscles. Tumors of the posterolateral oropharyngeal wall can extend into the nasopharynx and hypopharynx by way of either mucosal or submucosal spread (Figure 33-6).

Tongue Base

The tongue base is separated from the oral tongue anteriorly by the circumvallate papillae. It extends posteriorly and inferiorly to terminate near the level of the hyoid bone (see Figures 31-2 and 31-3). Laterally, it is separated from the palatine tonsils by the glossotonsillar sulcus. The lingual tonsils lie along the posterior surface of the tongue base. The lingual tonsils are variable in size and may be quite large in the first two decades of life and in patients with concurrent head and neck infections.

Neoplasms of the tongue base spread along several pathways as they increase in size. They may infiltrate along the intrinsic muscles of the tongue into the oral tongue and deep tongue musculature. It is especially important to identify involvement of the extrinsic muscles of the tongue (i.e., the hyoglossus, styloglossus, and genioglossus muscles) because this indicates a T4 lesion.[65] Tumor may track superolaterally along the mylohyoid muscle to invade the lingual surface of the mandible. Deep anterior extension may also involve the hypoglossal or lingual neurovascular bundles. Tumor can track posteriorly along these nerves between the superior and middle pharyngeal constrictor muscles into the parapharyngeal and masticator spaces.

Base-of-tongue cancer can also spread superficially along the mucosa. Posteroinferior extension can involve the vallecula, lingual surface of the epiglottis, and pharyngoepiglottic folds (Figure 33-7). There may be invasion of the preepiglottic space whenever the vallecula or glossoepiglottic folds are involved.

Nodal Involvement

Nodal metastasis has been reported in 40% to 66% of patients presenting with soft palate carcinoma.[66,67] Level II nodal involvement is most frequent, with extension into levels III and IV nodes commonly seen. Level I, level V, and lateral retropharyngeal nodal involvement is uncommon.[68] Lymph node metastasis from SCC of the palatine tonsils is common (69% to 74%) at the time of presentation.[67,69] The incidence of nodal involvement at diagnosis in patients diagnosed with tongue-base carcinoma has been reported to be between 64% and 78%.[66,67] Bilateral nodal disease is commonplace with base-of-tongue cancer, especially in patients with tumors near or crossing the midline. The incidence of nodal involvement in patients with oropharyngeal wall squamous carcinomas has been reported to be between 57% and 60%[70] (eFigures 33-3 to 33-5). Radiographic involvement of the retropharyngeal nodes is present in 16% of all patients with oropharynx cancer, rising to 23% with pathologic nodal disease in other neck sites. With nodal involvement elsewhere in the neck, retropharyngeal nodal involvement varies by subsite and is identified in 13% of base-of-tongue tumors, 14% of tonsillar tumors, 38% of posterior pharyngeal wall tumors, and 56% of soft-palate tumors.[71] This has implications for both primary treatment modality as well as design of the radiation treatment volumes.

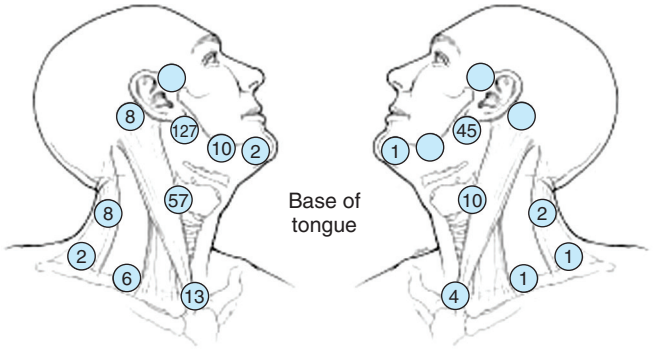
CLINICAL MANIFESTATIONS, PATIENT EVALUATION, AND STAGING

Symptoms at the time of diagnosis of an oropharyngeal cancer depend on the subsite but commonly include pain, either local or referred. Local pain is frequently described as a sore throat and may lead to dysphagia and weight loss secondary to the pain. Referred pain can occur through cranial nerves (CN) IX and X. CN IX (glossopharyngeal nerve) involvement can lead to referred pain via the tympanic nerve of Jacobson localized to the inner ear or temporomandibular joint. CN X (vagus nerve) causes referred pain through the auricular nerve of Arnold to the external auditory canal.

An asymptomatic mass within the upper neck is another frequent presenting symptom. More advanced symptoms can include odynophagia, dysphagia, dysarthria (including "hot potato" voice caused by CN XII involvement or narrowing of the pharyngeal air column), trismus (as a result of involvement of the pterygoids), and necrotic odor. Presentation with distant metastases is uncommon.

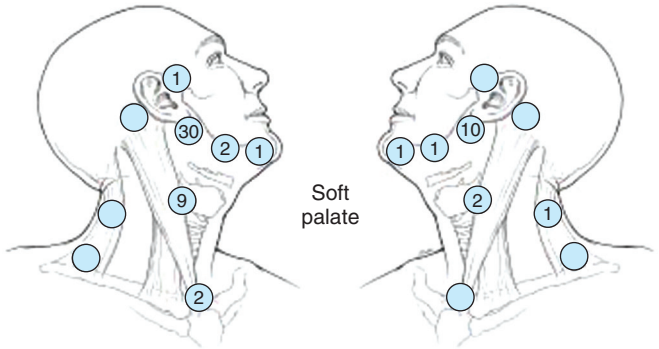
Patient Evaluation

A comprehensive history with an emphasis on head and neck–related symptoms should be taken for all patients, and a detailed physical examination of the head and neck region should be performed (Table 33-2). The examination should include a direct inspection of the oral cavity and proximal oropharynx; an indirect (mirror) examination of the distal oropharynx, hypopharynx, nasopharynx, and larynx; careful



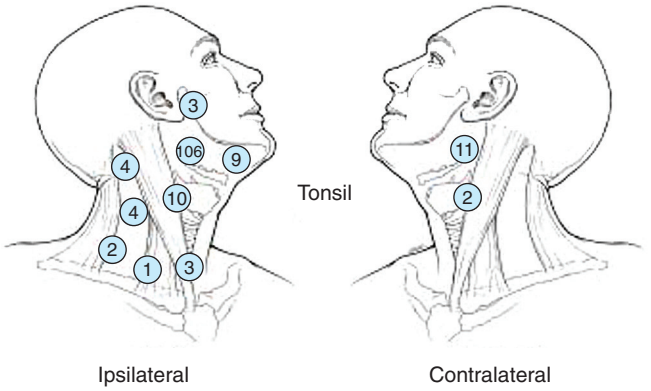
N_0	N_1	N_{2A}	N_{2B}	N_{3A}	N_{3B}	$N_1 - N_3$/Total
41	30	21	26	14	53	144/185 = 78%

eFigure 33-3 Distribution of positive nodes in patients with SCC of the base of the tongue on presentation to the M. D. Anderson Cancer Center, 1948 to 1965.
(Data from Lindberg RD: Distribution of cervical lymph node metastases from squamous cell carcinoma of the upper respiratory and digestive tracts. Cancer 29:1446, 1972, with permission.)



N_0	N_1	N_{2A}	N_{2B}	N_{3A}	N_{3B}	$N_1 - N_3$/Total
45	12	2	4	4	13	35/80 = 44%

eFigure 33-5 Distribution of positive nodes in patients with squamous carcinoma of the soft palate on presentation to the M. D. Anderson Cancer Center, 1948 to 1965.
(Data from Lindberg RD: Distribution of cervical lymph node metastases from squamous cell carcinoma of the upper respiratory and digestive tracts. Cancer 29:1446, 1972, with permission.)



eFigure 33-4 Distribution of positive nodes in patients with SCC of the tonsil on presentation to the M. D. Anderson Cancer Center, 1968 to 1979.
(Data from Remmler D, Medina JE, Byers RM, et al: Treatment of choice for squamous carcinoma of the tonsillar fossa. Head Neck Surg 7:206–211, 1985.)

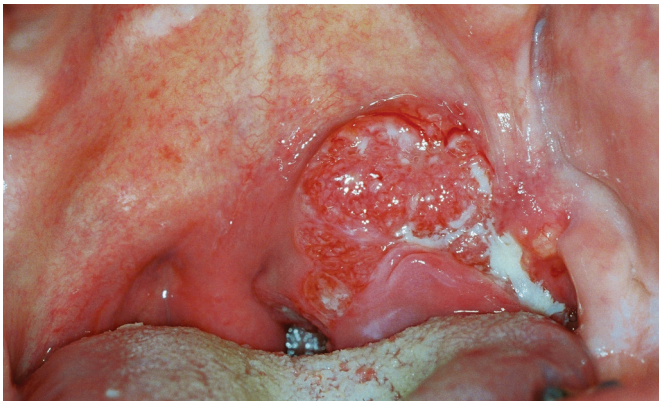


Figure 33-8 A 59-year-old male who presented in 2009 with a 3-week history of sore throat and dysphagia. An exophytic tumor is seen to arise from the left tonsillar complex, extending superiorly onto the proximal soft palate with a pushing, erythematous border causing the uvula to deviate contralaterally. The tumor involved both the anterior and posterior tonsillar pillars and measured more than 4 cm in greatest dimension with bilateral lymphadenopathy and was a stage IVA (T3N2cM0) lesion.

TABLE 33-2 Diagnostic Algorithm for Oropharyngeal Cancer

GENERAL
History
Physical examination
Visual inspection of oral cavity and proximal oropharynx
Palpation of oral cavity and proximal oropharynx
Mirror examination
Fiberoptic laryngoscopy (if indicated after mirror examination)
IMAGING
CT or MRI neck with contrast
Chest imaging
CT chest if high risk for distant disease
PET/CT
LABORATORY STUDIES
Basic metabolic panel
Complete blood count

palpation of the oral cavity and proximal oropharynx; and inspection and palpation of the cervical lymph nodes (Figure 33-8). Relaxing the sternocleidomastoid muscle by tilting the head slightly to the ipsilateral side allows easier palpation of the jugulodigastric nodes. Flexible fiberoptic nasopharyngoscopy is used as indicated by examination findings and the quality of the indirect examination.

Physical examination includes assessment of both the size and local extent of the primary tumor and the presence, size, and location of the cervical lymphadenopathy. The size of the primary tumor and nodal disease should be measured as this is the basis of the AJCC staging system for oropharyngeal cancers. Consideration should be given to documentation of the extent of disease before treatment with still photography and videography in the electronic medical record.

Additional staging information can be gleaned during the physical examination. Trismus, documented by measuring the distance between the upper and lower incisors, or alveolar ridges in edentulous patients, is a consequence of tumor invasion into the pterygoid musculature. Deviation of the tongue on protrusion suggests involvement of the deep or extrinsic muscles of the tongue or invasion or compression of the hypoglossal nerve (CN XII) (eFigure 33-6). A detailed physical examination is especially important with oropharyngeal cancers because treatment-altering findings may manifest themselves on visual inspection but not on radiographic evaluation and can alter both radiation treatment coverage and staging. For example, subtle superficial mucosal extension of a tonsillar tumor onto the adjacent soft palate or retromolar trigone may only be apparent during direct inspection and must be documented. Such regions may be more apparent during radiation treatment at approximately 20 Gy to 30 Gy because "tumoritis" causes increased erythema of these regions compared with the surrounding normal tissue (eFigure 33-7). With base-of-tongue tumors in particular, digital palpation is essential to determine the size and extent of local spread because these tumors are frequently not seen by or are underestimated by visual examination, especially if they are endophytic. All borders of the tumor must be determined precisely because this has a crucial impact on target volume delineation and treatment field arrangement. Precision in defining tumor borders becomes even more paramount when IMRT is anticipated. Detailed examination of the remainder of the head and neck is also important because of field cancerization and the risk of synchronous primary tumors.

Aside from a complete history and physical examination, the workup should include biopsy confirmation of the mass. Biopsy should be performed by the least invasive means possible and can include fine-needle aspiration of involved cervical nodes or biopsy of the primary site. In general, excisional biopsy of the primary site or involved lymph nodes is not recommended because of concerns about prolonged healing times that may delay definitive radiation and surgery-associated hypoxic changes. Patients who present with malignant jugulodigastric nodes or, less commonly, midcervical nodes and no clear primary tumor are statistically most likely to have a primary tumor of the oropharynx, and a thorough examination of the oropharynx should be performed as part of the evaluation.[72] Ipsilateral tonsillectomy is a recommended component of the evaluation for patients with head and neck cancers presenting with upper cervical or midcervical nodal metastases without an apparent mucosal primary tumor.

Given the significant prognostic importance and the implications for clinical investigation, assessing oropharynx SCCs for HPV has become routine. Immunohistochemical staining for p16 is a readily available and well correlated surrogate for HPV, although interpretation requires some experience.[73] In situ hybridization testing for HPV is also widely used although it is technically more challenging.

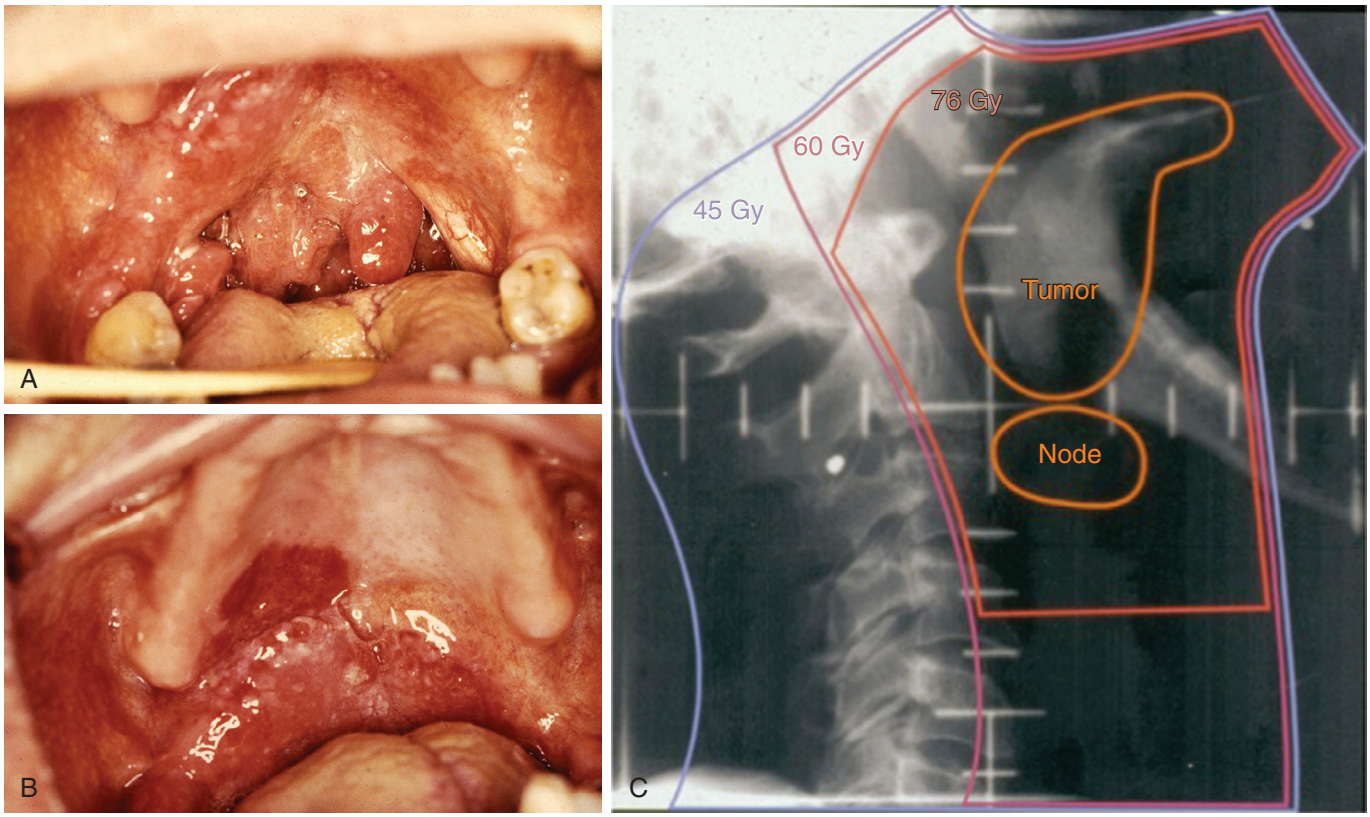
Imaging Studies

Selection of Imaging Studies

Recommended radiographic studies include CT or MRI scanning of the neck with contrast enhancement, chest imaging, and dental studies as indicated.[74] CT is generally considered to be the examination of choice for the initial diagnostic evaluation of oropharyngeal neoplasms when compared with MRI and PET imaging.[75-77] The benefits of CT include lower cost, faster acquisition speed, less motion artifact, better detection of bone invasion, higher spatial resolution, greater reproducibility on sequential examinations, and wide availability. MRI is superior to CT in specific situations, including delineating orbital or skull-base involvement and defining intracranial perineural tumor spread. MRI also has slightly superior multiplanar imaging capabilities and is better able to identify subtle soft-tissue involvement by tumor, deep osseous invasion and marrow replacement, perineural spread of disease, and extent of anterior spread of base-of-tongue tumors. MRI is also useful for patients in whom dental



eFigure 33-6 Atrophy of the right hemitongue with rightward deviation on protrusion consistent with right CN 12 palsy.



eFigure 33-7 **A,** T3N1 right tonsillar SCC before treatment in which precise tumor borders are difficult to demarcate. **B,** T3N1 right tonsil at approximately 24 Gy of comprehensive radiation using large lateral fields showing tumoritis well across the midline and extending into the ipsilateral hard palate mucosa and retromolar trigone. **C,** Schematic drawing of treatment field design with shrinking-field technique for hyperfractionated treatment.

amalgam artifact renders the CT examination suboptimal. MRI and PET/CT are used in most institutions as ancillary diagnostic studies for oropharyngeal cancers when CT imaging inadequately addresses specific clinical questions. Imaging modalities are often complementary, however, and both CT and MRI are useful in some instances. PET/CT studies can provide additive information relative to the extent of the primary tumor, nodal involvement, and metastatic disease.

Imaging is indispensable for assessing regional lymphatic spread.[78] This is particularly true in patients in whom clinical assessment of nodal disease is difficult (because of a large or muscular neck), in whom there is occult involvement of normal-sized nodes, or in whom nodal chains are involved that cannot be palpated on physical examination (i.e., retropharyngeal nodes). Multiple criteria must be used to determine whether a specific lymph node is involved by tumor on CT or MRI studies. These criteria include the node's size, homogeneity, distinctness of outer margin, focal areas of enhancement, location, loss of fatty hilum, and spherical shape and the presence of a clustering of lymph nodes. These criteria are best used as a whole and not considered in isolation. When imaging tests have been directly compared in the same patient population, PET and PET/CT studies have typically been found to be slightly more accurate in lymph node staging, followed by CT scanning and then by MRI.[77,79] See the Expert Consult website for further information on lymph node staging.

The overall incidence of pulmonary metastases has traditionally been placed at 1% to 2% in newly diagnosed patients with cancers of the head and neck. The traditional practice has been to obtain a chest radiograph to evaluate for pulmonary disease, but chest CTs allow better definition of the thoracic cavity and have a higher sensitivity for detection of pulmonary parenchymal metastases or mediastinal or hilar nodal disease. A review of the literature found a pooled prevalence of 7.9% for abnormalities on chest CT scans in patients with head and neck SCC.[81] Abnormal findings were more prevalent in patients with N2 or N3 nodal involvement or stage III or IV disease and less prevalent for oral cavity primary tumors. Not surprisingly, patients with recurrent disease had higher rates of positive chest CT scans (25.3%). These risk factors correlated closely with the clinical factors statistically associated with the development of distant metastases (T stage, N stage, gender, nodal level, and locoregional control [LRC]).[82] Although there is significant institutional variation regarding chest imaging, a measured approach would include chest CT scans for patients with advanced nodal involvement (N2b, N2c, and N3), locally advanced primary disease (T3 and T4), low cervical nodes, and other risk factors, including recurrent disease. A CT scan of the chest can be performed at the same time as the neck CT scan, and modern multislice scanners can provide contrast-enhanced images with the same contrast bolus.

Imaging Technique

The Expert Consult website contains information on imaging technique.

Staging

Table 33-3 shows the AJCC seventh edition staging system for oropharyngeal carcinomas.[61] Endoscopic, radiographic, and physical examination findings are included and collated when determining the clinical stage. Pathologic staging may also be performed using the same criteria as clinical staging. Even

TABLE 33-3 TNM Definitions and Stage Groupings for Oropharyngeal Carcinomas

Primary Tumor (T)	**Regional Lymph Nodes (N)**
TX: Primary tumor cannot be assessed	NX: Regional lymph nodes cannot be assessed
T0: No evidence of primary tumor	N0: No regional lymph node metastasis
Tis: Carcinoma in situ	N1: Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension
T1: Tumor 2 cm or less in greatest dimension	N2: Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension, or in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension, or in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension
T2: Tumor more than 2 cm but not more than 4 cm in greatest dimension	N2a: Metastasis in a single ipsilateral lymph node more than 3 cm but not more than 6 cm in greatest dimension
T3: Tumor more than 4 cm in greatest dimension	N2b: Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension
T4a: Tumor invades the larynx, deep/extrinsic muscle of tongue, medial pterygoid, hard palate, or mandible	N2c: Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension
T4b: Tumor invades lateral pterygoid muscle, pterygoid plates, lateral nasopharynx, or skull base or encases carotid artery	N3: Metastasis in a lymph node more than 6 cm in greatest dimension

Stage Grouping for Tumors of the Oropharynx			
Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T3 T1, T2, T3	N0 N1	M0 M0
Stage IVA	T4a T1, T2, T3, T4a	N0, N1 N2	M0 M0
Stage IVB	T4b Any T	Any N N3	M0 M0
Stage IVC	Any T	Any N	M1

There is varied opinion regarding size criteria and how to best measure lymph nodes in order to label them as radiographically involved. Measurements of 10 mm in the long axis and 8 mm in the short axis are often used as the upper limits of normal for nodes in most cervical levels. Upper level II nodes (jugulodigastric nodes) and level Ib nodes, however, may normally be slightly larger (12 mm to 15 mm). Lateral retropharyngeal nodes are considered abnormal if larger than 8 mm. Very young patients, those with severe dental disease, or those with concomitant head and neck infection may have reactive lymph nodes that are larger than the stated norm. Lymph node size should be considered as only one diagnostic criterion and must be modified in certain circumstances. One should specifically look for focal enhancement of a lymph node along its outer aspect where the afferent lymphatics enter the node. This is often the earliest evidence of lymphadenopathy and may even be seen in patients with normal-sized nodes. Assessment of lymphadenopathy on MRI scans can be more challenging than on CT scans.[75,77] In addition to the aforementioned criteria, one should look for areas of decreased signal intensity on T2-weighted images, which typically represent intranodal tumoral deposits. Meta-analysis suggests that the mean sensitivity of a neck CT scan for the detection of cervical lymph node metastasis is 81% (95% CI, 68% to 90%), of an MRI scan is 81% (95% CI, 65% to 91%), and of a PET scan is 79% (95% CI, 72% to 85%). The specificity of CT scanning has been found to be 76% (95% CI, 62% to 87%); of MRI scanning, 63% (95% CI, 43% to 80%); and of PET scanning, 86% (95% CI, 83% to 89%).[77,79] The quoted sensitivity and specificity for these studies depends greatly on the criteria that are used in declaring a lymph node positive. When imaging tests have been directly compared in the same patient population, PET and PET/CT studies have typically been found to be slightly more accurate in lymph node staging, followed by CT scanning and then by MRI.

PET/CT and PET can serve a complementary role in the imaging evaluation of oropharyngeal primary tumors. Besides the slightly improved accuracy for nodal disease, PET/CT is particularly useful in evaluating for a primary site in patients with cervical nodal disease but an unidentified primary site. An oropharyngeal origin remains the most likely source of an occult primary tumor in patients with level II or III lymph node involvement. PET/CT scanning can also identify synchronous second primary tumors in patients with oropharyngeal SCCs.[80] A PET/CT scan can also be used to screen for metastatic disease and excels at identifying atypical metastases outside of the standard metastatic search pattern, although metastatic spread at presentation is rare. The performance of PET/CT scanning can be improved with a dedicated head and neck protocol, which can also be incorporated into treatment planning. Although PET/CT in particular may have value in oropharyngeal cancer workup and staging, overuse of this expensive resource remains a persistent concern as more standard imaging modalities typically supply equivalent diagnostic information.

Limitations of imaging should also be acknowledged. CT and MRI have limited sensitivity for the detection of superficial mucosal disease, again emphasizing the necessity of a detailed head and neck examination. Also, dental amalgam artifact can limit visualization of the structures of interest, more so for CT than MRI. Motion artifact may degrade the image quality; this is particularly a problem with MRI, where images may be acquired over a several-minute time span. CT, MRI, and even physical examination are known to have limited sensitivity and specificity for the detection of small metastatic deposits within normal-sized lymph nodes. PET scans may be falsely negative in histologically low-grade lesions and in lesions that are less than 5 mm in size and falsely positive when inflammatory changes are present, particularly postoperatively or in the setting of poor dentition.

The development of multiple detector-row CT (MDCT) scanning in conjunction with helical acquisition techniques over the last decade has revolutionized the cross sectional imaging of patients with head and neck cancer. The ability to simultaneously obtain axial image information from 64 to 256 rows of detectors allows rapid scanning of patients with almost no motion artifact. The multiple rows of detectors can simultaneously produce 64 to 256 images, each with a slice thickness of 0.5 mm to 0.625 mm. This enables acquisition of a three-dimensional volume of image data that can be processed into images of varying slice thicknesses generated in sagittal, coronal, or oblique imaging planes. These two-dimensional reformations offer improved visualization of the three-dimensional extent of the primary neoplasm and involved cervical lymph nodes.

Because of the possibility that lower cervical and upper mediastinal nodes may be involved by tumor, it is important to start the CT acquisition just below the aortic arch at the level of the aortopulmonary window. The scans should extend superiorly to the level of the cavernous sinus and skull-base foramina to detect perineural tumor spread along cranial nerve branches, invasion of the masticator and parapharyngeal spaces, and skull-base invasion. Non–contrast-enhanced scans before contrast administration are rarely beneficial and do not need to be routinely obtained. Sufficient time must be allowed for the injected contrast material to enhance the primary tumor and lymph nodes before scanning begins. As a result, a scanner-specific time delay must be inserted between the start of the contrast injection and the initiation of the CT scan to obtain maximal enhancement, with the goal of providing differentiating tissue enhancement rather than vascular opacification. Tight compact bolus injection of the contrast medium (3 mL to 4 mL per second) offers superior enhancement of lesions. Bone and soft-tissue reconstruction algorithms should both be obtained for maximal diagnostic information.

MRI protocols should be constructed in a similar manner to cover the region from the skull base and cavernous sinuses to the aortic arch. It is particularly important to obtain both high-quality non–contrast-enhanced T1- and T2-weighted images because these are often more helpful than contrast-enhanced images at defining the extent of the primary neoplasm and assessing nodal disease. Post-contrast-enhanced T1-weighted images obtained with fat suppression are helpful for identifying perineural tumor spread, skull-base invasion, and deep spread to the masticator and parapharyngeal spaces, as well as for detecting intranodal tumor deposits. Because of the extensive pterygoid plexus of veins in the masticator space and normal enhancement of mucosal areas of the head and neck, contrast-enhanced scans are often challenging to interpret. These images must be carefully compared with non–contrast-enhanced images in the same plane.

when histologic evaluation of the disease is available, information obtained during clinical staging should be incorporated. Comparisons of surgical and radiation-based treatment outcomes should be based on clinical staging because up-staging and down-staging may occur with surgical intervention and both should be reported.

There are a few changes between the sixth and seventh editions of the AJCC oropharyngeal staging recommendations. Stage T4 lesions were previously divided between T4a (resectable) lesions and T4b (unresectable) lesions. Although the qualifications for stage T4a and T4b disease remain unchanged, the description has been altered in the seventh edition to account for advancement in surgical techniques with free-flap and other reconstructive options that allow previously "unresectable" primary lesions to be resected. Therefore, stage T4 is now divided into moderately advanced local disease (T4a) and very advanced local disease (T4b). Extracapsular spread has been added as a descriptor for nodal disease, although this does not currently alter nodal staging. The diagnosis of extracapsular spread is allowed clinically through identification of matted nodes adherent to the overlying skin or adjacent structures or through clinical evidence of extranodal invasion (e.g., cranial nerve palsies). Radiologic signs of extracapsular spread may include perinodal soft-tissue stranding seen before treatment and the presence of amorphous nodal margins. Nodal metastases to level VII are now considered regional disease in oropharyngeal and hypopharyngeal primaries. Level VII nodes are termed the *superior mediastinal group* and extend from the innominate artery to the suprasternal notch.

PRIMARY THERAPY

General Principles of Treatment

The primary goal of treatment is to maximize the chance for cancer cure while minimizing functional impairment and treatment-related morbidities. Selection of the treatment modality depends on the tumor stage, extent of nodal involvement, oropharyngeal subsite, and skill set of the healthcare team. As a whole, the effectiveness of radiation and the potential functional compromise from large surgical resections has historically made the oropharynx the realm of the radiation oncologist. The recent success of low-morbidity transoral surgical resection has challenged this assumption, however. Given the central role of radiotherapy in the treatment of oropharyngeal tumors, a substantial body of work has accumulated in an effort to optimize local control (LC) through altered treatment schedules such as accelerated fractionation, hyperfractionation, and accelerated hyperfractionation. The addition of concurrent chemotherapy over the past 15 years has also improved rates of LRC and OS, although at the expense of increased acute and late toxicities. IMRT provides LC rates similar to those of conventional irradiation while decreasing potential acute and late toxicities through dosimetric avoidance of critical structures.

To date, only a single randomized trial evaluating primary surgery versus radiation therapy has been conducted for primary oropharyngeal squamous cell carcinomas (RTOG 73-03).[83] Seventy patients were randomized to definitive radiotherapy, preoperative radiotherapy followed by surgery, or surgery followed by radiotherapy. No significant difference was identified in rates of either OS or LC, although the study was grossly underpowered.

The heterogeneity of tumors within the oropharynx given the multiple combinations of primary and nodal stages also makes broad treatment recommendations difficult. Furthermore, the recent epidemiologic shift in this disease, with the dramatic increase in good-prognosis HPV-initiated tumors, has brought into question the utility of historical comparisons.

Early-stage oropharyngeal carcinomas (T1 to T2, N0 to N1) can be treated with either radiation or surgery, with the addition of adjuvant radiation as indicated by surgical pathologic findings. Surgery and radiation therapy provide similar local and regional control rates.[84] Treatment selection is consequently based on the anticipated modality-specific functional and cosmetic outcome, the most appropriate treatment for lymph nodes at risk, and patient goals and preferences. Well-lateralized tumors, particularly of the tonsillar complex, can be treated with unilateral radiation and resultantly have a more favorable toxicity profile. Radiation has traditionally been used for early-stage oropharyngeal tumors based on excellent LC rates and acceptable morbidity and the higher rate of severe complications identified with surgery, particularly in older series. However, minimally invasive surgery with robotics or transoral laser microsurgery has demonstrated lower morbidity than older surgical techniques and is increasingly used in early stage disease.

Intermediate-stage carcinomas (large T2 lesions, nonextensive T3 lesions, with or without advanced nodal disease) are preferentially treated by primary radiation with or without chemotherapy because most patients undergoing surgical resection ultimately receive postoperative radiation therapy for the presence of multiple positive nodes, extranodal extension, or close resection margins. In this setting, definitive radiation spares the combined toxicity of both surgery and adjuvant radiation, particularly because resection of intermediate-stage carcinomas frequently leads to functional loss.

Locally advanced primary tumors (large, infiltrative T3 or T4 lesions) can be treated with radiation, preferably with concurrent chemotherapy, or with primary resection, nodal dissection, and postoperative irradiation with or without concurrent chemotherapy. The large tissue defects typically required for such a resection can be reconstructed with microvascular free flaps, which decrease the degree of functional loss. Because this functional loss exceeds that expected by radiation therapy, primary radiation plus concurrent chemotherapy is typically recommended. Surgical resection, however, is recommended for locally advanced cases with invasion of the mandible or other excisable osseous structures or if functional deficits such as gross aspiration or laryngeal impairment are present. Postoperative radiation follows surgical resection in these cases.

Surgery

Primary surgery followed by (chemo)radiation as indicated is a viable treatment approach. Surgical techniques continue to evolve and improve with less invasive procedures showing lower functional morbidity and equivalent oncologic outcomes. Traditional "open" surgical approaches include the lateral pharyngotomy, a transhyoid approach, or an anterior approach with a midline or lateral mandibulotomy with a combined lip-splitting incision. These procedures offer improved exposure of the tumor for oncologic resection at the expense of prolonged recovery and potential functional impairment.[85] Transoral approaches for tonsillar tumors have been used for years at some institutions because of the ready visibility and accessibility of the tonsillar fossa with standard surgical tools.[86] The more distal oropharynx, including the base of tongue, has less optimal transoral exposure, limiting transoral surgical excision with standard tools.[87] However, with the pioneering of a rod telescope for visualization and a carbon dioxide laser for excision, Steiner et al published results of 48 previously untreated patients with base-of-tongue tumors treated with this technique from 1986 to 1997.[88] These

transoral approaches have been labeled transoral laser microsurgery (TLM) and deviate from the previous standard for oncologic surgeries requiring en bloc resection of the tumor. As part of these procedures, the tumor is frequently removed piecemeal until the interface between tumor and normal tissue is identified, with an appropriate surgical margin taken at that point. TLM, particularly when used to resect base-of-tongue tumors, is challenging because the carbon dioxide laser is typically used in a line of sight fashion, requiring significant manipulation of the tumor. The carbon dioxide laser is also less robust than cautery in achieving hemostasis, leading to alternation between the two instruments intraoperatively. Finally, the microscope and laryngoscope can have limited exposure and illumination of the surgical site, frequently giving surgeons the impression that "they are operating with limited dexterity in a dark hole."[87]

Transoral robotic surgery (TORS) was first used in head and neck tumors in 2005, using a combination of the camera and two of the robotic arms.[89] Advantages of a TORS approach include improved field of view and illumination as well as more facile three-dimensional manipulation of the robotic arms. Mechanical limitations of the robotic device restrict its application for more distal tumors of the larynx and hypopharynx, but most oropharynx and supraglottic tumors are accessible via TORS.

Primary surgery offers the possibility for improved LC with a negative margin excision followed by radiation as needed, particularly in HPV-negative cancers. Primary surgery may also allow for lower radiation doses in the adjuvant setting and case-dependent omission of concurrent chemotherapy, diminishing potential treatment-related toxicities. This approach is currently being tested in clinical trials.[90]

The increasing use of transoral surgical approaches reflects accumulating institutional data showing good oncologic and functional outcomes (Table 33-4). The majority of data to date derives from single institution series. The Washington University experience[91] of 84 patients with stages III and IV oropharyngeal cancers treated with TLM followed by radiation as indicated described rates of disease-specific survival (DSS) and OS of 92% and 88%, respectively, at 5 years, with only one local failure and four regional failures; only 3.4% of patients remained gastrostomy-tube dependent at 3 years. Only 26% of the patients had stage T3 and T4 disease, however, and these patients had a statistically worse OS. In addition, 95% of the patients were HPV-16 positive, and this may have contributed to the high rates of LRC. Again, such potential benefits are weighed against the hazards of surgery, which included a 6% reoperation rate, an 11% temporary tracheotomy rate, and an 11% rate of velopharyngeal incompetence (although oral intake and speech were not interrupted).

Although the Mayo Clinic experience[96] details a similarly high LC rate with transoral excision, others have found higher rates of locoregional recurrence.[97] The Göttingen group, which pioneered TLM, has reported LRC of 76% and 79% in tonsillar and base-of-tongue resections, respectively.[94,95] These series contain a higher percentage of patients with locally advanced primary tumors, which in other series has significantly impacted locoregional control, with one series showing a 2.5 factor increase in death or recurrence when comparing T1 and T2 with T3 and T4 tumors.[92] Canis et al, however, found no internal differences in LRC or DFS when comparing the primary tumor stage.[94] Although the Göttingen series does not specify HPV positivity, the inclusion of patients extending back to 1986 infers a higher rate of HPV-negative patients, with an anticipated elevation of recurrence rates. The increasing rate of HPV-positivity and the likely impact of primary tumor stage on oncologic outcome underscores the challenge of comparing results from modern surgical series with selected surgically resectable tumors and older, randomized data evaluating radiation-based treatment.

Prior analysis of the patients treated at the University of Göttingen demonstrated a worse DSS and LRC in patients in which adjuvant split-course radiation was used when compared to conventional radiation.[98] The improved outcome with conventional radiation underscores the importance of adjuvant radiotherapy when indicated following transoral resection. Similarly, the largest series evaluating transoral resection found adjuvant radiation therapy, with or without chemotherapy, to favorably impact both OS and DFS (HR 0.33 to 0.48 and 0.38, respectively).[92] Primary tumor stage, HPV status, and margin status were also found impact OS on multivariate analysis.

Treatment Recommendations by Subsite

Tonsillar Region Carcinomas

A review of North American experiences[84] published between 1970 and 2000 compiled data comparing surgery with or without adjuvant radiation with definitive radiation with or without neck dissection. The 51 reported series represented approximately 6400 patients. Results for the tonsillar region showed strikingly similar oncologic outcomes between primary surgery and radiation therapy: LC (70% versus 68%), LRC (65% versus 69%), 5-year OS (47% versus 43%), and 5-year cause-specific survival (CSS) (57% versus 59%), none of which were statistically significant. However, rates of severe

TABLE 33-4 Outcomes Following Transoral Surgical Resection

Author/ Institution	No. Pts	Years	Median FU	Stage III or IV (%)	T3 or T4 (%)	LC	LRC	DFS	OS	Adjuv Tx (chemoRT)	PEG Tube at 1 Year (%)
Haughey[92]/Wash U, Mayo-J, Mayo-S	204	1996-2006	49 mo.	100	34	96% (ND)	93% (ND)	74% (5 yr)	78% (5 yr)	74% (16%)	19
Moore[93]/Mayo	66	2007-2009	36 mo.	88	18	97% (3 yr)	94% (3 yr)	95% (2 yr)	95% (ND)	83% (62.1%)	5
Canis (BOT)[94]/Göttingen	82	1986-2007	51 mo.	92	65	87% (ND)	79% (ND)	69% (5 yr)	59% (5 yr)	55% (23.1%)	6
Canis (Tonsil)[95]/Göttingen	102	1987-2006	63 mo.	87	54	ND	76% (5 yr)	71% (5 yr)	58% (5 yr)	66% (21%)	3

Adjuv Tx, *Adjuvant treatment;* BOT, *Base of tongue;* chemoRT, *Chemo-radiation;* DFS, *Disease-free survival;* FU, *Follow-up;* LC, *local control;* LRC, *localregional control;* Mayo-J, *Mayo Jacksonville;* Mayo-S, *Mayo Scottsdale;* mo., *months;* ND, *Not described;* No. Pts, *number of patients;* OS, *overall survival;* Wash U, *Washington University.*

TABLE 33-5 Outcomes Following Definitive IMRT

Author/Institution	No. Pts	Years	Median FU	Stage III or IV (%)	T3 or T4 (%)	LC	LRC	OS	Chemo (%)	Feeding Tube
Garden[104]/MDACC	776	2000-2007	54 mo.	93	26	94% (5 yr)	90% (5 yr)	84% (5 yr)	54	2.3%
Lok[105]/MSKCC	442	1998-2009	37 mo.	94	31.4	94.6% (3 yr)	89% (3 yr)	84.5% (3 yr)	91	7% (1 yr), 4% (2 yr)
Mendenhall[106]/Univ Florida	130	2001-2007	42 mo.	90	36	87% (5 yr)	84% (5 yr)	76% (5 yr)	61	4%

chemo, *Chemotherapy;* FU, *Follow-up;* LC, *local control;* LRC, *localregional control;* MDACC, *M. D. Anderson Cancer Center;* mo., *Months;* No. Pts, *number of patients;* OS, *Overall survival;* Univ, *University.*

TABLE 33-6 Outcomes Following Ipsilateral Radiation Therapy

Author/ Institution	No. Pts	Years	Median FU	T3 or T4 (%)	N2 or N3	Contralat Failure	LC	LRC	OS	Chemo (%)	Chronic Feeding Tube (%)
Jackson[100]/ British Columbia	178	1975-1993	ND	39	13% (N2-3)	2.3% (in N0 or N1)	75% (ND)	ND	56% (5 yr)	0	ND
O'Sullivan[107]/ Princess Margaret Hospital	228	1970-1991	84 mo.	16.2	11.8% (N2-3)	3.5%	77% (3 yr)	ND	ND	0	ND
Chronowski[108]/ MDACC	102	1970-2007	38 mo.	0	43% (N2a-b)	2%	100% (5 yr)	96% (5 yr)	95% (5 yr)	5	0
Al-Mamgani[109]/ Rotterdam	185	2000-2011	49 mo.	7 (T3 only)	27% (N2a-b)	1.1%	91% (5 yr)	87% (5 yr)	70% (5 yr)	6	0

chemo, *Chemotherapy;* Contralat, *contralateral;* FU, *follow-up;* LC, *local control;* LRC, *localregional control;* MDACC, *M. D. Anderson Cancer Center;* mo., *months;* ND, *not described;* No. Pts, *number of patients;* OS, *overall survival.*

complications (23% versus 6%) and fatal complications (3.2% versus 0.8%) were significantly higher in the surgical group. The less toxic side effect profile of definitive radiation therapy led the authors to recommend this approach for most patients with SCC of the tonsillar complex.

Oncologic and function outcomes from definitive radiation therapy have improved over time based on institutional series. eTable 33-1 summarizes historical institutional experiences with more than 100 patients treated with conventional radiation for SCC of the tonsillar region (with the exception of 17 patients in the Florida series receiving IMRT). The improved outcomes seen in recent reports are likely the result of improved imaging modalities leading to stage migration, improved planning techniques, the increased prevalence of HPV-positive tumors, and the concurrent use of chemotherapy when indicated (Table 33-5).

The largest study of radiation therapy for oropharyngeal cancer in the IMRT era reviewed 776 patients treated at M. D. Anderson Cancer Center (MDACC) with IMRT from 2000 onward.[104] Half of these patients had tonsillar tumors, 46% had base-of-tongue tumors, and small percentages had soft palate and pharyngeal wall primaries. LRC and OS were 90% and 84% at 5 years, respectively (Table 33-5). Sixteen percent of the patients had pretreatment tonsillectomies, largely for diagnostic purposes, and 9% had nodal excision biopsies. The implementation of IMRT has previously raised concern that LRC may be impaired as a result of marginal misses. This did not occur in this series as locoregional recurrences, when they occurred, were primarily in the high-dose volumes, with only 12 patients (2% of the cohort) experiencing recurrence outside of these volumes. Tumor stage, overall stage, current tobacco use, and low neck nodes all impacted OS. Memorial Sloan Kettering Cancer Center (MSKCC) and the University of Florida reported similar high rates of LC, LRC, and OS in the IMRT era (Table 33-5).[105,106] Of note, the rate of chronic gastrostomy tube dependence in these IMRT-based series was much lower (2.3% to 4%) than those reported for conventional radiation and concurrent chemotherapy and mirror those seen with transoral surgical resection.

Unilateral Radiation

Unilateral radiation, including coverage of the ipsilateral neck but not the contralateral neck, has been delivered in the past using conventional techniques in patients with well-lateralized tonsillar fossa tumors. Such an approach in the era before IMRT became available offered sparing of the contralateral parotid and submandibular glands and was designed to avoid permanent xerostomia. Jackson et al[100] reported a risk of contralateral node recurrence in 2.5% of patients treated with ipsilateral irradiation for a tonsillar primary tumor that was clinically N0 or N1 (Table 33-6). Of the 642 patients treated for carcinoma of the tonsillar region at Princess Margaret Hospital from 1970 to 1991, 228 patients were treated with ipsilateral irradiation.[107] Contralateral neck failures occurred in eight patients (3.5%), with only three patients having contralateral nodal failure alone (1.7% of patients). These three patients all had significant soft palate involvement (to within 1 cm of the midline in two cases and involving more than 1 cm of the soft palate in the other case) and ipsilateral neck disease. No contralateral neck failures were seen in patients who had clinical stage T1 disease, regardless of nodal disease extent, or N0 disease, regardless of tumor size or involvement of midline

eTABLE 33-1 Local Control Rates Reported for Treatment of SCC of the Tonsillar Fossa

Study/Institution	Years	No. Pts	T1 (%)	T2 (%)	T3 (%)	T4 (%)	Overall	Comments
Perez[99]/Wash U	1959-1991	154	76	63	59	33	56	Included patients treated with cobalt
Jackson[100]/Vancouver Cancer Centre, B.C.	1975-1993	271	94	79	58	56	75	60 Gy in 25 fx most common regimen, ipsilateral EBRT
Mendenhall[101]/ U Florida	1964-2003	503	88	84	78	61	79	64.8% with hyperfractionation
Bataini[102]/Institut Curie	1958-1983	465	90	84	64	47	64	Overall treatment time strongly predictive for local control
Wang[103]/MGH	1970-1993	102	91	91	80	ND	ND	Improved outcomes with hyperfractionation

EBRT, *External beam irradiation;* Fx, *fractions;* Institut, *institute;* ND, *not described;* No. Pts, *number of patients;* MGH, *Massachusetts General Hospital;* Wash U, *Washington University.*

structures. The margin of coverage placed on the primary site had a significant impact on LC rates, with a 30% LC rate for a margin of less than 1 cm and an 89% LC rate for a margin of more than 1 cm. O'Sullivan et al advocated ipsilateral irradiation after informed patient consent for all lateralized lesions with less than 1 cm of medial soft palate or tongue base extension.

Side effects appear to be reduced in patients treated to the ipsilateral neck only. The Aarhus University group found no impact on LRC or survival with ipsilateral radiation, but side effects were reduced for all endpoints (i.e., dysphagia, xerostomia, hoarseness, atrophy, fibrosis, and edema)[110] Moderate to severe toxicity was reduced by more than 50% for all endpoints except fibrosis. When compared to IMRT-based comprehensive MSKCC series 29% and 11% of IMRT patients had late greater than grade 2 xerostomia and dysphagia, respectively, compared to 7.5% and 5.4% with ipsilateral radiation.[105,109] In addition, in more modern experiences reporting ipsilateral radiation, no chronic gastrostomy tube reliance has been identified.

Our use of unilateral radiation at the University of Wisconsin has evolved over time, with increased frequency as studies confirming its safety have accumulated. We typically have confined ipsilateral radiation to patients with well-lateralized T1 to T2, N0 to N1 tonsillar cancers and ipsilateral radiation has not been employed when the primary tumor extends to involve midline structures such as the base of the tongue or more than minimal extension onto the soft palate. This is consistent with the American College of Radiology (ACR) consensus that deemed ipsilateral radiation appropriate in tonsillar tumors that have less than 1 cm invasion into the soft palate or base of tongue and a nodal stage of N0 or N1.[111] Others have argued that the contralateral neck only needs to be covered if the tumor extends beyond the midline of the soft palate (uvula) or beyond the lateral one third of the ipsilateral base of the tongue.[97,112] The dominant criticism of ipsilateral radiation is the potential risk of contralateral regional recurrence. In all large published series, however, the risk of contralateral nodal failure is significantly less than 5%, despite two studies including patients from before the CT era (see Table 33-6). This suggests that the current criteria for ipsilateral radiation may be overly conservative. Of note, in comparing late side effects of treatment, ipsilateral radiation seems to have more limited late toxicity than the transoral resections, although identifying the late toxicity of transoral resection can be confounded by adjuvant (chemo)radiation.

Surgery

The advances in surgical techniques and outcomes associated with transoral resections were discussed previously. Many patients present to the radiation oncology clinic having undergone tonsillectomy for either a tonsillar abnormality or as part of an evaluation for an unknown primary tumor in the setting of cervical nodal disease. Yildirim et al[113] evaluated 120 patients treated with radiotherapy at MDACC following gross removal of their disease by tonsillectomy. Most of these tonsillectomies were performed for diagnostic purposes, including 29% that had no preoperative tonsillar abnormality. The population included 36 patients with stage III disease and 64 patients with stage IV disease. Only 12 patients received systemic chemotherapy. Five-year LRC, recurrence-free survival (RFS), and OS were high at 97%, 92%, and 86%, respectively, with only a single patient experiencing disease recurrence at the primary site. Fifty-one percent of tumors had negative surgical margins, 35% had positive surgical margins, 10% had close margins (<5 mm), and 3% had an unknown margin status. The tonsillar bed received 66 Gy of radiation in 82% of patients. The authors concluded that the high LC rate present, particularly with T2 disease, may be a result of patient selection rather than the potential benefit of tonsillectomy because there was not invasion into adjacent mucosal sites such as the soft palate or base of the tongue in this patient group. Margin status and nodal disease dictated that adjuvant radiation be delivered, making the benefit from surgery with its associated toxicities, including potential velopharyngeal insufficiency, unclear. Surgery may be a reasonable approach for small, stage T1 or T2 primary tumors without nodal disease in which adjuvant radiation would not be required postoperatively, but this is a small subset of patients with early disease.[114]

Base-of-Tongue Cancers

SCCs of the base of the tongue tend to be more locally, regionally, and systemically aggressive with worse outcomes when compared with tonsillar primary cancers. Parsons et al[84] also reviewed the radiation oncology and surgical literature from 1970 to 2000 and compared reported outcomes between surgery with and without radiation and definitive radiation with or without a lymph node dissection for base-of-tongue primaries. For surgical-based versus radiation-based treatments, similar outcomes were identified for rates of LC (79% versus 76%), 5-year OS (49% versus 52%), and 5-year CSS (62% versus 63%). LRC rates were slightly better with radiation as the primary modality (60% versus 69%). Again, the rate of severe complications was higher if primary surgery was performed (32% versus 3.8%), as was the rate of fatal complications (3.5% versus 0.4%). The authors concluded that radiation therapy with or without lymph node dissection was preferable for the majority of SCCs of the base of the tongue based on the discrepant toxicity profiles.

Reported historical LC rates of large series published in the last 20 years are listed in eTable 33-2. The largest series from the University of Florida describes a LC rate of 93% for T1 to T2 tumors.[115] Multivariate analysis demonstrated that the T category, histologic differentiation, adjuvant chemotherapy (if T4 disease), and race all affected LC rates. More poorly differentiated cancers had better LC when compared with the more differentiated neoplasms, potentially acting as a surrogate for HPV-positivity. LRC rates were affected by the same factors and were also statistically associated with postradiotherapy neck dissections and overall stage. Seventy-five percent of patients in this series were treated with hyperfractionated regimens (twice-daily hyperfractionation or concomitant boost), although this was not correlated with LC or LRC. Compared with tonsillar fossa tumors, base-of-tongue tumors had lower rates of LC, particularly when clinically T3. Sixteen percent of patients (52 patients) developed one or more severe complications from treatment, including the need for a permanent gastrostomy tube (21 patients) and mandibular osteoradionecrosis (8 patients). Eleven patients had surgery-related complications following either a postradiation neck dissection or salvage surgery.[115]

Brachytherapy

High local and regional control rates have been achieved using a combination of external beam radiation therapy (EBRT) and a brachytherapy boost. Harrison et al[116] treated 68 patients with this approach, with a high overall LC of 89%. EBRT was delivered to the primary site and upper neck (54 Gy) and low neck (50 Gy), followed by a boost of 20 Gy to 30 Gy of iridium-192 (^{192}Ir) brachytherapy approximately 3 weeks later. Contraindications for a brachytherapy implant included disease extending below the hyoid bone, into the preepiglottic space, mandibular invasion, or posterior pharyngeal wall extension, with 15% to 20% of cases being unsuitable for brachytherapy. Similar high rates of LC have been identified at other institutions,[117,118] although the University of Florida discontinued

eTABLE 33-2 Local Control Rates Reported for Treatment of SCC of the Base of Tongue

Study/Institution	Years	No. Pts	T1 (%)	T2 (%)	T3 (%)	T4 (%)	Overall	Comments
Mendenhall[115]/Univ Florida	1964-2003	333	98	92	82	53	82*	75% altered fractionation
Harrison[116]/MSKCC	1981-1995	68	87	93	82	100 (2/2)	89	Ir-192 interstitial boost
Wang[103]/MGH	1970-1993	90	85	85	54	ND	ND	Improved outcome with hyperfractionation

MGH, *Massachusetts General Hospital;* MSKCC, *Memorial Sloan Kettering Cancer Center;* ND, *not described;* Univ, *university.*
**Locoregional control affected by T category, overall stage, adjuvant chemotherapy, and neck dissection.*

interstitial implant because of inferior results compared with conventional EBRT.[115]

Soft Palate Carcinomas

Carcinomas originating from the soft palate are a small minority of oropharyngeal cancers, occurring less frequently than cancer arising from the base of the tongue or tonsillar regions, and they typically account less than 10% of the total cases. A higher prevalence is seen in studies evaluating early-stage (stages I and II) carcinomas of the oropharynx because soft palate carcinomas are less likely to be locally advanced or regionally metastatic and resultantly represent a higher percentage of the early-stage tumors.[119] Because of the lower frequency of soft palate carcinomas, accumulation of large numbers of patients for studies is challenging. Generally, in patients who have not been previously radiated, definitive radiation is preferred to surgery. Surgical defects can lead to velopharyngeal incompetence, affecting both speech and swallowing. The drainage pattern from the soft palate can also include the retropharyngeal nodes, which are unaddressed in a standard neck dissection.

Chera et al[120] reviewed the University of Florida experience of 145 patients treated curatively with definitive radiation for soft palate carcinomas between 1963 and 2004. Hyperfractionation was used in 42% of patients, an orthovoltage intraoral cone in 27%, and an interstitial implant in 6%. Thirteen percent had synchronous SCCs elsewhere in the upper aerodigestive tract. At 5 years, LC rates were T1 90%, T2 91%, T3 67%, and T4 57%. The OS at 5 years was 44%, with many patients dying of comorbid disease and second primary tumors (CSS at 5 years was 73%). An overall treatment time of more than 47 days and a higher overall stage both adversely affected LRC rates, whereas nodal category affected OS. In an inter-era comparison, patients treated after 1985 had improved control rates (87% versus 73%). Similar high rates of LC were identified in older single-institution studies. Keus et al[121] reported on 146 patients treated at Institut Curie for soft palate carcinoma, 71% with EBRT alone and 29% with an intraoral applicator. Patients receiving radiation through the intraoral applicator had fewer normal tissue complications, although most patients receiving this had smaller primary tumors (stage T1 or T2). LC rates at 3 years for T1 and T2 tumors were 92% and 70%, respectively. Neck disease recurred in 19 patients, of whom 9 had no component of local recurrence; reexamination of the treatment portals suggested a marginal miss in 7 patients. No dose response was ascertained in locally advanced tumors receiving between 60 Gy and 75 Gy, leading the authors to recommend limiting the EBRT dose to 70 Gy to minimize complications.

Several French groups have described high LRC rates with a combination of interstitial brachytherapy and EBRT. Mazeron et al[122] described 5-year LC and nodal control of 91% and 95%, respectively, in patients treated with EBRT followed by a ^{192}Ir implant for T1 and T2 soft palate carcinomas. The 5-year necrosis rate in this group was just under 20%. When compared with rates for patients treated with EBRT alone, both LC and OS were improved.

Lateral and Posterior Pharyngeal Wall Tumors

SCC of the pharyngeal wall is a relatively uncommon primary location and has the lowest incidence of the oropharyngeal subsites. The oropharynx and hypopharynx are demarcated by an artificial plane placed at the superior surface of the hyoid bone. However, the fact that the lateral and posterior pharyngeal walls are in continuity can create challenges when one is attempting to assign a head and neck site to a tumor that may continuously involve a large segment of the pharyngeal wall.

Both surgery and radiation therapy have been employed to treat pharyngeal wall cancers, and comparison of the two modalities is problematic because of the low incidence and inherent staging variability of these lesions as well as the limited amount of literature addressing them. Hull et al[123] reported on 148 patients with SCCs of the pharyngeal wall treated with definitive radiation between 1964 and 2000; 93 lesions (63%) arose from the hypopharynx and 55 (37%) arose from the oropharynx. LC rates at 5 years were T1 93%, T2 82%, T3 59%, and T4 50%. With surgical salvage, the LC rate increased to 87% for T2 tumors. Earlier-stage disease (stages I and II), an oropharyngeal primary site, and twice-daily fractionation were all associated with improved LRC. Treatment complications resulted in the deaths of 5% of the patients, and 16% of patients experienced severe complications, the most frequent of which was the need for a permanent gastrostomy tube.

Julieron et al[124] reviewed 77 patients treated surgically for posterior pharyngeal wall tumors, of which 22 required a total laryngectomy. For previously untreated patients, local failure occurred in 11% of individuals treated with surgery and adjuvant radiation and in 18% with tumors larger than 4 cm. The total failure rate, including local, regional, and distant relapses and second primary tumors, was 50% in the primary surgery group. Nineteen percent continued to rely on a gastrostomy tube at 1 year. Local failure was seen in 52% of patients who had received prior radiation therapy, and 5-year OS was inferior to that of the nonrecurrent disease group; the authors concluded that conservative surgery should not be performed in the setting of postradiation failure.

LOCOREGIONALLY ADVANCED DISEASE AND PALLIATION

Chemotherapy/Concurrent Chemoradiation

The benefit of adding chemotherapy to the treatment of locoregionally advanced SCC of the head and neck has been established by the Meta-Analysis of Chemotherapy on Head and Neck Cancer (MACH-NC), a meta-analysis based on individual patient data, first published in 2000 and most recently updated in 2009.[125,126] The updated meta-analysis included 87 randomized trials that enrolled 16,485 patients comparing locoregional treatment versus the same locoregional treatment plus chemotherapy. An absolute survival benefit of 4.5% was observed at 5 years, but this benefit depended on how the chemotherapy was scheduled (induction, adjuvant, or concurrent) (Table 33-7).

Induction or Adjuvant Chemotherapy

Induction chemotherapy, the delivery of chemotherapy before definitive surgery or radiation therapy, is an approach based on the recognition that systemic chemotherapy is most active in previously untreated patients. Combination chemotherapy regimens with drugs such as fluorouracil and cisplatin can produce response rates of 80% to 90%, which are clinically complete in up to 40% of these patients.[127] Although the responses are temporary, the use of chemotherapy as the initial treatment modality is an attractive model and has the potential to maximize the benefit of the chemotherapy while both reducing the magnitude and improving the outcomes of the locoregional therapy.

Multiple Phase III trials of induction chemotherapy schedules have been conducted, but the results have been generally disappointing. In the updated MACH-NC meta-analysis, individual patient data from 31 induction trials (5311 patients) were analyzed, and no significant survival benefit was identified.[126] It is of note, however, that among the trials that used

TABLE 33-7 Meta-Analysis of Chemotherapy on Head and Neck Cancer (MACH-NC) Overall Survival[126]

Scheduling	No. of Trials	No. of Pts	HR (95%CI)	*p*-Value	5-yr OS Benefit
Induction chemotherapy	31	5311	0.96 (0.90-1.02)	NS	2.4%
Adjuvant chemotherapy	12	2567	1.06 (0.95-1.18)	NS	–1.0%
Concurrent Concurrent chemoradiation	50	9615	0.81 (0.78-0.86)	<0.0001	6.5%

HR, *Hazard ratio;* No., *number;* OS, *overall survival;* Pts, *patients.*

TABLE 33-8 Recently Reported Cooperative Group Phase III Trials of Concurrent Chemoradiation

Trial	Year	*N*	Stage IV	OP	p16+ OP	Treatment Arms	Primary Endpoint	Result	Secondary Observations
RTOG 0129[33]	2010	743	78%	60%	50%	1. SFX + DDP(×3) 2. AFX + DDP(×2)	OS	No difference	Better outcomes in HPV+(p16+) OP.
TROG 02.02[132,133]	2010	861	87%	55%	57%	1. SFX + DDP(×3) 2. SFX + DDP(×3) + TPZ	OS	No difference	1. Better outcomes in p16+ OP. 2. Worse outcomes if poor quality radiation.
RTOG 0522[134]	2011	940	86%	70%	73%	1. AFX + DDP(×2) 2. AFX + DDP(×2) + Cetuximab	PFS	No difference	Better outcomes In p16+ OP.
GORTEC 9902[135]	2012	840	NS	66%	NS	1. SFX +Cb/FU(×3) 2. AFX +Cb/FU(×2) 3. Very AFX	PFS	1. Arms 1 & 2 equivalent. 2. Arm 3 was inferior.	Mucositis was worse on Arms 2 and 3

AFX, *Accelerated fractionation radiation (70-72 Gy/6 weeks);* Cb/FU, *carboplatin and fluorouracil;* DDP, *cisplatin;* NS, *not stated;* OP, *oropharynx cancer patients;* OS, *overall survival;* PFS, *progression-free survival;* SFX, *standard fractionation radiation (70 Gy/7 weeks);* TPZ, *tirapazamine; Very AFX (64.8 Gy/3.5 weeks).*

induction regimens containing a platinum and fluorouracil, the hazard ratio was more favorable at 0.90 (95% CI, 0.82 to 0.99). Although induction chemotherapy significantly reduced distant metastases, it had only a minimal impact on LRC, the more frequent cause of treatment failure. Similarly, in 12 trials (2567 patients) which explored the use of adjuvant, single-modality chemotherapy after definitive locoregional management, no survival benefit was identified in this meta-analysis.

Concurrent Chemoradiation

The results were distinctly different for those trials using concomitant chemotherapy and radiation. This approach is based on the recognition that chemotherapy, in addition to its independent antineoplastic activity, has the potential to radiosensitize and thereby improves the outcomes achieved after radiation alone. Such radiosensitization, however, also increases the acute toxicity from treatment. In the MACH-NC meta-analysis of the 50 concomitant trials (9615 patients), the absolute benefit from chemotherapy was 6.5% at 5 years. The concomitant schedules markedly improved the LRC (HR, 0.74; 95% CI, 0.70 to 0.79; $p < 0.001$) with a significant but less impressive improvement in distant control (HR, 0.88; 95% CI, 0.77 to 1.00; $p = 0.04$).[126] This report solidified the role of concomitant chemoradiation as a treatment standard in the definitive management of locoregionally advanced head and neck squamous cell cancer.

The MACH-NC investigators also noted that the proportion of deaths not resulting from head and neck cancers increased progressively with age from 15% in patients younger than 50 years to 39% in those aged 71 years and over. There was a concomitant diminishing benefit of chemotherapy on survival such that patients aged 71 years or older essentially derived no improvement at 5 years. Others have suggested, however, that appropriately selected elderly patients have outcomes after treatment that are equivalent to their younger counterparts.[128]

Monotherapy with single-agent cisplatin and concomitant EBRT is the most frequently tested regimen and has become a standard of care.[129] Other acceptable alternatives include multiagent combinations of cisplatin or carboplatin with 5-fluorouracil (5-FU). Monotherapy with a drug other than cisplatin has led to inferior results and is not recommended in routine practice. The effect of the total dose of cisplatin administered may be relevant to clinical outcome but has not been addressed systematically.[130] Rates of acute toxicities, including mucositis, skin toxicity, and hematologic adverse events, are clearly increased by the addition of concurrent chemotherapy. Late toxicities, however, are less well described, although a trend toward an increase in severe late toxicity after chemoradiation was identified in the Phase III GORTEC 94-01 oropharynx cancer trial.[131]

Table 33-8 summarizes some of the recently published cooperative group randomized Phase III trials of concurrent chemoradiation. These studies have addressed the possibility of improving outcomes either by using accelerated radiation fractionation or by adding additional noncytotoxic systemic agents, such as cetuximab, a monoclonal antibody EGFR inhibitor, or tirapazamine, a hypoxic cell sensitizer. In general, these efforts have proven unsuccessful. Several important observations have nonetheless emerged from these trials. First, like most trials in head and neck cancers, eligibility was not restricted to patients with oropharynx tumors. Nonetheless it is apparent that the study populations were dominated by patients with stage IV oropharynx cancer who were largely p16 or HPV positive, and that in these large prospective trials the highly favorable prognostic import of HPV positivity was confirmed. This has led to the general consensus that, at the least, HPV status must be included as a stratification factor in all future clinical trials that include oropharyngeal cancer.

Ideally, separate clinical trials based on tumor HPV status should be designed.[34] In the HPV-negative cancers, continued efforts directed at improving outcomes remain the priority. In the good prognosis HPV-positive oropharyngeal cancer population, however, the focus should be on reducing acute and long-term toxicity, without loss of efficacy. The RTOG 1016 trial, which compares radiation with cisplatin to radiation with cetuximab, and the ECOG 1308 trial, a Phase II study exploring a reduced dose of radiation in patients with HPV-positive oropharynx cancer achieving a complete response to induction chemotherapy, are two examples of such trials in this population. Both studies await full analysis.

Additional observations from these recent randomized trials include the recognition that the highly accelerated fractionation schedule from the GORTEC trial[135] produced a significantly greater mucosal reaction. In the absence of a clear outcome improvement, such a schedule cannot be recommended. The TROG 02.02 trial confirmed the conventional wisdom that poor radiation therapy quality produces inferior outcomes, and it noted that the probability of receiving poor-quality radiation was highly correlated with lower enrollment on the trial, presumably reflecting lower overall patient volume and experience.[132] The TROG trial also identified a strong trend toward an improvement in LRC in the patients who were p16-negative treated with the hypoxic sensitizer; raising the possibility that such agents might be useful in that subset of patients.[133]

Although concurrent chemoradiation remains the standard of care for patients with locally advanced, nonmetastatic SCC of the head and neck, the short-term benefit of induction chemotherapy, and in particular its impact on the risk of distant metastases, has been of continued interest. Phase II testing of more intensive three-drug induction regimens adding a taxane (paclitaxel or docetaxel) to the well-tested cisplatin and fluorouracil backbone have suggested an improvement in overall response rate. To date, there have been four separate Phase III trials that have supported this observation (Table 33-9).[136-139] A meta-analysis has confirmed the findings.[140]

This has led several groups to explore more intensive sequential treatment schedules of induction chemotherapy followed by concurrent chemoradiation in an effort to optimize both distant and LRC effects. Four separate Phase III randomized trials have been completed attempting to define whether the addition of induction chemotherapy to concurrent chemoradiation will improve outcomes achieved with chemoradiation alone. Three of these studies have been reported and have all been negative.[141-143] No survival benefit was identified and the sequential regimens proved more toxic. Further use of this approach therefore remains investigational.

Biologic Therapy

In 2006, Bonner et al reported results from a landmark study that compared radiation therapy alone (once-daily dose of 70 Gy in 35 fractions; twice-daily dose of 72 Gy to 76.8 Gy in 60 to 64 fractions; or concomitant boost of 72 Gy in 42 fractions) with radiation plus the anti-EGFR monoclonal antibody cetuximab.[144] This study demonstrated that the use of a biologic agent in combination with EBRT could improve survival rates for locoregionally advanced SCC of the head and neck, and led to the approval of cetuximab by the U.S. Food and Drug Administration (FDA) in 2006 for this indication. The median duration of LRC, the primary endpoint, was 24.4 months in the combined-therapy arm and 14.9 months in the radiation alone arm (HR for locoregional progression or death, 0.68; 95% CI, 0.52 to 0.89; $p = 0.005$). Five-year OS was 45.6% versus 36.4%, with median survival durations of 49 versus 29.3 months (HR, 0.73; $p = 0.018$), respectively, favoring the combined-therapy arm.[145] With the exception of acneiform rash and infusion reactions, the incidence of grade III or greater toxic effects, including mucositis, did not differ significantly between the two groups. Rates of grade III or IV late toxicities were also similar.

In subgroup analyses, it would appear that patients who received radiation with the concomitant boost regimen derived the greatest benefit from the addition of cetuximab. When analyzed by disease site, patients with primary tumors in the oropharynx benefited most compared to those with primary tumors in the larynx (HR, 0.87) and in the hypopharynx (HR, 0.94), suggesting that there might be a relationship between HPV-related SCC and responsiveness to the anti-EGFR antibody, a postulate that requires verification by randomized data.

TABLE 33-9 Response Rates in Four Randomized Trials of a Taxane, Cisplatin, Fluorouracil (TPF) Versus Cisplatin, Fluorouracil (PF)-Induction Chemotherapy

Trial	Year	Taxane	PF (%)	TPF (%)	*P*-value
Hitt[136]	2005	paclitaxel	68	80	<0.001
Vermorken[137]	2007	docetaxel	54	68	0.006
Posner[138]	2007	docetaxel	64	72	0.07
Pointreau[139]	2009	docetaxel	59	80	0.002

Management of the Neck

Adjuvant Radiation or Chemoradiation

Two large, multicenter, randomized Phase III trials, EORTC 22931 and RTOG 9501, have evaluated the role of adjuvant high-dose cisplatin chemotherapy administered concomitantly on days 1, 22, and 43 with EBRT (60 Gy to 66 Gy in 30 to 33 fractions) in the postoperative setting for patients with locally advanced SCC of the head and neck.[146,147] Initial reports from both trials demonstrated statistically significant improvements in the rates of LRC and DFS or progression-free survival (PFS). The EORTC 22931 trial also demonstrated a significant OS benefit for postoperative chemoradiation, although the RTOG 9501 study only trended in that direction. The eligibility criteria of the two trials differed somewhat, and the overall patient population appeared to have somewhat worse baseline characteristics in the EORTC 22931 trial. A meta-analysis of these two trials has been published, identifying microscopically involved resection margins and extracapsular spread of tumor from neck nodes as the two most important prognostic factors for poor outcome.[148] Patients with these risk factors appear to gain the most benefit from concurrent chemoradiation. It is of note that in an analysis of the 10-year follow-up from the RTOG 9501 cohort, benefit was identified only in those patients with these two high-risk features.[149] Based on the results of these two studies, patients with one or both of these high-risk factors who are medically fit should be treated with postoperative chemoradiation using cisplatin, whereas radiation therapy alone should remain as the standard of care for those without these high-risk factors.

There have been subsequent efforts to improve on these results. The RTOG 0234 trial was a randomized Phase II trial of surgery followed by chemoradiation using cetuximab with either cisplatin or docetaxel in patients with resected stage III or IV SCC of the head and neck who had high-risk pathologic features, including microscopically positive resection margins, two or more metastatic neck nodes, or extranodal capsular spread. The trial accrued 238 patients and, with a median

follow-up of 4.4 years, the cetuximab-docetaxel arm compared favorably with the cetuximab-cisplatin arm, and appeared to produce an improvement in DFS when retrospectively compared to the cisplatin chemoradiation arm from RTOG 9501.[150] As a result, the RTOG has launched a follow-up Phase II-III trial (RTOG 1216) in high-risk postoperative patients comparing radiation with either single-agent cisplatin, single-agent docetaxel, or the cetuximab-docetaxel combination from RTOG 0234.

The RTOG has also activated a randomized Phase III trial (RTOG 0920) comparing radiation alone with radiation plus cetuximab in patients with locally advanced SCC of the oral cavity, oropharynx, or larynx whose tumors exhibited one or more "intermediate-risk" features. These intermediate-risk features include perineural invasion; lymphovascular invasion; a single lymph node greater than 3 cm or two or more lymph nodes (all <6 cm) and no extracapsular extension; close surgical resection margins (<5 mm); a T3 or T4a primary tumor; or a T2 oral cavity cancer with more than 5 mm depth of invasion.

Postradiation Neck Dissection

Current issues in the management of the neck in oropharyngeal SCCs revolve around the dose and volume of radiation delivered to nodal regions and the role of posttreatment neck dissections. Before the IMRT era, a common approach was to deliver 50 Gy to the draining regional lymphatics followed by a boost to the nodal disease using photon or electron beam therapy to 60 Gy in patients presenting with palpable cervical lymph node metastases. Radiation was subsequently followed by a postradiation planned neck dissection. Reported neck control rates with this approach at the MSKCC were 96% overall and 100% in patients who went on to have neck dissection.[151] Pathologic complete response was observed in 70% of patients. In the patients with residual disease, more than half had a complete clinical response and 83% had multiple residual pathologically positive nodes. The downside of this approach was overtreatment of the neck in the patients with a pathologic complete response who could have avoided neck dissection and the associated potential for complications and heightened late effects. The late side effects of neck dissection are not negligible; a meta-analysis of multiple RTOG studies showed that neck dissection after chemoradiation was one of the risk factors for severe late toxicity.[152]

Despite concern for side effects associated with neck dissection, some caution is warranted in choosing to forego a planned neck dissection in patients with N2-N3 nodal disease. Early, planned neck dissections have several distinct advantages. Most important are the potential improvements in oncologic outcomes such as DSS and regional control.[153] Most studies have found residual nodal disease in at least 20% of patients, with the caveat that pathologic presence following treatment does not establish cancer viability. Neck dissections performed during the 6 to 12 weeks immediately following the completion of radiation also take advantage of a window of time between the acute and late effects of radiation treatment. Although technically demanding in the postradiation setting, complications requiring additional surgery are typically around 5%, although they may be increased by high doses and concurrent chemotherapy.[154,155] Subcutaneous fibrosis is limited before the 12-week mark, allowing selective neck dissections to occur. In oropharyngeal cancer, a selective neck dissection involving levels II to IV is usually sufficient, although decision making regarding the neck dissection should be driven by pretreatment clinical and radiographic findings. In a primarily oropharyngeal cohort, residual nodal disease outside of levels II to IV was seen in less than 5% of patients following radiation.[156] Although salvage surgery can be performed in the undissected neck with recurrent disease, it carries a greater risk of complications, often requires a more extensive resection, and may lead to inferior regional control rates.

Most institutions have moved away from planned neck dissections despite these concerns. This treatment plan has relied on increasing the rate of pathologic complete responses and successfully detecting patients with residual disease following radiation. It has become common to deliver a full dose (70 Gy) to clinically and radiographically involved lymph nodes with IMRT technique. Radiographically involved lymph nodes are defined as being positive on PET scanning or having a maximal size of more than 1 cm. Critical structure toxicities are respected when planning full-dose nodal radiation. For example, involved lymph nodes within level IV and the supraclavicular fossa are frequently taken to 60 Gy with a planned neck dissection rather than risk an increased rate of brachial plexopathy by proceeding to 70 Gy.

Evaluation for residual disease occurs 8 to 12 weeks following completion of radiation with a PET/CT scan, diagnostic neck CT scan, and clinical neck examination. No isolated nodal failures were identified in a prospective trial in which neck dissection was foregone in patients with N2 and N3 disease and clinical and radiographic complete responses.[157] A radiographic complete response required that any previous lymphadenopathy measure less than 1 cm in maximum dimension and have no radiographically suspicious features. Of note, only 59% of patients with N2 and N3 disease had a clinical and radiologic complete response, and this dropped to 40% when considering N3 patients alone. Liauw et al[153] reported the University of Florida experience, which similarly found a negative predictive value of 94% for a radiographic complete response and no regional relapses in 34 patients with a radiographic complete response who did not undergo a postradiation neck dissection.

Locoregional Recurrent Disease

Locoregional recurrence after definitive treatment in the absence of distant metastases represents a challenging clinical scenario. Although the prognosis is limited, these patients are theoretically curable. Curative treatment options include salvage surgery, frequently made more challenging by prior radiation treatment, or reirradiation. Patients treated previously with surgery alone may have the option of surgery followed by adjuvant radiation or definitive radiation with or without chemotherapy. Factors to be considered in aggressive retreatment include time elapsed from initial definitive treatment; site, stage, and resectability of the tumor; patient performance status; and comorbidities.

Salvage Surgery

In patients with locally recurrent, resectable oropharyngeal tumors, salvage surgery provides the best opportunity for long-term locoregional control and potential cure. This is weighed against the morbidity of surgical resections, which may include permanent loss of swallowing function, poor cosmesis, and significant medical cost. In addition, such surgical procedures in patients who have had prior radiation carry higher complication rates than primary surgery alone. The introduction of free-flap reconstructions for large tissue defects has improved salvage surgery options and outcomes. This ability to transfer nonirradiated tissue with normal vasculature into the treatment field can decrease postsurgical complications.

A meta-analysis of 1080 patients treated with salvage surgery from 28 institutions showed a 5-year OS of 39%, with this better than expected outcome buoyed by the large number

of recurrent early-stage laryngeal cancers.[158] Pharyngeal primaries in this meta-analysis had a 2-year DFS of 25% and a 5-year OS of 26%. The operative mortality rate was 5.2%, with a complication rate of 39% and a major complication rate of 27%. Surgical complication rates appear to be significantly increased following primary chemoradiation compared with radiation alone.[159] A prospective trial that accompanied the meta-analysis found that OS declines progressively with a more advanced recurrent stage (24.3 months for stage I disease versus 9.3 months for stage IV disease) and the prior use of chemotherapy (26.9 months versus 8.8 months with prior chemotherapy).[158] The author concluded that patients with stages I and II recurrent cancer had a 70% chance of being disease-free at 2 years and a 60% to 85% probability of a successful outcome relative to quality of life and a low surgical complication rate. On the other hand, patients with recurrent cancer that initially had stage IV lesions had a less than 25% chance of being disease free at 2 years, with disease recurring in half of these patients within 5 months. Significant complications were present in 30% of stage IV salvage surgeries, and 30% of patients had a good quality-of-life outcome.

Bachar et al[160] reviewed the largest single-institution oropharynx salvage experience, in which 239 out of 640 patients treated definitively at the Princess Margaret Hospital with radiation for tonsillar carcinomas had subsequent recurrence. Of the 239, 175 (73.5%) were surgical salvage candidates. The median time to death was 1.3 years, and 5-year CSS and OS were 40% and 23%, respectively. The majority of patients died with disease. Both the T and N categories were predictors of time to death. Although the prognosis for recurrent disease was poor overall, the survivorship of 23% of patients at 5 years defines a finite group of patients cured by salvage surgery and argues in favor of a salvage surgical procedure when feasible.

Reirradiation

In attempting to determine which patients might benefit from repeating full-dose radiation to the head and neck, some have warned that "experience has shown that indiscriminate use of high-dose reirradiation often makes a bad matter worse."[161] Reirradiation has been pursued at some centers in the situation of a patient with good performance status, locoregional recurrence, and no other potentially curative treatment options. Appropriate patient selection is important, and patients should be fully informed of the increased complication rate incurred by cumulative radiation doses frequently topping 100 Gy. The use of systemic chemotherapy concurrently with reirradiation is an attractive option given its clear benefit in the previously untreated setting. This must be counterbalanced, however, by the further increase in toxicity expected with this approach.[162]

Investigations at several academic centers have demonstrated that between 10% and 20% of selected patients who are reirradiated can be long-term survivors. The University of Chicago reported on 115 patients who underwent reirradiation with a median lifetime dose of 131 Gy, including 30 patients with oropharyngeal carcinoma.[163] Radiation was delivered with concurrent chemotherapy as part of seven consecutive Phase I and II protocols in which radiation was given for five fractions every other week. Median OS and DFS were limited at 11 and 7 months, respectively. A subset of patients had long-term benefits from the repeat treatment, however, as 3-year OS, PFS, and LRC were 22%, 33%, and 51%, respectively. Improved outcomes were seen with higher doses of radiation (>58 Gy), multiagent chemotherapy, and surgery before repeat radiation. Conversely, only 11% of patients treated with repeat radiation alone were alive at 3 years. Side effects were substantial, with 19 patients (16.5%) dying of treatment-related complications and another 13 (11%) requiring surgery for osteoradionecrosis of the mandible.

The inability to undergo surgery as a negative prognostic indicator was reinforced by the RTOG 9610 clinical trial, which delivered 60 Gy at 1.5 Gy twice daily with concurrent chemotherapy. Patients were ineligible for surgical resection, and 2-year and 5-year OS were 15.2% and 3.8%, respectively.[164] A follow-up study (RTOG 9911) with concurrent cisplatin and paclitaxel found 2-year OS of 25.9%, which exceeded the results generally seen with chemotherapy alone, although 8% of patients still died of treatment-related complications.[165] Further study of this approach is ongoing, using other radiation schedules, and alternative cytotoxics or targeted therapies.[162]

The side effects of reirradiation may be partially tempered by employing highly conformal treatment techniques. An MDACC 5-year experience of 74 patients reirradiated with IMRT reported a 20% rate of major toxic events, defined as hospitalization or corrective surgery, and one patient death.[166] The median lifetime radiation dose was 116.1 Gy, and 41% of the lesions were oropharyngeal in origin. Two-year OS and LRC were encouraging at 58% and 64%, respectively. Salvage surgical resection had been previously performed in 27% of patients, and 81% of patients were treated for gross disease with margins only. Locoregional failure rates decreased with IMRT in the MSKCC experience, which described 2-year OS of 37% and a severe late complication rate of 11.4%.[167] Brachytherapy[168] and intraoperative radiation (IORT)[169] can also be used in the setting of focal reirradiation with reasonable LC. IORT as a treatment option is discussed further in the Head and Neck Overview.

Janot et al[170] reported on a randomized trial evaluating reirradiation with concurrent chemotherapy in patients who had recurrent disease or a second primary tumor in a previously irradiated region, no major sequelae from the prior treatment, a good performance status, no distant metastases, and salvage surgery with macroscopic complete resection. The radiation dose was 60 Gy over 11 weeks (five fractions, followed by the next week off) with concurrent 5-FU and hydroxyurea. Chemoreirradiation improved the DFS (HR, 1.68) but did not affect OS. Grade 3 or 4 late toxicities at 2 years were 39% in the radiation therapy arm and 10% in the observation arm ($p = 0.06$).

Locoregional radiation failures preferably undergo salvage surgery if feasible. Reirradiation following salvage surgery is not routinely added unless there is radiographic or clinical suspicion of residual gross disease or pathologic margins are diffusely positive. Reirradiation, with or without concurrent chemotherapy, is performed in a highly selected group of patients who are surgically unresectable, without marked sequelae from prior treatment, have a high performance status, are strongly motivated, and understand the high potential of significant treatment-related morbidity, and the modest likelihood of long-term survival. Generally, these patients also have limited-volume, well-circumscribed recurrent disease, and a prolonged time from initial definitive treatment. All attempts are made to limit the volume of full-dose retreatment, typically by the use of IMRT and daily image-guided radiation therapy (IGRT).

Recurrent or Metastatic Disease

Cytotoxic Chemotherapy

Large randomized clinical trials conducted over the last two decades evaluating cytotoxic chemotherapy in patients with recurrent or metastatic SCC of the head and neck have demonstrated little progress; the median survival time remains only 6 to 8 months. Single-agent chemotherapy with drugs

such as methotrexate, cisplatin, or fluorouracil typically yields lower objective response rates (8% to 17%) compared to cisplatin-based chemotherapy combinations (12% to 32%), but the latter have not demonstrated survival benefits in this patient population.[171-174] These chemotherapy combinations, however, can cause significant toxicity, and their effect on the quality of life in recurrent or metastatic disease has not been well studied. Intensification of chemotherapeutic regimens, such as the use of high-dose paclitaxel in combination with cisplatin and growth factor support in the ECOG study E1393, has led to excessive toxicity and failed to improve survival outcomes.[175] Such observations have motivated oncologists to continue to seek novel treatments to improve disease control and palliation for these patients.

Molecularly Targeted Agents

The biologic relevance of EGFR in SCC of the head and neck is validated not only through clinicopathologic correlations[176] but also by the results of the Bonner trial, which demonstrated improvements in both LRC and OS when cetuximab was added to definitive EBRT in locally advanced disease.[144,145] Multiple Phase II and III clinical trials of anti-EGFR molecularly targeted therapies in recurrent or metastatic SCC of the head and neck have been reported.[177-185] Overall, the large molecule monoclonal antibodies appear to produce higher objective response rates than the small molecule oral tyrosine kinase inhibitors although direct comparisons have not been performed. A Phase III comparison of single-agent chemotherapy with methotrexate and the oral tyrosine kinase inhibitor gefitinib failed to demonstrate a difference in outcome.[181]

In 2005, Burtness et al published the results of E5397, an ECOG trial comparing single-agent cisplatin with the combination of cisplatin and cetuximab in patients with recurrent or metastatic disease. The response rate was significantly better with the use of the cetuximab.[186] In 2008, Vermorken et al published the results of the EXTREME trial, which compared the combination of fluorouracil and a platinum with or without cetuximab in the same patient population. An improvement in overall response rate, and for the first time in recurrent/metastatic head and neck cancer, an improvement in PFS and OS was identified from the addition of cetuximab. However, an increased incidence of grade 3 or 4 sepsis, skin reactions, anorexia, and hypomagnesemia were also encountered in the cetuximab arm.[187] A similar trial (SPECTRUM) using the fully humanized anti-EGFR monoclonal antibody panitumumab instead of cetuximab, also demonstrated an improvement in PFS, although no statistically significant OS benefit was found.[188] Interestingly, median OS improved in patients who were p16-negative with no impact on OS in patients who were p16-positive.

There is continued intense interest in the use of targeted therapy in patients with recurrent/metastatic disease. The monoclonal anti-EGFR antibody zalutumumab has been tested in the second line setting,[189] as have other oral tyrosine kinase inhibitors such as afatinib.[190] Other molecular targets besides EGFR, including vascular endothelial growth factor receptor(VEGFR), PI3-kinase-Akt-mTOR, insulin-like growth factors, and cancer stem cell pathways, among others, are also being interrogated in the attempt to continue to identify promising therapies in head and neck SCC.

RADIATION TECHNIQUES AND TOLERANCE

Fractionation

Because radiation has served as a cornerstone of the treatment of head and neck cancers, a substantial amount of scientific and clinical effort has been devoted to optimizing radiation fractionation, treatment time, and total dose. Altered fractionation approaches were conceived to exploit the differential radiation response between normal tissues and tumors and resultantly improve the therapeutic ratio through either dose escalation or truncation of the overall treatment time. Radiobiologic modeling based on retrospective data from 676 patients with tonsillar carcinomas treated at nine centers found an increase of local tumor control probability by nearly 2% for each 1-Gy increase in total dose for a constant treatment duration.[191] Accelerated repopulation was estimated to begin approximately 30 days following treatment initiation, with a compensatory dose of 0.73 Gy per day required for treatments lasting beyond 30 days. Alternatively, the LC probability was decreased by at least 1% for each day that treatment was extended. This exquisite sensitivity of oropharyngeal tumor control to both total dose and treatment duration has highlighted the importance of optimizing treatment schedules.

Changes in radiation schedules generally fall under three general classifications, with some regimens containing elements of more than one group.[192] Hyperfractionation increases the total dose by using multiple small fractions daily over a conventional treatment time course. Accelerated fractionation without total dose reduction delivers a standard dose over 5 to 6 weeks rather than 7 weeks (i.e., concomitant boost or more treatments per week). Accelerated fractionation with total dose reduction involves a smaller total dose given over 3 to 4 weeks. Investigation of altered fractionation schedules was particularly prominent in the era immediately preceding the adoption of concurrent chemotherapy in locally advanced disease.

Hyperfractionation

A conventional course of radiotherapy, composed of a total dose of 70 Gy in 35 fractions of 2 Gy per day, 5 days per week for 7 weeks, is delivered to the primary tumor site and nodal disease, with lower doses to clinical regions without known disease. RTOG 9003 compared conventional radiation with hyperfractionation (81.6 Gy in 68 fractions, 1.2 Gy twice daily), accelerated fractionation with a concomitant boost (72 Gy in 42 fractions over 6 weeks; 54 Gy in 30 fractions of 1.8 Gy to initial fields plus 18 Gy in 1.5-Gy fractions to a cone-down boost field as a second daily dose during the final 12 treatments), and accelerated split-course fractionation (67.2 Gy in 42 fractions, 1.6 Gy twice daily with a 2-week break after 38.4 Gy), all delivered 5 days per week (Table 33-10).[193] All twice-daily treatments required 6 hours between fractions, and the concomitant boost field contained gross clinical disease. Improved LC rates were seen with both the hyperfractionation and accelerated fractionation with concomitant boost in this large, randomized study of 1113 patients, of whom 60% had oropharyngeal primary tumors. These schedules also trended toward improved DFS, although DFS and OS were not significantly different.

Significantly greater acute side effects were present with all three altered fractionation groups. Only the accelerated fractionation cohort had statistically worse late side effects when tabulated for events 90 days or more following treatment; however, late side effects at 6 to 24 months were equivalent between all four groups because some of the events initially scored as late effects at 90 days were acute toxicities that had persisted. The importance of total dose and treatment duration in the outcome of radiotherapy was emphasized by this trial, and altered fractionation was adopted as an acceptable standard for further RTOG trials. Split-course fractionation did not show a LC improvement despite increased acute side effects.

TABLE 33-10 RTOG 9003 Altered Fractionation 2-Year Outcomes

RTOG 9003	LRC (%)	2-yr DFS (%)	2-yr OS (%)	≥Gr 3 Acute (%)	≥Gr 3 Late (%)
Standard fractionation	46.0	31.7	46.1	35.0	26.8
Hyperfractionation	54.4*	37.6 ($p = 0.067$)	54.5	54.5*	28.0
Accelerated split course	47.5	33.2	46.2	50.4*	27.6
Accelerated concomitant boost	54.5*	39.3 ($p = 0.054$)	50.9	58.8*	37.2*

DFS, *Disease-free survival;* gr, *grade;* LRC, *locoregional control;* OS, *overall survival.*
*p < *0.05.*

Acceleration without Dose Reduction

Outcomes from the concomitant boost technique, which delivers doses slightly higher than those of conventional treatment (72 Gy versus 70 Gy) over a shortened time period of 6 weeks, are described previously. The Danish Head and Neck Cancer Study Group (DAHANCA) randomized 1485 patients between 1992 and 1999 treated with radiation alone to five or six fractions per week delivered to the same cumulative dose at 2 Gy per fraction.[194] Most patients had laryngeal cancer, but 29% had primary tumors of the pharynx. The median overall treatment time was reduced from 46 days to 39 days with the six-fraction-per-week group. The sixth fraction was given either on a weekend day or as a second fraction on a weekday, with a minimum of 6 hours elapsed between treatments. The shortened treatment time led to an improved 5-year LRC rate (70% versus 60%), which was significant for LC but not neck node control. DSS was also improved (73% versus 66%), but OS was not. Again, acute side effects were increased with accelerated treatment, but there was no difference in adherence to the treatment regimen and the increase in acute adverse events did not translate into worsened late side effects. The improvements in LC without associated late effects led the authors to adopt the six-fractions-per-week approach as their standard of care.

In the current era of conformal therapy, a simultaneous integrated boost assigns different dose levels to various target volumes within a single treatment. Radiobiologic advantages of this approach include potential hypofractionation to the gross tumor volume (GTV) and acceleration of the overall treatment time. The logistic benefit of a simultaneous integrated boost technique is the ability to deliver IMRT with a single treatment plan rather than sequential IMRT plans delivered to "shrinking-field" equivalent volumes. This approach has gained widespread adoption and is currently mandated for the RTOG trial evaluating postoperative radiation therapy (0920) with doses per fraction ranging from 1.8 Gy to 2.2 Gy. For example, the highest-risk clinical target volume (CTV) could receive a total of 66 Gy at 2.2 Gy per fraction, the high-risk CTV 60 Gy at 2 Gy per fraction, and the lower-risk CTV 56 Gy at 1.85 Gy per fraction. RTOG 0522 used a simultaneous integrated boost technique without a hypofractionated component, with doses ranging from 1.6 Gy to 2 Gy and a requirement that the treatment be completed in 6 weeks (six fractions per week). The optimal simultaneous integrated boost method remains unknown. Hypofractionating high-risk regions (2.2 Gy per day) may increase the risk of both acute and late side effects within the treated volumes, while capping the high-dose region at 2 Gy per day may deliver inadequate daily doses to lower-risk regions on a daily basis (1.5 Gy per fraction) or unnecessarily elevate cumulative doses to low-risk areas if higher fraction sizes are chosen (59.5 Gy in 35 fractions of 1.7 Gy per fraction to the supraclavicular region). The widespread adoption of the simultaneous integrated boost technique has been driven primarily by the potential radiobiologic benefits and logistic ease of use, despite the lack of randomized data comparing simultaneous integrated boost schemes to more studied radiation fractionation schemes.[195]

Acceleration with Dose Reduction

Continuous, hyperfractionated, accelerated radiotherapy (CHART) has been evaluated in the treatment of multiple cancers, including SCCs of the head and neck. Dische et al[196] reported on the largest CHART study, which randomized 552 patients to 54 Gy in 36 fractions delivered three times a day over 12 days and 366 patients to 66 Gy delivered in 33 fractions over 6.5 weeks. An interval of 6 hours was required between each of the three daily treatments. Primary tumors of the oropharynx were present in 26% of patients. CHART did not improve rates of LRC, DFS, or OS. Confluent mucositis was higher with CHART, occurring in 73% compared with 43% of those treated conventionally, and it peaked earlier. Skin desquamation was less with CHART, and the late side effects of telangiectasias, mucosal ulceration, and laryngeal edema were also diminished. A Trans-Tasman randomized study[197] had similar outcomes, with trends toward improved oncologic outcomes and a significant reduction in late effects, although late effects related to the mucosal membranes were similar between the treatment arms. Although the prospect of decreased late toxicity with similar oncologic outcomes and a markedly reduced treatment duration is appealing, the CHART regimen has not been widely pursued because of the logistic challenges of thrice-daily radiation administration over 12 consecutive days, the familiarity of clinicians with other altered fractionation schemes, and the inability to incorporate chemotherapy into the regimen given the already elevated acute side effects.

Fractionation Summary

A meta-analysis of altered fractionation regimens included 6515 patients from 15 trials, with most patients having laryngeal or oropharyngeal cancers and stage III or IV disease. The meta-analysis found a 3.4% 5-year OS benefit to altered fractionation radiotherapy, with a benefit of 8% and 2% for hyperfractionated and accelerated radiotherapy, respectively.[192] The LRC rate improved by 6.4% at 5 years with altered fractionation; greater benefit was seen with local compared with nodal control. The benefit of altered fractionation was most pronounced in younger patients, with a statistically lower impact with advancing age.

In conclusion, altered fractionation may be used to either decrease the probability of late complications or to improve the curative potential of a regimen. Altered fractionation appears to improve the rates of LRC, DFS, and, based on the meta-analysis, OS, at the expense of increased acute side effects. Because oropharyngeal primary lesions, like most head and neck cancers, are sensitive to both overall treatment time and total dose, altered fractionation should be used primarily in the definitive rather than the postoperative setting (Table 33-11). Concurrent chemotherapy has been added to

TABLE 33-11 Radiation Schedules

Regimen	Description	Advantages	Disadvantages
Standard fractionation	70 Gy in 35 Fx of 2 Gy	—	—
Hyperfractionation	81.6 Gy in 68 Fx, 1.2 Gy b.i.d.*	Largest improvement in meta-analysis data	Logistically challenging
Accelerated fractionation with concomitant boost	72 Gy in 42 Fx, 6 wks: initial field: 54 Gy/30Fx, 1.8 Gy/6 wks; boost field: 18 Gy, 1.5 Gy per day over the final 12 treatments	Fewer total fractions than hyperfractionation	May increase late side effects
DHANCA (6 fractions/week)	62-68 Gy at 2 Gy per Fx, 6 Fx/week	Logistically attractive, no increase in fraction total	
Simultaneous integrated boost	Differential dosing to different target volumes (1.6-2.2 Gy)	Single IMRT plan, hypofractionation to GTV, treatment acceleration	Lack of supportive randomized data

DAHANCA, *Danish Head and Neck Cancer Study Group;* Fx, *fractions;* Gy, *Gray;* GTV, *gross tumor volume;* HFX, *hyperfractionation;* IMRT, *intensity-modulated radiation therapy;* wks, *weeks.*
**Many HFX regimens have a maximum dose of 79.2 Gy in 66 fractions.*

both hyperfractionated and accelerated regimens in randomized trials and is discussed elsewhere in the chapter.

Radiation Treatment Planning

Radiation treatment planning for oropharyngeal cancer requires knowledge and commitment on the part of the radiation oncologist. Anatomic knowledge, head and neck physical examination skills, and imaging expertise are required to appropriately define regions of tumor involvement, and familiarity with pathophysiology and patterns of spread is necessary for appropriate selection of elective coverage areas. Given the complexity of head and neck planning, CT-based planning is standard.

Appropriate setup during patient simulation is vital because this forms the basis for subsequent radiotherapy planning. The supine position with the chin extended is used most commonly in the curative setting. A thermoplastic mask is created to provide daily reproducibility. Thermoplastic mask options include a mask covering the head and neck only or a mask that extends from the head and neck to include the shoulders. We most commonly recommend the head and shoulder mask because this improves daily reproducibility within the lower neck and shoulder region.[198] Shoulder straps can be used when warranted to lower the shoulders and improve beam accessibility to the lower neck. An intraoral stent can be considered in base-of-tongue cancers to diminish the dose to the palate and vice versa with soft palate tumors. A tongue depressor can be coupled to the mask to help to limit movement of the mandible and minimize flexion and extension during treatment.

CT images are obtained at 2.5-mm slices to balance image resolution and signal-to-noise issues. We typically administer bolus intravenous contrast medium when medically appropriate to better define gross disease and nodal structures. The treatment planning software can also be used to fuse prior diagnostic CT, PET-CT, or MRI studies. Fusion, however, can be challenging secondary to variations in patient positioning, particularly the changes brought about in cervical spine curvature and mandibular position by neck extension. In some centers, the PET-CT and MRI can be performed with patients in treatment planning position. Alternatively, software programs have become available that allow deformable registration, which helps to reduce the variability associated with differences in patient position for various imaging studies.

Precise localization of the tumor is essential, particularly when planning IMRT fields. Information from the physical examination, including fiberoptic pharyngoscopy, and imaging studies should be taken into account when defining target volumes. Even if three-dimensional conformal radiation therapy is to be employed, we still advocate precise contouring of the primary site as well as the radiographically and clinically involved lymph nodes. These regions are defined as the GTV, although the GTV may be subdivided into primary and nodal GTVs to assist in radiation planning. The CTV should extend at least 1 cm from the GTV in all dimensions, unless bounded by restrictive anatomic boundaries (such as skin, bone, air cavities, or central nervous system structures), and also covers the nodal volumes at risk for microscopic disease. Definition of the GTV should be generous, particularly with endophytic, infiltrative tumors in which the size can be frequently underestimated. SCCs of the base of the tongue are notoriously difficult to size accurately for deep extension on physical examination and with conventional imaging. Planning target volume (PTV) margins are dictated by institutional policy based on quality assurance measurement and the presence of image or optical guidance and are typically about 5 mm.

The primary and nodal CTVs receive 70 Gy in most instances, although 66 Gy can be delivered for stage T1 and small T2 primaries. We commonly use 2.12-Gy daily fractions to the GTV, thereby achieving 70 Gy in 33 fractions over 6.5 weeks. Many centers use 2 Gy per fraction to the GTV over 35 fractions. Nodal basins surrounding involved nodes receive 60 Gy to 66 Gy. Intermediate-risk nodal basins, typically an uninvolved level II to III basin contralateral to involved lymph nodes at the same level or a level IV basin ipsilateral to involved levels II or III nodes, are prescribed 54 Gy to 56 Gy. The low-risk neck can be treated via a separate anterior field and commonly receives 50 Gy in 2 Gy fractions prescribed most commonly to a 3-cm depth.

Clinical issues such as dental extractions or obtaining biopsy and imaging results as well as the complexity of radiation planning in oropharyngeal cancers can lead to delays in treatment initiation. Jensen et al[199] found a measurable increase in tumor volume in 62% of patients with SCCs of the head and neck at a mean interval of 28 days. Tumor volume increase correlated to length of the time delay and histologic differentiation. In 20% of patients, new lymph node metastases were seen, and 16% of patients had upstaging of their TNM classification. Head and neck radiation planning and treatment initiation are time-consuming processes but should proceed as expeditiously as possible (ideally, within 2 weeks) once definitive radiation is recommended to avoid not only the progression of disease but also potentially discrepant treatment fields and tumor volumes secondary to interval growth.

Conventional Radiation

Conventional radiation techniques remain a perfectly acceptable approach for patients who are not suitable candidates for IMRT. Reasons may include advanced N2c or N3 disease in which effective parotid gland sparing is contraindicated or patients with an inability to tolerate prolonged immobilization for IMRT. Nevertheless, IMRT may still afford some advantages beyond salivary gland sparing, such as improved GTV coverage at the skull base, sparing of critical optic and auditory structures, and avoidance of match-line inhomogeneities associated with photon-photon and photon-electron matches.

Conventional radiation is most commonly delivered using a "shrinking-field" technique for the primary tumor bed and upper neck, matched to an anterior-posterior (AP) supraclavicular field for the lower neck (Figure 33-9). Broad opposed lateral fields covering the primary tumor bed and upper neck extending to the thyroid notch are initially treated to 42 Gy to 44 Gy in 2-Gy fractions. Four-MV to 6-MV photons are used to avoid underdosing of superficial nodal disease. The isocenter is typically placed at approximately the C1 to C2 level just anterior to the intervertebral space. An off-cord boost is then created by shifting the posterior field border anteriorly to split the vertebral bodies vertically, and the cumulative dose is then taken to 50 Gy to 54 Gy. Electron fields (commonly, 6 MeV to 9 MeV; occasionally, 12 MeV for bulky nodal disease) are matched on the skin to abut the posterior aspect of the off-cord photon field and thereby treat the posterior neck to 50 Gy to 54 Gy, with higher doses if positive posterior nodes are present. Involved nodes at the match line warrant 2 mm to 3 mm of photon-electron field overlap to limit underdosing at depth. The posterior electron field border can be extended by

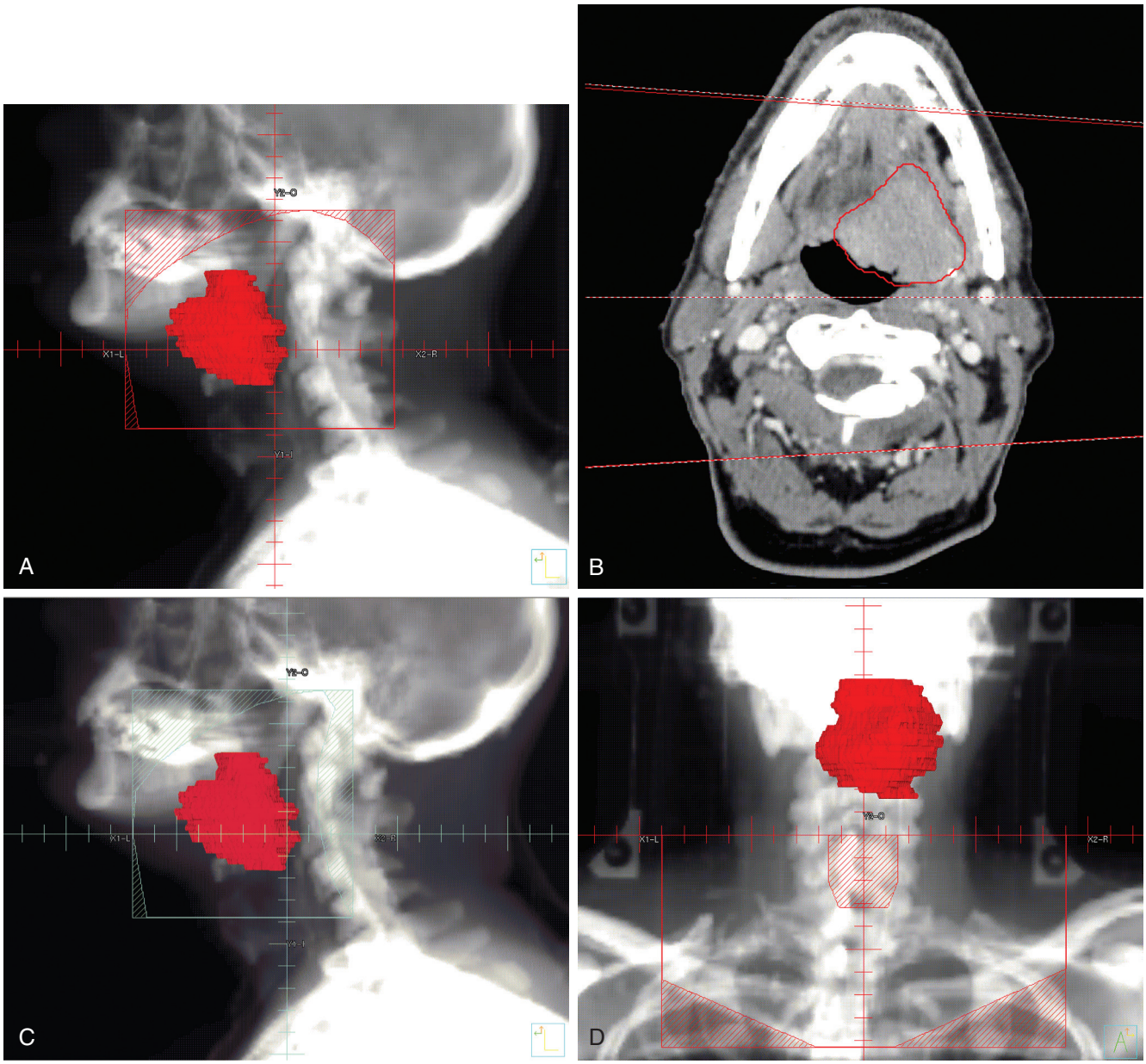


Figure 33-9 Two-dimensional conventional fields for an infiltrative stage IVA (T4aN2bM0) SCC of the left base of the tongue with deep tongue invasion. **A,** Initial lateral field with base of tongue gross tumor volume (GTV) represented by red colorwash. **B,** Axial CT image demonstrating lateral field coverage relative to the GTV with an anterior margin on the GTV. **C,** Off-cord lateral field providing a cord block while respecting the posterior extension of the primary tumor. **D,** Anterior-posterior supraclavicular field with a laryngeal/cord block.

5 mm to help compensate for electron dose constriction at depth. The final field reduction boost carries the tumor GTV plus a margin to 66 Gy to 70 Gy. If higher doses are required within the low neck and supraclavicular region, an AP (or AP:PA) hemineck supraclavicular field that blocks the spinal cord can be used for an additional 4 Gy to 16 Gy. Alternatively, an electron boost can supplement the dose to the supraclavicular regions.

Borders of the lateral photon fields are specific to the subsite and individual patient. More important than any generic field recommendations is the accurate identification of the involved primary site and inclusion of the defined GTV and regions of risk with adequate margins. In general, at least a 1-cm expansion is recommended on the GTV to create the CTV, with the PTV margin determined by institutional policy based on hardware-specific intrafraction and interfraction reproducibility. The beam penumbra must always be considered with conventional fields. General recommendations, to be tailored by individual findings, are as follows:

- *Superior border:* This should cover the retropharyngeal and jugulodigastric lymph nodes and approach the jugular fossa in patients with advanced nodal disease. The ipsilateral medial pterygoid insertion for early-stage tumors and the pterygoid plates for more advanced-stage tumors are worthy of coverage for tonsillar carcinomas.
- *Anterior border:* This is defined by the most anterior extent of the primary site with margin. This may be extended more anteriorly if level IB lymph node coverage is warranted. Tonsillar carcinoma fields have traditionally covered the ipsilateral retromolar trigone. Anterior coverage of base of tongue tumors should be generous (commonly, 2 cm) to respect the infiltrative nature of the primary tumor.
- *Posterior border:* This border is approximately 2 cm behind the mastoid process and just posterior to the cervical vertebral spinous processes, with additional posterior extension if warranted by level V nodal metastases. Adequate dosimetric margins must be ensured with posterior pharyngeal wall tumors, and the photon off-cord boost is typically placed at the posterior third of the vertebral body. The posterior margin may be moved 1 cm to 2 cm anteriorly for early-stage, node-negative tonsillar and soft palate tumors.
- *Inferior border:* This is placed just cranial to the arytenoids to limit posttreatment supraglottic edema. However, this border may be lowered to account for extension of the primary tumor into the larynx or hypopharynx. Location of the inferior border may also be affected by shoulder positioning.

The AP supraclavicular field extends from the inferior lateral photon border to the bottom of the sternoclavicular joints and covers the middle and lower neck nodes. Laterally, the supraclavicular field extends to the mid-clavicle and typically measures 18 cm to 20 cm in width, again tailored to known nodal disease. The isocenter is typically placed at the thyroid notch. A laryngeal block is created if no contraindications are present. This both decreases the toxicity to the central larynx and provides a "cheater block" to prevent three-field junctional overdosing to the spinal cord. The laryngeal block typically measures 3 cm to 4 cm in the craniocaudal dimension and 2 cm to 3 cm in the greatest width, with tapering inferiorly to avoid blocking of medial level IV and level VI nodes. The supraclavicular field can be half-beam blocked to prevent divergence into the lateral photon fields. Lateral fields can similarly be half-beam blocked to match the supraclavicular field, although this leads to increased divergence along the cranial aspect of the lateral field. We have preferentially allowed trace hot matching along the lateral and supraclavicular field junction rather than half-beam blocking the lateral field. The dose to the supraclavicular field is commonly 50 Gy with 6-MV photons to a depth of 3 cm or calculated to the optimal isodose line based on CT planning. Level VII within the superior mediastinum is typically not included within the supraclavicular field except when low nodal involvement is identified within the supraclavicular region for which level VII is the next potential echelon of nodal involvement or for advanced hypopharyngeal tumors, particularly those with inferior extension to the esophageal inlet.

Large jugulodigastric nodal disease is frequently located at the junction of the off-cord and electron fields. Rather than a 2-mm overlap "hot match," the coverage of the nodal disease may be improved by using oblique off-cord and boost fields, angled to prevent transection of nodal disease. Beam angles of 20 degrees to 30 degrees may be warranted to achieve this coverage. Alternatively, these may be patients in which IMRT is beneficial.

Unilateral Radiation for Tonsillar Cancer

Conventional radiation to the ipsilateral neck for early-stage tonsillar cancers typically consists of a two-field, wedge-pair beam arrangement covering the primary tumor and ipsilateral level II lymph nodes. The levels III and IV lymph nodes ipsilaterally are covered by an anterior supraclavicular field directed to the hemineck. Close attention should be paid to ensuring that adequate margins of primary tumors are treated because margins of less than 1 cm are strongly associated with local recurrence.[107] A risk of underdosing extension to the more medial structures (soft palate and base of the tongue) exists because the dose distribution significantly narrows along the medial portion of the volume, which can be partially compensated for by a narrower hinge angle. The use of five to six oblique beams can further reduce the dose to the contralateral parotid gland by a few Gray and better conform the prescribed dose to the PTV. In addition, disease involvement of the posterior tonsillar pillar can be challenging because coverage may be limited by the need to prevent the posterior oblique beam from traveling through the spinal cord and brainstem. Many institutions have adopted IMRT techniques for ipsilateral radiation with strict contralateral constraints (Figure 33-10).

Intensity-Modulated Radiation Therapy

IMRT can increase the dose gradient between target volumes and surrounding normal tissue. This improved conformality offers the potential of decreased acute and late side effects or, through dose escalation made available from the improved conformality, higher tumor control rates. The hazard of IMRT, however, is the potential for marginal misses and local failures from overly restrictive radiation deposition in regions that received comprehensive radiation with conventional techniques.[200] Multiinstitutional IMRT studies have found significantly more locoregional failures in patients who had a major underdose deviation of the target volume.[201] Benefit from IMRT requires appropriate patient selection, accurate delineation of organs at risk and treatment volumes, meticulous quality control in radiation planning and delivery, and limiting of interfraction and intrafraction variability.[202]

Patient Selection

IMRT has traditionally been championed to diminish the risk of long-term xerostomia by "sparing" the contralateral parotid gland. Locally advanced oropharyngeal cancers treated at MSKCC with IMRT had a diminished incidence of grade 2 or greater xerostomia at 2 years when compared with

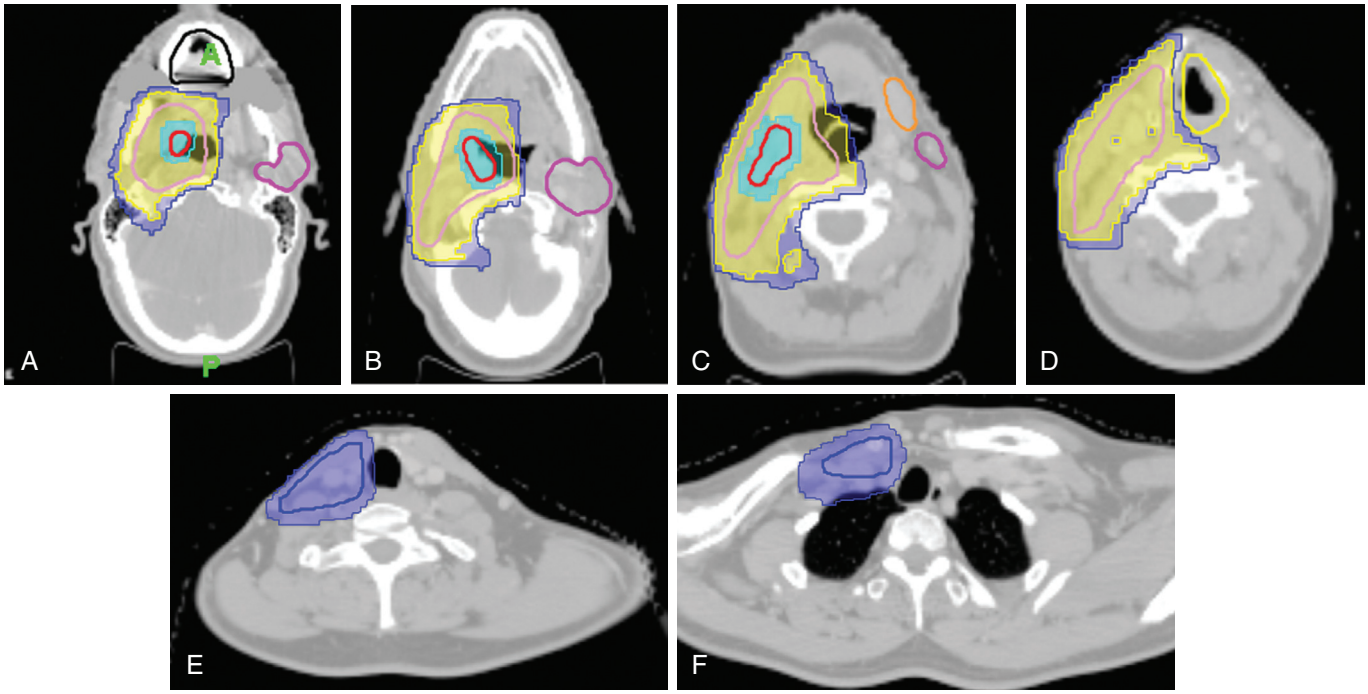


Figure 33-10 A 55-year-old man with a stage IVA (T1N2bM0) SCC of the right tonsil treated with radiation alone. The right tonsil (gross tumor volume [GTV]) was prescribed 70 Gy in 33 daily fractions of 2.12 Gy using tomotherapy IMRT with differential dosing to the upper neck (CTV1, 60 Gy) and lower neck (CTV2, 54 Gy). **A** to **F,** Axial CT images demonstrating contours and isodose distribution. Avoidance structures include an oral cavity block *(black)*, the left parotid gland *(pink)*, the left submandibular gland *(orange)*, and the larynx *(yellow).* Treatment volumes are GTV *(red)*, CTV1 *(peach)*, and CTV 2 *(blue)*; planning target volumes (PTVs) are not shown. Isodose lines in colorwash: 70 Gy *(teal)*, 60 Gy *(yellow)*, and 54 Gy *(blue).* Ipsilateral treatment was elected secondary to the small primary tumor and limited ipsilateral nodal disease.

conventional treatment techniques (12% versus 67%).[203] Xerostomia prevention has proven to be complex, with increasing recognition that the submandibular glands and oral cavity contribute to subjective and objective xerostomia.[204] The MSKCC study also found that gastrostomy dependence at 2 years was reduced with IMRT (4% versus 21%). Minimizing the late sequela of dysphagia has been a beneficial byproduct of IMRT and has evolved as an explicit goal within the IMRT treatment planning process. IMRT with concurrent chemotherapy that includes sparing of noninvolved swallowing structures has been shown to maintain high LRC rates and simultaneously reduce long-term dysphagia when compared to historical controls.[205]

Patients with bulky primary tumors and extensive bilateral nodal metastases may not derive significant benefit from IMRT approaches, at least in terms of salivary gland sparing. Some of these patients may be best served by the use of comprehensive conventional radiation techniques that broadly encompass regions at risk. Parotid gland sparing should be approached with caution in patients with ipsilateral cervical metastases, such as patients with N2c neck staging. Parotid sparing is particularly challenging for patients who are N+ with ipsilateral level II cervical metastases and may place patients with nodal disease at risk for superior cervical or periparotid recurrences.[200] Although conventional radiation is appropriate in patients with a heavy burden of disease particularly in the bilateral neck regions, IMRT is frequently used in these patients both as a practical matter of treatment planning and delivery flow within a clinic as well as the potential minimizing of long-term dysphagia.

Caution is also warranted when clinical factors exist that may impair accurate estimation of regions at risk. A neck dissection more than 1 year before treatment may contribute to the development of collateral lymphatic drainage patterns that circumvent conventional lymphatic flow. Neoadjuvant chemotherapy may also substantially reduce the disease burden and lead to an underestimation of regions at risk if pretreatment imaging is not used for radiation treatment planning.[201]

IMRT Planning

We generally begin head and neck radiation treatment planning by placing conventional fields on the digitally reconstructed radiographs (DRRs) to provide an "outer bound" contouring roadmap. The role of GTV, CTV, and PTV has been discussed previously. Contoured volumes and projected doses are described in Table 33-12. To provide adequate contralateral parotid gland sparing, the jugular chain in the N0 neck is contoured only up to the level of the posterior belly of the digastric muscle as it crosses the internal jugular vein. This is done because the first-echelon node within the jugulodigastric region lies below the junction of the posterior belly of the digastric muscle and the jugular vein, as described by Gregoire et al[206] in the consensus guidelines for the node-negative neck. This region is at low risk for recurrence provided the neck is clinically and radiographically negative.[207] The retropharyngeal lymph nodes can also be omitted given the low likelihood of involvement in the contralateral N0 neck.[208]

In general, the jugular digastric chains (levels II, III, and IV) are contoured to include the sternocleidomastoid muscle and the superficial paraspinal musculature if ipsilateral lymphadenopathy is present and particularly if there is clinical concern for extracapsular tumor extension.[209] At our institution, the ipsilateral CTV1 is typically extended to the ipsilateral base of the skull as well as levels IB and V when level II or III nodes are involved. When level IV is involved, contoured regions include the superior mediastinum, level V, and level VI. If no clinical ipsilateral lymphadenopathy is present, we extend the CTV only to the medial aspect of the sternocleidomastoid

muscle and typically do not cover level Va by terminating the contours approximately 1 cm to 2 cm posterior to the carotid and jugular vessels. CTV contours of the uninvolved hemineck typically cover the equivalent of the GTV and nodal extension from the involved side. Determining the appropriate CTVs continues to require physician expertise for each individual patient and may evolve as further clinical data are accumulated. For example, Sanguineti et al[210] found less than a 5% risk of level IB and V involvement when CT imaging was negative, even with ipsilaterally proven neck disease, and questioned the routine inclusion of these levels as part of the target volume.

Two traditional treatment options for IMRT planning are to incorporate the oropharynx and upper neck with an IMRT plan and match this to a conventional AP supraclavicular field or to treat the oropharynx and entire neck with an IMRT plan. A conventional AP supraclavicular field is reasonable if the region is without clinically involved lymph nodes because it offers simpler planning, good sparing of the larynx, reduced monitor units, and a shorter treatment time.[201] The potential for overdosing or underdosing at the junction of the IMRT and conventional fields, however, is present. IMRT to the low neck in higher-risk patients obviates this risk and also offers opportunities for dose sparing to the brachial plexus and upper esophagus.

The IMRT plan for the head and neck is most commonly a single plan with differential dosing (Figure 33-11). Sequential large- to small-volume IMRT plans can alternatively be created. The advantage of sequential IMRT plans is the ability to maintain standard fraction doses (1.8 Gy to 2 Gy) to all PTV volumes rather than employing hypofractionated doses to the higher dose volumes and frequently doses less than 1.8 Gy to the low risk volumes. The downside of sequential IMRT planning is the loss of conformality when two or more separate

TABLE 33-12 IMRT Treatment Volumes (University of Wisconsin)

Contour	Definition	Dose
GTV	Gross primary tumor and involved nodes	66 Gy-70 Gy
CTV1 (high-risk CTV)	GTV + 1 cm margin, nodal basins with involved lymph nodes, areas at high risk for subclinical spread	60 Gy-66 Gy
CTV2 (intermediate-risk CTV)	Nodal basins adjacent or contralateral to involved nodal regions	54 Gy-56 Gy
CTV3 (low risk)	Supraclavicular region with no ipsilateral high neck lymphadenopathy	50 Gy-54 Gy
CTVint (optional)	GTV + 1 cm margin for poorly defined or infiltrative tumors	63 Gy-66 Gy

CTV, *Clinical target volume;* GTV, *gross tumor volume;* int, *intermediate.*

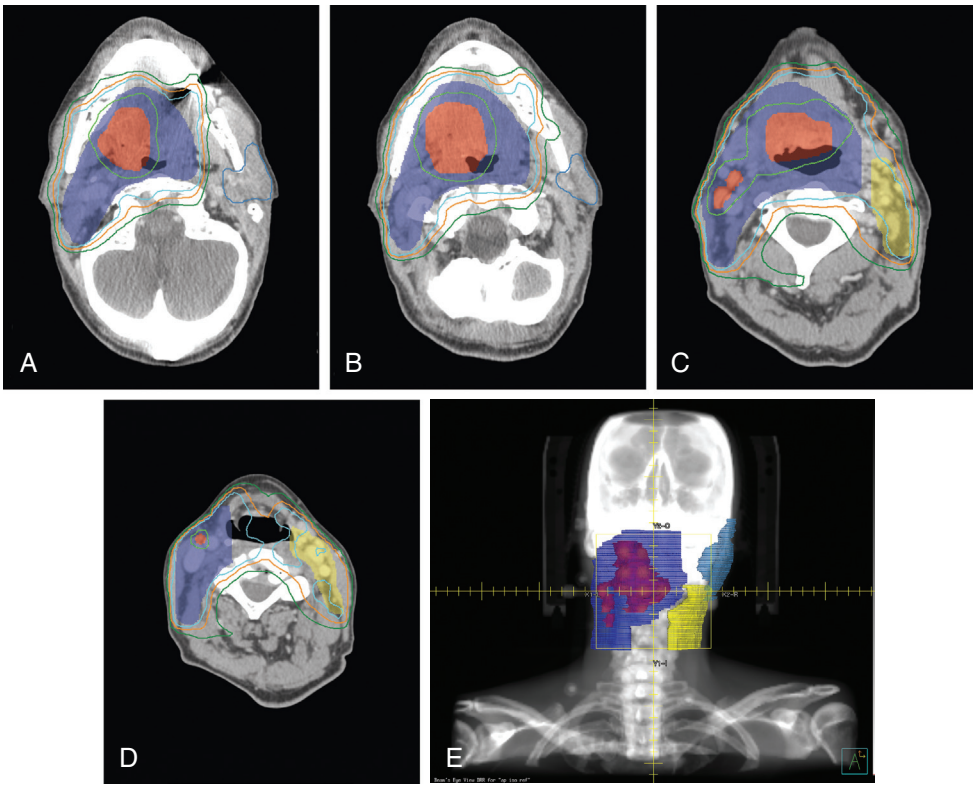


Figure 33-11 A 61-year-old woman who presented with otalgia and jaw pain. Physical examination confirmed a firm, right tongue base tumor with deep intrinsic tongue invasion and extension to the glossotonsillar fold (T4aN2bM0). The patient was treated with concurrent chemotherapy (cisplatin 30 mg/m^2 and avastin as part of a clinical trial) with the primary and nodal gross disease receiving 70 Gy using IMRT. Contours: red colorwash (GTV, 70 Gy), blue colorwash (CTV1, 60 Gy), yellow colorwash (CTV2, 56 Gy), blue (left parotid gland). Parts **A** to **D** are sequential axial isodose images with the following isodose lines: green (70 Gy), teal (60 Gy), orange (56 Gy), and dark green (50 Gy). **E,** A reconstructed AP radiographic study shows the contoured structures projected craniocaudally. Note the cessation of CTV2 at the level of the C1 transverse process (caudal to the majority of the contralateral parotid gland).

TABLE 33-13 IMRT Planning Avoidance Structures

High Priority	Complication
Spinal cord	Transverse myelitis
Brainstem	Neurologic deficits
Optic nerves and chiasm	Blindness
Intermediate Priority	
Parotid gland (contralateral)	Xerostomia (stimulated)
Additional Structures	
Oral cavity	Acute mucositis
Larynx	Voice changes, edema
Mandible	Osteoradionecrosis
Proposed Additional Structures	
Submandibular gland	Xerostomia (unstimulated)
Pharyngeal constrictors	Dysphagia
Cochlea	Sensorineural hearing loss
Brachial plexus	Brachial plexopathy
Esophagus	Dysphagia

IMRT plans are evaluated as a composite. Details of the simultaneous integrated boost are covered in the fractionation section.

IMRT Constraints

A critical component of high-quality IMRT head and neck plans is accurate contouring of critical organs and appropriate weighting during IMRT planning to optimize tumor coverage while minimizing the dose to these regions (Table 33-13). The primary goals of IMRT planning should be to provide adequate coverage of the contoured target volumes, particularly the GTV, and dose restriction to critical organs for which radiation damage may lead to death or severe morbidity (i.e., brainstem and spinal cord). Secondary, but important, goals include dose restriction to the salivary glands, optic and auditory structures, larynx (if appropriate), mandible, oral cavity, and other normal tissues, depending on the tumor extent and anatomy of the individual patient.

A substantial focus of IMRT in the treatment of head and neck cancers is to diminish the severity of xerostomia, initially by parotid sparing. Although historical data suggested a salivary gland tolerance dose of approximately 40 Gy,[211] it appears that the parotid gland tolerance may in fact be much lower. Eisbruch et al[212] reported in a seminal publication that a mean parotid dose of 26 Gy was associated with a threshold for impairment of stimulated salivary flow. In this report, most glands that received more than 26 Gy produced little saliva, with no significant recovery over time. Partial volume thresholds were also reported as well by these investigators. Since the publication of this report, numerous other reports have characterized the dose-response relationship.[213-216] Although a standard threshold of a mean dose of 26 Gy is commonly used, the parotid dose effect is clearly a continuum, with additional impact from concurrent treatments and intrinsic patient factors. Ultimately, the lower the integral dose to the parotid gland the more likely stimulated salivation will be retained. The submandibular gland produces unstimulated saliva, and the loss of submandibular salivary function may account for the xerostomia reported by many patients despite adequate parotid sparing. Submandibular salivary production appears to be partially maintained by a mean dose of less than 39 Gy.[217] Dose to the oral cavity also plays an independent role in the development of xerostomia.[218] Swallowing is a complex physiologic action, requiring timing and coordination of more than 30 pairs of muscles and six cranial nerves.[219] The reduction of dysphagia and aspiration via IMRT requires the identification of the appropriate structures and establishing dose correlates. The persistent dysphagia seen after head and neck radiation has been correlated with the dose delivered to the pharyngeal constrictors, with several dose thresholds reported.[220,221] The University of Michigan group reported aspiration in patients who received more than 60 Gy to the pharyngeal constrictors, and worsened liquid and solid swallowing was correlated with higher pharyngeal constrictor mean doses.[220] Dose to the glottic and supraglottic larynx and cervical esophagus also impacts long-term dysphagia.[205,222] Although various studies document separate structures as the most critical component in dysphagia prevention, improved dysphagia outcomes will likely be reliant on comprehensive avoidance of the pharyngeal constrictors, larynx, and cervical esophagus. As the dose effect on different structures and subsequent functional side effects are better defined, it is anticipated that IMRT planning can further incorporate these data as dose constraints. However, for each additional dose restriction applied to organs at risk, there is pressure brought to bear on the integrity of the overall IMRT plan in terms of target coverage and spread of dose to additional new regions. Physician overview of the comprehensive treatment plan selected for each patient with head and neck cancers is critical to ensure adequate tumor target coverage and personalize the therapy approach.

Reproducibility

Reproducible and accurate treatment delivery is required for the high-quality successful implementation of head and neck IMRT. The PTV is generally designed from a 3-mm to 5-mm expansion of the CTV. With a conventional thermoplastic mask, baseplate fixation, three-point laser alignment, and weekly port films, the mean daily setup error for patients with head and neck cancers can easily be several millimeters.[223] Not surprisingly, partial geographic tumor miss and overdosing of adjacent normal tissues can occur with daily setup variation, potentially contributing to reduced LC and worsened normal tissue complications. Daily setup variation with conventional approaches may also lead to higher than anticipated parotid doses.[224] Accurate oropharyngeal IMRT delivery therefore requires rigorous immobilization and setup verification with each fraction because imaging every other day may still lead to daily deviation rates of more than 5 mm.[225] Setup verification may occur through either pretreatment image guidance or optical tracking. Kilovoltage orthogonal filming or cross-sectional imaging with either cone-beam CT or megavoltage CT is adequate for daily imaging. For IMRT cases at the University of Wisconsin, delivery quality assurance is performed for each patient plan before the first treatment using a two-dimensional ion chamber array. As recommended in the TG-148 report, the agreement between the planned and delivered point dose measurement must be within ±3% for treatment to be initiated. Profound weight loss or rapid regression of bulky nodal disease can impair radiation accuracy by loosening the designing immobilization and altering the dose distribution. In such patients, adaptive radiation replanning is valuable.

Brachytherapy

Brachytherapy has a long history in the treatment of tonsillar fossa, soft palate, and base-of-tongue primary cancers. Most commonly, brachytherapy is used as a boost after 45 Gy to 50 Gy of EBRT, although it has also been used as monotherapy for small exophytic, node-negative tumors or in the recurrent

setting. Although IMRT can produce excellent conformality, the dose gradients and normal tissue sparing offered by brachytherapy are unmatched. The use of brachytherapy in head and neck cancers, however, has become less prevalent with the introduction of advanced planning and conformal treatment techniques, especially with the advent of IMRT. Challenges in the administration of interstitial brachytherapy include the necessity of an additional invasive procedure and the subspecialty expertise required; oropharyngeal brachytherapy can be performed in only a few select centers with physician expertise. The GEC-ESTRO guidelines nicely summarize appropriate brachytherapy patient selection, treatment strategies, target definition, implant technique, and different dose rates available.[226]

Treatment-Related Side Effects

Acute Toxicities

Toxicities secondary to head and neck radiation are commonly divided into acute and late categories. Potential acute side effects from radiation therapy to the oropharynx include mucositis, dermatitis, dysphagia, sore throat, odynophagia, thickened secretions, candidiasis, in-field alopecia, xerostomia, and taste disturbance with associated weight loss, dehydration, compromised nutrition, and pain sometimes necessitating placement of a feeding tube. Transient acute parotiditis (sialadenitis) can also develop within the first 24 to 48 hours of radiation in patients as a result of acinar cell apoptosis and typically resolves by 48 to 72 hours following treatment initiation. The frequency of acute side effects is dependent on field size and shape, total dose, fractionation, and the inclusion of cytotoxic chemotherapy.

The addition of concurrent chemotherapy to EBRT can substantially increase the risk of acute toxicity, with one postoperative study evaluating radiation with or without concurrent cisplatin demonstrating a doubling of acute grade 3 side effects from 34% to 77%.[146] This increase in toxicity has not been universally identified in randomized trials evaluating chemotherapy, which has been at least partially attributed to the challenges of recording, analyzing, and reporting toxicity data.[227]

Mucositis is characterized by ulceration and pseudomembranous formations along the mucosal surface and represents a complex interaction of mucosal injury, inflammatory response, and healing (eFigure 33-8). Mucositis is seen among virtually all patients receiving high-dose radiation for head and neck cancers. Self-reported mucositis was identified in 99% of 126 patients with oral cavity or oropharyngeal tumors, with 85% scoring it as severe to extreme.[228] The quality of life worsened concordantly with the severity of the mucositis. At least one study points toward cumulative point doses of less than 32 Gy leading to mucositis of limited severity (grade ≤1) and shorter duration (≤1 week),[229] but such low doses are typically not feasible, in part because of the multiple mucosal regions within the high-dose radiation volumes. The development of mucositis is the most problematic of the acute oropharyngeal radiation side effects, leading to dysphagia, sore throat, odynophagia, dehydration, weight loss, and narcotic use, and it often requires treatment breaks, hospitalization, and enteral nutrition. Concurrent chemotherapy with oropharyngeal radiation hastens the onset, increases the severity, and lengthens the duration of mucositis. Because of the anticipated severity of mucositis and associated dysphagia from combined chemotherapy and radiation, the majority of patients undergoing concurrent regimens at our institution have a gastrostomy tube placed before treatment to enable adequate nutrition. Prophylactic nutritional support leads to significantly less weight loss by the end of treatment and less grades 3 and 4 mucositis, although at least one study raised concerns about diminished LC with aggressive nutritional support.[230] Others have also reported diminished swallowing function with the use of a gastrostomy tube. Patients, however, are encouraged to continue oral intake and swallow at least liquids during the radiation course to help preserve swallowing function and potentially avert long-term dysphagia.

The altered dose distribution of IMRT may contribute to different acute toxicities than were seen with conventional techniques because some nontarget structures receive increased radiation exposure. A mean brainstem dose of more than 36 Gy, an occipital scalp dose of more than 30 Gy, and an anterior mandible dose of more than 34 Gy have been associated with increased nausea and vomiting, scalp alopecia, and anterior oral cavity mucositis, respectively.[231] Inclusion of these structures within the IMRT planning algorithm can help diminish such toxicities.

Late Toxicities

Late complications after oropharyngeal cancer radiation treatment include xerostomia, dental caries, osteoradionecrosis, prolonged dysphagia with gastrostomy tube reliance, trismus, hypothyroidism, cervical fibrosis, neck lymphedema, altered taste, hearing loss, and radiation-induced malignant disease. Radiation side effects are worsened by comorbidities such as diabetes mellitus and hypertension, tobacco use, as well as other less common autoimmune entities that produce microvascular changes before radiation initiation.

Xerostomia

Damage from radiation to the acinar cells and stromal matrix of the salivary glands induces a rapid loss of salivary production, also known as *hyposalivation*. Subjectively, the patient notes the sensation of oral dryness, or xerostomia. The diminishment of either stimulated or unstimulated salivary flow rates has significant implications for both patient quality of life and oral health. The presence of xerostomia can create difficulty in forming a food bolus and lead to associated dietary adaptations, with an impact on nutritional status and diet quality. Saliva also plays an integral role in maintaining dental integrity. Hyposalivation allows the oral pH to decrease because saliva typically contains bicarbonate and returns the pH to a neutral range following meals. Dental enamel is prone to demineralization within an acid environment. Saliva also bathes the enamel with calcium and phosphate, and loss of these substrates leads to an impedance of remineralization. Lastly, hyposalivation changes the oral flora, leading to an increase in acid-producing bacteria and resultantly increasing dental caries. Hyposalivation interferes with the delivery of food particles to the taste buds, resulting in altered taste.

This predisposition to dental caries can partially be counteracted by meticulous dental care, including frequent dental visits and custom-made fluoride carrier trays to be used on a daily basis. The bacterial component may be helped by chlorhexidine or Biotene rinses with reduction of the cariogenic flora. Interventions to ameliorate symptoms for patients with severe xerostomia can include secretagogues such as cevimeline and pilocarpine. The results with pilocarpine have been mixed, with one study showing an improvement in oral dryness and speaking ability,[232] another study demonstrating no difference in xerostomia or quality of life,[233] and a third, RTOG 97-09, showing objective preservation of salivary function but no impact on quality of life or subjective xerostomia.[234] Cevimeline was found to subjectively improve xerostomia in only one of two study groups, with an objective increase in unstimulated salivary flow.[235] Although some patients may find symptomatic relief from these secretagogues, there is no evidence that they counteract the adverse sequelae of



eFigure 33-8 Confluent mucositis at approximately 70 Gy for a T4 base-of-tongue tumor treated with conventional lateral fields. The confluent grade-3 mucositis extends from the oropharynx to the posterior oral cavity.

hyposalivation. Many patients compensate for the diminished salivary production by frequently rinsing with water or using other salivary substitutes.

The use of radioprotective agents in the prevention of xerostomia has also been evaluated, and amifostine is currently approved by the Food and Drug Administration for prevention of moderate to severe xerostomia in patients who have undergone complete resection of the cancer and are receiving postoperative adjuvant radiation. Amifostine was found to reduce acute xerostomia of grade 2 or higher from 78% to 51% ($p < 0.0001$) and chronic xerostomia of grade 2 or higher from 57% to 24% ($p = 0.002$) and to improve median salivary production in patients receiving head and neck cancer radiation where 75% or more of the parotid glands received 40 Gy or more of radiation.[236] Almost half of these patients had primary tumors arising in the oropharynx. Side effects included nausea, vomiting, hypotension, and allergic reactions and led to the discontinuation of amifostine in 21% of patients. Amifostine did not appear to have a tumor-protective effect because rates of LRC, DFS, and OS were similar between the treatment arms. A follow-up Phase III study did not find improvements in acute xerostomia, acute mucositis, or chronic xerostomia with the administration of amifostine.[237] These contradictory Phase III studies, concerns about side effects including nausea and significant hypotension during administration, the logistical challenges of daily delivery, the high cost associated with amifostine, and the introduction of IMRT have prevented more widespread adoption of amifostine in routine clinical use.

Transfer of a submandibular gland to the submental space (away from conventional radiation beams) has also been investigated as a means of reducing chronic xerostomia. Although the parotid glands are responsible for the bulk of saliva produced when stimulated by eating, the submandibular gland contributes 65% of the total volume of unstimulated saliva.[238] This basal, unstimulated saliva seems to correspond more to the subjective perception of xerostomia, making it a target for xerostomia prevention. In a randomized study after an initial Phase II evaluation,[239] the submandibular gland transfer was found to improve baseline salivary flow, stimulated salivary flow, and subjective evaluations of both saliva amount and consistency when compared with pilocarpine alone. Candidacy for this procedure was restrictive because patients with carcinomas of the nasopharynx, oral cavity, and salivary gland, N3 disease, recurrent disease, preepiglottic space involvement, or level I lymph node involvement were excluded. Submandibular gland transfer was performed on the contralateral neck or, for midline primary tumors, the clinically node-negative neck. If final pathologic studies found any lymph node involvement on the transferred side, no attempt was made to shield the transferred submandibular gland because of concerns about undertreating regions at risk. Although a significant improvement was seen over conventional radiation and pilocarpine, the median baseline and stimulated salivary flows were still found to drop by over half even with the submandibular gland transfer. This result was not unexpected as only one of the submandibular glands was salvaged. Submandibular gland transfer remains a viable option for the prevention of chronic xerostomia in appropriately selected patients, although the technical expertise and experience are not widespread.

Osteoradionecrosis

Osteoradionecrosis occurs in less than 5% to 10% of patients treated with definitive high-dose radiation and is primarily seen with cancers of the oral cavity and, to a lesser extent, the oropharynx.[240,241] Osteoradionecrosis rates have decreased over time with improved radiation techniques.[242] By definition, osteoradionecrosis occurs in previously radiated, often exposed bone that has failed to heal over a 3-month time period. As a process, osteoradionecrosis is characterized by hypocellularity, hypovascularity, and hypoxia, generating a failed ability to repair following injury. Symptoms can include pain, trismus, and anesthesia along the inferior alveolar nerve distribution. Findings may include exposed bone and spicule formation. Osteoradionecrosis is seen primarily involving the mandible, likely as a result of the combination of a more tenuous vascular supply when compared with the maxilla and more adjacent structures requiring full-dose radiotherapy. Lower rates of osteoradionecrosis are observed in patients that are edentulous. Given this finding and the clinical association of osteoradionecrosis with severe dental caries following radiation, removal of poorly conditioned teeth within the high-dose radiation field followed by a 10- to 14-day healing period before radiation initiation has been a standard practice in an attempt to limit osteoradionecrosis rates. Chang et al published the University of Florida experience, which did not identify an improvement in grade 2 or greater osteoradionecrosis rates with prophylactic extractions (edentulous, <1%; teeth in-field with preradiotherapy extractions, 15%; and teeth in-field without preradiotherapy extractions, 9%), bringing into question the utility of this approach.[241] Nevertheless, the authors of the paper still recommended prophylactic extractions of teeth in poor repair. Currently, we recommend a complete dental evaluation, including Panorex, before initiation of EBRT by a dental professional familiar with radiation treatments and toxicities. Teeth that are in poor repair and nonrestorable within the high-dose EBRT field are extracted; we typically do not recommend prophylactic extraction for teeth in good condition.[243]

The risk of osteoradionecrosis is dependent on the primary site, T category, proximity of bone to tumor, radiation dose, and dentition.[244] Simple steps toward preventing osteoradionecrosis include meticulous dental care following radiation and avoidance of poorly fitting dentures that can cause mucosal erosion, leading to bone exposure and increased osteoradionecrosis rates. See the Expert Consult website for further information on osteoradionecrosis.[237-239]

Dysphagia

Preservation of organ function is a driving force in the selection of the radiation regimen in the treatment of oropharyngeal cancer. Altered fractionation and concurrent chemotherapy have led to improved rates of LC and OS in head and neck cancers over the past two decades. However, this oncologic success has been accompanied by increased rates of chronic dysphagia, particularly before the advent of IMRT. Patients who exhibit chronic laryngopharyngeal dysfunction are a strong reminder of the potential toxicity cost that can be associated with definitive radiation techniques and are contrary to the goal of cancer cure with functional preservation.

Swallowing is a complex process with a series of coordinated actions involving more than 30 pairs of muscles and six cranial nerves. Many patients have an impaired swallowing mechanism before treatment. In one study, only 33% of patients had normal swallowing before treatment; aspiration and cervical esophageal impairment was seen more commonly with laryngeal or hypopharyngeal primary tumors.[248] Although pretreatment deficits may exist, radiation negatively affects swallowing initially through tissue edema, xerostomia, mucositis, pain, and viscous secretions during the acute phase. Late dysphagia results when tissues become fibrotic, leading to rigidity and loss of function, with potential contribution from late-effect lymphedema and neuropathy.[249] Strictures following treatment may also be contributory.[250] Chronic gastrostomy tube dependence, a surrogate for persistent dysphagia, is seen in approximately 20% of patients after concurrent

Osteoradionecrosis severity can range from asymptomatic bone exposures that are stable or improve with conservative management to more severe necrosis that requires more aggressive interventions. Small, asymptomatic bone spurs can be treated conservatively with surgical excision or polishing of bone spicules. For more severe osteoradionecrosis, hyperbaric oxygen and surgical excision, consisting of débridement and potential segmental mandibulectomy and reconstruction, may be required. Hyperbaric oxygen is typically recommended to counteract the hypoxia and hypovascularity that contribute to osteoradionecrosis. In patients requiring dental work following radiation therapy, hyperbaric oxygen delivered over 30 sessions (20 before and 10 following dental extraction) was found to decrease the rate of osteoradionecrosis when compared with penicillin alone.[245] Conversely, a randomized study examining hyperbaric oxygen for treatment of moderate osteoradionecrosis was stopped early because of a lack of improvement, and a trend toward detriment, within the hyperbaric arm.[246] Patients with more severe osteoradionecrosis, as demonstrated by bone resorption along the inferior mandible and mandibular fracture, were specifically excluded from this study, so it remains uncertain whether such patients may benefit from hyperbaric oxygen. However, the morbidity of persistent, unremitted osteoradionecrosis leads most clinicians to involve hyperbaric oxygen therapy in their treatment plan despite the lack of randomized data supporting its benefit. Delanian et al reported using a combination of pentoxifylline, vitamin E, clodronate, prednisone, and ciprofloxacin in patients with exteriorized, refractory mandibular osteoradionecrosis.[247] Remarkably, all 54 patients experienced a complete recovery at a median of 9 months, and this data warrants confirmation and repetition to solidify the promising results.

chemoradiation for head and neck cancers when delivered with conventional techniques. These rates are particularly elevated in patients who received concurrent chemoradiation and altered fractionation,[251,252] with Staar et al[253] reporting a rate of 51% at 2 years. Other factors in long-term dysphagia include primary site and increasing age.[222] The persistence of a gastrostomy tube strongly correlates with a poor quality of life following treatment.[254] Given the intimate relation of laryngeal action and swallowing, it is not surprising that aspiration is a frequent consequence of dysphagia. Before the implementation of IMRT designed to spare the important swallowing structures, Eisbruch et al found that 65% of their patients had aspiration shortly after the completion of radiation.[255] Nearly one-third of the patients with aspiration in post-therapy studies developed pneumonia.

Attempts to limit chronic dysphagia and aspiration have revolved around target avoidance during the planning process and prompt intervention both during and following treatment. Eisbruch et al[256] identified radiographic changes within the pharyngeal constrictors, supraglottic larynx, and glottic larynx after intensive chemotherapy and radiotherapy for head and neck cancers that correlated with functional detriment by videofluoroscopy. These structures were identified as "dysphagia/aspiration-related structures" (DARS), and, as discussed in the treatment planning section, partial dosimetric avoidance of these structures can be incorporated into IMRT planning. Limiting radiation to the uninvolved larynx can also be accomplished through a traditional anterior supraclavicular beam with a laryngeal block in place. Such limitations simultaneously decrease the dose to the adjacent cervical esophagus and cricopharyngeal inlet, potentially diminishing the risk of posttreatment dysphagia. As discussed previously, rates of long-term dysphagia and aspiration have been significantly reduced with IMRT when compared to three-dimensional conformal radiation therapy.[104,105] IMRT techniques to reduce dysphagia identify long-term patient-reported, objective, and observer-rated swallowing outcomes to be only slightly worse than pretherapy measures while maintaining excellent oncologic outcomes.[205]

Expert swallowing evaluation and therapy as appropriate before, during, and after treatment is valuable for patients undergoing head and neck cancers therapy. Modifications can include changes in diet to ensure safe and appropriate oral intake, exercises and routines that may improve swallowing function, and swallowing techniques to limit aspiration events. A modified barium swallow or fiberoptic endoscopic evaluation of swallowing is recommended for all patients with oropharyngeal cancer at risk for dysphagia or aspiration to assist in guiding interventions. Circumventing dysphagia through rehabilitation has had modest overall success. At least one retrospective study suggested that pretreatment swallowing exercises led to improvements in swallowing after therapy.[257] The same group found improvements in tongue base position and epiglottic inversion if swallowing exercises were used 2 weeks before and during concurrent chemoradiotherapy but no difference in gastrostomy tube rates 12 months after treatment.[258]

The role of feeding tubes to counteract dysphagia secondary to acute mucositis remains controversial. Dehydration from poor oral intake can lead to hospitalizations and treatment breaks. Malnourishment and weight loss may also prolong recovery from treatment-related side effects and have been shown to be prognostic for head and neck tumor outcomes.[219] Options for tube feedings include both nasogastric (NG) feeding tubes and percutaneous endoscopic gastrostomy (PEG) feeding tubes. Controversy exists as to which feeding tube should be used and whether it should be placed prophylactically or as needed during treatment.[259] NG tubes decrease cosmesis, mobility, and quality of life when compared with PEG tubes during treatment.[227,260] A randomized study comparing prophylactic PEG tubes versus a reactive initiation of enteral feeds demonstrated fewer malnourished patients and improved quality of life at 6 months at the expense of longer use of enteral nutrition.[261] A previous retrospective study comparing NG tubes with PEG tubes demonstrated worse outcomes with PEG tube placement independent of other tumor or clinical factors: worsened dysphagia at 3 and 6 months, increased median tube duration (28 weeks versus 8 weeks), and more patients undergoing pharyngoesophageal dilatation (23% versus 4%).[262] A prospective study found less weight loss immediately after treatment with PEG tubes but a higher rate of insertion site infection, longer median duration of use (146 days versus 57 days), and more grade 3 dysphagia at 6 months (25% versus 8%), leading the authors to conclude that PEG tube use should be selective rather than routine in patients requiring nutritional support.[263] These data point toward PEG tubes being more effective and convenient, leading to increased patient reliance with a greater period of diminished oral intake and atrophy of the muscles of deglutition. If prophylactic PEG placement is pursued, we recommend aggressive intervention from support staff, including speech pathologists, to maintain oral intake during and immediately after radiation treatment to preserve the swallowing mechanism. Alternatively, a reactive approach is viable, with placement of a feeding tube triggered by clinical concerns such as weight loss (e.g., >10%) or inadequate caloric intake (e.g., 50% to 60% of daily allotment). Such an approach allows avoidance of feeding tube placement in 25% to 50% of patients undergoing chemoradiation.[259]

Quality of Life

Despite clear toxicity from definitive radiation, particularly with the addition of concurrent chemotherapy, much of the toxicity in the treatment of locally advanced oropharyngeal cancer is dictated by tumor extent and location. Traditional surgical toxicity for oropharyngeal carcinomas is also marked with regard to functional and cosmetic outcome. Harrison et al found consistently better performance scores and quality of life for patients treated with a combination of EBRT and brachytherapy for base-of-tongue primaries when compared with primary surgical therapy.[264] Patients were more likely to eat out, have a normal diet, and have understandable speech. The differences were particularly marked when considering patients with more advanced disease. The same group found that despite long-term symptoms, including xerostomia, dysphagia, decreased energy, pain, and taste alteration in more than 30% of the patients, most individuals after base-of tongue radiation were still able to work full-time, had unchanged income, and had good to excellent overall functional status.[265] With the advent of transoral surgical techniques, quality of life is a major consideration in employing these surgical approaches and attempting to limit adjuvant treatments. Incorporation of quality of life as well as oncologic outcomes will ultimately guide the optimal selection of modalities in treating oropharyngeal carcinomas.

TREATMENT ALGORITHM, CHALLENGES, AND FUTURE POSSIBILITIES

A general treatment algorithm for SCC of the oropharynx is shown in Figures 33-12 and 33-13. Ipsilateral radiation is appropriate for small, well-lateralized tonsillar cancers with limited ipsilateral lymphadenopathy. Concurrent chemoradiation is generally pursued for T3 and T4 primary tumors or extensive lymphadenopathy.

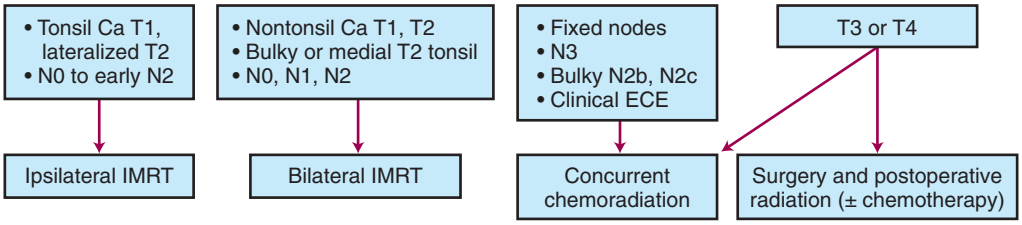


Figure 33-12 Treatment algorithm for primary tumor and regional nodes in oropharyngeal carcinoma. Indications for concurrent chemoradiation include local or regionally advanced disease (T3 or T4 primary; N3, fixed, bulky lymph nodes, or clinical extracapsular extension [ECE]).

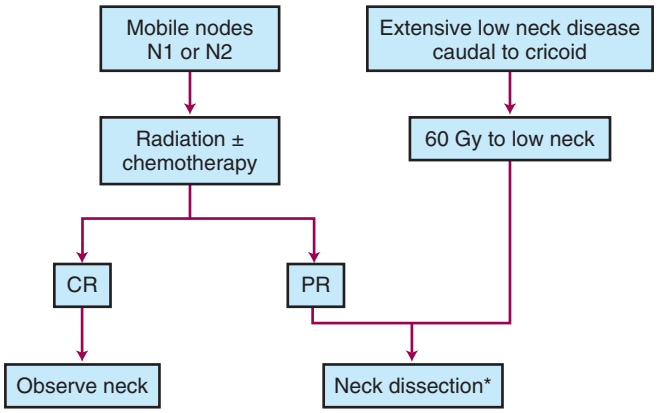


Figure 33-13 Treatment algorithm for addressing regional nodal disease identified before treatment. *CR*, Complete response (typically by CT and PET/CT imaging and clinical examination); *PR*, partial response. *Selective neck dissection is frequently appropriate treatment.

Potential deescalation of treatment intensity in HPV-positive oropharyngeal cancer is an ongoing focus of discussion and clinical research within the head and neck oncology community. Identification of HPV as a causative agent has highlighted a subgroup with improved LRC and OS rates. This discovery has come in an era of increased recognition of the significant acute and late toxicities associated with concurrent chemoradiation, albeit toxicities that have diminished with the broad implementation of IMRT. As these tumors appear more responsive to radiation, it may be possible to treat them with radiation alone and forego the additional toxicity of concurrent chemotherapy. Similarly, it may be possible to reduce the total radiation dose. However, to date, there are no data to confirm that the radiation or chemotherapy dose can be safely reduced. Ongoing clinical trials continue to examine potential avenues for deescalation in a controlled setting. Although these HPV-associated tumors may present with advanced stages, this is partially an artifact of the staging system as many have small (T1 or T2) primary tumors with advanced nodal disease that places them within the stage IV category. The relatively small primaries, however, may make them amenable to radiation alone, with neck dissection reserved for incomplete cervical nodal response. There is also renewed interest in the surgical community to consider transoral resections of small oropharyngeal tumors to maximize tumor control and maintain high-quality functional outcome.

Proton beam and heavy ion radiation may further minimize the dose to the surrounding normal tissues, improving the quality of life by reducing toxicity. At least one dosimetric study has demonstrated an improved ability to spare organs at risk when comparing intensity-modulated proton therapy with IMRT.[266] Clinical investigation is warranted, however, because the dose-depth characteristics of particle beam therapy make it susceptible to small changes in the treatment volume, which can frequently be seen in oropharyngeal cancers because of factors such as tumor shrinkage and patient weight loss.[267,268]

Conclusions

The evaluation and treatment of patients with cancer of the oropharynx are evolving. The implementation of IMRT in large series has reduced the spectrum and severity of normal tissue toxicities. The relatively recent advances in molecular targeting agents (e.g., cetuximab) are enabling new treatment options for patients with both locoregional and metastatic/recurrent disease. Advances in surgical technology (e.g., improved microvascular free-flap reconstruction and transoral surgery) are similarly affording new opportunities to tailor therapy and diminish toxicities. The emergence of HPV as a critical prognostic biomarker is changing the landscape of future clinical trials in oropharyngeal cancer. With each new tool there emerge new questions and opportunities to further refine treatment and thereby improve the ultimate outcome for patients with this challenging malignant disease.

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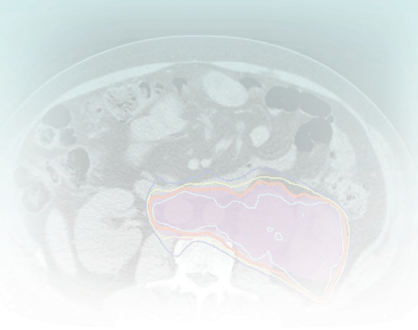
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CHAPTER

34 Nasopharyngeal Carcinoma



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INCIDENCE

In the United States, nasopharyngeal carcinoma (NPC) is uncommon, occurring at a rate of 0.2 to 0.5 cases per 100,000 people. In contrast, in southern China and Hong Kong, the incidence is 25 to 50 per 100,000 people and among the Inuit in Alaska and Greenland, 15 to 20 per 100,000 people.

BIOLOGY

A potential link between Epstein-Barr virus (EBV) and NPC was first described more than 30 years ago; advances in molecular biology have furthered our understanding of this association. The rate of positive EBV serology is higher with nonkeratinizing or poorly differentiated versus well-differentiated lesions, and EBV DNA is detected less frequently in patients with keratinizing squamous cell carcinomas.

STAGING EVALUATION

Evaluation for NPC includes detailed palpation of neck nodes, flexible nasopharyngoscopy with biopsy, computed tomography (CT), magnetic resonance imaging (MRI) of the head and neck, a complete blood count, a chemistry panel, and a chest radiograph. Positron emission tomography (PET) should be considered.

PRIMARY THERAPY

When treated with radiotherapy as a single modality, patients with NPC have a similar 10-year survival rate in the United States, Denmark, and Hong Kong (34%, 37%, and 43%, respectively).

Advancing technology promises to allow better optimization of radiotherapy, improving target coverage and minimizing morbidity.

The Intergroup study 0099 showed an advantage to the addition of concurrent plus adjuvant chemotherapy to radiotherapy for stages III and IV disease, with a survival advantage at 3 years (78% versus 48%; $p = 0.005$).[1] The advantage of concurrent chemotherapy for advanced disease is now well established, although the benefit of adjuvant chemotherapy remains unclear.

LOCALLY RECURRENT OR PERSISTENT DISEASE

For persistent or recurrent nodal disease, surgical resection is the preferred treatment if technically possible, but recurrent disease at the site of the primary lesion is difficult to approach surgically.

Radiation remains the mainstay of salvage therapy, and in the era of modern techniques can achieve local control without excessive risk of toxicity. Reirradiation for recurrent disease appears to be most effective in patients with a prolonged disease-free interval and small tumor volume treated to a high reirradiation dose (≥60 Gy).

Advances in clinical and basic science research have led to a better understanding of the carcinogenesis of NPC and to better treatment of this condition; however, such advances have also raised many new questions about this disease. This chapter provides an overview of the current understanding of etiologic factors, such as EBV, and the present diagnostic and therapeutic interventions for NPC. Therapeutic controversies are highlighted, and the data relevant to controversial issues are reviewed to guide treating physicians in applying clinical data to individual patients.

ETIOLOGY AND EPIDEMIOLOGY

NPC more commonly occurs in men than women, with up to a two- to threefold difference in incidence. It is an uncommon tumor in the United States, where the incidence is approximately 0.2 to 0.5 cases per 100,000 people.[2] In comparison, the incidence is considerably greater in southern China and Hong Kong (25 to 50 cases per 100,000 people) and among the Inuit residing in Alaska and Greenland (15 to 20 cases per 100,000 people). The incidence of NPC is also higher in other parts of Southeast Asia (Taiwan, Vietnam, and Thailand), the Philippines, and Malaysia and in some Mediterranean and North African populations (8 to 12 per 100,000 people). These areas of increased incidence of NPC are considered endemic areas, and the incidence outside endemic areas is much lower and more often associated with tobacco use. Although incidence of NPC has declined in some endemic areas over the past 20 years (Hong Kong, Taiwan), it has remained stable in other endemic regions.[3-5]

Several geographic-specific etiologic factors have been implicated in the incidence variations throughout the world. The high consumption of salted fish in southern China and Hong Kong has been implicated as a possible etiologic factor for NPC in these areas.[6,7] It has been suggested that various macromolecular lignins associated with these foods in southern China (and perhaps other areas such as Alaska) may activate EBV,[8] which has also been identified as a probable etiologic factor in NPC.[9,10] Studies by Bouvier et al[8] involved the fractionation of harissa, a homemade spice mixture used in Tunisia on various foods, including salted fish. Harissa was separated into various macromolecular fractions by column chromatography. The lignin-containing complexes extracted from harissa induced the EBV promoter in Raji cells.[8] The possibility that these environmental factors are important in the etiology of NPCs is further supported by the finding that incidence rates decrease for successive generations of people who originally emigrated from southern China to California.[11]

Other potential environmental etiologic factors that have been associated with NPC include alcohol consumption and exposure to dust, fumes, formaldehyde, and cigarette smoke.[12,13] Cigarette smoke and alcohol have long been associated with many other head and neck carcinomas, but their association with NPC has been controversial. Some studies have suggested that alcohol consumption and cigarette usage were not associated with NPC.[12-14] Nam et al[13] conducted a case-control study using a National Mortality Follow-Back Survey based on death certificates and found that cigarette smoking and alcohol consumption are independent statistically significant risk factors for NPC. The increased risk of NPC with heavy smoking (adjusted for alcohol consumption) was threefold, and an excess risk of 80% was demonstrated for heavy alcohol consumption (adjusted for cigarette usage).

In addition to environmental factors, genetic factors have also recently been discovered that may explain some of the risk of developing NPC. Multiple investigators have found genetic variation in human leukocyte antigen (HLA) region to be associated with the increased incidence of NPC in southern China.[15] Simons et al[16] originally described an association in Chinese patients with NPC and the HLA-A2 antigen with a deficit of the second antigen at the second locus (B locus). Two large genomewide association studies have subsequently confirmed the role of HLA locus in mediating risk of development of NPC.[17,18] It remains unclear whether specific HLA alleles may influence development of NPC directly, possibly by affecting the immune reaction to EBV, or whether, and perhaps more likely, the genetic susceptibility to NPC is encoded by a locus in close linkage disequilibrium. Several other single-nucleotide polymorphisms have also been implicated with risk for NPC, including genes involved in DNA repair and metabolism of various toxins. However, these latter studies have generally been smaller studies and have not yet been replicated.[19]

PREVENTION AND EARLY DETECTION

The nasopharynx cannot be visualized externally, and tumors of this area often present after they have eroded into vital structure and thus produced symptoms. The association of EBV and NPC has led some investigators to hypothesize that serologic screening (EBV titer) may be useful in certain high-risk populations to identify groups of patients who might benefit from frequent nasopharyngeal examinations.[20] In a study from China of 338,868 patients who underwent serologic screening for EBV titer, 9367 persons had immunoglobulin (Ig) A antibodies to EBV. Of these 9367 patients, 306 were positive for IgA to EBV early antigen. NPC was detected in 113 of the 9367 patients (1.2%) and in 63 of the 306 (20.5%) who were positive for IgA to EBV early antigen. Most of the tumors (>85%) were early-stage lesions. Serologic EBV IgA screening is currently being used in endemic areas.

In addition to EBV serologic screening as a means of early detection and possible prevention of advanced-stage disease, several environmental and genetic predisposing factors are being explored as possible markers that could identify groups of patients at high risk for NPC.[21] Real-time polymerase chain reaction (PCR) techniques show promise as screening tools for NPC.[22] EBV DNA detection, in particular detection of EBV nuclear antigen, eliminates many false-positive results and improves the sensitivity and specificity of EBV IgA serologic screening.[23] A retrospective analysis of blood samples from patients with disease relapse from previous clinical trials indicates that EBV nuclear antigen screening by PCR would have led to earlier detection of distant failure but, because of the quality of current imaging, would not have significantly affected detection of local recurrences.[24] Real-time PCR screening for EBV latent membrane protein 1 (LMP1) in nasopharyngeal swabs has also been shown to be a promising screening tool for high-risk populations, with a sensitivity of 87% and specificity of 98%.[25] These techniques are likely to replace serum IgA screening in endemic areas and have a promising role in screening for relapse in patients who are EBV-positive.[26] The further study of other environmental and genetic markers may lead to the identification of patient populations that could benefit from screening or chemoprevention.[21]

Chemoprevention has been tested extensively in patients with a prior diagnosis of head or neck malignant tumors because second primary tumors in the respiratory and digestive tracts are common in that population.[27-30] Hong et al[27,28] conducted a prevention trial for patients with head and neck carcinomas after curative surgery or radiotherapy, or both. Patients were randomly assigned to receive 1 year of 13-*cis*-retinoic acid (isotretinoin) as a chemoprevention agent (see Khuri et al[21] for a discussion of the biologic factors) or placebo. The treated group had significantly fewer second primary tumors (4%) than the placebo group (24%) ($p = 0.005$); however, there was no difference in rates of survival or incidence of relapse between the two groups. In addition, the chemopreventive effect appeared to abate after 3 years; the incidence of second primary tumors was similar in the two groups after 3 years. Acute toxicity was significant.[27]

The results of the trial by Hong et al[27] were not confirmed by a controlled trial of 316 patients by Bolla et al,[29] in which patients were randomly assigned to 2 years of etretinate (a retinoic acid similar to isotretinoin) at a maintenance dosage of 25 mg/day. Subsequently, a large intergroup effort was mounted, and 1302 patients with previously treated head and neck malignant tumors were randomly assigned to receive 3 years of isotretinoin or placebo.[30] Because of unacceptable toxicity seen with higher doses of isotretinoin (100 to 200 mg/m^2 [≈150 to 400 mg total]) in prior studies, the dosage was decreased to 30 mg/day in this trial. No difference was seen in the occurrence of second primary tumors (4.6% in both arms), which was the primary endpoint of the study.[31] A decrease in local recurrence was seen, however, and 13-*cis*-retinoic acid remains a topic of investigation.

The issue of whether retinoids or other chemopreventive agents should be used in the setting of premalignant lesions of the oral cavity has been considered, and many trials have suggested that retinoids can induce considerable responses in oral leukoplakia.[32,33] Toxicity has been a limiting issue in these trials, however. It will be important to determine whether these chemoprevention strategies, developed for leukoplakia, can be extrapolated to prevention of NPC in subgroups of patients at high risk for such malignant tumors.

Blockade of cyclooxygenase-2 (COX-2) has also shown some promise as a chemopreventive strategy, and COX-2 inhibitors were recently the topic of investigation for various malignant tumors, including head and neck cancers.[34] A Phase II study at Fox Chase Cancer Center evaluated a 3-month course of celecoxib in patients with biopsy-proven dysplastic or hyperplastic leukoplakia, with results pending (NCT00101335). In another pilot randomized study of celecoxib in oral premalignant lesions conducted by the M. D. Anderson Cancer Center (MDACC), doses of 100 mg and 200 mg twice daily were shown to be ineffective in controlling these lesions.[35] Most recent COX-2 inhibitor cancer prevention trials have been closed, except in very high-risk settings such as familial polyposis, because of the increased rate of cardiovascular events seen in a few of the celecoxib and rofecoxib prevention trials. Non-COX derivatives of nonsteroidal anti-inflammatory drugs have recently shown some promise as cancer prevention agents and may prove to have superior toxicity profile.[36]

PATHOLOGY

Malignant tumors of the nasopharyngeal area are generally carcinomas (90%), with lymphomas making up approximately 5% of lesions.[37] Histologic classification of carcinomas continues to evolve as we find out more about the biologic characteristics of these tumors. The most current pathologic classification of NPCs by the World Health Organization (WHO) includes three major categories: keratinizing squamous cell carcinoma (formerly, WHO type I), nonkeratinizing squamous cell carcinoma (including differentiated, or former WHO type II lesions, and undifferentiated, or former WHO type III lesions), as well as recently described basaloid squamous cell carcinoma.[38]

On histologic testing, keratinizing squamous cell carcinomas appear to be well differentiated with intercellular bridges. These lesions make up approximately 20% of carcinomas.[38,39] Differentiated nonkeratinizing carcinomas, representing 30% to 40% of NPCs, lack well-defined squamous cell characteristics but continue to show a "pavement stone pattern" characteristic of squamous cell histology.[38] Undifferentiated nonkeratinizing carcinomas, comprising 40% to 50% of carcinomas, also formerly known as lymphoepitheliomas, are characterized by a lymphoplasmacytic infiltrate.[38] On cytologic testing, the cells appear uniform, with round to oval nuclei and prominent nucleoli. The frequency of the different histologic types varies with geographic area. In the United States, the majority of NPCs have keratinizing squamous cell histologic findings, whereas in Asia, the undifferentiated histologic type is by far the most common (Table 34-1).

ANATOMY AND PATHWAYS OF SPREAD

The nasopharynx is a musculofascial tube that connects the nasal cavity and oropharynx. The anatomic borders of the nasopharynx are (1) the anterior border, consisting of the posterior nasal apertures and nasal septum; (2) the posterior border, the pharyngeal mucosa; (3) the superior border, the pharyngeal mucosa and body of the sphenoid; and (4) the inferior border, the oropharynx. The lateral wall of the nasopharynx contains the pharyngeal opening of the auditory tube. The medial cartilaginous extension of the auditory tube forms a protrusion from the lateral wall of the nasopharynx at the superior and posterior aspects of the opening of the auditory tube. This protrusion, with its overlying mucosa, creates the torus tubarius. Just posterior to the torus tubarius lies the pharyngeal fossa, or the fossa of Rosenmüller, which is formed by the junction of the lateral and posterior walls of the nasopharynx (Figure 34-1, *A* to *D*).

The superior wall of the nasopharynx warrants review. Extension of tumors superiorly often leads to invasion of structures, the symptoms of which are typical of the initial clinical presentation of patients. The sphenoid bone lies superior to the mucosa and pharyngobasilar fascia of the nasopharynx. Several cranial nerves exit the base of skull in this area. Critical foramina housed in the sphenoid include the superior orbital fissure (cranial nerves III, IV, V [ophthalmic division], and VI), the foramen rotundum (cranial nerve V [maxillary division]), the foramen ovale (cranial nerve V [mandibular division]), and the foramen spinosum (recurrent branch of cranial nerve V [mandibular division]). The foramen lacerum

TABLE 34-1 Irradiation Alone Results of Series in Three Diverse Locations

	Study		
	Sanguineti et al[40]	**Johansen**[41]	**Lee et al**[42]
Location	United States (MDACC)	Denmark	Hong Kong
Study size	378 patients	167 patients	5037 patients
Histologic type			
Well differentiated	5 patients	8%	0.3%*
Moderately differentiated	36 patients	5%	—
Poorly differentiated	109 patients	87%	—
Squamous cell carcinoma	193 patients	—	—
Not specified	43 patients	—	—
Lymphoepithelioma	154 patients	—	—
Undifferentiated	—	—	99.7%
Unknown	31 patients	—	—
N0 Category	21%	25%	39%
Primary treatment	60.2-72 Gy	57-68 Gy at 1.8-2 Gy/day	65 Gy†
Neck treatment	Yes	Yes	906 of 1290 N0 patients not treated
Primary control	66% (10-yr)	67% (10-yr)	87% (initial CR)
Nodal control	83% (10-yr)	86% overall, 60% if no irradiation	87% (initial CR)
Survival	48% (5-yr)	37% (10-yr)	52% (initial CR)
Complications	See Table 34-6	Xerostomia Edema Dysphagia Skin fibrosis/necrosis Osteonecrosis Radiation myelitis	9% Neurologic damage 7% Significant functional disturbance (soft tissue necrosis) 1% Death

CR, *complete response;* MDACC, *M. D. Anderson Cancer Center.*
**Well differentiated or nonkeratinizing type.*
†Median equivalent dose using time and dose fractionation (TDF) tables. Large (>2 Gy) fraction sizes were often used.

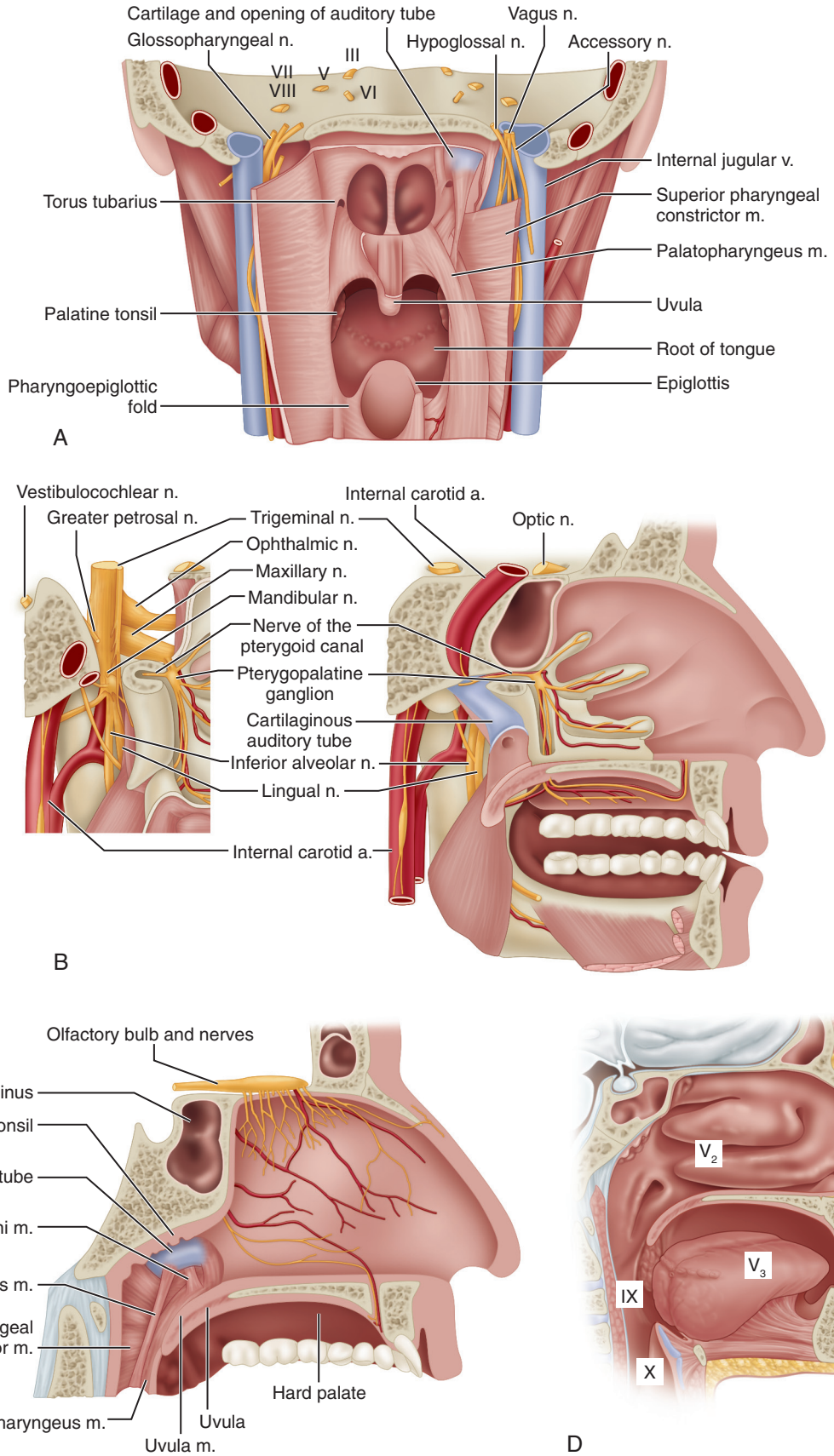


Figure 34-1 Anatomic relationships of the structures of the nasopharynx and adjacent structures. **A,** Coronal section through the center of the nasopharynx, with view of lateral structures. **B,** Sagittal section through the nasopharynx lateral to midline, with a view of the lateral relationships of the nasopharynx *(inset)*. **C,** Sagittal section through the nasopharynx, with a view of the anterior and adjacent structures. **D,** Sensory innervation of the nasopharynx. Roman numerals refer to cranial nerves. *a,* Artery; *m,* muscle; *n,* nerve; *v,* vein; V_1, ophthalmic division of trigeminal nerve; V_2, maxillary division of trigeminal nerve; V_3, mandibular division of trigeminal nerve.
***A** to **C,** Modified from Clemente CD: Anatomy: A regional atlas of the human body, Philadelphia, 1975, Lea & Febiger. **D,** Modified from Pernkopf E: In Ferner H, editor: Atlas of topographical and applied human anatomy, ed 2, Baltimore, 1980, Urban & Schwarzenberg.*

is formed by the junction of the sphenoid and temporal bones. The internal carotid artery passes over the superior opening of the foramen lacerum but does not traverse through the foramen. The nerve of the pterygoid canal and the meningeal branch of the ascending pharyngeal artery course through the foramen lacerum. Deep to the mucosa of the superior aspect of the lateral wall of the nasopharynx lies the superior pharyngeal constrictor muscle. Beyond this muscle lie cranial nerves IX, X, and XI, which exit the base of the skull from the jugular foramen in the temporal bone, and cranial nerve XII, which exits the base of the skull through the hypoglossal canal of the temporal bone.

The sensory innervation is shown in Figure 34-1, *D*. The maxillary division of the trigeminal nerve supplies the upper nasopharynx, the posterior part of the nasal cavity, and most of the palate and upper gums of the oral cavity. The general sensory branches of the lingual and pharyngeal branches of the glossopharyngeal nerve supply the sensory innervation of the lower part of the nasopharynx, the posterior third of the tongue, and part of the soft palate and oropharynx.

Understanding the anatomic relationships of the nasopharynx and adjacent structures is important to correctly diagnose patients with NPC. The importance of superior extension into the sphenoid bone of the base of the skull is exemplified by the fact that cranial nerves can be involved at presentation. The frequency of involvement of cranial nerves has been described in two large series.[40,43] Cranial nerves V and VI are the most commonly involved. These nerves traverse the sphenoid bone and can be involved when tumors erode superiorly through bone. Tumors of the nasopharynx can also gain access to the cranial nerves of the base of the skull by eroding superiorly through the foramen lacerum, which is bordered superiorly by the internal carotid artery (Figure 34-1, *B*).

Lateral extension of NPCs can lead to erosion of the medial opening of the auditory tube and the medial pterygoid plate and can involve cranial nerves IX, X, XI, and XII (Figure 34-1, *B* and *C*). Lateral extension can lead to involvement of the carotid artery and internal jugular vein.

Lymph node involvement is common; 65% to 80% of patients present with clinically involved cervical neck nodes. The level VA and level II lymph nodes are commonly involved. The frequency of involvement of these areas in two large series[40,43] is presented in the "Clinical Manifestations" section. Recent studies have shown that, for clinically N0 or N1 disease, microscopic involvement of the inferior neck and posterior neck (levels IV and VB) is less frequent.[44,45]

BIOLOGIC CHARACTERISTICS AND MOLECULAR BIOLOGY

The potential etiologic link between EBV and NPC was first described more than 30 years ago[9]; however, recent advances in molecular biology have shed further light on this association. Earlier work focused on the serologic response to EBV and showed elevated levels of IgA and IgG antibodies to the viral capsid antigen and a replication protein called early antigen in patients with NPC. Other studies have demonstrated the presence of EBV DNA and encoded proteins directly in the NPC tissue samples.[42] Latent infection of cells with EBV, initially studied in B lymphocytes, is associated with regulated expression of several viral genes, including latent membrane proteins (LMPs) 1, 2A, and 2B, six EBV nuclear antigens (EBNAs) 1, 2, 3A to C, and LP, and two small noncoding nuclear RNAs (EBERs).[46] Some of the molecular mechanisms by which expression of these genes can lead to transformation have been elucidated. For example, LMP1 induces expression of epidermal growth factor receptor (EGFR) and may therefore influence cellular growth. A restricted pattern of these EBV antigens is present in nasopharyngeal cancer cells, which may in part explain why immunotherapy directed against these antigens has been more successful in other EBV-associated diseases.[47] Allogeneic cytotoxic T cells to various EBV antigens have been developed and show some promise for treating locally recurrent nasopharyngeal carcinoma.[48]

Several studies have suggested that serologic responses to EBV may be more specific for the nonkeratinizing carcinoma (former WHO types II and III).[49] This, however, was not confirmed by another group.[50] Using the Southern blot technique to detect the viral DNA, Raab-Traub et al[51] showed the presence of EBV in all former histologic variants of NPC, but the EBV copy number was lowest in keratinizing squamous cell carcinomas. The presence of EBV in keratinizing squamous cell carcinoma has been consistently detected by other groups.[52-55] The differences in the rate of EBV detection by different investigators may stem from variability in the sensitivity of different assays. Alternatively, it may reflect differences in the sampled populations. The detection rate of EBV infection in keratinizing squamous cell NPC is highest in endemic areas.

Several groups have examined measuring circulating EBV DNA as a biomarker of tumor burden and response to treatment. The rationale for measuring circulating EBV DNA is that tumor cells are hypothesized to spill EBV DNA into the circulation, and as such pretreatment EBV DNA levels would serve as a measure of burden of disease and postradiotherapy EBV DNA levels might serve as an indicator of residual local or systemic disease. Lo et al demonstrated that using real-time quantitative PCR, cell-free EBV DNA was detectable in 96% of patients with NPC.[22] Investigators from Hong Kong then showed that EBV DNA levels 1 week postradiotherapy correlated with poor outcome,[56] with a 2 year overall survival (OS) of 56.3% for those with detectable EBV DNA compared to 96.7% for those with undetectable EBV DNA. Multiple other groups have also confirmed the prognostic value of posttreatment circulating EBV DNA.[57,58] At present, several Phase III studies are under way investigating whether the presence of circulating EBV DNA after definitive chemoradiotherapy can predict for the need of adjuvant chemotherapy.

Beyond examining the role of EBV in NPC, others are examining genomic alterations in NPC via genomic profiling. Initial investigations have focused either on copy number changes in nasopharyngeal tumors or alterations in gene expression. Deletions of the short arm of chromosome 3 (3p25, 3p14)[38] and of chromosome 9 (9p21-22)[59] are the most common cytogenetic changes. Candidate genes in these and other locations of interest are being identified. The first integrated genomic analysis, with whole exome sequencing and copy number profiling in over 50 tumors, and expression analysis in a limited set was published. (ref). These authors identified 9 significantly mutated genes (FDR $q < 0.2$), including TP53, PIK3CA, BAP1, MLL2, TSHZ3, ERBB2, ERBB3, KRAS, and NRAS. An integrated analysis identified multiple alterations in chromatin modifying genes, ERBB-PI3K signaling, and the autophagy machinery.[59a] These findings may lead to a greater understanding of the genetic basis of NPCs and eventually identify new therapies for treatment.

CLINICAL MANIFESTATIONS, PATIENT EVALUATION, AND STAGING

As mentioned, NPC is rare in the United States and, therefore, is not often suspected as a possible cause of a patient's early symptoms. In addition, the list of possible early symptoms of

NPCs includes many symptoms that could have more common causes. In a series of 378 patients from the MDACC,[40] the presenting symptoms included a neck mass in 41%; hearing loss, ear drainage, or otalgia in 27%; nasal bleeding or obstruction in 21%; cranial nerve deficits in 8%; and other nonspecific symptoms in 8%. Investigators from Washington University noted that the typical presentation involved multiple symptoms.[43] In this series of 143 patients, presenting symptoms included otitis in 43%, throat pain in 39%, nasal obstruction in 37%, a neck mass in 35%, nasal bleeding in 29%, cranial nerve involvement in 24%, and trismus or other symptoms in 5%.

Similar to these data, most series have shown that neck masses, obstructive ear symptoms, and cranial nerve deficits are common presenting symptoms for NPC. In the Washington University series,[43] 66% of patients were found to have ipsilateral neck masses and 28% had contralateral neck masses on examination, although only 35% of patients had reported a neck mass as the reason for seeking medical advice. Of the patients with clinically involved neck disease, 60% had enlarged ipsilateral level II lymph nodes and 32% had enlarged ipsilateral level V lymph nodes. The most frequently involved cranial nerves in the series were cranial nerve VI in 15% of patients, V in 7.7%, and VIII, X, and XII in 5.6% of patients each.

In the series from the MDACC,[40] the level VA lymph nodes were most commonly enlarged (54% of patients), followed by the level II nodes (49% of patients). The level III and lower level VA/upper level VB groups were involved in 24% and 22% of patients, respectively. The level IV lymph nodes, level VB lymph nodes, and supraclavicular lymph nodes were involved in 10%, 13%, and 10% of patients, respectively. Similar to the series from Washington University, cranial nerve VI was the most frequently involved nerve (6% of cases).

Patient Evaluation

The initial evaluation of patients with NPC should include a history and physical examination, with special attention to the level of nodal involvement (if any) (Figure 34-2).

Patients should undergo flexible fiberoptic nasopharyngoscopy to determine the involvement of mucosal surfaces. A diagram or digital photograph of these findings should also be made. Biopsy of the primary lesion should be attempted first. If this procedure gives indeterminate results, a needle biopsy of a potentially involved lymph node should be taken.

CT and MRI of the head and neck are useful in the evaluation of both erosion of tumor into the bony structures of the base of the skull and retropharyngeal and cervical lymphadenopathy. Although the same information is often provided by CT and MRI, some investigations have suggested that MRI may be more useful in delineating soft-tissue invasion outside the nasopharynx and the extent of retropharyngeal lymph node involvement,[60] whereas CT may be most useful in delineating skull base erosion.[61-63] Given the level of anatomic information required for the current T staging system, MRI is a critical imaging study in the evaluation of nasopharyngeal tumors.

PET can be useful for staging[64,65] as well as for posttherapy management where other imaging is unclear. PET/CT, which provides additional functional information, is more commonly used now and may be helpful for radiotherapy planning. Further PET/CT helps evaluate for distant metastatic disease before beginning definitive locoregional treatment.

The completion of the diagnostic evaluation involves acquiring routine complete blood counts, a chemistry panel, and a chest radiograph (see Figure 34-2). Further evaluation of possible metastases should be done on the basis of the clinical presentation of the patient.

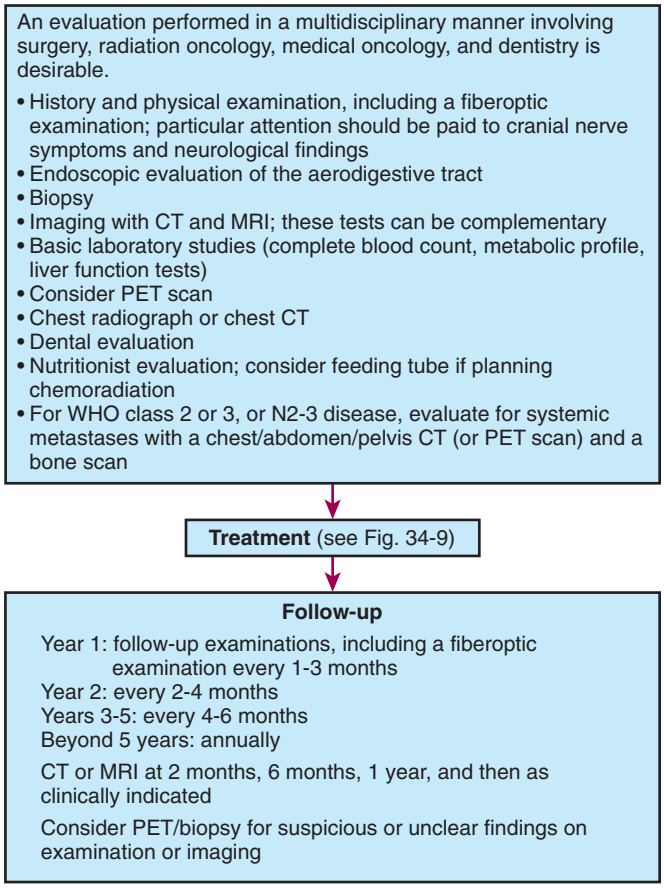


Figure 34-2 Diagnostic algorithm for nasopharyngeal carcinoma.

Staging

After a pathologic assessment has been made, the workup or evaluation leads to a clinical stage (Table 34-2). Clinical staging has been a matter of controversy, and the prognostic significance of the various TNM staging criteria remains under investigation. Several staging systems have been in use throughout the world. The most commonly used systems in North America and Europe are those of the American Joint Committee on Cancer (AJCC)[66] and the International Union Against Cancer (Union Internationale Contre le Cancer [UICC]),[67] which have become essentially analogous. In Asia, where NPC is endemic, the Ho[68] classification system was initially developed in Hong Kong. In addition, in 1992, Chinese physicians adopted an independent system similar to the Ho system.[69] All four systems, shown in Table 34-2, have limitations and continue to evolve, with researchers often drawing on each others' experience. Updated versions of the Chinese system and the AJCC system were released in 2008[70,71] and 2010,[72] respectively. The AJCC/UICC remains the most commonly used system in the English literature.

A well-recognized advantage of the Ho classification system lies in its approach to lymph node metastasis, namely, use of lymph node location in N-stage assignment and a more even distribution of nodal disease in stage grouping[68,74] (see Table 34-2). Nodal involvement appears in stage II, and supraclavicular nodal metastasis, which is known to carry a worse prognosis, is represented in a separate stage IV category (Table 34-2). The 1992 AJCC system used lymph node size and laterality in N-stage assignment, both of which carry some prognostic significance. However, only some patients with N1

TABLE 34-2 Comparison of Staging Systems

Classification	AJCC, 7th ed.[72]	2002/1997 AJCC[66,73]	Ho[68]	2008 Chinese[62]
T1	Confined to nasopharynx, or extends to oropharynx or nasal cavity	Confined to nasopharynx	Confined to nasopharynx	Confined to nasopharynx
T2	With parapharyngeal extension	Soft tissue invasion *A:* Without parapharyngeal extension *B:* With parapharyngeal extension	Nasal fossa, oropharynx, muscle, or nerves below base of skull	Nasal cavity, oropharynx, parapharyngeal extension
T3	Bony or paranasal sinus extension	Bony or paranasal sinus extension	*A:* Bone involvement below base of skull *B:* Involves base of skull *C:* Cranial nerves *D:* Orbits, laryngopharynx, or infratemporal fossa*	Skull base or medial pterygoid extension
T4	Intracranial extension, or cranial nerve or infratemporal fossa,* hypopharynx, or orbital involvement	Intracranial extension, or cranial nerve or infratemporal fossa,* hypopharynx, or orbital involvement	—	Cranial nerves, paranasal sinuses, masticator space* (excluding medial pterygoid muscles), intracranial (cavernous sinus, dural meninges) extension
N1	Unilateral, ≤6 cm or unilateral or bilateral retropharyngeal ≤6 cm	Unilateral, ≤6 cm	Upper neck above thyroid notch	*A:* Retropharyngeal *B:* Unilateral level Ib, II, III, and Va or ≤3 cm
N2	Bilateral, ≤6 cm	Bilateral, ≤6 cm	Below thyroid notch above line joining end of clavicle and superior margin of trapezius muscle	Bilateral level Ib, II, III, and Va or >3 cm or with extranodal spread
N3	*A:* >6-cm node *B:* Supraclavicular involvement	*A:* >6-cm node *B:* Supraclavicular involvement	Supraclavicular fossa† or skin involvement	Level IV or Vb involvement
M1	—	Metastases	Metastases	Metastases
Stage I	T1N0M0	T1N0M0	T1N0	T1N0M0
Stage II	T1N1 T2N0 T2N1	*A:* T2aN0M0 *B:* T1-2aN1M0 or T2bN0M0	T2 and/or N1	T1N1a-1bM0 or T2N0-1bM0
Stage III	T1N2M0 T2N2M0 T3N0-2M0	T1-2bN2M0 T3N0-2M0	T3 and/or N2	T1-2N2M0 or T3N0-2M0
Stage IV	*A:* T4N0-2M0 *B:* Any TN3M0 *C:* Any T any NM1	*A:* T4N0-2M0 *B:* Any TN3M0 *C:* Any T any NM1	N3 (any T)	*A:* T1-3N3M0 or T4N0-3M0 *B:* Any T any NM1
Stage V	—	—	M1	—

**Masticator space is defined as infratemporal fossa.*
†Supraclavicular fossa as described by Ho is a triangular space defined by three points: (1) the superior margin of the sternal end of the clavicle, (2) the superior margin of the lateral end of the clavicle, and (3) the point where the neck meets the shoulder. This includes the caudal portion of level IV and Vb lymph nodes.

disease were included in stage III, and most patients with nodal involvement were grouped into stage IV, together with patients with metastatic disease. Modifications to the AJCC classification implemented in1997[75] and maintained in 2002[73] and 2010[72] have incorporated lymph node location into N-category assignment, designating involvement of the supraclavicular fossa, as originally defined by the Ho system, as N3 disease, and have placed all N3M0 lesions in a separate stage IVA grouping. In addition, stage groupings were changed to provide a more even stage distribution. These changes improved risk stratification of the 1997 AJCC classification in comparison to both the prior version of the AJCC system and the 1978 Ho system.[76,77]

Important changes to the most recent AJCC system targeted T-category assignment. Invasion into the soft tissues of the nasopharynx was used in the 1997 and 2002 AJCC classification to segregate T1 and T2 lesions, but studies have shown that this carries no prognostic significance.[78-80] The parapharyngeal space involvement used to segregate T2a and T2b lesions does,[81-83] however, and therefore the new 2010 AJCC system segregates lesions with parapharyngeal involvement into the T2 subgroup, whereas all tumors either confined to the nasopharynx or extending into surrounding subsites but without parapharyngeal involvement are now in the T1 subgroup. Furthermore, cranial nerve involvement carries a significantly worse prognosis than base-of-skull involvement,[43,79,84-86] but both were aspects of the T4 subgroup in the 1997 and 2002 AJCC systems and of the T3 subgroup in the Ho system. In the 2003 and 2010 versions, akin to the 2008 Chinese classification system, base-of-skull involvement

has been downstaged to T3. Furthermore, data are emerging that extensive cranial nerve involvement, orbit involvement, and intracranial extension are associated with worse outcomes within the T4 subgroup.[77,86] Therefore, some of the proposed modifications to the AJCC system include a separation of the T4 subgroup into two categories. T4a would include tumors with involvement of the masticator space (infratemporal fossae), asymptomatic radiographic cranial nerve involvement, and involvement of the hypopharynx. T4b would include tumors with intracranial extension, orbital involvement, and symptomatic cranial nerve palsies. However, more data need to be collected to validate this proposed modification.

With respect to N-category classification, the seventh edition of the AJCC staging manual for the first time includes disease that has spread to the retropharyngeal lymph nodes in staging, placing it in the N1 category. On MRI evaluation, these nodes are involved in 83% of patients with NPC compared with 74% involvement of the level II to IV nodes and are considered to be the first echelon of nodal spread.[87] Therefore, their inclusion into the staging system is expected to improve the prognostic accuracy.[88,89]

The evolution of technology and, specifically, CT and MRI, has allowed for more precise evaluation of tumor invasion into surrounding structures and lymph node involvement and will undoubtedly lead to improvement in staging accuracy and risk stratification.

PRIMARY THERAPY

Traditionally, the nasopharyngeal area has not been easy to examine without fiberoptic technology and has been difficult to approach surgically. Surgical exposure of the area and resection of tumors with adequate tumor margins have long been challenging.[90] For these reasons, primary surgical intervention fell out of favor in the 1950s; primary treatment has generally consisted of radiotherapy for early stage disease and chemoradiotherapy for locally advanced disease.

Single-Modality Therapy

Although histologic presentations of nasopharyngeal tumors vary throughout the world, with more undifferentiated tumors found in southern China and Hong Kong, the 10-year survival rates for patients treated with radiation therapy alone in the United States (MDACC),[40] Denmark,[41] and Hong Kong[91] are similar, at 34%, 37%, and 43%, respectively (see Table 34-1). The rate from the Hong Kong study may be somewhat inflated because many patients had early-stage disease (node-negative disease in 39%), and few patients with the keratinizing histology (0.3%) were present in the series.[91] However, elevation of EBV titers has been correlated with a poor prognosis,[46] and higher titers would be expected in Hong Kong, an endemic area. The North American and European populations have a greater percentage of patients with keratinizing (WHO type I) histologic findings than with nonkeratinizing histologic findings (WHO types II and III), however, and the prognosis for the former has been poorer than for the latter.[78] Therefore, comparison of groups from various parts of the world is difficult, and our understanding of the role of EBV and histologic classifications is incomplete. Still, some general statements can be made.

The MDACC series elucidated the long-term outcome in a large population of patients treated with radiotherapy alone.[40] Using the 1992 AJCC staging system (see Table 34-2), researchers found that advanced T category, squamous histologic typing, and cranial nerve deficits were predictive of poor prognosis for local control in univariate and multivariate analyses. Five-year local control rates for T1, T2, T3, and T4 categories were 93%, 79%, 68%, and 53%, respectively. Similar results were observed in other, smaller series.[43,92-95]

The MDACC results illustrate the good tumor control that can be achieved with radiotherapy alone for early-stage lesions but demonstrate the need to explore multimodality options for more advanced lesions. Significant improvements were achieved with a combined chemoradiation approach and the evolution of radiotherapy techniques. Altered fractionation schemes were initially explored, but the improved therapeutic ratio associated with the use of intensity-modulated radiotherapy (IMRT) has made this technique the radiotherapy of choice.

Combined-Modality Therapy

In general, the dramatic improvement in outcomes with combined-modality treatment has limited the use of single-modality radiotherapy to patients with T1 disease. Results from randomized trials of combined-modality therapy will be discussed.

Irradiation Plus Chemotherapy

The randomized trial of Sanchiz et al[96] served as an introduction for using chemotherapy in NPC. However, only a small number of patients with NPC were included.

Brizel et al[97] reported a small randomized trial comparing twice-daily irradiation (1.25 Gy to 75 Gy) to twice-daily irradiation (1.25 Gy to 70 Gy) with concurrent cisplatin and 5-fluorouracil (5-FU) treatment. This trial included 121 patients with locally advanced (T3 and T4) squamous cell carcinomas of all head and neck sites (including some NPCs). With a median follow-up of 41 months, the locoregional control rate at 3 years was 70% for the combined-modality arm versus 44% for the irradiation alone arm ($p = 0.01$). The OS at 3 years was 55% for the combined-modality arm versus 34% for the irradiation alone arm ($p = 0.07$). Mucositis appeared to be more prevalent in the combined-modality arm; 45% of patients required feeding tubes compared with 28% in the irradiation alone arm. However, the severe late complications of soft-tissue necrosis or osteoradionecrosis were uncommon, with similar numbers in both arms (three patients in the irradiation group and five in the combined-modality group).

Several groups have conducted Phase III trials specific to nasopharyngeal primary tumors (instead of a wide array of head and neck cancers). The trial design compared chemotherapy plus irradiation versus irradiation alone (Table 34-3).[1,69,98-105]

Intergroup study 0099 showed a dramatic improvement in survival rates with combined-modality treatment.[1] The trial was closed at a planned interim analysis (October 1995) after review of the preliminary results by the Data Safety and Monitoring Committee for the Southwest Oncology Group. The results are shown in Table 34-3. Patients treated with standard irradiation received 70 Gy to gross disease in daily fractions of 1.8 Gy to 2 Gy. Patients enrolled in the combined-modality arm received 100 mg/m^2 of cisplatin on days 1, 22, and 43 of irradiation, and cisplatin (80 mg/m^2) and 5-FU (1000 mg/m^2) on days 1 to 4 every 3 weeks for three courses after irradiation. A marked statistically significant improvement in both disease-free survival (DFS) and OS in the combined-modality arm was documented at both initial analysis and in the final update of the trial published in 2001.[1] The 5-year OS for patients with the keratinizing squamous cell carcinoma histologic type (WHO type I) was 37%; the differentiated nonkeratinizing histologic type (WHO type II), 55%; and the undifferentiated nonkeratinizing histologic type (WHO type III), 60%. This landmark trial defined a new standard of care for NPC,

TABLE 34-3 Major Concurrent Chemotherapy and Radiotherapy Randomized Trials

Study	No. Pts	Stage	Randomization	DFS, 5 yr (%)	*p* Value	OS, 5 yr (%)	*p* Value
Intergroup study 0099[1]	150	AJCC 1992 stage III: T3N0; T1-3N1M0 AJCC 1992 stage IV: T4N0-1; any TN2-3M0	70 Gy/7-8 wk 70 Gy/7-8 wk with cisplatin, followed by three cycles of cisplatin/5-FU	29 58	<0.001	37 67	0.005
Chan et al[100,102]	350	Ho system[61] N2-3 or any nodes ≥4 cm	66 Gy/6.5 wk ±10-20 Gy boost 66 Gy/6.5 wk ± 10-20 Gy boost with cisplatin	52 60	NS	59 70	0.065
Lin et al[98]	284	AJCC 1992: III-IV (M0)	70-74 Gy/6-7 wk 70-74 Gy/6-7 wk with infusional cisplatin/5-FU × 2	53 72	0.0012	54 72	0.0022
Wee et al[104]	221	AJCC 1997: stage III or IV; WHO type 2 or 3	70 Gy/7 wk 70 Gy/7 wk with infusional cisplatin, followed by three cycles of cisplatin/5-FU	53 (3-yr) 72 (3-yr)	0.01	65 (3-yr) 80 (3-yr)	0.01
Lee et al[101]	348	AJCC 1997: T1-4N2-3M0; WHO type 2 or 3	>66 Gy/7-8 wk >66 Gy/7-8 wk with cisplatin, followed by three cycles of cisplatin/5-FU	62 72	0.027	78 78	0.97

5-FU, *5-Fluorouracil;* AJCC, *American Joint Committee on Cancer;* DFS, *disease-free survival;* NS, *not significant;* OS, *overall survival;* UICC, *Union Internationale Contre le Cancer;* WHO, *World Health Organization.*

resulting in the exclusion of nasopharyngeal cases from subsequent locally advanced head and neck cancers trials.

Although the first reported results from a chemoradiation trial conducted in an endemic area were disappointing,[100] the final update[102] as well as four additional independent trials conducted in Taiwan,[98] Hong Kong,[101,106] and Singapore[104] all confirmed an advantage to cisplatin-based chemoradiation (see Table 34-3). A randomized trial from Hong Kong of concurrent weekly cisplatin chemotherapy (40 mg/m^2), without adjuvant or neoadjuvant therapy, versus irradiation demonstrated a significant improvement in progression-free survival (PFS) at a median follow-up of 2.71 years[100] and in OS at a median follow-up of 5.5 years (hazard ratio [HR], 0.51; p = 0.013)[102] for a subset of patients with T3 to T4 disease. A trial conducted by Lin et al[98] in Taiwan randomized 284 patients to irradiation alone versus irradiation with two cycles of concurrent cisplatin (20 mg/m^2/day) and 5-FU (400 mg/m^2/day) by continuous infusion given over a course of 4 days. In this trial, combined-modality treatment was associated with a significant survival advantage. The differences in the degree of benefit derived from the combined-modality treatment in these two studies may stem from the different staging systems used to define entry criteria (AJCC system in the Lin study versus Ho system in the Chan et al study[100]), different histologic makeup of the tumors (73.2% differentiated nonkeratinizing carcinoma in the Lin study versus 93.7% undifferentiated carcinoma in the Chan study), or different chemotherapy or radiotherapy schedules. The role for concurrent chemotherapy in the management of NPC has been further supported by two other trials comparing concurrent and adjuvant chemotherapy with irradiation alone[101,104] (see Table 34-3).

A meta-analysis of seven endemic Phase III trials of concurrent chemoradiation versus radiotherapy alone, including 1608 patients, demonstrated an OS advantage of the concurrent regimen, with a relative risk of 0.74 at 5 years.[107] This survival advantage is less than that seen in trials from nonendemic regions.

Although the multiple aforementioned trials clearly established the role of concurrent chemoradiotherapy for stage III and IV disease, the role in stage II disease was ambiguous. The study by Chen et al randomized 230 patients with 1992 Chinese Stage II (vast majority AJCC stage II) disease to either radiotherapy alone or concurrent chemoradiotherapy with weekly cisplatin.[108] At a median follow-up of 5 years, the 5-year OS was 94.5% versus 85.8%, (p = 0.007) and PFS was 87.9% versus 77.8% (p = 0.017), both favoring the combined-modality arm. This trial more firmly establishes that patients with stage II disease should also receive combined-modality treatment.

Through the collective experience with cisplatin-based chemotherapy in these as well as other cancer trials, it became apparent that a weekly cisplatin regimen such as that used in the Chan study is better tolerated than the intergroup regimen. Ninety-five percent of the patients assigned to the concurrent chemoradiation arm with weekly cisplatin were compliant with the regimen, whereas only 65% of the patients in the high dose (every 3 weeks) combined treatment arm received all three cycles.

Many additional trials have been performed exploring combination chemotherapy and radiotherapy for NPC.[69,99,103,109] So far, no benefit was shown to neoadjuvant or adjuvant chemotherapy in these trials compared to radiotherapy alone. Likewise, a recent meta-analysis using combined individual data from eight randomized trials enrolling 1753 patients showed no OS benefit with either neoadjuvant or adjuvant chemotherapy, over radiotherapy alone, although a meaningful treatment effect was seen for concurrent chemoradiation.[110] However, the question remains whether addition of induction or adjuvant chemotherapy to concurrent chemoradiation may provide an additional advantage, by reducing the risk of distant metastasis.

A recent Phase III (n = 508) study compared concurrent chemoradiation plus adjuvant chemotherapy versus concurrent chemoradiation alone in patients with locally advanced NPC.[111] All patients received concurrent weekly cisplatin

(40 mg/m^2). Patients were randomized to receive adjuvant chemotherapy after definitive treatment with three cycles of 5-FU and cisplatin (251 patients) while 257 patients were randomized to observation. The 2 year failure-free survival was 86% in the adjuvant group and 84% in the observation group ($p = 0.13$). The authors concluded that there was no benefit to adjuvant chemotherapy. Limitations of this study include the short follow up (median of 37.8 months), the fact that the study was not designed as a noninferiority trial, and the borderline p-value. At present, National Comprehensive Cancer Network (NCCN) guidelines continue to recommend the use of adjuvant chemotherapy; however, its omission is available as a category 2B treatment recommendation. Multiple trials are under way to determine if circulating EBV DNA can be used to better determine which patients are at high risk for distant metastasis and may benefit the most from additional chemotherapy (see "Molecular Biology" section for more details).

Other ongoing trials that are examining induction and adjuvant chemotherapy regimens include a trial by the Nasopharyngeal Cancer Study Group of Hong Kong that is designed to compare induction versus adjuvant chemotherapy with cisplatin and 5-FU in combination with concurrent chemoradiation (NCT00379262). A multicenter Phase III trial opened by the Taiwan National Health Research Institutes is designed to compare a cisplatin-based multiagent induction regimen (mitomycin, epirubicin, cisplatin, 5-FU, and leucovorin) followed by concurrent chemoradiation with chemoradiation alone (NCT00201396). Both of these studies remain open and are near completion at the time of this publication. The potential benefit of sequential chemotherapy must be weighed against the increased morbidity and mortality from additional adjuvant or sequential chemotherapy.[112,113]

In addition to evaluating the best sequencing for chemotherapy and irradiation, investigators are also examining the role for other chemotherapeutic agents in the treatment of NPC. A recent study explored the efficacy of weekly carboplatin in the setting of concurrent chemoradiation for patients with locally advanced disease.[114] At a median time of 26 months, OS and DFS were similar in the cisplatin and carboplatin groups, with less toxicity noted in the latter group. Therefore, treatment with carboplatin is reasonable when use of cisplatin is precluded by patient comorbidities.

Several landmark randomized controlled Phase III studies have demonstrated that the addition of taxanes to induction cisplatin and 5FU in the neoadjuvant setting have the potential to improve outcomes in other head and neck carcinomas.[115,116] Phase II studies of patients with locally advanced NPC have already shown favorable results with paclitaxel, both in the neoadjuvant setting followed by concurrent therapy with platins or as a part of a concurrent regimen.[117-119] However, the DeCIDE and PARADIGM Phase III trials comparing taxane-based induction chemotherapy followed by concurrent chemoradiation, with concurrent chemoradiation alone, have so far failed to demonstrate an advantage to induction chemotherapy (at 2 years).[120,121] However, the relatively low incidence of distant metastases seen in the DeCIDE trial could translate to a survival advantage with longer follow-up. To further address this question, a Phase III trial was opened in 2009 by the international Groupe Oncologie Radiotherapie Tete et Cou (GORTEC), randomizing patients with NPC to receive induction chemotherapy with docetaxel, cisplatin, and 5-FU followed by concurrent chemoradiation with cisplatin or cisplatin-based concurrent chemoradiation alone (NCT00828386). This trial continues to accrue.

Molecular therapies are also under investigation. Although one trial showed a benefit to the use of cetuximab in other head and neck cancers,[122] it remains to be seen whether these data will be confirmed for squamous cell carcinomas of the head and neck in general[123] or for NPC in particular. The RTOG has conducted a 46 patient Phase II trial incorporating the vascular endothelial growth factor (VEGF) inhibitor bevacizumab into the standard chemoradiation regimen, with promising results in terms of distant disease control (90.8% freedom from distant metastases at 2 years).[124] Although there were grade 4 toxicities in nine patients, the treatment protocol was considered feasible.

Altered versus Standard Fractionation with or without Chemotherapy

In the last several decades, alongside trials exploring the role for chemotherapy in the treatment of NPC, other studies aimed to evaluate altered fractionation regimens. Hyperfractionation, accelerated fractionation, and a combination thereof were explored, either alone or in combination with concurrent chemotherapy. As in the trials focusing on chemotherapy, these were based on promising data from other head and neck sites.

A large randomized trial by Sanchiz et al[96] addressing the role of twice-daily versus once-daily irradiation for head and neck cancers included tumors of the nasopharynx. In this study, 892 patients (852 evaluable patients) with advanced head and neck cancers (T3-4N0-3M0 by UICC staging), including 92 patients with NPC, were randomly assigned to once-daily irradiation (group A), twice-daily irradiation (group B), and once-daily irradiation with 5-FU (group C). No differences were seen in median duration of response or OS between groups B and C; however, when either group B or C was compared individually with group A, there were significant improvements in both measures.

An accelerated fractionation regimen using six 2-Gy fractions per week to a total dose of 66 Gy to 68 Gy was compared with a conventional fractionation regimen to the same total dose in a large randomized Danish study of 1476 patients with head and neck cancers (435 patients with pharyngeal tumors, including nasopharyngeal tumors).[125] In this trial, accelerated fractionation resulted in significantly improved locoregional control and disease-specific survival (DSS) but not OS.

The same fractionation scheme, either with or without concurrent chemotherapy, was evaluated in a trial from the Hong Kong Nasopharyngeal Study Group of 189 patients with advanced NPC.[105] Patients were randomly assigned to one of four arms: (1) conventional fractionation alone, (2) accelerated fractionation alone, (3) conventional fractionation with concurrent cisplatin and 5-FU, and (4) accelerated fractionation with concurrent cisplatin and 5-FU. At 2.9 years of follow-up, accelerated fractionation with concurrent chemotherapy (arm 4) achieved the most substantial tumor control, with PFS of 97% versus 70% (arm 1), 63% (arm 2), and 74% (arm 3), without an improvement in OS. A significant increase in acute and late toxicity in the combined chemotherapy–accelerated fractionation arm was also noted.

Based on these and other experiences with altered fractionation schemes in NPC, as well as other head and neck cancers, it became apparent that both the total dose and overall treatment time were important determinants of outcome.[126] With the advent of IMRT, dose escalation (delivery of adequate doses to the gross and subclinical disease) has become possible without concomitant changes in the toxicity profile, significantly improving the therapeutic ratio of concurrent chemoradiation and rendering the above fractionation schemes obsolete.

Intensity-Modulated Radiotherapy with or without Chemotherapy

The proximity of numerous critical structures within the nasopharynx often makes it challenging to provide an adequate

TABLE 34-4 NPC: Results of IMRT Alone or IMRT Plus Chemotherapy*

Study	Year	No. Pts	Stage III or IV (%)	Dose (Gy)	Median FU Time (mo)	Time Point (yr)	LPFS (%)	OS (%)
Lee et al (UCSF)[127]	2002	67	67	65-70†	31	4	97	88
Kwong et al[128]	2004	33	0	68-70	24	3	100	100
Kam et al[129]	2004	63	57	66‡	29	3	92	90
Wolden et al[130]	2006	74	37	70	35	3	91	83
Lee et al (RTOG)[131]	2009	68	60	70	31	2	93	80
Tham et al[132]	2009	195	63	70§	>36	3	90	89

FU, *Follow-up;* Gy, *Gray;* LPFS, *local progression-free survival;* OS, *overall survival.*

**Chemotherapy was offered to all patients with advanced NPC in all of the trials except for the Kwong trial, in which only patients who were stage I and II were included.*

†*Twenty-seven patients also received either an intracavitary high-dose-rate boost of 5 Gy to 6 Gy in two fractions (26 patients) or a radiosurgery boost (1 patient).*

‡*Twenty patients with T1-2a tumors (100%) received an intracavitary boost, and 15 of 42 patients with T2b-4 tumors (36%) received a conformal boost of 8 Gy in four fractions.*

§*Twenty patients with T1-2 tumors received an intracavitary high-dose-rate boost of 4.5 Gy to 5 Gy per fraction for either one (12 patients) or two (8 patients) total fractions.*

dose to an irregularly shaped tumor while still keeping the dose to surrounding tissues within acceptable limits. Therefore the capacity of IMRT to provide highly conformal and precise coverage with sharp dose gradients has been widely embraced in the head and neck cancer community. In addition, the ability to assign different doses to a desired spatial distribution when using IMRT has allowed for simultaneous delivery of different fractionation schemes to different portions of the target. Multiple institutions both in the United States and the endemic regions have reported improved clinical outcomes since adoption of IMRT techniques for treatment of NPC (Table 34-4).

University of California–San Francisco (UCSF) researchers were the first to report their experience with IMRT in 67 patients with NPC, including 45 patients with stages III to IV disease, treated between 1995 and 2000.[127] Patients were prescribed 59.4 Gy in 1.8-Gy fractions to the planning target volume (PTV) encompassing microscopic and gross disease and typically received 65 Gy to 69.96 Gy to the gross disease and involved lymph nodes in 2.12-Gy to 2.25-Gy fractions. Twenty-six patients also had an intracavitary brachytherapy boost to a total dose of 5 Gy to 7 Gy at the discretion of the treating physician. Patients with advanced disease received concurrent and adjuvant chemotherapy. The reported 4-year estimates of local PFS, locoregional PFS, and OS were 97%, 98%, and 88%, respectively.[127] Long-term xerostomia was minimal at 2 years, with 66% of the patients having no xerostomia and no grade 2 or higher late xerostomia.

Locoregional control rates above 90% have since been noted in other single-institution prospective[128,130,133] and retrospective[132] series, as well as in a recently published multiinstitutional Radiation Therapy Oncology Group (RTOG) 0225 study.[131] Similar to the UCSF regimen, the RTOG 0225 trial used a simultaneous integration of the boost, with 2.12 Gy per fraction delivered to the gross disease with a minimal 5-mm margin (PTV_{70}), while 1.8 Gy was delivered to the subclinical PTV ($PTV_{59.4}$). Therefore, in 33 fractions, the PTV_{70} received a total dose of 69.96 Gy and the $PTV_{59.4}$ received 59.4 Gy. A total dose of 50.4 Gy in 28 fractions was delivered to the supraclavicular nodes using a non-IMRT technique. After a median follow-up of 2.6 years, the estimated 2-year local PFS, locoregional PFS, and OS rates were 92.6%, 89.3%, and 80.2%, respectively. Importantly, while providing similar or better locoregional tumor control in comparison with conventional irradiation techniques, IMRT has resulted in significantly lower rates of late complications. Only nine patients (13.5%) had grade 2 xerostomia at 1 year from the start of IMRT, two patients had grade 3 xerostomia, and none had grade 4 xerostomia. The improved toxicity profile of IMRT compared with conformal radiotherapy in the treatment of NPC has been since confirmed in two prospective randomized trials.[129,134]

LOCALLY RECURRENT OR PERSISTENT DISEASE

In contrast to other head and neck cancers, recurrent NPC can be successfully salvaged in a substantial number of patients. Therefore, aggressive management is usually advocated, and a number of different approaches, including surgery, brachytherapy, and external beam irradiation (EBRT), can be successfully used. Chemotherapy is generally used in combination with local treatment for all patients with advanced disease.

Surgical Management

Surgical resection is the preferred treatment for persistent or recurrent lymph node involvement in the neck. However, surgical management of recurrent NPC at the primary site is hampered by the same factors that make surgery at this site difficult as a primary treatment, such as difficulties in obtaining adequate exposure and surgical margins.[90,135-137] Salvage nasopharyngectomy has been achieved by several different approaches, the most common of which are the transpalatal, transmandibular, and transmaxillary approaches. Minimally invasive techniques, such as a transnasal approach and an endoscopic approach, have also been employed successfully in a select group of patients. The choice of surgical approach is dictated by the tumor size and its location. Generally, surgical treatment of recurrent NPC remains controversial, but it may offer a reasonable disease-free period in certain well-selected cases. Several recent surgical series reported locoregional control and OS of 40% to 72% and 30% to 54%, respectively.[138-141]

Reirradiation

Reirradiation remains the cornerstone of treatment for recurrent NPC within the nasopharynx. Early experiences with reirradiation were often associated with a high risk of late effects, including trismus, stricture, dysphagia requiring gastrostomy, hearing loss, unilateral blindness, cranial neuropathy, temporal lobe necrosis, and endocrinopathies. However, the evolution of radiotherapy techniques that allow for more precise

dose delivery, and imaging techniques that allow for earlier detection and more precise tumor delineation during treatment planning, have significantly improved the therapeutic ratio.

In general, earlier stage at recurrence and longer time to recurrence are associated with better outcomes for reirradiation.[142-144] Higher doses (≥60 Gy) are more effective than lower doses[144] and can be accomplished with EBRT alone or in combination with radiosurgery, or a brachytherapy boost (intracavitary or interstitial treatment).[142,144-147] Lee et al examined 654 patients with recurrent NPC reirradiated between 1976 and 1996 with conventional techniques and some without modern imaging.[142] Of these patients, 82% received external beam alone (median 45.6 Gy), and the other 18% had either brachytherapy or combined treatment. They found a 5-year actuarial local salvage rate of 23%. Investigators from Hong Kong examined 200 patients with local recurrence treated in the modern era (CT/MRI) and found a 3-year OS of 74%, suggesting a significant number of patients could be salvaged.[148] Of these 200 patients, 159 were salvaged with reirradiation, 108/159 with EBRT alone (dose > 60 Gy).

IMRT is particularly well suited for reirradiation, and results with this method are promising. At the Memorial Sloan-Kettering Cancer Center (MSKCC), 29 patients with recurrent NPC were treated with reirradiation between 1996 and 2008, in the era of modern techniques.[149] Sixteen patients received EBRT alone to an average dose of 59.4 Gy and 13 received EBRT to 45 Gy followed by intracavitary brachytherapy to 20 Gy (EBRT-brachy). Twenty-four patients, 14 in the EBRT alone group and 10 in the EBRT-brachy group, underwent IMRT. Choice of radiotherapy technique was at the discretion of the treating physician but was often dictated by the size and location of the recurrence. Thus, the EBRT-brachy group was primarily composed of patients with rT1 or T2 disease (85%), whereas the EBRT group included patients with more advanced disease (31%, rT1 or T2; 69%, rT3 or T4); 93% of the patients received chemotherapy. Five-year local control and OS were 52% and 60%, respectively. Although no significant differences were seen in local control or survival rates between the EBRT-brachy and EBRT groups, the EBRT-brachy approach was associated with fewer late complications (8% rate of grade 3 or greater late effects compared with 73% rate in patients receiving EBRT alone).

Hua et al examined 151 patients with NPC reirradiated with IMRT between 2001 and 2006.[150] They identified a 5-year OS for recurrent stages I, II, III, and IV of 71.4%, 62.9%, 35.5%, and 30.2%. The median reirradiation dose was 70.4 Gy (range 62.1 Gy to 77.6 Gy). Serious late toxicities included 12.6% with a cranial nerve palsy, 13.2% with hearing deficits, and 19.9% with radionecrosis detected by imaging. Qui et al reirradiated 70 patients with IMRT (median dose 70 Gy) between 2003 and 2009.[151] They found 2-year locoregional recurrence-free survival, DFS, and OS of 65.8%, 65.8%, and 67.4%. Significant late toxicity occurred in 35.7% of patients including cranial nerve palsies, posterior nasal space ulceration, and deafness.

Stereotactic radiosurgery (SRS), or stereotactic body radiotherapy (SBRT), treatment of recurrent head and neck lesions is another promising approach because the technique allows for rapid fall-off of the radiation dose outside of the tumor volume and nearby critical structures that surround this anatomic area. SRS has been used to treat recurrent nasopharyngeal lesions after prior irradiation, either alone or in combination with EBRT.[152-154] When used as the only local treatment modality, it is generally reserved for smaller lesions, and doses of 11 Gy to 35 Gy are used.[152,154-156] Fractionated SBRT in the reirradiation setting can provide satisfactory control with an improved late toxicity profile.[157]

Concurrent Chemoradiation

Concurrent chemoradiation is being used increasingly for treatment of recurrent head and neck cancer after primary radiotherapy.[158-161] In general, the late morbidity of these regimens is less severe than would be expected, given that reirradiation doses are comparable to the original radiotherapy doses.[160,161] These reirradiation trials have usually included few nasopharyngeal cases. Historically, reirradiation without chemotherapy, possibly including brachytherapy, has given better results for nasopharyngeal cases than for other head and neck sites.[158] However, given the superiority of chemoradiation over irradiation alone in the treatment of primary NPC, it is reasonable to extrapolate these results to recurrent disease. In fact, most of the recent salvage irradiation series have included concurrent cisplatin-based chemoradiation for advanced-stage recurrent disease (Table 34-5).

IRRADIATION TECHNIQUES AND TOLERANCE

The standard of care for patients treated with definitive radiotherapy per the NCCN guidelines is IMRT, but a brief

TABLE 34-5 Results of Select Locally Recurrent NPC Reirradiation Studies

Study	Year	No. Pts	T3/T4 (%)	Median FU (mo)	5-yr LC (%)	5-yr OS (%)	Major Complications (%)	Pts Retreated with Chemo (%)
CONVENTIONAL OR THREE-DIMENSIONAL CONFORMAL EBRT TECHNIQUES ALONE OR IN COMBINATION WITH RADIOSURGERY OR BRACHYTHERAPY								
Lee et al[142]	1997	654	48*	17	23	16	26	Unknown
Chua et al[162]	1998	97	70	18	—	36	34 (neurologic)	18
Hwang et al[147]	1998	74	66*	20	—	37	33	30
Teo et al[143]	1998	103	56	20	15	8	20% (neurologic)	16
Leung et al[163]	2000	91	44	27-55	38	30	57	19
IMRT ALONE OR IN COMBINATION WITH RADIOSURGERY OR BRACHYTHERAPY								
Lu et al[164]	2004	49	73	9	100 (9-mo)	—	N/A	6
Chua et al[146]	2005	31	74	11	65 (1-yr)	63	70, grade ≥3	68
Koutcher et al[149]	2010	29	48	45	52	69	31, grade ≥3	93

chemo, *Chemotherapy;* EBRT, *external beam irradiation;* FU, *follow-up;* IMRT, *intensity-modulated radiotherapy;* LC, *local control;* N/A, *not applicable;* OS, *overall survival;* Pts, *patients.*

**Eighty-three percent of the patients were treated with IMRT.*

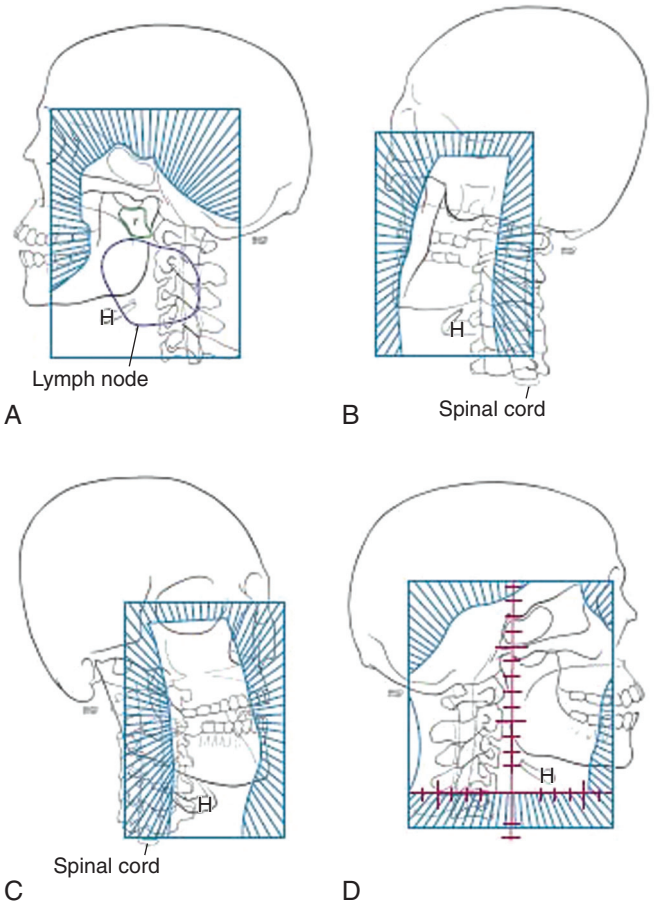


Figure 34-3 **A** to **C,** An example of a conventional field arrangement for stage T2 NPC. Pituitary shielding technique was used. The initial fields were opposed lateral fields **(A)**, followed by oblique fields **(B** and **C)**, with an electron field *(not shown)* to treat the contralateral neck. **D,** Base of skull included in the treatment of a stage T3 nasopharyngeal cancer. *H*, hyoid bone; *T*, thyroid. ***A*** *to* ***D,*** *Courtesy the Mayo Foundation, Rochester, Minnesota.*

description of conventional treatment techniques is provided for historical purposes.

Conventional Irradiation

Treatment Fields

Traditional two-dimensional radiation fields are arranged to cover the possible pathways of spread that account for the previously noted clinical manifestations (Figure 34-3, *A* to *D*). Intergroup study 0099[1] (see Table 34-3) provides a structure for general irradiation guidelines with opposed lateral fields. The borders of this field arrangement are described herein but can be modified on the basis of individual tumor characteristics as discussed in the subsequent section:

1. *Superiorly:* The field margin should be at least 2 cm beyond tumor that is visible on the head CT scan and should include the base of the skull and sphenoid sinus.
2. *Posteriorly:* The field should allow 2 cm of margin beyond the mastoid process. The posterior margin may extend further to allow at least a 1.5-cm margin on enlarged nodes.
3. *Anteriorly:* The field should include the posterior third of the maxillary sinus, posterior ethmoid air cells, and nasal cavity. This anterior border can be modified to accommodate adequate margins (2 cm) for tumors with anterior extension while excluding as much of the oral cavity as possible.
4. *Inferiorly:* The lower field margin is at the thyroid notch (superior to the arytenoids) to allow sparing of the larynx by a central block on the anterior lower neck field, which is matched to these lateral fields.

The lower neck is generally treated with an anterior field with a tapered central larynx block that extends inferiorly to the cricoid. This lower neck field is matched to the lower edge of the lateral fields and, therefore, the larynx block also prevents the spinal cord from receiving an excessive dose. The lower neck field should extend inferiorly to the level of the lower border of the clavicle at the sternoclavicular joint. It is convenient at the level of the match between the upper lateral fields and the lower anteroposterior (AP) v field, to avoid divergence. We often prefer treating the primary site with and high neck with IMRT, and if the low neck is uninvolved with disease, treating it with an AP field.

Field Modifications and Boost Techniques

In addition to the opposed lateral field arrangement described, several other techniques have been used to optimize target dose delivery. For example, patients may initially be treated with opposed lateral fields to the primary site and upper neck, and then continue with a boost reduced off the brainstem and spinal cord to the primary site with either oblique fields, a single central field, or a three-field technique. The use of oblique and smaller opposed lateral fields is generally accepted and has been shown to have acceptable tolerance[40] (see Figure 34-3). Interestingly, the use of three-dimensional conformal techniques to optimize the final or boost portion of treatment has not been shown to lead to a decrease in complications.[165,166]

Brachytherapy

Brachytherapy can be used to deliver a boost to T1 to T2 lesions after EBRT or alone in the setting of reirradiation. Intracavitary and interstitial[167-169] techniques have been used. Multiple applicators have been developed for intracavitary insertions. The Rotterdam Nasopharynx Applicator, developed in The Netherlands, is most commonly used today in conjunction with a remote-controlled high-dose-rate afterloading device[170] (Figure 34-4, *A* and *B*). The device, made out of pliable silicone and shaped to conform to the nasopharynx, is guided into position through the oral cavity. After it is immobilized and dummy sources are inserted, orthogonal radiographs are obtained to define the anatomy for treatment planning (see Figure 34-4, *C* and *D*). Dose is prescribed to a fixed anatomic point. In cases in which brachytherapy is used as a boost for EBRT, 5 Gy to 6 Gy in two fractions 5 to 6 hours apart is generally given. Given the excellent results with IMRT in treatment of NPC, however, many institutions employ brachytherapy almost exclusively for reirradiation.[144,147,171-177]

Permanent interstitial implantation of either iodine-125 (^{125}I) seeds or gold-198 (^{198}Au) grains should be considered for localized lesions and can be accomplished through several approaches, depending on the location of disease.[167,168,178] For lesions in the low- to midposterior wall, transoral or transnasal approaches have been used, whereas a transpalatal approach is favored for lesions in the high posterior wall.[167,168] Alternatively, a split-palate approach can be used.[178]

Intensity-Modulated Radiation Therapy

In the 1970s and 1980s it was becoming clear that advancing technology would make it possible to optimize radiotherapy by deriving the set of optimal incident stationary and moving beams to form a desired dose distribution.[179,180] These techniques deliver a set of beamlets of varying weights, with the

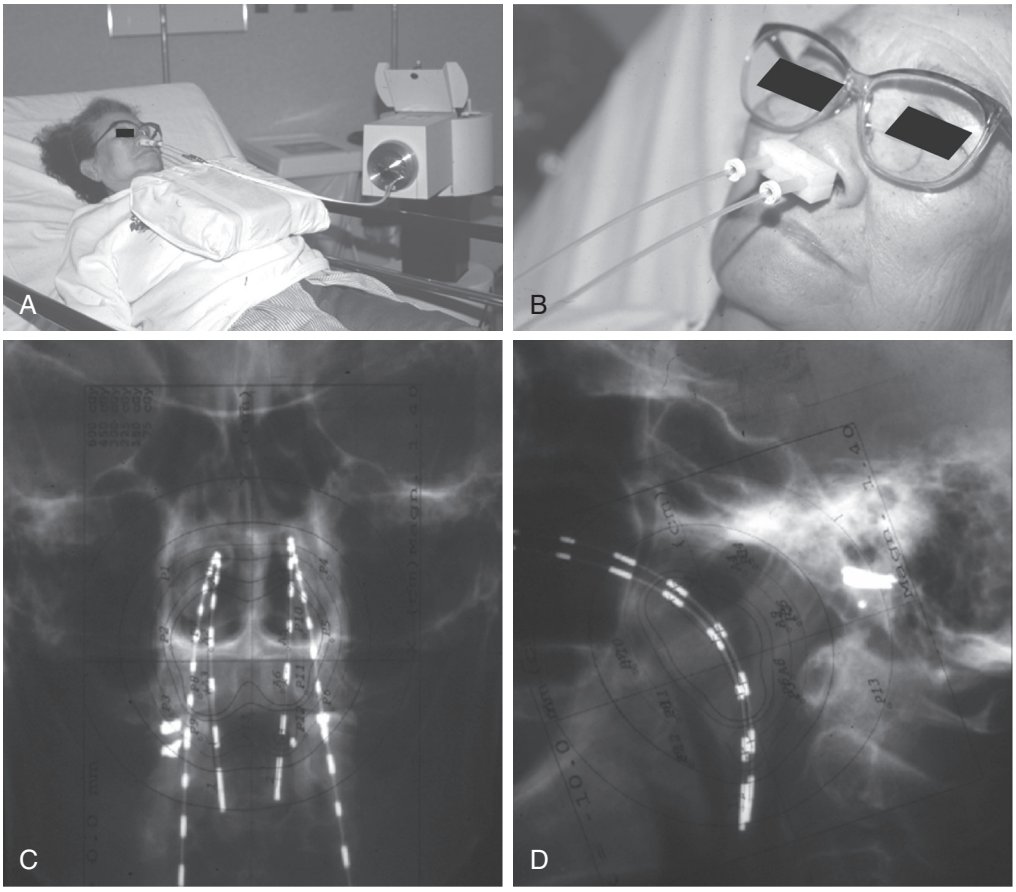


Figure 34-4 Use of brachytherapy to treat the nasopharynx. **A** and **B,** A patient with the Rotterdam Nasopharynx Applicator (RNA) in place. **A,** The afterloading catheters are connected to a remote-controlled high-dose-rate afterloading device (microSelectron HDR, Nucletron-Oldeft Nucletron). **B,** Close-up Close-up view of the RNA secured with a plastic clamp placed over the external portion of the applicator just outside the nose. Lateral **(C)** and anterior-posterior **(D)** localization radiographs with the dummy sources inserted.
***A** to **D,** Reprinted from Lee N, Fu KK: Cancer of the nasopharynx. In Leibel SA, Phillips TL, editors: Leibel and Phillips textbook of radiation oncology, ed 2, Philadelphia, 2004, Elsevier. Figures 27-16, A and B and 27-17, A and B.*

weights chosen to optimally conform the resulting distribution of dose to a target.[181,182] More generally, the optimization can be performed to optimize the biologic or physical objective functions, based on minimizing complications and maximizing tumor control probabilities.[183] The technique of optimizing beam delivery with inverse planning has become known as intensity-modulated radiation therapy (IMRT) for historical reasons, although typically the beam intensity is not modulated.

Target movement places a potential limitation on the applicability of IMRT. Movement during beam delivery could lead to the unintentional overlap of beamlets or possibly to untreated portions of the target volume. For this reason, IMRT is currently used in situations in which motion is minimal or can be controlled for with gating techniques. The head and neck is an area where target motion can be controlled reasonably well with immobilization devices, and for this reason much of the early work on IMRT centered on head and neck cancer. IMRT is particularly applicable to the nasopharynx, in that several critical structures are in close proximity to the target and the incidence of morbidity with conventional radiotherapy techniques is high. Helical tomotherapy, an image-guided IMRT system that was developed from the ideas of CT inventor Andrew Cormack, has shown particular promise with NPC.[184] In the future, intensity modulated proton therapy (IMPT) is likely to surpass x-ray–based technologies as a result of the geometrical advantages of charged particles.[185]

Several institutions have shown a potential dosimetric improvement for IMRT over conventional techniques and three-dimensional conformal techniques in the setting of NPC.[166,186-189] As discussed previously, several single-institution series as well as a Phase II RTOG trial have shown the efficacy of IMRT in the treatment of NPC.[131]

Simulation and Treatment Planning

CT simulation is necessary for IMRT treatment planning. The patient's head, neck, and shoulders are immobilized with a thermoplastic mask with a standard head rest. The head should be hyperextended to allow for maximal separation between the primary nasopharyngeal tumor and lymphatics.[127] At present, MSKCC is exploring the use of an open face mask, to improve tolerability of treatment for patients. A limited CT scan or orthogonal radiographs are obtained to allow for isocenter localization, after which planning CT images are acquired, with contiguous slices of 3 mm or less in the region of the tumor and of 5 mm elsewhere. Some treatment planning systems require equal spacing of slices throughout the entire scan. Alternatively, the CT images can be obtained first and then a treatment isocenter placed within the treatment volume.

IMRT treatment planning requires precise spatial information on the full extent of gross disease and thorough knowledge of the potential sanctuaries of microscopic disease along the lymphatic routes of tumor spread because the therapeutic

TABLE 34-6 IMRT Target Delineation for NPC

PRIMARY TUMOR AND UPPER NECK	
CTV_{70} or gross disease Dose: 2.12 Gy/Fr to 69.96 Gy	GTV Primary tumor All (+) lymph nodes + 5-mm to 10-mm margin (1 mm is acceptable near the brainstem or spinal cord, optic nerve, and chiasm)
$CTV_{59.4}$ or subclinical disease Dose: 1.8 Gy/Fr to 59.4 Gy Can consider 54 Gy in N0 disease	GTV and entire nasopharynx Clivus Base of skull Pterygoid fossae Parapharyngeal space Sphenoid sinus Posterior ⅓ to ½ of nasal cavity Posterior ⅓ of maxillary sinuses Posterior ethmoid sinuses Bilateral cervical lymph nodes: Level Ib-IV for N+ disease Omit level Ib for N0 disease Retropharyngeal lymph nodes

Based on MSKCC guidelines. Expansion is 3 mm to 5 mm for planning tumor volume, except near brainstem or spinal cord, where 1 mm is acceptable.
CTV, *Clinical target volume;* Fr, *fraction(s);* GTV, *gross tumor volume;* Gy, *Gray.*

dose will only be delivered to the designated areas. Therefore, MRI, CT, or PET imaging is instrumental in supplementing the information from clinical examination when delineating the tumor volume. It is recommended that fusion of diagnostic MRI or PET scans to the planning CT is performed to accurately define the gross tumor volume (GTV) and surrounding critical structures. Several clinical target volumes (CTVs) are delineated, $CTV_{gross\ disease}$ and $CTV_{subclinical\ disease}$, which will receive different doses per fraction and total doses (Table 34-6). This practice is known as simultaneous integrated boost or dose painting. In addition, in the absence of low neck lymphadenopathy, a third dose schedule may be administered to the low neck, either with separate AP fields matched to the IMRT plan (split-field technique) or with extension of the IMRT plan (extended whole-field technique). If the extended whole-field technique is used, then a third $CTV_{low\text{-}risk\ subclinical\ disease}$ may be outlined. However, in the presence of any pathologic low neck lymph node, the uninvolved low neck lymph nodes are incorporated into the $CTV_{subclinical\ disease}$.

The primary tumor in the nasopharynx and any cervical or retropharyngeal lymph nodes larger than 1 cm or with evidence of necrosis on imaging are considered $GTV_{gross\ disease}$. $CTV_{gross\ disease}$ is composed of $GTV_{gross\ disease}$ with a 5-mm to 10-mm margin to account for possible microscopic disease (see Table 34-6). A notable exception is near the brainstem or spinal cord, where normal tissue tolerances necessitate that the margin be reduced, sometimes to as little as 1 mm. The $CTV_{subclinical\ disease}$ includes all areas at risk for microscopic spread, including the entire nasopharynx, clivus, base of skull, pterygoid fossae, parapharyngeal space, sphenoid sinus, posterior one third to one half of the nasal cavity, posterior ethmoid sinuses, posterior one third of the maxillary sinuses, and the following lymph node regions: bilateral upper deep jugular (junctional, parapharyngeal), level Ib, level II, level III, level Va, and retropharyngeal nodes. In a patient with no clinically or radiographically detectable cervical lymph node involvement, no coverage of the submandibular region (level Ib) is required. The delineation of cervical lymph node stations on the planning CT scans is based on the published image-based consensus guidelines.[190-193] The PTV is generally a 3-mm to 5-mm expansion of all the CTVs to account for potential setup errors and patient motion. Once again, limiting the margin to 1 mm around the CTV is allowed near the brainstem and spinal cord.

When the split-field technique is used to cover the low-neck lymph node regions (levels IV and Vb), the match is typically placed just above the arytenoids, so that a tapered midline block in the anterior field can be used to shield the larynx.

Dose-limiting critical normal structures that should be outlined on the planning CT include the brainstem, spinal cord, optic nerves and chiasm, parotid glands, pituitary, middle and inner ears, oral cavity, submandibular glands, thyroid gland, brachial plexus, retinas, lenses, cochlea, and larynx.

Treatment Planning and Delivery

Several commercial treatment planning systems are available.[194-197] Inverse planning is generally used to generate a treatment plan. However, in the absence of sufficient experience with inverse planning, forward planning can be used with comparable clinical outcomes.[198] At the MSKCC, IMRT is delivered with the dynamic multileaf collimator system using a sliding-window approach and megavoltage 6-MV or greater x-rays are used. Megavoltage beams with energy above 6 MV should not be used for cervical lymph node irradiation.

Figure 34-5, *B* to *D*, provides an example of an IMRT plan for a patient with NPC treated in the RTOG 0225 trial. Seven coplanar nonopposed fields were used with a 0.5-cm multileaf collimator using the sliding-window technique, optimized with a gradient inverse planning engine. For comparison, a conventional plan for the same patient is also illustrated (see Figure 34-5, *A* to *C*). The conventional ports used for the comparison are shown in Figure 34-6. Considerable sparing of normal tissues, in particular the parotid glands, is achieved with IMRT, and there is better coverage of the base of the skull than can be achieved with lateral fields. Figure 34-7 shows the dose-volume histograms for this case, again comparing conventional technique with IMRT.

Figure 34-8 illustrates the dosimetric coverage that can be obtained with modern IMRT techniques in a sample reirradiation case. This is a situation in which the critical need to spare normal structures makes IMRT essential. Volumetric modulated arc therapy (VMAT)-based radiotherapy techniques may further improve conformality of treatment while simultaneously reducing treatment time, and thus perhaps limiting patient movement during treatment.

Radiotherapy Dose

Based on the early experience with IMRT (see Table 34-4) and the consensus opinion used in and subsequently validated by the RTOG 0225, the prescribed dose to the $PTV_{gross\ disease}$ is 69.96 Gy in 2.12-Gy fractions, the dose to the $PTV_{subclinical\ disease}$ is 59.4 Gy in 1.8-Gy fractions, and the dose to the $PTV_{low\text{-}risk\ subclinical\ disease}$ (if the extended whole-field technique is used) is 54.12 Gy in 1.64-Gy fractions. If the split-field technique is used, the AP fields receive 50.4 Gy in 1.8-Gy fractions or 50 Gy in 25 fractions to a depth of 3 cm in an average sized patient.

See Box 34-1 for normal tissue dose constraints currently used at the MSKCC. The aim of the treatment plan design and optimization process is to deliver the prescribed dose to the target while limiting the dose to normal structures. Strict adherence to the dose constraints for the brainstem, optic structures, and spinal cord is recommended. Limiting the dose to other critical normal structures listed previously is encouraged but should not compromise target coverage. In cases where all treatment planning goals cannot be met, clinical judgment must be used to determine the best compromise. In

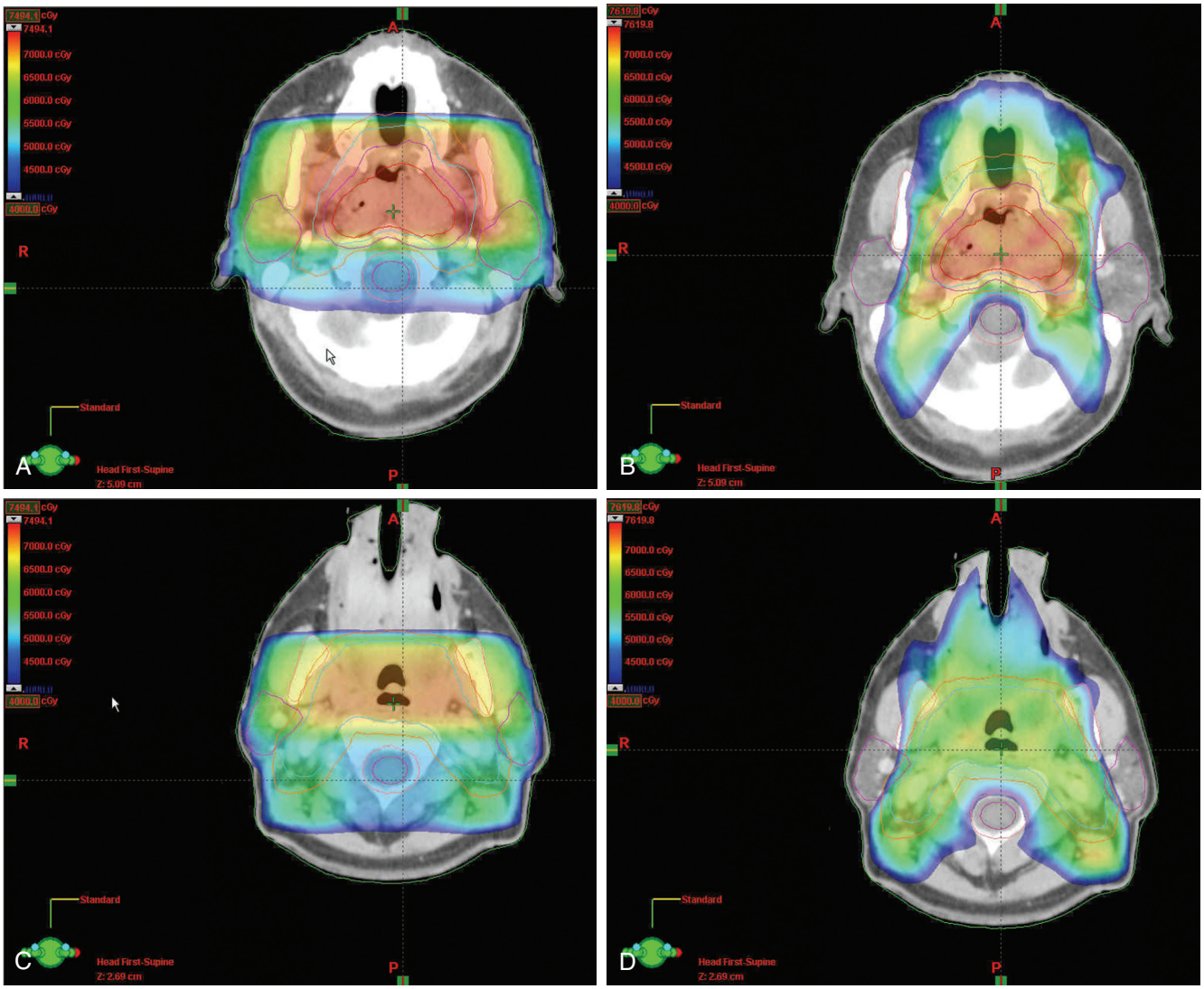


Figure 34-5 Dose colorwash comparison of coverage on a representative patient with stage T2bN0M0 NPC treated in the RTOG 0225 intensity-modulated radiotherapy (IMRT) trial. (For comparison, Figure 34-6 illustrates the conventional lateral ports used.) Computed tomography cuts are shown at the level of the pterygoid plates for conventional technique **(A)** and IMRT **(B)**. The level of the uvula is also shown for conventional radiotherapy **(C)** and IMRT **(D)**. The conventional plan is a composite of comprehensive head and neck fields with a boost to the primary lesion. Sparing of the parotid glands is the primary benefit of IMRT in this case. For the IMRT plan, seven coplanar nonopposed fields were used with a 0.5-cm multileaf collimator using the sliding-window technique, optimized with a gradient inverse planning algorithm.

addition to the listed constraints, no more than 5% of the nontarget tissue can receive more than 70 Gy. The dose constraints for noncritical normal structures listed are only suggestions and should be given the lowest priority in the treatment planning process.

Normal Tissue Tolerance and Complications

Because of the anatomic location and requirement for large treatment fields and high doses, conventional treatment of NPC was associated with complication rates of 31% to 66%[40,93,199] (see Table 34-1). Severe late complications included xerostomia, neck fibrosis, trismus, thyroid and hypothalamic-pituitary dysfunction, soft-tissue and bone necrosis, hearing loss, cranial nerve dysfunction, and transverse radiation myelitis.

The incidence and types of complications of irradiation for NPC at the MDACC between 1954 and 1992 are listed in Table 34-7. The actuarial frequency of grades-3 to -5 complications was 16%, 19%, and 29% at 5, 10, and 20 years, respectively.[32] However, the actuarial frequency of grades- 3 to -5 complications at 10 years decreased steadily over three consecutive time periods included in the study: 1954 to 1971, 14%; 1972 to 1982, 10%; and 1983 to 1992, 5%, respectively. Of nine severe spinal cord injuries, eight occurred in the early time period (1954 to 1971). On univariate analysis, the frequency of moderate-to-severe complications was dependent on treatment technique. The actuarial incidence of moderate-to-severe complications at 10 years was 58% for the single central field technique compared with 12% and 25% for the oblique fields and opposed lateral fields techniques, respectively ($p < 0.001$). It should be noted that patients treated with oblique and opposed lateral fields were treated in more recent periods, and the decreased frequency of complications may also be related to the use of custom blocking and CT treatment planning.

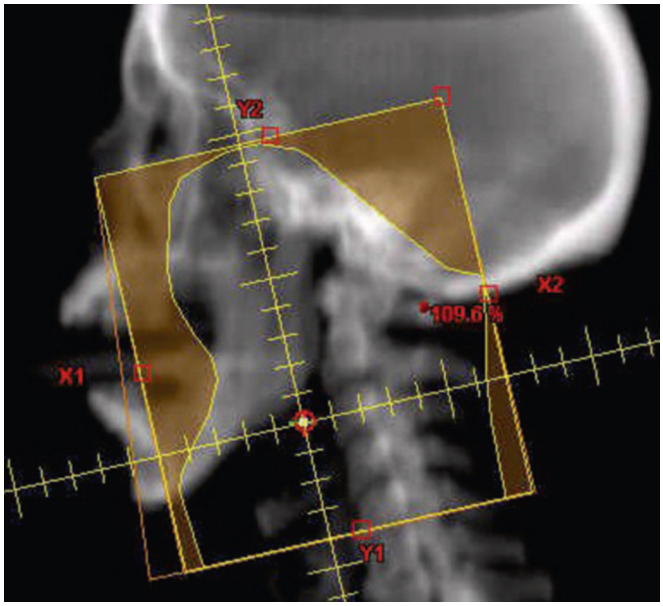


Figure 34-6 Digitally reconstructed radiograph of the conventional ports used in the comparison of intensity-modulated radiotherapy (IMRT) with conventional therapy illustrated (see Figures 34-5 and 34-7). The posterior neck was blocked and treated with electrons at 40 Gy, and the boost treated the primary tumor with margins using 15-MV photons.

TABLE 34-7 Serious Complications of Radiotherapy Alone for NPC in 378 Patients[31,32,40,43]

Complication	RTOG Grade 3	4	5	Total
Connective tissues				
Skin/mucosal ulcers	—	3	1	4
Fibrosis	13	3	—	16
Trismus	11	—	—	11
Bone	3	7	—	10
Larynx	1	1	—	2
Endocrine glands				
Pituitary gland	9	13	—	22
Thyroid gland	3	7	—	10
Nervous system				
Brain	2	2	—	4
Cranial nerve	3	8	6	17
Spinal cord	2	2	5	9
Hearing loss	10	—	—	10
Total	57	46	12	115

RTOG, *Radiation Therapy Oncology Group.*

The use of conformal techniques for the final boost portion of radiotherapy could potentially decrease the risk of complications, but this has not been shown to be the case. Conformal techniques are associated with a 25% incidence of grades-3 to -4 morbidity, including hearing loss, trismus, dysphagia, chronic sinusitis, and cranial neuropathy.[165] This result has led to an interest in delivering the full course of therapy with IMRT.[127,165,166,200]

Xerostomia is the most common toxicity associated with conventional therapy and may lead to dental caries. Strict dental hygiene and prophylactic fluoride treatment should be instituted to guard against dental decay. The use of IMRT allows for improved preservation and faster recovery of parotid gland function.[127,129,130,134]

BOX 34-1 Normal Organ/Tissue Dose Constraints, MSKCC

Critical organ/tissue; dose constraint at MSKCC	
Brainstem	D_{max} = 54 Gy or 60 Gy to 1% of the volume
Optic nerves	D_{max} = 54 Gy or 60 Gy to 1% of the volume
Optic chiasm	D_{max} = 54 Gy or 60 Gy to 1% of the volume
Spinal cord	D_{max} = 45 Gy or 50 Gy to 1% of the volume
Temporal lobes	D_{max} = 60 Gy or 65 Gy to 1% of the volume
Mandible and TM joint	D_{max} = 70 Gy or 75 Gy to 1 cc of the volume
Noncritical	
Parotid glands	D_{mean} = 26 Gy (in at least one gland)
Submandibular glands	As low as possible
Oral cavity	D_{mean} = 40 Gy
Larynx	D_{mean} = 40 to 45 Gy or D_{max} = 70 Gy or = 105% of prescription
Cochlea	D_{max} = 50 Gy
Retinas (globes)	D_{max} = 45 Gy
Lenses	D_{max} = 5 Gy
Brachial plexus	D_{max} = 65 Gy and D05 D_{max} = 70 Gy

MSKCC, *Memorial Sloan Kettering Cancer Center.*

Functional hearing loss was reported in up to 8% of patients treated with conventional technique, and at least 30% of those evaluated with audiograms showed a high-frequency sensorineural hearing loss.[199,201,202] This radiation sequel may also be negatively affected by concurrent treatment with ototoxic chemotherapy. Dose-dependent cochlear damage is the likely mechanism of radiation-induced ototoxicity and can be minimized by keeping the mean dose to the cochlea below 48 Gy to 50 Gy.[201,202] Lowering the dose to the external auditory canal also reduces the incidence and severity of acute external otitis. Excluding the mastoid air cells reduces the incidence and severity of chronic serous otitis media. Unfortunately, given the location of the primary tumor in the nasopharynx, chronic eustachian tube dysfunction is unavoidable.

When treating lesions with base-of-skull involvement, it is important to consider the potential for optic neuropathy. A University of Florida review of 106 patients receiving treatment encompassing the optic nerves reported that patients who received more than 60 Gy and daily fractions of more than 1.9 Gy had a 47% incidence of optic nerve injury, compared with 11% for patients treated with daily fractions of less than 1.9 Gy.[203]

Clinically significant endocrine dysfunction has been described in 5% to 10% of patients.[40,199] Given the availability of pharmacologic treatment, one should have a low threshold for evaluating long-term survivors for the presence of hypothalamic-pituitary or thyroid endocrinopathies. Routine evaluation of survivors with serum sodium, cortisol, thyroid-stimulating hormone (TSH), follicle-stimulating hormone, luteinizing hormone, and testosterone levels may be considered.

TREATMENT ALGORITHM, CONCLUSIONS, AND FUTURE POSSIBILITIES

A preferred treatment algorithm for patients with NPC is illustrated in Figure 34-9. With early-stage disease, irradiation

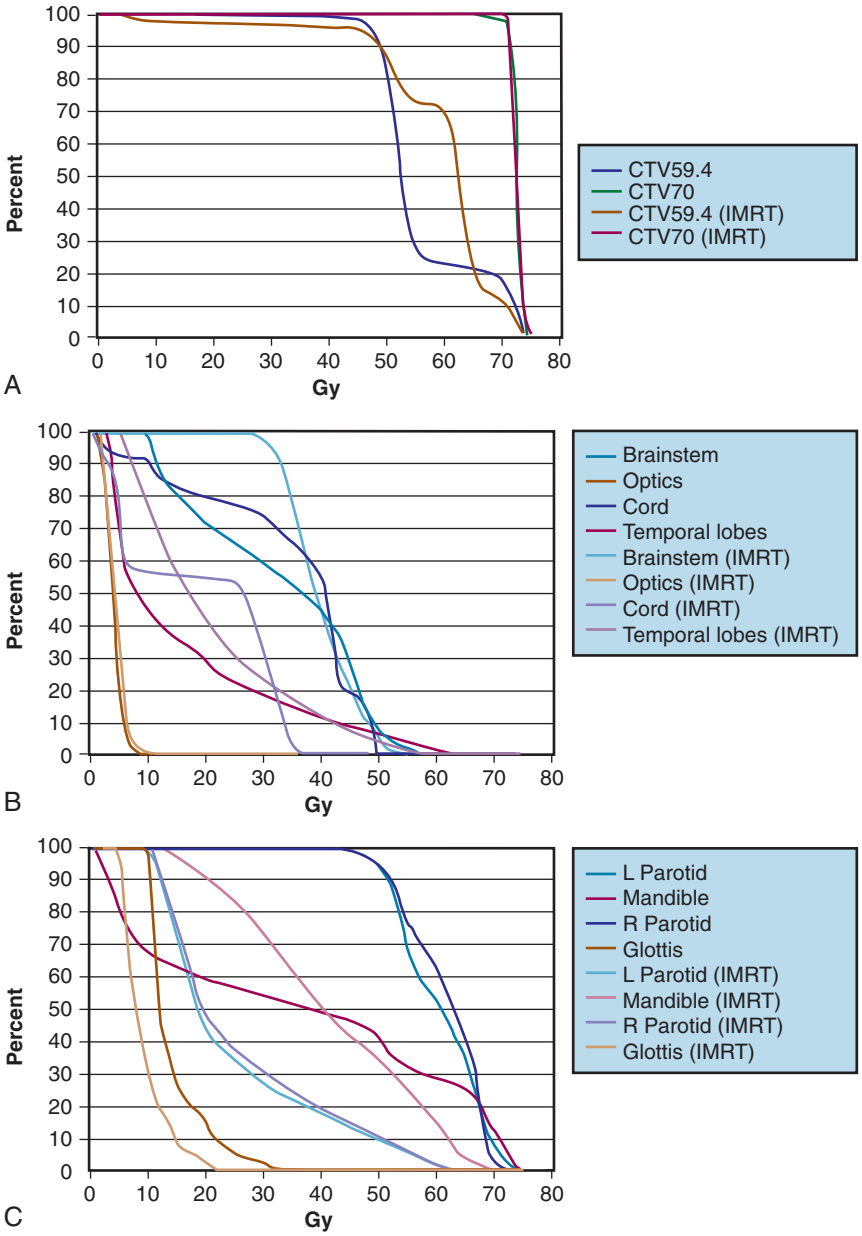


Figure 34-7 Dose-volume histograms (DVHs) for the patient in Figures 34-5 and 34-6, comparing intensity-modulated radiotherapy (IMRT) with conventional technique. Substantial gains can be made with IMRT in terms of target coverage and normal tissue sparing. **A,** Target coverage. Differences in the $CTV_{59.4}$ (clinical target volume to be covered by 59.4 Gy) target coverage reflect the relatively high dose given to subclinical risk areas per RTOG 0225, with much of this target volume being intentionally prescribed a dose of 50.4 Gy in the conventional plan. Also, a conventional anterior low-neck field was used in the IMRT plan, with a midline block over the spinal cord and larynx in that region, which blocked a portion of the $CTV_{59.4}$, a portion that was not included in the optimization but was included in the DVH. The DVHs for central nervous system (CNS) structures **(B)** and other normal structures **(C)** are also shown. Greater relative sparing of CNS structures by IMRT would be seen for higher-stage patients.

alone with once-daily fractionation generally yields excellent local control results. For locally advanced disease (nonmetastatic stage ≥T2 or ≥N1 in the current AJCC staging system), concomitant chemotherapy and radiotherapy results are encouraging, and entry of patients into further trials testing combined-modality treatment is indicated. Advancements in radiotherapy optimization and integration of functional imaging with radiotherapy planning both show promise for improvements in tumor control and decreased morbidity of treatment.

Because the rate of distant metastasis remains high in NPC, we continue to recommend adjuvant chemotherapy for most patients. Identifying which patients may benefit from adjuvant chemotherapy with the use of posttreatment circulating EBV DNA remains an area of active investigation. In the future, this may allow better selection of patients who require adjuvant chemotherapy and those that can be spared additional treatment. In addition the optimal combination of chemotherapeutics to serve as adjuvant therapy also remains to be determined.

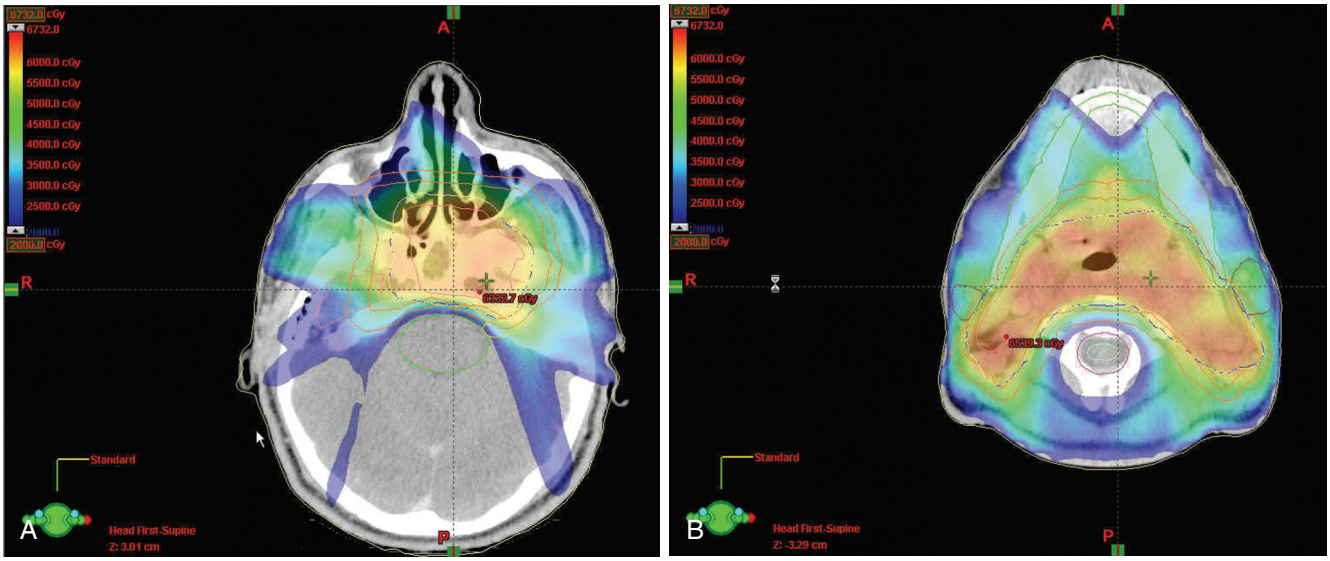


Figure 34-8 Dose colorwash illustrating radiotherapy coverage near the base of the skull for a case of recurrent NPC, in which intensity-modulated radiotherapy (IMRT) was used to minimize reirradiation risk to normal structures. Colorwash ranges between 20 Gy and maximum dose. **A,** The tolerance of the brainstem and temporal lobes places constraints on the dosimetry of the base of the skull. **B,** The mandible and spinal cord tolerance constraints the neck coverage. The IMRT technique used was similar to that in another case (see Figures 34-5 and 34-6) but with nine coplanar nonopposed fields.

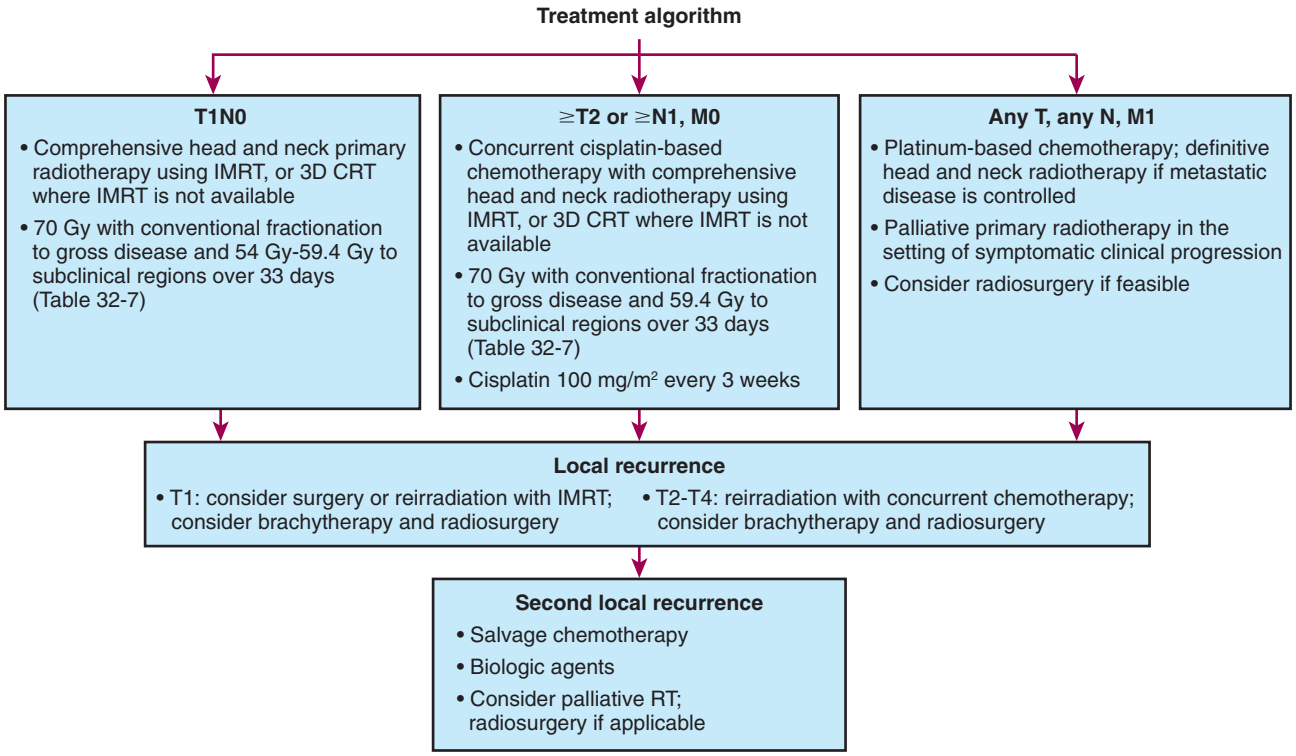


Figure 34-9 Treatment algorithm for NPC based on the AJCC, 7th edition staging system. Some patients with disease classified as stage II would have had stage III or IV disease when many of the chemoradiation trials were performed and are therefore included as having locally advanced disease. Intensity-modulated radiotherapy (IMRT) is generally recommended if available. In the case of local failure, reirradiation is a consideration if the time to recurrence exceeds 6 months. In elderly patients or in patients with multiple medical problems or poor performance status, concurrent chemotherapy should be used with caution. Such patients are not well represented in clinical trials, and meta-analysis of chemoradiation trials suggests less clinical benefit from chemotherapy. *5-FU,* 5-Fluorouracil; *MRI,* magnetic resonance imaging; *PET,* positron emission tomography; *WHO,* World Health Organization.

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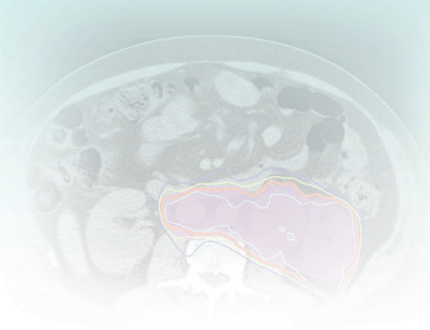
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CHAPTER

35 Larynx and Hypopharynx Cancer



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INCIDENCE

Larynx and hypopharynx cancers account for about one third of all head and neck neoplasms, affecting about 15,000 Americans per year.

BIOLOGIC CHARACTERISTICS

Prognosis for all tumors is primarily dependent on extent of disease, although it is also influenced by the anatomic site of origin.

Glottic tumors have the lowest incidence of metastases because they more commonly present with earlier-stage lesions and the true cords do not have a rich lymphatic supply compared with supraglottic and hypopharyngeal neoplasms. Hypopharyngeal cancers have a relatively high metastatic rate among head and neck cancers.

STAGING EVALUATION

Staging includes history, complete head and neck examination including indirect and direct laryngoscopy, contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI) of the head and neck region, blood chemistry, and chest radiography.

PRIMARY THERAPY

Early-stage disease can be treated with a single modality, either surgery or radiation therapy (RT). Reported cure rates range from 65% to 95% and depend primarily on the bulk of disease.

ADJUVANT THERAPY

High cure rates have not justified adjuvant therapies for early-stage disease.

Chemoprevention remains an area of active research for this group at high risk for second primary tumors.

LOCALLY ADVANCED DISEASE

The concept of larynx preservation has been validated as an option for patients with T3 disease.

Concurrent chemoradiation has been demonstrated to improve the larynx preservation rate compared with irradiation alone or treatment with neoadjuvant chemotherapy; the latter does not compromise survival compared with laryngectomy. Approximate 5-year survival rates for these patients are 50% to 55%.

For elderly patients in whom the toxicity of chemotherapy is a concern, irradiation alone is a valid alternative for patients desiring larynx preservation. Altered fractionation may be employed in these cases to improve locoregional control.

Surgery remains the mainstay for advanced, but resectable disease (category T4a), with adjuvant postoperative RT used for patients at high risk for local regional failure.

Concurrent chemoradiation is advocated for patients with inadequate margins or extranodal or soft-tissue disease extension. Local control rates for this group range from 60% to 90%, but 5-year survival rates are between 20% and 40%.

PALLIATION

Palliative therapies are dependent on prior therapies received and disease location and extent. RT, chemotherapy, and surgery are all used but are individualized.

Management of cancers of the larynx is a special challenge for head and neck oncologists. Laryngeal cancer, even in locally advanced stages, has a relatively high cure rate if managed appropriately. Because of this factor, it has become the paradigm for the concept of organ preservation in oncologic patient management. Curing the patient is not the only consideration in the management of this disease. Voice preservation and avoidance of tracheal stoma are important priorities.

In previous decades, surgery, RT, or a combination of the two therapies were used and individualized to best meet these endpoints. Both modalities have improved in eradicating the disease and preserving function over the years. Newer, more technically sophisticated voice-conserving surgical procedures have been developed. Similarly, radiation oncologists have grown in their understanding of the influences of dose, treatment duration, and target volumes to improve the results in managing these diseases. Important improvements in defining disease extent, by both physical examination with fiberoptic laryngoscopy and radiologic images obtained with CT MRI, have allowed for better selection of the appropriate therapy for an individual patient. Systemic therapies have been incorporated into the management of these diseases, thus increasing the options in trying to cure patients with this disease while maintaining function.

Carcinomas of the hypopharynx are often considered together with carcinomas of the larynx, because the anatomy of the hypopharynx is essentially created by the location of the voice box in the throat. Hypopharyngeal tumors frequently involve the larynx and vice versa. In these situations, it is one's best guess whether the epicenter of a large tumor is laryngeal or hypopharyngeal. It is therefore not unexpected that the concept of voice preservation also applies to the management of cancers of the hypopharynx. The pharynx is also involved in deglutition, and issues of preservation of swallowing are also important in the management of these tumors.

Although affecting the area immediately adjacent to the larynx and thus having similar management concerns to laryngeal carcinoma, hypopharyngeal cancers typically have different natural histories compared with cancers arising in the larynx. At diagnosis, hypopharyngeal tumors have much

higher rates of spread beyond the primary tumor; thus, even with successful local treatment, survival rates tend to be worse than other cancers of the head and neck.

Primary tumors of the hypopharynx also tend to present in locally advanced stages. However, local therapies have improved in recent years. Surgical grafting techniques have been developed to replace the resected pharyngeal tissues and allow the patient a better swallowing mechanism. Without these techniques, larger hypopharyngeal lesions would be unresectable. Improved control with altered RT schedules may allow preservation of the larynx and pharynx for intermediate-stage lesions. Adding systemic agents may also allow for organ preservation and help with the problem of distant disease prevalent in cancers of this site.

EPIDEMIOLOGY AND ETIOLOGY

Laryngeal cancer occurs in roughly 12,000 Americans per year, accounting for approximately one fourth to one third of all head and neck cancer cases. However, mortality resulting from cancers of the larynx is relatively low, accounting for approximately 4200 deaths per year in the United States.

The median age of patients presenting with larynx cancer is 65 years. Less than 4% of patients are younger than 45 years old. Laryngeal cancer remains predominantly a disease affecting men. The most recent data from the Surveillance, Epidemiology, and End Results (SEER) program (2003-2007)[1] estimated an overall incidence of 3.4 cases per 100,000 people per year, a slight decrease of 0.4 cases per 100,000 compared with the previous 5 years of data.[2] Comparisons reveal case incidences of 6.1 versus 1.3 in males and females, respectively. There is a higher incidence among blacks than among whites for both men and women.

Tobacco use is strongly associated with the development of cancer of the larynx, with the highest risk among active heavy smokers and an intermediate risk among ex-smokers.[3,4] More than 95% of patients with laryngeal cancer have a history of tobacco use.[5] Cigar and pipe smoking have also been associated with cancer of the larynx,[4] but studies on this issue have been more controversial.[3,6,7] In the years between 1965 and 2004, rates of cigarette smoking by adults in the United States were halved (42% to 21%); from 2005 to 2010, there was a less dramatic decrease in the rates of smoking (20.9% to 19.3%).[8] Given the correlation between smoking and the development of larynx cancer, these reductions would be expected to translate into a lower incidence of larynx cancer. Indeed, there have been statistically significant reductions in the age-adjusted incidence rates for glottic and supraglottic cancers, as measured from 1973 to 2003.[9]

Alcohol use is also associated with laryngeal cancer but is believed to act synergistically with tobacco rather than independently. It is unusual to see laryngeal cancer in nonsmoking patients with alcohol abuse histories.[7] A history of heavy alcohol use is more strongly associated with supraglottic and hypopharyngeal cancers.[4,10] Likewise, occupational exposures to asbestos,[4,11,12] mustard gas, nickel, soot, and tars have been linked to laryngeal cancer, but generally a tobacco use history is also present.[13] Several authors have evaluated the influence of diet on the development of larynx cancer and have found, while controlling for tobacco and alcohol use, a higher incidence among patients with vitamin- and nutrient-deficient diets.[6,14,15]

Attention has been directed at the influence of gastroesophageal reflux disease (GERD) on laryngeal diseases, including carcinomas. Three separate studies[16-18] have described cohorts of nonsmoking patients with GERD and larynx cancer. Bacciu et al[19] compared 36 consecutive patients with no history of tobacco and alcohol consumption who developed laryngeal carcinoma to a group of 125 lifetime nonsmokers who were cancer free. They found a much higher prevalence of GERD among the patients with laryngeal cancer. It is believed that chronic irritation on the larynx from acid may predispose these patients to cancer. It is thought that if this cancer is seen in nonsmokers, the influence of GERD on the development of laryngeal cancer in smokers and alcohol users (who are at higher risk for GERD) may be significant.

Human papillomavirus (HPV) has been causally linked to multiple cancers, including head and neck cancers,[20,21] particularly cancers of the tonsil. HPV has also been demonstrated to be associated with laryngeal cancers, although studies are, in general, retrospective, and the reported prevalence rates vary widely. The evidence for HPV having a role in laryngeal cancer is less obvious than in other malignancies, and its interaction with other carcinogens such as tobacco is unclear. As in cervical cancer in women and tonsillar cancer, HPV-16 is the most common type noted.

Hypopharyngeal cancers are less common than laryngeal tumors. The estimated incidence in the United States is 2500 cases per year. Etiologic risk factors are similar to those for laryngeal tumors,[14] with a predominance among men and older individuals. This type of cancer is closely linked to tobacco and alcohol use, and the ties to heavy alcohol use seem stronger than those for laryngeal cancer.

PREVENTION AND EARLY DETECTION

Prevention

The primary preventive methods taken to eliminate malignancies of the upper aerodigestive tract have come from public awareness that tobacco and alcohol are the major causative agents of these cancers. National public health measures have been directed at diminishing the prevalence of smoking and drinking. A by-product of these policies may be a decline in the incidence of laryngeal and hypopharyngeal carcinomas. The most recent SEER data have identified a decrease in the incidence of larynx cancer over the past two decades (1988-2007).[1] The annual percentage decrease over this time period is 2.6%.

Although government policies have been directed at diminishing carcinogenic etiologic agents for the general population, investigators have tried to identify high-risk groups in whom more direct measures can be taken. The major group identified consists of patients who have been cured of a cancer of the upper aerodigestive tract,[22-25] particularly patients who have smoking or alcohol use histories.[26] The incidence of second primary cancers of the upper aerodigestive tract ranges from 10% to 30%. The locations of these second cancers are evenly divided between the lungs, esophagus, and head and neck mucosal sites, including the larynx and hypopharynx.[26]

The high incidence of new cancers in this patient population has led investigators to develop programs designed to diminish the occurrence of second primary tumors. Hong et al[27] studied 13-*cis*-retinoic acid as a possible agent to prevent new cancers in patients with a history of head and neck malignancy. A randomized trial showed a 14% versus 31% incidence of second primary tumors in patients who received a relatively high dose of 13-*cis*-retinoic acid versus placebo.[28] In 2002, the Radiation Therapy Oncology Group (RTOG) completed accrual to a trial testing chemoprevention with 13-*cis*-retinoic acid in a multiinstitutional setting.[29] Nearly 1400 patients with stage I or II cancer were accrued. The dose of 13-*cis*-retinoic acid was lower than that used by Hong et al to ensure more compliance and less side effects. Unfortunately, the RTOG trial was negative and did not show any benefit to low-dose isotretinoin in the prevention of second primary cancers. The RTOG study did show that the continuation of smoking had adverse

effects on outcome and those who smoked were more likely to develop second cancers.

Papadimitralopoulou et al[30,31] investigated α-tocopherol, interferon-alfa, and isotretinoin in patients with laryngeal dysplasia and reported a 50% complete response rate at 12 months. The current thinking is that these agents may delay or prevent subclinical cancer from manifesting as clinical disease but are less likely to prevent cellular transformation. This three-drug combination was subsequently tested in a randomized trial adding a maintenance phase for non-progressors.[32] The drugs had only modest activity, and more than one third of patients developed cancer. The authors did find that cyclin D1 genotype and protein expression were risk markers for laryngeal cancer and suggested future trials target upstream regulators of *CD1* transcription.

New compounds for chemoprevention are currently being investigated. These include green tea extracts, curcumin analogs, soybeans, celecoxib, erlotinib, and rapamycin. These agents are being tested in coordination with efforts to identify molecular prognostic markers. Once these markers are identified, ideally they will be incorporated into randomized clinical trials by using these markers for risk stratification purposes.

Early Detection

Similar to the issues surrounding prevention, early detection of laryngeal and hypopharyngeal cancers centers on targeting the population at highest risk for developing these carcinomas. Cancers of the larynx and hypopharynx affect roughly 15,000 Americans a year and therefore is not considered a large enough health problem to warrant screening of the general population. Some investigators have studied the role of screening a more focused population, such as tobacco users who work at high-risk occupations, and question the value of screening even a more limited population.[33] However, Prout et al[34] argue that a primary care practitioner can, as part of a general evaluation, inquire about hoarseness in a patient from an at-risk population. If a positive response is obtained, the patient can be referred to an otolaryngologist for appropriate evaluations. The laryngeal carcinoma detection rate in this situation ranges between 3% and 4%.[34,35]

PATHOLOGY AND PATHWAYS OF SPREAD

Pathology

The majority of laryngeal and hypopharyngeal cancers are squamous cell carcinomas. Laryngeal carcinomas are usually well differentiated. Because patients with laryngeal tumors often present with early-stage disease, it is common to see a spectrum of pathologic tissue changes, ranging from premalignant atypia or dysplasia to carcinoma in situ and superficially invasive carcinomas, within the larynx.

Carcinoma in situ is a pathologic entity representing carcinomatous changes confined to the thickened epithelium without breaching the lamina propria. The clinical appearance of carcinoma in situ is a white or grayish white thickening of the mucosa. Penetration through the lamina propria makes the diagnosis of invasive carcinoma. Invasive tumor may be missed if biopsy samples are too small or too superficial for proper histologic evaluation.

Less frequently, the larynx and hypopharynx can give rise to variants of squamous cell carcinoma. The most common of these cancers is verrucous carcinoma, accounting for approximately 4% of all larynx cancers.[36] These are classically slow-growing tumors with a gross warty appearance. A less common variant with numerous nomenclatures is squamous cell carcinoma with spindle cell features. As its name implies, along with typical squamous cells, carcinoma cells are spindle cells. The significance of these spindle cells is the subject of debate, because theories range from these cells being a benign reactionary process with little clinical significance to highly malignant elements with adverse outcome.[37] Molecular evidence suggests the sarcomatoid carcinoma evolves from the conventional epithelium-type component and the sarcomatoid component has a malignant nature.[38] Grossly, they can often present as large polypoid lesions that sometimes act as ball valves in the larynx. Basaloid squamous cell carcinoma and lymphoepithelioma of non-nasopharyngeal origin are rare tumors seen in numerous head and neck mucosal sites, including the larynx and hypopharynx.

The remaining 5% of larynx cancers are composed of neoplasms more commonly found in other locations. Salivary gland cancers, neuroendocrine tumors[39] (including small cell carcinomas), sarcomas, and lymphomas have all been reported in the literature.[40]

Pathways of Spread

Primary Site and Regional Lymphatics

Larynx

The larynx is divided into three regions: the supraglottis, glottis, and subglottis. The supraglottic larynx lies above the level where the mucosa of the upper surface of the true vocal cords turns upward to form the lateral wall of the ventricle. It consists of the false vocal cords, arytenoids, aryepiglottic folds, and infrahyoid and suprahyoid epiglottis. The glottic region by definition includes the true vocal cords and extends 0.5 cm inferiorly, and the subglottic region extends from there to the superior aspect of the trachea (Figure 35-1).

Primary glottic cancers are about three times more common than supraglottic carcinomas, whereas subglottic carcinomas are extremely rare (about 2% of larynx cancers). At diagnosis, nearly two thirds of patients with laryngeal cancer have their disease confined to the laryngeal structures and less than 10% present with distant metastases. The patterns of spread, presentations, and management of cancers arising from these three subsites are different.

Glottis. Most glottic lesions arise on the free margin and upper surface of the anterior two thirds of the true cord. These

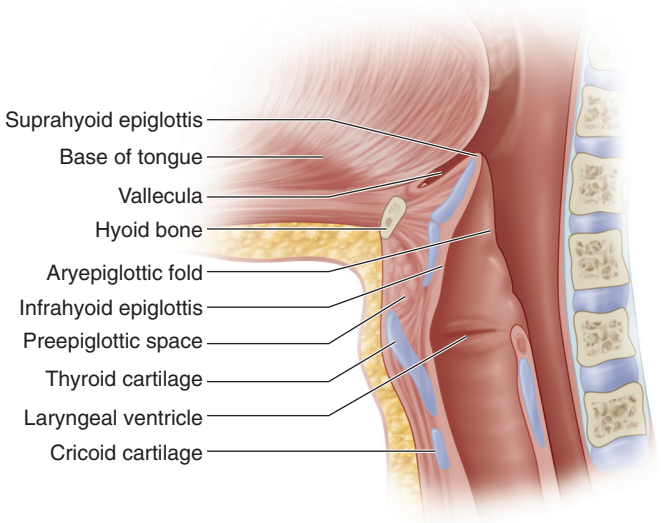


Figure 35-1 Anatomy of the larynx and its subdivisions.

tumors tend to grow slowly and remain confined to the mucosa of the true cords. Eventually they will spread superiorly or inferiorly onto the mucosa of the supraglottic or subglottic structures. Some tumors may grow outward, in an exophytic fashion, leading to voice changes and subsequently respiratory obstruction. Invasion into the intrinsic musculature and joints of the larynx decreases vocal cord mobility and ultimately causes vocal cord fixation. Noteworthy is that tumor bulk alone can cause impaired mobility. Less commonly, infiltration of the recurrent laryngeal nerve may also cause impairment of mobility.

Infiltrative tumors will breach into the paraglottic and preepiglottic spaces. These spaces lie between the external frame of the larynx (thyroid-cricoid cartilages and hyoid bone) and the internal components of the larynx (epiglottis, muscles, and ligaments) and are filled with fat and hence offer little resistance to infiltration. From these spaces, infiltrative tumors may break through ligaments above or below the thyroid cartilage into the neck or may invade the cartilage directly.

The mucosa of the true vocal cords has a sparse lymphatic supply. Thus, glottic carcinomas have a low propensity for lymphatic spread. The incidence of lymphadenopathy at diagnosis is approximately 5% for T1 and T2 lesions and approximately 20% for T3 and T4 tumors.[41] The frequency of occult nodal involvement is also low. Byers et al[42] found microscopic nodal involvement in 9 of 57 patients who underwent elective nodal dissection for T3 or T4 vocal cord lesions; most frequently involved nodes were the upper jugular (level II), midjugular (level III), and paratracheal groups (level VI).

Supraglottis. There are some variations of growth patterns within subsites of the supraglottic larynx. Suprahyoid epiglottic tumors sometimes grow in an exophytic pattern off the tip of the epiglottis, causing no symptoms until they become quite large. At other times they spread inferiorly, infiltrating and eroding the epiglottis. These lesions can eventually autoamputate the tip of the epiglottis. Complete regression of these tumors after RT may leave only a small epiglottic stump. Such an anatomic aberration increases the risk for aspiration.

Infrahyoid epiglottic lesions tend to spread anteriorly or circumferentially. They can invade directly through the base of the epiglottis into the preepiglottic space, spread onto the lingual epiglottis, and subsequently invade the vallecula, pharyngoepiglottic folds, and tongue base. At other times, they spread onto the aryepiglottic folds, usually spreading from their midline position in both directions to involve both folds, producing a horseshoe-like appearance. They then spread either inferiorly onto the false vocal cords or over the aryepiglottic folds into the piriform sinuses.

Lesions originating on the aryepiglottic folds can spread in all directions, that is, anteromedially onto the epiglottis, posteriorly to the arytenoids, inferiorly to the false cords, or laterally into the piriform sinus. Similar to lesions of the false vocal cords, they have variable growth patterns but often are infiltrative with easy access to the paraglottic space. They can frequently involve the cricoarytenoid joints or the musculature of the larynx, impairing mobility.

The primary difference between supraglottic cancers and true glottic cancers is the likelihood of developing cervical nodal metastases. At diagnosis, 55% of patients with supraglottic cancers have clinically involved lymph nodes. Lymphatic vessels in the supraglottic larynx collect in channels that pass through the piriform sinuses to drain to nodes along the jugular chain, particularly the upper (level II) and midjugular (level III) lymph nodes. Lee et al[43] reported on the data of a subgroup of patients with intermediate-stage disease who underwent supraglottic laryngectomy with neck dissections. One third of patients had palpable nodes on presentation, and nearly an additional third of patients had pathologic nodal involvement.

Subglottis. Subglottic tumors spread inferiorly to the trachea, extend through the cricothyroid membrane into the neck, or directly invade the cricoid cartilage. Superiorly, they almost always involve the undersurface of the true glottis; from a staging perspective, it is sometimes difficult to differentiate between a tumor truly originating from the subglottis and a glottic tumor with significant subglottic extension.

Primary subglottic tumors drain to the paratracheal nodes (levels VI and VII). The jugular nodes (levels II, III, and IV) are a secondary echelon and are rarely involved in the absence of metastases to the paratracheal nodes. Because of the rarity of subglottic tumors, the true incidence of involvement of nodes is difficult to determine, with estimates varying from <5% to 25%.[44]

Hypopharynx

The hypopharynx is the inferior portion of the three divisions of the pharynx (Figure 35-2). It extends from the hyoid bone superiorly to the cricoid inferiorly. Valleculae, pharyngoepiglottic fold, and lateral projections of aryepiglottic folds are considered the superior border separating the hypopharynx from oropharynx. Inferiorly, the hypopharynx ends at the cervical esophageal inlet. The hypopharynx is subdivided into three components: the pharyngeal walls, the piriform sinus, and the postcricoid pharynx. The hypopharyngeal walls are a continuation of the lateral and posterior oropharyngeal walls. The pair of piriform sinuses is created by the invagination of the larynx into the hypopharynx. They are conical (more truly pear shaped, hence the derivation of its name). Each sinus (or recess) consists of three walls. The medial wall is essentially the lateral aspect of the larynx; superiorly, it becomes the aryepiglottic fold. The lateral wall is a continuation of the lateral wall of the oropharynx. Anteriorly, the medial and lateral walls converge to form the narrow anterior wall. Superior is

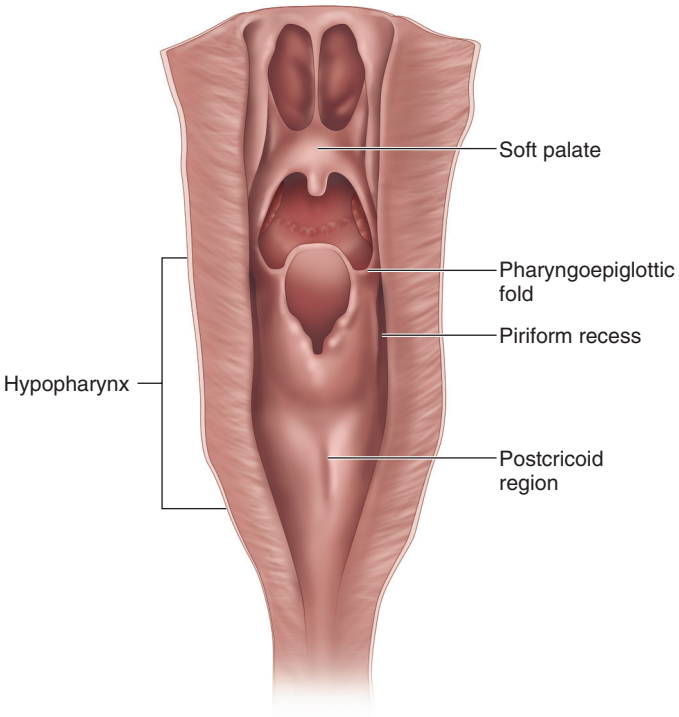


Figure 35-2 Anatomic relationship of the hypopharynx to the pharyngeal axis.

the base or vestibule formed by the rim of the three walls. Inferiorly, the three walls merge to form the apex.

The postcricoid pharynx begins superiorly at the level of the arytenoids and ends inferiorly at the esophagus, covering the posterior aspect of the cricoid cartilage. The posterior larynx makes its anterior border, and posteriorly it again is a continuation of the posterior pharyngeal wall.

Hypopharyngeal cancers also commonly present with nodal metastases. Lindberg[45] reported a 75% incidence of nodal metastases in patients presenting to the M. D. Anderson Cancer Center (MDACC) with hypopharyngeal tumors. Levels II and III nodes were most frequently involved, and bilateral lymphadenopathy was seen in 15% of patients. These tumors also have access to deep jugular and retropharyngeal lymph nodes.

Piriform Sinus Tumors. Piriform sinus tumors account for 70% of cancers originating in the hypopharynx. Tumors originating from the medial wall of the piriform sinus behave similarly to supraglottic tumors arising from the aryepiglottic folds, and it is often difficult to know the true origin of some of these lesions. Posteriorly, there is little to impede tumor extension into the postcricoid space or crossing from the ipsilateral arytenoid to the contralateral arytenoid. Lateral wall tumors also have few barriers to growth. They can extend medially along the mucosa to involve the posterior hypopharyngeal wall or anteromedially to involve the other two walls of the piriform sinus. Inferiorly, they have quick access to the apex and usually extend deep to the sinus submucosally to involve other adjacent structures, including the thyroid and cricoid cartilages, or directly into the thyroid gland. It is not uncommon to see advanced tumors from this location that have direct soft-tissue extension into the neck. These tumors can also extend into the cervical esophagus, primarily through submucosal routes, making a true definition of disease extent extremely difficult. They can also behave similarly to more classic esophageal tumors with extensive spread along lymphatic spaces and with skip lesions.

Hypopharyngeal Wall Tumors. Tumors originating from the hypopharyngeal walls are less common. Because early presentations are infrequent, it is unusual to see a lesion confined to and clearly originating from the lateral or posterior hypopharyngeal wall. Hypopharyngeal wall tumors frequently spread along the walls to involve either the posterior or lateral oropharyngeal walls and can also spread inferiorly and invade the cervical esophagus. Posterior wall tumors can also invade the prevertebral tissues or invade even more deeply to the bones of the cervical spine.

Postcricoid Tumors. Postcricoid tumors are the least common hypopharyngeal tumors. They almost always present in advanced stages. They can extend laterally into one or both piriform sinuses, directly invade laryngeal structures and can also spread inferiorly and invade the cervical esophagus.

Distant Metastases

The incidence of distant metastases from cancers of the head and neck and specifically laryngeal and hypopharyngeal cancers is low and is generally thought to be less than 10%. An often-referenced study by Crile in 1906[46] reported an incidence of 1% distant metastases in 4500 patients with epidermoid cancers of the head and neck. In subsets of patients with head and neck squamous cell cancers, patients with glottic tumors usually have the lowest rates of distant metastases whereas patients with hypopharyngeal carcinomas often have the highest rates.

Merino et al[47] analyzed the incidence of distant disease in more than 5000 patients with head and neck squamous cell carcinomas treated from 1948 through 1967. Among patients with control of disease above the clavicle, the incidence of distant failure was 1%, 13%, and 23% for patients with carcinomas of the true vocal cords, supraglottic larynx, and hypopharynx, respectively. Similarly, Marks et al[47a] found that 23% of patients with piriform sinus cancers developed distant metastases, with a higher rate among patients who underwent total laryngectomies as part of their therapy. The incidence of metastases is associated with stage of disease because the clinical incidence of metastases is approximately 20% in patients with stage IV disease.

The sites of presentation of distant metastases are similar for cancers of the larynx and hypopharynx.[43] The lungs are the most common site and are the first site of presentation in nearly 60% of patients. Bones are the next most common site because 20% of patients with distant disease develop osseous metastases. Liver metastases are common in autopsy studies, but clinical liver metastases develop in only 10% of patients with hematogenous spread of disease from the larynx and hypopharynx.[48] Spread to mediastinal lymph nodes, the brain, or other organs is uncommon.

MOLECULAR BIOLOGY

The critical events of carcinogenesis and tumor progression occurring at a molecular level have been heavily studied over several decades. Paradoxically, as our knowledge of molecular tumor biology increases, the complexity of tumorigenesis at this level also appears to increase. This is in part as a result of the realization that laryngeal and hypopharyngeal tumors, while developing in a "single" site, represent a heterogeneous group of neoplasms. Investigators have found genotypic markers, either chromosomal rearrangements or the presence of an oncogene, tumor suppressor gene, or other markers but have only found them in some varying percentage of laryngeal and hypopharyngeal tumors.

A general view is that tumorigenesis of head and neck malignancies occur because of a combination of factors. Carcinogen exposure (primarily tobacco) results in genetic damage. However, not all smokers develop cancer. The genetic damage in individuals varies based on the degree of exposure to the offending agent as well as the individual's inherent sensitivity to genetic damage. The latter can be tested indirectly in individuals using an assay quantifying chromosomal breakage induced by in vitro exposure to bleomycin. Patients with upper aerodigestive tract malignancies were compared with healthy controls. Mutagen-sensitive individuals had a higher likelihood of having a cancer, and mutagen-sensitive smokers were at the highest risk.[49]

A field of mucosa is placed at risk for developing carcinoma by the exposure and sensitivity described previously, but it requires a number of events to develop a frank cancer. The concept of field cancerization was first described in 1953 by Slaughter et al.[50] These researchers found widespread microscopic abnormalities in "normal" mucosa adjacent to tumor obtained from resected specimens. These abnormalities ranged from hyperplasia to areas of carcinoma both invasive and in situ away from the known resected cancer. Califano et al[51] proposed a genetic progression model in which the local clinical phenomenon of field cancerization involves the expansion and migration of clonally related preneoplastic cells.

The molecular events leading to the development of carcinomas are believed to occur by a multistep process and have been described for other cancers.[52] This theory is applicable to head and neck cancers and appears consistent with the pathologic findings of field cancerization. Genotypic alterations in histologically normal epithelium adjacent to invasive carcinomas have been described. Voravud et al[53] found increased chromosomal polysomies in normal mucosa of smokers with invasive carcinomas but not in mucosa of healthy nonsmoking

volunteers. The most frequent findings in premalignant tissue are deletions of one of the two alleles at chromosomes 3p and 9p21.[54] These regions harbor tumor suppressor genes and thus may be involved with malignant transformation. It has also been observed that telomerase is activated in head and neck squamous carcinoma and dysplasia and may be an early event in the tumorigenic process.[54]

TP53 is a tumor suppressor gene. A mutation in *TP53* is regarded as the most common related genetic change in human cancers.[55] The normal TP53 protein has a short half-life, so its detection is thought to represent *TP53* mutation. Shin et al[56] found *TP53* expression in normal tissue and premalignant lesions adjacent to head and neck tumors but not in normal tissues from normal control patients. Numerous investigators have found overexpression of TP53 protein in laryngeal carcinomas, typically in approximately half the tumors studied.[56,57] Alterations in *TP53* are thought to be an important step early in the carcinogenic process but not a necessary step for all laryngeal and hypopharyngeal tumors. The finding of this protein in laryngeal specimens is also unclear; although there are diverging study results, most investigators have not found a prognostic value to the finding of TP53 protein in larynx tumor specimens.[57-60]

Other cellular changes in laryngeal carcinogenesis involve epidermal growth factor receptor (EGFR), CCND1 (formerly cyclin D1), and CDKN2A. Weichselbaum et al[61] described elevations in EGFR expression in head and neck tumor cell lines. In an analysis of premalignant and malignant head and neck tumor specimens, EGFR levels correlated with increasing severity of dysplasia.[62] Furthermore, Shin et al[63] found elevated EGFR levels in premalignant tissues but dramatic up-regulation in invasive carcinoma specimens. EGFR was amplified in DNA from 29% of sampled hypopharyngeal cancers, and it is overexpressed in at least 80% of head and neck cancers. This overexpression has been demonstrated to be an independent prognosticator in head and neck cancer.[62]

CLINICAL MANIFESTATIONS, PATIENT EVALUATION, AND STAGING

Clinical Manifestations

Hoarseness is the main presenting symptom in patients with glottic carcinoma. Patients with neglected advanced disease can also present with airway obstruction, pain, or dysphagia. Recurrent laryngeal nerve involvement may cause local pain or referred otalgia.

Patients with supraglottic cancers have differing symptomatology depending on the location of the primary lesion. Patients with false vocal cord lesions can present with hoarseness, whereas patients with epiglottic tumors can have voice changes often referred to as a supraglottic or "hot potato" voice. Patients can also present with throat pain, referred otalgia, and sometimes dysphagia. On rare occasions, patients may present with an asymptomatic neck metastasis. Similar to glottic cancers, advanced tumors can cause airway obstruction and have direct extension into the neck.

Patients with hypopharyngeal cancer usually present with throat pain with or without referred otalgia. Other symptoms include varying degree of dysphagia, ranging from the sensation of food "hanging up" in the throat to inability to swallow solids. Weight loss develops frequently in these patients, who often have malnutrition and poor performance status. Hoarseness occurs with larynx invasion that impairs vocal cord mobility. Because of the high incidence of nodal involvement, patients with hypopharyngeal cancer can occasionally present with asymptomatic neck masses.

TABLE 35-1 Evaluation of Patients with Suspected Laryngeal or Hypopharyngeal Cancer

Medical history
Physical examination
Directed examination of oral tissues and neck
Fiberoptic laryngopharyngoscopy
Chest radiography
Thin-slice CT or MRI of the larynx
Direct laryngoscopy and biopsy of the primary tumor
*Optional examinations**
CT of chest
PET
Barium swallow
Esophagogastroduodenoscopy (EGD)

**In patients with more advanced disease, these tests may augment the workup for metastatic disease; PET and barium studies may help better define the inferior extent of advanced hypopharyngeal cancers.*

Patient Evaluation

Laryngeal Cancer

Clinical evaluation of laryngeal cancer includes indirect laryngoscopy with a mirror that is frequently supplemented by fiberoptic endoscopy (Table 35-1). Similar to other tumors in the head and neck, the examiner assesses the tumor size, morphology, infiltration (defect, distortion) of adjacent structures, and vocal cord mobility. It is important to palpate the base of the tongue to determine direct invasion from the supraglottic larynx and to look for indirect signs of preepiglottic space invasion such as fullness of the vallecula or ulceration of the infrahyoid epiglottis. A direct laryngoscopy is often the final step in evaluation. It is needed to further outline the disease extent and, in particular, to obtain biopsy specimens for tissue diagnosis.

Examination of the neck is important to detect lymphadenopathy or direct tumor extension manifesting as tenderness of the thyroid cartilage or the presence of a subcutaneous mass. Firm fullness over the thyroid notch is suggestive for preepiglottic space involvement.

Radiologic studies are indicated when there is the suggestion of deep infiltration. CT (Figure 35-3) or MRI is useful for the assessment of the preepiglottic space, tongue base, paraglottic region, and subglottis (which is sometimes difficult to evaluate from above with the mirror or fiberoptic scope). These images may help differentiate direct primary tumor extension to the soft tissue of the neck from nodal involvement. Anterior commissure lesions may have subtle thyroid cartilage invasion only detectable by CT.

Hypopharyngeal Cancer

Evaluation of hypopharyngeal tumors is similar to that of larynx cancers. Because these lesions are typically at an advanced stage, it is not uncommon to palpate disease in the neck by direct extension. The thyroid click may be lost owing to anterior displacement of the larynx by a posteriorly located (particularly postcricoid) lesion. Phonation may provide better visualization of the piriform sinus on indirect mirror and fiberoptic examination. If unsuccessful, a Valsalva maneuver may open the sinus. Deep infiltrative lesions in the apex may be hard to see but are suspected by either pooling of secretions or arytenoid edema. Assessment of laryngeal mobility is important in medial wall lesions because they can invade directly into the laryngeal framework. In addition to CT (Figure 35-4), combined ^{20}F-fluorodeoxyglucose–labeled positron emission tomography and CT (FDG-PET/CT) may be helpful in defining tumor extent, particularly the inferior

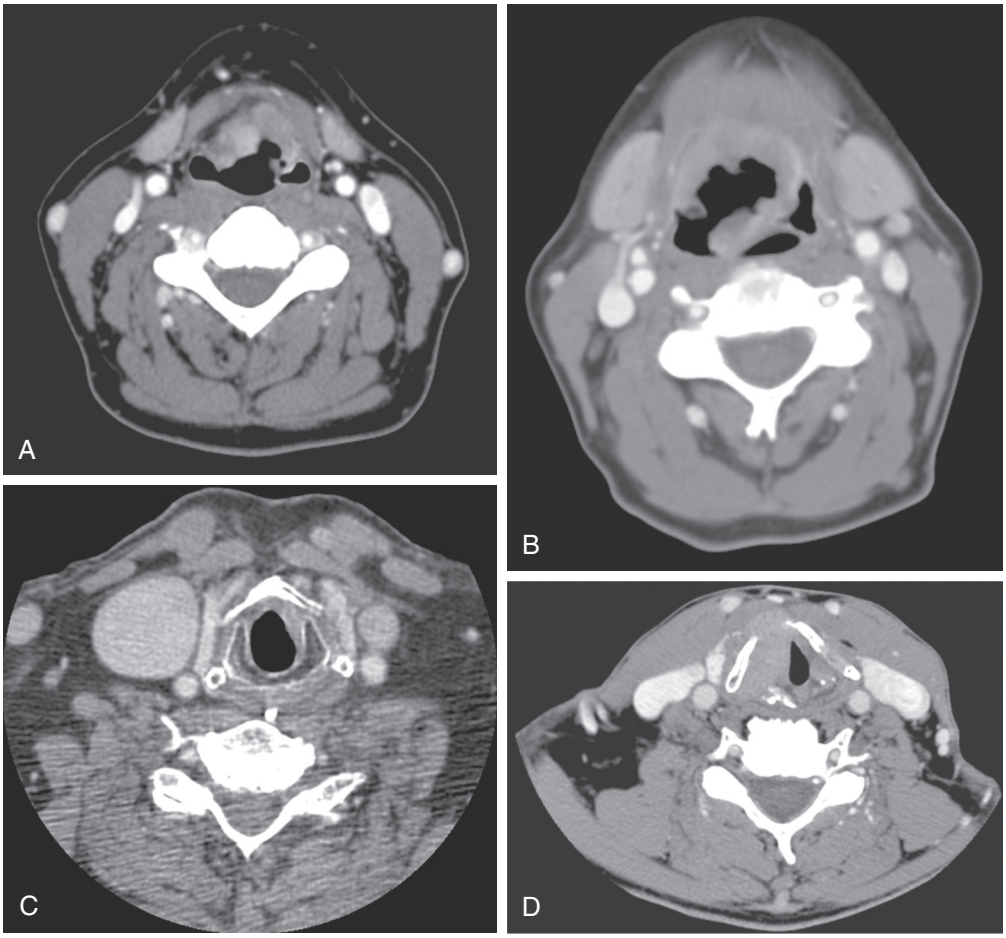


Figure 35-3 CT of laryngeal cancers. **A,** Cancer of the supraglottis invades the preepiglottic space *(left).* **B,** Cancer of the epiglottis with direct extension into the base of the tongue. **C,** Cancer of the true vocal cord with subglottic extension *(left).* **D,** T4 laryngeal cancer, with destruction of the cartilage and invasion of the anterior strap muscles.

border where subtle changes in the inferior hypopharynx and superior cervical esophagus may be hard to identify solely on anatomic images. A laryngoscopy and biopsy is often required to confirm the diagnosis. At that time, esophagoscopy is prudent to assess disease extent inferiorly.

Staging

Larynx

Tumors are staged using the American Joint Committee for Cancer (AJCC) TNM system[29] (Table 35-2). The system is currently in its seventh iteration, most recently revised in 2010. The system classifies/categorizes larynx cancer primary tumors (T) by sites of extension and cord mobility but not size. For glottic tumors, stage T1 is disease limited to the vocal cord(s). The AJCC staging system further divides T1 glottic tumors into T1a for tumors confined to one true vocal cord and T1b for tumors involving both vocal cords. In general, this subdivision is more useful for communication and may influence the treatment decision (i.e., limited surgery versus RT) but does not have a strong impact on prognosis. T2 glottic tumors have either supraglottic or subglottic extension or impaired mobility (but not fixation). Although not defined by the AJCC, T2 glottic lesions can be subdivided into T2a for normal mobility and T2b for impaired mobility. This subdivision is not uniformly used, however, because there is no general agreement that treatment outcomes differ among the substages.

Two significant revisions were made to the sixth edition of the staging system.[64] Historically, the definition of T3 glottic disease has been fixation of the vocal cord. The sixth edition expanded on this definition and included paraglottic space invasion or minor thyroid cartilage invasion. Previous editions had defined T4 disease as invasion *through* the thyroid cartilage, but a common misinterpretation was to include any thyroid cartilage invasion into the T4 category. The new definition was made to clarify this point. The significance of this distinction is in the era of larynx preservation (see discussion in this chapter); many still think that the presentation of invasion through the cartilage into the extralaryngeal tissues precludes a nonsurgical approach, but patients presenting with minimal invasion into the inner cortex may have disease suitable for larynx preservation.

The second modification is the subdivision of T4 disease. For head and neck cancers in general, the sixth edition had subdivided stage T4 into resectable (T4a) and unresectable (T4b) categories. Thus, glottic cancer T4a disease has been defined as tumor that invades through the thyroid cartilage or invades tissues beyond the larynx (e.g., trachea, soft tissues of neck including deep extrinsic muscle of the tongue, strap muscles, thyroid, or esophagus), and T4b is tumor invading prevertebral space, encasing carotid artery, or invading mediastinal structures. Subsequently, the only change made in the seventh edition was descriptive. Category T4a now describes moderately advanced local disease, and T4b describes advanced local disease.

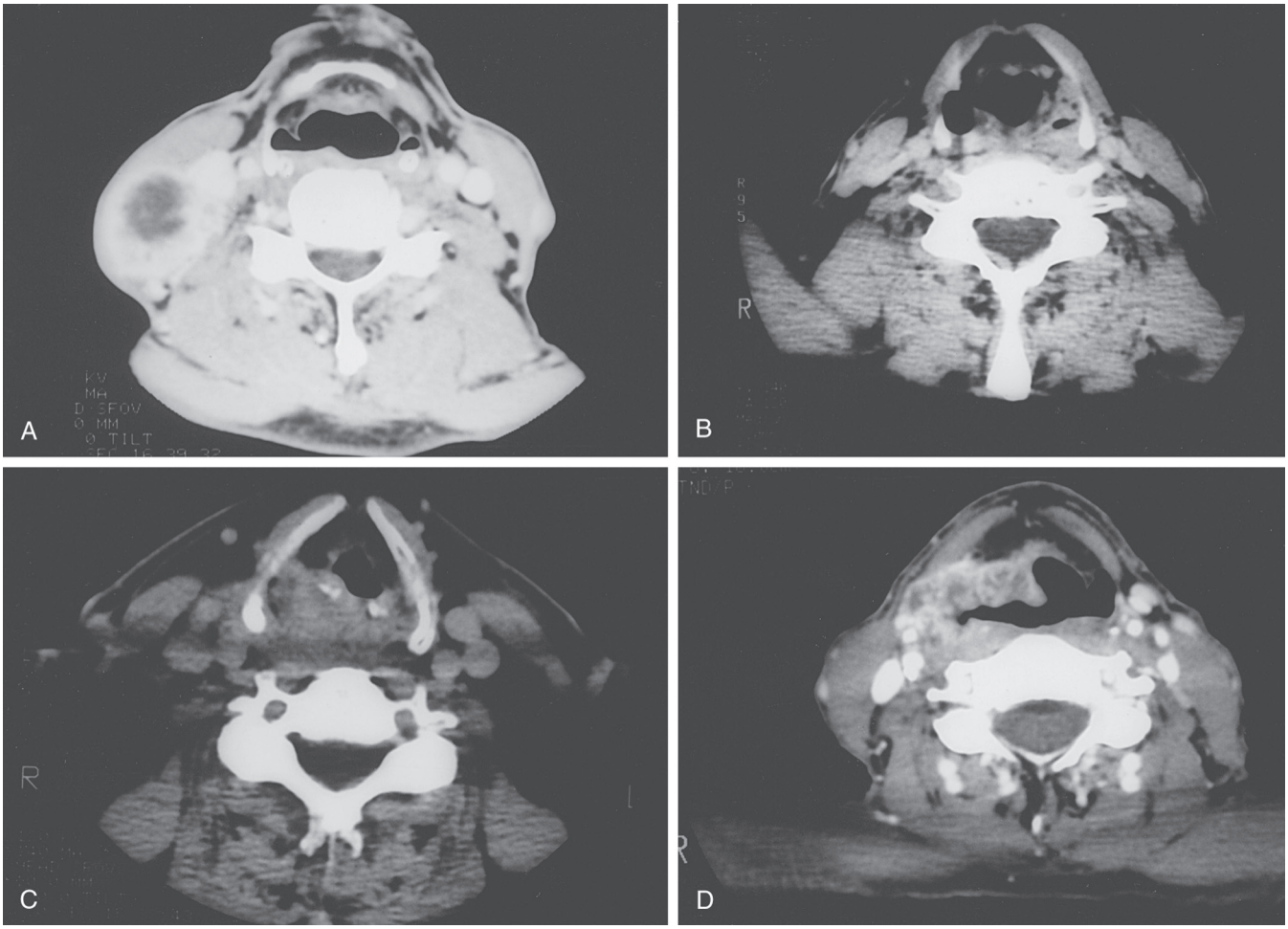


Figure 35-4 CT of hypopharyngeal cancers. **A,** A small (<1-cm) lesion arises off the posterior hypopharyngeal wall (T1) with large (N3) neck metastases. The primary tumor was managed with irradiation only, and the neck was treated with combined irradiation and surgery. **B,** An exophytic lesion was confined to the walls of the left piriform sinus (T2) and was treated with hyperfractionated RT. **C,** An infiltrative lesion off the medial wall of the piriform sinus invaded and fixed the hemilarynx (T3). This patient was treated within the framework of a study of induction chemotherapy and irradiation. **D,** An advanced lesion of the piriform sinus extended directly into the soft tissues of the neck. This lesion required a resection with a free jejunal autograft repair followed by postoperative RT.

The staging of supraglottic cancers requires the division of the supraglottis into five subsites: the suprahyoid epiglottis, infrahyoid epiglottis, aryepiglottic folds, arytenoids, and ventricular bands (false cords). T1 disease is disease confined to one subsite (with normal vocal cord mobility). T2 disease invades more than one adjacent subsite or region outside the supraglottis (mucosa of base of tongue, vallecula, or medial wall of the piriform sinus). T3 disease is similar to glottic carcinoma, although it also includes preepiglottic space invasion or postcricoid involvement. Last, in the newest edition, the definition of T4 supraglottic cancer is the same as that for glottic cancer with subdivisions into moderately advanced and advanced (T4a and T4b) categories.

Hypopharynx

T category for hypopharyngeal tumors is also based on sites of involvement and larynx motion (an indirect measurement of disease extension). The fifth edition of this staging classification had a significant modification to also include the size of the tumor in staging.[65] This change addressed a major deficiency in prior systems because the older systems tended to understage hypopharynx tumors relative to other head and neck mucosal cancers. The hypopharyngeal T category still does not reflect morphology, which remains an important criterion for selection of local therapies because exophytic tumors in this site are usually selected more frequently than infiltrative lesions for organ-preserving therapies. The sixth edition made one additional modification. As described for laryngeal cancers, resectable T4a and unresectable T4b categories were defined. T4a hypopharyngeal disease can invade thyroid or cricoid cartilages, hyoid bone, thyroid gland, esophagus, or central compartment, whereas T4b disease invades prevertebral fascia, encases carotid artery, or involves mediastinal structures. The newest edition now defines T4a and T4b as moderately advanced and very advanced.

Regional Classification and Categorization

The nodal (N) category is uniform for all head and neck cancers, including laryngeal and hypopharyngeal tumors. No changes were made in the seventh edition. The details of T and N categories for laryngeal (glottic and supraglottic) and hypopharyngeal cancers are summarized in Table 35-2.

TABLE 35-2 American Joint Committee on Cancer Staging of Laryngeal and Hypopharyngeal Cancers

GLOTTIS	
Tis	Carcinoma in situ
T1	Tumor limited to the vocal cord(s) with normal mobility
T2	Tumor extends to supraglottis or subglottis or with impaired cord mobility
T3	Tumor limited to the larynx with vocal cord fixation or invades paraglottic space or minor thyroid cartilage erosion
T4a	Tumor invades through the thyroid cartilage or invades tissues beyond the larynx
T4b	Tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures
SUPRAGLOTTIS	
Tis	Carcinoma in situ
T1	Tumor limited to one subsite of the supraglottis with normal vocal cord mobility
T2	Tumor invades mucosa of more than one subsite of the supraglottis or glottis or adjacent site outside the glottis, without fixation of the larynx
T3	Tumor limited to the larynx with vocal cord fixation and/or invades any of the following: the preepiglottic space, the postcricoid area, or minor thyroid cartilage erosion
T4a	Tumor invades through the thyroid cartilage or invades tissues beyond the larynx
T4b	Tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures
HYPOPHARYNX	
T1	Tumor limited to one subsite of hypopharynx and 2 cm or less in greatest dimension
T2	Tumor invades more than one subsite of hypopharynx or an adjacent site or measures between 2 cm and 4 cm in greatest dimension, without fixation of hemilarynx
T3	Tumor measures greater than 4 cm or with fixation of hemilarynx
T4a	Tumor invades thyroid/cricoid cartilage, hyoid bone, thyroid gland, esophagus, or central compartment soft tissue
T4b	Tumor invades prevertebral fascia, encases carotid artery, or involves mediastinal structures
NODAL INVOLVEMENT (N)	
Nx	Nodes cannot be assessed
N0	No clinically positive node
N1	Single clinically positive ipsilateral node 3 cm or less in diameter
N2	Single clinically positive ipsilateral node more than 3 cm, but not more than 6 cm in diameter or multiple clinically positive ipsilateral or bilateral or contralateral nodes, none more than 6 cm in diameter
N2a	Single clinically positive ipsilateral node more than 3 cm, but not more than 6 cm in diameter
N2b	Multiple clinically positive ipsilateral nodes, none more than 6 cm in diameter
N2c	Bilateral or contralateral lymph node, none more than 6 cm in greatest dimension
N3	Metastases in a lymph node more than 6 cm in greatest dimension
STAGE GROUPINGS	
Stage I	T1N0M0
Stage II	T2N0M0
Stage III	T3N0M0 T1-3N1
Stage IVA	T4aN0-1M0 T1-4aN2M0
Stage IVB	T4bN0-3M0 T1-4bN3M0
Stage IVC	T1-4N0-3M1

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PRIMARY THERAPY

Early Carcinomas

T1 and T2 Glottic Tumors

The management of early glottic carcinomas is controversial and is often determined by the preferences and expertise of the attending physicians. Oncologists advocate either irradiation or voice-preserving partial laryngectomy. Large published series have for all practical purposes demonstrated equivalent control rates with surgery (excision, cordectomy, or hemilaryngectomy) and RT. There has not been a true comparative study between these two modalities, and it is highly unlikely that a prospective trial will be performed. Therefore, it is imperative that the patient visit with both a surgeon and radiation oncologist before making a treatment decision so that their preferences, desires, and goals can be considered in the treatment making decision.

There are several difficulties in comparing the results of various treatment options. Nearly all series are retrospective single-institutional studies. It is thus difficult to ascertain if small differences in control rates between series are real.

TABLE 35-3 Results of Irradiation for T1 Carcinomas of the True Vocal Cords

Study/Author	Year	No. Patients	Local Control	Salvage
Harwood[78]	1979	333	86% (5-yr a)	ND
Fletcher[79]	1980	332	89% (c)	84% (c)
Lustig[80]	1984	342	90% (3-yr a)	ND
Hendrickson[81]	1985	364	90% (c)	ND
Akine[82]	1991	154	89% (c)	94% (c)
Schwaab[77]	1994	194	86% (c)	89% (c)
Wang[83]	1996	665	93% (5-yr a)	98% (5-yr DSS)
Le[84]	1997	315	84% (c)	83% (c)
Warde[85]	1998	449	91% T1a 82% T1b (5-yr a)	ND
Gowda[86]	2003	200	93% (5-yr a)	50% (c)
Cellai[87]	2005	831	84% (5-yr a)	58% (c)
Groome[88]	2006	491*	82% (5-yr a)	ND
Nomiya[89]	2009	163	92% T1a 85% T1b (5-yr a)	ND
Chera[90]	2010	325	94% T1a 93% T1b (5-yr a)	98% (ULC) 97% (ULC)

a, *Actuarial;* c, *crude;* DSS, *disease-specific survival;* ND, *no data.* ULC, *ultimate local control.*
**4.5% of patients treated with surgery alone. Data given for T1a and T1b separately.*

TABLE 35-4 Results of Radiation for T2N0 Glottic Carcinomas

Study/ Author	Year	No. Patients	Local Control	Salvage
Van den Boegart[96]	1983	83	76% (c)	65% (c)
Lustig[80]	1984	109	78% (3-yr a)	ND
Hendrickson[81]	1985	76	73% (c)	50% (c)
Karim[97]	1987	156	78% (5-yr a)	92%
Barton[98]	1992	327	69% (5-yr a)	ND
Wang[83]	1996	237	71%-77% (5-yr a)	84%-92% (5-yr DSS)
Klintenberg[99]	1996	94	74% (c)	38% (c)
Le[84]	1997	83	67% (c)	74% (c)
Warde[85]	1998	230	69% (5-yr a)	ND
Garden[100]	2003	230	72% (5-yr a)	68% (c)
Frata[101]	2005	256	73% (5-yr a)	46% (c)
Groome[88]	2006	213*	63% (5-yr a)	ND
Chera[102]	2010	260	T2a 80% (5-yr a) T2b 70% (5-yr a)	T2a 96% (ULC) T2b 93% (ULC)

a, *Actuarial;* c, *crude;* DSS, *disease-specific survival;* ND, *no data;* ULC, *ultimate local control.*
**4.2% treated with initial total laryngectomy. Data given for T2a and T2b separately.*

Mendenhall et al[66] address this issue by defining the surgical procedure that would have been recommended in their patients who were irradiated. They found that the surgical treatment option would have required total laryngectomy, rather than partial voice-conserving procedures, in 10% of patients with T1 disease and 55% of those with T2 disease. However, the supracricoid laryngectomy, a procedure that removes an entire circumferential portion of the larynx and subsequently reconstitutes the larynx, has largely been developed during the past decade.[67] Many patients described by Mendenhall et al in 1993 deemed suitable only for total laryngectomy may now be managed with this voice-preserving surgery. Olsen[68] states that it is unusual for disease that does not fix the arytenoids to require total laryngectomy. Although this is possibly true from a technical standpoint, many patients who have larynx cancer are older, have long histories of tobacco exposure, and medically may not be suitable for partial laryngeal surgery other than excisions of small T1 lesions on the midcord.

In general, T1 tumors can be treated effectively with transoral laser excision,[69] laryngofissure,[70] partial laryngectomy,[71,72] or irradiation. Table 35-3 summarizes the results of RT. Local control rates of RT range from 85% to 95%, and ultimate control rates after salvage surgery for recurrences are greater than 95%. Surgical salvage for the uncommon local relapse often requires a total laryngectomy, but an occasional patient can have a lesion amenable to a voice-conserving partial laryngectomy.[73-77]

An important factor in selecting therapy for individual patients is the anticipated voice quality after therapy. Unfortunately, studies comparing voice quality between laser excision and RT have yielded conflicting conclusions. Hirano et al[91] concluded in their analysis that hoarseness and incomplete glottic closure were more frequently seen in patients treated with laser. McGuirt et al[92] had physicians, patients, and speech pathologists compare voice quality of patients who received RT or laser excision for early glottic cancer. They concluded that patients treated with limited excisions of tumors of the midcord had equivalent quality compared with those receiving RT. Using computerized-assisted voice analysis, Harrison et al[93] demonstrated that most of their patients irradiated for early vocal cord cancer maintained excellent voices. Mittal et al[94] reported a cost savings with radiation compared with hemilaryngectomy and thought this should be an important component in treatment decisions if other important criteria are equivalent. A recent meta-analysis performed by Higgins et al[95] of more than 7600 patients suggested a trend toward improved voice quality with RT as compared with transoral laser excision.

The outcome of RT for T2 cancers is, as expected, less favorable than that for T1 tumors. Local control rates range from 65% to 80%, and ultimate control rate is about 90% (Table 35-4). The wider range in the reported local control rates can, at least in part, be ascribed to a considerable heterogeneity of presentations within this stage, that is, varying from a superficial tumor spilling into the ventricle to a more bulky lesion transgressing the paraglottic space and impairing motion.

Oncologists have searched for prognostic determinants in this group of patients. Several reports showed that impairment in cord mobility adversely affects tumor control by RT (Table 35-5). Some physicians favor a hemilaryngectomy, if feasible, for T2b tumors.[71,72,103] However, Karim et al[97] did not find impaired cord mobility to result in a worse outcome and attributed this observation to prescribing higher radiation doses to patients with such a tumor feature. Similarly, a report from MDACC did not show a relationship between mobility and outcome, but some patients were treated with altered fractionation schedules that were theorized to have a

TABLE 35-5 Control of T2 Glottic Cancer as a Function of Cord Mobility

Study/Author	No. Patients (T2a/T2b)	Local Control T2a	Local Control T2b	Statistics
Harwood[105]	156/80	80% (5-yr a)	52% (5-yr a)	$p < 0.001$
Van den Boegart[96]	33/28	62%	65%	NS
Karim[97]	111/45	75%-80%*	71%-82%	NS
Kelly[106]	37/16	91%	50%	$p < 0.001$
Wiggenraad[107]	50/21	78%	71%	NS
Pellitteri[108]	34/14	80%	57%	Not given
Schwaab[77]	53/12	64%	75%	Not given
Wang[83]	145/72	77% (5-yr a)	71% (5-yr a)	$p = 0.16$
Klintenberg[99]	76/18	75% (5-yr a)	60% (5-yr a)	$p = 0.02$ NS (MV)
Le[84]	60/23	79% (5-yr a)	40% (5-yr a)	$p = 0.02$ (MV)
Mendenhall[109]	146/82	80% (5-yr a)	72% (5-yr a)	$p = 0.0003$* (MV)
Garden[100]	116/114	74% (5-yr a)	70% (5-yr a)	$p = 0.37$ (MV)
Frata[101]	177/79	77% (5-yr a)	65% (5-yr a)	$p = 0.03$ (MV)

a, *Actuarial;* MV, *multivariate;* NS, *not significant.*
**T1 patients included in stage analysis.*

therapeutic advantage.[104] An update of this report reinforced the lack of impact of mobility on prognosis, independent of fractionation.[100] This was contrary to the finding of Wang,[83] who found that twice-daily radiation improved local control of T2 tumors with normal mobility but not those with impaired mobility.

Several studies were also undertaken to assess the influence of impaired cord mobility on the success rate of salvage surgery for patients who developed recurrences. Schwaab et al[77] noted difficulties in attempting salvage on a small cohort of patients presenting with T2b tumors (although, surprisingly, the initial control rate of T2b tumors in this series was better than that of T2a lesions). Wiggenraad et al[107] reported ultimate control rates of 98% for T2a and 76% for T2b tumors ($p < 0.05$). Other groups, however, have reported equivalent ultimate local control rates for tumors with normal or impaired cord mobility.[77,100,110] Ang and Peters[111] suggested that the timeliness of diagnosis and the extent of surgery, rather than the initial disease presentation, might account for the difference in the salvage results.

Anterior commissure involvement was considered a potential prognostic factor because it may carry an increased risk for unsuspected thyroid cartilage invasion. However, this feature was not found to be a prognostic determinant in most recent series. Sessions et al[112] found that anterior commissure[109] involvement was more frequently associated with larger tumors, and it was the extent of disease rather than commissure involvement per se that impacted on outcome. Le et al[84] found, in a multivariate analysis, that patients with anterior commissure involvement had a poorer local control rate but concluded that these patients also had a larger tumor burden and sometimes unsuspected subglottic disease. Modern high-resolution imaging techniques can detect clinically unsuspected thyroid cartilage invasion and eliminate the clinical significance of anterior commissure involvement.

Glottic Carcinoma in Situ

Controversies of management even exist for carcinoma in situ of true vocal cords. Although not all lesions progress to invasive cancer, Hintz et al[113] reported that with a watchful waiting policy nearly two thirds of patients developed invasive cancer that was not always suitable to voice-preserving therapies. Ferlito et al[114] polled otolaryngologists and found practices of management ranging from postbiopsy observation, vocal cord stripping, cordectomy, open partial laryngectomy, to primary irradiation.

TABLE 35-6 Results of Radiation for Carcinoma in Situ of the True Vocal Cords

Study/Author	Year	No. Patients	Local Control	Salvage
Pene[118]	1976	86	85%	92%
Sung[121]	1979	21	90%	100%
Harwood[78]	1979	45	90%	ND
Kalter[123]	1987	62	100%	—
Fernberg[124]	1989	40	90%	ND
Macleod[120]	1990	20	70%	67%
Smitt[119]	1993	29	93%	100%
Small[125]	1993	21	95%	—
Wang[83]	1996	60	92% (5-yr a)	98% (u)
Le[126]	2000	54	79% (10-yr a)	85%*
Spayne[127]	2001	67	98% (5-yr a)	100% (u)
Sengupta[128]	2010	37	91% (5-yr a)	91% (u)

a, *Actuarial;* ND, *no data;* u, *ultimate local control (5-yr actuarial).*
**Ten-year actuarial larynx preservation rate*

Primary RT is an effective treatment for carcinoma in situ of the larynx. However, conservative surgical approaches such as microexcision, laser ablation,[115,116] or vocal cord stripping[117] are considered sufficient for initial treatment. Repeated biopsies, strippings, or laser excisions may be counterproductive and lead to worsening of voice quality. RT is usually reserved for recurrences or for diffuse lesions that are not suitable for limited surgery as the first therapy.

The local control rates reported in modern series of patients with carcinoma in situ treated with radiation ranges from 70% to 100% and are similar to rates described for invasive T1 disease (Table 35-6). It should be recognized that, owing to limited biopsy sampling, many radiation series may include patients with unrecognized invasive disease. For example, nearly one third of the patients in the series of Pene and Fletcher[118] diagnosed with carcinoma in situ had clinical T2 disease. Most patients developing recurrent laryngeal

TABLE 35-7 Comparison of Once-Daily versus Twice-Daily Fractionated Radiation for T2-3 Supraglottic Carcinomas

Study/Author	Institution	T Category	Once-Daily % Control	Twice-Daily % Control
Garden[100,142]	M.D. Anderson Cancer Center	T2-3	76% (2-yr a) (*n* = 98, 76% T2)	80% (2-yr a) (*n* = 102, 57% T2)
Hinerman[137]	University of Florida	T2	80% (c) (*n* = 44)	89% (c) (*n* = 65)
		T3	30% (c) (*n* = 10)	66% (c) (*n* = 77)
Wang[83]	Massachusetts General Hospital	T2	61% (5-yr a) (*n* = 85)	83% (5-yr a) (*n* = 126)
		T3	56% (5-yr a) (*n* = 47)	71% (5-yr a) (*n* = 136)

a, *Actuarial;* c, *crude.*

carcinoma in situ undergo salvage surgery, most often with total laryngectomy, although some series have reported salvage with voice-preserving surgery.[119,120] Although control rates after irradiation are similar to those reported for early invasive disease, recurrences in patients with carcinoma in situ take longer to manifest. Most series report median times to failure of greater than 2 years, but the majority of tumors recur within 5 years of treatment.[113,118,120-122]

T1, T2, and Selected T3 Supraglottic Tumors

Similar to glottic cancer, the optimal management of supraglottic carcinomas is still being debated. Confounding the issue even more is the necessity to manage the neck lymphatics in addition to the primary tumor. As mentioned previously, nearly one third of patients with early- to intermediate-stage supraglottic neoplasms present with palpable cervical lymphadenopathy[44,78] and another third have subclinical nodal involvement detected by elective neck dissections.[129]

Voice-preserving treatment options for early- and intermediate-stage tumors are supraglottic laryngectomy or primary RT.[44,71,74,130-134] Local control rates in most surgical series range from 80% to 90%. Bocca et al from Milan reported a local control rate of 85% in one of the largest series of more than 400 patients with predominantly T2 tumors. Of note is that postoperative RT is often given to many patients undergoing partial laryngectomy. Common indications are presence of multiple nodes, extracapsular spread of nodal disease, and close or positive surgical margins. For example, 50 of 60 (83%) patients who underwent supraglottic laryngectomy at MDACC from 1974 to 1987 had indications for postoperative RT.[44] The leading complication of supraglottic laryngectomy is aspiration, which can be morbid in heavy smokers (the majority of patients) with chronic pulmonary disease. Although preliminary data of endoscopic removal of early supraglottic lesions have been reported recently,[135,136] more experience is needed to determine its relative value.

Most surgical series selected middle-aged men who are medically fit for supraglottic laryngectomy. Hinerman et al[137] analyzed 274 patients who underwent primary RT at the University of Florida and retrospectively grouped these patients into three groups: (1) suitable for conservation surgery, (2) anatomically suitable but medically unsuitable, and (3) anatomically unsuitable. Using 1998 AJCC criteria, they reported that 45% of T1 patients, 36% of T2 patients, and 14% of T3 patients were suitable for conservation surgery. Only 14% of T1 patients were anatomically unsuitable, compared with 46% and 68% of T2 and T3 patients, respectively. Of note, results after RT for all their patients were dependent on T category but were not dependent on suitability for conservation surgery. Similar to the situation in patients with glottic carcinomas, the development of the supracricoid laryngectomy would alter the balance of patients with T2 and T3 patients thought to be anatomically unsuitable for a conservative procedure. In a small series, Laccourreye et al[138] reported on 19 patients treated with supracricoid laryngectomy. This cohort had disease in the infrahyoid epiglottis that was not suitable for more traditional conservative procedures.

In 1974, Bataini et al[139] published an overall locoregional control rate of 76% for a relatively large series of patients with T1-2, N0-2 supraglottic carcinomas treated by RT alone. Subsequent series reported control rates of 84% to 100% for T1 tumors.[79,83,140] Table 35-7 summarizes the outcome of RT in T2 and favorable T3 lesions. Fletcher and Goepfert[79] obtained a local control rate of 76% in this subset of patients by escalating the total dose of the conventional daily irradiation to 70 Gy. Application of altered fractionation regimens appear to have resulted in a trend toward further improvement in local control.[83,129,142] In the Danish Head and Neck Cancer Group (DAHANCA) randomized fractionation trials, the benefit of accelerated treatment for head and neck cancers in general was most noticeable in the subgroup of patients with supraglottic cancers.[141]

The impact of clinically positive nodal disease on local control has been evaluated in several series. Wall et al[143] found the presence of lymphadenopathy was associated with a significantly lower local control rate. Similarly, Wang et al[144] describe a marked worsening of local control in patients who were node-positive. The 5-year actuarial local control rate obtained with accelerated fractionation was 86% in patients with no adenopathy as opposed to 46% in patients with N2-3 disease. In contrast, Freeman et al[145] did not find an association between local control and the presence of lymph nodes.

The potential impact of tumor volume, estimated by CT measurements, on the results of RT was addressed by Freeman et al[146] in patients with T3 supraglottic tumors. They found a control rate of 83% for tumors of less than 6 cm^3 compared with 46% for tumors of greater than 6 cm^3. This latter group may be more suitable for surgery, particularly if voice-conserving surgery is feasible. Kraas et al[147] also studied tumor volume measurements, and although their threshold was 8 cm^3, the concept of increasing tumor volume predicting worse outcome with RT was validated in a separate cohort.

Comparative studies have been undertaken in an attempt to delineate therapy recommendations for different subsets of patients. Fein et al[134] analyzed the University of Florida experience and concluded that RT yielded a local control rate equivalent to that obtained by conservative surgery but was associated with a lower complication rate. Robbins et al[131] from MDACC compared the outcome of patients who underwent supraglottic laryngectomy with that of patients who received RT for tumors judged suitable for partial laryngectomy. They found a better tumor control rate in the surgically

TABLE 35-8 Results of Radiation Alone for Early (T1-2) Squamous Cell Carcinoma of the Hypopharynx

Study/Author	Institution	Yr	Site	T Category (No. Patients)	Control
Vandenbrouck[151]	Institut Gustave-Roussy	1987	Piriform sinus	T1 (19) T2 (39)	90% 78% (c at 6 wk; 17% of patients subsequently experienced recurrence)
Rabbini[152]	University of Florida	2008	Piriform sinus	T1 (23) T2 (100)	85% (5-yr a) 85% (5-yr a)
Garden[149]	M. D. Anderson Cancer Center	1996	All hypopharynx	T1 (18) T2 (46)	89% (c) 77% (c)
Wang[153]	Massachusetts General Hospital	1997	All hypopharynx	T1 (24) T2 (51)	74% (5-yr a) 76% (5-yr a)

a, *Actuarial;* c, *crude.;* yr, *year.*

treated group, but the incidence of morbidity as a result of chronic aspiration was rather high. This finding contributed to the development of the current treatment policy at this institution. Briefly, supraglottic laryngectomy, with postoperative RT when indicated, is recommended for medically fit patients with bulky, infiltrative T2 and T3 tumors (e.g., invasion into the false cords or infrahyoid epiglottis). RT is selected for patients with either smaller or exophytic lesions (T2 or favorable T3) or patients with bulky lesions who are medically unfit for voice-conserving surgery.

T1 and T2 Hypopharyngeal Tumors

Although uncommon, these tumors can be treated with RT. Because of the high propensity for neck metastases, it is not unusual to see patients with small-volume primary disease suitable for RT but with large neck disease that requires multimodality treatment. In this situation, the options are to irradiate the primary tumor and neck nodes to high doses and dissect the residual neck mass about 6 weeks after RT or to perform a neck dissection followed by definitive RT to the primary tumor and with adjunctive RT to the neck. The latter approach is frequently recommended to patients who need to undergo dental extractions, requiring a delay in initiation of irradiation.[148]

Some results with primary RT for early-stage hypopharynx lesions are shown in Table 35-8. Compared with historical control data, local control rates seem to have improved with the use of hyperfractionated regimens. For example, analysis of MDACC data revealed actuarial local control rates of 86% for hyperfractionation (35 patients) and 63% for conventional fractionation (23 patients).[149] Similarly, for for T2 category piriform sinus tumors T2 piriform sinus primary tumors, Amdur et al[150] reported local control in 89% of patients treated with twice-a-day irradiation compared with 73% for those treated only once per day ($p = 0.09$). Although it is believed that hyperfractionation has improved the results, it should be realized that refinements in RT technique, including customized Cerrobend portal shaping, more generous coverage of the posterior route of spread, and the use of 6-MV x-rays with smaller penumbra, may all have contributed to the improvement of outcome. In addition, it is difficult to discern whether the rather subjective patient selection criteria have changed over the years and what impact this has on the results. Superficial and exophytic tumors, particularly in the vestibule, tend to be selected for primary RT, whereas infiltrative tumors of similar stage, especially in the apex, are chosen for multimodality treatment.

Management of Squamous Carcinoma Variants

Verrucous Carcinoma

Verrucous carcinoma is generally a well-differentiated, slow-growing, wartlike lesion. This tumor has a reputation for its relative radioresistance and a tendency for converting to a highly anaplastic neoplasm after RT.[36] However, no firm data are available to support this belief. A 5-year control rate of 66% was achieved in a series of 62 patients treated with RT at the Princess Margaret Hospital.[154] The majority of these patients had early-stage disease, although in more than half, the disease was T2 category. The majority of patients with recurrence were treated with surgery, and only 50% required a total laryngectomy, resulting in a laryngeal preservation rate of 81%. Only 3 (5%) patients died of the disease. Therefore, it is reasonable to treat patients with early verrucous carcinoma with radiation if the surgical option is a total laryngectomy. However, those with well-lateralized early tumors may be better suited for conservative surgery.

Sarcomatoid Carcinoma

Sarcomatoid carcinoma of the larynx has a similar reputation for radioresistance and for dedifferentiation after RT. In a review of 28 patients with T1-2 glottic sarcomatoid carcinoma who were irradiated, we found a 5-year actuarial control rate of 89%, which is similar to that obtained for ordinary squamous cell carcinoma.[155] Although the control rate for 7 patients with T2 tumor was only 57%, all patients with recurrences could undergo salvage surgery and only 1 patient died of the disease.

Neuroendocrine Carcinoma

Neuroendocrine carcinomas of the head and neck are extremely uncommon. They can be subgrouped into three categories. The most common is small cell undifferentiated carcinoma. Moderately differentiated and well-differentiated tumors have also been described and are sometimes referred to as atypical and typical carcinoids, respectively. The latter is extremely rare. The behavior of these three subtypes is similar to their more common counterpart in the lung.

In a report[156] describing the results of patients presenting with nonsinonasal neuroendocrine cancer, we found that the majority of patients (65%) presented with laryngeal or hypopharyngeal disease. RT was effective for locoregional control, but most patients succumb to distant metastases. The addition of chemotherapy appeared to decrease the risk of distant failure and translated into improved survival. Our current policy is to recommend neoadjuvant chemotherapy, typically with cisplatin and etoposide, followed by RT to the primary tumor and lymphatics. Concurrent chemoradiation is offered to patients who have initial large primary tumors or have a suboptimal response to chemotherapy alone.

LOCALLY ADVANCED CARCINOMAS

These tumors have been traditionally managed with total laryngectomy with or without postoperative RT. It had been

TABLE 35-9 Comparison of the EORTC and RTOG/Intergroup "High-Risk" Postoperative Radiation with or without Concurrent High-Dose Cisplatin Trials

	No. Patients	No. Patients by Primary Site		Median Follow-up	Locoregional Failure*		Grade 3 Toxicity*	
		Control	Exp		Control	Exp	Control	Exp
EORTC 22931[159]	334			60 mo				
Larynx		38	37		31%	18%	21%	41%
Hypopharynx		34	34		$p = 0.007$†		$p = 0.001$	
RTOG/Intergroup[160]	459			46 mo				
Larynx		44	42		28%	18%	34%	77%
Hypopharynx		26	15		$p = 0.01$‡		$p < 0.001$	

Exp, *Experimental.*
**Locoregional failure and grade 3 toxicity rates are for the combined larynx/hypopharynx group of patients in both trials.*
†EORTC 5-yr actuarial rate. ‡RTOG 2-yr actuarial rate.

believed that although primary RT can preserve the larynx for some patients, this approach generally results in a lower survival rate than does surgery. Series describing RT alone tended to be small, retrospective, and influenced by patient selection bias, so they were not generally accepted despite reporting results similar to surgery. Additionally, data from large national databases on patient outcomes suggest that patients treated with RT alone have worse survival outcome compared with those who undergo total laryngectomy.[157] However, as opposed to Phase III data, these patients are possibly not truly comparable, and it is likely that patients treated by RT alone often have worse performance status and increased comorbidities.

Although it remains debatable whether induction chemotherapy has a role in the management of head and neck cancers, it was randomized trials using induction therapy that popularized the concept of larynx preservation. This led to the RTOG/Intergroup Phase III trial 91-11, which randomized patients between three approaches: RT alone, induction chemotherapy and local treatment based on response, and concurrent chemoradiation[158] (see later discussion). This study added to our knowledge of the role of combined-modality treatment (concurrent chemotherapy and RT) and gave further validity to nonsurgical approaches for locally advanced larynx cancers.

Although tremendous advances have been made in laryngeal preservation, progress has also been made in rehabilitation of the patient postlaryngectomy. In particular, the popularity of tracheoesophageal hands-free speech has been a tremendous advantage for patients. Thus, whereas RTOG/Intergroup 91-11 demonstrated that high larynx preservation rates can be achieved with concurrent chemotherapy and RT, patients with large-volume T4 disease were not eligible for this approach and are still usually referred for surgery and postoperative RT. Although it may be debated whether equivalent cancer control rates can be achieved with nonsurgical approaches for advanced larynx and hypopharynx disease, many of these patients have such vast destruction of their laryngeal structure that it would be unlikely to retain good laryngeal function even after successful therapy. In particular, this problem makes these patients at high risk of aspiration. Thus, a laryngectomy with rehabilitation may offer them a better quality of life than larynx preservation.

Randomized trials evaluating concurrent chemoradiation in the post–head and neck surgical setting have recently been reported. For patients deemed to be at high risk of locoregional recurrence, both the EORTC and RTOG/Intergroup[159,160] trials demonstrated that RT plus concurrent chemotherapy improve locoregional tumor control compared with RT alone. The definitions of high risk were different in the two studies. Thirty percent to 40% of patients in both studies had laryngeal or hypopharyngeal cancers. The findings of these two important trials are summarized and contrasted in Table 35-9.

TABLE 35-10 Results of Radiation Alone for T3 Glottic Cancer

Study/ Author	Year	No. Patients	Local Control	Salvage
Lustig[80]	1984	47	65% (3-yr a)	ND
Hendrickson[81]	1985	39	56%	47%
Lundgren[163]	1988	141	44%	59%
Croll[164]	1989	30	70%	66%
Terhaard[165]	1991	104*	53% (3-yr a)	53%
Bryant[162]	1995	55	55%	ND
Wang[83]	1996	65	57% (5-yr a)	75%
Wylie[166]	1999	114	68% (5-yr a)	42%
Jackson[167]	2001	70	65%	25%
Hinerman[168]	2007	87	78%	ND

a, *Actuarial;* DSS, *disease-specific survival;* ND, *no data.*
**Includes all larynx.*

T3 Glottic Cancer

Most series of primary RT for T3 glottic tumors are relatively small. The available data are summarized in Table 35-10. Initial control rates range from 44% to 70%. Various twice-a-day fractionation schedules were found to control disease in approximately two thirds of patients.[153,161] In a comparative study, Bryant et al[162] found that the disease-specific survival of patients treated with RT and surgical salvage was not significantly different from that of patients who underwent surgery and, occasionally, postoperative RT. They noted, however, that the control rate of patients requiring an emergency tracheotomy before RT was very low (18%). Mendenhall et al[161] also found similar disease-free and overall survival (OS) between patients treated with RT and those treated with total laryngectomy (occasionally with postoperative RT). The success rate of salvage surgery for radiation recurrences is on average 50% but decreases with increasing initial disease extent.

Bulky Supraglottic Cancer

Most patients with bulky, infiltrative T3 supraglottic primary tumors (often with vocal cord fixation) have been treated with total laryngectomy with or without postoperative RT. Clinical trials addressing the role of neoadjuvant chemotherapy have enrolled predominantly this subset of patients.[169-171] The Veterans Affairs study,[169] for example, randomized patients to either surgery at the outset (standard therapy arm) or neoadjuvant chemotherapy, with the responders receiving radiation and the nonresponders undergoing surgery. This trial showed that no difference in survival and larynx preservation was achieved in a substantial number of patients. However, this trial did not answer the important question of whether induction chemotherapy was more beneficial than RT alone.

Subsequently, the RTOG/Intergroup trial 91-11 tested differing larynx preservation approaches.[158] An initial report was written in 2003,[158] and an update of long-term outcomes was published 10 years later.[172] Induction chemotherapy was the control arm, and RT alone or combined with concurrent cisplatin were two experimental arms. The primary endpoint of the trial was laryngectomy-free survival, and the updated manuscript demonstrated that both induction chemotherapy and concomitant therapy showed similar efficacy with regard to this endpoint and were superior to radiation alone. The results of this trial addressed several issues. In the initial report, survival rates were equivalent for all three approaches. However, in the update, the authors noted "a possibility of worse outcome with concomitant relative to induction chemotherapy."[172] Although no difference in late effects was detected, patients who had concomitant therapy had a much higher rate of deaths not as a result of treatment or the index cancer. Locoregional control and larynx preservation were superior with concurrent chemoradiation. The addition of chemotherapy did increase the toxicity of treatment, principally acute toxicity. The suspected grade 5 toxicity rate in patients receiving concurrent chemoradiation was 5%, and the total rate of severe toxic effects was 20% in patients receiving chemotherapy.[158] The 10-year cumulative rates of grades-3 to -5 toxicity did not differ between the three arms, and ranged from 31% to 38%. However, the authors did note that in patients alive with larynx and disease free, less than 5% were limited to liquids or unable to swallow. The authors were cautious in this conclusion because of the small numbers available for long-term followup.[172]

In Europe, investigators have looked at other methods of larynx preservation. One group followed up on data demonstrating that a taxane added to the induction regimen of cisplatin and 5-fluorouracil improved outcomes in patients with head and neck cancers[173] by testing this approach for larynx preservation. Pointreau et al reported a Phase III trial for advanced laryngeal and hypopharyngeal cancers comparing the three-drug combination to the standard two-drug combination of cisplatin and 5-fluorouracil.[174] Responders received RT (with or without concurrent chemotherapy) and nonresponders underwent laryngectomies followed by RT (with or without chemotherapy). Patients receiving the three-drug combination had more infections, but despite this, these patients had a better response rate. In addition, those randomized to receive docetaxel had a 70% larynx preservation rate compared with 58% for those patients who did not receive the taxane.

A second approach investigated in Europe was to compare sequential chemoradiation to alternating chemoradiation.[175] It was hoped that the alternating chemotherapy approach, which used lower doses of chemotherapy and RT (60 Gy compared with 70 Gy in the sequential arm) would mimic results seem with concurrent chemotherapy as in RTOG 91-11. Ultimately there was no difference in either toxicity or outcomes between the two approaches.

Other than cisplatin, there is little evidence for alternative agents to be used concurrently with radiation in the treatment of larynx cancer. Cetuximab is advocated as an alternative, particularly for patients who can not receive cisplatin, but data supporting this for larynx cancer is minimal. Although the trial testing the addition of cetuximab to radiation did show a general benefit[176] an unplanned subgroup analysis only showed a benefit for patients with oropharyngeal cancer. The TREMPLIN[177] study tested concurrent cisplatin versus cetuximab for patients with advanced larynx or hypopharynx cancer. All patients were treated with induction docetaxel, cisplatin, and 5-fluorouracil (5-FU), and responders were randomly assigned to concurrent high-dose cisplatin versus weekly cetuximab. In this Phase II trial with short follow-up, the authors could not detect differences in varying outcome endpoints. Further, the study did not demonstrate better results than those seen in the GORTEC 2000-01 trial[173] using the three-drug induction regimen followed by radiation alone for responders. Although questions remain regarding cisplatin or cetuximab as the optimal concurrent agent, the RTOG recently demonstrated no benefit to combining the two drugs rather than using cisplatin alone.[178]

T4 Larynx Cancer

Patients with T4 glottic and supraglottic tumors are best treated with total laryngectomy and irradiation, especially those with nonfunctioning larynges. The larynx preservation clinical trials testing neoadjuvant chemotherapy have not yielded encouraging results for patients with T4 disease.[169,171] Only 10% of the RTOG-Intergroup trial cohort had "T4" disease, most likely with minimal thyroid cartilage invasion that has been downstaged by the criteria of the current AJCC classification. In addition, many patients with large bulky disease often will be left with dysfunctional larynges, leading to aspiration if the therapy is successful in eradicating the tumors.

In addition to general indications of postoperative RT in head and neck cancers (i.e., close or positive margins, multiple nodes, extracapsular spread of nodal disease, or extension of the primary lesion into the soft tissues of the neck), post–total laryngectomy RT is also recommended when thyroid/cricoid cartilage invasion and extensive subglottic disease are present or emergency tracheotomy is performed before RT. In a series by Klein and Fletcher,[175] stomal recurrence occurred in 13 of 54 patients (24%) with radiologic evidence of subglottic disease who did not receive postoperative RT. None of these patients was salvaged. Yuen et al[179] analyzed the data of patients with T3 and T4 glottic lesions and found that surgery alone achieved locoregional control in 90% of patients without the adverse features listed previous compared with 73% of those with some of the adverse features; with surgery and postoperative RT, locoregional control was obtained in 46 of 50 patients (92%). In patients with stage IV supraglottic cancer, Goepfert et al[180] reported a 2-year determinate control rate of 37% for surgery alone as opposed to 63% for combined surgery and postoperative RT.

Several groups have investigated chemoradiation for T4 disease. Clinicians from the University of Chicago used an aggressive concurrent regimen of paclitaxel, 5-FU, hydroxyurea, and twice-daily RT and reported 4-year locoregional control and laryngectomy-free survival rates of 71% and 87%, respectively.[181] They suggested that patients who received induction chemotherapy in addition to concurrent chemoradiation fared best. At the University of Michigan, investigators are using a strategy of chemoselection.[182] Patients with

T4 disease are treated with one cycle of neoadjuvant chemotherapy. Those with a greater than 50% response are treated with chemoradiation, whereas the remaining patients go immediately to laryngectomy. Using this approach in 36 patients, 27 underwent chemoradiation, with a 58% laryngeal preservation rate. In both the Chicago and Michigan series, there were modest rates of permanent tracheostomies and gastrostomies.[181,182]

Locally Advanced Hypopharynx Cancer

Surgery is the treatment of choice for patients with T3-4 hypopharyngeal cancer, but adjuvant irradiation is almost always indicated. Vandenbrouck et al[183] performed a randomized trial comparing preoperative and postoperative RT in the treatment of hypopharyngeal tumors. They reported a statistically better 5-year OS in patients treated postoperatively (56%) compared with those treated preoperatively (20%). Table 35-11 lists the results of postoperative RT. Analyzing a series of patients treated between 1949 and 1976, El Badawi et al found that patients who received surgery and RT had significantly higher local control and 5-year OS than those who underwent surgery alone.[184] Frank et al[185] found that, despite having higher stages, patients who received postoperative irradiation had only a 14% locoregional failure rate compared with 57% in those treated with surgery only. When adjusted for confounding variables, particularly the stage discrepancy, they also found that patients receiving postoperative irradiation had an improvement in OS.

The issue of larynx preservation in hypopharyngeal cancer has been addressed by the European Organization for Research and Treatment of Cancer (EORTC) in a multiinstitutional Phase III trial.[188] Similar to the trial of the U.S. Department of Veterans Affairs for larynx cancer, the EORTC compared induction chemotherapy, followed by RT or surgery depending on the response, with immediate total laryngectomy and partial pharyngectomy. The 5-year actuarial voice-preservation rate was 35% in patients receiving chemotherapy, and there was no difference in survival among the two arms. This trial was recently updated, and the conclusions regarding the feasibility of larynx preservation without a compromise in survival are unchanged.[189] Long-term followup suggests a poor prognosis for these patients as 10-year OS in each arm approximated 13%, with overall disease recurrence rates of approximately 50%.

Patients with locally advanced hypopharynx cancer may be suitable for therapy with concurrent chemoradiation. These patients have often been included in trials in which the eligibility has been broad and included patients with locally advanced cancers of multiple head and neck sites.[190,191] In most studies, as a subgroup, hypopharyngeal cancers represent a minority of patients. These studies have demonstrated an advantage to concurrent chemoradiation, and none of the studies has suggested that this general conclusion does not apply to locally advanced hypopharyngeal cancers. With regard to organ preservation for patients with locally advanced hypopharynx cancer, the same principles used for patient selection of larynx cancer should be applied.[192,193]

TABLE 35-11 Results of Postoperative Radiation for Piriform Sinus Tumors

Study/Author	Year	No. Pts	Failure Above Clavicle	Overall Survival
El Badawi[184]	1982	125	14 (11%)	40% (5-yr)
Mendenhall[186]	1987	65	32 (49%)	28% (5-yr)
Vandenbrouck[151]	1987	199	35 (18%)	33% (5-yr)
Frank[185]	1994	35	5 (14%)	55% (3-yr†)
Slotman[187]	1994	32	5 (16%)	22% (5-yr)
Lefebvre[188]	1996	94*	25 (27%)	43% (5-yr)

*Intent to treat: only 89 patients received postoperative irradiation.
†Estimated from curve.

IRRADIATION TECHNIQUES AND TOLERANCE

Primary Radiation Therapy

T1-2N0 Glottic Carcinomas

T1-2N0 glottic carcinomas are typically treated with a pair of small, lateral, opposed photon fields that encompass only the larynx proper (Figure 35-5). In patients with a short neck, a 5- to 10-degree inferior tilt may be necessary to avoid irradiation through the shoulders. Other techniques include anterior wedged pairs or a four-field technique as described by Wang.[83] For T1 lesions, the field is centered on the true vocal cord and extends at or above the top of the thyroid notch superiorly to the lower edge of the cricoid cartilage inferiorly and from the anterior margin of the vertebral bodies posteriorly to approximately 1-cm falloff anteriorly. The superior and inferior borders are adjusted for T2 lesions that extend out of the glottis. When there is subglottic disease, at least one tracheal ring must be included in the fields. Typical field sizes range from 25 cm^2 (5 × 5 cm) to 36 cm^2 (6 × 6 cm). Harwood et al[78] reported better results with larger fields but acknowledged that at the time they used a free setup that likely accounted for some cases of geographic misses. Teshima et al randomized patients with stage I glottis cancers to treatment with either 25 cm^2 or 36 cm^2 fields and found that results were not different between the two field sizes. The authors emphasize that technique (appropriate coverage of the larynx and wedging to optimize the dose distribution) were critical in obtaining good outcomes, rather than field size per se.[194]

It is acceptable to use cobalt-60 gamma rays for treating glottic cancer because higher-energy beams (6 MV or greater) may underdose the anterior commissure region, particularly in thin patients. Most modern radiation oncology centers no longer have cobalt-60 units and thus rely on linear accelerators. Local control rates of more than 90% have been obtained for T1 lesions treated with 6-MV photons.[82,195] Sombeck et al[196] performed a dosimetric comparison between cobalt-60 and 6-MV beams and found a similar dose distribution except for the most anterior tissues (3 mm below the surface) where underdosing occurred with the 6-MV beam. Consequently, these authors cautioned against using the 6-MV beam for anterior commissure lesions. However, advocates of 6-MV photons for glottic cancer recommend either using tissue-equivalent bolus material for buildup or using a beam spoiler for thin patients or patients with anterior lesions.[195]

A contour or CT plan is obtained to evaluate the dose distribution and determine the need for wedges (Figure 35-6). Fifteen- or 30-degree wedges are often used and improve the dose distribution to the vocal cord, particularly for mid and posterior lesions. Some modern linear accelerators now have dynamic internal wedging to optimize the dosimetry. In the absence of wedging, optimizing the dosimetry can be achieved with "field in field" compensation. This is accomplished by using the internal multileaf collimation system built into the accelerator to create smaller fields within the larger fields to add the needed dose to areas being underdosed by the large "open" field. Some refer to this technique as intensity-modulated radiation therapy (IMRT), though this technique

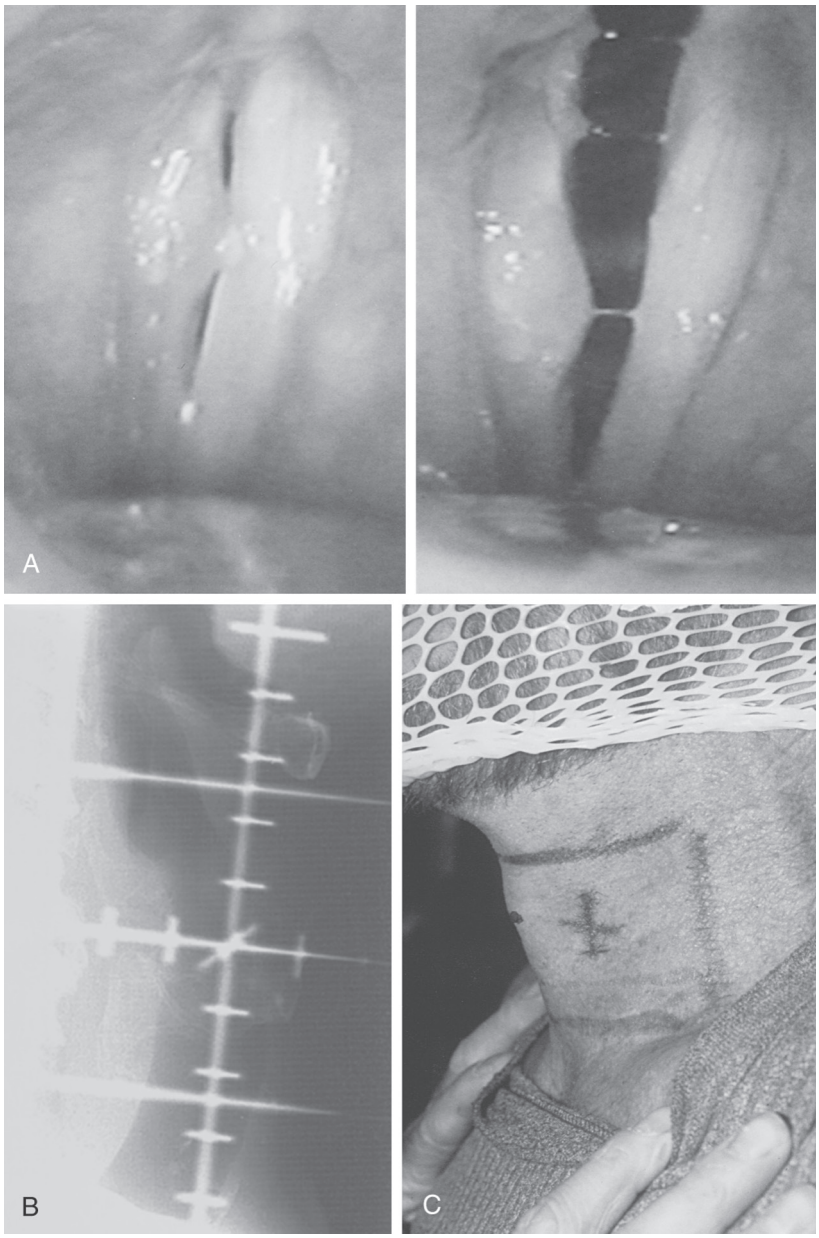


Figure 35-5 **A,** T1 glottic cancer. **B,** Simulation radiograph of a 5 × 5-cm field covering the glottis only for treatment of an early glottic tumor. **C,** Field for a T1 glottic cancer is outlined on the patient's skin.

has fewer fields than true IMRT and also is not inversed planned like true IMRT. Treating without wedges or other forms of compensation results in a less homogeneous distribution, but this may be advantageous for anterior lesions when the built-in dose differential (5% to 10%) is desirable. Unilateral lesions can be treated by unequally weighting (e.g., 3:2) the fields, favoring the side of the lesion.

Radiation doses range from 60 Gy to 70 Gy given in 2-Gy fractions. In general, a dose of 60 Gy is given to patients with no obvious clinical disease after stripping, 66 Gy to those with bulky T1, and 68 Gy to 70 Gy to patients with T2 lesions. Most centers deliver 2 Gy per day, five fractions a week. Several studies evaluating the importance of dose per fraction principally for T1 disease show that 2 Gy per fraction yields better control rates than 1.8 Gy per treatment (Table 35-12). Some centers even advocate the use of larger fraction sizes.[197] Investigators from Osaka randomized patients to either 2 Gy or 2.25 Gy per fraction and demonstrated an improvement in control in patients receiving the higher dose per fraction.[198] Many groups now treat patients with T1 glottic disease with more hypofractionated regimens, and 63 Gy in 28 fractions is a common regimen.[199]

Based on biologic rationale, it has been attempted to improve the control rate of T2 glottic carcinoma by increasing the total dose through hyperfractionation.[104] Two large retrospective studies have since been reported and both have suggested a trend ($p > 0.05$ but < 0.1) toward improved control with twice-daily treatments.[100,109] Mendenhall et al[109] compared 182 patients treated with once-daily or twice-daily treatment and reported the following 5-year actuarial local control rates: T2a, 82% and 83%, respectively; and T2b, 71% and 69%, respectively. The authors contemplated that the advantages of hyperfractionation were mitigated by selection bias. Garden et al[100] analyzed 230 patients, of whom 89 were treated with twice-daily fractionation. Local control rates were 79% and 67%, respectively, for patients treated with twice-daily or once-daily schedules. The authors hypothesized that although there may be a benefit to twice-daily treatment the data more

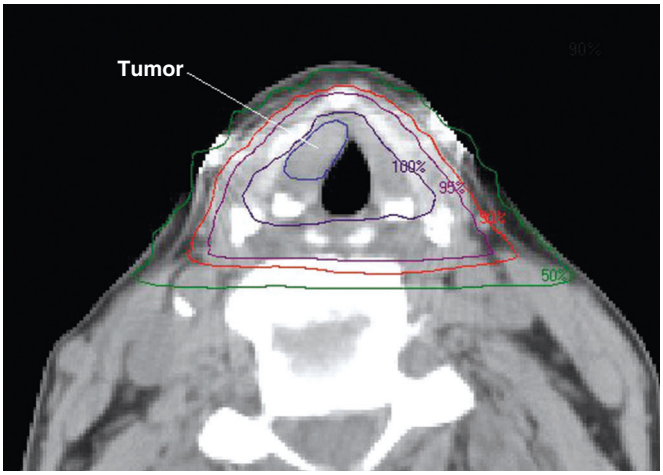


Figure 35-6 Dosimetry of parallel-opposed fields for early glottic carcinoma. Parallel-opposed, 5- × 5-cm fields were used with 30-degree wedges (heel anterior).

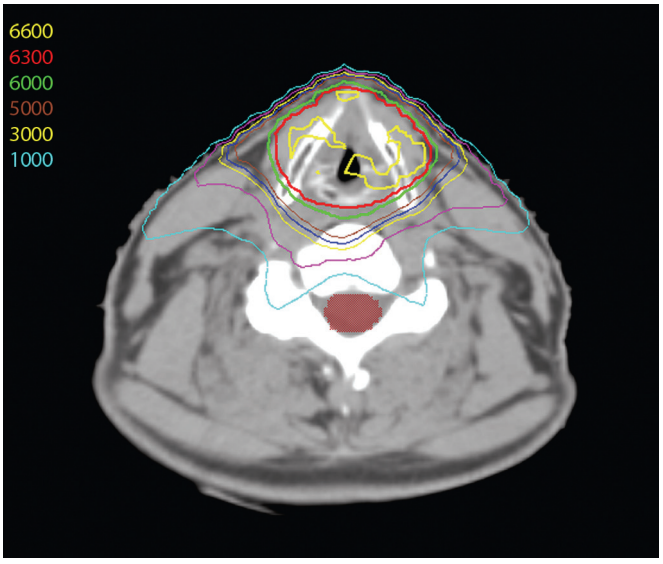


Figure 35-7 Dosimetric plan of three-field IMRT for a patient with T1 cancer of the true vocal cord. A dose of 63 Gy was prescribed in 28 fractions. Note the 3000-cGy isodose line at the anteromedial edges of the carotid vessels.

TABLE 35-12 Results of Irradiation for T1 Glottic Tumors by Fraction Size

Study/ Author	Year	No. Patients	Control Rate by Fraction Size	*p* Value
Schwaibold[200]	1988	56	1.8 Gy: 75% 2.0 Gy: 100%	<0.01
Mendenhall[201]	1988	75	2.0-2.2 Gy: 88% 2.25-2.3 Gy: 96%*	None
Kim[202]	1992	85	1.8 Gy: 79% 2.0 Gy: 96%	0.05
Rudoltz[203]	1993	91	2.0 Gy: 62% ≥2.0 Gy: 87%	0.006
Ricciardelli[204]	1994	42	1.8 Gy: 70% 2.0 Gy: 100%	<0.01
Yu[197]	1997	126	2.0 Gy: 66% 2.25-2.5 Gy: 84%	0.03
Burke[205]	1997	100†	<2.0 Gy: 44% ≥2.0 Gy: 92%	<0.01
Le[84]	1997	315	<1.8 Gy: 79% ≥1.8 Gy: 81-94%	0.05‡
Yamazaki[198]	2006	180	2 Gy: 77% 2.25 Gy: 92%	0.004

**Control in patients receiving > 60 Gy.*
†Includes T1 and T2 patients.
‡Tested continuous variable.

strongly favored a higher daily dose as a more important treatment factor because those patients treated with less than 2 Gy per day had control rates of 59% compared with an 80% control rate for those treated with more than 2 Gy per day.

The RTOG has completed accrual to a randomized trial designed to address this issue, and the results were presented in 2006. Hyperfractionation was associated with an increase in local control of approximately 9% compared with conventional RT at 5 years. Although this result was not statistically significant, it was noted that this small improvement was consistent with results seen in other hyperfractionation studies.[206]

If hyperfractionation is not feasible, daily fractions of greater than 2 Gy per day result in superior outcomes to smaller daily doses. If patients can be treated occasionally twice daily, but not for the entire course, altered schedules such as concomitant boost or those of the DAHANCA are appropriate.

RT of early glottic cancers with small fields rarely induces severe complications. Fletcher and Goepfert[79] described a 1% crude incidence of late edema in patients treated from 1962 to 1979. An analysis of late complications in 230 patients with T2 tumors revealed a 4% incidence of severe complications.[100] The complications were five cases of dysfunctional larynx or chondronecrosis requiring tracheotomy, one case of reversible laryngeal edema, and four cases of postoperative complications related to salvage.

Despite the absence of obvious complications, questions have arisen as to whether irradiation to the neck can lead to an increase in the incidence of stroke.[207] This has led several groups to assess the role of IMRT in irradiating the larynx while sparing the carotid vessels. Two recent reports[102,208] have demonstrated that IMRT can reduce the dose to the carotid arteries (Figure 35-7). A study by MDACC investigators also describes a preliminary experience using IMRT to treat 12 patients, and early data suggest local control rates equivalent to those expected for patients with stages I and II glottic cancer.[208]

T3N0 Glottic, T1-3 Supraglottic, T Any N Glottic, or Hypopharyngeal Carcinomas

T3N0 glottic and T1-3N0 supraglottic carcinomas have historically been treated with parallel, opposed, lateral portals covering the primary tumor and the subdigastric (level II) and midjugular (level III) lymph nodes. A matching anterior portal (with superior midline block to prevent overlap on the spinal cord) encompassing the lower jugular (level IV) and supraclavicular lymph nodes is also used (Figures 35-8 and 35-9). Hypopharyngeal cancers and larynx carcinomas with nodal involvement are treated with larger lateral portals covering the primary disease and the upper (level II) and midjugular (level III) nodes (under the insertion of the sternocleidomastoid muscle) and a matching anterior portal encompassing lower jugular (level IV) and supraclavicular lymph nodes. For



Figure 35-8 This 55-year-old man had squamous cell carcinoma of the right true vocal cord. The entire cord was involved, and there was subglottic extension. The cord was fixed, and the patient's disease was staged as T3N0M0. He received 70 Gy in 35 fractions with the shrinking fields shown and has been without disease for 30 months after therapy.

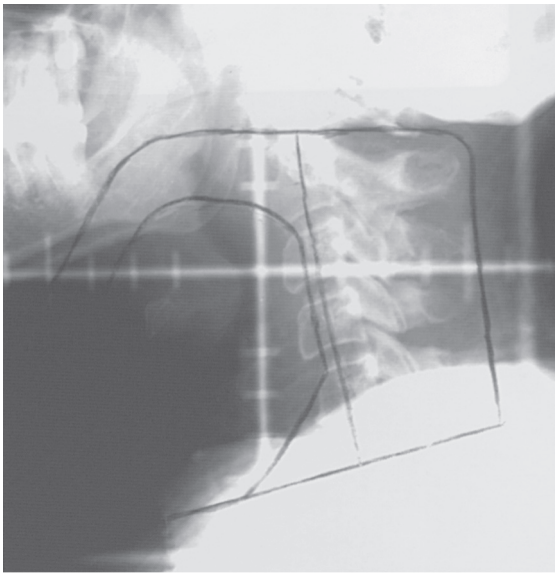


Figure 35-9 A 57-year-old woman presented with right otalgia and had a biopsy-proven squamous cell carcinoma of the epiglottis with extension of disease onto the aryepiglottic fold. The staging was T2N0M0, and she received 76.8 Gy at 1.2 Gy twice daily to the fields shown. She remains without evidence of disease.

hypopharyngeal tumors the inferior border must cover the entire piriform sinus including the apex (Figures 35-10 and 35-11). Because of the posterior location of the majority of these tumors, the off-spinal cord fields extend slightly more posteriorly than for other head and neck primary tumors. This necessitates more frequent portal verification. It is important to encompass the retropharyngeal lymph nodes generously in patients with hypopharyngeal tumors. However, supraglottic



Figure 35-10 This 74-year-old man had a biopsy-proven squamous cell carcinoma arising from the medial wall of the right piriform sinus. The lesion was 1 cm in diameter. The patient's disease was staged T1N0M0. He received 66 Gy in 33 fractions. The initial fields included draining lymphatics and retropharyngeal nodes; an off-spinal cord reduction was made at 42 Gy, and the large fields continued to 50 Gy. A final reduction was made to the total dose. The patient remained without evidence of disease until his death 8 years later.

lesions invading the medial wall of the piriform sinus only do not necessitate wide coverage of the retropharyngeal nodes.

The initial large field, on-cord RT can be accomplished with either cobalt-60 gamma rays or 6-MV photons depending on the neck diameter and the depth of the nodes. It is preferable to irradiate thick patients and those with deep-seated neck nodes with 6-MV beams. The off-cord and boost irradiations are administered with 6-MV beam with delivery of a supplemental dose to the posterior cervical nodes overlying the spinal cord with electron beams of appropriate energy.

Treatment of head and neck cancers with IMRT has rapidly increased since the early 2000s.[209,210] However, preliminary reports of IMRT have focused on treatment of nasopharynx and oropharynx cancer. In trials reporting more general head and neck results, the percentage of patients with laryngeal or hypopharyngeal cancers is extremely low.[211,212] However, particularly for hypopharyngeal cancers or patients with extensive nodal disease, the appeal of IMRT for potentially reducing xerostomia exists. The clinical target volume (CTV) for the primary tumor is the gross target volume (GTV) plus a minimum of 1 cm. In general, the entire larynx is included in the CTV. Planning target volume (PTV) expansion varies dependent on the method of treatment setup and verification; smaller PTVs can be used with image guided therapy (IGRT). However, more generous coverage is recommended in the cranial-caudal dimension, as swallowing can effect the location of the larynx in this plane. Examples of selected target delineation and isodose distributions for patients with advanced supraglottic cancer and a patient with hypopharyngeal cancer are shown in Figures 35-12 to 35-14.

Patients with T1 disease usually receive daily 2-Gy fractions to 64 Gy to 68 Gy. Patients with T2 to T3 lesions receive either daily 2-Gy fractions to 70 Gy, although preferably if they are to be treated with RT and no chemotherapy, they should be treated with either hyperfractionated twice-daily RT

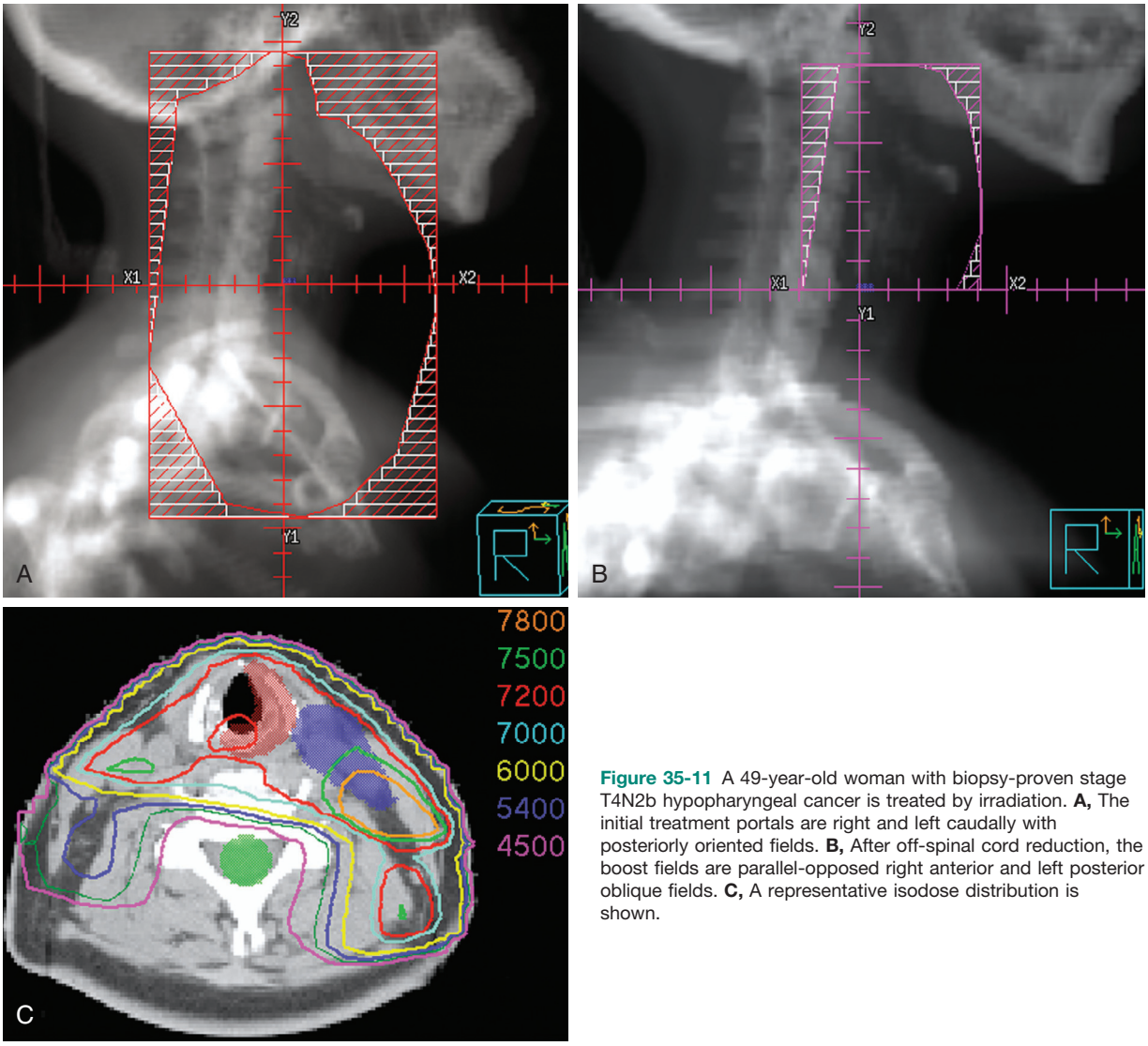


Figure 35-11 A 49-year-old woman with biopsy-proven stage T4N2b hypopharyngeal cancer is treated by irradiation. **A,** The initial treatment portals are right and left caudally with posteriorly oriented fields. **B,** After off-spinal cord reduction, the boost fields are parallel-opposed right anterior and left posterior oblique fields. **C,** A representative isodose distribution is shown.

with fraction size of 1.2 Gy to 76.8 Gy or, alternatively, are treated with an accelerated schedule such as concomitant boost or the DAHANCA schedule.[141] The concomitant boost schedule[213] treats patients to their large fields with 1.8-Gy fractions to 54 Gy and delivers the boost dose with fraction size of 1.5 Gy per fraction during the last 2.5 weeks as a second daily fraction to bring the total dose to gross disease to 72 Gy delivered in 6 weeks. The DAHANCA regimen also treats patients in 6 weeks but in 35 fractions. This is accomplished by delivering the boost as a second daily fraction once per week (for 5 weeks). Portal size is reduced to encompass the gross primary disease with 1-cm to 2-cm margins after reaching an elective dose of 50 Gy (2-Gy fractions) to 54 (1.8-Gy fractions) or 55.2 Gy (1.2-Gy fractions).

Because of larger radiation volume, RT of supraglottic and hypopharyngeal tumors induces a higher complication rate than treatment of early-stage glottic carcinomas. Mendenhall et al[140] have reported a 6% severe acute and late complication rate in 211 patients receiving primary RT for supraglottic carcinomas. In a series of 236 patients treated with hyperfractionation at MDACC, 21 patients developed grade 3 late complications; this includes two patients who died of massive hemoptysis 2 months posttherapy and tracheal necrosis after a tracheotomy, respectively, and two patients who underwent laryngectomy for necrosis.[142] However, the 3-year actuarial complication rate has decreased from 14% to 8% since increasing the interfraction interval from 4 to 6 hours. We currently maintain the 6-hour interfraction interval for twice-daily irradiation.

Postoperative Radiation Therapy

The technique for postoperative RT is similar to that for primary RT. Briefly, initial fields cover the operative and tumor bed. Patients with adverse features requiring postoperative irradiation are at increased risk for stomal failure. Patients were historically treated with a three-field technique: two lateral-opposed fields and an anterior low-neck portal (Figure 35-15). The inferior borders of the lateral fields are in close proximity or even include the superior aspect of the stoma. The stoma itself is included in the anterior low-neck field. Occasionally it is complicated to find the ideal location for the match because of the stomal location. Caudally oriented fields often provide a simple solution for this problem and obviate concerns regarding matching through the stoma or needing to block the stoma for safety reasons.[214]

IMRT is being used more often to treat these patients. This allows tailoring of the dose to high- and intermediate-risk

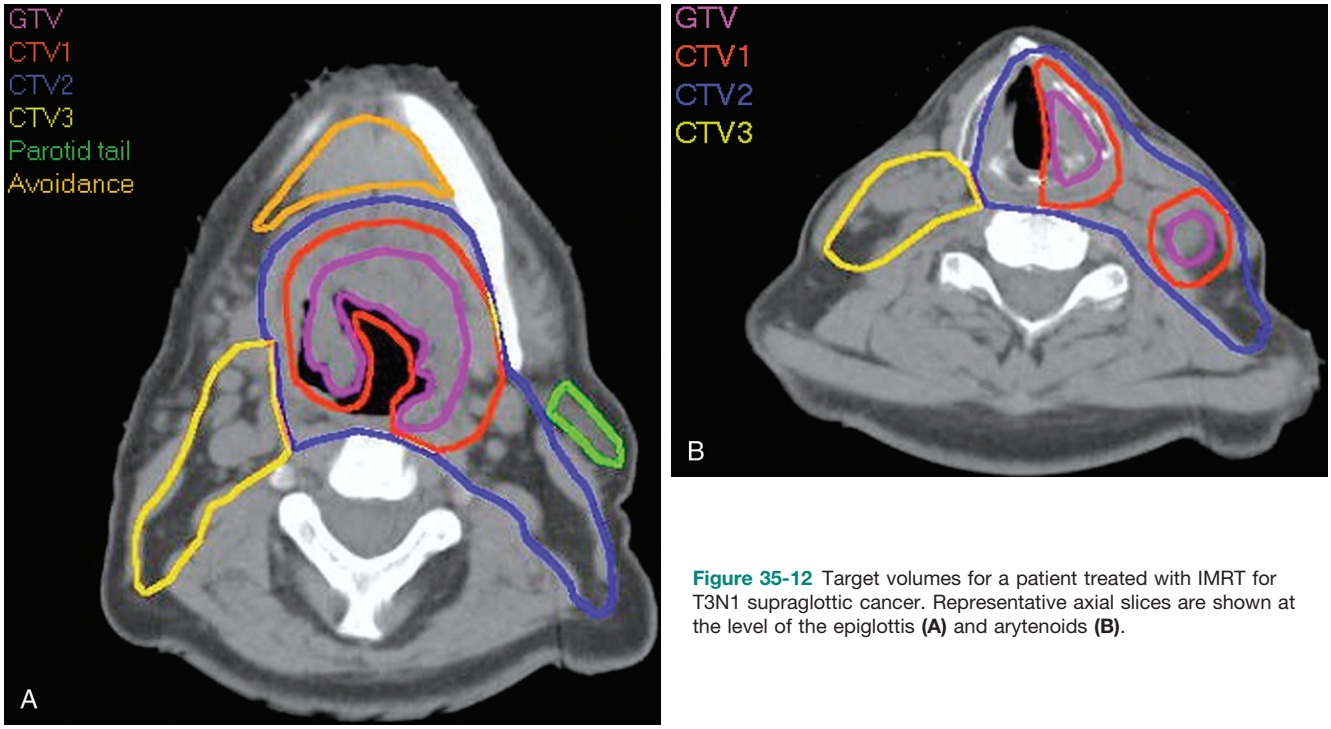


Figure 35-12 Target volumes for a patient treated with IMRT for T3N1 supraglottic cancer. Representative axial slices are shown at the level of the epiglottis **(A)** and arytenoids **(B)**.

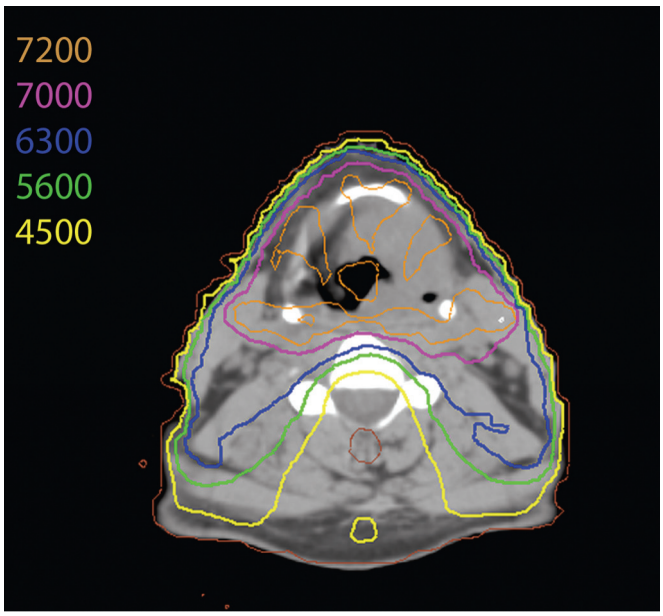


Figure 35-13 Dosimetric plan shown on an axial CT slice of a patient with T3N0 epiglottic cancer treated by IMRT. The bulky tumor can be seen at the level of the superior aspect of the hyoid. The tumor involves the epiglottis, fills the left preepiglottic space, and involves the left aryepiglottic fold and arytenoid. A dose of 70 Gy was prescribed to CTV1 (gross disease and margin). Because of concerns of larynx motion, the entire supraglottic larynx is included in CTV1. CTV2 and CTV3 are dosed to 63 Gy and 56 Gy, respectively. CTV2 included level 3 nodes, and CTV3 included level 2 and 4 nodes. The patient was treated with concurrent cisplatin.

regions, avoids a match because the entire volume can be encompassed by the fields, and, particularly in patients who are node-positive, may allow for parotid sparing (Figure 35-16).

The operative bed is treated to 57.6 Gy, and areas of increased risk are boosted to 63 Gy given in 1.8-Gy fractions[215] or 56 Gy and 60 Gy, respectively, given in 2-Gy fractions. These dose prescriptions are also applicable to targets delineated with IMRT. No dose reduction is applied for patients who have had free jejunal autograft reconstruction because no significant complications have been observed in a series of 29 patients treated to these doses.[216] The dose delivered to surgically undisturbed elective sites is 50 Gy to 54 Gy. The stoma is treated to 50 Gy to 54 Gy and boosted only if there was extensive paratracheal or soft-tissue extension in the region of the stoma.

TREATMENT ALGORITHM, CONTROVERSIES, CHALLENGES, AND FUTURE POSSIBILITIES

Treatment Algorithm

A treatment algorithm for laryngeal and hypopharyngeal cancer is shown in Figure 35-17.

Tis, T1, T2 tumors: These tumors nearly always can be treated with a single modality, either voice-sparing surgery or RT. Infiltrative T2 hypopharyngeal tumors may be considered similar to T3 disease.

T3: Options include either total laryngectomy (with pharyngectomy for a hypopharyngeal primary tumor) or a voice-preservation approach. Concurrent cisplatin and RT has been demonstrated to result in higher rates of larynx preservation than neoadjuvant chemotherapy or RT alone and is usually the treatment of choice, although it does have a modest toxicity profile. RT alone is an option for selected

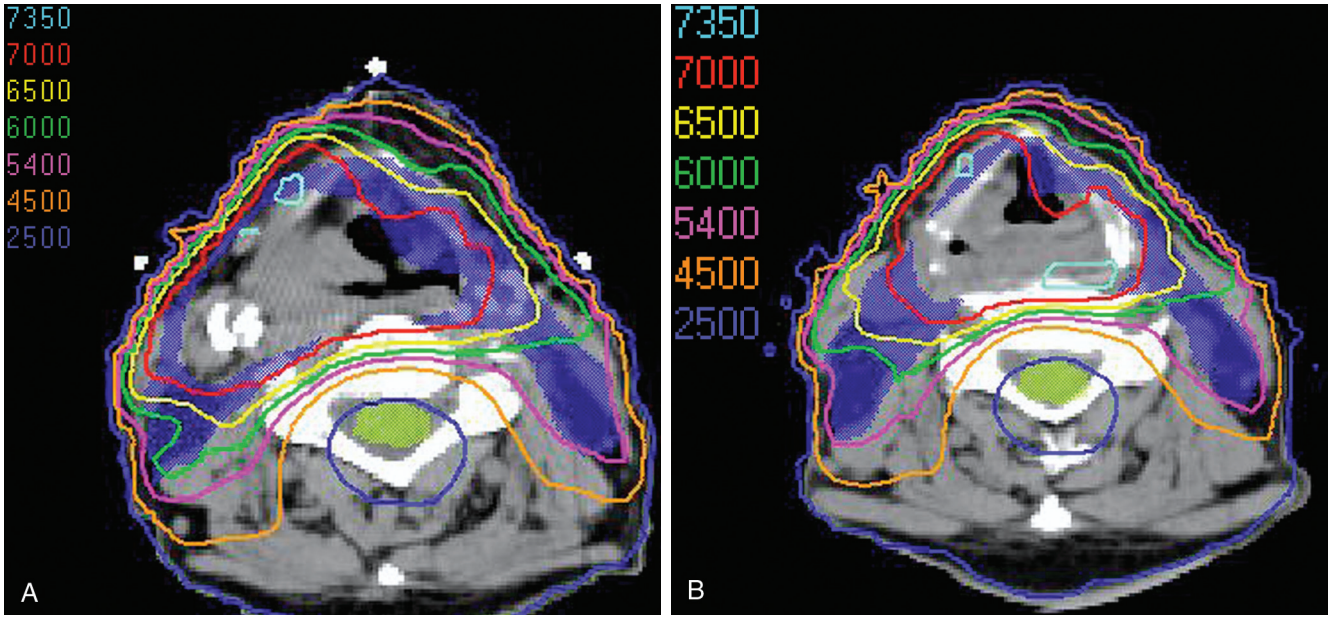


Figure 35-14 Isodose distributions on axial CT images of a patient with T3 carcinoma of the hypopharynx treated with concurrent chemotherapy and IMRT. Representative slices through the vestibule **(A)** and apex **(B)** of the piriform sinus are shown. The high-dose target volume for gross disease and the margin (CTV1) is transparent so the underlying tumor can be visualized. CTV1 was planned to 70 Gy and CTV2 *(blue)* was planned to 50 Gy. Treatment was planned with two sequential plans so that both targets would be fractionated at 2 Gy per fraction.

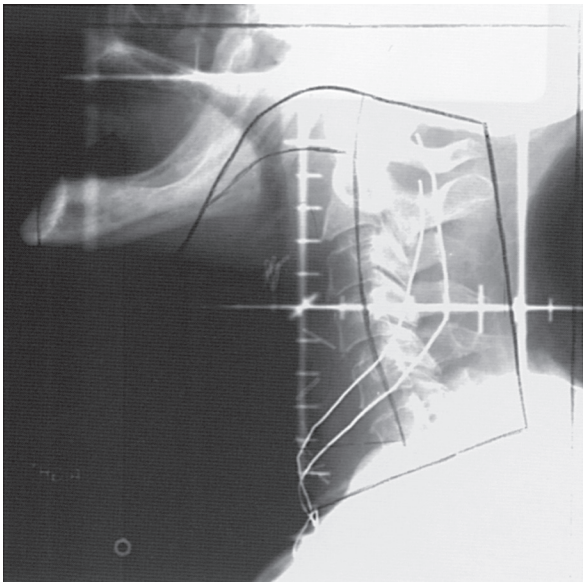


Figure 35-15 A 46-year-old man was diagnosed with squamous cell carcinoma of the right piriform sinus. He underwent a laryngopharyngectomy with jejunal autograft for repair. The tumor was 6 cm in the largest dimension, and it had invaded the soft tissues of the neck. He received postoperative radiation of 60 Gy to the fields shown. The scar and stoma are wired on the skin. One year after his therapy he developed pulmonary metastases and died with metastatic disease.

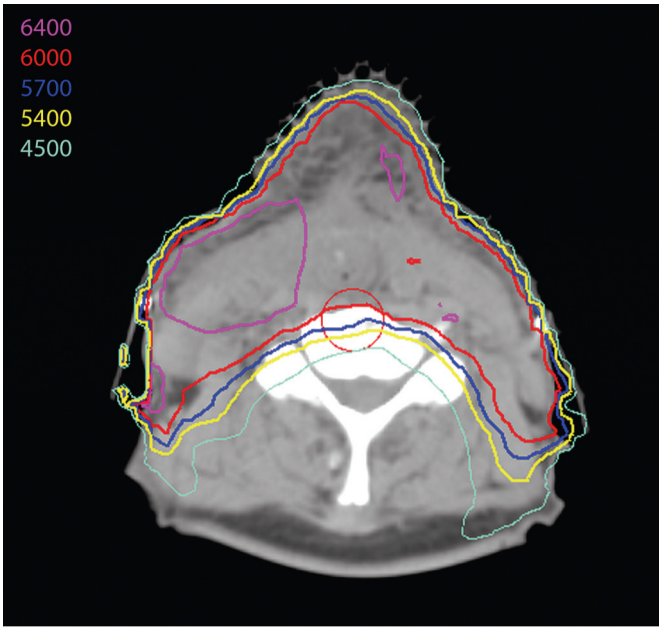


Figure 35-16 Dosimetric plan used for treatment of a patient with advanced supraglottic cancer. His disease was staged T4N2c, and he was treated initially with total laryngectomy and bilateral neck dissections. The pathology report demonstrated extracapsular spread in his right-sided levels 2 and 3 nodes. Radiation was delivered postoperatively in 30 fractions. The tumor bed was specified a dose of 60 Gy, although the area of right-sided nodal disease was specified a dose of 64 Gy. He was also treated with concurrent chemotherapy.

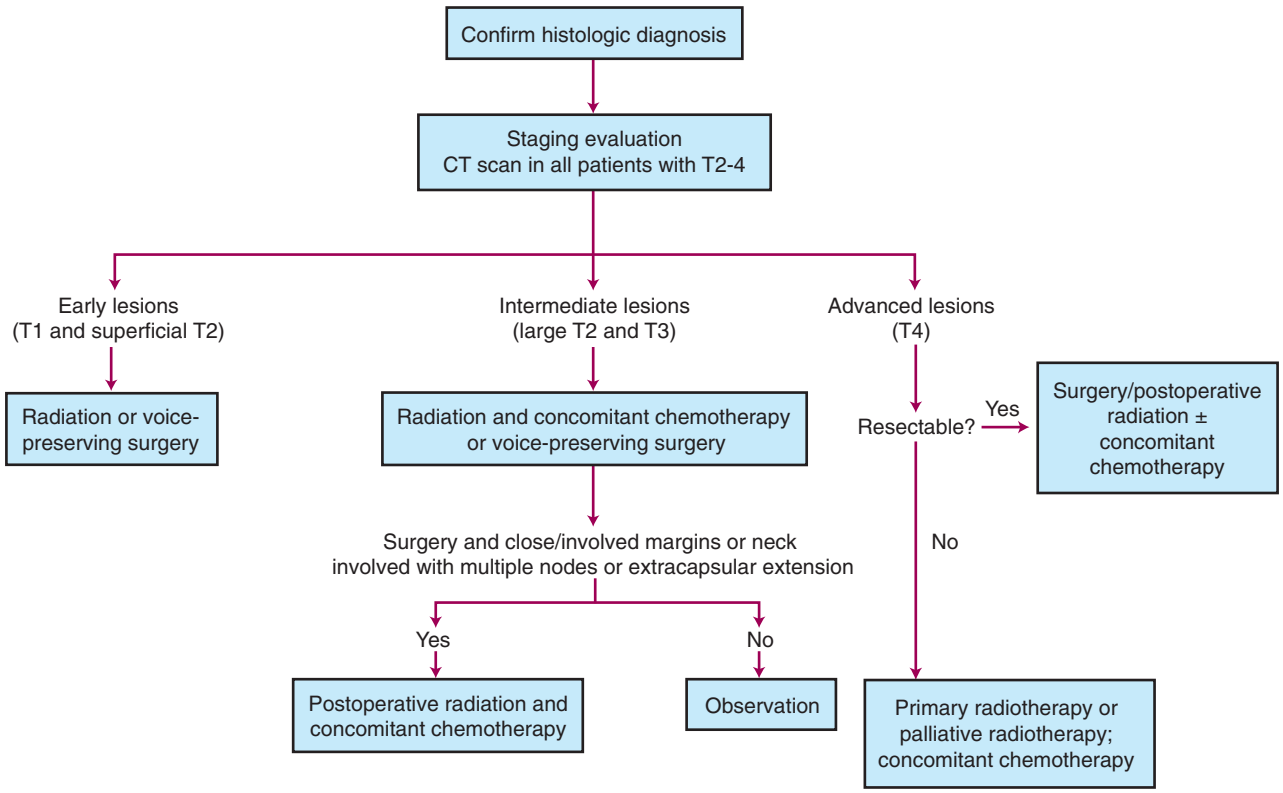


Figure 35-17 Treatment algorithm for patients with cancer of the larynx or hypopharynx.

patients who may desire larynx preservation but are deemed medically unsuitable for chemotherapy.

T4: Surgery with adjuvant postoperative RT remains the treatment of choice. Patients considered to have high-risk features (inadequate surgical margins or soft-tissue spread of disease) may require concurrent chemoradiation in the adjuvant postoperative setting. Highly selected patients with T4 disease may be treated similar to those with T3 disease using concurrent chemoradiation in an attempt at larynx preservation.

N1: If RT is used to treat the primary tumor, then surgery is reserved for any residual nodal mass. If surgery is chosen for primary treatment, then neck dissection is performed and RT is used if there is extracapsular extension or >2 pathologically involved nodes.

N2 and N3: Combined surgery and RT is used for the neck disease and sequencing chosen based on the preferred modality for treatment of the primary tumor.

M1: Systemic therapies are used for patients with good performance status; local therapies are provided for palliation if required.

Controversies, Challenges, and Future Possibilities

In the past two to three decades, we have seen seminal trials performed to maximize preservation of the larynx in patients requiring treatment for laryngeal and hypopharyngeal carcinoma. Ultimately, the concept of larynx preservation was vaguely defined. Trials designed with a primary endpoint of an intact larynx ignored the multiple functions in addition to voice that the larynx provided, particularly swallowing functions (at least with regard to the primary endpoints). Thus, although in 2014 it can be proclaimed that high-dose cisplatin delivered concurrently with radiation is the standard of care for managing locally advanced larynx cancer, this conclusion should be accompanied with caveats.

The results of RTOG 91-11 led us to conclude that most patients with laryngeal cancer can be managed without surgery except for those with T4 disease.[158] This conclusion has come under more scrutiny because SEER data have suggested that survival rates for larynx cancer have decreased in recent years.[157] However, whether this change in survival can be attributed to a greater use of larynx preservation remains moot.[80]

Future directions depend on both our continued understanding of the disease and a better understanding of the impact our therapies have on the laryngopharyngeal structures and how alterations from either disease or therapy impact quality of life. To date, several decades of investigations have not necessarily improved survival rates but have made assumptions that we have improved the quality of life in our patients because we have preserved the larynx in many patients that otherwise would have been treated with laryngectomy. What is required is developing treatments with less toxicity or better prediction models of either the efficacy (with regard to the cancer) of varying treatments in specific individuals or the impact a treatment will have in an individual with regard to function.

In cancer therapy, in general, there has been great interest in targeted therapy with the use of biologic agents. In head and neck cancers, EGFR has been attractive as a target, and preliminary results with concurrent radiation and EGFR blockade have been interesting in terms of potential enhancement of radiation response without an increase in tissue toxicity. In patients who have high levels of EGFR with larynx cancer, this approach has great theoretical appeal in lieu of concurrent RT and chemotherapy. Future directions in treatment of cancer of

the larynx may actually have a de-intensification of therapy for selected patients in whom an effective therapy can be selected with less toxicity. To date, however, in the United States, there has not been a follow-up to RTOG 91-11.

Additional directions will be in better understanding which patients will, after effective tumoricidal therapy, have a functioning larynx and which patients will be subject to chronic aspiration or swallowing dysfunction. The full integration of speech and swallowing assessments before treatment disposition is becoming a critical component in the treatment selection process.

Laryngeal carcinoma (and, to a lesser extent, hypopharyngeal carcinoma) is a curable disease. Great challenges remain, however. We still need to understand which subgroups do not benefit from their selected therapies and have disease relapse and determine if we can further improve survival rates by selecting the appropriate treatment in these patients. In the remaining patients who can be cured, we need to determine the least toxic approaches and continue to explore second primary cancer prevention because the development of less curable malignancies remains an obstacle to prolonged survival in this patient population.

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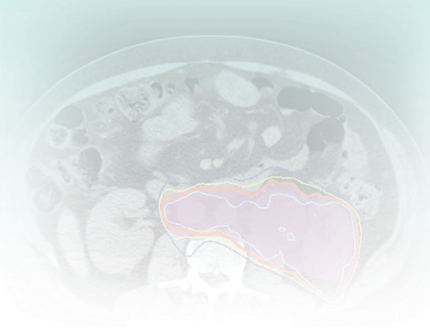
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CHAPTER

36 Sinonasal Cancer



Jonathan J. Beitler, Mark W. McDonald, J. Trad Wadsworth, and Patricia A. Hudgins

INCIDENCE AND EPIDEMIOLOGY

Sinonasal cancers comprise less than 1% of all malignant neoplasms and the American Cancer society estimates 2,000 Americans develop cancers of the nasal cavity and paranasal sinuses annually. Men are 50% more likely to be affected. Approximately 40% to 50% occur within the nasal cavity, 30% to 40% within the maxillary sinus, 10% in the ethmoids, and less than 5% in the frontal and sphenoid sinuses.

Sinonasal cancers are more common in carpenters, sawmill personnel, and nickel workers. These tumors are more frequently diagnosed in regions outside the United States, such as Japan and South Africa.

BIOLOGIC CHARACTERISTICS

The natural history of sinonasal cancer depends on the anatomic site, the histologic type, and the stage of the tumor. Distinct from other head and neck sites, nonsquamous cell cancers predominate. In a series of 386 patients with nasal and paranasal sinus tumors treated from 1975 to 1995, squamous cell carcinoma was the most frequent histology but was found in only one third of the patients. The incidence of squamous cell cancers of the paranasal sinuses appears to be decreasing (Annual Percentage Change –1.5% from 1973 to 2009).

Three quarters of sinonasal cancers have TP53 mutations with more than half the mutations being missense mutations.

STAGING EVALUATION

Staging includes a history, head and neck examination including fiberoptic exam, computed tomography (CT) with contrast, magnetic resonance imaging (MRI), and especially in advanced disease, positron emission tomography (PET)/CT scanning.

PRIMARY THERAPY

Radiation is generally selected for the treatment of the nasal vestibule and anterior nasal fossa and yields high locoregional control (LRC) rates with good cosmetic results. Most paranasal sinus tumors should undergo primary surgery, if resectable. Patients who are nonresectable undergo preoperative or definitive photon or proton therapy with or without concurrent chemotherapy, dependent on histology and patient suitability.

ADJUVANT THERAPY

A combination of surgery and radiotherapy (usually given in postoperative setting) is recommended for the management of more advanced resectable cancers. Because of the rarity of these cancers, as well as the varied histologies, randomized studies showing the value of adjuvant radiation therapy, with or without concurrent chemotherapy, are not available.

LOCALLY ADVANCED DISEASE AND PALLIATION

For squamous cell cancers, concurrent chemotherapy is frequently used with definitive radiotherapy in the management of inoperable tumors. The use of concurrent chemotherapy is based on data from other head and neck cancer sites.

Definitive radiotherapy can yield local control in a few patients with locally advanced carcinomas who are medically or surgically unresectable.

INTRODUCTION

Sinonasal neoplasms are so rare and encompass such a broad range of anatomical sites and differing histologies that obtaining clinical expertise at one center is particularly difficult. Surgery and radiotherapy are complicated because these tumors are often located close to multiple critical structures (the eye, brain, optic nerves and chiasm, brainstem, and cranial nerves). Aesthetic considerations argue for less radical surgical resection especially if cure is unlikely.

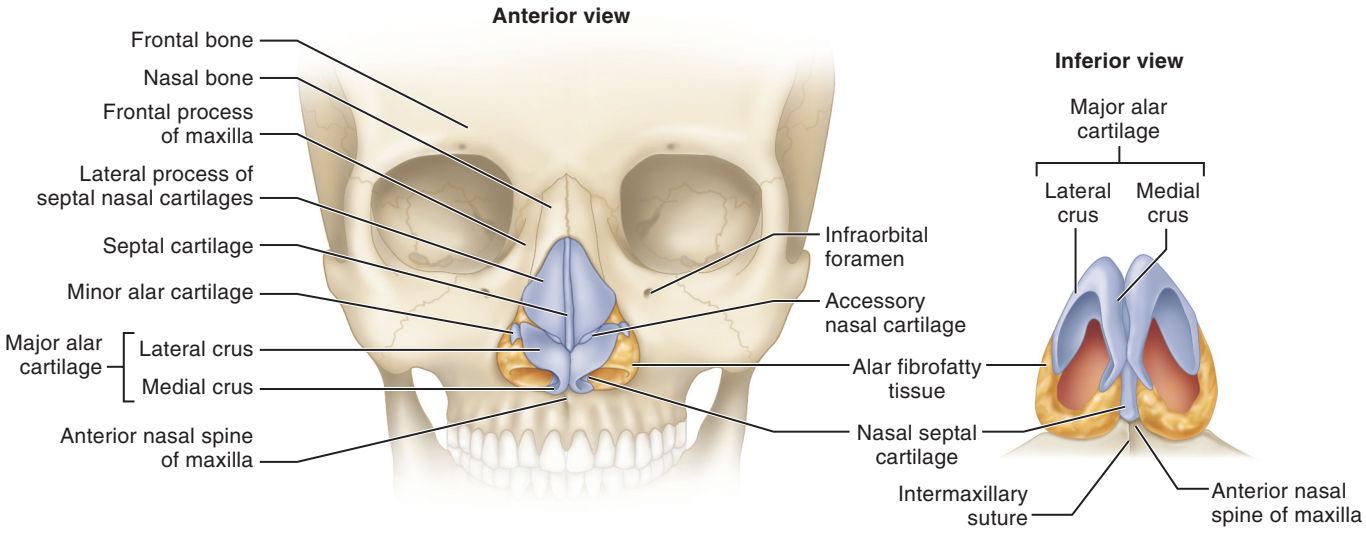
Although the American Joint Committee on Cancer (AJCC) divides the nasal cavity into four subsites[1] (the septum, floor, lateral wall, and vestibule; Figure 36-1 and eFigure 36-1) the nasal vestibule is best considered independently because cancers of the nasal vestibule remain confined until late in their course.

The treatment outcome of patients with carcinoma of the maxillary and ethmoid sinuses has improved if one compares the results, by decades from the 1960s to the 1990s.[2] Using the Danish Head and Neck Cancer Group (DAHANCA) database, the overall 5-year survival from sinonasal cancers treated from 1995 to 2004 were 20% superior to the 1982 to 1991 reference study.[3] In this review of 204 patients, treatment failures occurred in 46% with primary site being involved in 81% of failures. There was a component of nodal failure in 24% and component of distant failure in 14%. The predominant pattern of failure being local is echoed by other publications.[4] Advances have been made in methods of extirpation including skull-base surgery, reconstruction, and highly conformal proton and photon techniques that enable avoidance of adjacent critical normal tissues.[5] Many are gaining experience with endoscopic resections but long-term data on efficacy of this technique as well as radiation using protons is still lacking. The role of chemotherapy for most of these neoplasms has yet to be defined.[5]

This chapter focuses on epithelial neoplasms originating in the nasal cavity or paranasal sinuses. Other histologic types such as sarcomas, lymphomas, and melanomas are discussed in their respective chapters.

ETIOLOGY AND EPIDEMIOLOGY

Cancers of the nasal cavity and paranasal sinuses are uncommon neoplasms, with approximately 2000 Americans diagnosed per year.[6] Tumors of the maxillary sinus are twice as frequent as those of the nasal cavity and ethmoid sinus, and



eFigure 36-1 Anatomy of sinuses: Anterior/lateral and inferior views.

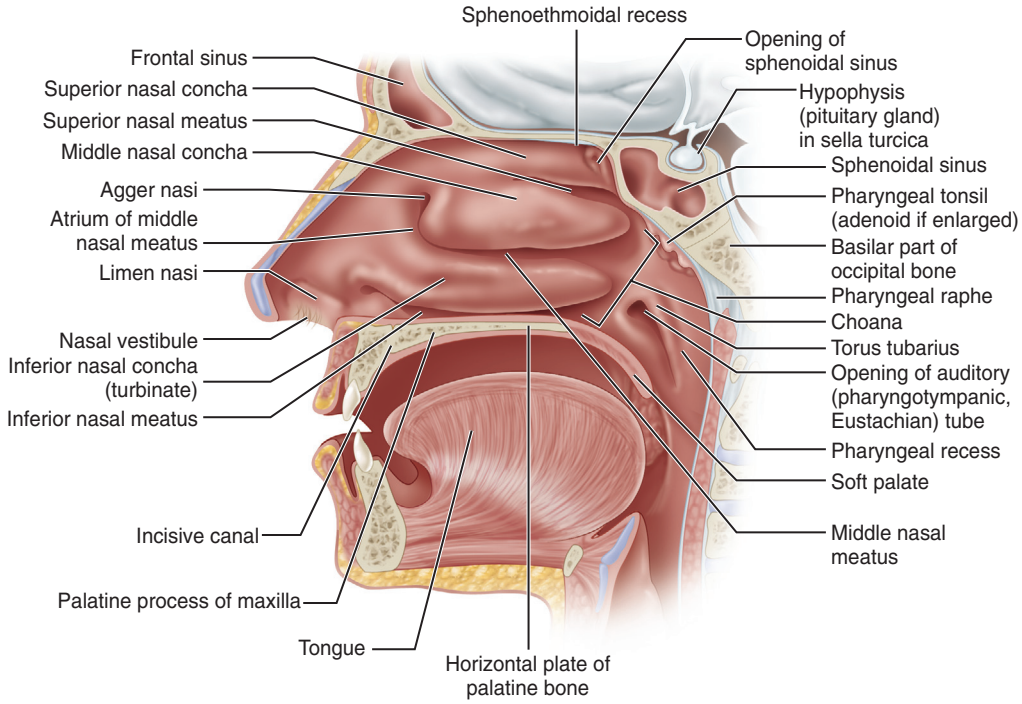


Figure 36-1 Anatomy of sinuses.

neoplasms of the frontal and sphenoid sinuses are extremely rare. Sinonasal neoplasms occur twice as frequently in men as in women. These tumors are more frequently diagnosed in regions outside the United States, such as Japan and South Africa.

A number of sinonasal cancers are relatively more common in people engaged in certain occupations or exposed to some chemical compounds.[7-12] Excessive numbers of sinonasal squamous cell cancers were seen in bakers, pastry cooks, grain millers, construction workers, carpenters and joiners with at least 15 years in the wood manufacturing industry, farm workers, and female textile workers.[13] Squamous cell carcinoma of the nasal cavity develops more often in nickel workers.[14] Adenocarcinoma of the nasal cavity and ethmoid sinus occurs more frequently in carpenters and sawmill workers who are exposed to the dust of mainly hard and exotic woods.[7,8,10,12] From a review of 358 sinonasal cancers with or without exposure to wood dust, TP53 mutations occurred in all histologies with an overall frequency of 77% but were most common in adenocarcinoma (overall rate 2.0 compared with squamous cell cancer).[15] The risk of TP53 mutations was significantly increased in association with duration, average level, and cumulative level of wood dust exposure. K-ras mutations were reported in 13% of sinonasal adenocarcinomas.[16] Synthetic wood, binding agents, and glues may also be involved as cocarcinogens.[10]

A pooled analysis of 12 case-controlled studies evaluated occupational exposure to formaldehyde, silica dust, textile dust, coal dust, flour dust, asbestos, and man-made vitreous fibers as risk factors for the development of sinonasal cancers.[17] Pooled analysis suggested that formaldehyde was a risk factor for sinonasal adenocarcinoma development but there was a strong association between wood dust and formaldehyde exposure and there were not sufficient formaldehyde only subjects to answer the question. The International Agency for Research on Cancer found that with high professional exposure to formaldehyde and limited wood dust exposure (e.g., embalmers, pathologists, chemical workers) there was no increased mortality from sinonasal cancers.[18]

Maxillary sinus carcinoma was associated with a radioactive thorium-containing contrast material, thorium dioxide (Thorotrast), which was used for radiographic study of the maxillary sinuses decades ago.[9,10] Occupational exposure in the production of chromium, mustard gas, isopropyl alcohol, and radium also increases the risk for sinonasal carcinomas.[9]

Cigarette smoking is reported to increase the risk of nasal cancer, with a doubling of risk among heavy or long-term smokers and a reduction in risk after long-term cessation. After adjustment for smoking, a significant dose-response relation was also noted between alcohol drinking and risk of nasal cancer.[12]

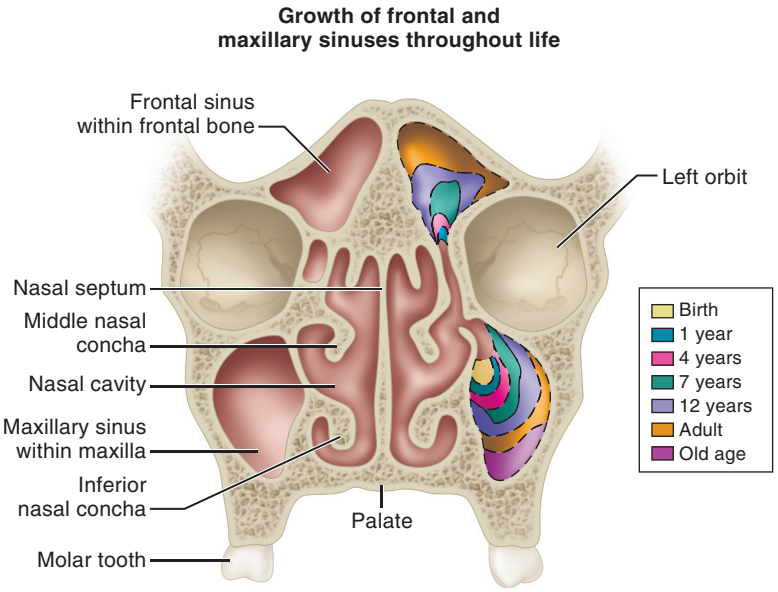
PREVENTION AND EARLY DETECTION

In general, carpenters, sawmill workers, and workers involved in the production of nickel, chromium, mustard gas, isopropyl alcohol, and radium should use appropriate face masks or other strategies to reduce occupational exposure to potential carcinogens. Individuals who develop persistent nasal or sinus symptoms should undergo evaluation.

PATHOLOGY, BIOLOGY, AND PATHWAYS OF SPREAD

The disease course depends on the anatomic site, the histologic type, and the stage of the tumor. The size and configuration of the paranasal sinuses change with age (eFigure 36-2).

Classifying cancers into the bins of squamous cell carcinoma (squamous cell, transitional, and verrucous), adenocarcinoma, glandular carcinoma (adenoid cystic carcinoma and mucoepidermoid carcinoma), and undifferentiated carcinoma, Dulguerov et al[2] identified 386 patients with nasal and paranasal sinus tumors treated between 1975 and 1995 and



eFigure 36-2 Paranasal sinuses: Size and configuration change with age.

TABLE 36-1 Sinonasal Cancer Histology

Histology	*n*	%
Squamous Cell	126	32.6
Sarcoma	52	13.5
Esthesioneuroblastoma	42	10.9
Glandular	39	10.1
Adenoid cystic	35	9.1
Lymphomas	38	9.8
Melanoma	34	8.8
Undifferentiated	30	7.8
Adenocarcinoma	25	6.5

Data from Dulguerov P, Jacobsen MS, Allal AS, et al: Nasal and paranasal sinus carcinoma. Are we making progress? A series of 220 patients and a systemic review. Cancer 92(12):3012–3020, 2001.

excluded nasal vestibule cancers. Squamous cell carcinoma was the most frequent histology but was only found in one third of the patients (Table 36-1).

Nasal Vestibule

The nasal vestibules are the two entry points into the nasal cavity. Each is a triangle-shaped space situated in front of the limen nasi and defined *laterally* by the lateral crus and alar fibrofatty tissue, *medially* by the medial crus of the alar cartilage and the nasal septum and the distal end of the cartilaginous septum, and columella (see Figures 36-1 and eFigure 36-1). The nasal vestibule is covered by skin and, therefore, lesions at this location are essentially squamous cell skin cancers[19] but may occasionally be basal cell carcinoma,[20] sebaceous carcinoma,[21] melanoma,[22] or non-Hodgkin's lymphoma.[23] Nasal vestibule cancers are analogous to cancers of the anal margin. Human papilloma virus has been implicated in the development of nasal septal cancers.[24]

Cancers of the nasal vestibule are said to arise preferentially on the medial wall, which is the nasal septum.[25] Nasal vestibule carcinomas can spread by invasion of the upper lip, gingiva-labial sulcus, premaxilla, or nasal cavity. Vertical invasion may result in septal (membranous or cartilaginous) perforation or alar cartilage destruction. Lymphatic spread from nasal vestibule carcinomas is usually to the ipsilateral facial (buccinator and mandibular) and submandibular nodes. The buccinators nodes[26] can be found on the buccinator muscle or in the fat of the buccinator space (Figure 36-2 *A,B*).

The buccinators nodes are divided into anterior or posterior buccinator depending on their relationship to the facial vein. The mandibular nodes[26] include the supramaxillary nodes, the supramandibular nodes, and the inframandibular nodes and lie along the external surface of the mandible adjacent to the facial artery and anterior to the masseter muscle. Large lesions extending across the midline may spread to the contralateral facial or submandibular nodes. The average incidence of nodal metastasis at diagnosis is approximately 5%.[27-31] Without elective lymphatic treatment, about 15% of patients develop nodal relapse.[27-29,31] In the intensity-modulated radiation therapy (IMRT) era, when parotid sparing is de rigueur, the 15% incidence of nodal relapse makes consideration of elective nodal irradiation mandatory. Hematogenous metastases are rare in nasal vestibule carcinomas.[31]

Examples of nasal vestibule tumors are shown in the photographs and magnetic resonance (MR) images in Figures 36-3 and eFigure 36-3 *A,B*.

BOX 36-1 Paranasal Sinus Drainage Pathways

SINUS	ORIFICE	DESTINATION
Posterior ethmoid	Sphenoethmoidal recess	Superior meatus
Sphenoid sinus	Sphenoethmoidal recess	Superior meatus
Anterior ethmoids	Ethmoid bulla	Middle meatus
Frontal sinus	Osteomeatal complex	Middle meatus
Maxillary sinus	Osteomeatal complex	Middle meatus
Nasolacrimal duct	Nasolacrimal duct	Inferior meatus

Nasal Cavity and Ethmoid Air Cells

Nasal cavity and ethmoid sinus tumors now share a common staging system.[1] The *nasal cavity proper* (nasal fossa), which excludes the nasal vestibule, begins at the limen nasi anteriorly and ends at the choana posteriorly. It extends from the hard palate inferiorly to the cribriform plate superiorly. The lateral walls consist of three thin bony structures, the superior, middle, and inferior turbinates (or concha) that project inferomedially into the nasal cavity (eFigure 36-4). The middle turbinate attaches to the cribriform plate superiorly and then posteriorly and laterally to the lamina papyracea[32] (Figure 36-4 and see eFigure 36-4).

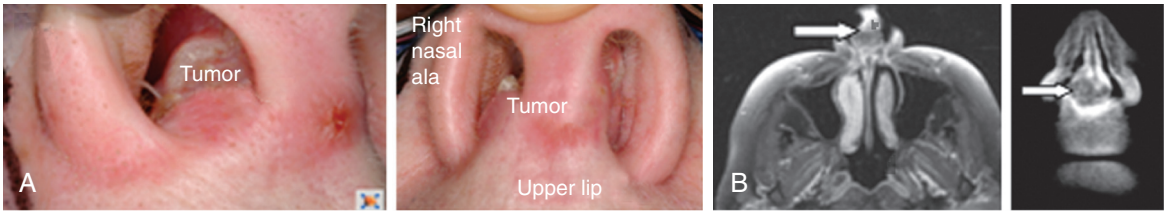
The region inferior to each turbinate is defined as the superior, middle, and inferior meati (see Figure 36-4). The superior meatus receives drainage from the posterior ethmoid air cells and the sphenoid sinus at the sphenoethmoidal recess (Box 36-1). The middle meatus is a particularly important site of drainage, taking drainage from the anterior ethmoids, the frontal sinus, and the maxilla. The anterior ethmoid air cells drain into the ethmoid bulla at the superior aspect of the osteomeatal complex, the frontal sinus drains into the middle meatus at the anterior portion of the osteomeatal complex, whereas the maxillary sinus dumps its content past the infundibulum (a valve at the superior medial aspect of the maxilla) into the middle meatus by way of the maxillary ostium at the inferior osteomeatal complex (see pink arrow in Figure 36-5). Of course, the inferior meatus receives drainage from each nasolacrimal duct.

The septum divides the nasal cavity into right and left halves (Figure 36-6). The olfactory nerves penetrate the cribriform plate and innervate the roof of the nasal cavity, superior nasal turbinate, and the upper third of the septum. This portion of the nasal cavity is referred to as the *olfactory region.* The remaining part of the cavity, the respiratory region, contains orifices connecting the nasal cavity with the paranasal sinuses.

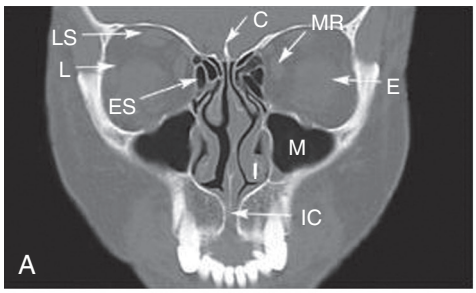
The *ethmoid sinuses* comprise several small cavities, called ethmoid air cells, within the ethmoidal labyrinth located below the anterior cranial fossa and between the nasal cavity and the orbit (eFigure 36-5). They are separated from the orbital cavity by a thin, porous bone called the *lamina papyracea* and from the anterior cranial fossa by a portion of the frontal bone, the *fovea ethmoidalis.*

Neoplasms originating in the respiratory region of the nasal cavity and ethmoid cells are squamous cell carcinoma, adenocarcinoma, and adenoid cystic carcinoma. Carcinoma may arise from inverted papilloma.

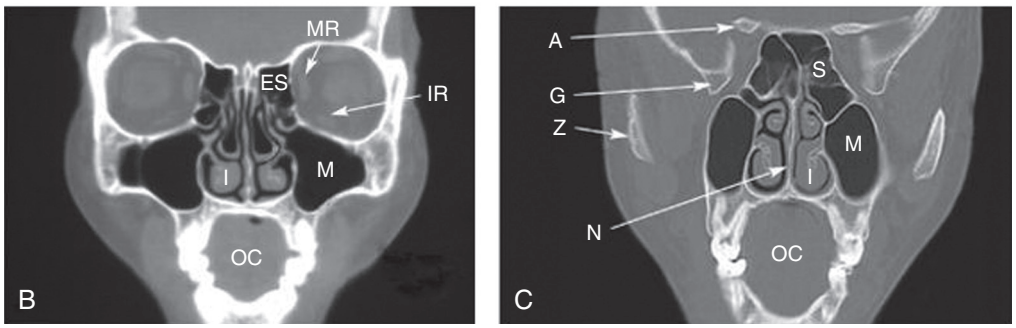
The pattern of contiguous spread of carcinomas varies with the location of the primary lesion. Tumors arising in the upper nasal cavity and ethmoid air cells extend to the orbit through the lamina papyracea and to the anterior cranial fossa via the cribriform plate, or grow through the nasal bone to the subcutaneous tissue and skin. Lateral wall primaries invade the maxillary antrum, ethmoid airs cells, orbit, pterygopalatine fossa, and nasopharynx. Primaries of the floor and lower



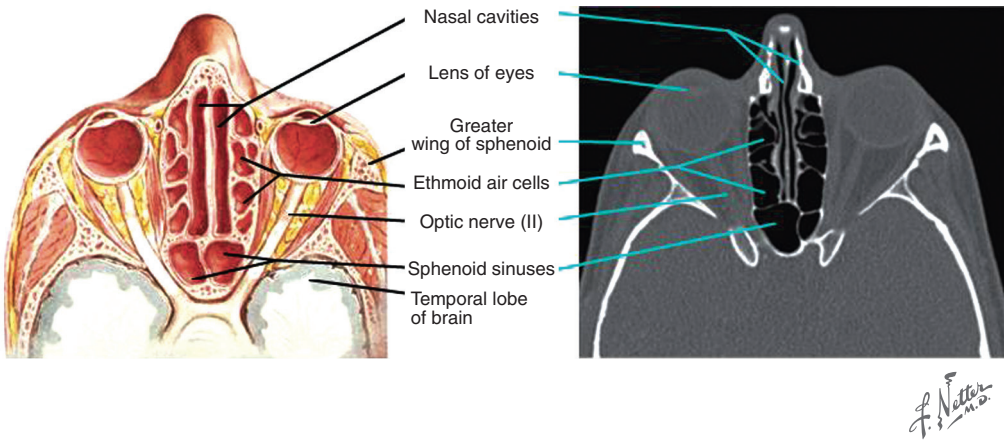
eFigure 36-3 **A,** T2N0 carcinoma of tumor of the left and right nasal septum, vestibules, and columella; photograph of the tumor. **B,** In the transverse and coronal magnetic resonance images, the arrow points to the tumor.



A	Anterior clinoid process
C	Crista galli
E	Eye (vitreous chamber)
ES	Ethmoid sinus
G	Greater wing of the sphenoid
I	Inferior nasal concha
IC	Incisive canal
IR	Inferior rectus muscle
L	Lateral rectus muscle
LS	Levator palpebrae superioris and superior rectus muscles
M	Maxillary sinus
MR	Medial rectus muscle
N	Nasal septum
OC	Oral cavity
S	Sphenoid sinus
Z	Zygomatic arch

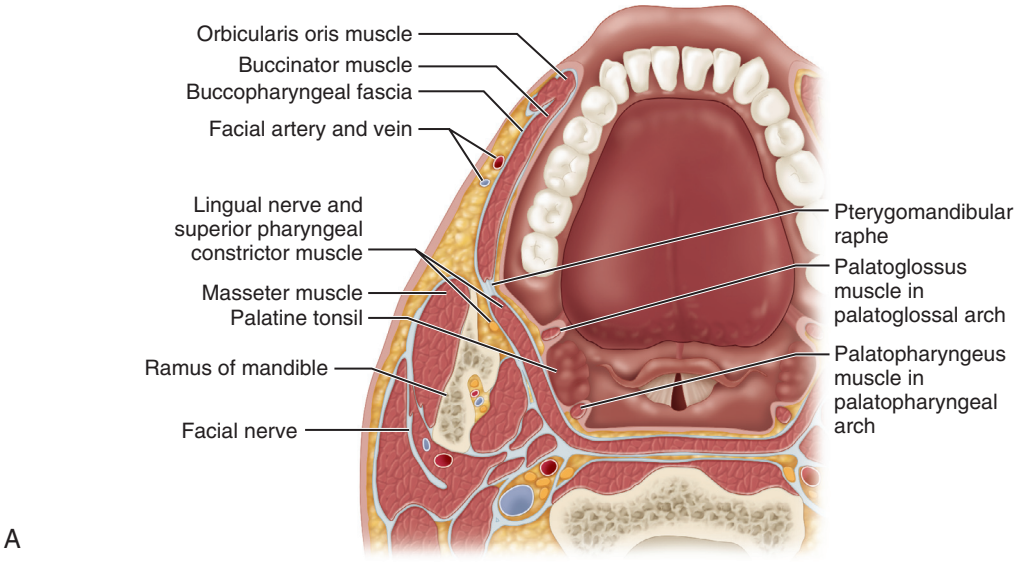


eFigure 36-4 **A-C,** Coronal CT images of the head from anterior **(A)** to posterior **(C)**.

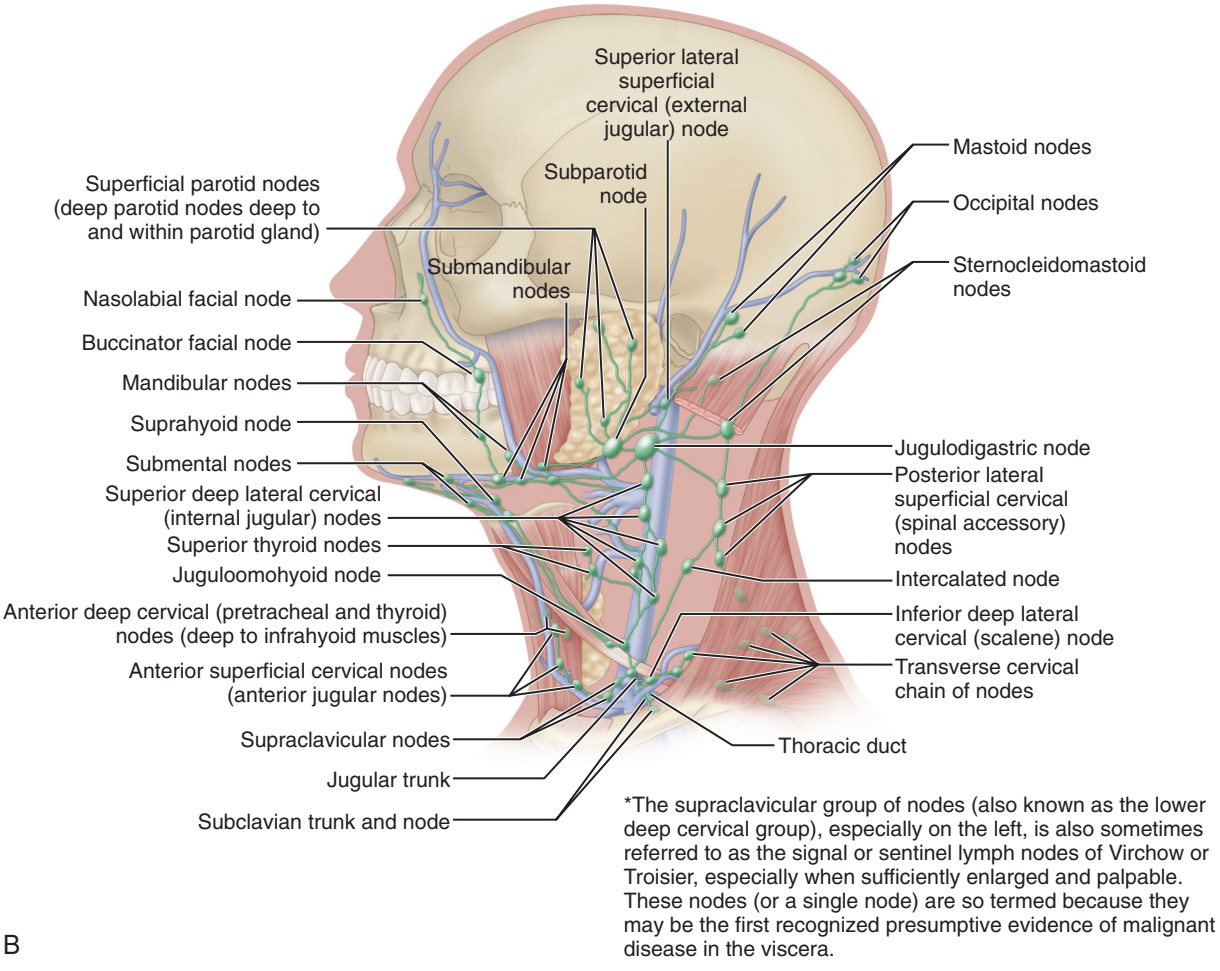


eFigure 36-5 Paranasal sinuses, axial CT.

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A



B

Figure 36-2 **A,** Tongue and salivary gland: horizontal section, superior view. **B,** Lymph vessels and nodes of head and neck.



Figure 36-3 A 2.5-cm squamous cell carcinoma (T2 N0) located on the right side of the columella.

septum may invade the palate and maxillary antrum. Spreading may also occur through perineural spaces especially when the histology is adenoid cystic cancer (Figure 36-7 A-I).

Lymphatic spread of respiratory region primaries is variable. Turning first to nasal cavity, where approximately 50% of the patients have a squamous cell histology,[33] a review of 23 studies with a median follow-up of 4.4 years found the weighted average regional recurrence rate for squamous cell cancers of the nasal cavity to be 18.1%.[34] At least some patients from 7 of the 23 studies received prophylactic cervical nodal irradiation, which significantly lowered the rate of neck failure.

Review of the Istituto Nazionale per lo Studio e la Cura dei Tumori of Milan experience from 1968 to 2003[35] identified 305 consecutive tumors of the ethmoid sinus. There was a striking

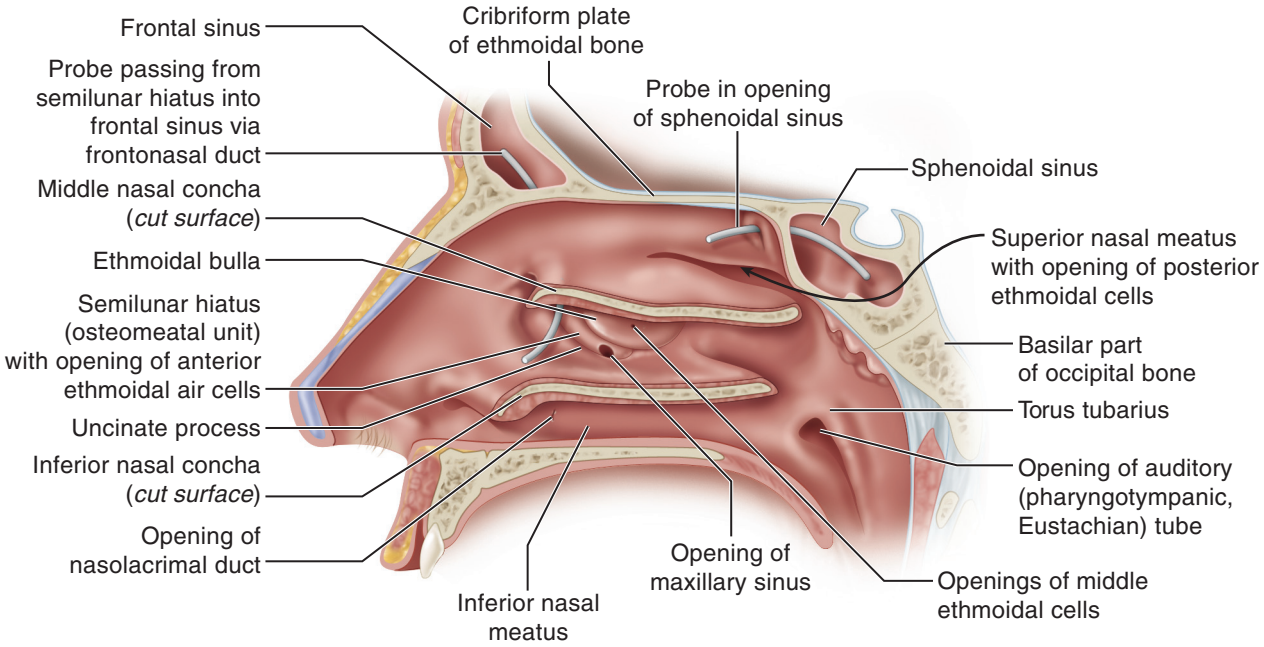


Figure 36-4 Lateral wall of nasal cavity with nasal conchae removed.

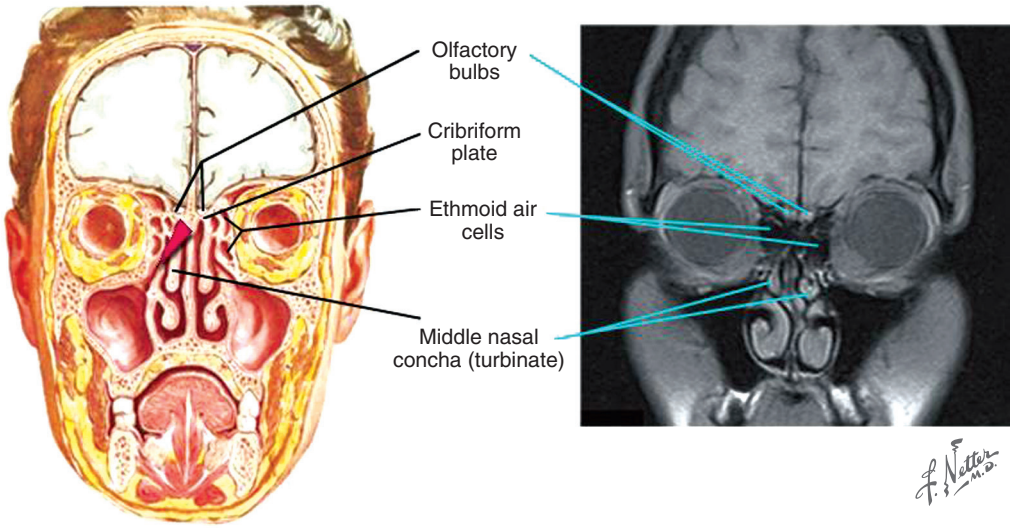


Figure 36-5 Olfactory bulbs: coronal frontal section and maxillofacial MRI.
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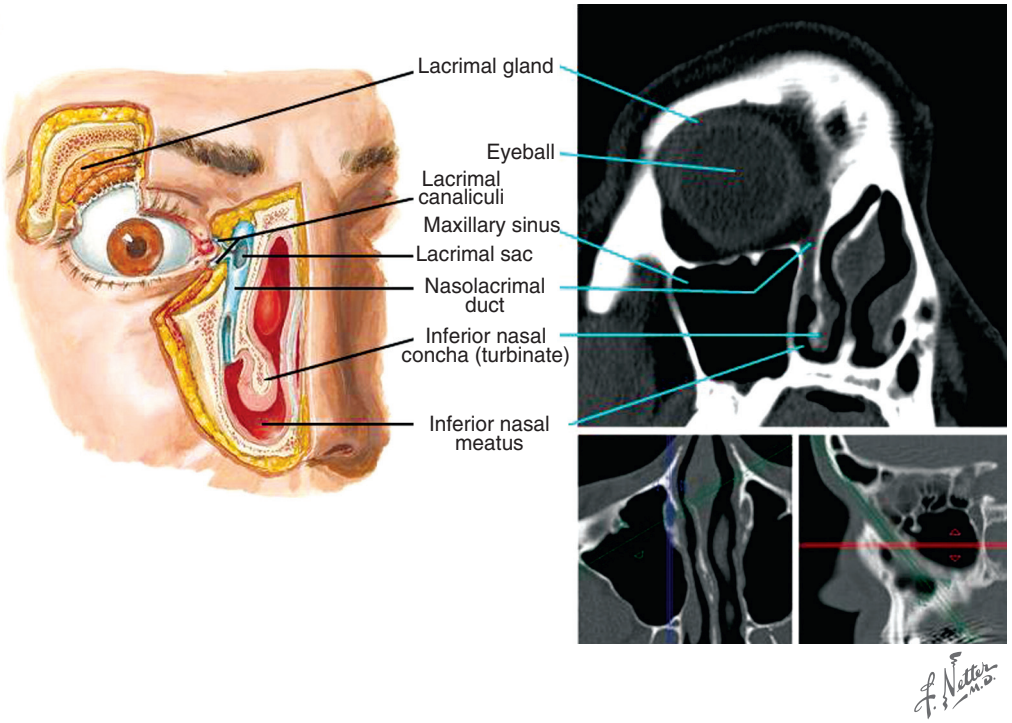


Figure 36-6 Oblique coronal reconstruction, maxillofacial CT (green lines in the reference images indicate the position and orientation of the main image).

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male predominance, 70.8% versus 29.2%. Intestinal type adenocarcinoma was the most frequent histology, 50.2%, with only 10.8% of patients with ethmoid sinus cancer having squamous cell cancer. The strong male predominance was confirmed in a 202-person study of European patients with adenocarcinomas of the ethmoid sinus.[35] Only 1.6% of 305 patients with ethmoid sinus cancer presented with adenopathy, and with a median follow-up of 109 months, the cumulative incidence of lymphatic recurrence was 4.3%.[35] It is important to note that most neck recurrences were accompanied by recurrence of the primary tumor. The 5-year cumulative incidence of metastases was just 3.6%.

The olfactory region is located at the roof of the nasal cavity. It represents a narrow strip demarcated by the lamina cribrosa and the adjoining septum and lateral walls. The olfactory region is the site of origin of esthesioneuroblastoma and, occasionally, adenocarcinomas.

Esthesioneuroblastoma is a tumor of neural crest origin first reported by Berger and Luc in 1924 as esthesioneuroepithelioma olfactif.[36] It has been given a variety of other names, including *olfactory neuroblastoma*, and *esthesioneurocytoma.* Esthesioneuroblastoma constitutes approximately 3% of all intranasal neoplasms. About 250 cases were reported in the literature between 1924 and 1990.[37] A typical histologic feature of esthesioneuroblastoma is that of a tumor comprised of round, oval, or fusiform cells containing neurofibrils with pseudorosette formation and diffusely increased microvascularity.[38] Perivascular palisading of cells can be observed in the absence of pseudorosette formation.

Esthesioneuroblastoma may be mistaken for any other "small round-cell tumor": a group of aggressive malignant tumors composed of relatively small and monotonous undifferentiated blue staining cells. These include Ewing's sarcoma, peripheral neuroepithelioma (also referred to as primitive neuroectodermal tumor or extraskeletal Ewing's), peripheral neuroblastoma ("classic-type"), rhabdomyosarcoma, desmoplastic small round-cell tumor, lymphoma, leukemia, small-cell osteosarcoma, small-cell carcinoma (either undifferentiated or neuroendocrine), cutaneous neuroendocrine carcinoma (Merkel-cell carcinoma), small-cell melanoma, and mesenchymal chondrosarcoma. Their clinical presentations often overlap but clinicopathologic features and immunohistochemistry may help in differentiation.

The route of contiguous spread of esthesioneuroblastomas is similar to that of ethmoid carcinomas. Multiple and late local and regional recurrences are the rule. Eventual development of neck disease has been reported in 21% of 110 patients[39] and in 20.2% of 678 patients,[40] with 61.7% of the cervical disease occurring more than 6 months after the diagnosis.

Maxillary Sinus

Maxillary sinuses, the largest of the paranasal sinuses, are pyramid-shaped cavities located in the maxillae. The base of the maxillary sinus forms the inferior part of the lateral wall of the nasal cavity. The roof of the maxillary sinus is formed by the floor of the orbit, which contains the infraorbital canal, and the floor is composed of the alveolar process. The apex extends toward, and frequently into, the zygomatic bone. Ohngren's line is a theoretical line passing from the medial canthus of the eye to the angle of the mandible and divides the maxillary sinus cancers into suprastructure and infrastructure tumors. Tumors superior to this arbitrary plane invade vital structures such as the orbit and middle cranial fossa earlier and thus have a worse prognosis.[41] Also of importance when understanding the anatomy of the maxillary sinus is the pterygopalatine fossa. The pterygopalatine fossa, also known as the sphenopalatine fossa, can be thought of as a box, with its anterior wall being the posterior wall of

the maxillary sinus. The posterior wall is the pterygoid plates and inferior aspect of the sphenoid bone, the roof is the inferior orbital fissure. The floor is the palantine canal and contains the greater palantine nerve. Medially it is defined by the perpendicular plane of the palatine bone. The pterygopalatine fossa contains the maxillary nerve (V2), which enters from the brain via the foramen rotundum, as well as the pterygopalatine ganglion and the distal maxillary artery, which enters via the pterygomaxillary fissure. The pterygopalatine ganglion is the largest head and neck parasympathetic ganglion and has sensory, motor, and sympathetic function.

Sixty-two percent of maxillary sinus cancers are squamous cell carcinomas.[2,42] Other histologic types and survivals are shown in Table 36-2.

The pattern of spread of maxillary sinus cancer varies with the site of origin. Neoplasms of the suprastructure tend to extend into the nasal cavity, nasopharynx, ethmoid cells, inferior or medial wall of the orbit, orbital contents, pterygopalatine fossa, masticator space, infratemporal fossa, base of the skull, parasellar region and cavernous sinus, and middle cranial fossa. Tumors of the infrastructure extend to the palate, alveolar process, gingivobuccal sulcus, soft tissue of the cheek, nasal cavity, masseter muscle, pterygopalatine space, and pterygoid fossa. It is sometimes difficult to differentiate from tumors extending from the upper alveolus and hard palate.

Overall, the incidence of clinical lymphadenopathy is relatively uncommon at diagnosis but because regional recurrence is common the presumption is that subclinical nodal disease

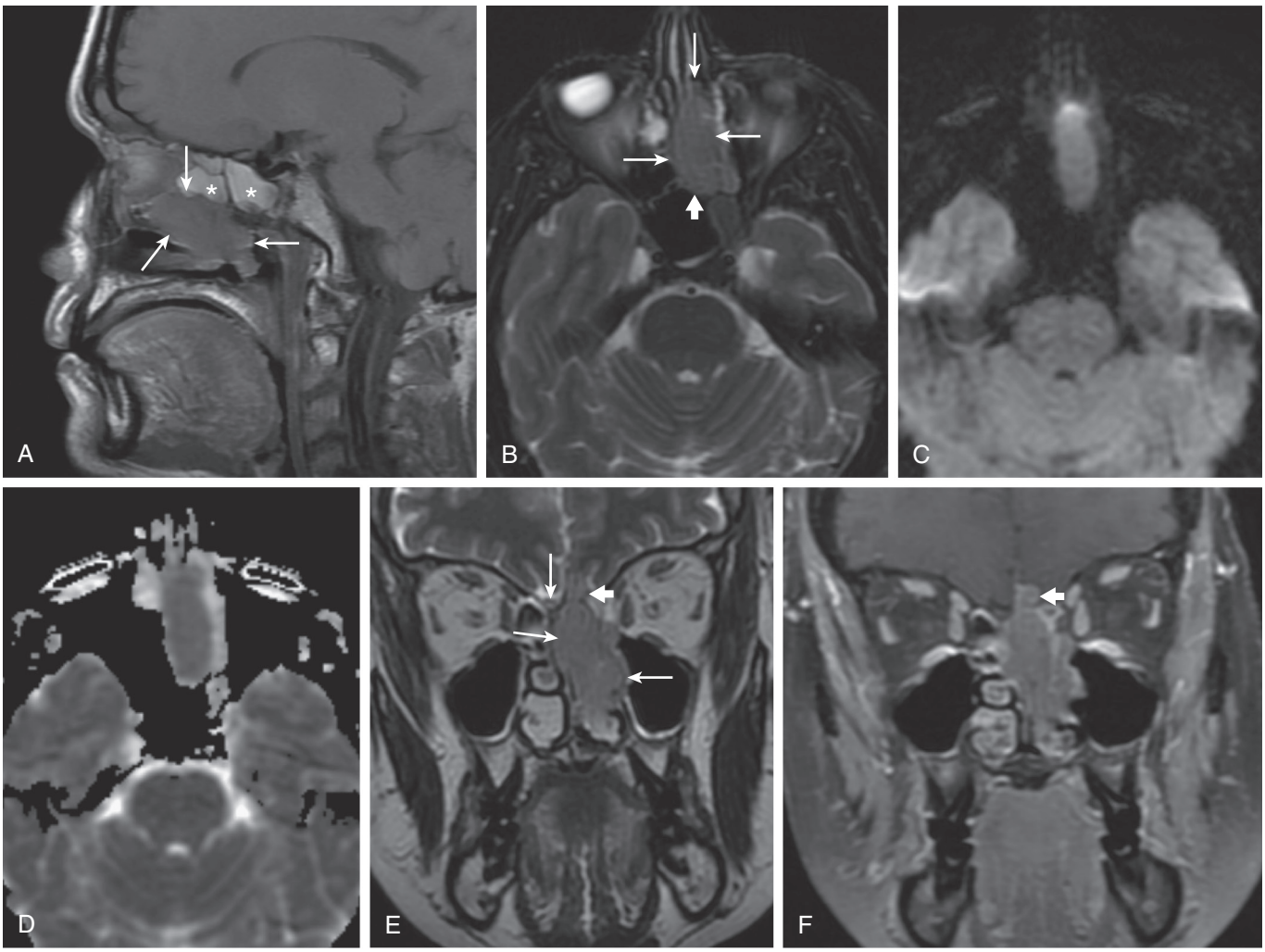


Figure 36-7 **(A-F)** Patient with nasal cavity tumor with left sphenoid sinus and intracranial extension. **A,** T1 sagittal image shows relatively low signal intensity (SI) tumor *(arrows)* in nasal cavity, extending to nasopharynx. Posterior ethmoids and sphenoid sinus are completely opacified *(asterisks)* with high SI chronic proteinaceous debris. **B,** T2-weighted fat saturated axial image shows the tumor *(arrows)* in left nasal cavity, with invasion through the anterior left sphenoid sinus wall *(arrowhead)*. Note high SI benign secretions in right ethmoid sinus. **C,** Diffusion-weighted image (DWI) shows relatively high signal in tumor. **D,** Apparent diffusion coefficient (ADC) map confirms the "restricted diffusion" because the lesion is low signal on the map. DWI can be helpful in determining whether a lesion is benign or malignant but should never be used in isolation. **E,** T2 coronal image through the left nasal cavity mass shows extension across the bony perpendicular ethmoid bone *(long arrow)*, into the right nasal cavity roof, and laterally through the medial left maxillary sinus wall *(short arrow)*. The tumor has extended across the left cribriform plate, and fills the olfactory recess, obliterating the left olfactory bulb *(white arrowhead)*. Note normal right olfactory bulb *(black arrow)*. **F,** T1 fat saturated gadolinium enhanced coronal image at same level as 3A confirms intracranial extension *(arrowhead)* on left. The smooth interface between the tumor and the gyrus rectus suggests no intradural invasion. The boundaries of the tumor are better appreciated on the T2 image, as all the normal mucosa enhances with gadolinium contrast on T1, similar to the mass.

Continued

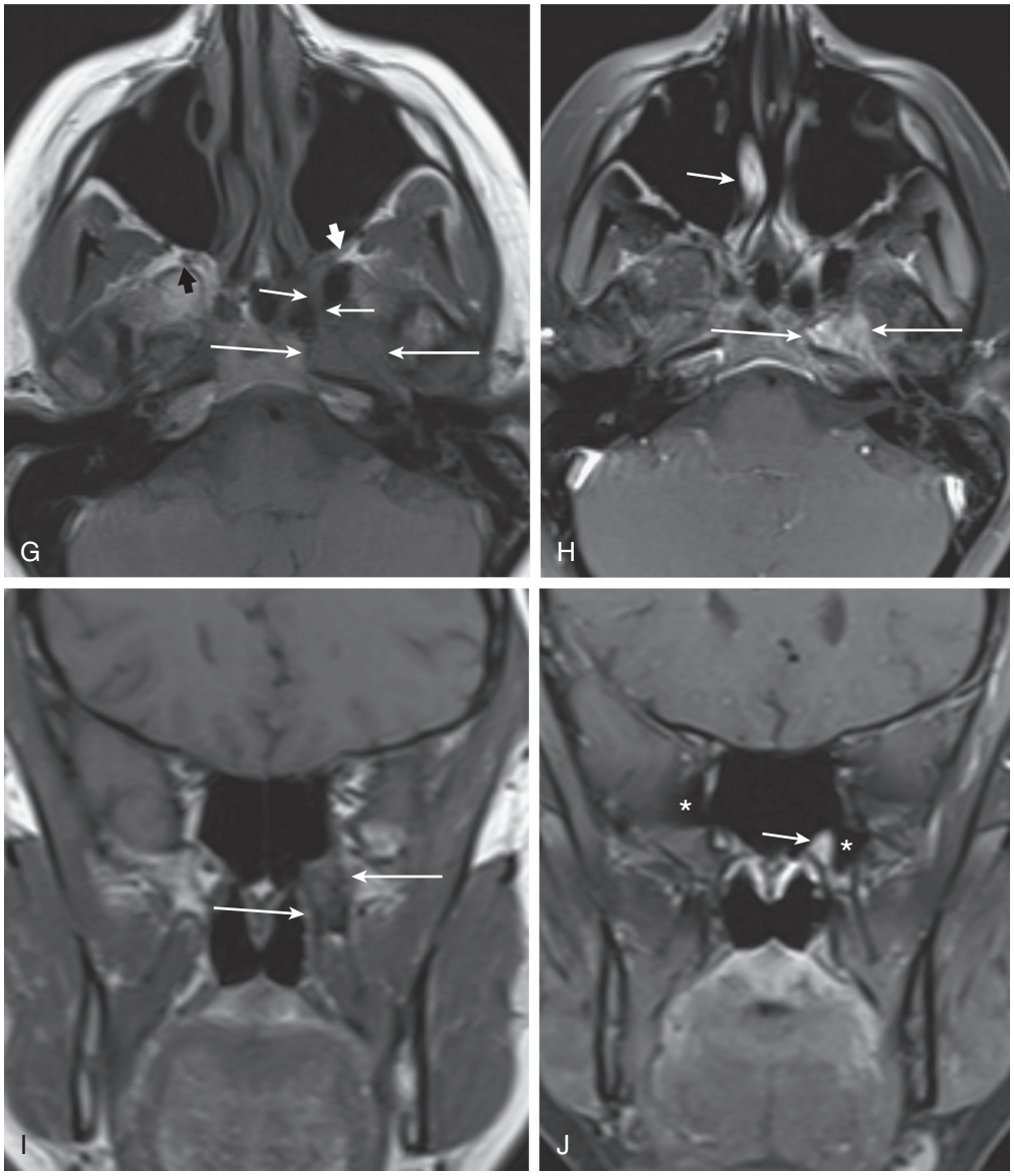


Figure 36-7, cont'd Patient with adenoid cystic carcinoma of sinus shown on axial and coronal T1 images **(G, I)** and axial and coronal T1 fat-saturated gadolinium enhanced images **(H, J)**. Imaging findings of perineural tumor are enlargement of a skull-base foramen, thickening and enhancement of the nerve, and replacement of fat that is always present at the extracranial side of the foramen. **G,** Image through the central skull base shows abnormal SI of bone *(long arrows)*, and replacement of fat in left pterygopalatine fossa *(arrowhead)*. Right pterygopalatine fossa is normal, with high SI fat *(black arrowhead)*. Note perineural tumor in left vidian *canal (short arrows)*. **H,** Robust enhancement in the abnormal bony skull base *(long arrows)* makes the tumor less conspicuous, as normal marrow is also high SI. Even perineural tumor is more difficult to appreciate, as there is normal enhancement in the nasal cavity mucosa *(short arrow)* and bright susceptibility artifact from the fat-saturation technique. **I,** T1 coronal image, without gadolinium, clearly shows abnormal SI of left pterygoid plates *(arrows)* from replacement by tumor. **J,** Gadolinium-enhanced image shows thickening and abnormal enhancement of left vidian nerve *(short arrow)* from perineural tumor spread. The osseous tumor is better seen on the precontrast image. Note band of black artifact through skull base *(asterisks)*, a limitation of fat-saturation technique at bone-air interface. Both pre- and gadolinium-enhanced T1 images are recommended to detect skull-base invasion and perineural tumor. Both sets of images must be carefully evaluated because some lesions are better seen without gadolinium and some better seen after contrast.

exists at presentation.[25] Cantu et al reported that 8.3% of 399 patients presented with lymphadenopathy, and during follow-up (median 109 months) 12.5% developed regional recurrence. Squamous cell primary cancers of the maxilla had a 10.3% incidence of nodal disease at presentation, with a 36.4% recurrence rate in patients who were N+.[35] The cumulative incidence of neck recurrence for patients with squamous cell cancer of the maxilla was 20.7%.[35] Le[43] has published the location of nodal presentation and failure and found that Levels IB, II, V, and the preauricular area can be involved ipsilaterally, and Levels II contralaterally.

Sinonasal Undifferentiated Carcinoma (SNUC)

Sinonasal undifferentiated carcinoma (SNUC) has recently been identified by the World Health Organization[44] as a distinct sinonasal neoplasm that should be differentiated from esthesioneuroblastoma and other cancers.[45] There is a male predominance and tumors typically are aggressive presenting with locally extensive disease. Etiology is unknown. Immunohistochemical studies are noncontributory and stains for epithelial mucin are negative. The nuclear to cytoplasmic ratio is high with a high mitotic rate. In 2005 there were fewer than

TABLE 36-2 Tumor Types and Survival for Maxillary Sinus Cancer

Tumor Type	No. Pts.	%	Survival	
			Median (mo.)	5-yr (%)
Squamous cell	401	61.7	18	29.2
Other	70	10.8	27	38.7
Adenoid cystic	64	9.8	118	57.5
Sarcoma	46	7.1	47	44.8
Adenocarcinoma	31	4.8	50	47.7
Melanoma	23	3.5	18	25.9
Mucoepidermoid	15	2.3	53	35.9
	650	100.0		

Data from Bhattacharyya N: Factors affecting survival in maxillary sinus cancer. J Oral Maxillofac Surg 61(9):1016–1021, 2003.
5-yr, *5-year;* CA, *carcinoma;* mo., *month;* No. pts, *number of patients.*

100 cases of SNUC described, by 2008 approximately 200 cases were described,[46] and a review from 2009[45] as well as anecdotal experience suggested that the diagnosis is becoming more common. Scanty evidence ($n = 17$) reported that SNUC is one of the few ethmoid sinus cancers with a 25.5% rate of regional failure. A 13% rate of regional failure in 26 SNUCs from the maxilla was reported.[35] Mendenhall's review of the literature found 10% to 30% of patients with SNUC have clinically positive adenopathy and the cure rates varied from 20% to 50%.[47]

CLINICAL MANIFESTATION, PATIENT EVALUATION, AND STAGING

Table 36-3 summarizes the updated AJCC TNM classification (seventh edition) for cancers of the maxillary sinus, the ethmoid sinus, and the nasal cavity.[1] Significant updates in the seventh edition are as follows:

- T4 lesions are divided into T4a (moderately advanced local disease) and T4b (very advanced local disease).
- Stage IVB is defined by either T4b or N3 disease and IVC disease is defined as M1 disease.

For purposes of staging, the nasal cavity and ethmoids are considered different sites, and the maxillary sinus and ethmoid sinus are each divided into a left and right subsite. The subsites of the nasal cavity have already been identified.

Nasal Vestibule

Small carcinomas of the nasal vestibule usually present as asymptomatic plaques or nodules, often with crusting and scabbing. The septum is the most common location.[25,48] Advanced lesions may extend to adjacent structures, such as upper nasal septum, upper lip, infranasal depression (philtrum), skin of nose, nasolabial fold, hard palate, buccogingival sulcus, etc. Deep muscle and bone and nerve involvement may cause pain accompanied by bleeding or ulceration. Large ulcerated lesions may become infected, leading to severe tenderness that hinders complete clinical assessment. The contiguous spread is best assessed by bimanual palpation and examination through a nasal speculum or fiberoptic endoscopy after mucosal decongestion and topical anesthesia. Early buccinator and submandibular nodal involvement may be detected by bimanual palpation or by imaging.[26] Staging of nasal vestibule carcinoma is by the TNM classification system for the skin. However, other staging systems have been used in reporting data.[49,50]

Nasal Cavity and Ethmoid Air Cells

Carcinoma

The presenting symptoms and signs of nasal fossa tumors are similar to those associated with nasal polyps; chronic unilateral nasal discharge, ulcer, obstruction, anterior headache, and intermittent nosebleeds. This similarity often leads to delays in diagnosis. Other symptoms and signs include nasal ulcer, tenderness, facial swelling, or pain.[22] Invasion of the orbital cavity may produce a palpable medial orbital mass, proptosis, and diplopia; obstruction of the nasolacrimal duct causes epiphora (overflow of tears); involvement of the olfactory region may produce anosmia (inability to perceive odors) and expansion of the nasal bridge; and extension through the cribriform plate results in frontal headache.

The presenting symptoms and signs of ethmoid air cell tumors are sinus ache and referred pain to the nasal or retrobulbar region, subcutaneous mass at the inner canthus, nasal obstruction and discharge, diplopia, and proptosis.

Physical assessment should include examination of the nasal cavity and nasopharynx with an endoscope after mucosal decongestion and topical anesthesia, evaluation of cranial nerves (particularly cranial nerves III, IV, V, and VI), and palpation of the nose bridge, cheek, and medial orbital cavity.

Imaging information on CT and MRI can be found on the Expert Consult website.

Primary tumors of the lateral wall and floor tend to be diagnosed in more advanced stages. Of the patients referred to the M. D. Anderson Cancer Center (MDACC) between 1969 and 1985, 3 (21%) of 14 patients with septal lesions versus 20 (65%) of 31 patients with lateral wall or floor primaries had disease extension beyond the nasal cavity (stages II and III).[52,53]

Esthesioneuroblastoma

The natural history of esthesioneuroblastomas is long and multiple recurrences are the rule. A literature review of 97 patients reported between 1969 and 1977 found that the age distribution is bimodal, with a first peak incidence occurring between 11 and 20 years and a second higher peak incidence between 51 and 60 years.[54] Surveillance, Epidemiology and End Results (SEER) analysis of 311 patients found the age distribution to be unimodal with the mean age being 53.[55] SEER analysis described the primary site as the nasal cavity in over three fourths of the cases and 12.3% presented with nodal involvement.

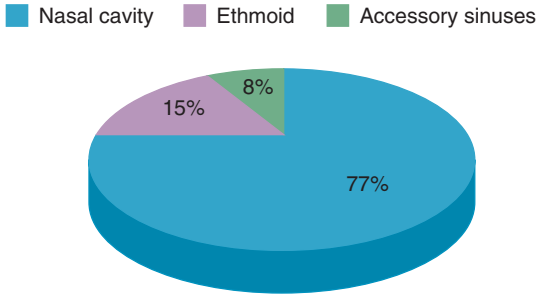
The most common presenting symptoms are nasal obstruction and epistaxis. Anosmia (inability to perceive odors) can precede diagnosis by many years.[56] Other symptoms are related to contiguous disease extension into the orbit (proptosis, visual field defects, orbital pain, epiphora), paranasal sinuses (medial canthus mass, facial swelling), anterior cranial fossa (headache), and manifestation of inappropriate antidiuretic hormone secretion. Most present in the nasal cavity (eFigure 36-6).

Physical evaluation and recommended staging workup procedures for esthesioneuroblastoma are similar to those for nasal fossa tumors. The commonly used staging system, proposed by Kadish et al,[38] is as follows:

- Stage A: disease confined to the nasal cavity
- Stage B: disease confined to the nasal cavity and one or more paranasal sinuses
- Stage C: disease extending beyond the nasal cavity and the paranasal sinuses, including involvement of the orbit, the base of the skull or intracranial cavity, cervical lymph nodes, or distant metastasis

The stage distribution of the 97 patients reviewed by Elkon et al[54] at diagnosis is 30% stage A, 42% stage B, and 28% stage C. Of the 22 patients who had stage C disease, 9 had orbital

CT or MRI is essential to determine the disease extent and invasion of adjacent structures (e.g., orbital cavity and anterior cranial fossa). Regarding the imaging modality, CT is best for cortical bone erosion or deossification, and the prospective use of a high-resolution bone algorithm, perhaps with dual-energy photons,[51] is recommended for assessment of the anterior and central skull base and the lamina papyracea. The coronal plane of the MRI is best for determination of intracranial extension, with fat-saturated postgadolinium–enhanced T1-weighted imaging being the "workhorse" sequence for detecting epidural disease. MRI can help differentiate tumors in the sinonasal cavity from edematous mucosa. Generally benign mucosal disease is hyperintense on T2-weighted images in distinction to malignant disease, which is less hyperintense. Tumors of glandular origin, however, tend to be exceptions and can be high signal intensity on T2-weighted images.



eFigure 36-6 Esthesioneuroblastoma, primary site of disease.

TABLE 36-3 Nasal Cavity and Paranasal Sinuses TNM Staging Classification by the American Joint Committee on Cancer[26]

PRIMARY TUMOR (T)	
Maxillary Sinus	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Tumor limited to maxillary sinus mucosa with no erosion or destruction of bone
T2	Tumor causing bone erosion or destruction including extension into the hard palate or the middle of the nasal meatus, except extension to the posterior wall of maxillary sinus and pterygoid plates
T3	Tumor invades any of the following: bone of the posterior wall of maxillary sinus, subcutaneous tissues, floor or medial wall of orbit, pterygoid fossa, ethmoid sinuses
T4a	Moderately advanced local disease Tumor invades anterior orbital contents, skin of cheek, pterygoid plates, infratemporal fossa, cribriform plate, sphenoid or frontal sinuses
T4b	Very advanced local disease Tumor invades any of the following: orbital apex, dura, brain, middle cranial fossa, cranial nerves other than maxillary division of trigeminal nerve (V_2), nasopharynx, or clivus
Nasal Cavity and Ethmoid Sinus	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Tumor restricted to any one subsite, with or without bony invasion
T2	Tumor invading two subsites in a single region or extending to involve an adjacent region within the nasoethmoidal complex, with or without bony invasion
T3	Tumor extends to invade the medial wall or floor of the orbit, maxillary sinus, palate, or cribriform plate
T4a	Moderately advanced local disease Tumor invades any of the following: anterior orbital contents, skin of nose or cheek, minimal extension to anterior cranial fossa, pterygoid plates, sphenoid or frontal sinuses
T4b	Very Advanced Local Disease Tumor invades any of the following: orbital apex, dura, brain, middle cranial fossa, cranial nerves other than V_2, nasopharynx, or clivus
REGIONAL LYMPH NODES (N)	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single ipsilateral lymph node, ≤3 cm in greatest dimension
N2	Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension, or in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension, or in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension
N2a	Metastasis in a single ipsilateral lymph node more than 3 cm but not more than 6 cm in greatest dimension
N2b	Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension
N2c	Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension. N3 Metastasis in a lymph node more than 6 cm in greatest dimension Metastasis in a lymph node more than 6 cm in greatest dimension
DISTANT METASTASIS (M)	
MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis
AJCC STAGE GROUPINGS	
Stage 0	Tis N0M0
Stage I	T1N0M0
Stage II	T2N0M0
Stage III	T3N0M0 or T1-3N1M0
Stage IVA	T4aN0-1M0 or T1-4aN2M0
Stage IVB	T4b any NM0 or any TN3M0
Stage IVC	Any T or any NM1

From Edge SB, Byrd DR, Compton CC, et al, editors: AJCC Cancer Staging Handbook, ed 7, New York, 2010, Springer.
Authors comment: In clinical evaluation, the actual size of the nodal mass should be measured, and allowance should be made for intervening soft tissues. Most masses more than 3 cm in diameter are not single nodes but confluent nodes or tumors in soft tissues of the neck. There are three stages of clinically positive nodes: N1, N2, and N3. The use of subgroups a, b, and c is not required but recommended. Midline nodes are considered homolateral nodes.

involvement, 6 had invasion of the cribriform plate or cranial fossa, 11 had palpable neck nodes, and only 1 had distant metastasis.

Maxillary Sinus

Because of their relatively silent presentations, maxillary cancers are often diagnosed late. Of the 73 patients referred to MDACC for treatment between 1969 and 1985, for example, symptoms and signs related to extension to the premaxillary region (facial swelling, pain, or paresthesia of the cheek) occurred in 26 (36%). Symptoms resulting from tumor spread to the nasal cavity (e.g., epistaxis, nasal discharge or obstruction) or oral cavity (e.g., ill-fitting denture, alveolar or palatal mass, or unhealed tooth socket after extraction) occurred in 20 (27%) and 19 (26%), respectively. Five patients (7%) presented with symptoms and signs of orbital invasion such as proptosis, diplopia, impaired vision, or orbital pain.[57]

Physical examination should include assessment of the oral and nasal cavities, palpation of the cheek, evaluation of the eye movement and function, and assessment of the trigeminal nerve, particularly the branches of the maxillary division (infraorbital, anterior superior alveolar, posterior superior alveolar, and greater palatine nerves). Numbness of the incisor teeth and upper lip, however, can result from biopsy through a Caldwell-Luc procedure. CT or MRI with appropriate contrast are essential to determine the disease extent and invasion of adjacent structures (e.g., orbital cavity, infratemporal, pterygopalatine, and anterior cranial fossae).

The T classification description by the AJCC staging system is shown in Table 36-3 and is based on clinical and radiologic evidence of involvement of various adjoining anatomic structures.

PRIMARY THERAPY

Nasal Vestibule

Nasal vestibule cancers are skin cancers that are in a cosmetically important location. Radiotherapy is generally preferred for carcinoma of the nasal vestibule because of better cosmetic outcome, but if local excision of a medial tumor of the nasal septum can be performed with clear margins and no cosmetic deformity, that treatment may well be more appropriate.[25] Surgery can yield a high control rate with excellent cosmetic results in selected small, superficial lesions. Depending on the location and size of the primary lesion, radiation treatment can be accomplished by external beam irradiation (EBRT), brachytherapy, or a combination of both. Cartilage invasion per se is not a contraindication for radiation therapy because the risk of necrosis is low with fractionated irradiation.[58] Rare cases of large primaries with extensive tissue destruction and distortion are best managed by resection in combination with preoperative or postoperative radiotherapy. Experienced prosthodontists can design custom-made nasal prostheses for large defects. Smaller defects can be reconstructed with a rotational or advancement flap.

Because of disagreement regarding the applicability of the AJCC staging system, some authors use the Wang staging system and some use the AJCC skin cancer staging system, which makes comparing results in a relatively rare tumor precarious. Additionally there are parochial concerns about whether nasal vestibule is a surgical disease or not. Eloquent editorials aside,[25] there is a dearth of randomized data, and endpoints such as cosmetic results are difficult to quantify.

University of Florida, Gainesville, reported that 32 of 34 patients with disease 5 cm or smaller who were treated with definitive radiation were locally controlled (Table 36-4).[59] Generally, radiation doses were high (65 Gy to 75 Gy), but techniques varied between definitive EBRT, a combination of brachytherapy and EBRT and brachytherapy alone. The authors conclude that definitive radiation gives both good local control and cosmesis for early tumors, but tumors involving bone that are more than 4 cm should be treated with a combination of surgery and radiation. The importance of both size and bone invasion are seen in Table 36-5.

Elective nodal irradiation (ENI) was only recommended for tumors involving bone that are more than 4 cm in size but the 5-year neck control and ultimate neck control were 87% and 97%, respectively, suggesting excellent follow-up because seven of the nine neck failures were successfully salvaged. The control rates of the N0 neck when the primary tumor was continuously controlled appear in Table 36-6.

DAHANCA's retrospective review[60] noted that 54 Gy in 18 fractions was more effective than 62 Gy to 66 Gy in 31 to 33 fractions for T1 lesions. However, complications were not discussed.

An overall local control of 93% was found on analysis of irradiation of 1676 carcinomas of the skin of the nose and nasal vestibule performed by the Groupe Europen de Curietherapie

TABLE 36-4 Nasal Vestibule Tumors, Local Control, University of Florida

Treatment	Size	Controlled/Treated	Salvaged/Attempts	Ultimate Local Control
RT alone	≤5 cm	32/34 (94%)	1/2	32/34 (94%)
	T4-"Extradermal"	16/25 (64%)	4/7	20/25 (80%)
	≤5 cm but recurrent	9/9	nd	9/9
	T4-"Extradermal" Recurrent	3/3	nd	3/3
Surgery + RT	T4-"Extradermal"	8/8	nd	8/8

nd, *No data;* RT, *radiotherapy.*

TABLE 36-5 Local Control of T4 "Extradermal" Nasal Vestibule Tumors, University of Florida

Treatment	Prior Treatment	<4 cm, no BI	<4 cm, +BI	≥4 cm, no BI	≥4 cm, + BI
RT alone	No	12/16 (75%)	4/5	0/1	0/3
	Yes	1/1	2/2	nd	nd
RT + Surgery	No	nd	nd	nd	8/8

BI, *Bone invasion;* nd, *no data;* RT, *radiotherapy.*

in France.[20] Local control was dependent on tumor size (<2 cm, 96%; 2 cm to 3.9 cm, 88%; ≥4 cm, 81%), site (external surface, 94%; vestibule, 75%), and on whether a tumor was recurrent or new (88% versus 95%). Local control was independent of histology for tumors less than 4 cm, but for those larger than 4 cm, basal cell carcinomas were more frequently controlled than squamous cell carcinomas. There were few complications (necrosis, 2%). The local control rate with surgery was ~90%.

TABLE 36-6 Initial Control of the N0 Neck when the Primary Tumor Was Controlled, University of Florida

Treatment	Size	Without ENI	ENI
RT alone	≤5 cm	29/31 (94%)	nd
	T4-"Extradermal"	11/15 (73%)	8/8
	≤5 cm but recurrent	6/6	1/1
	T4-"Extradermal" Recurrent	1/2	1/1
	Total	47/54 (87%)	10/10

ENI, *Elective node irradiation;* nd, *no data;* RT, *radiotherapy.*

Other series conclude that more advanced lesions, such as Wang stage T2 or T3 are better handled by combined modality treatment.[48,60]

Table 36-7 summarizes the results of six series of patients treated by radiotherapy.[28,31,49,61,62] Patients received brachytherapy, EBRT, or a combination. A number of conclusions can be derived from these data sets. First, brachytherapy or EBRT cures, on average, about 90% of nasal vestibule lesions smaller than 2 cm. Surgery offers equivalent results.[60] Second, for tumors 2 cm to 4 cm in size, the University of Florida[59] showed 94% control for lesions less than 5 cm. Others have shown 70% to 80% local control with radiation alone with surgical salvage bringing the ultimate local control to 94%.[63] Third, occult nodal spread is extremely rare in lesions smaller than 2 cm but can be as high as about 40% in larger primary tumors. Once again surgical salvage of neck failures is high. Fourth, University of Florida[59] has documented a relatively high rate of radiation salvage for surgical failures. Finally, complications from radiation therapy alone are relatively mild. In 71 patients treated with definitive radiation at the University of Florida, there was a 21% incidence of complications with the majority being soft-tissue necrosis and no complication required hospitalization or surgical intervention. Perhaps counterintuitively, 3 of 8 patients treated with surgery and radiation developed severe complications.

TABLE 36-7 Reported Local and Regional Control Rates of Nasal Vestibule Carcinomas Treated by Definitive Radiotherapy

Institution	Local Control	Nodal Control	Late Complications
University of Texas M. D. Anderson Cancer Center[18]	Brachytherapy: 11/11 EBRT: 20/21 (95%) Total: 31/32 (97%)	Small lesions: 11/11 Large lesions: ELR: 12/12 (100%) No ELR: 5/9 (56%) Total: 28/32 (88%)	Osteonecrosis (at area of hot spot): 1 Nosebleeds: 1
University of Florida[33]	Brachytherapy: 9/9 EBRT: 8/11 (73%) Combination: 12/16 (75%) Total: 29/36 (81%)	ELR: 3/3 No ELR: 23/27 (85%); 4 relapses were salvaged Total: 26/30* (87%)	Transient soft-tissue necrosis after implants: 4 Nasal stenosis: 1
Rotterdam Radiotherapy Institute[34]	≤1.5 cm (n = 15): 72%* >1.5 cm (n = 17): 50%* <54 Gy†: 37%* ≥54 Gy†: 82%*	Details not presented	Details not presented
Princess Margaret Hospital[17]	<2 cm (n = 34): 97%* ≥2 cm (n = 16) and size not recorded (n = 6): 57%* <55 Gy/5 wk: 30% ≥55 Gy/5 wk: 82%	No ELR: 51/54, 94% (2 patients presented with nodes)	Osteonecrosis: 2 (1 resulting in fistula) Nasal stenosis: 2 Massive epistaxis: 1
VU University Medical Center, Amsterdam[28]	Overall: 79% (ultimate local control: 95%) <1.5 cm (n = 43): 83% (ultimate: 94%) 1.5 cm (n = 24): 74%; (ultimate: 96%)	Routine ELR to the mustache region 2-year regional control rate: 87% (6 of 7 neck relapses were salvaged) Ultimate regional control rate at 5 years was 97%	Rhinorrhea: 45% Nasal dryness: 39% Epistaxis: 15% Adhesions: 4%
DAHANCA	Wang T1 (n = 63): 61% LR control; 54 Gy/18 fractions (n = 23), LR control was 87%	No data	Skin necrosis in 3 patients (all in IDR brachytherapy group)

EBRT, *External beam irradiation therapy;* ELR, *elective lymphatic radiation;* IDR, *intermediate-dose-rate of 2.7 Gy/hr (range, 0.7 Gy-7.1 Gy), median dose per fraction of IDR brachytherapy was 15 Gy (range, 3.2 Gy-26 Gy).*
Total dose of IDR brachytherapy was 16 Gy (range, 8-40 Gy).
**5-year actuarial rates.*
†2.5-3 Gy/fraction.

Nasal Cavity and Ethmoid Air Cells

Carcinoma

Radiotherapy and surgery are effective in curing stage-I lesions of the respiratory region. The choice of therapy depends on the size and location of the tumor and the anticipated cosmetic outcome. Posterior nasal septum lesions are generally treated by surgery. In contrast, for aesthetic reasons interstitial brachytherapy (iridium-192 [^{192}Ir] wire implant) is an excellent treatment option for small anteroinferior septal lesions (1.5 cm) to avoid partial removal of the anterior nasal septum. It is preferable to treat lateral wall lesions extending to the lateral alar (eFigure 36-1) nasi with EBRT for cosmetic reasons.

Stage II and operable stage III neoplasms are best treated with surgery. In most cases, postoperative irradiation is indicated.

After excluding cancers of the nasal vestibule,[3] cancers of the nasal cavity ($n = 136$) have a far better 5-year actuarial LRC (61% versus 24%), cancer-specific survival (CSS; 74% versus 49%), and overall survival (OS; 66% versus 35%) when compared to cancers of the maxillary and ethmoid sinuses ($n = 68$), which is a trend reflected in a meta-analysis.[2] Distinct from ethmoid and maxillary cancers, looking at results from the 1960s to 1990s, there has been no improvement in survival for nasal cavity tumors through those decades.[2] The later Danish series on sinonasal cancers, which is dominated (67%) by nasal cavity tumors, documents an improvement in 5-year survival when the national experience from 1982 to 1991 is compared to the results from 1995 to 2004.[3]

Table 36-8 shows the pattern of failure in a series from MDACC. All 14 patients with carcinoma of the nasal septum had the disease controlled (10 after initial therapy and 4 after salvage therapy). Nine of 31 patients with lesions of the lateral wall and floor died of the disease, 5 of uncontrolled local disease, 2 of distant metastases, and 2 of both. The CSS rates at 5 and 10 years were 83% and 80%, respectively. The corresponding OS were 69% and 58%, respectively.

The Danish series also reflected that 81% of the failures involved the primary site with T site failure being 31%.[3] Having combined surgery and radiation therapy improved LRC.

Just as in esthesioneuroblastoma and maxillary sinus cancer, the incidence of lymphatic involvement in nasal cavity cancer is being reevaluated. A meta-analysis reviewed 23 studies of squamous cell cancers of the nasal cavity (series reporting on maxillary cancers were excluded) published between 1974 and 2002.[34] With 927 patients and a mean follow-up of 4.4 years, the regional recurrence rate was 18.1%; prophylactic irradiation was done in 7 studies. Pooled analysis of the 5 studies that reported their rates of control for the electively irradiated patients separately, suggested that the relative risk of nodal failure after elective irradiation, when compared to observation, was 0.18 or 0.16 respectively, both relative risks being statistically significant.

Nasal Cavity: Comparative Outcome by Series

Table 36-9 summarizes the results of relatively large series focusing on nasal cavity tumors. LRC rates range from 60% to 80%.[53,64-66] The incidence of isolated regional recurrence in patients who did not receive elective nodal treatment was approximately 5% in the MDACC series. Treatment morbidity was proportional to disease extent, which dictates the magnitude of surgical resection and the target volume of radiotherapy. Most frequent complications were soft-tissue necrosis, nasal stenosis, and visual impairment.

Nasal Cavity: Comparative Outcome by Histology, Stage, and Pathologic Features

The data on 783 of a total of 981 cases of nasal cavity cancer extracted from the SEER database from 1988 to 1998 were analyzed.[33] Squamous cell carcinoma was the most common tumor type (49.3%), followed by esthesioneuroblastoma (13.2%). More than half of the cases presented with a small primary tumor (T1), and only 5% had positive nodes at

TABLE 36-8 Pattern of Failure of Nasal Cavity Carcinomas, MDACC

Relapse	No. of Patients	LR	N	LR + DM	DM Only
AFTER INITIAL THERAPY					
Septum	14	2	2	0	0
Lateral and floor	31	9	0	1	2
AFTER SALVAGE THERAPY					
Septum	4	0	0	0	0
Lateral and floor	5	1	0	1	0

Modified from Ang KK, Jiang GL, Frankenthaler RA, et al: Carcinomas of the nasal cavity. Radiother Oncol 24:163–168, 1992.
DM, *Distant metastasis;* LR, *local recurrence;* MDACC, *M. D. Anderson Cancer Center;* N, *nodal relapse.*

TABLE 36-9 Outcome of Patients with Nasal Cavity Cancers of Various Histologies Treated by Radiation, Surgery, or Both

Institution	Treatment	Survival	Late Complications
University of Texas M. D. Anderson Cancer Center[20]	RT only: 18 pts RT + surgery: 2 pts Surgery + RT: 25 pts	5-year OS: 75% All 14 nasal septum lesions and 22/31 tumors of lateral wall and floor were controlled	Radiation-induced blindness: 2 pts Surgical blindness: 2 pts Maxilla necrosis: 2 pts Stenosis/perforation: 3 pts
Roswell Park Memorial Institute*[35]	RT only: 30 pts Surgery only: 13 pts Surgery + RT: 14 pts	5-year OS: 67% Patients with WDSCC had the best outcome	Not presented
University of Puerto Rico*[36]	RT only: 34 pts Surgery only: 6 pts	5-year OS: 56%	Not presented
Mallinckrodt Institute of Radiology*[37]	RT only: 28 pts RT + surgery: 18 pts Surgery + RT: 10 pts	5-year OS: 52% Survival not significantly affected by histology Neck relapse occurred in 10/52 N0 pts	Complications (soft-tissue necrosis, cataract, synechiae, otitis media) requiring surgery: 5 pts

OS, *Overall survival;* pts, *patients;* RT, *radiotherapy;* WDSCC, *well-differentiated squamous cell carcinoma.*
**Includes patients with nasal vestibule carcinomas.*

TABLE 36-10 Treatment Results of the Nasal Cavity Cancer from the Analysis of the Surveillance, Epidemiology, and End Results Database for 1988 to 1998

Tumor Type	5-year Survival (%)
Adenocarcinoma	49.0
Adenoid cystic carcinoma	59.1
Melanoma	22.1
Other tumors	59.5
Sarcoma	78.0
Squamous cell carcinoma	61.6
Esthesioneuroblastoma	63.6
SNUC	49.5
Overall	56.7
Classification	**5-year Survival (%)**
T	
T1	66.4
T2	51.8
T3	45.6
T4	40.2
N	
N0	62.3
N1	28.4
N2	NA
N3	NA
GRADE	
Well differentiated (I)	75.3
Moderately differentiated (II)	61.9
Poorly differentiated (III)	47.6
Undifferentiated(IV)	36.8

Data from Bhattacharyya N: Cancer of the nasal cavity. Survival and factors influencing prognosis. Arch Otolaryngol Head Neck Surg 128:1079–1083, 2002.
NA, *Not applicable;* SNUC, *sinonasal undifferentiated carcinomas.*

diagnosis. Overall mean (median) survival was 76 (81) months, with 5-year OS of 56.7%. On multivariate analysis, male gender, increasing age, T classification, N classification, and higher tumor grade adversely affected survival independently ($p < .05$). Radiotherapy was administered in 50.5% of patients and also independently predicted poorer survival ($p = .03$), which is likely the result of the selection of patients with poor prognostic features, such as perineural invasion, positive margins, or poor performance status (medically unfit for surgery) for radiotherapy. The median and 5-year OS by histology, T classification, and differentiation are shown in Table 36-10.

Sinonasal Undifferentiated Carcinoma

With a 10% to 30% incidence of adenopathy at presentation, aggressive therapy seems appropriate.[47,67] University of Florida recommends craniofacial resection with postoperative radiation.[68] Elective nodal irradiation should be considered. Some suggest systemic therapy, and some conclude that the use of surgery has little impact on the end result.[69]

Ethmoid Sinus Cancer

The Italian experience showed a 50.2% rate of adenocarcinomas and 5-year OS of 44.6%.[35] A review of 34 patients found 44% incidence of squamous cell cancer, with a 41% incidence of ethmoid sinus cancer patients having adenocarcinoma. Five-year OS was 44% with surgery and postoperative radiation providing good local control. Local control was one eighth with dura or brain involvement. Prophylactic neck irradiation was not recommended despite a 13% incidence of nodal involvement.[70] The European continental experience with 204 adenocarcinomas of the ethmoid sinus showed a very similar 5-yr OS of 46%.[71]

Esthesioneuroblastoma

Being especially rare, treatment recommendations for esthesioneuroblastoma are tenuous. With a mean recurrence time of 82 months,[72] any initial treatment gives early encouraging results. Whereas treatment with radiation therapy alone might be satisfactory for the uncommon Kadish stage A patient, with a mean follow-up of "only" 56.1 months, radiation therapy alone produced 58% local control for stage B disease ($n = 12$) and 18.9% local control for patients who were stage C ($n = 37$).[73]

Early in Dr Beitler's career, he noted an unexpected rate of neck failures[39,74] and attempted to publish a Kaplan-Meier meta-analysis showing that at 5 years the cumulative rate of late failure in the untreated neck was 27%.[39] At the time this was "unconventional" and the graph of the cumulative incidence of neck failure was not published (see eFigure 36-7).

Monroe[75] published a review of nine other studies and examined the rates of nodal disease. At initial presentation, 7.5% of 212 patients had nodal disease and after interval neck recurrences, the overall rate of disease in the neck was 24.3%.

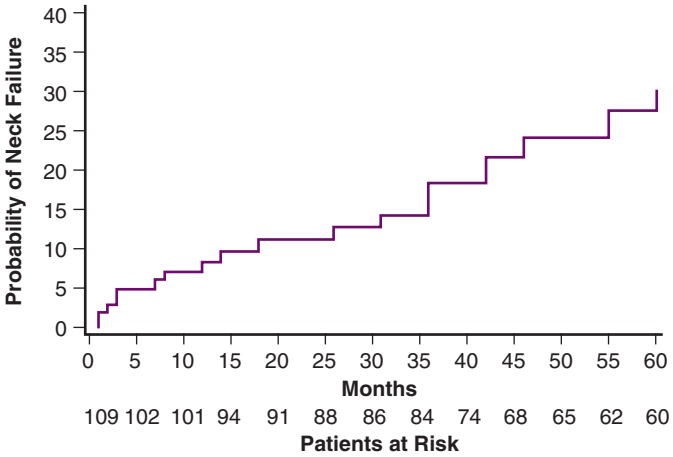
SEER[55] and another retrospective analysis[76] demonstrate that survival is improved when patients receive both surgery and radiation therapy. Surgery runs the gamut from craniofacial resection to endoscopic resection.[77] Whereas a meta-analysis of 379 patients showed that endoscopic resection of esthesioneuroblastoma showed improved survival over patients treated with open surgery,[78] the authors were quite clear that their data had limitations, including patient selection. Though endoscopic surgery is comparable to open surgery for less invasive disease (which may have meant Kadish stage A and B disease), more study is needed especially regarding more invasive tumors before a definite conclusion is reached. Dr. Levine, in the Ogura Lecture to the Triological Society,[77] was more doubtful. "Despite the zeal with which endoscopic resection of esthesioneuroblastomas has been adopted, owing to limited data in terms of numbers of patients and follow-up, there is no statistically significant data at this time to support that approach."

Nishimura et al reported results of proton therapy for esthesioneuroblastoma in 14 patients, primarily with Kadish stage B and C tumors with or without surgery and chemotherapy. A dose of 65 Gy (RBE) in 26 fractions was delivered. The 5-year OS was 94% and local progression-free survival 84%. No late grade-3 or higher toxicities were observed.[79]

The role of preoperative and concurrent chemotherapy and autologous bone marrow transplant is similarly unclear.[56,80-82] Globally, surgical irradiation, or combined-modality salvage of neck recurrence is successful in approximately 30%,[40] with combined-modality salvage being more effective (71%) than either surgery (21%) or radiation alone (7%). Esthesioneuroblastoma is almost a chronic disease, requires very long follow-up, and is one of the few paranasal sinus cancers in which surgical salvage at the primary site is possible.[83]

Maxillary Sinus

The occasional patient with T1 or T2 tumors of the infrastructure can be cured by surgery alone, which may be limited to



eFigure 36-7 Cumulative incidence of neck failure.

TABLE 36-11 Cox Regression Analysis for Survival for Maxillary Cancer

Variable	Significance	Hazard Ratio
Increasing age	<0.001	1.034
Gender	0.822	0.975
T Stage	<0.001	1.424
N Stage	<0.001	1.671
Tumor grade	0.006	1.26
Adenoid cystic histology	<0.001	0.437
Mucoepidermoid histology	0.049	0.44
Radiation therapy	<0.001	0.575

Data from Bhattacharyya N: Factors affecting survival in maxillary sinus cancer. J Oral Maxillofac Surg 61(9):1016–1021, 2003.

a partial maxillectomy. However, most of these tumors present at fairly advanced stages, and the combination of surgery and radiotherapy is considered standard treatment. Nonetheless, these operations still carry significant morbidity.

A meta-analysis[2] suggested the treatment outcome of patients with maxillary sinus carcinomas has improved over the last four decades ($p = 0.02$; eFigure 36-8). However, treatment outcome is still poor, and fewer than 50% of patients survive longer than 5 years. Local recurrence at the primary site and distant metastasis are the most common patterns of treatment failure. Factors that influenced survival for maxillary sinus cancer are seen in Table 36-11.

Stratified analysis found that radiation significantly improved survival only for T4 lesions, and not for T1-T3 lesions, but slightly more than half the patients in the SEER analysis had T4 disease,[42] which limits the power of such an analysis for the patients who are T1-T3. The available literature reveals that the combination of surgery and irradiation yields a 53% to 78% 5-year local control rate and a 39% to 64% 5-year OS.[31,49,56,58,61,62,64,65,84,85]

An MDACC experience with postoperative radiation therapy for maxillary sinus cancer published in 1991 showed that (1) local recurrence was significantly higher in patients with pathologically proven nerve invasion when compared to those patients who did not have perineural invasion (36% versus 10%, $p = 0.05$); (2) the nodal relapse rate without elective nodal irradiation was >30% for those patients with squamous or undifferentiated carcinoma; and (3) complications were related to technique and fraction size >2 Gy.[57] As a result of this experience, MDACC made three modifications to their technique. (1) For patients with perineural extension, the fields included the base of skull, including the trigeminal ganglion; (2) for patients with T2-4 squamous cell or undifferentiated cancers, ipsilateral neck irradiation was included; and (3) dose homogeneity was improved. Important to the last treatment recommendation, it should be noted that of the 90 patients reviewed by Jiang et al, 88 underwent XRT using cobalt and other, now antiquated treatment techniques.

Comparing a more recent cohort of patients whom had presumably benefited from the recommendations, MDACC found that though local control and survival were not significantly impacted, there were hints of improvement.[86] Presumably because of the improved coverage of the base of skull, perineural invasion was no longer a significant predictor of local control in the newer cohort.

Elective nodal irradiation of T2-4 squamous or undifferentiated cancers reduced the risk of neck recurrence from 36% to 7% ($p < 0.001$). Of the 13 neck recurrences in the group that was not electively irradiated, 7 were in the ipsilateral level II neck, 4 in the ipsilateral Ib station, but 1 patient recurred bilaterally in the II nodal stations and 1 in the contralateral level II neck. These last two patients would not have been helped by ipsilateral elective treatment bringing the ipsilateral only neck failure rate to 30%.

Not to be forgotten was that the strongest predictor of distant disease was histopathology. Patients with squamous cell cancers had a 5-year rate of distant metastases of 11%, versus a rate of 33% to 40% for other histologic subtypes. Both nonsquamous histology and nodal disease were independent predictors of the development of an increased rate of distant metastases.

Between 1969 and 2006 the University of Florida[87] treated 54 patients with squamous cell cancer of the maxillary sinus with 96% of their patients having T3-4 disease. With a mixture of patients who were preoperative, postoperative, and received definitive radiation, the median doses to the primary site were 71.2 Gy, 67.8 Gy, and 70 Gy, respectively. The 5-year local control was 41%. Perhaps because only 1 of 54 patients had IMRT treatment, the severe complication rate was 33% ($n = 18$) with mostly ocular complications, but one fatal fistula and one fatal carotid blowout. Eight patients suffered neck failure, 3 of which were initially cN0. Three recurrences were in the contralateral neck. For the 22 patients with cN0 necks who did not receive elective neck irradiation, 2 failed in the ipsilateral neck. For the 23 cN0 patients who received either unilateral ($n = 14$) or bilateral ($n = 9$), one patient who received unilateral neck irradiation failed in the contralateral neck.

Memorial Sloan Kettering Cancer Center (MSKCC)[88] reported a postoperative sinonasal series where the median dose was 63 Gy. With more moderate dosing and one third of patients receiving IMRT there were no late grade-3 or -4 complications. The definitive-radiation MSKCC series of 39 patients[89] found that despite a median BED dose of 70 Gy, local recurrence developed in 25 of 39 (64%) patients and regional recurrence developed in 9 patients (23%). With the higher doses, more complications were seen. One patient who presented with unilateral blindness developed a corneal ulcer during radiation. One patient developed optic neuropathy and blindness 7 years after radiation; this patient received 77 Gy to the optic nerve and had been forewarned that unilateral blindness was likely. Three patients developed unilateral blindness attributable to disease progression and one patient developed radionecrosis with the dose to the temporal lobe being 77 Gy.

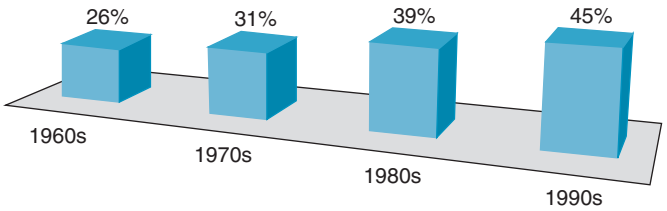
High dose intraarterial chemotherapy is theoretically appealing for advanced maxillary cancers. The clinical results have been disappointing.[90-93]

Conclusions

First, there is no doubt that unresectable maxillary sinus cancer has poor control despite aggressive doses of radiation, with little obvious benefit from intraarterial chemotherapy. Second, high-dose radiation therapy is prone to high complication rates, and whether an aggressive dose (70 Gy or higher) is chosen depends on the risk tolerance of the patient and the physician. Third, lymphatic spread is not trivial and ipsilateral upper nodal elective irradiation should be considered for T2 disease or higher. Fourth, contralateral upper nodal irradiation should be considered for patients who are node positive and patients with advanced disease or disease approaching or crossing the midline.

Sphenoid Sinus

Owing to the rarity of the disease, there are relatively few articles which concentrate on cancers originating in the



eFigure 36-8 Maxillary sinus cancer, survival by decade.
Dulguerov 2001.

sphenoid sinus. Their prognosis, when compared to other paranasal sites is said to be inferior but even a series of 220 patients only claims 7 cancers originating in the sphenoid sinus.[2] Headaches and visual disturbances are the most common presenting symptoms with squamous cell cancer being the most common histology.[94,95] Most series report high local failures, but the Massachusetts General Hospital (MGH) series of multimodality therapy, including proton therapy-median dose 76 Gy (RBE) showed an 86% 2-year local control rate, an 86% 2-year regional control rate, but only a 50% 2-year freedom from distant failure rate.[95] There were no cases of visual loss.

LOCALLY ADVANCED DISEASE AND PALLIATION

Primary Radiotherapy

Patients with locally advanced inoperable tumors or who are unfit for surgery are often treated with primary radiotherapy. Compilation of literature data reveals that primary radiotherapy yields a 22% to 39% 5-year local control rate and 22% to 40% 5-year OS.[96-103]

Proton therapy may have the potential to do better. In a proton series of 39 patients with unresectable malignancies of the nasal cavity and paranasal sinuses, all of whom had N0M0 disease, the 5-year OS was 55% but there were 5 patients with grades-3 to -5 late toxicity.[104] The treatment related fatality was caused by a persistent cerebrospinal fluid (CSF) leak. There were 9 (23%), 5 (12.8%), and 9 (23%) local, regional, and distant failures.

Chemotherapy: Neoadjuvant and Concurrent

Neoadjuvant Chemotherapy

Neoadjuvant chemotherapy in addition to standard radiotherapy failed to demonstrate any therapeutic advantage over radiation alone in a matched-control study from Seoul, Korea, comparing standard radiotherapy versus the combination of neoadjuvant chemotherapy and radiation.[105] Thirty-four patients with inoperable maxillary squamous cell cancer were treated with three cycles of neoadjuvant chemotherapy (cisplatin and a 5-day continuous infusion of 5-fluorouracil with or without intravenous vinblastine) followed by radiotherapy (66 Gy to 75 Gy; median, 70 Gy). The outcomes were compared with those for 34 patients treated with radiation alone who were matched for age, sex, performance status, tumor grade, and stage and local extent of tumor. Despite a higher response rate to neoadjuvant chemotherapy, the relapse rate and patterns of treatment failure were not influenced by the addition of neoadjuvant chemotherapy. Treatment-induced late complications occurred equally in both treatment groups. After a median follow-up of 48 months, there was no significant difference in 5-year OS or disease-free survival between the two treatment groups. Both groups had a 65% rate of local recurrence. The 5-year OS was 32% after radiotherapy alone and 30% after neoadjuvant chemotherapy followed by radiotherapy.

Concurrent Chemoradiation

Concurrent chemotherapy and radiotherapy using accelerated fractionation (concomitant boost radiotherapy) produced surprisingly good local control and survival in a prospective study from MSKCC.[106] Among 82 patients with unresectable cancers of the head and neck, 12 had T4 paranasal sinus cancer. Patients received 70 Gy in 6 weeks using a concomitant-boost technique with cisplatin (100 mg/m^2) given on days 1 and 22 of radiotherapy. Three-year local control rates for T4 paranasal sinus cancer was 78% and 3-year OS was 42%.

Concurrent cisplatin (single agent) or carboplatin chemotherapy is often used during EBRT to treat patients with newly diagnosed unresectable squamous cell carcinoma. The addition of chemotherapy enhances acute mucosal and cutaneous toxicity associated with radiation and brings toxicities unique to the specific systemic agent.

Chemotherapy can be given concurrently with radiation for patients with esthesioneuroblastoma but even the University of Virginia has questioned its efficacy.[56] Some believe that chemotherapy is of benefit for patients with high grade, stage C disease.[81] Local therapy alone with surgery and postoperative radiotherapy[40] yields excellent results at 5 years with regard to both OS (93.1%) and local control (96.2%). Concurrent chemotherapy during radiation may be considered in inoperable cases.

Palliation

The symptoms of incurable sinonasal cancer are particularly distressing. Multidisciplinary input is required even with advanced cases because palliation may involve limited surgery, palliative EBRT, investigational chemotherapy studies, or best supportive care. The morbidity of each modality has to be balanced with the benefit to symptom control and improvement in quality of life. Attention is required to

- Control of pain and discomfort as a first priority;
- Communicate the incurable status of the tumor;
- Deal with the psychological effect of incurable status;
- Help with the impact of disfigurement and dysfunction that are frequently present; and
- Collaborate with caregivers, social services, and home and hospice care, as needed.

Chemotherapy is often single agent or investigational. If radiation therapy is given, concurrent chemotherapy may be added. Although larger dose per fraction EBRT is the usual practice for palliative cases to reduce the duration of treatment, if concurrent chemotherapy is added, consideration may be given to reducing the dose to 1.8 Gy to 2 Gy/fraction to avoid severe acute effects.

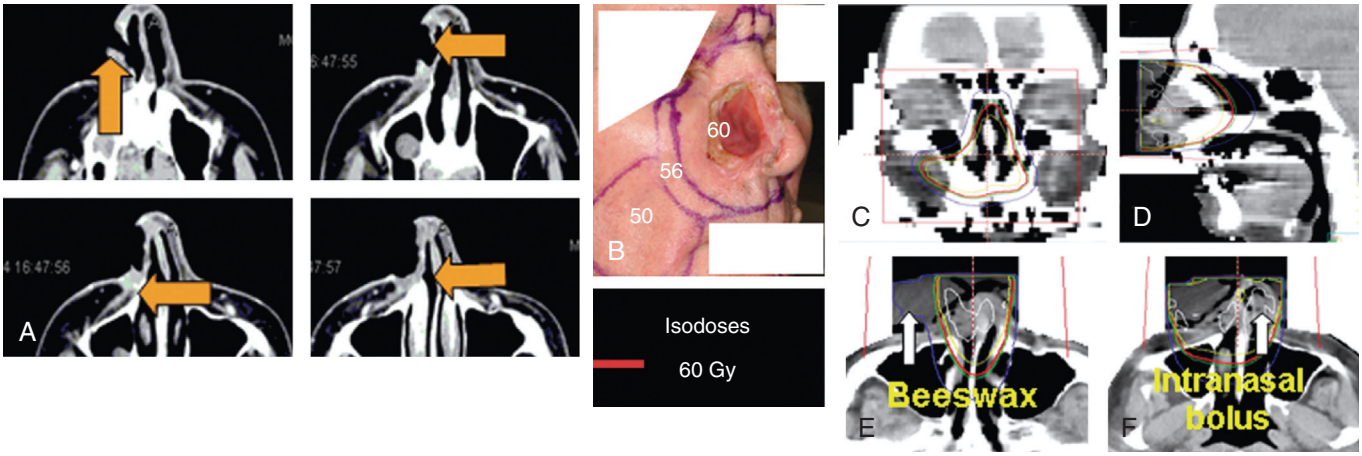
Treatment with radiotherapy or chemotherapy is often effective in reduction of tumor bulk to provide relief of symptoms such as disfiguring masses, proptosis, discomfort or neuropathic pain, headache, epistaxis or other bleeding, nasal obstruction or discharge, and trismus.

IRRADIATION TECHNIQUES AND TOLERANCE

Nasal Vestibule

Target Volume

For a small, delineated, well-differentiated carcinoma measuring up to 2 cm, small fields with a 1-cm or 2-cm margin are appropriate. The initial target volume for all poorly differentiated tumors and well-differentiated primaries larger than 2 cm without palpable lymphadenopathy encompasses both nasal vestibules with at least 2-cm or 3-cm margins around the primary tumor (wider margins for infiltrative tumor) (eFigure 36-9). Bilateral facial ("Manchu mustache area"),[107] submandibular, and subdigastric node inclusion is optional and partially dependent on how reliable the patient will be for follow-up. The most recent Danish national experience of sinonasal carcinomas treated from 1995 to 2004, with no patients receiving elective neck treatment, showed 23 neck failures in their series of 204 patients.[3] For extension to "extradermal" structures such as the bone, elective nodal radiation should be more strongly considered because there was a 27%



eFigure 36-9 Adjuvant radiotherapy for a recurrent squamous cell carcinoma of the nasal cavity after partial rhinectomy. **A,** CT images show a small amount of tissue with heterogeneous enhancement. The patient had a complete resection, and pathologic analysis demonstrated invasion of bone, but the surgical section margins were negative. **B,** Fields were drawn at simulation before placing the beeswax bolus and intranasal bolus. The ipsilateral facial lymphatics (i.e., mustache field), the surgical bed with a wide margin (including the residual portion of his nostril and nasal septum), and the tumor bed with a 1.5-cm margin received 50 Gy, 56 Gy, and 60 Gy, respectively, with all doses given in 2-Gy fractions. The nostril was treated using 20-MeV electrons, and the mustache field was treated with 9-MeV electrons. A second set of skin collimation was fabricated for the reduced boost field. A wax bolus to compensate for surface obliquity was used for the whole treatment. An additional bolus was placed in the nostrils to reduce the perturbation of the electron beam with the air cavity and the air bone interfaces. **C-H,** Dose distributions.

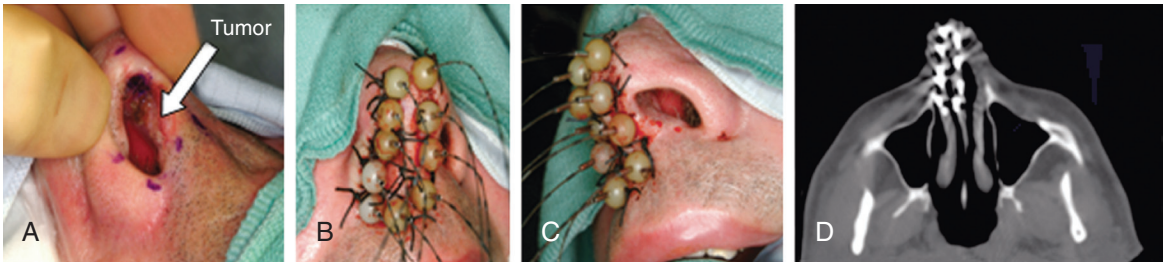


Figure 36-8 **A,** A 2.5-cm squamous cell carcinoma (T2 N0) located on the right side of the columella. **B** and **C,** The entry points are shown for the hollow stainless steel needles that are inserted for afterloading with low-dose-rate iridium-192 interstitial implants. **D,** Needle positions are seen on CT images. A dose of 60 Gy was administered at 68 cGy per hour (total treatment time was 90.6 hours).

nodal failure rate with observation and a controlled primary tumor.[59] When lymph node involvement is present at diagnosis, the lower neck nodes are also irradiated.

For postoperative radiotherapy, the initial target volume includes the operative bed plus a 1-cm to 1.5-cm margin and quite possibly elective nodal irradiation. The undissected nodal region should receive 50 Gy to 56 Gy and the primary site 60 Gy unless there were positive margins or a limited excision was done in which case the dose might be increased to 66 Gy to 70 Gy.

Setup, Field Arrangement, and Dose Fractionation Schedule

Brachytherapy

Brachytherapy for small lesions is accomplished by ^{192}Ir wire implant or, in selected cases, by intracavitary ^{192}Ir mold. Hollow needles for afterloading are inserted, often under general anesthesia, which allows good exposure of the tumor as well as protection of the airway in the event of bleeding from the vascular Kiesselbach's plexus on the anterior nasal septum or from posterior hemorrhages originating from larger vessels near the sphenopalatine artery, behind the middle turbinate. Implantation of a T2 squamous cell carcinoma of the columella is shown in Figure 36-8 and eFigure 36-10. The recommended dose for low-dose rate brachytherapy has evolved empirically and ranges from 60 Gy to 65 Gy delivered over 5 to 7 days. An example of needle placement is shown in Figure 36-8.

Brachytherapy boosts may be given to T1 or T2 nasal vestibule tumors following initial larger field EBRT. At 50 Gy, the patient is assessed, and if there is good reduction of tumor volume, a boost of 20 Gy to 25 Gy may be chosen.

High-dose-rate (HDR) brachytherapy has also been used as a boost. A custom mold of the nasal vestibule is fabricated and tumor is marked in the mold. Two to four plastic tubes with a 1.0-cm spacing are inserted in the mold alongside the tumor. With tumors of the lateral part of the vestibule, two catheters are placed on the inner aspects of the nasal vestibule. For medially localized tumors, catheters are placed on both sides of the vestibule. Following an EBRT dose of 50 Gy in 4 weeks, HDR brachytherapy is delivered in week 6. The dose per fraction is 3 Gy (twice a day) to a total dose of 18 Gy. For tumors of the lateral nasal vestibule, dose is prescribed to a point 0.5 cm lateral to the tumor and for tumors of the septum, the dose was prescribed to the center of the tumor[49] (eFigure 36-11). With a median overall treatment time (EBRT and brachytherapy) of 36 days, this technique yielded a 2-year local control of 86% and ultimate LRC of 100%.

External Beam Irradiation

The patient lies supine and is immobilized with the head positioned (usually slightly flexed) such that the anterior surface of the maxilla is parallel to the top of the couch. This setup allows irradiation of the primary lesion through a vertical appositional field, which can be done with a combination of electrons and photons in a ratio of approximately 4:1. The position is maintained with a custom made head and neck mask. Skin collimation using a lead cut-out, is used to reduce the penumbra of the electron field and, thereby, protect adjacent structures such as the nasolacrimal duct and eye. Custom fabricated bolus material (usually beeswax) is applied to reduce the obliquity of the incident electrons at the sloping surface contour of the nose and to fill the nares for electron beam treatment to improve dose homogeneity (see eFigure 36-9). Additional bolus material may be inserted into the nasal cavity (see eFigure 36-9). The bolus is removed for photon treatments to achieve skin sparing of the dorsum and the nasal tip. Using clinical examination and any appropriate imaging the depth of the lesion is carefully assessed to select the appropriate energy. To protect the mandible, the mouth is opened and lead may be used behind the upper lips to limit dose to the upper gingiva.

The EBRT schedule for irradiating lesions of up to 5 cm with a combination of electrons and photons is 65 Gy to 70 Gy in 1.8- to 2-Gy fractions to gross primary or nodal disease plus, if using electrons, a ≥2 cm margin. Alternatively, when accessible, it is reasonable to deliver a brachytherapy boost dose after an initial 50 Gy.

The schedule for elective nodal irradiation is 50 Gy in 25 fractions. Palpable nodes are given a boost to a total dose of 65 Gy to 70 Gy in 33 to 35 fractions, depending on the size of the nodes and IMRT techniques can be used to deliver this treatment.

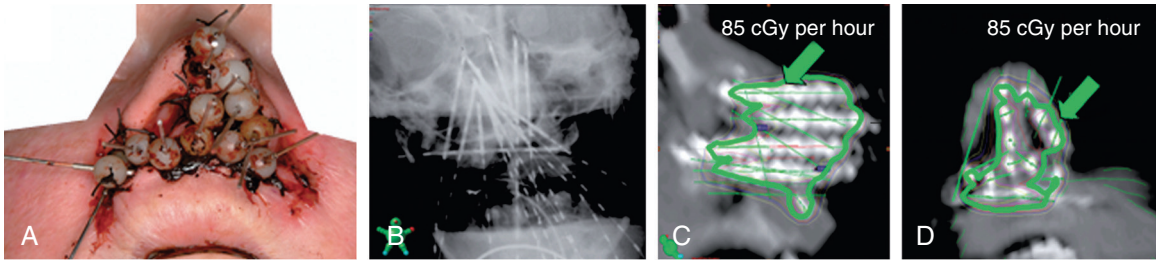
Nasal Cavity and Ethmoid Air Cells

Target Volume

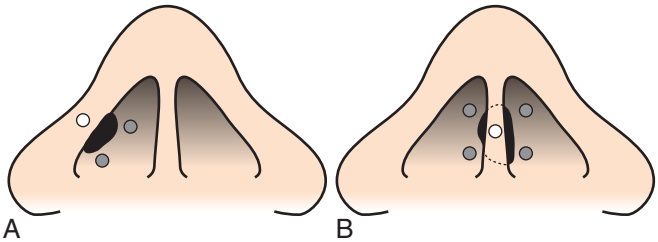
The technique for primary or postoperative EBRT of nasal cavity tumors depends on the depth of the tumor. A margin of at least 1 cm deep to the posterior edge should be included in the full dose volume. CT-based treatment planning is necessary for accurate target localization and dose calculation.

IMRT (Figure 36-9) or proton therapy (Figure 36-10) is recommended for tumors of the nasal cavity or for tumors of the ethmoid sinus. These techniques deliver the desired dose to the target volume while minimizing the dose to critical organs such as cornea, lens, lacrimal glands, retina, optic nerve, optic chiasm, brain, and brainstem.

For postoperative radiotherapy, the primary clinical target volume (CTV) descriptions are given in Table 36-12. CTV_1 consists of the primary tumor bed with 1.0-cm to 1.5-cm margins of normal tissue. A boost subvolume consisting of high-risk region (sites of positive margins and any gross macroscopic residual tumor) to be treated to higher dose may be



eFigure 36-10 A 2.5-cm squamous cell carcinoma (T2 N0) located on the right side of the columella treated with external beam irradiation (50 Gy/fractionated) and brachytherapy implant boost (25 Gy at 85 cGy/hr). **A,** Positions of needles, with the left nasal ala apposed to the septum by two additional sutures to close the air gap of the left nostril for optimal dosimetry. **B,** Anteroposterior radiograph taken in the operating room. **C** and **D,** Sagittal and transverse sections of the final brachytherapy plan, which shows that the 85 cGy/hr line adequately covers the tumor volume (*green line*).



eFigure 36-11 Placement of catheters (gray dots) for tumor of lateral **(A)** and medial **(B)** part of nasal vestibule. White dots indicate dose specification point. Dose specified 0.5 cm lateral from tumor for lateral tumors; for tumors of septum, dose specified in center of tumor. Catheter fixed with ColdPlast mold.
From Langendijk[49] (Elsevier). Used with permission.

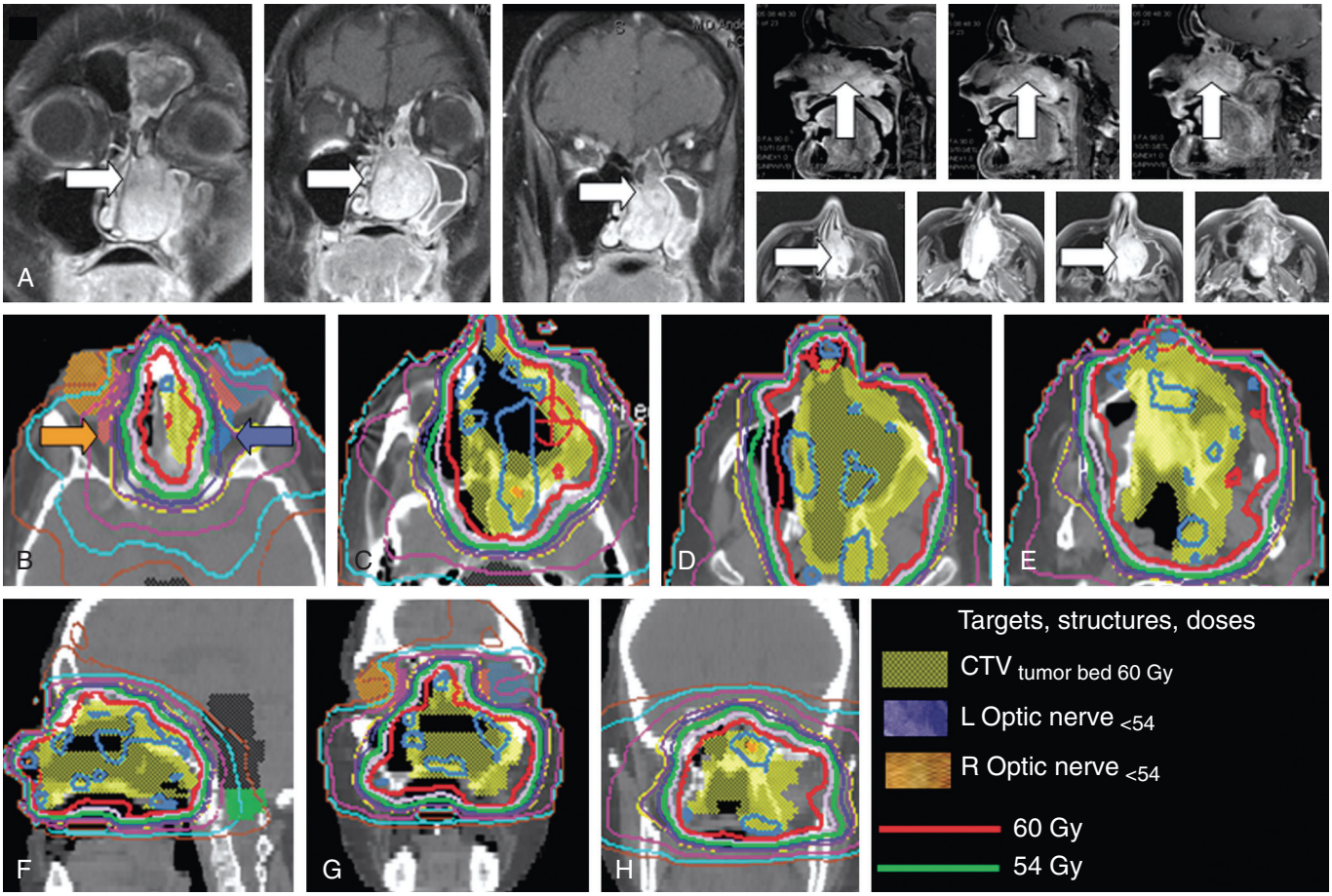


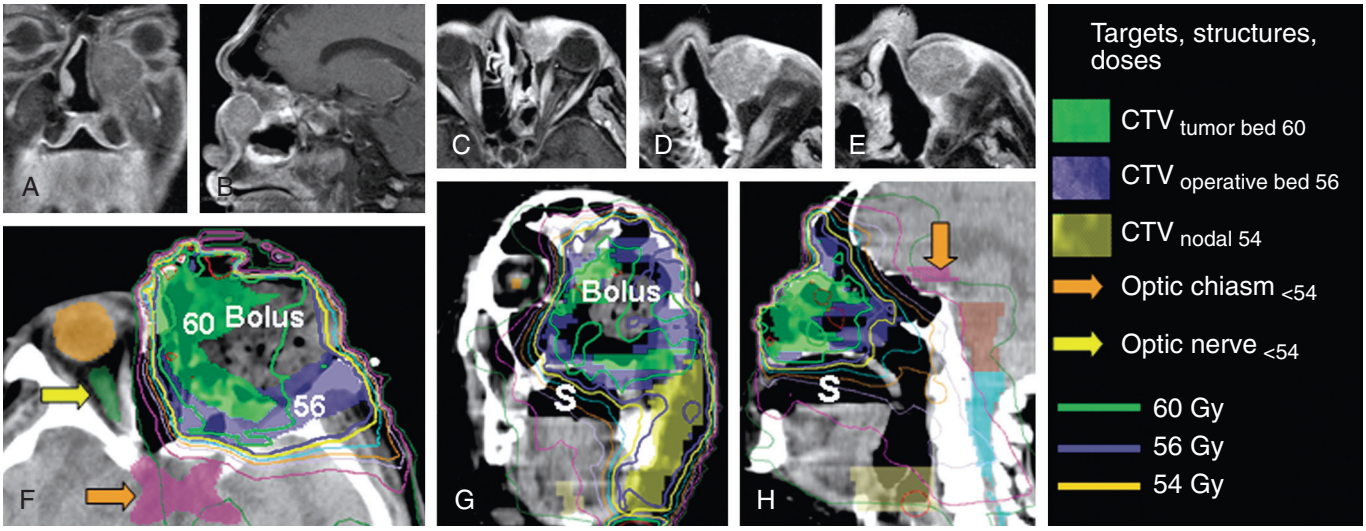
Figure 36-9 Adjuvant radiotherapy for a large tumor of the left nasal cavity after gross total resection with negative margins. **A,** In preoperative MRI, *the white arrows* indicate the primary tumor. **B-E,** Dose distributions at transverse sections. The depth of the target volume precludes the use of an electron beam. The proximity of the target volume to the optic chiasm, brainstem, eyes, and optic nerves (*arrow* in **B**) motivates the use of intensity-modulated radiation therapy. The dose limit for the chiasm and the contralateral optic nerve was set at 54 Gy and the limit for the ipsilateral optic nerve was set at 56 Gy. **F-H,** Sagittal and coronal dose distributions.

TABLE 36-12 Target Volumes for Radiotherapy of Paranasal Sinuses Using IMRT

PRIMARY RADIOTHERAPY		
Target	**Description**	**Dose (30-62 Fractions)**
GTV	Gross tumor volume (represents prechemotherapy volume)	60 Gy-74.4 Gy
CTV_1 (primary CTV)	GTV + 1.0 cm-1.5 cm	60 Gy-74.4 Gy
CTV_2 (intermediate dose)	Primary CTV + 1.0 cm-1.5 cm	59 Gy-66 Gy
CTV_3 (elective CTV)	Nodal volumes, nerve tract, and base-of-skull margin	56 Gy-57 Gy
ADJUVANT (POSTOPERATIVE RADIOTHERAPY)		
Target	**Description**	**Dose (30-35 Fractions)**
CTV_{HR} (high-risk CTV)	Sites of suspected positive margins or gross macroscopic residual tumor	66 Gy-70 Gy
CTV_1 (primary CTV)	Primary tumor bed with 1.0-cm to 1.5-cm margin	60 Gy
CTV_2 (intermediate dose)	Surgical bed	56 Gy
CTV_3 (low-dose CTV)	Tract of V2 if there is perineural invasion, additional skull-base margin, elective nodal volume if indicated	54 Gy

outlined. A secondary CTV_2 includes the entire operative bed. For ethmoid sinus tumors the frontal sinus, maxillary sinus, and sphenoid sinus may be explored during surgery; therefore, these areas are included as part of the operative bed. The bony orbit is part of the operative bed when orbital exenteration is performed as a result of tumor invasion (eFigure 36-12). A third CTV may be delineated to encompass the tract of V2 to the foramen rotundum if there is extensive perineural invasion (Table 36-12).

For primary radiotherapy using IMRT, the gross tumor volume (GTV) plus a 1-cm to 1.5-cm margin of normal appearing tissue is considered the CTV_1 to receive the full dose of 66 Gy to 70 Gy. Any neoadjuvant chemotherapy should not alter the target volumes. Other secondary CTV include the rest of the involved sinus and region around the primary target to an intermediate dose (59 Gy to 63 Gy), the tracts of nerves if there is perineural invasion, and elective nodal regions to a lower dose (56 Gy to 57 Gy) (see Table 36-12).



eFigure 36-12 The patient underwent partial rhinectomy and septectomy for a nasal cavity carcinoma. One year later, disease recurred with an irregular, fungating mass measuring 4.5 × 3.5 × 0.7 cm, which was removed en bloc with clear margins by a medial maxillectomy. **A-E,** Follow-up MRI showed a 2.3 × 2.3-cm, enhancing soft-tissue mass centered in the superior portion of the nasolacrimal duct and invading the medial inferior portion of the left orbit, displacing the globe laterally and involving the medial portion of the left inferior oblique muscle. The patient underwent left suprastructure maxillectomy with left orbital exenteration and removal of medial cheek skin. All margins were clear. Final pathologic analysis revealed an invasive schneiderian squamous cell carcinoma infiltrating the skeletal muscle. **F-H,** The intensity-modulated radiation therapy plan demonstrates target coverage and sparing of the optic nerve and chiasm. Notice the bolus material filling the orbital defect. *S* indicates the position of an intraoral stent used to depress the tongue.

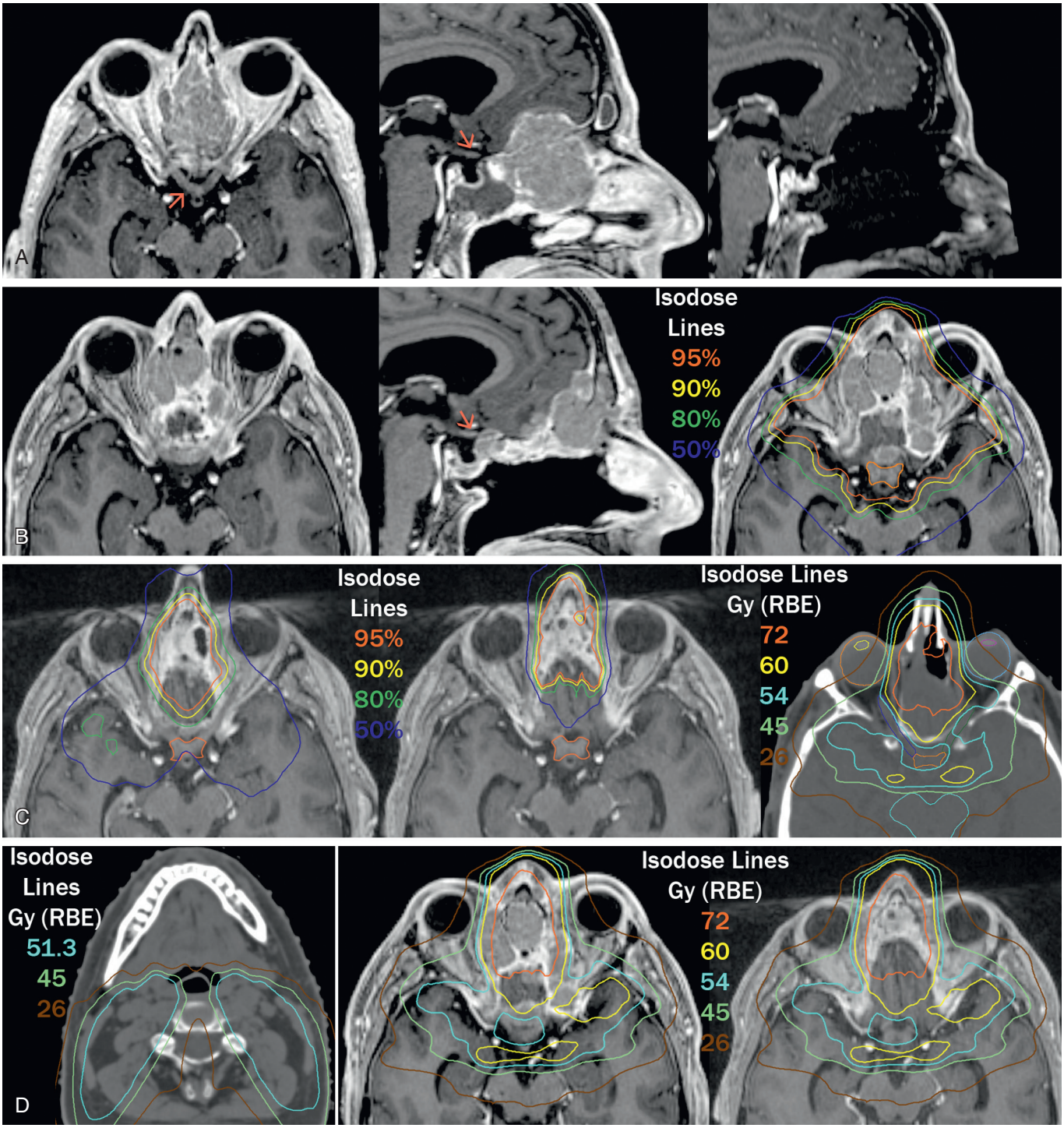
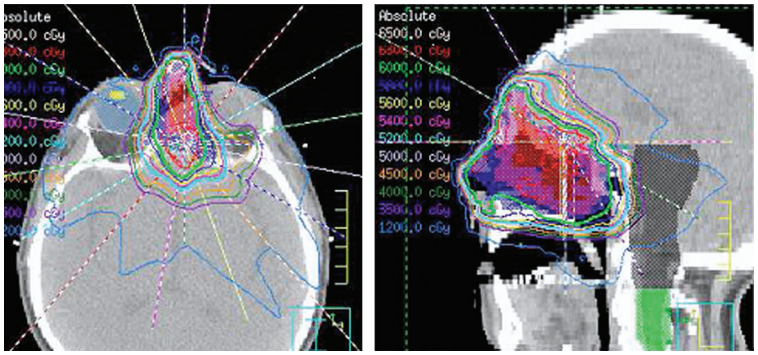


Figure 36-10 Proton therapy for a T4 N0 M0 sinonasal poorly differentiated neuroendocrine carcinoma. **A,** Preoperative axial and sagittal MRI demonstrated a large mass centered on the cribriform plate with bilateral medial orbital involvement and intracranial tumor extension, in close proximity to the optic chiasm *(arrow)*. An endoscopic craniofacial resection was performed achieving macroscopic complete resection with positive margins. **B,** Social circumstances delayed presentation for postoperative radiation for 2 months, at which time MRI demonstrated extensive recurrent disease with recurrent proptosis. An initial radiation plan was developed with delivery of concurrent cisplatin and etoposide. **C,** As the tumor responded to treatment and proptosis resolved, the plan was adapted to begin introducing a dose gradient across the optic apparatus and a smaller volume was boosted to the total dose *(middle)*. The composite plan to 75.6 Gy (RBE) on CT shows *(right)* shows generous coverage of the periorbita because of prior tumor involvement, but overestimates the dose to the globes, which were laterally displaced at onset of treatment. **D,** Elective nodal irradiation was delivered to 54 Gy (RBE), with sparing of the oral cavity. The composite plan on the preradiation MRI and the midcourse MRI is shown. A complete response was maintained at 1 year without visual complications.



Noncoplanar beam orientation					
Beam	Couch	Gantry	Beam	Couch	Gantry
1	000	220	7	000	100
2	000	260	8	000	140
3	000	300	9	090	030
4	000	340	10	300	355
5	000	010	11	090	345
6	000	060			

Figure 36-11 An example of noncoplanar beam arrangement for irradiation of an ethmoid sinus cancer. Beams 9, 10, and 11 are noncoplanar.

Setup and Field Arrangement

Treatment devices include lead skin collimation to obtain a sharp penumbra if electrons are part of the plan as well as bolus material in the nasal cavity, on postoperative defects, and on skin scars. An intraoral stent can be used to depress the tongue, provide a patent airway, and aid in immobilization. Tungsten internal eye shields may be used if the target volume approaches the orbits (when using low-energy electrons but not high-energy electrons or photons).

For EBRT, the patient is immobilized in a supine position with the head positioned such that the hard palate is perpendicular to the treatment table. Caution should be used with metal-containing shielding devices placed on the skin during simulation, which have the potential to perturb the CT images. Other devices and bolus are positioned, scars are marked with thin radioopaque wires, and transverse CT images are obtained from the vertex to the upper mediastinum.

An example of an 11-field noncoplanar arrangement is shown in Figure 36-11. The beam angle selections are based on the same principles as for three-dimensional conformal radiation therapy (3D CRT): (1) preference for the shortest path to the target; (2) avoidance of direct irradiation of the critical structures (e.g., avoidance of beam segment entry through the contralateral eye after ipsilateral exenteration); and (3) use of as large a beam separation as possible.

For 3D CRT, anterior oblique wedge-pair photon fields are most suited for lesions located in the anterior lower half of the nasal cavity. Opposed lateral fields may be applied to treat tumors at the posterior part of the nasal fossa, provided the ethmoid cells are not involved. The optic pathway can be excluded from the radiation fields with this setup. For primaries of the upper nasal cavity and ethmoidal air cells, a three-field setup allows coverage of the ethmoid cells without delivering high doses to the optic apparatus (eFigure 36-13).

Dose Fractionation Schedule

The dose schedule of (LDR) brachytherapy is 60 Gy to 65 Gy over 5 to 7 days. The EBRT schedule for definitive radiotherapy is 66 Gy to 70 Gy in 33 to 35 fractions. For postoperative adjuvant radiotherapy, the schedule is 60 Gy to 66 Gy depending on risk factors such as close or positive surgical margins and perineural invasion. The dose regimens for primary or adjuvant radiotherapy using IMRT are summarized in Table 36-12.

Maxillary Sinus

Target Volume, Field Arrangement, and Dose Fractionation Schedule

Delineation of target volumes of *postoperative radiotherapy* is based on compilation of four sources of information (Table 36-12). These are pretreatment physical examination, pretreatment imaging, intraoperative findings (e.g., tumor extension relative to critical structures such as orbital wall, cribriform plate, cranial nerve foramina, etc., and ease of resection), and outcome of histologic examination (e.g., positive margin, perineural invasion).

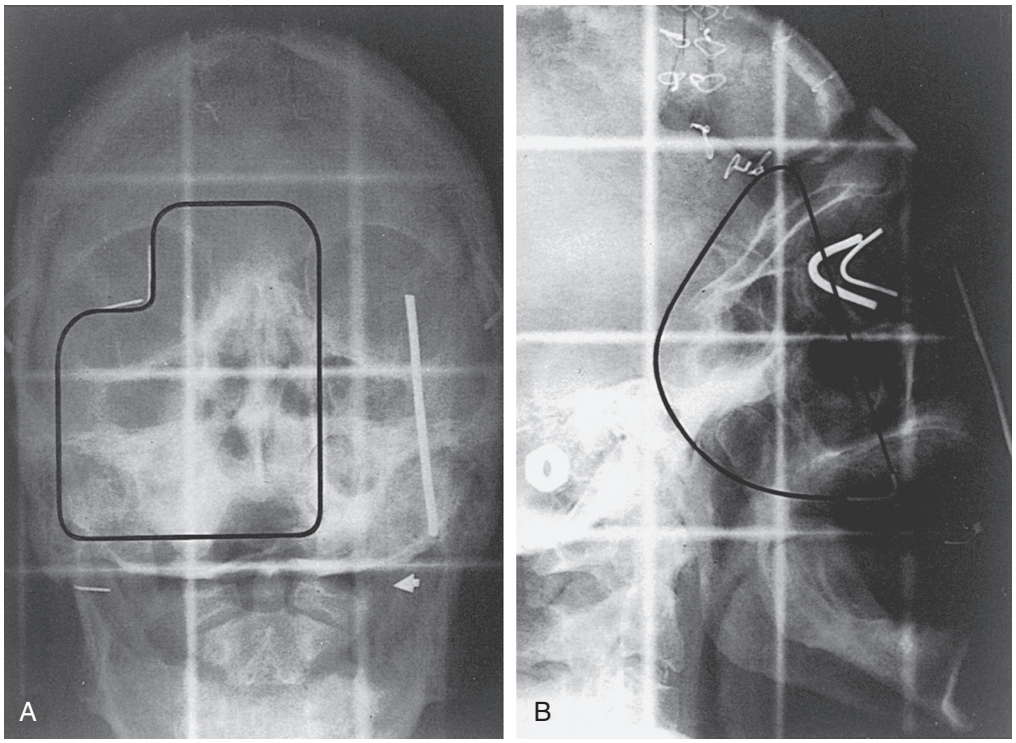
IMRT or proton therapy are the preferred treatment methods because they generally yield better dose distributions in terms of tumor coverage and normal tissue sparing than 3D CRT. Nonionic intravenous contrast should be used at the time of the simulation whenever medically safe. Fusion of the PET/CT or MRI should be performed whenever this will help delineate the target volumes. For postoperative radiotherapy, CTV_1 consists of the primary tumor bed with 1.0-cm to 1.5-cm margin of normal tissue. CTV_2 encompasses the entire operative bed including the bony orbit after exenteration and the ethmoid, frontal, or sphenoid sinuses if explored during surgery. A third CTV may be delineated to encompass the tract of V2 to the foramen rotundum if there is extensive perineural invasion as shown in Figure 36-12. CTV_{HR} may be outlined, which encompasses sites of positive margins, gross macroscopic residual tumor where a higher dose may be delivered. Serious side effects from disease and treatment are common and are shown in Table 36-13. Examples of an IMRT plan for postoperative radiotherapy are shown in Figure 36-13 (an infrastructure tumor) and eFigure 36-12 (a recurrent tumor requiring left suprastructure maxillectomy and orbital exenteration).

Table 36-12 summarizes the dose regimens for IMRT. For primary radiotherapy using IMRT, the prescription doses are 66 Gy to 70 Gy to the gross tumor volume (GTV), prechemotherapy GTV for those receiving induction/neoadjuvant systemic treatment, plus a 1-cm to 1.5-cm margin of normal appearing tissue (CTV_1), 59 Gy to 63 Gy to other secondary clinical target volumes such as the rest of the involved sinus and wider region around the primary target, and 56 Gy to 57 Gy to the tracts of nerves if there is perineural invasion and elective nodal regions (Table 36-13). An example of an IMRT plan for primary radiotherapy of a sinonasal undifferentiated carcinoma is shown in Figure 36-14.

When the primary lesion invades structures adjacent to the optic chiasm, such as posterior ethmoid cells and sphenoid sinus, a dose of up to 60 Gy to the chiasm may carry a higher therapeutic ratio (potentially higher control probability with a relatively low risk for visual impairment) and thus may be acceptable after clear discussion of the therapy rationale with the patient.

Setup

The patient is immobilized in a supine position with the head slightly hyperextended to bring the floor of the orbit parallel



eFigure 36-13 A 56-year-old man sought medical attention because of nasal stuffiness and pressure discomfort below the right eye. A polypoid mass was removed from the right nasal cavity, which was diagnosed as an adenocarcinoma. CT revealed a tumor in the right ethmoid sinuses and the upper part of the right nasal cavity. The floor of the right orbit was involved. The tumor was resected through a craniofacial approach. The right antrum and the sphenoid sinus were inspected and found free of gross disease, but the mucosal lining was removed. Pathologic examination revealed an adenocarcinoma in the ethmoid sinuses spreading to the mucosa of the nasal septum. The surgical bed was treated with an anterior field **(A)** and right **(B)** and left lateral fields using 6-MV photons. The lateral orbital canthi, external auditory canals, oral commissures, and position of the cornea of the right eye were marked at simulation. The thick, straight wire indicated the slope of the face. A dose of 56 Gy was delivered to the isocenter in 28 fractions.
From Ang KK, Kaanders JHAM, Peters LJ, editors: Radiotherapy for head and neck cancers: indications and techniques, Philadelphia, 1994, Lea & Febiger.

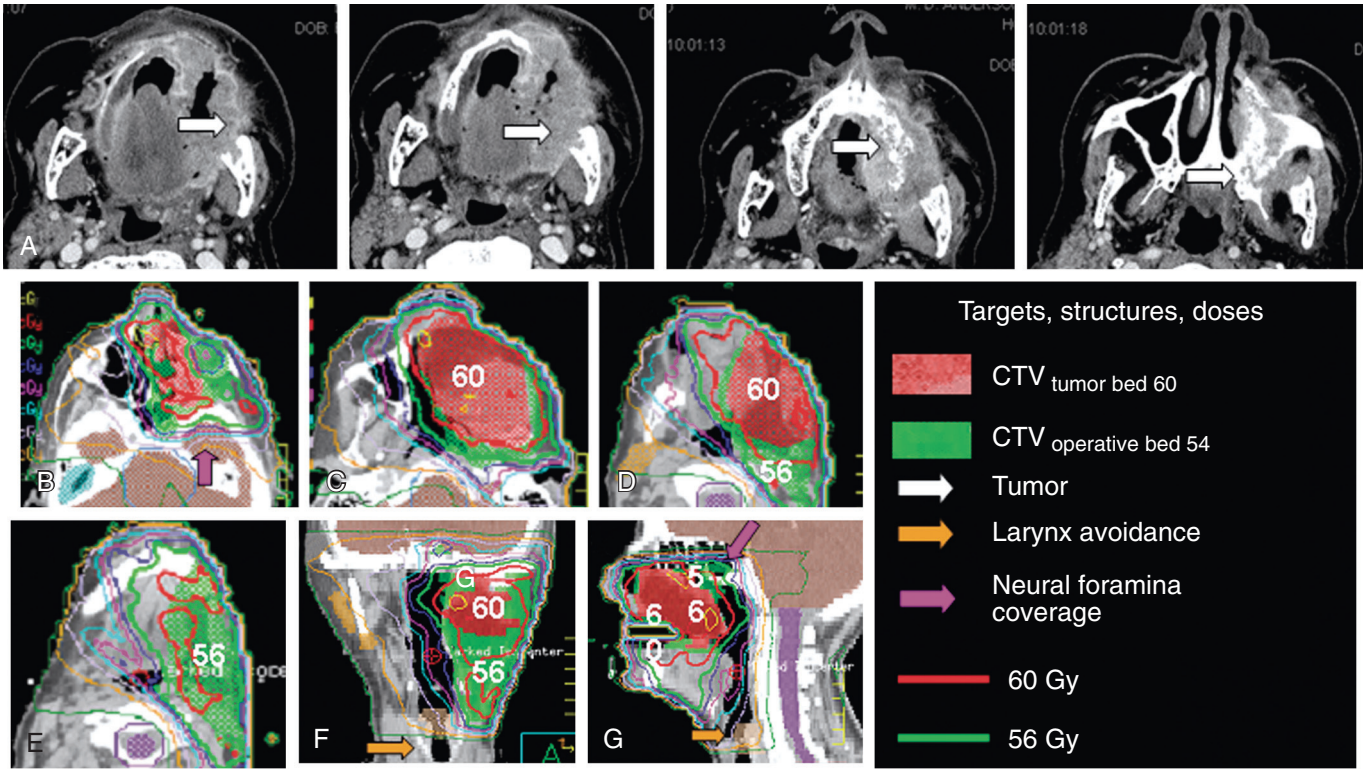


Figure 36-12 A 60-year-old woman had primary radiation therapy in 1999 to a total dose of 66.6 Gy for a left buccal cancer. In 2004, she developed a recurrence centered on the left side of the hard palate and left maxillary alveolar ridge, involving the left buccal mucosa and retromolar trigone, with gross destruction of the mandible and maxilla and the floor of the left maxillary sinus **(A)**. She underwent salvage surgery, which identified poorly differentiated squamous carcinoma with negative margins and found involvement of lymphovascular space and obvious invasion of the infraorbital nerve. She had adjuvant radiotherapy to 60 Gy using intensity-modulated radiation therapy with concurrent chemotherapy. **B-G,** Isodose distributions. The 54-Gy target volume encompasses the floor of the orbit and foramen rotundum at the base of the skull because of perineural invasion *(pink arrow)*, and the larynx was outlined for avoidance *(orange arrows)*.

TABLE 36-13 Side Effects That May Result from a Combination of Tumor, Surgery, and Radiotherapy in Patients with Paranasal Sinus Cancers

Vestibulocochlear	Vestibular dysfunction (imbalance), persistent otitis, tinnitus, hearing impairment
Ophthalmologic (lacrimal gland, eyes, lens, optic nerves, and chiasm)	Retinopathy, xerophthalmia, keratopathy, cataracts, visual impairment
Neurologic (brain, brainstem, spinal cord, temporal lobe)	Neurocognitive impairment, cranial neuropathy, myelopathy, brain necrosis
Endocrine (pituitary gland, hypothalamus, thyroid gland if neck irradiated)	Multiple endocrine dysfunction: hyperprolactinemia, syndromes associated with decreased GH, FSH, LH, T_4, TSH, ACTH, and their downstream hormones
Oral (major salivary glands, oral mucosa, mandible and temporomandibular joint)	Xerostomia, dental caries, dysgeusia, mandible exposure and necrosis, trismus
Connective tissue complications (oral cavity, soft palate musculature, pharynx, larynx, skin and subcutaneous tissues, skull bones)	Soft-tissue necrosis, skin changes, persistent lymphedema, subcutaneous fibrosis, cartilage necrosis, nasal dryness, choanal stenosis, swallowing, voice dysfunction, bone necrosis

to the axis of the anterior field. This position allows irradiation of the entire orbital floor while sparing most of the cornea and most of the globe. An intraoral stent may be considered to open the mouth and depress the tongue out of the radiation fields. Following palatectomy, a stent can be designed to hold a water-filled balloon to obliterate the large air cavity in the surgical defect and thereby improve dose homogeneity. Critical structures, including the optic chiasm, optic nerves, cochlea, parotids, superior pharyngeal constrictors, eyes (retina), brainstem, brain, and larynx should be contoured and identified as organ at risk.

Patient Care during and after Radiotherapy

Patients should be informed about the specific acute and late side effects. The keys to tolerating radiation are adequate nutrition, hydration, and hygiene. Skin and mucosal reactions as well as hydration, hygiene, and nutrition should be monitored and managed during treatment. Saline nasal rinses are initiated during the period of confluent mucositis to prevent crusting and secondary infection. Patients are instructed to use sun block with SPF greater than 15 over the irradiated area after completion of treatment. Regular follow-up examinations

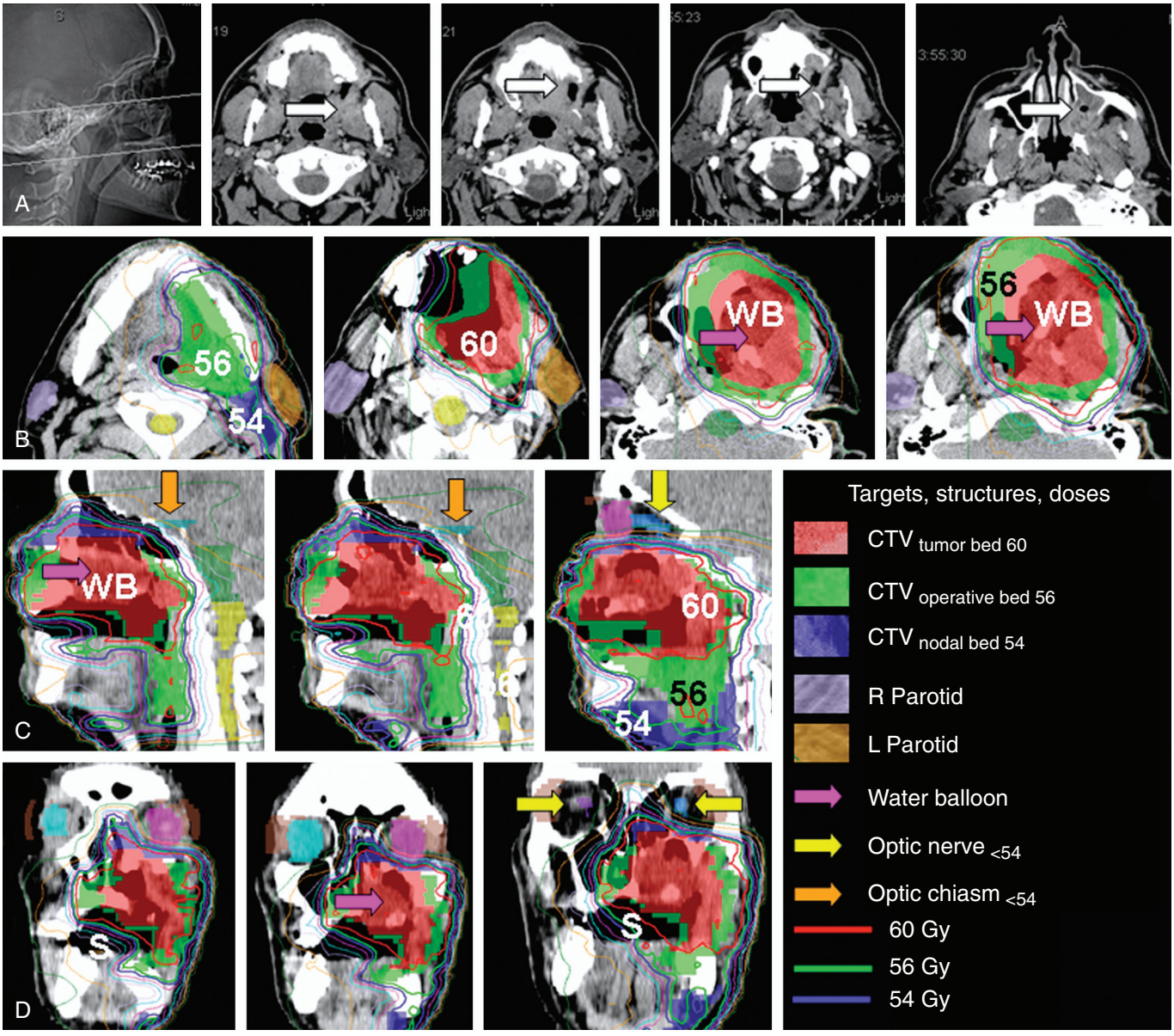


Figure 36-13 Adjuvant radiotherapy for a large, destructive T4 N0 squamous cell carcinoma centered in the left hard palate and inferior maxilla, with extension up into the left descending pterygoid canal. **A,** Tumor *(white arrows)* is demonstrated in the base of the pterygoid plates, left pterygoid musculature, and floor of the left maxillary sinus, along with destruction of the left maxillary alveolar ridge and the left soft palate. The tumor extent was confirmed at resection, and pathologic analysis showed perineural invasion (PNI). **B-D,** Transverse, sagittal, and coronal images show the dose distribution using intensity-modulated radiation therapy. The 54-Gy target volume encompasses the floor of the orbit and foramen rotundum at the base of the skull because of perineural invasion. *Pink arrows* point to a water balloon used to fill the space to provide scatter and reduce dose heterogeneity.

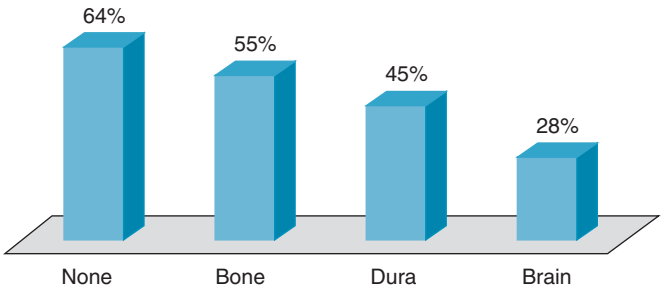
include evaluation of the treated area for late complications. A list of possible side effects is given in Table 36-13.

DIAGNOSTIC AND TREATMENT ALGORITHM AND FUTURE POSSIBILITIES

New Therapy Directions and Clinical Studies

Surgical Techniques

"It is the best of times and it is the worst of times, it was the age of foolishness, it was the epoch of belief, it was the epoch of incredulity, …"[108] Craniofacial resection and plastic reconstruction surgical techniques provide better access for complete tumor resection, while preserving and reconstructing some functionally important structures. Unfortunately, survival is not a certainty (eFigure 36-14). The International Collaborative Study[109] of 334 patients undergoing craniofacial resection for paranasal sinus tumors at 17 prestigious and experienced centers documented a not inconsiderable 4.5% operative mortality rate and a nontrivial complication rate of 33%. Esthesioneuroblastomas were excluded from the analysis as they have a far better prognosis. Surgical margins were "close" (12.9%) or positive (15.6%) in 28.5% and those patients had a 5-year CSS of only 25% versus 64% for those who had negative margins (relative risk, 2.3; $p < 0.0001$). The poor results



eFigure 36-14 5-year disease specific survival (DSS) after craniofacial resection.

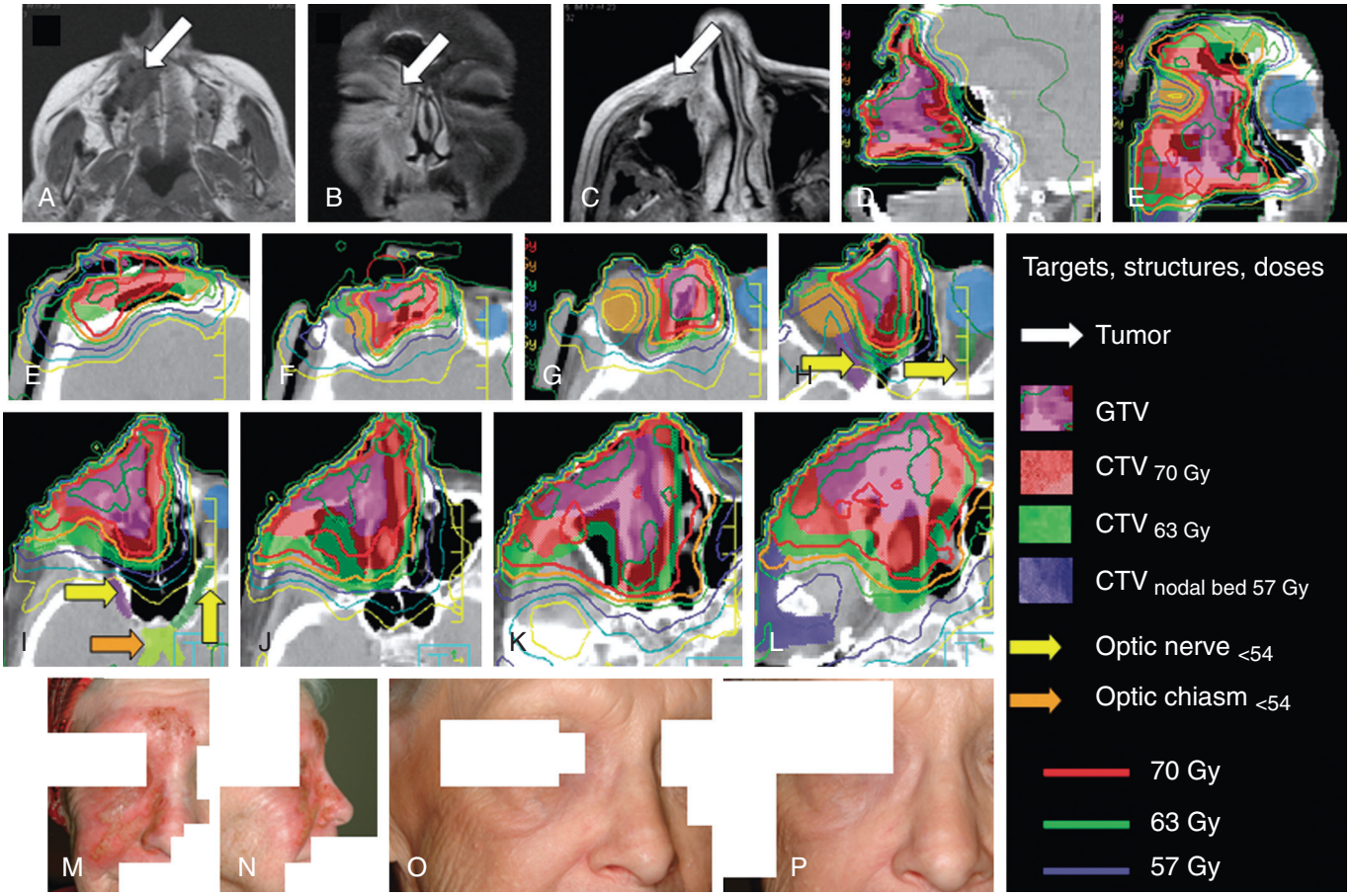


Figure 36-14 Primary radiotherapy for sinonasal undifferentiated small cell carcinoma (SNUC). **A-C,** MRI reveals an extensive infiltrating tumor that is partially enhancing and centered over the upper right nasolacrimal duct. There is penetration through the subdermal layers of the skin and spreading to the right maxillary antrum, the right ostiomeatal complex down to the hard palate, and to the inferior portion of the right frontal sinus. The patient had two cycles of induction chemotherapy consisting of cisplatin and etoposide, which had minimal effect. She received intensity-modulated radiation therapy to 70 Gy in 35 fractions with concurrent cisplatin administered during weeks 1, 4, and 7. **E-L,** The dose distribution is shown for various transverse sections. **M** and **N**, Brisk erythema can be seen on the skin of the face over the high-dose region, along with areas of moist desquamation and crusting. The patient was prescribed prophylactic antibiotic eye drops. **O** and **P**, Skin at 6 weeks after completion of therapy. The patient had no evidence of disease at the last follow-up visit.

with inadequate surgical margins bring into question the value of the surgery. Likewise, bone, dura, and brain involvement each carry a significantly worse prognosis with only a 28% 5-year disease-specific survival for those undergoing craniofacial resection, and for patients with brain involvement, the utility of the procedure must be questioned.

Endoscopic sinus surgery certainly has its practitioners but long-term evidence of its efficacy is lacking. In the largest review of endoscopic resection of sinonasal cancers with or without accompanying craniotomy, Hanna et al[110] reported on 120 patients. The local control was an excellent 85% with a median follow-up of 37 months. Practically these patients were well selected with 63% of patients treated with endoscopic resection alone having T1-T2 disease, whereas 95% of those whose treatment included craniotomy had T3 or T4 disease. As sensibly stated by the authors, endoscopic resection alone should be reserved for patients with relatively early stage disease with no, or limited, involvement of the skull base.

We seem to have the school of radical surgeons who believe in the necessity of the most complete resection possible and the minimalists who feel that considering lack of progress that less invasive surgery makes the most sense. Although opinions are plentiful, randomized data is not.

Chemoradiotherapy

In the setting of squamous cell carcinomas of the head and neck, despite a great deal of enthusiasm, the role of induction chemotherapy is unclear.[111] Based on principles[112,113] it seems reasonable to include concurrent chemotherapy for advanced squamous cell cancers of the paranasal sinuses. Unfortunately, because of the rarity of the disease, it will take many years to assess the relative value of these new developments in improving the overall outcome of patients with sinonasal cancers.

Proton Radiotherapy

Protons are charged particles with a finite, energy-dependent range in tissue. Their energy transfer increases as protons lose momentum, resulting in a large deposition of energy as the protons comes to rest in what is termed the Bragg peak. Unlike photons, the maximal dose deposition of an individual beam occurs in the target, with a slightly sharper beam penumbra[114] and small dose beyond the target ("exiting"), providing

dosimetric advantages in treatment of many disease sites. In a review of published reports of treatment planning comparisons between proton therapy and photon techniques for paranasal sinus and other head and neck cancers, proton therapy provided advantages including markedly lower doses to organs at risk (OARs), the ability to dose escalate the target without increasing dose to OARs, and the ability to maintain superior PTV coverage compared to IMRT as dose constraints to OARs became more stringent.[115]

Emerging proton techniques include active beam scanning and intensity modulation, which can further improve dose conformality, although the great majority of proton clinical results to date are based on three-dimensional conformal proton therapy (CPT). Some published clinical reports have included a component of photon therapy either because historical limited availability of proton beam time or to integrate photons for potential skin sparing and homogeneity optimization of the composite treatment plan.

Given the tremendous heterogeneity of patients with sinonasal malignancies, and institutional variation in treatment approaches, it is difficult to draw conclusions from comparison of different published series. However, most series of proton therapy have focused on patients with particularly advanced or anatomically difficult tumors, with encouraging local control and, despite delivery of aggressive doses, reported visual complications have been low.[116]

A dosimetric comparison of 3D CPT with IMRT for the treatment of a patient with maxillary sinus cancer was performed at the Florida Proton Therapy Institute.[117] The total dose to be delivered was a optimistic 74.4 Gy or 74.4 cobalt gray equivalent (CGE), to be delivered in 1.2 Gy or CGE twice-daily fractions with concurrent weekly cisplatin. The proton plan was normalized so that the CTV received 90% of the prescription dose. Both IMRT and 3D CPT covered the target volumes, but the mean and integral doses for all normal tissues were lower with 3D CPT. Both plans had maximal doses that violated normal tissue tolerances for the ipsilateral optic nerve/retina/lens, temporal lobe, pituitary, and brain. Though the protons reduced the dose to the ipsilateral optic structures, the planned dose to these normal structures was still above tolerance. 3D CPT was able to completely spare the contralateral lens, parotid, and lacrimal glands. Other centers have also reported modest benefit with 3D CPT.[118-120]

Fitzek et al reported results of a prospective study of chemotherapy, surgery, and combined photon-proton therapy in 19 patients with esthesioneuroblastomas or sinonasal neuroendocrine carcinomas, primarily Kadish stage C. Biopsy or subtotal resection was followed by two cycles of cisplatin and etoposide, followed by an aggressive hyperfractionated approach combining photons and protons to deliver a median total dose of 69.2 GyE in a median of 40 fractions. The 5-year OS was 74% and local control 88%. Both patients with local failures were salvaged by surgery. There were no late visual complications.[121]

Zedna et al reported on results of definitive proton therapy in 39 patients with unresectable tumors of the nasal cavity and paranasal sinuses, including several histologies. Approximately a quarter received induction chemotherapy. The most common dose and fractionation was 65 GyE in 26 fractions. The 3-year OS was 59% and progression-free survival 49%; 23% of patients had local progression. One patient suffered vision loss and there was one treatment related death from a CSF leak, with 13% of patients experiencing grades-3 to -5 late toxicity.[104]

Okano et al reported on 13 patients with T4b nasal and sinonasal malignancies of varied histologies treated with induction chemotherapy using docetaxel, cisplatin, and S-1, followed by concurrent cisplatin given with proton therapy to 65 GyE in 26 fractions. The 5-year OS was 75.5%, progression-free survival 34%, with three patients developing local failures. No instances of brain radionecrosis or visual loss were observed.[122]

Proton dosimetry is significantly influenced by air-tissue inhomogenities. Application of proton therapy in treatment of paranasal sinus tumors requires careful attention to dynamic changes that typically occur during radiation therapy from tumor regression and changes in mucosal thickening and filling of the sinuses with fluid. Beam arrangements are selected to provide a dosimetrically robust treatment plan, which is not reliant on the distal range of the beam to provide sparing of critical OARs.[123] When nodal irradiation is indicated, it may be incorporated with proton therapy or with matched photon fields.

TABLE 36-14 Treatment Algorithms for Cancer of the Nasal Vestibule, Nasal Cavity, and Ethmoid Sinus

Site/Extent	Preferred Treatment	Comments
NASAL VESTIBULE		
Small tumors	Brachytherapy	Suited for septal lesions
Larger tumors	EBRT	Suited for nasal floor tumors
Advanced tumors	Surgery + EBRT	—
NASAL CAVITY/ETHMOIDS		
Stage I (A)	Surgery or EBRT	Based on expected esthetic outcome
Stage II (B), III (C)	Surgery + EBRT ± chemotherapy	EBRT ± chemotherapy if high risk for anesthesia

EBRT, *External beam radiotherapy.*

Follow-Up

Although we feel ethically compelled to follow our patients, data regarding the cost-effectiveness of rigorous surveillance is lacking. The relative surveillance modalities are endoscopy for extracranial disease, multiplanar MRI with gadolinium and fat-saturation techniques for endoscopically inaccessible locations, and PET scanning for metastatic disease.

Treatment Algorithms and Conclusions

Treatment algorithms for cancers of the nasal vestibule, nasal cavity and ethmoid sinus are seen in Table 36-14 and the diagnostic and treatment algorithm for maxillary sinus in Figure 36-15. In summary, acknowledging that the literature on the subject of nasal and paranasal sinus cancers comes mostly from retrospective reviews from single institutions, "appropriate" surgery plus postoperative radiation for the aggressive sinonasal cancers is the guiding principle.[124] Especially in the IMRT era, trends toward increased use of elective nodal irradiation seem reasonable, as does the use of concurrent chemotherapy for squamous cell histologies.

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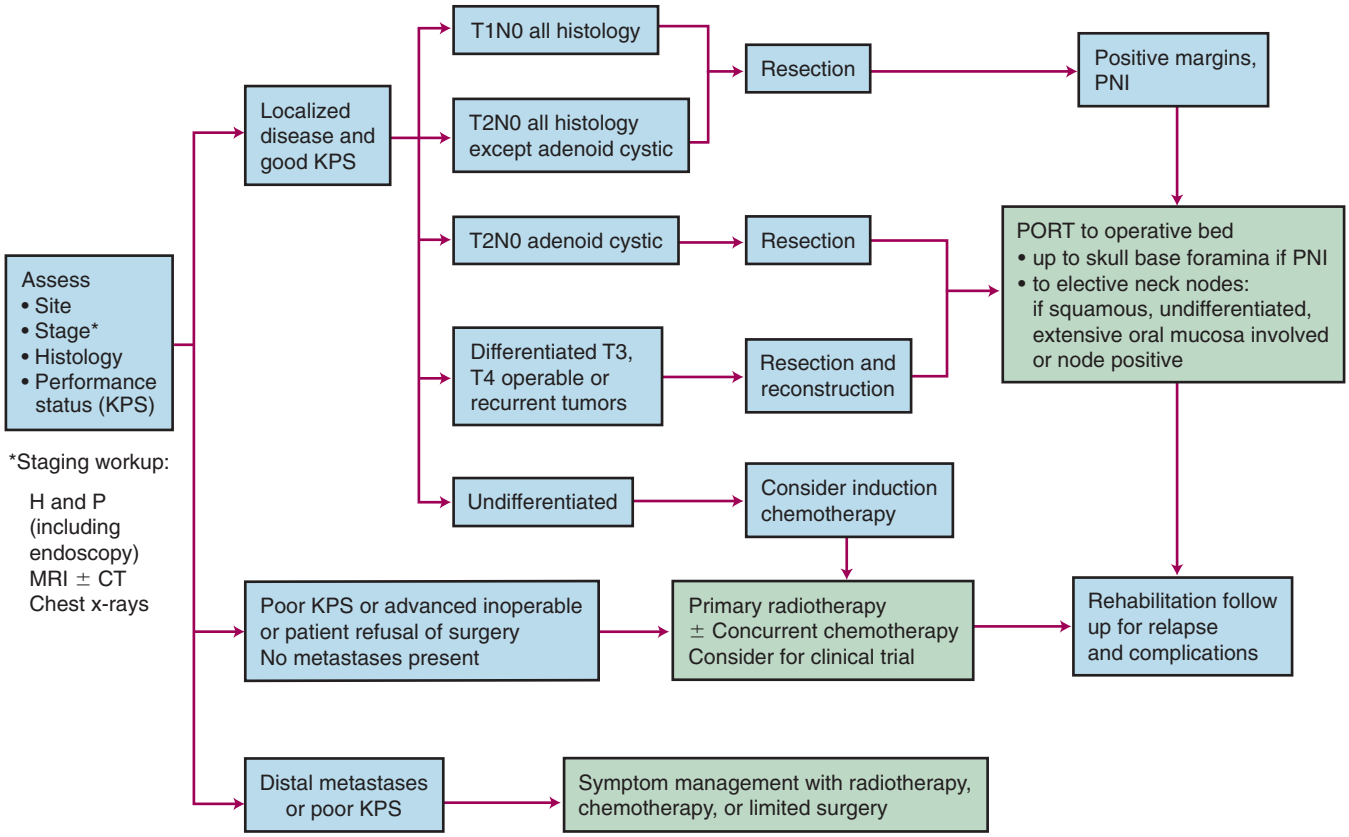


Figure 36-15 Diagnostic algorithm, staging workup, and treatment algorithm for patients with maxillary sinus carcinomas.
CT, Computed tomography; *H&P*, histologic and pathologic examinations; *KPS*, Karnofsky performance score; *MRI*, magnetic resonance imaging; *PNI*, perineural invasion.

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CHAPTER

37 Salivary Gland Malignancies

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INCIDENCE

The overall incidence of salivary gland malignancies in the general population is about 0.9 to 4.0 new cases per 100,000 population per year.

BIOLOGIC CHARACTERISTICS

Prognostic factors relate to histology, grade, primary tumor size and extent, lymph node involvement, gender, and age.

For mucoepidermoid carcinomas, the presence of the hallmark t(11;19)(q21;p13) translocation is a key oncogenic event associated with lower rates of local and distant relapse in fusion positive malignancies.

STAGING EVALUATION

Staging includes a thorough history and physical examination, chest radiography, contrast-enhanced computed tomography (CT) scan or magnetic resonance imaging (MRI) of the head and neck region, positron emission tomography (PET) scan, and liver function tests.

PRIMARY THERAPY

Compete surgical resection is the primary therapy for major and minor salivary gland cancers. Small cancers, typically arising within minor salivary glands in cosmetically or functionally critical areas, may be treated with primary radiation therapy with moderate success in the patient who refuses surgery. New surgical options including transoral robotic surgery (TORS) now exist, offering improved function preserving surgical options especially for minor salivary gland malignancies.

ADJUVANT THERAPY

Adjuvant radiotherapy has an established role to reduce the risk of locoregional relapse in high-risk indications. These include the presence of a positive or close surgical margin, perineural invasion, high-grade histology, extraglandular extension, bone invasion, and the presence of lymph node metastasis.

EARLY STAGE DISEASE

The 10-year locoregional disease control and overall survival (OS) rates for stages I to III disease treated with surgery and postoperative radiotherapy are ≥80% and ~60%, respectively. When treated with radiotherapy alone, these are ~70% and ~65%, respectively.

LOCALLY ADVANCED DISEASE

The 10-year locoregional disease control and OS rates for stage IV disease treated with surgery and postoperative radiotherapy are ~65% and ~30%, respectively. When treated with radiotherapy alone, these are ~25% and ~20%, respectively.

When treated with neutron beam alone, the 6-year actuarial locoregional and OS rates are ~60% and ~60%, respectively. The use of neutron beam radiation can increase the rate of severe late effects including central nervous system (CNS) injury at the skull base.

PALLIATION

Combination chemotherapy regimens have poor response rates, typically less than 25%. Multiple targeted agents have been investigated, demonstrating less toxicity and the suggestion of disease stabilization but even poorer objective response rates.

The salivary glands are exocrine glands that function to produce saliva. The salivary gland unit is composed of acini of serous or mucinous cells that drain into a branching ductal system composed of cells forming the intercalated duct, striated duct, and excretory duct. Myoepithelial cells surround the acinar cells and the intercalated ducts and function by contracting and forcing saliva through the ductal system. Stem cells are present in the basal layer of the excretory and intercalated ducts that can differentiate into the different elements of the salivary glands.

There are three major paired salivary glands (parotid, submandibular, and sublingual) producing the majority of the saliva. The remaining saliva is produced from more than 600 minor simple unencapsulated tubuloalveolar glands, located throughout the lamina propria of the upper aerodigestive tract mucosa. Approximately 50% of the minor salivary glands are located within the mucosa of the hard palate. These glands are predominately mucous secreting. Minor salivary glands may also be seen in the nasal cavity and paranasal sinuses.

Benign and malignant tumors of diverse histologies may occur in a variety of anatomic sites adding to the complexity in understanding the natural history of salivary gland tumors (SGTs). This heterogeneity and the rare incidence of SGTs add to the challenge in determining the optimal management approach.

ETIOLOGY AND EPIDEMIOLOGY

The causes of SGTs, both benign and malignant, have not been clearly established. Reports consistently suggest etiologic associations with nutritional deficiencies, exposure to ionizing radiation, ultraviolet exposure, genetic predisposition, history

of previous cancer of the skin of the face, occupational exposure, viral (Epstein-Barr virus) infection, alcohol use, hair dye use, and higher educational attainment.[1-5]

Of these associations, exposure to ionizing radiation is associated with a statistically significant, though small risk of for SGTs, both benign and malignant. Radiation-induced malignant SGTs (MSGTs) may occur with higher frequency in the minor salivary glands. Studies have demonstrated not only a strong association[6] but also that the risk has a temporal latency (10 years to 25 years) and a dose-response relationship with the exposure especially for mucoepidermoid carcinomas suggesting a cause-and-effect relationship.[4,7,8] The relative risk is greater for MSGTs than benign SGTs (BSGTs).[4,8] These observations are based on several independent long-term cohort studies of victims of atomic bomb exposure[6,7,9] and patients receiving therapeutic radiation for benign[8] and malignant indications.[4] Although investigators have concluded that higher doses and repeated exposure to radiotherapy increases the develop of radiation-induced SGTs, the nature of the dose-response curve for radiation-induced SGTs is unclear beyond doses ≥4 Gy and may not necessarily always increase the risk of second malignancies.[10,11] However, the atomic bomb data does demonstrate that second malignancies are increased with single exposures up to approximately 3 Gy and that this relationship is at least linear up to 2 Gy. Unlike radiation-induced sarcomas, which appear to be primarily limited to the high doses seen within radiotherapy prescription volumes, SGTs can also be seen to occur in areas receiving low therapeutic doses of radiation with the risk increasing with higher doses.

Salivary gland tumors are regarded as rare with a reported overall incidence in the Western world of approximately 2.5 cases to 3.0 cases per 100,000 per year.[12] MSGTs account for more than 0.5% of all malignancies and approximately 3% to 5% of all head and neck cancers.[12] They comprise approximately 11% of all oropharyngeal cancers.[13] Most patients with MSGTs are in the sixth or seventh decade of life.[14]

The incidence patterns of salivary gland cancers were recently reported in a Surveillance, Epidemiology, and End Results (SEER) population-based study that offers the advantage of eliminating the inherent biases of clinical series.[15] Almost 6400 major salivary gland carcinomas were estimated to have been diagnosed from 1992 to 2006. The most common nonsquamous salivary gland cancers were mucoepidermoid carcinomas followed by adenoid cystic and acinic carcinomas of comparable incidence rates. Males had a 51% higher incidence rate compared to females. The parotid gland accounted for 80% of all major salivary gland malignancies,[15] but tumors of the parotid are in general less likely to be malignant compared to the other major salivary glands and the minor salivary glands of the palate.[12] Except for adenoid cystic carcinomas (ACCs), which were equally seen in the parotid and submandibular glands, other histologies occurred mainly in the parotid gland. Notably, squamous cell carcinomas found in the parotid region usually represent lymph node metastases from cutaneous squamous cell carcinomas rather than primary parotid gland carcinomas.[16]

Among males, the most common nonsquamous salivary gland cancers were mucoepidermoid and adenocarcinoma–not otherwise specified (NOS).[15] Among females, the most common nonsquamous salivary gland cancers were mucoepidermoid, acinic cell, and ACCs. Squamous cell, adenocarcinoma–NOS, and salivary duct carcinomas occurred with more than a twofold higher incidence among males. In contrast, females had a higher incidence of acinic cell carcinoma and ACCs.

Acinic cell carcinomas were more likely to be diagnosed at younger ages compared to other cell types.[15] Incidence ratios of salivary gland cancers were significantly lower among African Americans, Asians, and Pacific Islanders compared to whites. However, incidences of mucoepidermoid carcinoma and ACC were similar among all races.

PREVENTION AND EARLY DETECTION

The recognition that radiation exposure is a risk factor for BSGTs and MSGTs (especially mucoepidermoid carcinomas) argues that long-term surveillance is likely a prudent recommendation for patients with a known history of accidental, diagnostic or therapeutic head and neck radiation exposure. These patients should be counseled about the potential risk of late MSGTs manifesting, especially if their anticipated life span is on the order of 10 years to 25 years given the latency period noted for development of radiation-induced SGTs. It is not clear if younger patients receiving therapeutic radiation are at an increased risk,[4,8] which would necessitate more vigilant observation. Gender does not appear to be a risk factor. Issues of cost-effectiveness of various surveillance investigations and the frequency of follow-up have not been established.

Because a dose-response relationship for developing SGTs from therapeutic radiation has been described (especially for mucoepidermoid carcinomas), this raises the intriguing question of whether this risk may be mitigated with modern radiation treatment planning techniques. Modern radiotherapy techniques have the advantage that the dose and volume of normal tissue irradiated may be reduced. This includes the use of proton radiation with its favorable Bragg peak physical beam characteristic. Details of this are further discussed in considering the role of protons in the management of SGTs. At this time, the possibility that conformal radiotherapy such as protons will reduce the risk of developing SGTs remains speculative and unproven. SGTs have been demonstrated, even with low doses, including doses less than 280 cGy to the parotid glands.[8] Hence, judicious use of diagnostic and therapeutic radiation and avoidance of any unnecessary radiation exposure are currently the most effective preventive strategies that can be recommended.

BIOLOGIC CHARACTERISTICS AND MOLECULAR BIOLOGY

Significant progress has been made in the understanding of the genetics and molecular biology of salivary gland malignancies. These considerations may be organized based on biologic characteristics of the tumor cell and of the tumor microenvironment. Although many biomarkers have been evaluated and shown to have differential expression compared to normal cells, this review will highlight several that have important potential therapeutic implications especially when shown to have independent prognostic significance.

Salivary Gland Genetic and Molecular Biology

Chromosomal Rearrangements

In recent years, investigations have demonstrated recurrent, nonrandom, and hallmark chromosomal rearrangements, especially translocations that characterize both benign and malignant salivary gland tumors (reviewed in Stenman[17]). These translocations result in fusion oncogenes that affect the apoptotic threshold, cell cycle regulation, tumor angiogenesis, and growth independence. Similar rearrangements have been a common theme among leukemias, lymphomas, sarcomas, and more recently with various epithelial malignancies including thyroid, prostate, and breast carcinomas. Characterizing these recurring translocations and their clinical significance is

an active area of investigation in hopes of identifying future prognostic and therapeutic targets. Several noteworthy observations have been made to date.

In 2003, the recurrent and hallmark t(11;19)(q21;p13) translocation involving CRTC1 at 19p13 and MAML2 at 11q21 was described by several groups demonstrating it to be a key pathogenic event that underlies the development of mucoepidermoid carcinomas (MECs).[18,19] This translocation has been shown to result in the mucoepidermoid carcinoma translocated gene 1–mastermind-like gene family (MECT1–MAML2) (MECT1/TORC1/CRTC1–MAML2) fusion transcript that results in a transcription factor acting on the Notch and the CREB pathways (reviewed in O'Neill[20]).

Okabe et al have demonstrated that this fusion transcript was associated with a longer disease-free survival (DFS) and overall survival (OS) on univariate and multivariate analysis.[21] Others have reported on its favorable independent prognostic impact on survival.[22,23] Lower rates of local and distant relapses have been reported in fusion-positive MECs.[23] It is important to note that these investigations have been retrospective in nature and that prospective evaluation of the prognostic significance of MAML2 translocations remains an area of study.[24] Despite this translocation correlating with low-grade MEC, in multivariate analysis for OS, this translocation was found to be independent of tumor grading raising some to question its ultimate prognostic value.[24,25] Hence, this translocation may be of diagnostic benefit and may potentially identify a favorable cohort of high-grade MECs[26] and help identify a subgroup of high-grade MECs that may be more appropriately categorized as aggressive MEC mimics, such as adenosquamous carcinomas.[23,25] This fusion offers not only the promise of future risk stratified treatment approaches but also insights into the development of novel therapeutic targets. For example, unfavorable fusion-positive MECs are believed to have acquired further somatic mutations conferring increased invasiveness such as deletion in the *CDKN2A (p16)* gene.[27]

Deletions or translocations of the terminal regions of the long arm on chromosome 6 appear to be a consistent and unique event in the development of salivary gland ACCs.[28] Of these, reciprocal translocations involving 6q and the short arm of chromosome 9 have been frequently reported.[29,30] Persson et al have also demonstrated a recurrent and hallmark t(6:9) translocation in ACCs, resulting in the MYB–NFIB fusion oncoprotein.[31] These investigators suggest that this may also be a key oncogenic event in the pathogenesis of ACC[31] leading to the induction of high MYB oncogene expression.[28,31] MYB transcription factors regulate cell proliferation, apoptosis, and differentiation. In turn, high MYB expression can also be seen in MYB–NFIB fusion-negative ACCs as well and may be helpful for future disease stratification because it appears to have potential prognostic significance as part of a molecular prognostic profile.[32]

Mutation Analysis

With advances in massive parallel sequencing, the whole exome and genome sequences of ACCs were recently completed.[33,34] Consistent with the previous report by Persson et al,[31] the whole genome sequencing data confirms frequent t(6, 9) translocation resulting in the MYB–NFIB fusion oncoprotein and frequent chromosomal loss of 1p36, 6q24, 9p, 12q13, and 14q.[33,34] These analyses also demonstrate that ACCs have a lower somatic mutation rate (13 mutations per exome) relative to most adult solid tumors with a wide mutational diversity.[34] Many of the mutated genes encode chromatin remodeling regulators and chromatin-state modifiers (i.e., MGEA5, SMARCA2, SMARCE1, CREBBP, EP300, KDM6A, ATRX, ARID1A, ARID4B, and ARID5B) suggesting epigenetic regulation is important in the development of ACCs. Additionally, genes involved in DNA damage response (i.e., TP53, BRCA1, ATM, ERCC2, and PTPRK), protein kinase A signaling (i.e., PTPRG, PTPRH, RYR2, RYR3, and CALM2), Notch signaling (i.e., NOTCH1, NOTCH2, and SPEN), and FGF-IGF-PI3K signaling (i.e., PIK3CA, PTEN, MAGI1, MAGI2, FGFR2, and FGFR4) are shown to be mutated.[33,34] Presence of activating mutations in the FGF-IGF-PI3K pathway has a particular importance because of the existence of therapeutic agents targeting the pathway in this particularly chemotherapy resistant tumor.

Dysregulation in Growth Factor Receptors

Epidermal growth factor receptor (EGFR) and human epidermal growth factor receptor 2 (erbB2 or HER2/neu) are members of the EGFR transmembrane receptor family, and when activated, transduce mitogenic signals. Several studies have reported high immunohistochemical expression levels that may be more dominantly expressed in non-ACCs.[35-37] However, the clinical significance of EGFR protein overexpression remains controversial with some multivariate analyses demonstrating both an independent association with poor survival[38] and others demonstrating no independent association with poor survival.[37]

Similarly, erbB2 overexpression has been reported for MSGTs. These include strong overexpression in MECs and in salivary ductal carcinomas (SDCs)[39,40] but rarely for ACCs.[39] Univariate[41,42] and multivariate independent prognostic significance has been reported for erbB2 overexpression.[43,44] Agulnik et al suggest that greater clinical activity with the dual EGFR and erbB2 inhibitor lapatinib may be possible in tumors with both high EGFR and erbB2 expression and that erbB2 may be especially important.[35] Recently, patients with SDCs and erbB2 amplification treated with a trastuzumab-containing regimen containing other targeted agents based on actionable mutations were found to have improved survival compared to patients who did not have actionable mutations.[45] Identifying subgroups of patients more dependent on erbB2 signaling may be important in further defining the therapeutic benefit with erbB2 inhibition because tailoring therapies based on molecular abnormalities may be have therapeutic benefits.

c-KIT/CD117

The KIT protein is a membrane tyrosine kinase receptor, which when activated through binding to the ligands stem cell factor or mast cell growth factor, provide signals for cell survival, proliferation, and differentiation. Its overexpression has been particularly noted in ACCs[46] and has been suggested as one way in which ACCs may be distinguished from polymorphous low-grade adenocarcinomas (PLGAs),[47] though contradictory findings have also been reported.[48]

Although the independent prognostic significance for KIT overexpression has not been evaluated, it has remained an attractive therapeutic target because of the clinical success of imatinib, a small molecule tyrosine kinase inhibitor that competitively inhibits the activation of the KIT receptor and several other structurally similar receptor tyrosine kinases. However, it is clear that it is the nature of any point mutations in the protein that impacts on its response to inhibition with imatinib, a small molecule tyrosine kinase inhibitor, which competitively inhibits the activation of the KIT receptor and several other structurally similar receptor tyrosine kinases. Although several investigators have not demonstrated the presence of mutations, recent studies using more sensitive polymerase chain reaction techniques confirm the presence of multiple mutations in the *c-kit* gene in ACCs.[49] While both gain of function (activating function of the receptor) and loss of function *c-kit* mutations have been described for other malignancies, the therapeutic implications of these recently

described mutations in the therapeutic management of ACCs remains to be determined. Although the independent prognostic significance for KIT overexpression has not been evaluated, it has remained an attractive therapeutic target because of the clinical success of imatinib.

Salivary Gland Tumor Microenvironment

Neoneurogenesis

The study of perineural invasion (PNI) is an important biologic consideration for many cancers especially for MSGTs such as ACCs. The molecular determinants of this mechanism of spread have only begun to receive attention in recent years and have yielded insights to view this spread pattern as an active and reciprocal interaction between malignant cells and peripheral nerves. Observations in other cancer sites currently suggest that PNI is the result of a mutual neurotropic interaction with cancer cells characterized by the release of various paracrine growth factors.[50] As with neoangiogenesis, it is clear that the in-growth of nerve endings into a tumor may be stimulated by the tumor release of various neurotrophins such as brain-derived neurotrophic factor (BDNF),[51] nerve growth factor (NGF), and its receptor tyrosine kinase A (TrkA).[52] Neurotrophin staining has been demonstrated to be present in ACCs. NGF and TrkA have both been correlated with the presence of perineural invasion.[52] Recently, the expression of neurotrophin-3 (NT3) and its receptor TrkC/NTRK3 was demonstrated in ACCs.[53] These tumor-innervating nerve cells may release neurotransmitters that function as proliferative and pro-migratory signals for the tumor cells. Furthermore, nerve fibers are used as routes for tumor cell dissemination. For pancreatic carcinoma, detailed studies of serial sections have demonstrated that tumor cells can progress along branching nerve fascicles in a continuous fashion.[54]

Therapeutically, these insights offer the potential for the development of small molecule inhibitors such as Trk tyrosine kinase inhibitors especially for ACCs in hopes of addressing this pattern of spread.[55] Importantly, radiation has recently been shown to impair PNI not only through direct cancer cytotoxicity but also with prophylactic treatment of the nerve, disruption of paracrine signaling preventing perineural spread in an animal model system.[56] Such observations are important because they have potential radiotherapy treatment planning implications.

Hypoxia

In contrast to other solid malignancies of the head and neck, the role of tumor hypoxia has not been as extensively evaluated in MSGTs. This is an important consideration for MSGTs given their relative resistance to radiotherapy and the improved results seen with neutron radiation, which is less oxygen dependent.

Preliminary investigations using methodologies such as immunohistochemical staining for the oxygen-dependent binding of 2-nitroimidazoles suggest that salivary gland malignancies may be well-oxygenated tumors.[57] This observation would not support the hypothesis that an underlying mechanism for not only the radioresistance but also high rates of distant metastasis characterizing MSGTs is the presence of tumor hypoxia. In a study of 12 patients receiving surgery, the hypoxia-marker pimonidazole was administered preoperatively. Of the 8 patients yielding sufficient tumor specimen for analysis, immunohistochemical staining was not seen for pimonidazole and for the hypoxia inducible factor (HIF)-α or the HIF-1α regulated carbonic anhydrase (CA) IX and glucose transporters (GLUT) 1 and 3. Given that salivary gland malignancies are rare and of diverse histologies, further evaluation is needed before more generalized conclusions can be made.

PATHOLOGY AND PATHWAYS OF SPREAD

Pathology

The classification of SGTs is primarily based on morphologic patterns with two classification systems often recognized. This includes the Armed Forces Institute of Pathology (AFIP) and the World Health Organization (WHO). In 2005, the WHO further developed the classification scheme for salivary cancers originally set forth by Foote and Frazell (Box 37-1).[58] The WHO classification includes the following categories: adenomas, carcinomas, nonepithelial tumors, malignant lymphomas, secondary tumors, unclassified tumors, and tumorlike lesions. In contrast, the AFIP classification includes the following categories: benign epithelial neoplasms, malignant epithelial neoplasms, mesenchymal neoplasms, malignant lymphomas, metastatic tumors, and nonneoplastic tumorlike conditions. Speight and Barrett have reported a comprehensive summary of salivary gland histopathology.[12] Given the histologic diversity, this review will highlight histopathologies that impact the pattern of spread and its clinical manifestations.

Important prognostic factors for disease-relapse and survival are summarized in Table 37-1. Practically, histologies may be categorized as high-grade histologies with at a greater risk of nodal and distant metastases or low-grade histologies with a lower risk of nodal metastasis. The former includes high-grade MECs, high-grade adenocarcinoma–NOS, carcinoma ex-pleomorphic adenoma, salivary ductal carcinomas (SDCs), and squamous cell carcinomas. Low-grade histologies include low-grade MECs, ACCs, acinic cell carcinomas (AcCCs), and PLGAs. An intermediate group has also been described consisting of intermediate MECs.

For MECs, the histologic grading has been shown to be of prognostic significance. Several three-tiered grading schemes have been shown to be reproducible and predictive of the patient's outcome by defining low-, intermediate-, and

BOX 37-1 Classification of MSGTs

Carcinoma ex-pleomorphic adenoma
Adenoid cystic carcinoma
Mucoepidermoid carcinoma
Adenocarcinoma (NOS)
Acinic cell carcinoma
Squamous cell carcinoma
Myoepithelial carcinoma
Cystadenocarcinoma
Small cell carcinoma
Polymorphous low-grade adenocarcinoma
Epithelial myoepithelial carcinoma
Clear cell carcinoma (NOS)
Basal cell adenocarcinoma
Salivary duct carcinoma
Carcino-sarcoma
Metastasizing pleomorphic adenoma
Large cell undifferentiated carcinoma
Lymphoepithelial carcinomas
Other rare histologic subtypes include malignant sebaceous tumors, mucinous adenocarcinoma, oncocytic carcinoma, and sialoblastoma. In addition, metastatic tumors, hematolymphoid tumors, and sarcomas may involve the salivary glands.

Classification from Barnes L, Eveson J, Reichart PA, et al, editors: World Health Organization classification of tumors. Pathology and genetics of tumors of the head and neck. Lyon, France, 2005, IARC Press.
NOS, *Not otherwise specified.*

high-grade tumors using five histopathologic features yielding a numerical score for differentiation.[59,60] High-grade MEC has a greater proportion of epidermoid cells than mucous-producing cells with a solid tumor appearance often mistaken for squamous cell carcinoma. High-grade disease also increases the risk of nodal metastasis sufficient to warrant elective management (such as a neck dissection). Despite this, the risk of nodal metastasis with low grade (LG) and especially intermediate grade (IG) can still be significant. Ozawa et al reported that, using the Goode grading schema, low- and intermediate-grade MECs had nodal metastases in 24% and 30%, respectively.[61] High grade (HG) MECs demonstrated nodal metastases in 56% of patients. In the modified Healey grading schema, lymph node involvement was 0% (LG), 22% (IG), and 72% (HG). T category also is associated with an increased risk of nodal metastasis for both major and minor salivary gland MECs.[62] T1 HG disease may be at low risk for nodal metastasis in major salivary glands, that is, anatomic sites not involving the mucosa.[62]

TABLE 37-1 Summary of Prognostic Factors

Endpoint	Prognostic Factors
Local relapse	T3 and T4 category, unresectability, and skull-base invasion
Neck metastasis	Male sex, T3 and T4 category, primary site involving the pharynx, high-grade histology especially mucoepidermoid and adenocarcinoma–NOS
Distant metastasis	Clinical perineural invasion, skull-base invasion, nodal metastasis
Survival	Stage IV, nodal metastasis

NOS, *Not otherwise specified.*

Pathways of Spread

When considering all histologies together, the risk of lymph node metastasis is increased with T3 and T4 disease, involvement of a pharyngeal site and high-grade MECs and adenocarcinoma–NOS.[63] Similar observations have been reported with T stage, anatomic site, and histology (Table 37-2).[64] For minor salivary glands, the density of the lymphatics in the anatomic site has a significant influence on the risk of nodal metastases. In general, cancers arising within the

TABLE 37-2 Incidence of Lymph Node Metastases at Initial Diagnosis by Site, Grade, T Category, Size, and Facial Nerve Paralysis

	Clinically Positive (%)	Clinical or Pathologic Positive (%)	Elective Neck Dissection, Occult Metastases (%)	Clinically Negative, Delayed Neck Metastases (%)
SITE				
Parotid	16-25	—	9	8
Submandibular/sublingual	8-44	—	21	8
Minor		—	—	10
Palate	16			
Sinuses or nasal	15			
Tongue	42			
Cheek or lips	15			
Gingiva	21			
Floor of mouth	41			
Larynx	67			
Tonsil	65			
Pharynx	0			
Adenoid cystic	14			
Mucoepidermoid	30			
Adenocarcinoma	24-28			
Malignant mixed	38			
Acinic cell	0			
Small cell	50			
GRADE				
Low	—	2	7	—
Intermediate	—	16	7	—
High	20-40	34	15-49	—
T CATEGORY				
T1-T2	—	—	7	—
T3	—	—	16	—
T4	—	—	24	—
SIZE				
<4 cm	—	—	17	—
≥4 cm	—	—	61	—
FACIAL NERVE PARALYSIS	—	>60	—	—

Data from Armstrong JG, Harrison LB, Thaler HT, et al: Indications for elective treatment of the neck in cancer of the major salivary glands. Cancer 69:615–619, 1992; Byers RM, Jesse RH, Guillamondegui ON, et al: Malignant tumors of the submaxillary gland. Am J Surg 126:458–463, 1973; and Spiro RH, Koss LG, Hajdu SI, et al: Tumors of minor salivary origin: A clinical pathologic study of 492 cases. Cancer 31:117–129, 1973.

oropharynx or nasopharynx have about a 60% incidence of lymph node metastasis compared with 5% to 10% for hard palate and paranasal sinus sites. Minor salivary gland cancers arising within the tongue and floor of mouth have an approximately 40% incidence of lymph node metastasis; those arising within the gingiva have a 20% incidence of lymph node metastasis; nasal cavity, buccal mucosa, and lip have a 15% incidence or less.

ACCs at the primary site have a predilection for PNI as a unique pattern of local disease extension. ACCs occur most commonly in the palate and frequently spread by PNI. PNI may be seen in >50% of cases and spread may occur in both directions along the nerve. Growth along the nerve has been shown to have "skip" areas of involvement and noninvolvement, so that a negative nerve margin does not guarantee a final negative margin. However, a recent study of serial sections for pancreatic carcinoma suggests that PNI may in fact be contiguous along the branching nerve fascicles and that it is the branching nature of the nerve and pathologic sampling of the sections evaluated that contributes to the uncertainty in margin assessment.[65]

The risk of distant metastases is increased with the presence of lymph node metastasis, skull-base involvement, and high-grade histology.[66] Common distant metastatic sites include lung, liver, and brain and are also associated with the histologic grade.

CLINICAL MANIFESTATIONS, PATIENT EVALUATION, AND STAGING

Clinical Manifestations

Most patients presenting with SGTs are asymptomatic and present typically with a solitary, painless mass. Low-grade SGTs tend to be slow-growing tumors that rarely invade local structures. Symptoms are largely related to the anatomic location from which it originates. Symptoms may include local pain with involvement of the parotid gland, and facial paralysis with involvement of cranial nerve VII. Local obstructive symptoms and possibly drainage from the ipsilateral ear can result from extension to involve the external auditory canal. Trismus may develop with involvement of the deeper parapharyngeal space or pterygoid muscles. Involvement of the skull base can result in other cranial nerve deficits, including symptoms of dysphagia. Minor salivary gland MSGTs commonly involve the palate where they are typically asymptomatic or cause a vague sensation of a mass. SGTs may also present with mass effect symptoms in the submandibular gland, maxillary sinus, oropharynx and larynx. Tumor involvement of functionally sensitive sites, like the larynx, is more likely to lead to symptoms and an earlier disease presentation.

PNI may result in symptoms of pain and numbness but more commonly presents as a painless mass with an indolent history of growth. Clinical symptoms are more likely to be associated with radiologic evidence of PNI (Figure 37-1). Extension through the skull base with intracranial growth can also occur and result in mass effect symptoms. Because ACCs commonly occur in the palate, spread along the palatine nerves through the greater and lesser palatine foramen is an important route of local spread.

Patient Evaluation

As with any patient with a suspected or documented malignancy, proper evaluation begins with a detailed history and physical (Box 37-2). Presence of a new mass in the face, neck, or mouth should be investigated for associated symptoms based on the surrounding anatomic structures that may be affected by disease extension. This should also include symptoms that may relate to perineural spread of the cancer. Physical examination should include a full oral cavity inspection

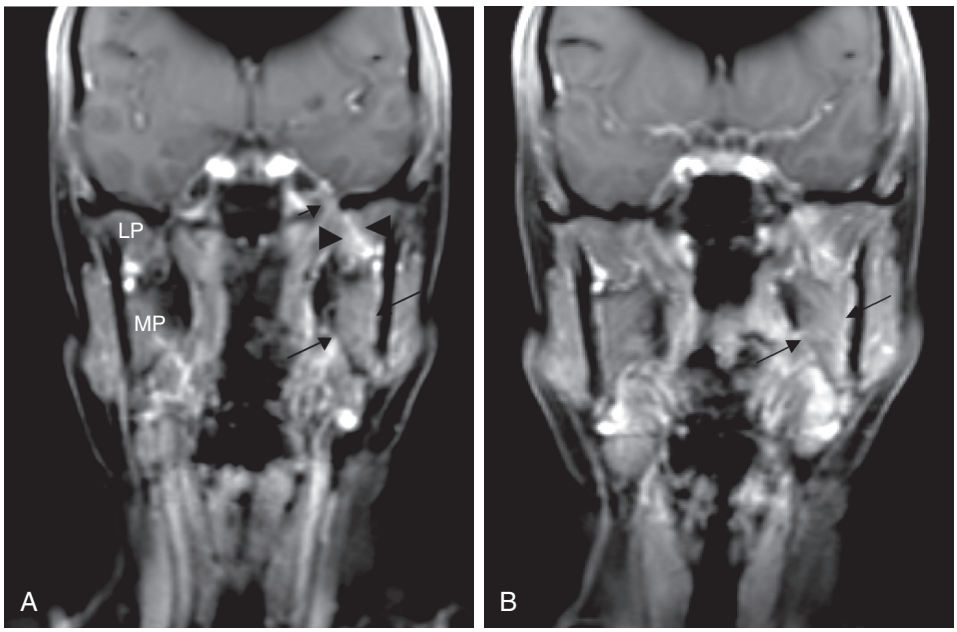


Figure 37-1 Preoperative T1 postcontrast **(A)** coronal images demonstrating an adenoid cystic carcinoma of the left submandibular gland with clinical perineural invasion (PNI) extending along the thickened mandibular branch of the cranial nerve V *(between arrow heads)* between the medial pterygoid (MP) and the lateral pterygoid (LP) muscles to involve the foramen ovale *(short arrow)*. There is also abnormal signal intensity and tissue in the region of the mandibular foramen along the left ascending ramus of the mandible and in the adjacent medial pterygoid muscle *(between long arrow heads)* **(A** and **B)**.

BOX 37-2 Diagnostic Algorithm for MSGTs

GENERAL

History
Physical examination

RADIOGRAPHIC STUDIES

Chest radiograph or CT
CT scan of the head and neck with contrast or MRI of the head and neck with contrast
PET-CT scan for high-grade aggressive histologies

LABORATORY STUDIES

Liver function tests (lactate dehydrogenase, alkaline phosphatase, aspartate aminotransferase)

CT, *Computed tomography;* MRI, *magnetic resonance imaging;* PET, *positron emission tomography.*

TABLE 37-3 Primary Tumor Staging Criteria

Tx	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor 2 cm or less in greatest dimension without extraparenchymal extension*
T2	Tumor ≥2 cm but <4 cm in greatest dimension without extraparenchymal extension*
T3	Tumor ≥4 cm or tumor having extraparenchymal extension*
T4a	Tumor invades skin, mandible, ear canal, or facial nerve
T4b	Tumor invades base of skull or pterygoid plates or encases the carotid artery

**Extraparenchymal extension is defined as the presence of any clinical or macroscopic evidence of invasion of the adjacent soft tissues. Microscopic evidence alone does not constitute extraparenchymal extension for classification purposes.*

and bimanual palpation of structures that are or may be involved. Minor salivary gland tumors typically appear as a submucosal mass and commonly involve the palate. The proximity of the mass and any changes to the greater and lesser palatine foramina should be noted. Flexible fiberoptic nasopharyngolaryngoscopy should be performed to assess for the location and extent of any mucosal lesions in the pharynx or to assess the function of critical cranial nerves that may be suspected to be involved due to a mass at the skull base.

Fine needle aspiration or ultrasound-guided core needle biopsy of suspicious lesions may be useful to distinguish a malignant from benign processes. In a recent retrospective study of 879 patients, fine needle aspiration demonstrated a sensitivity of 83% and specificity of 99%, with overall accuracy of 93%.[67] However, other studies have demonstrated false negative rates as high as 33% and 43% for adenoid cystic carcinoma and low-grade mucoepidermoid carcinoma, respectively.[68] FNA is strongly preferred for the diagnosis of parotid gland masses as it is associated with minimal risk of tumor seeding along the biopsy tract or facial nerve injury. This is particularly important as benign tumors such as pleomorphic adenomas can be very difficult to control after local tumor seeding.

Both CT and MRI are necessary to assess the extent of the disease though the later may be particularly helpful. MRI provides better delineation of soft-tumor infiltration, PNI, and intracranial spread.[69] Bony destruction and regional lymph node metastases are better visualized with CT. CT with contrast may be complementary to MRI for minor SGTs.[69] Both pre- and postcontrast images are needed for optimal evaluation. Recently, MRI techniques such as diffusion-weighted MRI (DW-MRI), dynamic contrast-enhanced MRI (DCE-MRI), and MR spectroscopy (MR) have shown potential for discriminating malignant from benign SGTs.[70] Although the role of PET-CT imaging for salivary gland cancers has yet to be established, early studies have demonstrated an accuracy of more than 90% for detection of the primary tumor and an increased ability in identifying unrecognized local, nodal, and distant metastases.[71,72] The role of sentinel lymph node biopsy for parotid MSGTs remains a promising method to evaluate the risk of nodal metastases but warrants further evaluation before its routine recommendation.[73,74]

Staging of Major and Minor Salivary Gland Malignancies

Unlike minor salivary gland tumors, which are staged according to the anatomic site of origin, major salivary gland cancers have their own staging system. In general, tumors of the major salivary glands are staged according to the tumor size, and whether there is any extraparenchymal extension (Table 37-3). Extraparenchymal extension is described as either clinical or macroscopic evidence of invasion of the soft tissues. Microscopic extension does not constitute extraparenchymal extension. For parotid tumors, the prognostic significance of facial nerve involvement is also considered. Although tumor grade does affect outcome, the current AJCC seventh edition does not incorporate tumor grade as a component of the staging system.

Nodal staging and group staging for major salivary gland tumors follows other head and neck cancer sites and are described here.[75]

PRIMARY THERAPY

The treatment approach for SGTs continues to be based on a surgical resectability paradigm. The therapeutic dilemma occurs when there is significant involvement of a functional region in the head and neck involved in the speech or swallow function or if there is unresectable disease. Therapeutic advancements in recent years include the development of novel organ-preserving surgical approaches (Figures 37-2 and 37-3). Radiotherapy advancements include the development of more conformal radiotherapy techniques and the advent of particle beam therapy. Advancements in systemic agents have included the translation of molecular therapeutics, offering a potentially more favorable therapeutic ratio.

Surgery

The surgical treatment of salivary malignancies can be divided into categories based on the gland involved. The most common site for salivary malignancy is the parotid gland. The submandibular gland and the minor salivary glands have a lower absolute number of cancers; however, the risk of a neoplasm being malignant is higher in submandibular and minor salivary glands than it is in the parotid gland.[76]

Parotid Gland Malignancy

The mainstay of surgical management of parotid malignancies is the parotidectomy, and the extent of the surgery is dictated by the tumor extent. The gland itself is divided into superficial and deep lobes by the seventh cranial nerve (facial nerve), and tumors can exist and arise in either or both lobes of the gland. Although there is no embryologic boundary between the two components of the gland, most tumors arise from the superficial lobe.



eFigure 37-1 This demonstrates a modified Blair incision used for a surgical access for a left parotid salivary gland tumor. The incision includes a preauricular incision that transitions under the ear into a postauricular and upper neck incision.

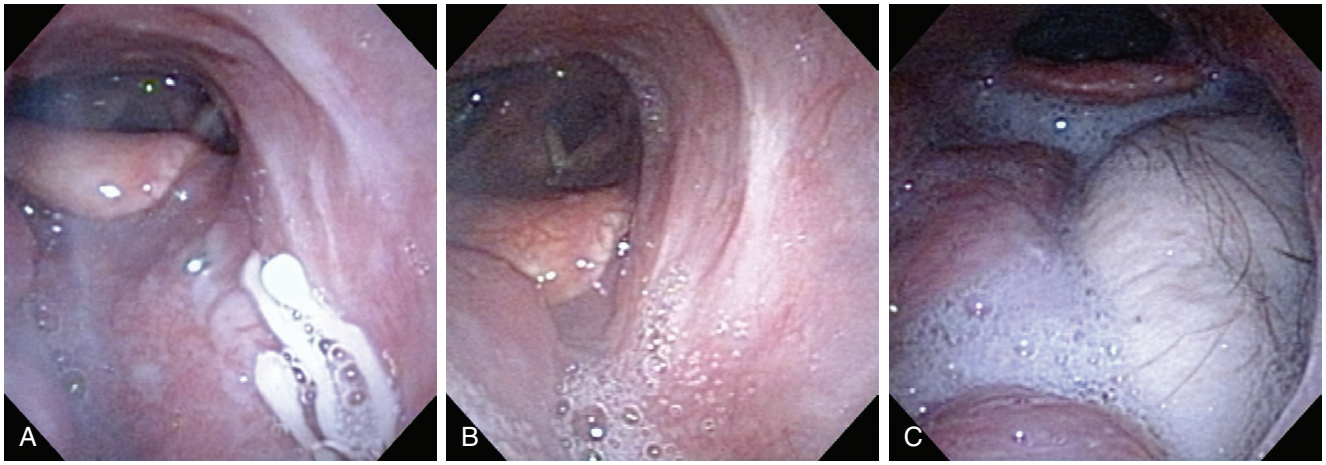


Figure 37-2 Transoral robotic resection (TORS) for an adenoid cystic carcinoma of the base of tongue. The patient was swallowing a full oral diet in the early postoperative setting **(A)** and did not require a mandibulotomy. Very good swallow function can be seen with no pooling of secretions in the vallecula with further wound healing **(B)**. In contrast, a second patient was treated with a traditional mandibulotomy and a radial forearm free-flap reconstruction in the left base of tongue demonstrating more limited swallow function with pooling of secretions in the vallecula **(C)**.

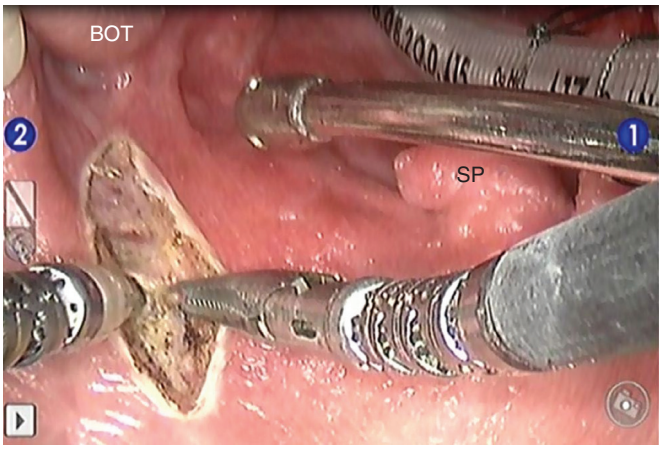


Figure 37-3 Transoral robotic surgery (TORS) of a parapharyngeal space pleomorphic adenoma. This demonstrates the robotic wristed instruments performing the early incision and dissection through the left lateral oropharyngeal wall adjacent to the base of tongue (*BOT*) and soft palate (*SP*). Excellent visualization can be demonstrated through the magnified optics.

Surgery involves an incision in the preauricular crease extending postauricularly and then into the upper neck (eFigure 37-1). This incision, known as the modified Blair incision, gives access to the facial nerve as it comes out of the stylomastoid foramen. A facelift incision is an alternative for select patients. The goal of the surgery is to identify and protect the facial nerve, trace it out along its main branches, and then manage the tumor once its relationship to the nerve has been clarified. In cases where the nerve is compromised by the tumor, or in which the tumor abuts the stylomastoid foramen, it may be necessary to identify the nerve before it comes out of the mastoid bone. This can be accomplished by drilling out the mastoid bone and identifying the nerve before it comes out of the foramen.

Once the appropriate branches of the nerve have been identified, the tumor is removed. Great care is taken to avoid entry into the tumor, and attempts are made to avoid residual positive margins as this is a known poor prognostic indicator.[77,78] Because most tumors involve only the superficial lobe of the parotid, dissecting the tumor carefully off the facial nerve is appropriate surgical care. Tumors that involve the deep lobe of the parotid gland or that involve the parapharyngeal space just medial to the parotid gland may require extended procedures to perform complete resections. These procedures are often possible through the same parotid incision but occasionally require extension of the neck incision or a mandibulotomy.[79] Excision of soft tissue, skin, muscle, and neurovascular structures in the region is appropriate if they are involved with tumor.

All attempts should be made to preserve the facial nerve during parotid surgery. Complete paralysis of the facial nerve will not only cause a significant cosmetic deficit but has the potential to affect many aspects of a patient's outcome. Corneal abrasion, nasal congestion, poor oral competence, and slurred speech are some of the common complaints after this event. Most surgeons would agree that tumor proximity to the nerve is not adequate justification for its sacrifice. However, there are circumstances under which most surgeons would agree that sacrifice of all or a part of the nerve is reasonable. Complete or partial paralysis of the face preoperatively often heralds an intraoperative finding of direct invasion of the facial nerve by tumor. If the tumor extends into the nerve, or grossly encases the nerve, then sacrifice of the nerve is warranted.

Submandibular Gland Malignancy

Although the absolute number of malignancies of the submandibular gland is far less than the parotid gland, the chance of a lesion being malignant is much higher, nearing 50%.[80] For this reason, a high level of vigilance must be in place when managing masses in the submandibular region. Most commonly, patients present with a painless mass in the region. Less commonly, painful masses or neck adenopathy may occur. Any of these presentations warrants a workup of the area, including possibly a CT or MRI and a fine-needle aspiration biopsy.

As with parotid cancers, SGT of the submandibular gland is a surgical disease. Definitive treatment often includes a combination of therapies but almost always begins with surgical excision. The surgical approach should include, at the minimum, a complete submandibular gland excision with clear margins. There is no role for enucleation of the tumor because this has been clearly associated with a higher rate of local recurrence.[81] In patients who have undergone subtotal

surgery, only to be diagnosed with cancer postoperatively, imaging studies should be performed and reoperation performed if there is residual gross tumor to obtain negative margins before considering further therapy.[54]

Sublingual and Minor Salivary Malignancy

Malignancies of the sublingual gland and minor salivary glands are rare. Minor salivary glands are present throughout the upper aerodigestive tract, and SGTs can occur at any of the sites. The oral cavity and oropharynx are the most common sites of disease, but the nasal cavity, paranasal sinuses, hypopharynx, larynx, nasopharynx, and parapharyngeal space (PPS) are all at risk for these cancers.[82]

As is the case with other salivary cancers, surgical therapy with negative margins is the mainstay of therapy. Depending on the site of the cancer, this may include a variety of surgical approaches. The challenge for these MSGTs is the functional impact that surgery can have on the speech-and-swallow function. Unlike the more common squamous carcinomas of the head and neck, the role of nonsurgical therapy has not been well established.

The role of organ-preserving surgical approaches that do not use transcervical exposure techniques are valuable in limiting the swallowing complications resulting from surgery. These include various transoral approaches including the TORS approach (Figures 37-2 and 37-3).[83] TORS has several advantages including the improved visualization of the tumor resection in three dimensions avoiding sight-line limitations with magnified optics. Its application has included function preserving resection of SGTs in the base of tongue[84,85] and in the PPS (Figure 37-3).[86]

Management of the Neck

Patients who present with clinically palpable or radiologically evident disease in the neck lymph nodes require management of this disease. This generally involves planned neck dissection at the time of the primary surgery with or without radiation.[87] What remains more controversial is the role of treatment in patients with no clinicoradiologic evidence of disease in the neck.

Some studies have demonstrated that all high-grade malignancies, (regardless of histology) would benefit from elective management of the neck.[88] Other studies have suggested elective management of the neck based on histologic type or size. This includes elective neck surgery for all squamous cell carcinomas, adenocarcinomas, high-grade MECs, undifferentiated carcinomas, and all T2 or higher tumors.[62,89,90] Still, other groups have suggested either nodal sampling of the upper neck lymph nodes at the time of the primary surgery, or including the neck in the primary treatment field for certain cancers.[91,92] What does appear clear is that high-grade, high-stage cancers benefit from aggressive multimodality therapy, including treatment of the primary site and the lymphatic drainage pathway for the tumors.

Radiotherapy

Postoperative Radiotherapy

At present no randomized studies have been conducted to establish the value of postoperative radiotherapy. Tables 37-4, 37-5, and 37-6 summarize the treatment results from modern series comparing surgery with surgery and postoperative, adjuvant radiation therapy for malignant major salivary gland, submandibular gland, and minor salivary gland cancers, respectively. These demonstrate that the addition of postoperative radiation therapy, when indicated, appears to be associated with improved local control rates and survival in patients with malignant salivary gland cancers. Frequent pathologic indications reported for the use of postoperative radiotherapy include the presence of a positive or close surgical margin (not well defined in the scientific literature), PNI, high-grade histology, extraglandular extension, bone invasion, tumor size, T category, and the presence of nodal metastases (Box 37-3). Because these pathologic indications have not been prospectively evaluated, the absolute risk of relapse and the incremental risk reduction with adjuvant radiotherapy cannot be determined. Recently, a postoperative nomogram predicting for survival in the individual patient with MSGTs of the major glands was developed further confirming the importance of these pathologic risk factors.[93]

TABLE 37-4 Results of Surgery Alone and Combined Surgery and Postoperative External Irradiation for MSGTs

Institution (Reference)	No. of Patients	Median Follow-up (yrs)	Prognostic Factors	Disease Outcomes, 5-yr (%)			
				Local Control		Survival	
				S	S + RT	S	S + RT
MSKCC[73]	92	S: 10.5 S + RT: 5.8	Stage I/II	79	91	96	82 (det.)
			Stage III/IV	17	51 $p = 0.14$	9.5	51 (det.) $p = 0.015$
			Positive Nodes	40 (LRC)	69 $p = 0.05$	19	49 (det.) $p = 0.015$
			High-grade	44	63	28	57 (det.)
Johns Hopkins[74]	87	—	All patients	58	92 $p = 0.001$	59	75 (det.) $p = 0.01$
MDACC[71]	155	7.5	All patients	58	86	50-56*	66-72*
PMH[75]	271	10	All patients	—	—	60	75 (CSS) $p = 0.039$
						29	69 (RFS) $p = 0.0005$
MGH[76]	62	5.5	All patients	—	95	—	77 (DFS)

CSS, *Cause-specific survival;* det, *determinate;* DFS, *disease-free survival;* LRC, *locoregional control;* MDACC, *M. D. Anderson Cancer Center;* MGH, *Massachusetts General Hospital;* MSKCC, *Memorial Sloan Kettering Cancer Center;* PMH, *Princess Margaret Hospital;* RFS, *relapse-free survival;* S, *surgery alone;* S + RT, *surgery and postoperative radiation therapy;* yr, *year.*

**Survival varies by presence of high-grade or perineural invasion*

TABLE 37-5 Results of Surgery and Surgery with Postoperative, Adjuvant Radiation Therapy for Malignant Tumors of the Submandibular Gland

Institution (Reference)	No. of Pts	Minimum Follow-up	Prognostic Factor	Local Control (%)		Survival, 5-yr (%)	
				S	S + RT	S	S + RT
PMH[77]	91	—	All patients	30 (5 yr LRC)	69 $p < 0.05$	60 27	65 (CSS) 52 (RFS) $p < 0.1$
MDACC[78]	86	24 mo	All patients	— Crude	—	71	60
			Soft tissue extension	48	85 $p < 0.034$	—	—
			Perineural invasion	62	92	—	—
			Adenoid cystic CA*	29	100 $p < 0.01$	—	—

CSS, *Cause-specific survival;* det, *determinate;* LRC, *locoregional control;* MDACC, *M. D. Anderson Cancer Center;* PMH, *Princess Margaret Hospital;* RFS, *relapse-free survival;* S, *surgery alone;* S + RT, *surgery and postoperative radiation therapy;* yr, *year.*
**With soft tissue and perineural invasion*

TABLE 37-6 Results of Surgery and Surgery with Postoperative, Adjuvant Radiation Therapy for Malignant Minor Salivary Gland Tumors

Institution (Reference)	No. of Patients	Median Follow-up	Treatment	Local Control (%)	Survival (5-yr) (%)
MSKCC[79]	434	—	S	53 (crude)	42 44.5 det
UF[80]	87	≥2 yr	S + RT	87.5 (crude)	63-100 CSS 56-100 OS 50-93 RFS
			RT	51.3 (crude)	38-90 CSS 39-82 OS 25-73 RFS
MDACC[81]	160	110 mo	S + RT	96 (5-yr)	81
Stanford[82]	54	7.8 yr	S + RT	88 (10-yr)	81 10-yr CSS 63 10-yr OS

CSS, *Cause-specific survival;* det, *determinate;* MDACC, *M. D. Anderson Cancer Center;* MSKCC, *Memorial Sloan Kettering Cancer Center;* OS, *overall survival;* RFS, *relapse-free survival;* RT, *radiation therapy;* S, *surgery;* UF, *University of Florida.*

BOX 37-3 Indications for Postoperative, Adjuvant Radiation Therapy for MSGTs

- Close or microscopically positive surgical margins or gross residual disease
- High-grade cancer
- Involvement of skin, bone, nerve (gross invasion or extensive perineural involvement), and tumor extension beyond the capsule of the gland with periglandular and soft-tissue invasion
- Lymph node metastases
- Large tumors (T3 or T4 disease) requiring radical resection
- Tumor spillage during operation
- Recurrent cancer (including benign histologies such as recurrent pleomorphic adenoma)

In general, the use of postoperative radiotherapy doses typically to 60 Gy appear to be sufficient for MSGTs with PNI of unnamed nerves.[64] In a retrospective review of 140 patients, skull-base relapses may be reduced from 15% to 5% with elective skull-base irradiation especially for T4 disease.[94] Patients with skull-base relapses had a poorer survival when compared to those who did not experience a relapse. For MSGTs with PNI of a major named nerve, elective skull-base irradiation has also been shown to be effective.[95]

Doses between 50 Gy and 60 Gy have also been used for elective irradiation of the neck with relapses less than 5%.[96] Terhaard et al observed a trend to a lower rate of neck control with elective irradiation <46 Gy compared ≥46 Gy ($p = 0.07$).[64] Again, patients with neck relapses have been associated with a poorer survival compared to those patients without neck relapses. When a higher burden of microscopic disease is suspected based on the presence of a positive margin or PNI of a major named nerve, doses <56 Gy are insufficient and doses >60 Gy may be associated with improved local control rates.[97]

With surgery and postoperative radiotherapy to the doses described, long-term locoregional control rates on the order of 80% to 90% may be expected for patients with T1-3 with N0-1 disease. With T4 or multiple nodes, locoregional control rates are significantly lower on the order of 60% to 70%.

Definitive Radiotherapy

Definitive radiotherapy is used primarily for patients with locally unresectable SGTs and will be discussed in the next section.

LOCALLY ADVANCED DISEASE AND PALLIATION

Definitive Radiotherapy: Conventional Fractionation

With locally unresectable salivary gland malignancies, the use of definitive radiotherapy on the order of 70 Gy with

conventionally fractionated schedules typically results in locoregional control rates on the order of ≤20% to 30%.[86-88] These results are also limited by the inherent biases seen with retrospective institutional reviews but are significant in their independent verification of a consistently poor outcome for unresectable salivary gland malignancies when treated with photon radiotherapy alone. These results are also consistent with the standard arm (photon) in a randomized trial of neutron versus photon radiotherapy for unresectable salivary gland malignancies.[98]

Altered Fractionation

Although RTOG 9003 demonstrated that altered fractionation improves locoregional control in other sites of the head and neck,[99] its role in salivary gland tumors is unclear. Wang and Goodman reported results using high-dose, accelerated, hyperfractionated photon beam therapy in patients with inoperable and unresectable major and minor salivary gland cancers.[100] All patients were treated with 1.6 Gy per fraction, twice a day, combined with various boost techniques to obtain a total dose of 65 Gy to 70 Gy. Local control and survival rates were promising, with a 5-year 100% local control and 65% survival rate for parotid gland lesions, and a 5-year 78% local control and 93% survival rate for minor salivary gland lesions. Late complications were minimal. However, the follow-up was relatively short, and thus far, no update has been reported.

Although this suggests a potential role for altered fractionation, it should be regarded as investigational until further data adequately addresses this issue.

Neutrons and Heavy Charged Particle Therapy

High linear energy transfer (LET) radiation from neutrons and heavy charged particles causes direct damage to DNA and is characterized by a reduced oxygen enhancement factor (OER). Compared to low LET radiation from standard photon therapy, damage from high LET radiation is less repairable, and less dependent on cell cycle state. These characteristics make high LET potentially suitable for MSGTs, which are thought to be radioresistant due to a low growth fraction and a long doubling time.

The only randomized trial comparing neutron radiation to conventional photon irradiation was conducted by the Radiation Therapy Oncology Group (RTOG) and the Medical Research Council (MRC) for patients with locally unresectable primary and recurrent MSGTs.[98] The study closed early as a result of ethical concerns because an interim analysis performed at 2 years of 25 patients demonstrated significantly better local control with neutron compared with photon irradiation (67 versus 17%, $p < 0.005$) and a trend toward improved survival (62 versus 25%, $p = 0.1$). The local control rate of 67% was consistent with prior single-institution reports associated with the use of fast neutrons.[101-103] A median survival of 2.97 years with neutrons versus 1.23 years with photons was initially reported. With longer follow-up, the overall survival curves showed no difference. The majority of failures in the neutron arm were systemic. In contrast, the major relapse pattern in the photon arm was predominantly locoregional failures. The incidence of severe or life-threatening toxicity was greater in patients treated with neutrons, with 9 patients treated with neutrons having at least one "severe or greater" complication, compared to 4 patients in the photon arm. This finding of a relatively high rate of severe complications from neutrons has been observed in another comparative series.[104]

Overall, the lack of survival difference from the randomized trial, and the high rate of severe complications coupled with the lack of institutions with available treatment capabilities, limited the broad use of fast neutron therapy. However, mature uncontrolled, single-institution studies continue to demonstrate impressive results, with lower rates of toxicity. Douglas et al published a retrospective study of 148 patients with major salivary gland tumors treated at the University of Washington with a 5-year actuarial locoregional control rate of 100% for tumors <4 cm in size, and only a 6% grade 3 or 4 complication rate.[105] An updated larger series of 279 patients from the same institution demonstrated a 6-year actuarial locoregional control rate of 59% with a grade 3 or 4 toxicity rate of 10%.[66] Neutrons have also been used in the postoperative setting for microscopic residual disease with a 100% 5-year actuarial locoregional control rate reported.[106]

In part, the increased complication rates are the result of the use of neutrons at the skull base and the adjacent CNS. The sensitivity of the CNS structures to high LET radiation often precludes safe delivery of therapeutic doses of high LET radiation to tumors with skull-base involvement. Despite this, it is interesting to observe that neutron radiation does not appear to be associated with an increased risk of facial nerve palsy as a treatment complication.[102,107] Complicating the risk of CNS injury is the recognition that skull-base involvement is associated with a poorer prognosis, local control, and survival in a group of 159 patients with unresectable ACCs.[106]

To address this technical limitation of neutrons, investigators from the University of Washington have been investigating the role of boosting the superior portion of the tumor with stereotactic radiosurgery, after reduced dose neutron beam radiotherapy, in patients with skull-base disease. In 34 patients with skull-base disease treated with a Gamma Knife boost (for details, see discussion), the 40-month actuarial local control was 82%, compared to a historical control rate of 39% in patients with skull-base disease treated with neutrons alone ($p = 0.04$).[108] Heavy charged particle radiation may also hold promise because it combines the biologic qualities of high LET with rapid Bragg Peak dose fall-off. Limited data with carbon ion radiation suggests similar tumor control as neutron beam, with less late effects.[109]

In summary, for patients with locally advanced, unresectable disease of the salivary glands, neutrons offer superior locoregional control compared to standard photon radiation, but with a potential increased risk of severe toxicity. For postoperative radiation, it is not clear that the therapeutic ratio is improved upon given the potential for increased late normal tissue toxicities. Techniques to improve the therapeutic ratio, such as those seen with stereotactic boost or with heavy charged particle radiation therapy, are warranted and are the subject of ongoing investigations.

Stereotactic Radiosurgery

Whether or not the use of hypofractionated doses of radiotherapy in the form of stereotactic radiosurgery (SRS) or fractionated stereotactic radiotherapy (SRT) can overcome the radioresistance associated with conventionally fractionated photon therapy has not been clearly established. There have been two main indications that are relevant for MSGTs and have been the subject of clinical investigations.

The first is the study of SRS at the skull base as a treatment strategy to more safely escalate the effective biologic radiotherapy dose delivered. This largely reflects the experience reported by the University of Washington as described previously. Douglas et al used a Gamma Knife radiosurgery boost as a strategy to reduce the relative biologic neutron dose to the skull base and minimize the risk of CNS injury while improving on the local control rates.[108] The median prescribed Gamma Knife dose was 12 Gy to the 50% isodose line resulting in a median neutron dose of 19.2 nGy to the isocenter. The

median number of isocenters was 17. The median target volume treated was 12.4 cm^3 (range, 1.9 cm^3 to 28.9 cm^3) with a median total volume treated of 18.3 cm^3 (range, 5.9 cm^3 to 53.9 cm^3). This resulted in a median dose of 11.98 nGy to the adjacent tip of the temporal lobe. In total, 34 patients were treated. With a median follow up of 20.5 months, the actuarial 24-month and 40-month local control rates were 82% and 82% compared to 81% and 39% in historical patients not receiving SRS boost. A total of four failures in the SRS group were described with two in-field and two out-of-field relapses. Noteworthy complications included three cases of radionecrosis with only one third of cases with symptomatic headaches responsive to steroids. Comparable risk of brain necrosis (i.e., <10%) has recently been reported by Owen et al in a retrospective analysis of 184 patients with head and neck cancers treated with SRS alone or in combination with external beam radiotherapy.[110]

The other major indication for SRS or SRT has been for *palliative indications*. The rationale for the use of an SRT approach is twofold. First, the stereotactic approach affords greater confidence in the accuracy of the target lesion to be irradiated allowing a smaller margin of uncertainty and thus reducing the volume of normal tissues that receive both unnecessary entry and exit radiation. The second is the potential greater therapeutic benefit that *may* be achieved with higher doses delivered over a single fraction or just a few fractions. To date, the reported experiences are limited and largely amount to small case reports and heterogeneous cohorts for the use of SRS or SRT for head and neck cancers including some recurrent salivary gland malignancies.[111-113] These observations limit the ability to draw any definitive generalized conclusions about the risks and benefits of SRS and SRT at this time including the optimal prescribed dose. The range in prescribed dose includes single fractions of 11 Gy to 18 Gy and hypofractionated schedules including 30 Gy in 6 fractions. In the only series reporting sole on MSGTs, effective palliation of pain was achieved with durable responses including freedom from local tumor progression ranging from 10 months to 35 months.[113] In general, the major serious but infrequent risk associated with this palliative treatment approach includes the risk of optic, facial, and trigeminal nerve injury. At this time, the use of SRS or SRT for MSGTs should be limited to treatment on a clinical protocol or treatment at institutions with a broad stereotactic experience at the skull base for other malignancies where the risks are well defined.

Proton Radiotherapy

There is limited published experience with the use of proton therapy for salivary gland tumors, although the sharp dose fall-off at depths beyond the Bragg peak may potentially allow for safer dose escalation. The Paul Scherrer Institute in Switzerland published a comparative dosimetry study of intensity-modulated photon and proton therapy in the treatment of head and neck tumors.[114] The primary endpoint was the risk of secondary cancers based on the risk estimated using the organ equivalent dose model. For proton plans, both the scatter and the neutron dose contributions were accounted for. Their modeling demonstrated that the risk of secondary malignancies may be reduced with the use of intensity-modulated proton therapy (IMPT) compared to intensity-modulated radiation therapy (IMRT) with photons. The risk was particularly reduced when the number of proton fields was limited.

Pommier et al at the Francis H. Burr Proton Center in Boston have treated 23 patients with ACCs of the skull base with a combination of proton and photon radiotherapy.[115] Only 2 of 23 patients had a complete gross resection but with residual positive margins. The mean total dose to the primary tumor was 75.9 cobalt-gray equivalent (CGE). With a median follow-up of 64 months, the 5-year actuarial local control rate was 93%. The 5-year disease-free survival (DFS) and OS rates were 56% and 77%, respectively. Multivariate analysis demonstrated that tumor involvement of the sphenoid sinus and the clivus and the presence of vision change at presentation were significant adverse risk factors for overall survival. No grade-4 or grade-5 ocular toxicities were reported. Significant grade-3 neurologic toxicities were observed in 10 patients and 2 patients developed grade-5 toxicity. These findings suggest that radiotherapy dose-escalation with protons may result in improved local control rates beyond the historic 20% to 30% local control rates with photons.[116] Recently, with a median follow-up of 25 months (7 months to 54 months), Linton et al reported similar findings using passive scatter proton radiotherapy in 26 patients with ACCs treated to a median dose of 72 Gy (CGE) with or without surgery.[117] The 2-year local control rate was 95% for previously untreated patients with two grade-3, one grade-4, and one grade-5 toxicity observed. The single case of grade-5 toxicity was observed in a patient who previously was irradiated with IMRT and SRS boost for a nasopharyngeal ACC with the prior treatment plan not archived digitally limiting reconstruction and proton planning considerations.

Chemoradiation

The data for concurrent chemoradiation (chemoRT) is scant (typically case reports and small series) and the subject of an extensive review by the French Rare Head and Neck Cancer Network. These investigators concluded that cisplatin-based chemoRT chemoradiation was the most common regimen typically used for adverse pathologic high-risk situations with low evidence to support its efficacy.[118] In the adjuvant context, a single case-control study compared 12 patients with a variety of histologies treated with chemoRT to 12 matched controls treated with radiation alone.[119] This analysis showed a significant survival and local control advantage with chemoRT, with a 3-year OS and DFS survival of 83% and 77% compared to 44% and 52% for radiotherapy alone. However, in addition to the small number of patients analyzed, several other key caveats must be noted. Performance status and comorbidity of the two groups were not reported, IMRT was used more frequently in the chemoradiation group, and a variety of histologies were treated. Thus, adjuvant chemoRT must be considered experimental. However, in the absence of level I data to support its efficacy, it is commonly used for patients with aggressive disease, positive margins, extracapsular extension, and other factors associated with a high risk of recurrence. This practice is largely based on the extrapolated experience in patients with head and neck squamous cell carcinoma (HNSCC). Hence, in the absence of established efficacy, its use should be limited to the use of chemotherapy agents in dose ranges and with schedules of administration where the toxicity spectrum and risks have been well established if it is being considered.

Much of the available literature on chemoRT for SGTs involves small single-institution series. One case report describes definitive concurrent chemoRT with intraarterial cisplatin and docetaxel in 2 patients.[120] A retrospective study of 13 patients treated with cisplatin chemoRT demonstrated complete response to initial therapy in all patients.[121] A single patient developed delayed local failure at 39 months (but achieved successful surgical salvage) and a second patient developed distant metastases; 5-year OS was 83%. Although also experimental, definitive chemoradiation is reasonable for patients who are not candidates for surgery, either based on

anatomic constraints or medical inoperability. Finally, a case series of 14 patients with recurrent MSGTs reported a 3-year locoregional control rate of 51.6% and a 3-year actuarial survival of 35.7% with 5-fluorouracil and hydroxyurea chemoRT following a median radiation treatment interval of 48 months.[122]

Palliation: Role of Chemotherapy

Data on the efficacy of chemotherapy for salivary gland malignancies is limited to case reports, retrospective reviews, and small Phase II studies.

Once metastatic, salivary gland malignancies are not curable. Nonetheless, their course can frequently be indolent, especially for ACC with metastatic disease limited to the lung. Median survival with metastatic disease with ACC is approximately 3 years[123] with some patients living substantially longer. Results with systemic agents, both chemotherapeutic and molecular-targeted agents, have been disappointing. Therefore, careful consideration must be given to administration of supportive care, with systemic therapy reserved for rapid or symptomatic progression.

Chemotherapeutic agents are of limited efficacy in salivary gland malignancies, with particularly poor responses in adenoid cystic histology. A variety of single-agent chemotherapies have been studied in the Phase II setting. Limited responses have been observed with cisplatin, vinorelbine, mitoxantrone, epirubicin, methotrexate, and paclitaxel. For example, ECOG1394 evaluated paclitaxel, given at 200 mg/m^2 every 3 weeks.[124] No responses were seen in 14 patients with ACC, whereas a 26% response rate was seen in patients with mucoepidermoid or adenocarcinoma histologies.

The best studied combination regimen is cyclophosphamide, doxorubicin and cisplatin (CAP).[125] Although CAP has demonstrated good response rates across histologies, there is no clear evidence for superior efficacy as compared to single-agent chemotherapy. Only a single randomized study compared single agent therapy to a platinum-based doublet. Airoldi et al compared vinorelbine (given at 30 mg/m^2 on days 1 and 8 every 3 weeks) to cisplatin plus vinorelbine (with cisplatin administered at 80 mg/m^2 on day 1 and vinorelbine at 25 mg/m^2 on days 1 and 8).[126] This study showed a doubling of response rate from 20% to 44% and a strong trend toward improved median survival (8.5 months versus 11 months, $p = 0.058$) with use of the doublet. Of particular note was the 44.4% response rate in the typically chemoresistant ACC. Many oncologists consider cisplatin plus vinorelbine as the standard of care when cytotoxic chemotherapy is chosen, with paclitaxel as a reasonable consideration in non-ACC disease.

Malignant salivary gland tumors commonly over express a variety of molecular targets. Given the success of targeted agents in other cancers overexpressing these markers[127-130] and the relative tolerability of the agents targeting these markers, investigators have sought to apply these agents to the MSGTs (see eTable 37-1).

Given the paucity of data, no regimen may be considered a standard of care for any histology of MSGT. Thus, when therapy is required, the authors consider a clinical trial to be the preferred option. When no Phase II trial is available, Phase I studies with agents directed at relevant targets, with low expected toxicity should be considered. In the absence of available trials and the need for therapy, it is reasonable to evaluate for molecular markers of interest (ER, EGFR, HER2, AR, and c-Kit) and consider treatment targeting any biomarker that is present. Although response rates are low for targeted agents, multiple studies suggest the possibility of prolonged stable disease. For rapidly progressive disease, especially in the patient with good functional status, good renal function, and good bone marrow function, the combination of cisplatin plus vinorelbine may be considered. Additional clinical trials are desperately needed, but the rarity of these tumors will likely require novel cooperative strategies to promote successful accrual. Ideally, studies of targeted agents aimed at promoting stable disease would be tested using creative study designs, such as a randomized discontinuation design, but the rarity of these tumors may make such definitive trials impossible.

TECHNIQUES OF IRRADIATION

Target Volume Delineation

Parotid Gland

Target volumes include the location of the primary tumor or the surgical bed for SGTs meeting the indications for radiation. The ipsilateral neck should be included in the setting of cervical lymph node metastases or high-grade primary tumor histology (especially for MEC and adenocarcinoma–NOS). It is unclear whether a primary tumor recurrence increases the risk of cervical nodal metastases. Involvement of the facial nerve requires coverage of the course of the nerve, via the facial canal, to the base of skull through the stylomastoid foramen. This should be a consideration for ACC. A boost should be considered to areas at high risk of incomplete resection.

Anatomic landmarks for the parotid should include the zygoma superiorly, styloid process medially, the soft tissues of the neck laterally, including possibly the skin and the surgical scar if there was evidence of tumor spillage or direct tumor infiltration, the masseter muscle anteriorly, the hyoid bone inferiorly, and the mastoid bone posteriorly. Careful review of preoperative imaging and the intraoperative findings are also important to consider in delineating the parotid surgical bed as is noting the location of the contralateral parotid gland.

For the cervical neck, anatomic landmarks for the N0 neck have been referenced. Briefly, cervical levels II to IV are located along the course of the sternocleidomastoid anterolaterally and the scalenus muscles posteromedially. The nodal levels at risk typically include levels II to IV but may require consideration of level V in the setting of known cervical nodal metastases or evidence of metastases to level V.

Submandibular Gland

The primary target volume includes the location of the primary tumor or surgical bed for SGTs meeting indications for radiotherapy. A boost is given to areas of unresected disease. When PNI is present, but limited to small, unnamed nerves, the target volumes are enlarged in the area of the postoperative bed, but the nerve pathways are not treated comprehensively. If named nerves are involved, such as the lingual or hypoglossal nerves, their course should be treated to the base of skull. This involves delineation of the course of the mandibular (V3) branch of cranial nerve V to the foramen ovale. The V3 branch runs from the submandibular space extending into the parapharyngeal and masseter space medial to the course of the medial pterygoid muscle to the foramen ovale (Figure 37-4). Review of preoperative imaging and intraoperative and pathologic findings are imperative in treatment planning.

Indications for treatment of the elective neck are similar to those described previously in the section for the parotid gland. However, because of the proximity of the submandibular gland to the midline of the neck, irradiation of the adjacent and contralateral upper cervical nodal regions should be a consideration when treatment of the ipsilateral neck is indicated.

eTABLE 37-1 Summary Table of Clinical Trials of Molecular Targeted Agents for MSGTs

Agent	Molecular Target	Response Rate for Adenoid Cystic Carcinoma (%)	Response Rate for Nonadenoid Cystic (%)
Imatinib mesylate	c-kit, Bcr-Abl, PDGF-R	0/16[131] 0/14[132] 0/5*[133]	N/A N/A
Trastuzumab	HER2	0/2[39,134]	1/11†
Lapatinib	HER2, EGFR	0/19[35]	0/17
Gefitinib	EGFR	0/19[135]	0/2
Cetuximab	EGFR	0/19[136]	0/9
Bortezomib	26S proteosome NF-kappa-B (indirectly)	0/23[137]	N/A

N/A, *Not applicable.*

**Study closed early because three fifths of patients had rapidly progressive disease.*

†*One of three patients with mucoepidermoid histology had a durable response out to 45 months of follow-up.*

As c-kit is expressed by the majority of ACC, imatinib mesylate, an inhibitor of the c-kit, Bcr-Abl and PDGF-R tyrosine kinases was studied. Although responses were noted in three case reports[138,139] there were no responses in 30 patients with ACC treated in two Phase II studies.[131,132] KIT was assessed only by immunohistochemistry with no mutational analysis performed. Stable disease was common in these studies, including stable disease longer than 6 months. However, the lack of a control group and the indolent behavior of many ACC leave unclear whether this stability was the result of the activity of imatinib or the underlying indolent nature of the tumors. Pending more effective therapies, many clinicians still consider imatinib for c-kit expressing ACC because of its lack of toxicity relative to cytotoxic therapies. An ongoing Phase II study is evaluating the more potent c-kit inhibitor dasatinib.[123,140]

The anti-HER2 antibody trastuzumab and the tyrosine kinase inhibitor lapatinib have demonstrated efficacy in HER-2 overexpressing breast cancer. All histologies of MSGTs have been reported to overexpress HER2 at rates from 24% to 56%, depending on the histology, leading to a Phase II study of trastuzumab with planned accrual of 50 patients.[119,141] A total of 137 tumors were screened for HER2/neu with 17% found to be overexpressed at 2+ or 3+.[39] This result was substantially lower than previously reported in smaller series and the study was closed early with only 14 patients treated. A single patient with MEC histology achieved a long-lasting partial response (PR).[134] It is relevant to note for future investigations of HER2 as a therapeutic target, that HER2 overexpression in ACC was rare at 4%, but common in secretory duct cancers, with 21% in MEC, 83% in salivary duct, and 60% in squamous histologies.[39] A SWOG trial of trastuzumab also closed early as a result of poor accrual. In this trial, 3 patients were enrolled and treated; 1 had stable disease for almost a year and the other progressed on therapy.[129,142]

Lapatinib is an oral tyrosine kinase inhibitor (TKI) that targets both HER2 and EGFR. A Phase II study of this agent enrolled 29 patients with ACC and 28 patients with non-ACC MSGT.[35] In total, 88% of patients with ACC and 97% of patients with non-ACC expressed EGFR or erbB2. There were no responses in either group, but 47% of patients with ACC and 24% of patients with non-ACC had stable disease (SD) lasting at least 6 months. Although the indolent nature of the disease itself likely contributed to some of this stability, biologic activity of lapatinib was likely greater than that represented by the response rate. To meet response criteria, a tumor must shrink by 30%. Many patients classified as having SD experienced reductions in tumor volumes that failed to meet this threshold but nonetheless are suggestive of activity. Further, 36% of the patients with SD for more than 6 months were progressing before starting therapy, suggesting that although the therapy may not have been sufficiently active to shrink the cancer, it could at least stop its growth.

Similar results were found with the TKI gefitinib, which targets primarily EGFR. At the time of presentation, 21 patients were assessable for response, with 0 of 21 responses.[135] Thirteen of 14 patients with SD had ACC, but the median duration of SD was only 13 weeks, again raising concerns that the SD was secondary to the indolent nature of the cancer, rather than efficacy of therapy. Similarly, a Phase II study of cetuximab failed to achieve any responses. However, 20 of 23 (87%) of patients with ACC achieved SD, with 12 of these 23 (52%) achieving stability lasting at least 6 months.[136] Of note, 11 patients with ACC were actively progressing at the time of study entry; all of these patients achieved SD for at least 6 months.

Bortezomib inhibits the 26S proteosome, indirectly inhibiting NF-KB activity. A Phase II study treated 25 patients with ACC.[137] Again, no responses were seen. Patients with progressive disease were treated with the combination of bortezomib and liposomal doxorubicin based on preclinical data for synergy. Four patients were treated with this combination; one achieved a PR and 2 had SD. A Phase II study of the combination of bortezomib and doxil just closed secondary to poor accrual.[130,143]

Data for the efficacy of the hormonal agent tamoxifen is limited to three case reports of long-term SD.[144,145] Case reports also describe responses, including a complete response, to luteinizing hormone–releasing hormone analogues in patients with androgen-receptor–positive adenocarcinoma.[146]

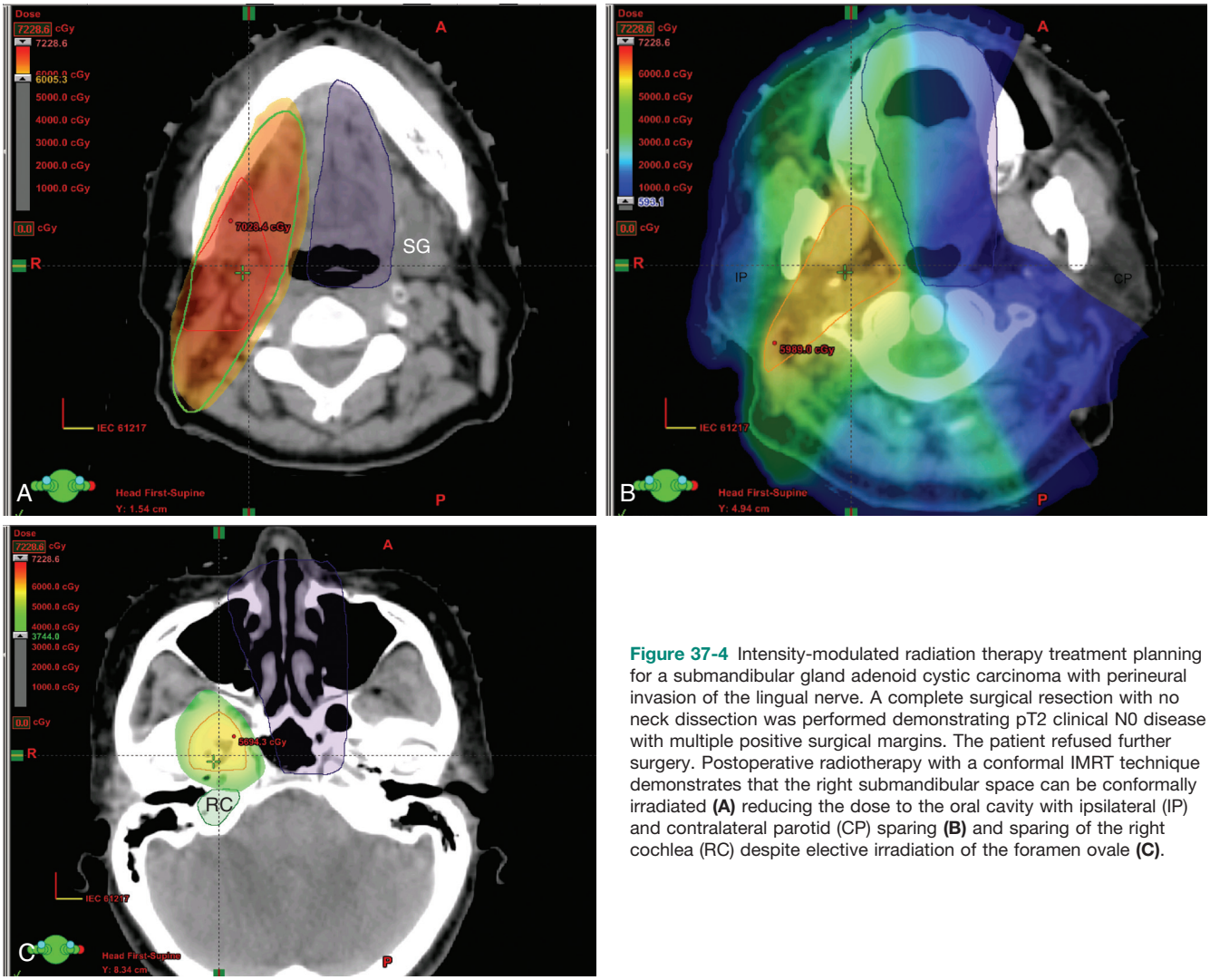


Figure 37-4 Intensity-modulated radiation therapy treatment planning for a submandibular gland adenoid cystic carcinoma with perineural invasion of the lingual nerve. A complete surgical resection with no neck dissection was performed demonstrating pT2 clinical N0 disease with multiple positive surgical margins. The patient refused further surgery. Postoperative radiotherapy with a conformal IMRT technique demonstrates that the right submandibular space can be conformally irradiated **(A)** reducing the dose to the oral cavity with ipsilateral (IP) and contralateral parotid (CP) sparing **(B)** and sparing of the right cochlea (RC) despite elective irradiation of the foramen ovale **(C)**.

Minor Salivary Glands

Target volumes include the primary tumor or surgical bed for small or low-grade cancers meeting indications for radiation therapy. These areas are determined by preoperative imaging and intraoperative and pathologic findings. Areas of unresected disease are given a boost.

Elective neck treatment varies with the histology, grade, T category, anatomic site, and nodal category.[63] Lloyd et al analyzed the SEER database identifying 2667 cases of minor salivary gland cancers with known lymph node status from 1988 to 2004. Although there are inherent limitations with SEER database analyses, the results are consistent with smaller clinical series that in turn lack the size for a multivariate analysis. Analysis demonstrated that male sex, T3-T4 category, primary site involving the pharynx and high-grade adenocarcinoma or high-grade MECs were independent risk factors for the development of nodal metastasis for minor salivary glands.

Although these findings suggest that the biology of salivary gland malignancies influences the risk of nodal metastases, they also suggest that lymphatic-rich anatomic sites may have higher rates of nodal metastases, as seen with squamous carcinomas. For ACCs, Mendenhall et al reported that this was a significant consideration in their institutional approach. They reported a 10-year neck control rate of 90% when the neck was observed compared with 98% with elective irradiation.[96] Other relevant but unestablished anatomic factors that have been well described for squamous carcinomas can also be considered during treatment planning for malignant SGTs. These include the presence of mucosal disease at the coronal midline, increasing the risk for contralateral nodal metastases,[147] and the involvement of the posterior pharyngeal mucosa, increasing the risk of retropharyngeal lymph node metastases.[148]

Simulation and Field Arrangements

A CT scan is obtained in the treatment position. Patients are typically positioned supine, with arms down, and the head and neck in the hyperextended position to move the orbits out of the radiation field. A thermoplastic face mask is used for immobilization. For cases with skull-base or intracranial involvement, a MRI can be obtained and fused to the CT to assist in target delineation. The target volumes and normal critical structures are defined on the representative CT or MRI axial images.

Traditional standard techniques used to treat parotid tumors include wedged pair or mixed beam techniques, whereas IMRT is now commonly used as well. It is our preference to use either a wedged pair technique or an IMRT

technique (allows for comprehensive coverage of the parotid bed and cervical lymph nodes, while avoiding the potential impact on the mandible of electron beam dosimetry). IMRT also allows for improved conformality at the skull base, especially when the surgical bed and scar extends superiorly above the plane of the middle and inner ear complex and may lie adjacent to the temporal lobe. Traditional radiotherapy techniques have often relied on matched fields typically with electrons to treat the course of the surgical scar if it was deemed to be at risk. This results in potential dosimetric uncertainties with a photon-electron match with the potential for a dosimetric hotspot that may lie in the temporal lobe.

IMRT may also allow for additional sparing of structures such as the cochlea, semicircular canal, mastoid air cells, and temporal lobes. Historically, hearing deficits, and soft-tissue and bone necrosis have been observed in approximately 20% of patients treated with a traditional beam arrangements especially with wedge-pair fields.[149] Using these techniques to treat the tumor bed with or without the ipsilateral neck, mean doses to the contralateral salivary glands can be effectively limited to less than 10% of the prescription dose, thereby preventing any grade-3 symptoms of xerostomia during and after treatment.

Dose, Fractionation and Pathologic Considerations

Frequent pathologic indications reported for the use of postoperative RT include the presence of a close if not positive surgical margin, PNI, high-grade histology, extraglandular extension, bone invasion, tumor size, T category, and the presence of nodal metastases. It is important to recognize that these pathologic indications have not been prospectively evaluated to determine what the absolute risk level is and the incremental risk reduction with adjuvant radiotherapy.

The typical postoperative dose to the surgical bed that has been reported has typically ranged from 60 Gy to 66 Gy with a conventional daily fractionated schedule. For a positive or close surgical margin, localization of the area of concern based on preoperative imaging and intraoperative findings for a boost dose of radiation typically of 6 Gy to a total dose of 66 Gy is an important consideration. Other risk stratified radiotherapy dose recommendations have not been clearly established. Hence, it is unclear if areas involved with extraglandular extension (i.e., T3 and T4) or nodal metastases necessitate a dose higher than 60 Gy.

PNI has been correlated with an increased risk of locoregional relapse, especially for ACCs. Recent detailed histologic studies of serial sections suggest that the mechanism in which PNI may be contributing to relapse is the result of the direct contiguous spread of cancer along the branches of the nerves.[65] Hence, a judicious clinical target volume (3 cm to 5 cm) surrounding the primary tumor bed should be created, to reflect the potential subclinical extent of cancer. The use of postoperative radiation therapy appears to be effective in reducing the risk of local relapse resulting from PNI (10-year local control rates of tumors with PNI treated with surgery compared with surgery and postoperative RT was 60% versus 88%, $p = 0.01$).[64]

For more extensive PNI resulting in clinical symptoms or radiologic nerve abnormalities, there is a further increased risk of locoregional relapse, especially with ACCs.[96] This observation is consistent with other cancer sites in which the size of the involved nerve appears to increase the risk of relapse.[150] With involvement of major named nerves, there is an increased risk of relapse including spread to the skull base and increased risk of distant relapses. Hence, elective irradiation along the course of the nerve is recommended.

For elective nodal irradiation, the anatomic draining lymphatics should be encompassed. The usual dose has ranged from 50 Gy to 54 Gy with a conventional daily fractionated schedule. However, it should be recognized that the optimal elective nodal irradiation dose for MSGTs is unknown.

Gross, unresectable disease has typically been treated to 70 Gy again with a conventional daily fractionated schedule. It is important to note that the optimal dose and fractionation schedule has not been clearly defined especially for unresectable gross disease. This is important to consider in light of evidence suggesting that radiotherapy dose escalation with photons[108] and protons[115] may offer additional improvements in local control rates. Unknown at this time is whether or not there may be incremental gains in locoregional disease control rates with the practice of a simultaneous in-field boost ("dose painting") that is now possible with the use of IMRT.

Treatment Side Effects

The side effects associated with radiation therapy are dependent on several factors: the site and volume treated, the dose fractionation regimen, and total dose delivered, whether treatment is delivered definitively or adjuvantly, the type of radiation used (low LET versus high LET), and whether concomitant chemotherapy is used.

In the treatment of salivary gland tumors, acute phase reactions (within first 90 days of completion of RT) are generally limited to rapidly proliferating tissues, such as the skin, and the oral and pharyngeal mucosa. Skin reactions can range from a mild erythema to moist desquamation, which would require aggressive skin care and antibiotic treatment. Xerostomia and dysgeusia may also occur during RT, but the risk of long-term xerostomia can be minimized with appropriate field arrangements and treatment planning, by excluding the contralateral parotid and submandibular gland. Acute mucositis is commonly observed if the oral cavity or pharyngeal mucosa is in the field. The risk of developing severe mucositis is increased with approaches such as accelerated fractionation, concurrent chemotherapy, or high LET radiation. Attention to pain control, close monitoring for the development of oral candidiasis, and aggressive nutritional support (with the placement of a percutaneous gastrostomy [PEG] tube, if needed) are required with severe mucositis.

Late complications (occurring >90 days after completion of treatment) are associated with slower proliferating tissues, with side effects limited to the particular region treated. In treatment of the base of skull, careful treatment planning is required to limit the dose delivered to critical structures, thereby minimizing the risks of side effects such as pituitary dysfunction, temporal lobe necrosis, optic neuropathy, keratitis, and hearing loss. With conventional 1.8 Gy to 2 Gy fractionation, the dose to the spinal cord should be limited to 45 Gy (maximum [max]), cochlea to 45 Gy (mean), lacrimal gland to 30 Gy (mean), optic nerves and chiasm to 54 Gy (max), temporal lobes to 65 Gy (max), and brainstem to 60 Gy (max). These doses need to be appropriately adjusted if nonstandard approaches (concurrent chemotherapy, altered fractionation, high LET radiation) are used. Every patient should undergo preradiation dental evaluation, with any necessary extractions to be done before initiation of radiation, and if dentition is to be preserved, custom fluoride trays should be applied daily using custom trays. If extractions or oral surgery needs to be done following radiation therapy, hyperbaric oxygen therapy is recommended to minimize the risk of developing osteoradionecrosis. Another common late side effect in patients receiving neck radiation therapy is hypothyroidism. In patients receiving unilateral radiation therapy, the risk of xerostomia can be minimized through conformal delivery (via

TABLE 37-7 Treatment Algorithm for Malignant Major and Minor Salivary Gland Cancers

Clinical Situation	Standard Therapy	Proposed Clinical Trial
Complete resection, adjuvant therapy	Postoperative, adjuvant EBRT when indicated (see Box 37-3)	Intergroup trial of surgical resection plus postoperative adjuvant EBRT versus surgical resection plus postoperative adjuvant EBRT with concomitant and maintenance chemotherapy
Locally advanced (primary or recurrent; unresectable or resected but residual)	1. High-dose conventional photon irradiation (consider altered fractionation) 2. Maximal surgical resection, IOERT, or brachytherapy and conventional EBRT 3. Neutron beam therapy with or without SRS boost	1. Neoadjuvant chemotherapy followed by resection (with or without IOERT or brachytherapy), and EBRT (photons or protons) with concomitant and maintenance chemotherapy 2. High-dose conventional or altered-fractionation EBRT (photons or protons) with concomitant and maintenance chemotherapy 3. Carbon ion therapy
Locally recurrent, prior irradiation	Low- to moderate-dose EBRT plus hyperthermia Palliative chemotherapy	Low to moderate dose CCRT, resection, IORT (electrons or HDR brachytherapy)

CCRT, *Concurrent chemoradiation;* EBRT, *external beam irradiation;* IOERT, *intraoperative electron beam irradiation.*

three-dimensional conformal radiation therapy, IMRT, proton therapy, or heavy charged particle therapy). Limiting the mean dose to contralateral major salivary glands to <10% of the prescription dose has commonly been recommended.

TREATMENT ALGORITHM, CONCLUSIONS, CONTROVERSIES, AND FUTURE POSSIBILITIES

In summary, SGTs are characterized by their rare incidence, diverse histology, and the potential for an indolent natural history. It is this heterogeneity that has hampered clinical progress in the management of SGTs. In recent years, progress has been made in further understanding the genetic and molecular characteristics of these tumors, but this has not yet yielded any significant therapeutic insights. However, the favorable survival associated with expression of the *CRTC1-MAML2* fusion oncogene in MECs is an important advancement toward improved classification of MECs. Therapeutic progress has been made with technical advances in surgical techniques such as the transoral robotic technique, and in radiation oncology, with the maturation of the use of fast neutron radiotherapy. The increasing study of charged particle beam radiotherapy, both protons and heavy ion beams offer the potential to further reduce toxicities with improved locoregional control rates. Although various molecular targeted therapeutics have been introduced into clinical trials, none have yet realized the goal of significantly decreasing the risk of distant metastasis. However, the toxicities associated with these systemic approaches are acceptable and manageable, and disease stabilization may be possible with several targeted agents.

In conclusion, the treatment options for patients with SGTs have significantly improved in recent years offering the potential for more effective function preserving locoregional therapy. Our preferred treatment algorithm is seen in Table 37-7. Major survival gains will likely only be realized with the development of more effective systemic therapy.

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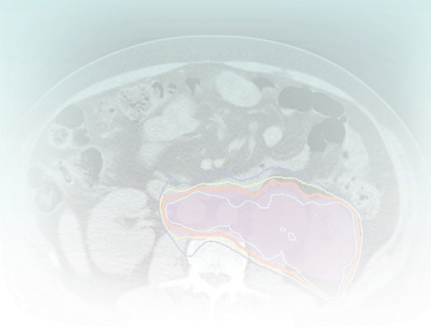
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CHAPTER

38 Thyroid Cancer



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INCIDENCE

In the United States the incidence of well-differentiated thyroid cancer increased from 4.9 per 100,000 to 14.3 per 100,000 between 1975 and 2009. It was estimated that 62,450 new cases would occur in the United States in 2015. Carcinomas are of follicular or parafollicular cell (C cell) origin, and 95% are well differentiated.

BIOLOGIC CHARACTERISTICS

Prognostic factors include patient age, histology, grade, tumor size, neoplastic extent, and completeness of initial surgical resection. Reliable prognostic scoring systems permit accurate outcome prediction.

Only a few patients with thyroid carcinoma are at risk for cause-specific mortality.

STAGING EVALUATION

Staging includes the patient's history, physical examination of the neck, fine-needle aspiration (FNA) biopsy, ultrasound neck examination, and a chest radiograph.

Additional studies may include vocal cord examination, chest computed tomography (CT), skeletal magnetic resonance imaging (MRI), and 18F-fluorodeoxyglucose (18F-FDG) positron emission tomography with CT (fused PET/CT).

PRIMARY THERAPY

Surgical resection is the primary therapy for resectable, well-differentiated thyroid carcinomas. Most are treated by near-total or total thyroidectomy with excision of involved regional nodes. Cause-specific survival (CSS) rates exceed 90% at 20 years.

ADJUVANT THERAPY

Thyroxine-suppressive therapy of thyroid-stimulating hormone (TSH) is standard postoperative management of papillary and follicular cancers.

Radioactive iodine (RAI) therapy is used for treating distant metastasis, unresectable or residual papillary thyroid carcinoma (PTC), and most cases of follicular thyroid carcinoma (FTC) or Hürthle cell carcinoma (HCC). Radioiodine remnant ablation (RRA) is widely used in high-risk follicular cell–derived cancers (FCDCs) but may not benefit patients with low-risk tumors.

External beam radiotherapy (EBRT) is reserved for selected patients with locally advanced disease and with high-risk surgical pathologic features and patients with recurrent or metastatic disease nonresponsive to RAI therapy.

UNDIFFERENTIATED TUMORS AND PALLIATIVE THERAPY

Anaplastic cancer is preferably treated by resection, EBRT, and chemotherapy.

Thyroid lymphomas typically are diffuse, large cell lymphomas of B-cell origin. These tumors are best controlled with combination chemotherapy (rituximab, cyclophosphamide, hydroxydaunomycin, Oncovin [vincristine], and prednisone) and involved field EBRT.

Thyroid tumors are the most common endocrine neoplasms. They usually manifest as anterior neck nodules, which in most cases can be localized to the thyroid gland by palpation. Most nodules are benign hyperplastic (or colloid) nodules, but 5% to 20% of nodules that come to medical attention are true neoplasms: benign follicular adenomas or carcinomas of follicular or parafollicular cell (C cell) origin. Differentiating true neoplasms from hyperplastic nodules and distinguishing benign from malignant tumors are major diagnostic challenges for clinical endocrinologists. High-resolution ultrasound studies assessing large groups of normal volunteers suggested that the prevalence of incidentally discovered nodular thyroid disease in healthy adults is more than 60%.[1] In the United States during 2015, 62,450 new cases of thyroid cancer were expected. It has been estimated that a half-million people are currently living with thyroid cancer in the United States.[2]

In the current era, when patients are increasingly being advised on the advantages of self-examination to detect cancer at an early stage, the finding of a palpable mass in such a superficial and visibly obvious location as the thyroid gland can be disconcerting, and the patient is likely to seek prompt medical evaluation. At the conclusion of an appropriate investigation, the patient can usually be reassured that the nodule is benign. If the discovered lesion is suspected to be malignant, the patient can be advised that the management of typical thyroid cancer is effective[3] and usually consists of surgical resection,[4] followed by medical therapy[5] and regular postoperative surveillance.[6] In recent years, a degree of consensus has been achieved with regard to the initial evaluation of nodular thyroid disease[7,8] and the management of differentiated thyroid cancer,[7,9,10] but important biologic and clinical questions remain unanswered.[11-13]

From a radiation oncologic standpoint, FCDC of the thyroid has some historic interest. In 1940, Hamilton et al[14] at the University of California–San Francisco, first reported evidence of uptake of RAI in FCDC. In 1942 at Columbia University, Keston et al[15] gave a patient with an iodophilic femoral metastasis a 10-mCi therapeutic dose of RAI. Since that time, RAI therapy has become the primary treatment for iodophilic distant metastases in the papillary or follicular histologic type of FCDC.[16] The concept of RRA to "complete" a thyroidectomy

in FCDC, which was derived from pioneering work by Blahd et al[17] at the University of California–Los Angeles, in the late 1950s, has been increasingly employed in the routine management of FCDC.[18] The use of EBRT in managing thyroid cancer has its origin in the 1960s.[19] Subsequently, the role of EBRT generally has been restricted to the treatment of locoregional advanced FCDC, but it has also been employed as primary therapy in the management of two rare malignancies: anaplastic (undifferentiated) thyroid carcinoma and primary malignant lymphoma of the thyroid.[20] In this chapter, we discuss the more common FCDCs, but where indicated, less common tumors derived from nonfollicular cell origin are considered.

ETIOLOGY AND EPIDEMIOLOGY

The annual incidence of thyroid cancer is 0.5 to 10 per 100,000 people in the general population in most countries. Between 1975 and 2009, the incidence of thyroid cancer increased from 4.9 to 14.3 cases per 100,000 individuals in the United States; with a more pronounced increase in women (from 6.5 to 21.4 cases per 100,000 women).[21] In South Korea the incidence of thyroid cancer has increased from 10.6 per 100,000 per year in 1996 to 111.3 per 100,000 per year in 2010.[22]

Clinical thyroid malignancy is relatively uncommon, accounting for only about 2% of human malignancies.[23] Nonetheless, it was estimated that thyroid cancers would account for 96% of endocrine malignancies in the United States in 2014.[2] It was estimated that 1890 patients with thyroid cancer would die during 2014, accounting for 67% of deaths from endocrine malignancies.[2]

Most thyroid cancers are derived from follicular epithelium. In most countries, incidence rates for PTC generally exceed the incidence rates for FTC, and either PTC or FTC is far more common than the usually lethal anaplastic (undifferentiated) thyroid carcinoma.[24,25] Similar data on the frequency of the various histologic types are contained in two large series of thyroid cancer cases reported from the United States and Japan.[26,27] These data are summarized in Table 38-1.

Anaplastic carcinomas and FTCs tend to be relatively more common in areas endemic for goiter, and numerous case-control studies have strongly suggested that dietary iodine content is responsible for the increased incidence rates in these areas.[28] This hypothesis is supported by the fact that dietary iodine supplementation has been shown to increase the relative proportion of PTC and to decrease the frequency of FTC.[29]

PTC and FTC are more than twice as common in women as men and tend to occur much more commonly in middle age and later, although patients with PTC are younger than patients with FTC.[24,25] The preponderance of women with FCDC has led to speculation about the role of estrogen as a risk factor. Other putatively estrogen-dependent tumors, particularly breast cancer, and thyroid cancer occur more frequently in the same individual than expected by chance.[30] Case-control studies have suggested a correlation between pregnancy, a high estrogen state, and the onset of thyroid cancer.[31] Other studies have suggested that pregnancy per se, rather than the associated estrogen levels, may be associated with increased thyroid cancer risk.[32] The role of female sex hormones as a risk factor for thyroid cancer development must still be considered unresolved.

The most firmly established risk factor for development of thyroid cancer is prior exposure to ionizing radiation, particularly to the head and neck region during childhood, which used to be a common problem in some exposed populations in Japan and the Pacific during the 1960s and 1970s in the aftermath of atomic bomb use at the end of World War II and in areas exposed to atmospheric nuclear bomb tests during the 1950s and 1960s.[33,34] In most other countries, radiation treatments for benign medical conditions, such as acne vulgaris, thymic enlargement, tinea capitis, or inflammatory connective tissue disorders, contributed to increasing numbers of patients with thyroid cancer.[35,36] These practices have largely been abandoned, and radiation exposure as a risk factor for the most part has ceased to be of significant importance.[36] Exceptions are areas of high natural background radiation; radiotherapy used for malignant conditions[37]; and areas where radioactive contamination of the environment from military or civilian sources is a notable problem, particularly in many countries in the southern part of the former Soviet Union that were heavily contaminated in the wake of the Chernobyl nuclear reactor accident.[38] The contamination in parts of Belarus and Ukraine was significant and prolonged, and there is mounting clinical evidence that this contamination has led to increased rates of thyroid malignancies, often of an unexpectedly aggressive nature.[39-41] In the United States, it has been disclosed that a significant segment of the U.S. population was exposed to radioiodine during a series of nuclear bomb explosions at the Nevada test site in the 1950s.[42] Predictions of excess relative risk of thyroid cancer vary but may prove to be significant. However, it is impossible to determine whether individual thyroid cancers arose as a result of radiation exposure or as sporadic events.[42,43] It has been also suggested that the surge of cases of thyroid cancer is not as a result of a new risk factor but rather, because of the exponential increase in the use of diagnostic imaging.[43] This argument is supported by the steady incidence of mortality from thyroid cancer despite a large increase in thyroid cancer incidence; many of which are small and papillary in nature. Additionally, many autopsy studies, conducted around the world, have demonstrated that thyroid cancer is common, occurring in 24% to 36% of patients who died from nonthyroid related causes.[44]

Although most cases of thyroid cancer are sporadic occurrences, a small proportion of thyroid cancers may be familial, and in the case of C cell–derived malignancy, medullary thyroid carcinoma (MTC) may be associated with multiple endocrine neoplasia (MEN) type II (MEN-II) syndrome and its associated adrenal medullary tumors (pheochromocytomas). In patients with the MEN-II syndrome, a strong and typical family history can often be obtained. PTC may also be associated with other nonthyroid malignancies and with premalignant conditions such as Cowden's syndrome and familial adenomatous polyposis coli (i.e., Gardner's syndrome).[45] Several cases of familial PTC have been described.[46] No such distinct associations exist for FTC, but aggregation of FTC cases in families with dyshormonogenesis has been described.[47]

TABLE 38-1 Frequency of Various Histologic Types of Thyroid Cancers

Study	Years	Papillary, *N* (%)	Follicular, *N* (%)	Medullary, *N* (%)	Anaplastic, *N* (%)
SEER program of the NCI	1992-2006	36,583 (85)	4560 (11)	976 (2)	556 (1)
Japanese Society of Thyroid Surgery[27]	1977-1995	22,307 (80)	3320 (12)	369 (1)	489 (2)

NCI, *National Cancer Institute;* SEER, *Surveillance, Epidemiology and End Results.*

PREVENTION AND EARLY DETECTION

Most thyroid cancers are sporadic and not caused by an avoidable environmental agent. Prevention of thyroid malignancy is impossible.

Nodular thyroid disease generally can be detected early by careful neck palpation in the course of routine physical examinations. High-resolution ultrasound can readily detect impalpable thyroid nodules 2 mm to 3 mm in diameter. There is no evidence, however, that population screening for nodular thyroid disease using ultrasound is warranted because 70% to 90% of diagnosed thyroid malignancies are of the papillary histologic type. In such incidentally discovered papillary tumors, 85% to 90% are deemed low risk and are associated with mortality rates close to rates predicted by actuarial curves and comparable to rates for nonmelanoma skin cancer.

In contrast, early detection of the often more aggressive, familial MTC is possible when there is evidence within the family of an inherited mutation of the *RET* proto-oncogene in the pericentromeric region of the short arm of chromosome 10. Such mutations have been found in more than 90% of familial MTC cases, and since the successful cloning and sequencing of the *RET* gene, asymptomatic members of affected families can be tested for the presence of a mutation at this locus.[48] A positive test result obviates the need for any further testing. The present recommendation for persons shown to harbor the mutation is to undergo prophylactic total thyroidectomy, which completely prevents the development of the invariably multicentric MTC associated with these conditions.[10,49] If such a mutation is found in infancy, the current practice is to perform a total thyroidectomy when the child is 3 to 5 years old.[10,50]

PATHOLOGY AND PATHWAYS OF SPREAD

Most thyroid cancers are well-differentiated tumors derived from follicular cells. PTC accounts for 40% to 90% of cases, and 15% to 40% are classified as FTC, which includes the so-called oxyphilic or Hürthle cell variant. Anaplastic thyroid cancer (ATC), also derived from the follicular cell, is the least common FCDC, typically constituting 1% to 5% of most series. The frequency of C cell–derived MTC depends on the diligence with which reporting centers pursue the early diagnosis of patients with familial MTC and MEN-II, but it may account for 2% to 8% of thyroid cancers. Nonepithelial thyroid tumors include sarcomas, malignant hemangioendotheliomas, and malignant lymphomas. Lymphomas may involve the thyroid as the only manifestation of the disease or as part of a systemic disease; such tumors may rarely complicate Hashimoto's (autoimmune) chronic lymphocytic thyroiditis, which in the United States is the most common cause of goiter and noniatrogenic hypothyroidism. Blood-borne metastases to the thyroid are common at autopsy in patients with widespread malignancy, but they rarely cause clinically detectable thyroid enlargement.

PTC most often occurs in patients 30 to 50 years old; the mean age at diagnosis is about 45 years. Most primary tumors are 1 cm to 4 cm in diameter; the average is about 2 cm to 3 cm in the greatest dimension. Of tumors, 95% are classified on the basis of degree of differentiation as histologic grade 1 (of 4); 80% of primary PTC tumors are assessed to be DNA diploid by flow cytometry.[51] Extrathyroidal invasion of adjacent soft tissues is present in about 15% (range 5% to 34%) at primary surgery, and about one third of patients with PTC have clinically evident lymphadenopathy at presentation.[52] About 35% to 50% of excised neck nodes have histologic evidence of involvement, and in patients 17 years old or younger, nodal involvement may be present in up to 90%.[53] The primary disease is confined to the neck in 93% to 99% of patients with PTC at diagnosis.[51,52] Spread to superior mediastinal nodes is usually associated with extensive neck nodal involvement. Distant metastases are diagnosed in only 1% to 7% of patients with PTC before or within 30 days of primary treatment.[51,54]

FTC occurs in older patients, and the mean age in most studies is more than 50 years, about 10 years older than for typical PTC.[25,55] Women affected by FTC outnumber men by more than 2:1. Patients with FTC rarely (4% to 6%) have clinically evident lymphadenopathy at presentation.[56] In most series, the average tumor size in FTC is larger than in PTC.[55] When tumor grading is performed, higher grade tumors are more common than with PTC.[55] DNA aneuploidy is present in about 60% of FTC tumors and in up to 90% of patients with oxyphilic or Hürthle cell variant tumors.[25,57] Direct extrathyroidal extension into adjacent soft tissues does not occur in the common "minimally invasive" FTC, but it is not unusual in the rare patient with "widely invasive" FTC. Of patients with FTC, 5% to 20% may have distant metastases at presentation, and the most common sites of distant spread are lung and bone.[25,58]

MTC arises from the C cells of the thyroid rather than the follicular epithelium; secretes a characteristic hormone, calcitonin; is frequently associated with one or more paraendocrine manifestations; and provides an early biochemical signal (i.e., hypersecretion of calcitonin) that permits its early detection, treatment, and cure.[10,59] The tumor occurs in sporadic and familial forms, with the latter constituting about 20% of the total. The familial variety usually appears at a younger age, is almost invariably bilateral, is less likely to have associated cervical metastases at presentation, and has a better prognosis.[10,59] Most importantly, the familial variety is preceded by a premalignant C-cell hyperplasia that can be cured by total thyroidectomy.[60]

ATC is the least common FCDC and typically constitutes less than 5% of most reported series.[61] It usually occurs after age 60 years, and it is only slightly more common in women than men (1.3:1 to 1.5:1). It is highly malignant, rapidly invading adjacent structures and metastasizing throughout the body. Pathologic examination of tumor biopsy specimens may reveal evidence of PTC or FTC, which may represent a precursor of ATC. Thorough biopsy sampling may be necessary to detect residual well-differentiated thyroid tissue. On histologic examination, the tumor is usually composed of atypical cells that exhibit numerous mitoses and form a variety of patterns. Spindle-shaped cells and multinucleated giant cells usually predominate, but in a third histologic pattern described as squamoid, the cells are undifferentiated but retain an epithelial appearance. It was formerly thought that there was a small cell ATC, but most of these tumors have been classified as malignant thyroid lymphomas.

BIOLOGIC CHARACTERISTICS, PROGNOSTIC FACTORS, AND STAGING

It has long been recognized that prognosis in thyroid cancer largely depends on the age of the patient, the histology of the tumor, and the anatomic extent of disease at presentation. Although head and neck cancer is staged entirely on the basis of anatomic extent, thyroid cancer staging is unique in that the histologic diagnosis and the age of the patient are included because of their prognostic importance.

The seventh edition of the TNM (primary tumor, regional nodes, metastases) staging scheme for thyroid carcinoma, approved in 2009 by the International Union Against Cancer[62] and in 2010 by the American Joint Committee on Cancer (AJCC),[63] is presented in Table 38-2. The primary tumor status

TABLE 38-2 American Joint Committee on Cancer Stage Groupings for Thyroid Carcinoma

	Papillary or Follicular			
Category*	**Age <45 yr**	**Age ≥45 yr**	**Medullary (Any Age)**	**Anaplastic (Any Age)**
I	M0	T1 N0 M0	T1 N0 M0	—
II	M1	T2 N0 M0	T2 N0 M0 T3 N0 M0	—
III	—	T3 N0 M0 T1-3 N1a M0	T1-3 N1a M0	— —
IVA	—	T4a N0-1a M0 T1-4a N1b M0	T4a N0-1a M0 T1-4a N1b M0	T4a Any N M0
IVB	—	T4b Any N M0	T4b Any N M0	T4b Any N M0
IVC	—	Any T Any N M1	Any T Any N M1	Any T Any N M1

Data from Edge SB, Byrd DR, Compton CC, et al: American Joint Committee on Cancer: AJCC Cancer Staging Manual, ed 7, New York, 2010, Springer.
**T-category definition:* T1, *greatest dimension ≤2 cm, limited to the thyroid;* T2, *>2 cm but ≤4 cm, limited to the thyroid;* T3, *>4 cm, limited to thyroid or any tumor with minimal extrathyroid extension;* T4a, *tumor of any size extending beyond thyroid capsule to invade subcutaneous soft tissues, larynx, trachea, esophagus, or recurrent laryngeal nerve;* T4b, *tumor invades prevertebral fascia or encases carotid artery or mediastinal vessels.*

is defined in this scheme on the basis of the size of the primary lesion (diameter in centimeters) and the presence of extrathyroidal extension. A T1 tumor is 2 cm or smaller and limited to the thyroid. T1a refers to tumors of 1 cm or less, and T1b refers to a tumor more than 1 cm but not more than 2 cm in greatest dimension. A T2 tumor is 2.1 cm to 4.0 cm in diameter and limited to the thyroid. A T3 tumor is larger than 4 cm and limited to the thyroid or any tumor with minimal extrathyroidal extension (i.e., to sternothyroid muscles or perithyroidal soft tissues). A T4a tumor represents moderately advanced disease, which extends beyond the thyroid capsule and invades subcutaneous soft tissue, larynx, trachea, esophagus, or recurrent laryngeal nerve, and a T4b tumor represents locally advanced disease, typically invading prevertebral fascia or encasing carotid artery or mediastinal vessels.

When tumor spreads to lymph nodes, it is classified as N1. N1a refers to metastasis in level VI (e.g., pretracheal and paratracheal nodes, including prelaryngeal and Delphian nodes), and N1b describes metastasis to other unilateral, bilateral, or contralateral cervical or superior mediastinal lymph nodes. M1 refers to the presence of distant metastasis involving nonregional lymph nodes, internal organs, or bones.

To make this TNM information clearer, several of these TNM descriptions can be grouped together into stages I through IV. For the seventh edition of the TNM/AJCC staging system, the grouping for MTC is the same as for PTC or FTC in patients older than 45 years with one exception. A T3 N0 M0 MTC patient is considered stage II, whereas such a patient with papillary and follicular cancers is considered stage III. All patients with ATC are considered stage IV, reflecting the poor prognosis of this type of cancer.

For patients younger than 45 years with a diagnosis of PTC or FTC, the TNM stage is I (any T, any N, M0) if there is no distant spread and stage II (any T, any N, M1) if there are distant metastases beyond the neck or upper mediastinal lymph nodes. For patients with MTC or who are 45 years or older with PTC or FTC, the seventh edition of the TNM/AJCC staging system is more complicated than before.

In patients with PTC or FTC who are 45 years of age or older, stage I (T1 N0 M0) cancers are 2 cm or smaller and have not spread to lymph nodes or distant sites. Stage II (T2 N0 M0) cancers are more than 2 cm in diameter but not bigger than 4 cm, and they are localized to the thyroid. Stage III (T3 N0 M0 or T1-3 N1a M0) encompasses tumors larger than 4 cm or with minimal extrathyroidal extension and tumors of any size that have spread to central neck nodes.

In former TNM/AJCC classifications, stage IV referred only to patients who had distant spread, but the later editions (since 2002) define these patients as IVC (any T, any N, M1), and the designations IVA and IVB define more aggressive tumors that have not spread to distant sites. Stage IVB (T4b, any N, M0) refers to the unusual situation of a tumor that has grown back to the spine (e.g., prevertebral fascia) or into nearby large blood vessels (e.g., carotid artery or mediastinal vessels). The new stage IVA (T1-4a, N0-1b, M0) was formerly considered to be stage III, and it encompasses locally invasive T4a tumors (i.e., with or without nodal involvement [any N]) and node-positive N1b tumors (with primary tumors of any size but localized or showing only minimal extrathyroidal extension [T1-3]).

Because of significant differences in the tumor biology displayed by the four principal types of thyroid carcinomas, the remainder of this discussion of tumors is divided according to histologic type.

Papillary Thyroid Carcinoma

Most patients with PTC present with localized, node-negative disease.[51,64,65] Patients 45 years old or older with nodal metastases or extrathyroidal extension account for less than 20% of cases.[51] Only about 1% to 3% of older patients with PTC present with distant metastases. Figure 38-1, *A* shows CSS according to pathologic TNM (pTNM) stage in a cohort of 1851 patients who underwent surgical treatment at Mayo Clinic during the period 1940 to 1990.[66]

Three types of tumor relapse may occur with PTC: postoperative regional nodal metastasis, local recurrences, and postoperative distant metastases. Local recurrence has been defined as "histologically confirmed tumor occurring in the resected thyroid bed, thyroid remnant, or other adjacent tissues of the neck (excluding lymph nodes)" after complete surgical removal of the primary tumor.[67] Nodal or distant spread is considered postoperative if the metastases are discovered within 180 days or 30 days, respectively. In a cohort of 2370 patients with PTC who did not have initial distant metastases and had complete surgical resection of their primary tumors during treatment at Mayo Clinic from 1945 to 2000, relapse rates at nodal, local, and distant sites were 9.8%, 5.5%, and 4.6%, respectively, after 25 years of follow-up.[65] In a larger cohort of 2512 PTC patients treated during the period 1940-1990 at Mayo Clinic, the CSS rates at 5, 10, and 20 postoperative years were 98%, 96%, and 95%, respectively.[65]

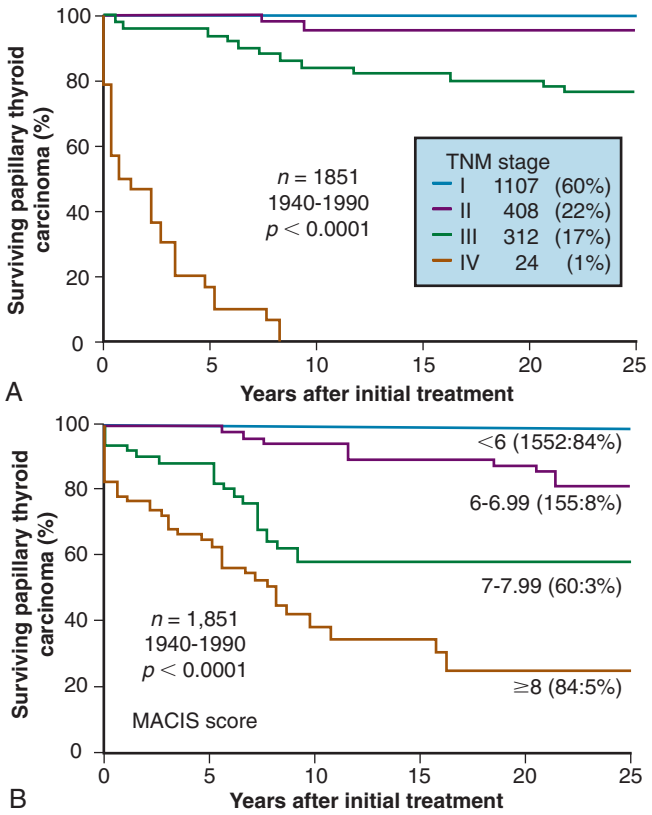


Figure 38-1 Cause-specific survival (CSS) for a cohort of 1851 patients with papillary thyroid carcinoma treated at the Mayo Clinic during the period 1940 to 1990. **A,** CSS by pathologic TNM (primary tumor, regional nodes, metastases) stage; numbers in parentheses are the percentages of patients in each pathologic TNM stage grouping. **B,** CSS by MACIS (metastasis, age, completeness of resection, invasion, and size) scores of <6, 6-6.99, 7-7.99, and ≥8; numbers in parentheses are the numbers and percentages of patients with PTC in each of the four risk groups.
From Larsen PR, Davies TF, Hay ID: The thyroid gland. In Wilson JD, Foster DW, Kronenberg HM, et al, editors: Williams Textbook of Endocrinology, ed 9, Philadelphia, 1998, WB Saunders, pp 389–515.

Of patients with lethal PTC, 20% of deaths occurred within the first year after diagnosis, and 80% of the deaths occurred within 10 postoperative years.[51,52,65]

Only a fraction (≈15%) of patients with PTC have relapse of disease, and even fewer (≈5%) have a lethal outcome.[51-53,65] The exceptional patient who experiences an aggressive course tends to relapse early, and the rare fatalities usually occur within 5 to 10 years of initial diagnoses.[51,52,65]

Multivariate analyses have been used to identify variables predictive of cause-specific mortality.[68-71] Increasing patient age and presence of extrathyroidal invasion are independent prognostic factors in all such studies.[68-71] The presence of initial distant metastases and large size of the primary tumor are also significant variables in most studies,[68,70] and some groups[51,64,68,69,72] have reported that histopathologic grade (i.e., degree of differentiation) is an independent variable. The completeness of initial tumor resection (i.e., postoperative status) is also a predictor of mortality.[51,71] The presence of initial neck nodal metastasis, although relevant to future nodal relapse, does not apparently influence cause-specific mortality.[51,52,71]

From a multivariate analysis of more than 14,200 patient-years of experience, a prognostic scoring system was devised and named the AGES system after five independent variables: patient's *a*ge, tumor *g*rade, tumor *e*xtent (e.g., local invasion, distant metastasis), and tumor *s*ize.[51,68] With the use of such a scoring system, 86% of patients with PTC were in the minimal-risk group (AGES score <4), and they had a cause-specific mortality rate of only 1%.[51] In contrast, patients with AGES scores of 4 or greater (i.e., high-risk group is 14% of the total) had a 20-year cause-specific mortality rate of 40%. Based on the description of the Mayo Clinic–derived AGES system,[68] Cady and Rossi,[73] working at the Lahey Clinic, devised a simplified version of the AGES system, which they called the AMES multifactorial system. The AMES system disregarded tumor grade because this information was not readily available to the authors, but they took advantage of the other four variables: *a*ge, *m*etastasis, *e*xtent, and *s*ize. The details of the AMES system are presented in Table 38-3. Of the 1961 to 1980 cohort of patients studied by Cady and Rossi, 89% were deemed low risk and had a death rate of 1.8%; outcome results virtually identical to results defined by the AGES prognostic scores.[51,68]

TABLE 38-3 Classification of Risk Group Categories According to the AMES System

LOW RISK
1. Younger patients (men <41 years; women <51 years), no distant metastasis
2. Older patients with (a) minor tumor capsule involvement *and* (b) primary cancers <5 cm in diameter *and* (c) no distant metastasis
HIGH RISK
1. All patients with distant metastasis
2. All older patients with (a) major tumor capsule involvement *or* (b) primary cancers ≥5 cm in diameter

Data from Cady B, Rossi R: An expanded view of risk-group definition in differentiated thyroid carcinoma. Surgery 104:947–953, 1988.
AMES, *Age, metastasis, extent, and size.*

Although the AGES scheme had the potential for universal application, some academic centers could not include the differentiation variable (tumor grade [G]) because their surgical pathologists did not recognize higher grade PTC tumors.[74] Another prognostic scoring system for predicting PTC mortality rates was devised with the use of candidate variables that included completeness of primary tumor resection but excluded histologic grade.[71] Cox model analysis and stepwise variable selection led to a final prognostic model that included five variables: *m*etastasis, *a*ge, *c*ompleteness of resection, *i*nvasion, and *s*ize (MACIS). The final score was defined as MACIS = 3.1 (if age is ≤39 years) or 0.08 × age (if age is ≥40 years), +0.3 × tumor size (in centimeters), +1 (if tumor not completely resected), +1 (if locally invasive), +3 (if distant metastases are present). As illustrated by Figure 38-1, *B*, the MACIS scoring system permitted identification of patient groups with a broad range of risk of death from PTC. Twenty-year CSS rates for patients with MACIS scores of less than 6, 6 to 6.99, 7 to 7.99, and 8 or more were 99%, 84%, 56%, and 24%, respectively. When cumulative mortality from all causes of death was considered, approximately 85% of patients with PTC (who had AGES scores <4 or MACIS scores <6) experienced no excess mortality over rates predicted for control subjects.[51,65,68,71]

Follicular Thyroid Carcinoma

When more than 75% of cells in an FTC exhibit Hürthle cell or oncocytic features, the tumor is classified as an HCC, oncocytic carcinoma, or oxyphilic variant FTC.[25] Most patients with FTC or HCC present with tumors that are 2 cm or larger and confined to the neck. Patients 45 years old or older with nodal

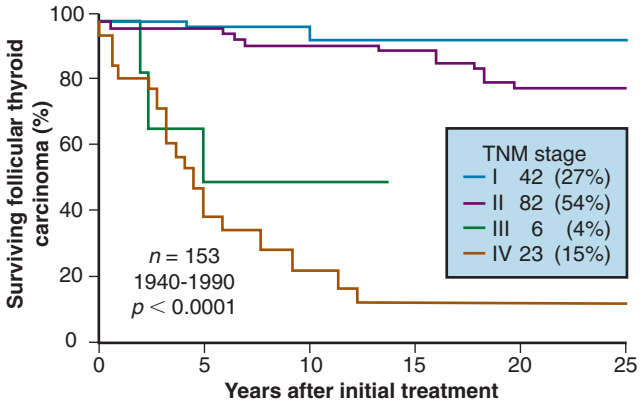


Figure 38-2 Cause-specific survival according to pathologic TNM (primary tumor, regional nodes, metastases) stages for a cohort of 153 patients with nonoxyphilic follicular thyroid carcinoma treated at the Mayo Clinic during the period 1940 to 1990. Numbers in parentheses are the percentages of patients in each pathologic TNM stage grouping. *From Larsen PR, Davies TF, Hay ID: The thyroid gland. In Wilson JD, Foster DW, Kronenberg HM, et al, editors: Williams Textbook of Endocrinology, ed 9, Philadelphia, 1998, WB Saunders, pp 389–515.*

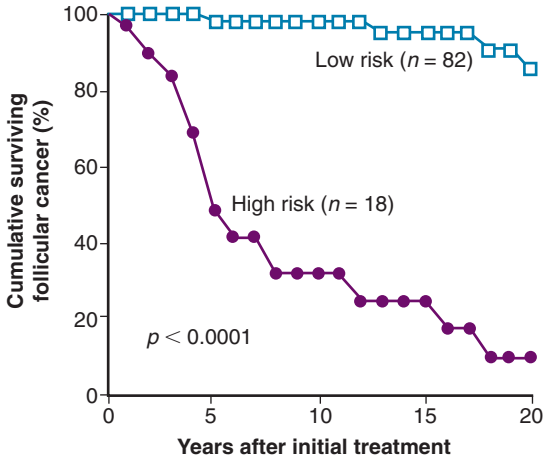


Figure 38-3 Cause-specific survival among 100 patients with nonoxyphilic follicular thyroid carcinoma treated at the Mayo Clinic during the period 1946-1970 and plotted by high-risk and low-risk categories. High risk is characterized by two or more of the following factors: age older than 50 years, marked vascular invasion, and metastatic disease at the time of initial diagnosis.
From Brennan MD, Bergstralh EJ, van Heerden JA, et al: Follicular thyroid cancer treated at Mayo Clinic, 1946 through 1970: initial manifestations, pathologic findings, therapy, and outcome. Mayo Clin Proc 66:11–19, 1991.

metastases or extrathyroidal extension account for only about 4% to 7% of FTCs and 8% to 10% of HCCs.[64,66] In contrast to patients with PTC, among whom only 1% to 3% present with distant metastases, about 4% to 6% of patients with HCC and 7% to 15% of patients with nonoxyphilic variant FTC have distant metastases at the time of initial diagnosis.[25,64,66] Figure 38-2 shows CSS according to pTNM stage in a cohort of 153 patients with nonoxyphilic FTC surgically treated at Mayo Clinic during the period 1940-1990.[66]

Nodal metastases are rare in typical FTC, and nodal relapse rates at 10 and 20 postoperative years are 1% and 2%, respectively. About 6% of patients with HCC have nodal involvement at presentation,[56] but at 20 and 30 years after primary surgery, 18% and 24%, respectively, of these patients have nodal relapse.[25] When relapse at neck or distant sites is considered, patients with HCC have the highest rates of tumor relapse after 10 or 20 years. Local recurrences account for most of these postoperative events because the numbers of distant metastases in patients with HCC are comparable with the numbers of metastases found in nonoxyphilic FTC (i.e., about 20% after 20 postoperative years).[25]

Cause-specific mortality rates vary with the presenting TNM stage for patients with FTC or HCC. The death rates tend to parallel the curves for development of distant metastases. In five decades of Mayo Clinic experience, the mortality rate for FTC initially exceeded that of HCC, but by 20 and 30 postoperative years, there were no significant differences in CSS rates between FTC and HCC,[25] with both survival rates about 80% at 20 postoperative years and 70% at 30 postoperative years.

The risk factors that predict outcome of patients with FTC are largely the same as for patients with PTC: distant metastases at presentation, increased patient age, large tumor size, and presence of local (extrathyroidal) invasion.[25] To a lesser degree, increased mortality is associated with male sex and higher grade tumors. Vascular invasiveness, lymphatic involvement at presentation, DNA aneuploidy, and oxyphilic histology are potential prognostic variables unique to FTC.[25] The importance of vascular invasion is underscored by a study showing that patients with FTC with minimal capsular invasion and no evidence of vascular invasion had 0% cause-specific mortality after 10 years of postoperative follow-up.[75]

Prognostic scoring systems for FTC allow stratification of patients into high-risk and low-risk categories.[25,76] A multivariate analysis at the Mayo Clinic found that distant metastases, patient age older than 50 years, and marked vascular invasion predicted a poor outcome.[55] As illustrated by Figure 38-3, if two or more of these factors are present, the 5-year survival rate is 47%, and the 20-year survival rate is 8%. If only one of these factors is present, the 5-year survival rate is 94%, and the 20-year survival rate is 86%.[55]

Systems developed to predict outcomes for PTC or FTC have been applied to patients with FTC. Specifically, the AMES risk-group categorization by Cady and Rossi has proved useful in FTC.[64,73] From a multivariate analysis of 228 patients with FTC treated at Memorial Sloan Kettering Cancer Center, the independent adverse prognostic factors were identified as age older than 45 years, Hürthle cell histologic type, extrathyroidal extension, tumor size exceeding 4 cm, and presence of distant metastasis.[77] The prognostic importance in FTC of histologic grade has also been confirmed[77,78] by the Memorial Sloan Kettering group, who have included this factor in their assignment of risk groups to low-risk, intermediate-risk, and high-risk categories, with 20-year survival rates of 97%, 87%, and 49%, respectively.[77] The AGES and MACIS prognostic scoring systems, originally developed for PTC, have also been successfully applied to FTC.[79,80] It seems that scoring systems used in PTC can be cautiously applied in FTC as long as some of the unique features of this tumor, such as vascular invasiveness and the remarkable significance of DNA aneuploidy in HCC, are considered.[25]

Medullary Thyroid Carcinoma

In reported studies of treated MTC, the proportion of patients with intrathyroidal node-negative tumors of 2 cm in diameter or smaller (TNM stage I) varies, depending on the number of familial cases detected by biochemical testing or DNA screening. The number of patients who present with TNM stage I MTC ranges from 5% to 25%, with the lower numbers

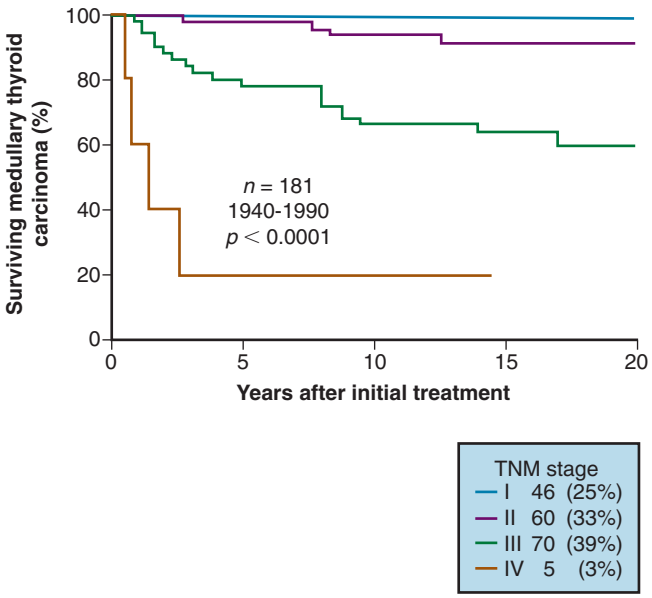


Figure 38-4 Cause-specific survival according to pathologic TNM (primary tumor, regional nodes, metastases) stage for a cohort of 181 patients with medullary thyroid carcinoma treated at the Mayo Clinic during the period 1940 to 1990. Numbers in parentheses are the percentages of patients in each pathologic TNM stage grouping.
From Larsen PR, Davies TF, Hay ID: The thyroid gland. In Wilson JD, Foster DW, Kronenberg HM, Larsen PR, editors: Williams Textbook of Endocrinology, ed 9, Philadelphia, 1998, WB Saunders, pp 389–515.

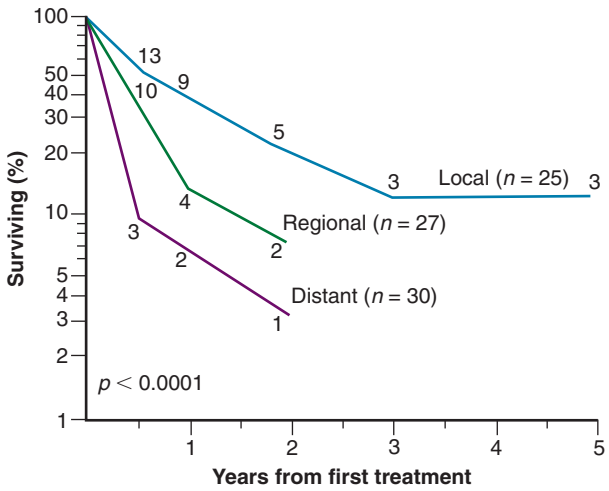


Figure 38-5 Survival to death from anaplastic thyroid cancer is plotted by extent of disease at presentation. Notice the logarithmic scale of the ordinate.
From Nel CJ, van Heerden JA, Goellner JR, et al: Anaplastic carcinoma of the thyroid: a clinicopathological study of 82 cases. Mayo Clin Proc 60:51–58, 1985.

representing the older series. Of patients, 25% to 50% present with positive neck nodes; the proportion of patients presenting with distant metastases usually exceeds the proportion with PTC but is typically less than the proportion with FTC. Stage IV cases constitute 3% to 10% of most MTC series. Figure 38-4 illustrates cause specific survival according to pTNM stage in a cohort of 181 patients with MTC surgically treated at Mayo Clinic during the period 1940-1990.[66]

Other prognostic factors relevant to outcome in MTC include age at diagnosis, male gender, vascular invasion, calcitonin immunoreactivity, amyloid staining, presence or absence of postoperative gross residual disease, and abnormal postoperative plasma calcitonin levels.[10,81-83] In a multivariate analysis from Toronto, only the presence of extrathyroidal invasion and postoperative gross residual disease were significant in the prediction of CSS.[83] In another multivariate study from Mayo Clinic, however, the only factors remaining in the final Cox model were pTNM stage III or IV disease, negative Congo red staining for amyloid, and postoperative gross residual disease.[82] Based on these three independent prognostic variables, a scoring system was devised to define four risk groups with 10-year mortality rates ranging from 5% to 100%.[82]

Anaplastic Carcinoma

Patients with ATC have a poor prognosis, and survival beyond 1 year is rare. There is no real use for an elaborate staging system for these patients, although distant and lymphatic spread at presentation, advanced age, and extremely poor differentiation have been identified as factors that make an already grim picture worse.[61,84] Figure 38-5 shows survival curves for 82 patients with ATC, stratified by extent of disease at presentation.[61]

CLINICAL MANIFESTATIONS AND PATIENT EVALUATION

At initial assessment, most patients with thyroid cancer have a palpable neck mass, which may represent the primary intrathyroidal tumor or metastatic regional lymphadenopathy. In some patients, the tumor may be clinically occult, and the impalpable lesion may first be recognized on high-resolution neck imaging[85] or during the course of a neck exploration for presumed benign thyroid disease. In patients with a family history of MTC or MEN-II syndrome, the finding of an *RET* oncogene mutation (identical to the proband) or abnormal calcitonin (or stimulated calcitonin) levels, or both, may necessitate elective prophylactic thyroidectomy in a patient who may prove to have early MTC visible only under the surgical pathologist's microscope.[49,50]

Features of the history and physical examination rarely provide convincing evidence for a diagnosis of thyroid malignancy.[7,8] The diagnosis of thyroid cancer necessitates pathologic confirmation from cytologic or histologic material. It is generally recognized that FNA biopsy is the most effective method available of preoperatively distinguishing between benign and malignant thyroid nodules.[7,8] All cancer diagnoses should be verified, however, by careful examination of histologic material after surgical excision of affected tissues. This approach is particularly relevant to the problem of the cellular follicular lesions described by cytologists as "suspicious" for follicular or Hürthle cell neoplasm. The diagnosis of FTC or HCC depends on the demonstration of invasion of the thyroid capsule or the adjacent blood vessels (i.e., angioinvasion), a process that typically necessitates careful evaluation of serial sections from the excised specimen for the presence or absence of such microinvasion. Even if FTC or HCC is apparently excluded at intraoperative frozen section, the resected specimen must be carefully reviewed in multiple sections from paraffin-embedded material.[25]

FNA biopsy can usually allow a confident diagnosis of PTC, which typically represents more than 75% of clinically recognized thyroid cancers in most contemporary series.[11,51,64,72]

Some authorities claim that the characteristic nuclear abnormalities diagnostic for PTC may be best seen in cytologic preparations from an FNA biopsy specimen, rather than in frozen sections or in paraffin-embedded histologic material. MTC may be readily diagnosed by FNA biopsy, but in equivocal cases, amyloid stained by Congo red or immunoperoxidase labeling of intracytoplasmic calcitonin may allow a definitive preoperative diagnosis.[10,59] ATC may often be diagnosed by FNA biopsy, but it sometimes may be difficult to distinguish from carcinoma metastatic to the thyroid.[61] When the biopsy specimen is found to be suspicious for ATC, immunostaining for thyroglobulin can help confirm the diagnosis of ATC. FNA diagnosis of thyroid lymphoma is difficult to make, and verification may necessitate examination of open biopsy material and specific immunostaining for clonal B-cell and T-cell populations.[86]

The evaluation of a patient with thyroid cancer requires obtaining a thorough history and performing physical examination with particular attention to signs and symptoms associated with local (extrathyroidal) invasion, involvement of regional (neck) nodes, and distant spread. Historical features suggesting a possible thyroid cancer include growth of a thyroid nodule over weeks or months; changes in speaking, breathing, or swallowing; and systemic symptoms of malignancy, such as weight loss, fatigue, and night sweats. On thyroid palpation, typical signs may include firm consistency of the dominant nodule, irregular shape, and fixation to underlying or overlying tissues. Evidence of suspicious regional lymphadenopathy may be present in up to one third of patients with PTC and MTC, but it is absent in most patients with FTC.

Patients with thyroid cancer are typically euthyroid, and when measured, the serum TSH level is usually normal. FNA biopsy can provide a confident diagnosis of PTC, MTC, and usually ATC. Diagnosing follicular cancer preoperatively remains a problem because capsule or vascular invasion cannot be shown in cytologic material. When FCDC is suspected and the decision is made for surgical exploration, it is often advisable to draw blood for a baseline serum thyroglobulin. This thyroid-specific protein can be used as a tumor marker to assess the efficacy of future therapies. Similarly, for patients with MTC, baseline measurements of calcitonin and carcinoembryonic antigen may permit a more accurate subsequent assessment of tumor control.

A preoperative vocal cord examination may permit the demonstration of unilateral vocal cord paralysis, which may raise suspicion about pressure or invasion of the ipsilateral recurrent laryngeal nerve. Particularly with PTC, MTC, and HCC, in which initial nodal involvement is common, high-resolution, real-time ultrasound examination of the neck can provide a surgeon with valuable information regarding the extent of disease within the thyroid gland and in adjacent regional lymph nodes. With extensive nodal disease or suspected locally invasive thyroid cancer, examination of the lower central neck with CT may delineate the presence of an intraluminal tumor or show more subtle evidence of tracheal or esophageal involvement with invasive disease. A high-resolution spiral CT scan of the chest or a whole skeleton isotopic bone scan is not routinely performed before initial neck exploration, but it can be useful postoperatively to exclude metastases in the mediastinum, lung, or bone, especially in patients without gross residual disease but with persistently elevated tumor markers.

Scanning with RAI has little role to play in the preoperative evaluation of thyroid malignancy. However, a postoperative whole body scan has become the gold standard for identification of iodophilic distant metastasis in patients with PTC or FTC.[7,9]

PRIMARY THERAPY

Surgery

Surgery is the standard primary treatment for differentiated thyroid cancers, but the extent of initial surgery is an area of considerable controversy.[4,68,87,88] Various investigators have advocated ipsilateral thyroid lobectomy with isthmectomy, bilateral subtotal thyroidectomy, and near-total or total thyroidectomy. Most institutions favor the initial resection of both lobes of the thyroid. Clinical guidelines promote near-total or total thyroidectomy as the recommended operative procedure for FCDC and total thyroidectomy for MTC.[7,9,10] Even thyroid carcinomas that are locally extensive, involving extrathyroidal structures, may be most effectively treated by a more aggressive surgical approach.[89,90] Most studies that have evaluated the impact of surgical treatment in thyroid cancers have compared total or near-total thyroidectomy with less aggressive surgical procedures.[4,67,68,91] These reports suggest that survival rates in higher risk cases are significantly improved after the more extensive surgery.[4,68]

An often-cited reason for removing all or nearly all of the thyroid gland is reducing the risk of future recurrence of FCDC in the contralateral thyroid lobe. This approach may be most appropriate in cases of PTC, in which multicentricity is a frequent phenomenon. Some investigators claim, however, that a subsequent local recurrence in the contralateral lobe also can be managed with a secondary operative procedure.[92] Such "completion" thyroidectomies carry a higher morbidity except in the hands of highly skilled surgeons.[67,93] One advantage of initial resection of the entire gland is the subsequent ability to follow serum thyroglobulin levels and to perform meaningful radioiodine scanning more easily.[6,7,9] Whole body scans may be difficult to interpret in the setting of residual thyroid remnant, as would be found after unilateral or bilateral subtotal resection.

In addition to the initial resection of the thyroid, the question of the extent of neck node removal remains controversial. When clinically evident nodal metastases are identified by palpation or ultrasound examination, surgical removal is performed. The role of prophylactic or prognostic lymph node dissections is unclear. For patients undergoing total or near-total thyroidectomy, removal of the central compartment lymph nodes may not add significantly to the morbidity of the procedure and should be included routinely with the primary resection.[7,93-96] Modified radical neck dissection is indicated for gross nodal metastases found before or during surgery, and it may improve the outcome of older patients with PTC with larger tumors or evidence of extrathyroidal invasion.[97,98]

The advantage of total thyroidectomy over near-total thyroidectomy may be nonexistent or limited to patients with more advanced malignancies.[67,68,99] The use of more limited surgery, such as unilateral total lobectomy, is probably appropriate only for a selected population of low-risk patients, such as patients with papillary microcarcinoma.[7,9,100]

Adjuvant Therapy

Thyroid Hormone

Postoperative thyroid suppression therapy for FCDC is based on administration of supraphysiologic oral doses of levothyroxine. This therapy has been widely used for more than 40 years, and it is assumed that suppression of endogenous TSH deprives TSH-dependent differentiated FCDC cells of an important growth-promoting influence. Traditionally, the goal of thyroxine therapy has been complete suppression of pituitary TSH secretion, as indicated by undetectable levels of serum TSH when measured in sensitive immunometric assays.

Uncertainty surrounds the level to which the serum TSH level must be suppressed to maximize benefit while avoiding potential long-term complications.[3,5,7,9]

With the increasing availability of sensitive TSH assays, meticulous titration of the level of TSH suppression has become possible. If patients with FCDC are deemed to be at high risk for relapse or mortality on the basis of scoring or staging systems,[63,71,73] or if they have persistent or recurrent carcinoma that cannot be eradicated by surgery, RAI, or other therapeutic measures, the goal would be to maintain the TSH level at less than 0.1 mU/L indefinitely in the absence of specific contraindications. In most patients with PTC who would be classified as low risk by prognostic scoring systems,[68,71,73,78] it is generally accepted that the degree of TSH suppression would be less stringent, and the goal for basal serum TSH should be in the readily detectable, barely subnormal range of 0.1 mU/L to 0.5 mU/L.[5,7,9,66,99]

Radioactive Iodine Therapy

Similar to the use of thyroid hormone for TSH suppression, the concept of adjuvant RAI therapy originated from treatment approaches to metastatic thyroid carcinoma and was based on an equally compelling physiologic premise. Because most FCDC cells retain some architectural and functional features of normal thyrocytes, iodine trapping and sometimes organification may be preserved in the tumors. It seemed appropriate to take advantage of this trapping by trying to eradicate microscopic residual postoperative tumor foci with RAI.

RRA has been defined as "the destruction of residual macroscopically normal thyroid tissue after surgical thyroidectomy."[99,101] Typically, RRA is used to complete the initial therapy in a patient whose FCDC has been completely resected (i.e., no gross residual disease is reported at the conclusion of the primary neck exploration). RRA is a procedure that is offered to patients with FCDC who have undergone "potentially curative" surgical treatment, and it should not be confused with RAI therapy, in which larger doses of iodine-131[102] (^{131}I) are used in an attempt to destroy persistent neck disease or distant metastatic lesions.[86,99,101,103,104]

Proponents of RRA describe at least three advantages for this adjunctive therapy. First, by being actively trapped by normal thyroid cells, RRA is thought to destroy occult microscopic carcinoma cells within the thyroid remnant. Second, the later detection of persistent or recurrent disease, particularly in the neck by RAI scanning, is facilitated by the destruction of remaining normal tissue. Third, the performance of RRA is thought to increase the value of serum thyroglobulin measurement during follow-up. This last benefit has convinced many physicians to consider RRA in patients with FCDC who are, by prognostic scoring or staging, deemed to be at low risk for tumor relapse or cause-specific mortality.[18,101] Other physicians have not advocated RRA in these low-risk patients, however, because of a lack of evidence of improved outcome.[98,99,101,103]

Investigators have reported benefit and a lack of benefit from the use of RRA. It is unclear from these reports whether outcome is improved with the routine use of RRA in the initial therapy of all patients with differentiated thyroid carcinoma, largely because of difficulties obtaining a comparable control group and the potential for selection biases, which may account for the outcomes reported. Sawka et al[101] systematically reviewed 1543 English references to determine whether RRA decreases the risk of thyroid cancer–related death or relapse after bilateral thyroidectomy for PTC or FTC. In 18 cohort studies not adjusted for prognostic factors or interventions, the benefit of RRA in decreasing thyroid cancer–related mortality and any relapse by 10 years was inconsistent among centers. However, pooled analyses suggested a statistically significant treatment effect of RRA in terms of 10-year outcomes for locoregional recurrence (relative risk, 0.31) and distant metastases (absolute decrease in risk, 3%). The conclusion of this meta-analysis was that RRA might be beneficial in decreasing relapse of well-differentiated thyroid cancer; however, Sawka et al[101] said that "the incremental benefit of remnant ablation in low-risk patients treated with bilateral thyroidectomy and thyroid hormone suppressive therapy is unclear."

The National Thyroid Cancer Treatment Cooperative Study Group (NTCTCSG) was founded in 1986 and has maintained over more than two decades a registry contributed to by 11 North American institutions prospectively following a large nonrandomized cohort of patients with FCDC, with the objective of assessing the effects of initial and longitudinal management on outcomes. By June 2001, 2936 patients were registered, and the more recently published results of outcome showed that "no treatment modality, including lack of radioactive iodine, was associated with altered survival in stage I patients." Jonklaas et al[3] "were unable to show any impact, positive or negative, of specific therapies in stage I patients." These authors concluded that "postoperative RAI (RRA) therapy does not provide significant benefit in stage I patients, and could even be harmful," and suggested that "further evaluation of the potential risks and benefits of treatment in stage I patients is, therefore, indicated."[3]

Use of prognostic scoring schemes may help to define patients at significant risk for relapse and who are more appropriate for consideration of remnant ablation. At the Mayo Clinic, patients with PTC who have MACIS scores greater than 6.0 or are found to have persistent elevation of serum thyroglobulin levels after 6 to 8 postoperative weeks are considered for an ablative procedure. Use of such a scheme is applicable only if the patient undergoes a near-total or total thyroidectomy. If the goal is to minimize the use of RAI, more extensive surgery such as near-total or total thyroidectomy is more appropriate in low-risk patients. However, if RRA is planned, more extensive surgery may not give any advantage. In high-risk patients, the use of RAI in addition to more aggressive surgery seems warranted.[98,103,105]

After determining the need for remnant ablation, the question of dose after the primary surgical procedure is also an important consideration. In the United States, low-dose regimens of less than 30 mCi have been used when the amount of residual thyroid tissue is small. Higher doses of 75 mCi to 150 mCi may be appropriate when microscopic residual is present or when the initial scan suggests an unsuspected metastatic site. Use of low-dose RAI in such a patient may decrease the ability of the tumor subsequently to concentrate sufficient radioiodine and should be avoided.

Further treatment with RAI ideally should reflect the local or distant uptake of iodine in residual differentiated thyroid cancer tissue. Adequate ability of thyroid cancer cells to concentrate radioiodine is variable, and this approach may not be appropriate in all patients. Patients with FTC may concentrate RAI better than patients with PTC.[104] In a multicenter Canadian study, Simpson et al[104] reviewed the outcomes of more than 1500 patients with PTC or FTC and studied 321 patients who were treated with RAI. The use of RAI resulted in significantly improved local control in patients with microscopic residual disease. CSS was also significantly better for patients with PTC with microscopic residual disease who received RAI. Most patients received only thyroid remnant ablation doses (50 mCi to 125 mCi), but total (cumulative) therapeutic doses given in one to seven treatments ranged from 75 mCi to 1000 mCi.

The definitive role of RRA continues to evolve.[105,106] Multiple studies have suggested that RRA be used routinely in

high-risk patients. Although the definition of "high risk" varies, most investigators favor using RAI in patients with large tumors or extensive extrathyroidal invasion and in patients with incompletely resected disease or distant metastases. Robbins and Schlumberger[105] recommended RRA for "any individual with a carcinoma larger than 1.5 cm or with a thyroid carcinoma of any size with obvious lymph node involvement, extrathyroidal extension, or multicentricity." The clinical guidelines proposed by the European Thyroid Association and the American Thyroid Association should allow some greater uniformity of treatment approach.[7,9,106]

External Beam Radiation Therapy (EBRT)

The appropriate application of EBRT in PTC and FTC is controversial, and this modality is not uniformly used.[106,107] A better understanding of prognostic factors that are specific to local recurrence may help identify an appropriate population of patients who would be candidates for EBRT. Most prognostic schemes consider only the overall risk of relapse and CSS.

Historically, indications for EBRT have included residual macroscopic or microscopic disease, extrathyroidal extension, multiple lymph node involvement, Hürthle cell histology, older age of patients, large tumor size, and residual disease that does not take up RAI. Several investigators have retrospectively reviewed their experience with EBRT and suggested improved local control or survival benefit or both. The patient populations in these studies are not uniform with respect to other treatments that also effect local control, making interpretation difficult.

Most series support the use of adjuvant EBRT for patients with microscopic residual disease or narrow surgical margins of resection. An early Canadian study of follicular and papillary carcinomas evaluated the role of EBRT according to completeness of surgical resection.[108] Table 38-4 summarizes these findings. Although the overall numbers are small, they suggest that patients with surgically narrow or microscopically positive margins may benefit from the addition of EBRT in moderate doses. These results were achieved with minimal morbidity.

A larger synopsis of 13 Canadian institutions in which EBRT was used predominantly in patients with high-risk features, such as extrathyroidal invasion, high-grade malignancies, and older age, revealed a significant improvement in local control for patients who had microscopically positive or narrow surgical margins.[106] In this study, the overall survival (OS) of patients with PTC with presumed or microscopic residual was significantly improved with the addition of adjuvant EBRT. These improvements were seen with or without the use of RAI. Results from Germany for patients with pathologic T4 disease (based on the older staging system) with or without lymph node involvement also suggest a benefit from EBRT with respect to local control and distant failure rates, especially in patients older than 40 years.[109] However, in a review from Princess Margaret Hospital in Toronto of 207 patients with microscopic residual, the addition of EBRT did not significantly improve the CSS or the local control ($p = 0.38$ and $p = 014$).[110] A more recent review with a larger number of patients and longer follow-up revealed an improved 10-year CSS in high-risk patients (age >60 years, extrathyroid extension, microscopic residual disease, no gross residual disease) with the addition of EBRT.[111,112] A review from Mount Sinai Hospital in Toronto found that the use of EBRT was the only predictor of significantly improved disease-specific survival and OS in patients with well-differentiated thyroid cancer with extrathyroidal extension.[113]

Benker et al[114] described 932 patients with differentiated thyroid malignancies and found no OS benefit with the addition of EBRT. On subset analysis, however, patients older than 40 years with T3 or T4 disease experienced improved survival that approached statistical significance ($p = 0.09$). All patients in this series received thyroxine-suppressive therapy and RAI.

The role of EBRT in the setting of gross residual disease has been evaluated by multiple investigators, with a wide range of outcomes. A study from the Royal Marsden Hospital showed complete response in 37% of patients and partial response in an additional 25%.[115] The Princess Margaret Hospital study had 33 patients with macroscopic disease treated with EBRT with or without RAI; the 5-year local recurrence-free rate was 62%.[110] Tubiana et al[116] from Institut Gustav-Roussy evaluated 97 patients with macroscopic residual based on the surgeon's clinical assessment. Local recurrence after EBRT was only 15% compared with 32% in a similar surgical category without postoperative EBRT. None of these patients received RAI. With the ability to deliver higher doses of EBRT using techniques such as intensity-modulated radiotherapy (IMRT) or proton beam therapy (IMPT), it may be feasible to give higher doses than were used in these studies and perhaps increase the long-term control of disease in this difficult patient population.

Although the definitive role of EBRT for differentiated thyroid carcinoma remains controversial, retrospective data support its use in a selected population of patients who have microscopic or presumed microscopic residual cancer.[117] Evidence exists not only for PTC and FTC but also for HCC and MTC.[118-120] The only randomized trial evaluating the role of EBRT was initiated in 2000 in patients with pathologic T4, N0-1, M0 disease after surgical resection and ablative ^{131}I therapy.[121] The study closed because of inadequate accrual in March 2003 despite acceptable toxicity.[122] The study authors indicated that at early follow-up, there are lower than expected relapse rates in the nontreatment arm. The improvements in surgical management of these patients and the appropriate application of RAI may have accounted for the decreased relapse and mortality rates compared with historical studies.

The use of EBRT for patients with differentiated thyroid cancer needs to be carefully tailored to the specific patient and applied after use of RAI. Although efforts to improve on surgical outcome have focused mainly on RAI treatment in patients with a high risk of relapse, there seems to be an evolving role for EBRT in their management. The rationale for inclusion of EBRT upfront in the management of this subset of patients is to (1) treat tissues that are known to take up less RAI (areas of extrathyroidal or extranodal extension, which are known poor prognostic indicators); (2) treat carcinomas that fail to concentrate and retain RAI (20% of all differentiated thyroid cancers, patients with Hürthle cell tumors, and patients >40 years old who commonly have less sodium iodide symporter); (3) spare some of the systemic toxicity of RAI treatment (when adequate treatment of residual disease entails excessive doses of radioiodine or when repeated treatments are likely to be

TABLE 38-4 Local Recurrence of PTC and FTC at Princess Margaret Hospital by Method of Treatment

	Surgery Alone		EBRT		RAI	
Extent of Disease	***N***	**%**	***N***	**%**	***N***	**%**
No residual disease	11/24	46	1/11	9	1/5	20
Probable residual	5/9	56	1/22	5	1/10	10
Microscopic residual	1/1	—	0/16	0	1/4	25

Data from Simpson WJ, Carruthers JS: The role of external irradiation in the management of papillary and follicular thyroid cancer. Am J Surg 1365:457–463, 1978.

EBRT, *External beam radiotherapy;* RAI, *radioactive iodine.*

necessary, increasing cumulative systemic toxicity); and (4) spare some of the morbidity associated with uncontrolled locoregional cancer, such as obstruction of the esophagus or trachea or both, neurovascular compromise, pain, hemorrhage, need for laryngectomy, and need for repeated surgical procedures.

The current American Thyroid Association and National Comprehensive Cancer Network guidelines suggest that EBRT should be considered in patients older than age 45 with grossly visible extrathyroid extension at the time of surgery and a high likelihood of microscopic residual disease and patients with gross residual tumor in whom further surgery or RAI would likely be ineffective.[123] Changes in the staging of locally advanced thyroid cancers in 2002 by categorizing minimal extrathyroidal extension as T3 disease and creating two T4 categories should help delineate further the highest-risk population. In the clinical setting of T4b disease, it is unlikely that complete surgical resection can be achieved, and use of EBRT in addition to RAI seems to help control gross disease. For patients with locally recurrent disease, early use of EBRT as a component of treatment should be considered.

Treatment of the thyroid bed or gland and its draining lymph node areas has historically been a challenging undertaking. Advances in treatment modalities include three-dimensional conformal multiple-beam treatments, IMRT, and IMPT treatments. Although there is no definitive evidence of a dose-response relationship between radiation dose and local control probability, there is some suggestion that higher doses are associated with lower local recurrence rates.[116,124] With the increasing availability of IMRT and IMPT, dose escalation may be more readily achievable in the adjuvant setting without increasing toxicity.[125-127] Stereotactic body radiotherapy (SBRT) has been proposed as a highly targeted technique that is efficient (one to three treatments) and effective in controlling cervical lymph node recurrence of nonanaplastic thyroid cancer (100% tumor control) with no serious adverse events.[128]

Chemotherapy

Although most thyroid cancers, FCDC, and medullary cancers respond to historical therapeutic approaches, radioiodine-refractory metastatic differentiated thyroid cancer (FDTC) and advanced medullary thyroid cancer (MTC) have, until recently, had few treatment options. The role of systemic therapies, such as cytotoxic chemotherapy in the treatment of these advance thyroid cancers is limited. Most agents have low response rates. The most active single agent reported in the treatment of thyroid cancers is doxorubicin (Adriamycin). Other reportedly active agents include cisplatin, carboplatin, and etoposide (VP-16).

The Eastern Cooperative Oncology Group (ECOG) reported the only randomized study of the use of chemotherapy in advanced thyroid cancer.[129] Patients with locally advanced or metastatic FTC, PTC, MTC, and ATC were eligible. In this study, patients were randomly assigned to chemotherapy with doxorubicin alone or doxorubicin with cisplatin. Of the 84 eligible patients, the investigators reported a complete response rate of 6% and a partial response rate of 15%. A partial or complete response to chemotherapy occurred in 8 (23%) of 35 patients with advanced differentiated thyroid carcinomas. Overall, there was no advantage to the combination-drug regimen over doxorubicin alone. All five complete responders were in the combination arm, however.

Targeted Therapy for Advanced Thyroid Cancer

The most promising targeted therapies for advanced thyroid cancer are tyrosine kinase inhibitors (TKIs). TKIs are oral therapies that inhibit various altered intracellular metabolic pathways. In clinical trials these therapies induce significant regression in differentiated and medullary thyroid cancer without improvement in survival (Table 38-5). The only TKI approved for advanced FDTC is sorafenib. Among patients with well-differentiated thyroid cancer that has metastasized, recurred, or has not responded to radioactive iodine, this therapy increased the length of progression-free survival (PFS) by 41% and led to a median PFS of 10.8 months.[130] Vandetanib and Cabozantinib are two TKIs approved for progressive and metastasized medullary thyroid cancer. Both therapies are associated with improvements in mean PFS and reduction in tumor size compared to patients receiving placebo. At Mayo Clinic, two recently published multicenter Phase II studies described a initial experience with pazopanib in both FDTC[131] and, more recently, MTC.[102] Among patients with metastatic, rapidly progressive, and radioiodine-refractory FDTC, pazopanib induced a partial response (30% decrease in the sum of the longest diameter of target lesions) in about 49%; with an estimated 66% likelihood of having responses longer than 1 year's duration. Promising results were also observed for patients with progressive and metastatic medullary thyroid cancer, where pazopanib induced a partial response in 14.3% of patients with median PFS of 9.4 months.

TABLE 38-5 Tyrosine Kinase Inhibitors for Advanced Thyroid Cancer

	Tumor Type	Target	Partial Response (%)	Progression-Free Survival (Months)	Most Frequent Adverse Effects (%)
FDA APPROVED					
Sorafenib	PTC	BRAF, RET, other TKRs	13-41	10-18	Hand-foot-skin reaction (30%), diarrhea (43%), fatigue (37%)
Vandetanib	MTC	RET, other TKRs	16-45	20-27	Hypertension (33%), rash (53%), diarrhea (57%)
Cabozantinib	MTC	RET, other TKRs	28	11.2	Diarrhea (15.9%), hand-foot-skin reaction (12.6%), and fatigue (9.3%)
NON-FDA APPROVED					
Axitinib	PTC, FTC	Other TKRs	26-40	NA	Diarrhea (55%), increased creatinine (55%), hypertension (40%)
Pazopanib	PTC, FTC	RET, other TKRs	49	11.7	Liver enzymes elevation (53%), weight loss (52%), diarrhea (52%)
Sunitinib	PTC, FTC	RET, other TKRs	28	10-21	Diarrhea (61%), liver enzymes elevation (56%), fatigue (54%)

BRAF, *v-Raf murine sarcoma viral oncogene homolog B;* RET, *rearranged during transfection;* FTC, *follicular thyroid cancer;* MTC, *medullary thyroid cancer;* NA, *not assessed;* PTC, *papillary thyroid cancer,* TKR, *tyrosine kinase receptor.*

The most common side effect of these TKIs is fatigue, hand-foot skin reaction, gastrointestinal and abdominal pains, and hypertension. It has been estimated that TKIs cause mortality in about 1.5% of patients.[132] Also important to consider is that even in the presence of radioiodine-refractory disease, advanced thyroid cancer does not always progress to cause symptoms or result in decreased quality of life.[133] Therefore, it is important to offer these treatments to those patients where the benefits may outweigh the potential harm. A potential subgroup, where this is true, are patients with radioiodine-refractory, previously irradiated disease and nonsurgical, non-EBRT candidates with progressive or threatening symptoms.

THYROID LYMPHOMA AND ANAPLASTIC THYROID CARCINOMA

The most common poorly differentiated tumors of the thyroid, lymphoma and ATC, are treated differently from well-differentiated FCDC and MTC. For that reason, these two tumors and their treatment plans are considered separately.

Primary Thyroid Lymphoma

For a thorough and in-depth review of lymphoma, please refer to Chapters 76 and 77 "Hodgkin's Disease" and "Non-Hodgkin's Disease.

Most thyroid lymphomas are diffuse, large B-cell lymphomas (DLBCLs), but significant numbers are in the category of lymphomas known as mucosa-associated lymphoid tissue (MALT) lymphomas or mixed tumors containing elements of DLBCL and MALT. Rarely, other types of lymphoma, including follicular lymphomas and Hodgkin's lymphomas, have been reported.[134,135] Thyroid lymphomas usually manifest with a rapidly enlarging mass that is sometimes associated with respiratory and esophageal symptoms. These lymphomas typically occur in middle-aged and older women and are often associated with chronic thyroiditis.[134,135] MALT lymphomas have a more indolent natural history, whereas DLBCLs tend to be more aggressive.

In general, early stage, indolent, low grade lymphoma (including MALT lymphoma) is treated with EBRT alone to a dose of 24 Gy in 12 fractions to an involved-field. Stages III-IV disease (indolent follicular lymphoma, marginal zone lymphoma) is also treated with radiation therapy alone to 24 Gy in 12 fractions to involved-fields.[136-139] In cases where the treatment intent is palliative, 4 Gy in 2 fractions may be sufficient.[139] For early stage (I, II) diffuse aggressive (large B-cell) lymphoma, the treatment is typically 8 cycles of Rituximab, Cyclophosphamide, Doxorubicin Hydrochloride, Vincristine Sulfate, Prednisone (R-CHOP) usually followed by 30 Gy in 15 fractions EBRT to the involved field if there has been a complete response to chemotherapy. The addition of EBRT to chemotherapy in this situation has been reported to improve disease free or PFS and OS when compared to chemotherapy alone.[137,138,140-143]

In stages III-IV DLBCL involving the thyroid gland, the treatment would generally be R-CHOP alone. Further improvement in outcomes for DLBCLs has been shown with the addition of monoclonal antibodies, especially rituximab, to combination chemotherapy.[144,145] Other immunologic and radiolabeled agents are being evaluated.

Anaplastic Thyroid Carcinoma

The treatment of ATC is frustrating because of the rapidly progressive nature of this disease and its high fatality rate. Most patients are women presenting in the sixth to seventh decade of life, typically with a mass rapidly enlarging over a short time interval. Symptoms of hoarseness, dyspnea, dysphagia, and pain are common in this form of thyroid malignancy. Persistent or recurrent local disease is often the cause of death. Distant metastases are present in almost half of patients at presentation.

The optimal role of surgery has not been well defined. Surgery may be performed initially in some patients, but this probably reflects the selection of a favorable population of patients. The M. D. Anderson Cancer Center reported that more extensive surgery by itself did not provide a survival advantage.[84] Overall, most patients present with unresectable or metastatic disease, and the initial surgery in these situations is primarily for diagnostic purposes. In most reports, however, the only long-term survivors were patients who had undergone surgical resection.[61,146-149] For this reason, surgery should be strongly considered as a component of treatment. Surgery has been performed before or after EBRT, chemotherapy, or both.[84,150] The sequence of surgery relative to EBRT and chemotherapy may be primarily a reflection of the extent of disease at time of patient presentation to the treating physicians.[151]

EBRT has been used in the treatment of these advanced tumors, but because of the high metastatic rate and high rate of local failure with EBRT alone, the investigation of chemotherapy in addition to EBRT is warranted.[152] Multiple studies have investigated the use of multimodality therapy.[146,147,150,153] The use of hyperfractionated EBRT has been examined because of the rapid proliferation rate of these malignancies.[147,150,153,154] Various approaches have been reported, but most studies use doxorubicin-based chemotherapy given concurrently with local EBRT.[129,147,153,155]

In approaching ATC, we view two issues to be paramount: (1) the eradication of localized disease in the neck, with protection of the airway, esophagus, and neurovascular structures, and (2) the control of metastatic disease, which almost always contributes to the death of patients with ATC. It follows that a strategy combining locoregional and systemic therapy may offer the greatest promise in ATC.

Although long-term survival (>1 year) after combined-modality therapy in ATC has been so rare as to provoke reports of single cases,[156] subsequent series support the benefit of combined-modality approaches. Swaak-Kragten et al[157] conducted a study of 30 patients with ATC treated with an adjuvant approach combining surgery, EBRT, and single-agent chemotherapy with doxorubicin administered concurrently with EBRT and continued after EBRT completion and reported an encouraging improvement in 1-year survival from 9% (historical controls) to 23% (new patient cohort). Haigh et al[158] reported a 75% 2-year survival in 8 patients undergoing complete surgical resection and adjuvant EBRT and chemotherapy. Tan et al[159] reported an estimated 5-year survival of 60% for 5 patients who underwent complete resection. Four patients had received postoperative EBRT, 3 with post-EBRT doxorubicin-based chemotherapy. Pudney et al[160] reported a median OS of 13 months for 5 patients with stage IVB ATC treated with either EBRT concurrent with doxorubicin or induction docetaxel, doxorubicin, and cyclophosphamide. Three patients developed progression of local disease, and 1 developed distant metastases. Higashiyama et al[161] reported a 12-month survival rate of 44% in 9 patients with stage IVb ATC treated with induction paclitaxel. This survival rate compared favorably with a historical control group of 50 patients treated without induction paclitaxel; their 12-month survival was just 5.9%. A retrospective review of 10 consecutive patients with stage IVA and IVB ATC from Mayo Clinic who were treated with aggressive combined modality therapy (surgery if feasible, early initiation of docetaxel and doxorubicin, with the addition of concurrent EBRT followed by adjuvant

chemotherapy as tolerated) had an unexpectedly long median OS of 60 months, compared to a 5- to 6-month median OS among an analogous historical group of patients.[162] NRG Oncology is currently studying such aggressive combined modality therapy in a randomized Phase II clinical trial (RTOG 0912) using surgery when possible, concurrent IMRT and paclitaxel with or without pazopanib.

The optimal EBRT fractionation schedule has not yet been determined. Of patients treated with a moderate dose (57.6 Gy) slightly accelerated radiotherapy, given twice daily 3 days per week, combined with concurrent weekly doxorubicin, 70% required a 1-week interruption in treatment because of pharyngoesophagitis and tracheitis.[153] Moderate-dose (60.8 Gy) accelerated fractionation even without concurrent chemotherapy may be too toxic with a median OS of just 10 weeks.[163] Low-dose (40 Gy) hyperfractionated accelerated radiotherapy with sequential but not concurrent chemotherapy (doxorubicin) seems to be well tolerated with 1-year and 3-year OS of 50% and 35%, respectively.[155] Moderate-dose (60 Gy) hyperfractionated accelerated radiotherapy without concurrent chemotherapy seems to be well tolerated with a median OS of 13.6 months and 1-year and 5-year OS of 66.7% and 0%, respectively.[164] However, others have reported less than 10% 1-year survival with hyperfractionated accelerated radiotherapy to a median dose of 57 Gy in patients with nonmetastatic disease.[165] In the current NRG Oncology clinical trial, IMRT is being used with conventional daily fractionation to a total dose of 66 Gy in 33 fractions of 2 Gy each over a 6.5 week period of time.

In a report of the Surveillance, Epidemiology and End Results (SEER) database from the National Cancer Institute, the only factors predicting for lower cause-specific mortality were age younger than 60 years, intrathyroidal tumor, and combined use of surgery and EBRT.[166] However, the overall cause-specific mortality rate was 80.7% at 1 year. The use of multimodality therapy, including surgery, EBRT, and chemotherapy, is appropriate and offers the best chance for long-term survival, but more active systemic agents need to be found to improve survival significantly.

IRRADIATION TECHNIQUES AND TOLERANCE

EBRT Treatment Volumes and Doses

Treatment of the thyroid bed or gland and the regional lymph nodes is challenging because of the contour of the body in this anatomic area; the potential extension of disease to the upper mediastinum; involvement of lymph nodes in the central and lateral neck and mediastinum; and the close proximity of the lungs, spinal cord, esophagus, larynx, pharyngeal constrictors, and brachial plexus. Historically, several approaches have been reported for the initial extended fields, including a single anterior electron field,[110] an anterior field with a posterior supplemental field for the mediastinum, and lateral fields.[116]

For optimal treatment in an adjuvant setting or for locoregionally advanced or recurrent disease treated with curative intent, the clinical target volume should include the thyroid bed (including gross disease if present), lymph nodes of the central and lateral neck (typically bilateral levels II through VI, consider adding level VII when level II is involved or in the case of bulky adenopathy), and upper mediastinum. When treating for palliation, it is reasonable to consider treating only the gross tumor volume plus margin. Treatment planning should be image based (CT simulation) and incorporate CT, ^{18}F-fluorodeoxyglucose (^{18}F-FDG) fused PET/CT, and MRI.

At Mayo Clinic, we have chosen to use IMRT or intensity-modulated arc therapy (VMAT) in the treatment of these patients, which allows us to quickly administer a more conformal high dose (60 Gy to 70 Gy) with improved homogeneity to the thyroid bed or gross disease and high-risk areas (lymph nodes and tracheoesophageal groove), while lowering the dose to normal organs at risk, including the salivary glands, epiglottis, false vocal cords, true vocal cords, arytenoids, central and posterior aspects of the pharyngeal constrictors and esophagus, brachial plexus, and spinal cord. The use of IMRT and VMAT has allowed for more elegant treatment of this disease site compared with conventional two-dimensional and three-dimensional treatment planning (Figure 38-6). IMRT improves the minimum and mean dose to the planning tumor volume and significantly reduces the dose to the spinal cord.[125,127,167,168] This is true for treatment of the thyroid tumor bed and locoregional nodal sites.

The radiation dose used in the postoperative setting for microscopic residual disease should be 60 Gy in 6 weeks. However, some centers have suggested 40 Gy given over 3 to 3.5 weeks is adequate.[108] For known gross residual disease, dose escalation to 66 Gy to 70 Gy is reasonable. One retrospective study from the United Kingdom suggested a possible dose-response effect at greater than 50 Gy for patients treated with curative intent.[107] The use of higher doses without added morbidity may be feasible with IMRT, VMAT, and IMPT. Although there is no definitive evidence of a dose-response relationship between radiation dose and local control probability, there is some suggestion that higher doses are associated with lower local recurrence rates.[116,124]

Treatment Tolerance

With the increasing availability of IMRT, VMAT, and IMPT, dose escalation may be more readily achievable in the primary setting without increasing toxicity while lowering toxicity in the adjuvant setting.[125-127] Ideal planning target volumes and dose remain inadequately characterized, however. Early experiences with IMRT seem to suggest that escalation of dose to subclinical sites of possible involvement (nodal regions outside the thyroid bed to 54 Gy), the margin-negative thyroid bed (60 Gy-63 Gy), margin-positive regions (66 Gy), and gross disease (70 Gy) is technically feasible without increasing toxicity.[125,127] One treatment is given each day, 5 days a week, 1.8 Gy to 2.0 Gy per treatment. Acute radiation reactions include dermatitis, laryngitis, pharyngitis, tracheitis, and esophagitis. Late sequelae are uncommon but may include laryngeal edema, cartilage necrosis, esophageal stenosis, myelitis, brachial plexopathy, and pulmonary fibrosis.

TREATMENT ALGORITHM, CONCLUSIONS, AND FUTURE POSSIBILITIES

Treatment Algorithm

The initial approach to a potentially malignant thyroid mass is to perform FNA biopsy. This technique permits the identification of patients with definite cancer or for whom there is a high degree of suspicion for malignancy. At initial operation (i.e., open biopsy, thyroid lobectomy, and near-total or total thyroidectomy), the surgeon can assess tumor size, determine the presence or absence of gross local invasion or regional lymph nodal metastasis, and define the postoperative status (i.e., presence or absence of gross residual disease). The surgical pathologist can identify the degree of tumor differentiation (i.e., histologic grade); the tumor histologic type; and, if requested, the DNA ploidy.

Typically, FCDC is treated by near-total or total thyroidectomy unless the primary tumor is 1 cm or less in diameter. MTC is treated by total thyroidectomy, whereas ATC and lymphoma probably require only an open biopsy for verification

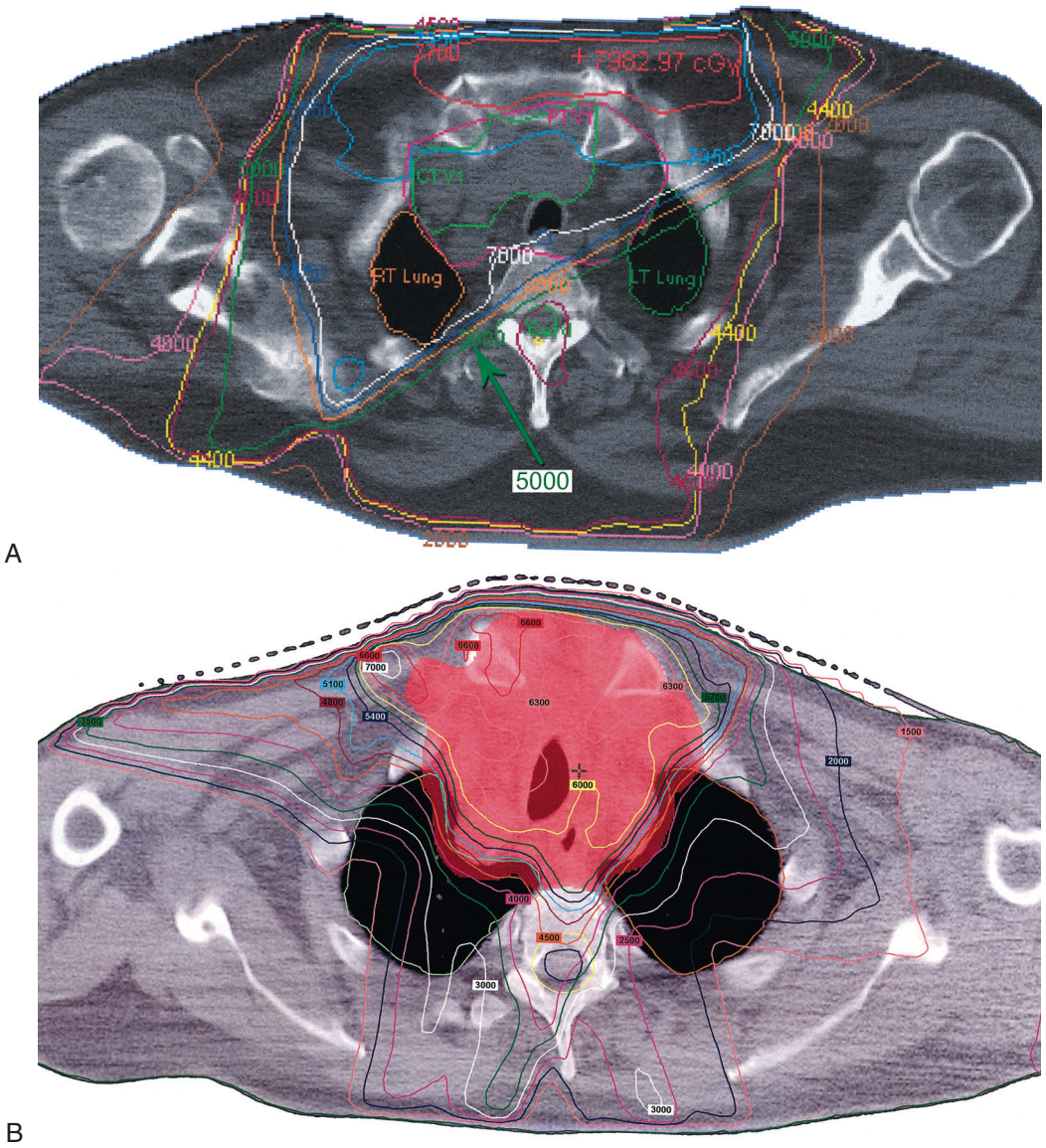


Figure 38-6 **A,** Three-dimensional treatment planning isodose curves for a patient with locally recurrent and progressive papillary thyroid carcinoma, deemed unresectable. Treatment uses anteroposterior fields followed by oblique fields to the left neck for a total dose of 70 Gy. **B,** Intensity-modulated radiotherapy (IMRT) treatment plan for a patient with resected recurrent Hürthle cell carcinoma. Treatment uses nine IMRT fields delivering 60 Gy to central lower neck and 54 Gy to lateral upper neck and mediastinum.

of diagnosis. Postoperatively, all patients undergoing more than a lobectomy require thyroid hormone therapy, but only patients with FCDC should receive TSH-suppressive doses of thyroxine.

Knowledge of patient age, cell type, pTNM stage, and postoperative status permits classification of patients into risk groups, which may influence the selection of subsequent postoperative adjuvant therapy. The treatment of patients with different tumor histologies is outlined in the following paragraphs and summarized as four steps in the accompanying treatment algorithm (Table 38-6).

Papillary Thyroid Carcinoma, Follicular Thyroid Carcinoma, and Hürthle Cell Carcinoma

Patients with FCDC with documented distant metastases (e.g., lung, bone) at presentation undergo RAI scanning 6 to 8 weeks postoperatively and are treated with ^{131}I therapy; the dose depends on the extent of metastases and avidity for RAI. Subsequent repeat whole body scans are performed at 3- to 6-month intervals until no further uptake is observed in the neck or distant sites. Serum thyroglobulin levels are obtained before RAI therapy and are closely monitored while on and off thyroxine to gauge progress in terms of tumor control.

Patients with unresectable or resected but residual FCDC are typically given the opportunity of whole-body scan and possible RAI therapy. If a whole-body scan reveals no significant uptake after therapy, a course of EBRT is considered.

Patients 45 years old or older with locally invasive disease usually are given RAI therapy. Some authorities consider the addition of EBRT, especially if serum thyroglobulin levels continue to be elevated despite apparently adequate treatment with RAI.

The role of remnant ablation in patients with intrathyroidal or node-positive PTC remains controversial. Use of the AGES,

TABLE 38-6 Treatment Algorithm

Step I	*Initial neck exploration/thyroid resection* FCDC: usually near-total or total thyroidectomy MTC: total thyroidectomy ATC: open biopsy or subtotal thyroidectomy Lymphoma: FNA or open biopsy Lymph nodes: removal of central compartment nodes in FCDC and MTC; modified radical neck dissection for involved lateral nodes
Step II	*Thyroid hormone therapy* Replacement doses for MTC, ATC, lymphoma TSH-suppressive doses for FCDC except microcarcinoma
Step III	*Outcome prediction by risk-group classification* Gauged according to age, stage, histologic type, and cancer type-specific scoring systems (e.g., AMES, MACIS)
Step IV	*Patient selection for RAI therapy, EBRT, chemotherapy, or combinations* FCDC: RAI therapy indicated for distant spread, unresectable or residual neck tumor, possibly invasive disease in PTC and most cases of FTC or HCC; EBRT for local or metastatic tumor nonresponsive to RAI therapy; almost no role for chemotherapy in differentiated FCDC MTC: residual or recurrent neck disease considered for EBRT; octreotide or chemotherapy considered for palliation only ATC: postbiopsy EBRT and concurrent chemotherapy Lymphoma: CHOP chemotherapy plus EBRT

AMES, *Age, metastasis, extent, and size;* ATC, *anaplastic thyroid cancer;* CHOP, *cyclophosphamide, hydroxydaunomycin, Oncovin (vincristine), prednisone; EBRT, external beam radiotherapy;* FNA, *fine-needle aspiration,* FCDC, *follicular cell–derived cancer;* FTC, *follicular thyroid carcinoma;* HCC, *Hürthle cell carcinoma;* MACIS, *metastasis, age, completeness of resection, invasion, and size;* MTC, *medullary thyroid carcinoma;* PTC, *papillary thyroid carcinoma;* RAI, *radioactive iodine;* TSH, *thyroid-stimulating hormone.*

AMES, or MACIS prognostic classifications may permit a more selective use of RAI. Generally, most patients with FTC or HCC undergo postoperative whole-body scans and are considered candidates for RRA. This may be an overaggressive position because the prognosis is excellent for minimally invasive FTC after surgery alone, and HCC usually does not avidly uptake RAI.

Medullary Thyroid Carcinoma

Because MTC may be bilateral and multicentric and because nodal metastases are common at presentation, most authorities recommend an initial surgical approach of total thyroidectomy, central compartment node removal, and possible modified radical neck dissection if the lateral neck is involved with disease. There is no role for TSH-suppressive or RAI therapy in this condition. Recurrent disease in the neck or mediastinum is typically treated by repeat surgical exploration. EBRT may have a role in local control if disease becomes unresectable, and it can be usefully employed in the treatment of osseous metastases, especially when vertebral deposits threaten the spinal cord. Combination chemotherapy has been used in stage IV MTC, as has subcutaneous octreotide therapy. These treatments have not been shown to improve CSS in disseminated, symptomatic MTC.

Anaplastic Thyroid Cancer

Usually only an open biopsy is performed at surgery when ATC is first diagnosed. More extensive initial resection should be considered if it can be achieved without significant morbidity. Most patients with ATC are given EBRT postoperatively, and many are given the option of concurrent chemotherapy during EBRT. There is no generally approved efficacious chemotherapeutic program available to patients with ATC.

Primary Thyroid Lymphoma

In contrast to the outlook for ATC, much greater optimism is expressed in managing primary thyroid lymphomas. There has been a gradual shift from subtotal thyroidectomy to open biopsy and FNA biopsy in diagnosing this condition. Recognition of the probably systemic nature of the disease led initially to an acceptance of the role of EBRT to the involved thyroid gland and regional nodes. More definitive data point to the use of combined-modality therapy in the management of this disease, typically combining R-CHOP chemotherapy with EBRT.

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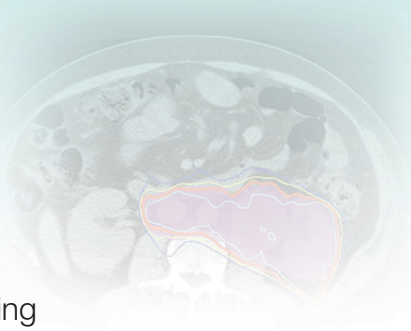
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CHAPTER

39 Unknown Head and Neck Primary Site



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INCIDENCE
Approximately 3% of head and neck squamous cell carcinomas metastasize to the neck from an unknown head and neck primary site.

BIOLOGIC CHARACTERISTICS
Biologic characteristics are similar to head and neck mucosal squamous cell carcinomas with known primary sites.

STAGING EVALUATION
Evaluation includes history and physical examination, computed tomography (CT) of the head and neck, chest radiography, direct laryngoscopy with ipsilateral tonsillectomy, and directed biopsies. Optional studies include chest CT and positron emission tomography (PET).

PRIMARY THERAPY AND RESULTS
Therapy consists of neck dissection to the involved neck or radiotherapy (RT) to the neck, oropharynx, and nasopharynx if RT is indicated for treatment of neck disease. The 5-year survival is approximately 50%.

ADJUVANT THERAPY
Concomitant cisplatin chemotherapy is administered for N2 and N3 neck disease and for close and positive margins or extracapsular extension following an initial neck dissection.

LOCALLY ADVANCED DISEASE
RT is administered to the oropharynx, nasopharynx, and both sides of the neck with concomitant chemotherapy followed by evaluation for a neck dissection.

PALLIATION
Moderate dose RT (30 Gy/10 fractions or 20 Gy/2 fractions with a 1-week interfraction interval) is administered to the involved neck.

In a small percentage of patients with squamous cell carcinoma metastatic to the cervical lymph nodes, the primary lesion cannot be found, even after an extensive evaluation. Patients with metastatic adenopathy in the upper neck have a good prognosis when treated aggressively, compared with those with metastatic lymph nodes in the level IV nodes or supraclavicular fossa.[1] The latter group is more likely to have a primary lesion located below the clavicles and the probability of cure is remote. Most patients have either squamous cell carcinoma or poorly differentiated carcinoma. Patients with adenocarcinoma almost always have a primary lesion below the clavicles, although if the nodes are located in the upper neck, one must exclude a salivary gland, thyroid, or parathyroid primary tumor.

This chapter addresses the management of patients presenting with squamous cell or poorly differentiated carcinoma in the upper or middle neck. Squamous cell carcinoma presenting in a parotid area lymph node is almost always metastatic from a cutaneous primary site and will not be addressed.[2]

DIAGNOSTIC EVALUATION

Patients should be evaluated with a thorough physical examination including careful evaluation of the head and neck by multiple examiners. A needle biopsy of the lymph node should be performed; fine-needle aspiration (FNA) is preferred to a biopsy because it is less traumatic, and there is a lower likelihood of seeding tumor cells along the needle track.[3-7] Evaluation of the neck node biopsy for Epstein-Barr virus (EBV) DNA, via polymerase chain reaction, may be useful in detecting a nasopharyngeal primary tumor in geographic areas where this malignancy is prevalent.[8] Similarly, evaluation of the biopsy for high-risk human papilloma virus (HR-HPV) may be useful for detecting an oropharyngeal carcinoma.[9] Most occult primary cancers that are detected in the United States are in the oropharynx so that, depending on the situation, testing in the biopsy for HR-HPV may be useful for determining the aggressiveness of the treatment plan.[10] HPV-positive oropharyngeal cancers have a better prognosis, and it may be possible to eliminate concomitant chemotherapy or use a lower RT dose. The necessity of adding a neck dissection may also be lower.

After chest roentgenography, CT or magnetic resonance imaging (MRI) of the head and neck is obtained to detect an unknown primary lesion arising from the mucosa of the head and neck. We use CT initially and follow with MRI only in cases with equivocal findings in which MRI might yield additional useful information, such as a suspected primary site in the nasopharynx. A complete blood count is obtained to evaluate the patient for anemia, which may reduce the likelihood of local regional control after irradiation alone. A chest CT should be considered for patents with N3 neck disease, as well as those with N2b to N2c disease and bulky adenopathy in the low neck, to assess the lungs for pulmonary metastases.[11] The recommended diagnostic algorithm is depicted in Box 39-1.[12]

Preliminary evidence suggested that fluorodeoxyglucose (FDG) single-photon-emission computed tomography (SPECT) or PET scans may identify primary lesions that would not otherwise be identifiable.[13,14] Theoretically, tumor cells have a higher metabolic rate than normal tissues, and therefore, take up more FDG so that they appear "hot" on a PET or SPECT scan. If an FDG-SPECT or PET scan is obtained as part of the workup, it should be performed before panendoscopy so that any suspicious areas of increased uptake can be biopsied.

BOX 39-1 Diagnostic Algorithm

GENERAL

History
Physical examination
Careful examination of the neck and supraclavicular regions
Examination of oral cavity, pharynx, and larynx (indirect laryngoscopy with a flexible endoscope)

RADIOGRAPHIC STUDIES

Chest roentgenogram
Computed tomography (CT) or magnetic resonance imaging (MRI) scans of head and neck (special attention to nasopharynx, pharynx, and larynx)

LABORATORY STUDIES

Complete blood cell count
Blood chemistry profile

DIRECT ENDOSCOPY AND DIRECTED BIOPSIES

Nasopharynx, both tonsils, base of tongue, both pyriform sinuses, and any suspicious or abnormal mucosal areas
Ipsilateral tonsillectomy
Fine needle aspirate (FNA) or core-needle biopsy of the cervical node

From Mendenhall WM, Parsons JT, Mancuso AA, et al: Head and neck: management of the neck. In Perez CA, Brady LW, editors: Principles and practice of radiation oncology, ed 3, Philadelphia, 1998, J. B. Lippincott, pp 1135-1156.[12] [Table 44-20, p 1152]

TABLE 39-1 Detection of the Primary Site on FDG-SPECT

Patient Group	FDG-SPECT Negative*	FDG-SPECT Positive*
PEØ/RadØ	No data	1/5
PE+ or Rad+	2/6	6/15 (40.0%)
Total	2/6	7/20 (35.0%)

From Cianchetti M, Mancuso AA, Amdur R, et al: Diagnostic evaluation of squamous cell carcinoma metastatic to cervical lymph nodes from an unknown head and neck primary site. Laryngoscope 119(12):2348-2854, 2009.
PEØ, Physical exam negative; PE+, physical exam suspicious, not definitely positive; radø, radiological exam negative; rad+, radiological exam (CT or MR) suspicious, not definitely positive.
**Number of primaries detected/number of patients.*

TABLE 39-2 Detection of the Primary Site by FDG-PET or FDG-PET/CT

Patient Group	FDG-PET Negative*	FDG-PET Positive*
PEØ/RadØ	3/4	No data
PE+ or Rad+	8/12	3/5
Total	11/16 (68.8%)	3/5 (60%)

From Cianchetti M, Mancuso AA, Amdur R, et al: Diagnostic evaluation of squamous cell carcinoma metastatic to cervical lymph nodes from an unknown head and neck primary site. Laryngoscope 119(12):2348-2354, 2009.
PEØ, Physical exam negative; PE+, physical exam suspicious, not definitely positive; RadØ, radiological exam negative; Rad+, radiological exam (CT or MR) suspicious, not definitely positive.
**Number of primaries detected/number of patients.*

TABLE 39-3 Detection of a Primary Site versus Patient Group

Patient Group	Biopsy-Proven Primary Site/No. Pts (%)
PEØ/RadØ	21/72 (29.2%)
PEØ/Rad+	51/82 (62.2%)
PE+/RadØ	15/25 (60.0%)
PE+/Rad+	39/57 (68.4%)
Total	126/236 (53.4%)

From Cianchetti M, Mancuso AA, Amdur R, et al: Diagnostic evaluation of squamous cell carcinoma metastatic to cervical lymph nodes from an unknown head and neck primary site. Laryngoscope 119(12):2348-2354, 2009.
PEØ, Physical exam negative; PE+, physical exam suspicious, not definitely positive; RadØ, radiological exam negative; Rad+, radiological exam (CT or MR) suspicious, not definitely positive.

Limited data pertaining to the usefulness of FDG-SPECT and FDG-PET scans suggest these procedures may identify the primary site in a relatively small subset of patients.[15-17] The FDG-SPECT scan was the sole procedure that correctly identified the occult primary site in only 1 of 26 patients (4%) at our institution (Table 39-1).[10] Similarly, FDG-PET was the only means of detecting a primary site in none of 21 patients at the University of Florida (Table 39-2).[10] Currently, FDG-PET-CT scans are not routinely obtained at our institution as part of the diagnostic evaluation of these patients. When obtained, they may be useful in detecting distant metastases in patients with advanced neck disease and for evaluating suspicious cervical lymph nodes in areas that would otherwise not receive definitive RT, as opposed to a moderate dose employed for suspected subclinical disease.

Direct laryngoscopy with fiberoptic endoscopic visualization under general anesthesia is performed with directed biopsies of the nasopharynx, tonsils, base of tongue, and pyriform sinuses, and of any abnormalities noted on CT or MRI or suspicious mucosal lesions observed during endoscopy. A subset of patients will have the primary tumor site discovered at direct laryngoscopy. The likelihood of discovering the primary site is related to whether or not a suspected (but not definite) primary site is discovered on physical examination or radiographic evaluation (Table 39-3).[10] Most suspected primary sites are detected by pretreatment radiographic workup as opposed to physical examination.

An ipsilateral[10,15,18] tonsillectomy should be performed in patients who have not had a prior tonsillectomy and who have adequate lymphoid tissue remaining in the tonsillar fossa. Although some authors recommend a bilateral tonsillectomy,[19] the likelihood of finding the primary site in the contralateral tonsil for patients with ipsilateral neck nodes is probably quite low. Lapeyre et al[18] reported 87 patients who were evaluated between 1969 and 1992 and underwent a unilateral tonsillectomy; 26% of patients were found to have a tonsillar cancer. Seventy-nine of 236 patients who were evaluated as the University of Florida underwent a tonsillectomy at the time of direct laryngoscopy; the primary site was detected in the tonsil in 35 patients (44%).[10] The likelihood of detecting the primary site was related to whether there were suspicious findings on physical examination or radiographic evaluation (Table 39-4).[10]

Fifty-eight primary head and neck cancers were found in 126 of 236 patients (53%) in the University of Florida series.[10] The most common primary sites were tonsillar fossa (59 patients, 45%) and base of tongue (58 patients, 44%).[10] The reason for the decreased likelihood of detecting cancers in other sites may be that they are found on physical examination with fiberoptic endoscopy and on radiographic evaluation.[7,20,21] In contrast, it is still difficult to discern a small primary cancer hidden in the lymphoid tissue of the tonsillar fossa or tongue base.

PRIMARY THERAPY AND RESULTS

Treatment Techniques and Algorithm

Treatment options range from treatment of the involved neck alone with a neck dissection or RT to irradiation of the suspected primary site and both sides of the neck followed by evaluation for a planned neck dissection.[22-24] Although treatment of the potential mucosal primary site and contralateral neck appears to reduce the risk of a local regional recurrence, the impact on survival is modest at best. Therefore, patients with a single positive node without extracapsular extension may be treated with a neck dissection alone and followed closely, provided that the neck was not violated with an open procedure prior to surgery.[25-27]

If RT is indicated to treat the involved neck, we usually irradiate the nasopharynx and oropharynx, as well as both sides of the neck (Figure 39-1, *A*).[1] Although it may be tempting to irradiate the involved neck alone or combined with RT to the ipsilateral mucosal sites deemed to be at risk, the base of tongue is a midline structure that probably harbors the undetected primary site as often as the tonsillar fossa, so it has been our policy to treat the entire oropharynx.[28] Failure to do so is likely associated with an increased risk of a local regional recurrence and further RT would be complicated by the initial treatment.[29] It is not necessary to irradiate the oral cavity unless the patient has submandibular (level I) adenopathy, in which case we either do a neck dissection and observe the patient or irradiate the oral cavity and oropharynx. At one

TABLE 39-4 Detection of the Primary Site on Tonsillectomy

Patient Group	No. of Patients with Pathologically Proven Site in Tonsillar Fossa/ No. Patients Having Tonsillectomy
PEØ/RADØ*	9/22 (41.1%)
PE+ and/or RAD+*	26/57 (45.6%)
Total	35/79 (44.3%)

From CianchettiM, Mancuso AA, Amdur R, et al: Diagnostic evaluation of squamous cell carcinoma metastatic to cervical lymph nodes from an unknown head and neck primary site. Laryngoscope 119(12):2348-2354, 2009.
PEØ, Physical exam negative; PE+, physical exam suspicious, not definitely positive; RadØ, radiological exam negative; Rad+, radiological exam (CT or MR) suspicious, not definitely positive.
**Radiographic evaluation = CT or MRI with or without FDG-SPECT or FDG-PET or FDG-PET/CT.*

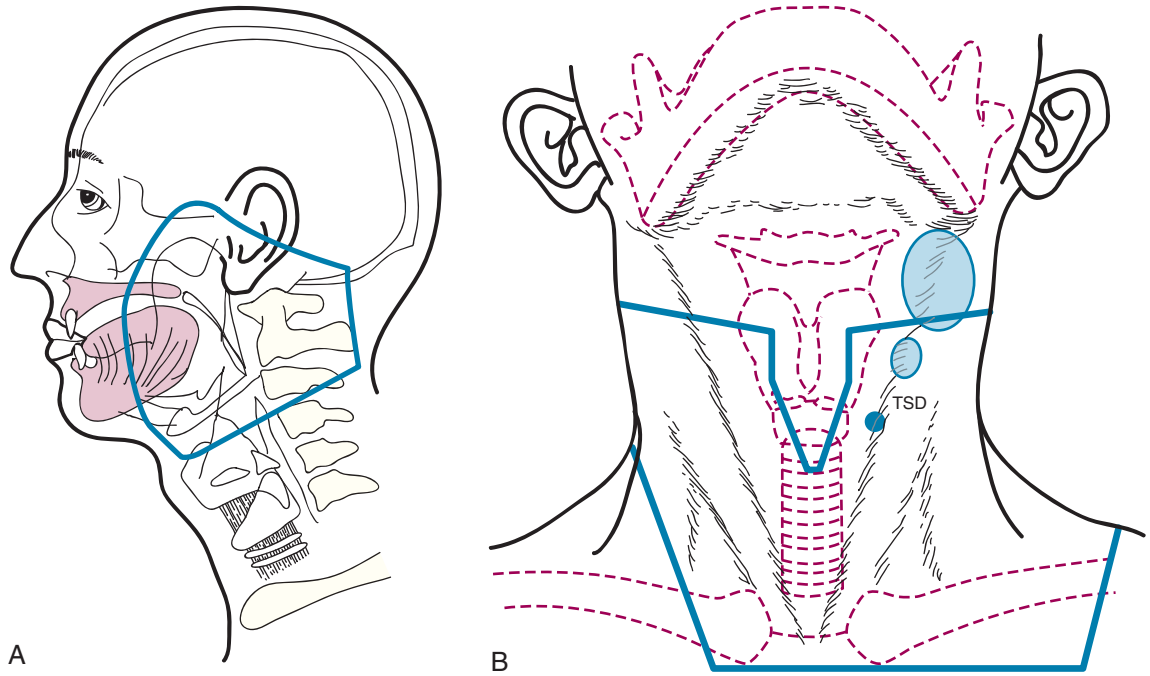


Figure 39-1 **A,** Radiation treatment technique for carcinoma from an unknown primary site. Superiorly, the portal treats the nasopharynx and the jugular (level II) and spinal accessory (level V) lymph nodes to the base of skull. The posterior border is behind the spinous process of C2. The inferior border is at the thyroid notch. Antero-inferiorly, the skin and subcutaneous tissues of the submentum are shielded, except in the case of advanced neck disease. The anterior tongue margin is set so as to obtain a 2-cm margin on the base of tongue and tonsillar fossa, as well as the nasopharynx. One portal reduction is shown (reduce off spinal cord). **B,** Fields for bilateral lower neck radiotherapy. The larynx shield should be carefully designed. Because the internal jugular vein lymph nodes (level III) lie adjacent to the posterolateral margin of the thyroid cartilage, the shield cannot cover the entire thyroid cartilage without producing a low-dose area in these nodes. A common error in the treatment of the lower neck is to extend the low neck portal laterally out to the shoulders, encompassing lateral supraclavicular lymph nodes that are at negligible risk while partially shielding the high-risk midjugular lymph nodes with a large rectangular laryngeal block. The inferior extent of the shield is at the cricoid cartilage or first or second tracheal ring; the shield must be tapered because the nodes tend to lie closer to the midline as the lower neck is approached. Lateral borders of the low-neck portals are set to cover only the lymph nodes in the root of the neck when the risk of low-neck disease on that side is small (i.e., stage N0 or N1 disease). If there are clinically positive lymph nodes in the lower neck or if major disease is present in the upper neck, the lateral border of the low-neck field is widened on that side to cover the entire supraclavicular region out to the junction of the trapezius muscle with the clavicle. *TSD,* Target-to-skin distance.
***A,** From Mendenhall WM, Mancuso AA, Amdur RJ, et al: Squamous cell carcinoma metastatic to the neck from an unknown head and neck primary site. Am J Otolaryngol 22(4):261-267, 2001. **B,** From Million RR, Cassisi NJ, Mancuso AA, et al: Management of the neck for squamous cell carcinoma. In Million RR, Cassisi NJ, editors: Management of head and neck cancer: A multidisciplinary approach, ed 2, Philadelphia, 1994, J. B. Lippincott Company, pp 75-142.*

time, it was our policy to irradiate the larynx and hypopharynx, but because the likelihood of a primary tumor in these sites is low, and because the morbidity of irradiating these areas is significant, we modified our technique in approximately 1997.[28] It could be argued that the nasopharynx should also be eliminated from the primary treatment volumes. However, the incidence of positive retropharyngeal nodes is relatively high in patients presenting with advanced neck disease[30] so that the volumes must include the skull base (jugular foramen and retropharyngeal nodes) and at least part of the nasopharynx. It is our belief that a modest increase in the size of the treatment volumes to adequately irradiate the nasopharynx does not significantly increase morbidity.

Patients are treated with parallel-opposed fields at 1.8 Gy per fraction to a midline dose of 64.8 Gy with reduction off the spinal cord at 45-Gy tumor dose (see Figure 39-1, *B*).[31] The lower neck is treated through a separate en face anterior field. Treatment is administered with cobalt-60, 4-MV x-rays, or 6-MV x-rays. Dosimetry is obtained at the level of the central axis (which usually corresponds to the oropharynx) and the nasopharynx. The dose to the nasopharynx is usually 3 Gy to 5 Gy lower than the central axis. Currently, the majority of radiation oncologists obtain a multilevel three-dimensional dosimetric analysis to evaluate the dose delivered to the clinical target volume (CTV), planning target volume (PTV), and organs at risk (OARs). Patients with ipsilateral nodes may be treated with intensity-modulated radiotherapy (IMRT) to reduce the dose to the contralateral parotid (≤26 Gy mean dose) to reduce the likelihood of long-term xerostomia. Patients with bilateral-positive nodes are better treated with parallel-opposed fields to reduce the risk of a marginal miss.[32] Patients with advanced, fixed adenopathy undergo a boost to the involved part of the neck using anteroposterior wedged beams to a total dose in the range of 70 Gy to 75 Gy. Concomitant chemotherapy should be considered for patients with N2 and N3 neck disease. Our preference is to use weekly cisplatin (30 mg/m^2) or cisplatin 100 mg/m^2 every 3 weeks for two cycles.[33]

Treatment of the neck depends on the extent and location of the adenopathy. Patients with N1 and early N2B neck disease located in the high-dose fields may be treated with irradiation alone if the nodes have resolved completely.[34-36] Similarly, if the patient has undergone an excisional biopsy of a single positive node, the neck may be treated with radiation alone with a 95% likelihood of neck control.[37] Patients undergo a CT scan of the neck 1 month after completing RT at our institution and the decision whether to proceed with neck dissection depends on the likelihood that viable tumor remains in the neck.[38-40] The criteria employed for determining whether a neck dissection should be performed are outlined in Table 39-5.[38,40] Because the likelihood of cure is low if a regional recurrence develops in a clinically positive neck after treatment with radiotherapy alone, we usually proceed with a modified neck dissection if the risk of residual disease exceeds 5%.[41] In practice, patients with N2-N3 neck disease and those with gross disease neck disease after an open neck biopsy often undergo a planned neck dissection after radiation therapy.[36,42]

The treatment algorithm is depicted in Figure 39-2.

Results

One hundred thirty-six patients were treated at the M. D. Anderson Hospital between 1968 and 1992 and had a median duration of follow-up of 8.7 years.[43] Both sides of the neck and potential head and neck mucosal primary sites were irradiated. A mucosal head and neck cancer developed in 14 patients (10%); 6 of the 14 cancers were located in unirradiated sites. Recurrent disease in the neck developed in 12 patients (9%). The 5-year cause-specific survival rate was 74%.

The incidence of subsequent mucosal primary lesions was compared by Erkal et al[44] for patients with a known primary site and a series of 126 patients treated for an unknown primary site at the University of Florida. The incidence for both groups was similar at 5 years, suggesting either that mucosal irradiation significantly reduced the risk of primary site failure or that patients with unknown primary sites have a much lower risk of a second primary head and neck cancer developing subsequently (Figure 39-3).[44] The 5-year absolute and cause-specific survival rates for the 126 patients with an unknown primary were 47% and 67%, respectively. The 5-year outcomes stratified by N-category are shown in Figures 39-4, *A-D*.[44]

Reddy and Marks[29] reported 52 patients treated to the neck alone (16 patients) or to the neck and potential head and neck primary sites (36 patients). Failure in the head and neck mucosa occurred in 44% of those who underwent treatment to the neck alone, compared with 8% in those who underwent irradiation of the head and neck mucosa ($p = 0.0005$). The 5-year survival rates were similar for the two treatment groups.

Grau et al[45] reported 273 patients treated with curative intent at five cancer centers in Denmark between 1975 and 1995 with surgery alone (23 patients), RT to the ipsilateral neck alone or combined with surgery (26 patients), and RT to the neck and head and neck mucosa alone or combined with

TABLE 39-5 Predictive Value of Postradiotherapy CT Findings at 4 Weeks in the Hemi-Neck Correlated to Neck Dissection Pathology (n = 193 Hemi-Necks)

	NPV		PPV	
Finding	**No./Total No.**	**%**	**No./Total No.**	**%**
Any lymph node >1.5 cm	85/118	72	24/75	32
Any focally abnormal lymph node*	49/57	86	49/136	36
Any lymph node with focal lucency	75/98	77	34/95	36
Any lymph node enhancement	111/147	76	21/46	46
Any lymph node with calcification	102/144	71	15/49	31
Two or more focally abnormal lymph nodes*	90/113	80	34/80	43
Any lymph node >1.5 cm and any focally abnormal lymph node	32/34	94	55/159	35

From Liauw SL, Mancuso AA, Amdur RJ, et al: Postradiotherapy neck dissection for lymph node-positive head and neck cancer: The use of computed tomography to manage the neck. J Clin Oncol 24:1421–1427, 2006.

CT, *computed tomography;* NPV, *negative predictive value;* PPV, *positive predictive value.*

**Focally abnormal lymph node = grades 3 to 4 focal lucency, focal enhancement, or focal calcification.*

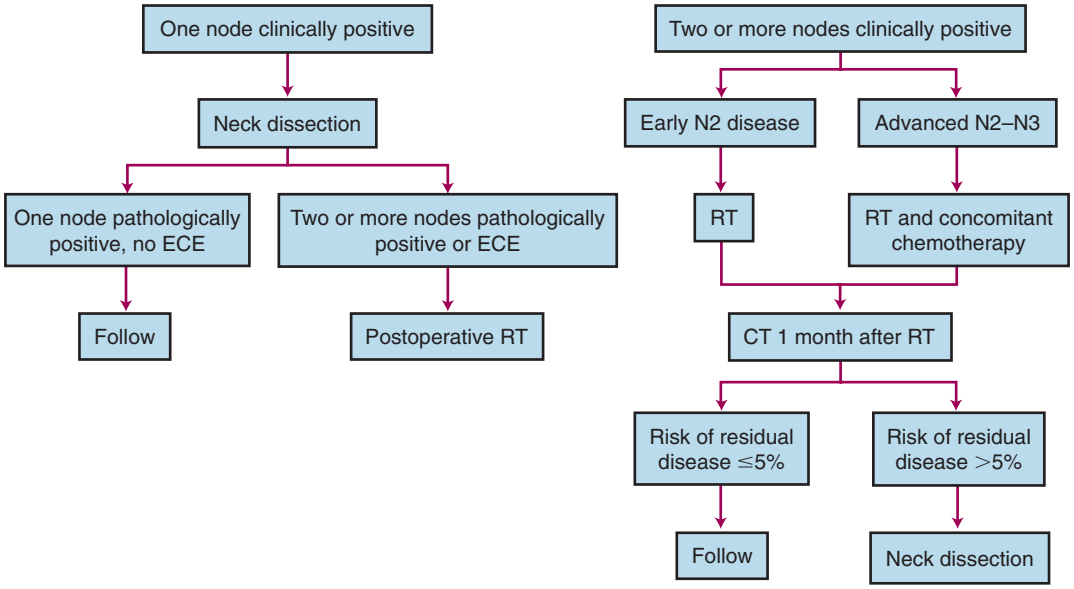


Figure 39-2 **Treatment algorithm.** *CT,* Computed tomography; *ECE,* extracapsular extension; *RT,* radiotherapy.

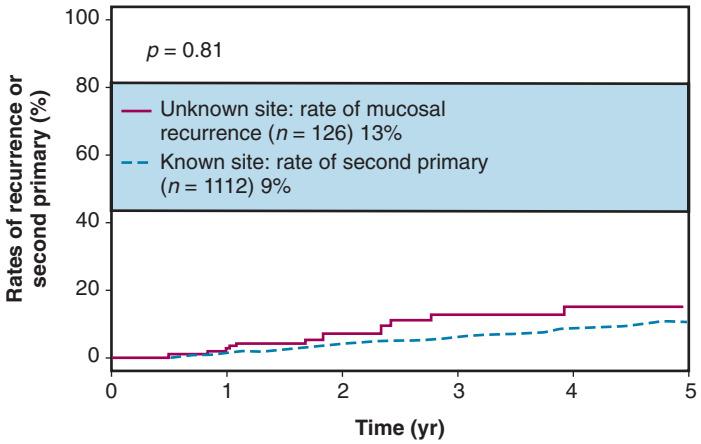


Figure 39-3 The rate of developing carcinomas in head and neck mucosal sites for patients treated for carcinomas with an unknown head and neck mucosal site compared to the rate for developing metachronous carcinomas in head and neck mucosal sites for patients treated for carcinomas with a known head and neck mucosal site.
From Erkal HS, Mendenhall WM, Amdur RJ, et al: Squamous cell carcinomas metastatic to cervical lymph nodes from an unknown head-and-neck mucosal site treated with radiation therapy alone or in combination with neck dissection. Int J Radiat Oncol Biol Phys 50(1):55-63, 2001.[44]

surgery (224 patients). The ipsilateral oropharynx unintentionally received some irradiation in patients treated to the ipsilateral neck alone, depending on the treatment technique.[45] The 5-year rates of freedom from failure in the head and neck mucosa were as follows: surgery alone, 45%; RT with or without surgery to the ipsilateral neck, 77%; and RT to the head and neck mucosa with or without surgery 87%. Failure in the oropharynx, particularly the base of tongue, was the most common location of mucosal site failure.

Complications

The main complication of radiation therapy for patients treated for an unknown head and neck primary tumor is xerostomia. The likelihood of long-term problems with altered taste or difficulty swallowing is relatively low. IMRT may be used to reduce the dose to the contralateral parotid gland so long as the patient does not have bilateral clinically positive neck nodes. It is difficult to limit the dose to the parotid if there are positive nodes in the same side of the neck without risking underdosing the adenopathy and increasing the risk of a marginal miss.[32] The risk of bone exposure, radiation myelitis, or radiation-induced malignancy is low.

The complications of neck irradiation include subcutaneous fibrosis and lymphedema of the larynx and submentum. The latter complications may be minimized by sparing an anterior strip of skin when designing the parallel-opposed lateral portals used to encompass the suspected primary site. This will also reduce the risk of desquamation, particularly in patients who receive concomitant chemotherapy. A 5-mm-wide midline block in the en face low-neck field may also diminish the likelihood of postirradiation edema. The probability of complications is directly related to radiation dose and volume.

Complications of neck dissection include hematoma, seroma, lymphedema, wound infection, wound dehiscence, chyle fistula, damage to cranial nerves VII, X, XI, and XII, carotid exposure, and carotid rupture. The incidence of complications after neck dissection is probably higher when the operation follows a course of radiation therapy.

The incidence of postoperative complications in a series of 143 patients treated with radiation to the primary lesion and neck followed by unilateral neck dissection was 23%.[36] Seventeen patients (12%) required a second operation and four patients (3%) experienced fatal complications.[36] The incidence of complications was higher for maximum subcutaneous doses higher than 60 Gy. Taylor et al[46] updated the University of Florida experience with an analysis of the incidence of moderate (2+) and severe (3+) wound complications in a series of 205 patients who underwent a planned unilateral neck

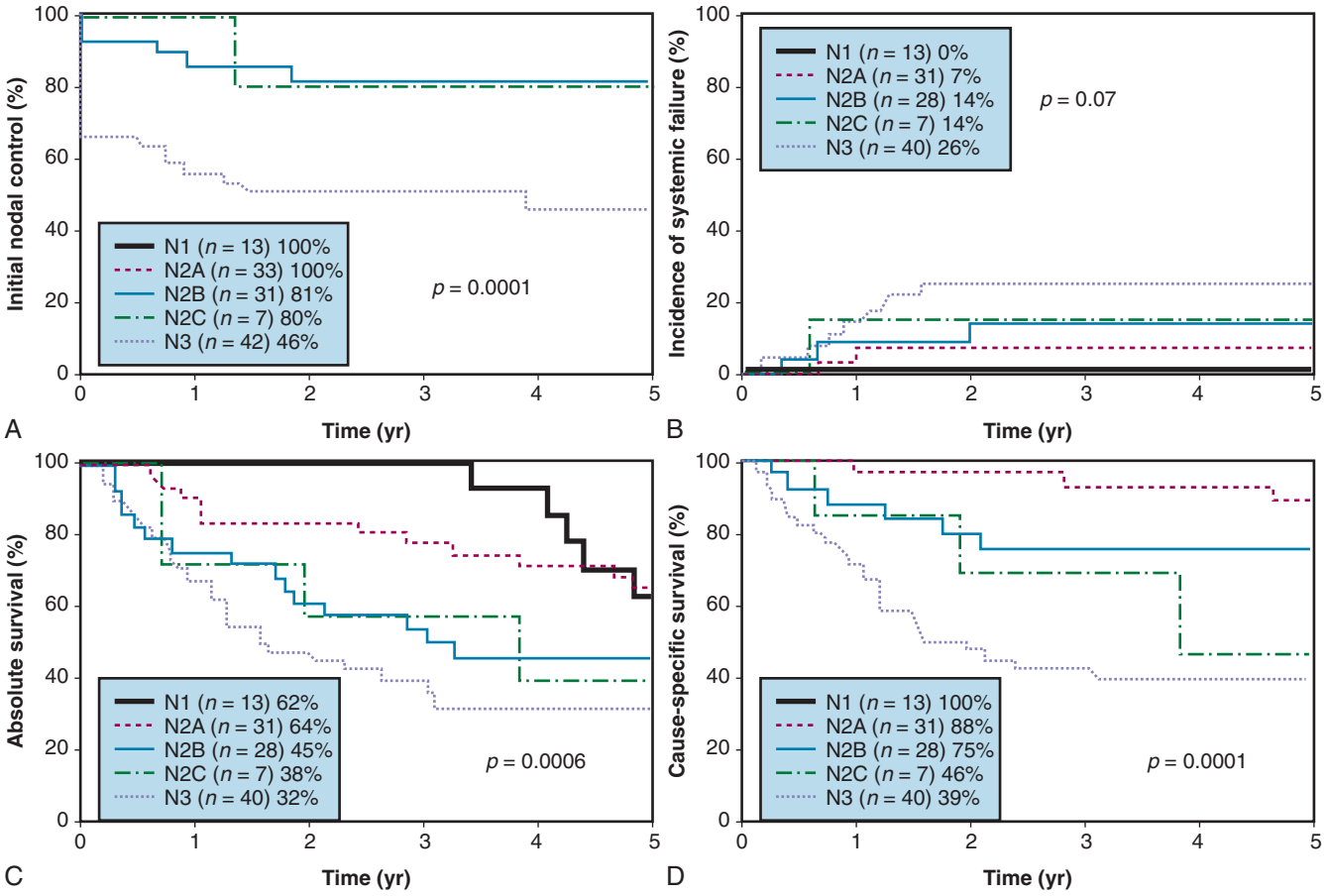


Figure 39-4 Disease and survival outcomes according to N category after initial treatment. **A,** Nodal control rates. **B,** Systemic failure (distant metastases). **C,** Absolute survival. **D,** Cause-specific survival.
From Erkal HS, Mendenhall WM, Amdur RJ, et al: Squamous cell carcinomas metastatic to cervical lymph nodes from an unknown head-and-neck mucosal site treated with radiation therapy alone or in combination with neck dissection. Int J Radiat Oncol Biol Phys 50(1):55-63, 2001.[44]
[Figure 3-6, pp 58–60]

dissection after radiation therapy. Radiation therapy was given once daily in 123 patients, twice daily in 80 patients, and with both techniques in the remaining 2 patients. The incidence of wound complications tended to increase with total dose and dose per fraction.

CONCLUSIONS

The diagnostic evaluation of patients with squamous cell carcinoma of the head and neck from an unknown primary site includes multiple head and neck examinations by experienced examiners, FNA of the neck node, CT from the skull base to the clavicles, direct laryngoscopy and biopsies, and an ipsilateral tonsillectomy. The primary site will be detected in approximately 40% to 50% of patients and will be located in the oropharynx in more than 80% of patients. The management of these patients is controversial. Treatment usually includes irradiation of both sides of the neck (levels II, III, IV, and V) and the potential mucosal primary sites. The likelihood of 5-year survival is approximately 50% and is related to the extent of disease in the neck.

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CHAPTER

40 Management of the Neck

Vincent Grégoire, Thierry P. Duprez, Benoît Lengelé, and Marc Hamoir

Assessment and treatment of regional lymph nodes in the neck are of utmost importance in the management of patients with head and neck squamous cell carcinoma (HNSCC). The philosophy of treatment of the neck has evolved over the past several decades. Radiation oncologists and head and neck surgeons progressively realized that extensive treatments were associated with more morbidity but not always with a better oncologic outcome than less extensive procedures. Today, a comprehensive approach to the treatment of the neck needs to be multidisciplinary, taking into account the patient's quality of life without jeopardizing cure and survival. A better understanding of the patterns of lymph node metastasis promoted the use not only of selective dissection but also of selective irradiation in selected patients. Concepts are still evolving; for example, the need and extent of postconcomitant chemoradiation neck node dissection continues to be evaluated.

In this chapter, the discussion will be limited to management of the neck for oral cavity, oropharyngeal, hypopharyngeal, and laryngeal squamous cell carcinoma.

ANATOMY OF THE LYMPHATIC SYSTEM OF THE NECK

The head and neck region has a rich network of lymphatic vessels draining from the base of the skull through the jugular nodes, spinal accessory nodes, and transverse cervical nodes to the venous jugulosubclavian confluence or the thoracic duct on the left side and the lymphatic duct on the right side.[1,2] A comprehensive anatomic description of this network was made by Rouvière more than 50 years ago.[1] The whole lymphatic system of the neck is contained in the celluloadipose tissue delineated by the aponeurosis enveloping the muscles, vessels, and nerves (Figure 40-1). The lymphatic drainage is mainly ipsilateral, but structures such as the soft palate, tonsils, base of the tongue, posterior pharyngeal wall, and especially the nasopharynx have bilateral drainage. On the other hand, sites such as the true vocal cord, paranasal sinuses, and middle ear have few or no lymphatic vessels at all. The nomenclature of head and neck lymph nodes has been complicated by various confusing synonyms that are still in use in major textbooks and articles. Several expert bodies have proposed the adoption of systematic classifications aimed at standardizing the terminology. Following the description by Rouvière, the TNM (primary tumor, regional nodes, metastases) atlas proposed a terminology that divides the head and neck lymph nodes into 12 groups.[3] In parallel to this classification, the Committee for Head and Neck Surgery and Oncology of the American Academy for Otolaryngology–Head and Neck Surgery has been working on a classification (the so-called Robbins classification), dividing the neck into six levels, including 8 node groups.[4] This classification is based on the description of a level system that has been used for a long time by the Head and Neck Service at the Memorial Sloan Kettering Cancer Center (MSKCC).[5] Because one of the objectives in developing the Robbins classification was to create a standardized system of terminology for neck dissection procedures, only the lymph node groups routinely removed during neck dissection were considered. The terminology proposed by Robbins was recommended by the International Union Against Cancer (UICC).[6] Recently a task force comprising worldwide opinion leaders in the field of head and neck radiation oncology reviewed and updated the previously published guidelines on nodal level delineation, and came up with a proposal corresponding more closely with the TNM atlas (Table 40-1).[7] The major advantage of this new proposal (the so-called modified from Robbins classification) over the TNM terminology is the definition of the boundaries of the node levels. The delineation of these boundaries is based on anatomic structures such as major blood vessels, muscles, nerves, bones, and cartilage that are easily identifiable on computed tomography (CT) or magnetic resonance (MR) axial imaging sections. The anatomic boundaries are oriented to a patient lying in a supine position with the neck in a neutral position.

Level Ia is a unique median region that contains the submental nodes. The lymph nodes are located in a triangular region limited anteriorly by the platysma muscle, posteriorly by the mylohyoid muscles, cranially by the symphysis of the mandible, caudally by the hyoid bone, and laterally by the anterior belly of the digastric muscle. The medial limit of level Ia is virtual because the region continues into the contralateral level Ia. Nodes in level Ia drain the skin of the chin, mid lower lip, tip of the tongue, and anterior floor of the mouth. Level Ia is at greatest risk for harboring metastases from cancer arising from the floor of the mouth, anterior oral tongue, anterior mandibular alveolar ridge, and lower lip. *Level Ib* contains the submandibular nodes located in the space between the inner side of the mandible laterally and the digastric muscle medially, from the symphysis menti anteriorly to the submandibular gland posteriorly. The submandibular nodes receive efferent lymphatics from the submental lymph nodes, lower nasal cavity, hard and soft palate, maxillary and mandibular alveolar ridges, cheek, upper and lower lips, and most of the anterior tongue. Nodes in level Ib are at risk for developing metastases from cancers of the oral cavity, anterior nasal cavity, soft-tissue structures of the mid-face, and submandibular gland.

Level II contains the upper jugular lymph nodes located around the upper one third of the internal jugular vein (IJV) and upper spinal accessory nerve. It extends from the insertion of the posterior belly of the digastric muscle to the mastoid cranially to the carotid bifurcation (a surgical landmark) or the caudal border of the body of the hyoid bone (a clinical landmark) caudally. Level II can be further subdivided into level IIa and IIb by the posterior edge of the internal jugular vein. Level II receives efferent lymphatics from the face, parotid gland, and submandibular, submental, and retropharyngeal nodes. Level II also directly receives the collecting lymphatics from the nasal cavity, pharynx, larynx, external auditory canal, middle ear, and sublingual and submandibular glands. The nodes in level II are therefore at greatest risk for harboring metastases from cancers arising from the nasal cavity, oral cavity, nasopharynx, oropharynx, hypopharynx, larynx, and major salivary glands. Level IIb is more likely associated with primary tumors arising in the oropharynx or nasopharynx and

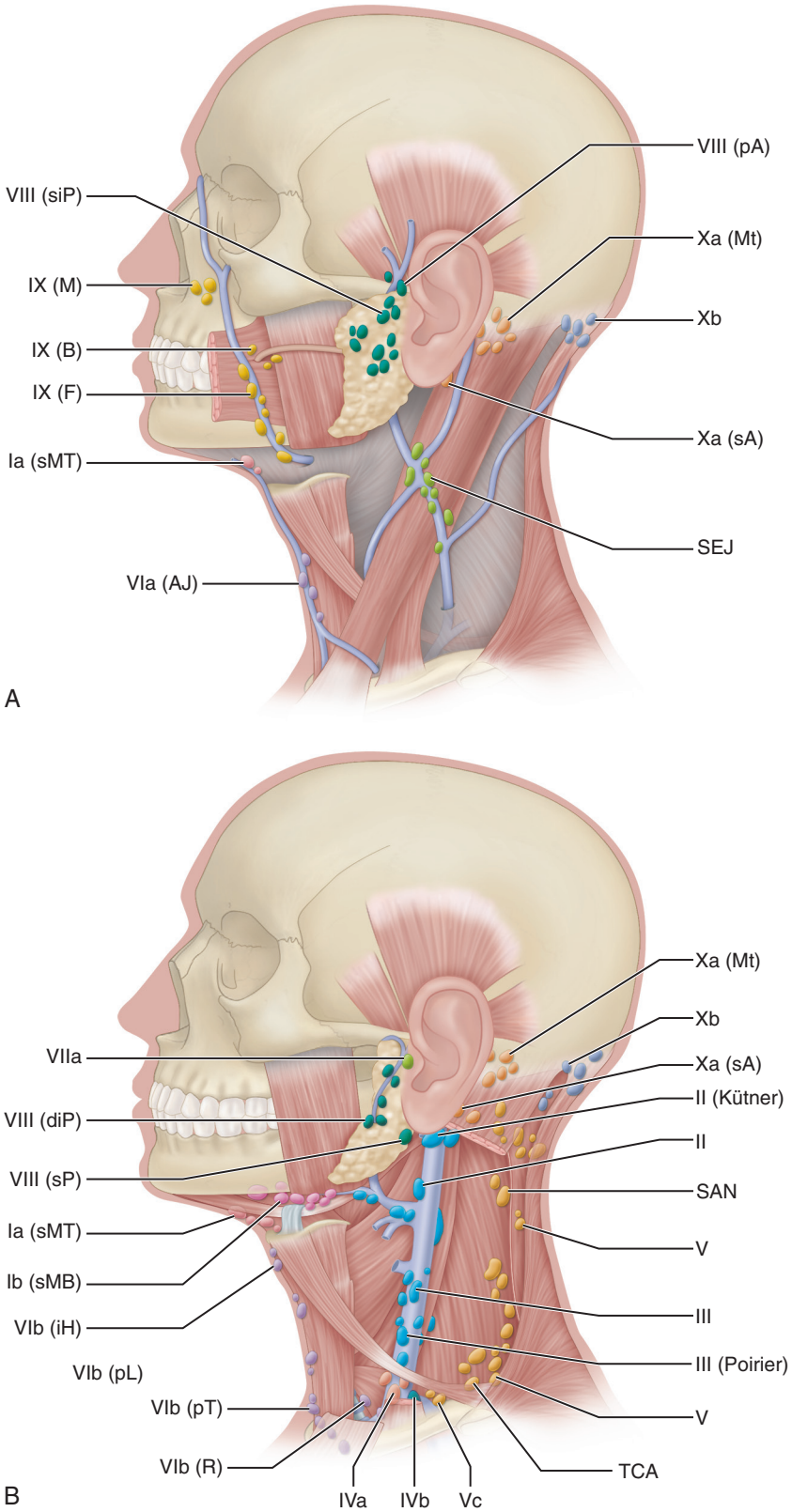


Figure 40-1 Superficial *(top)* and deep *(bottom)* lymphatic node groups of the head and neck. *AJ,* Anterior jugular; *B,* buccal; *diP,* deep intraparotid; *F,* facial; *iH,* infrahyoid; *M,* malar; *Mt,* mastoid; *pA,* preauricular; *pL,* prelaryngeal; *pT,* pretracheal; *R,* recurrent or paratracheal; *sA,* subauricular; *SAN,* spinal accessory nerve; *SEJ,* superficial external jugular; *siP,* superficial intraparotid; *sMb,* submandibular; *sMt,* submental; *sP,* subparotid; *TCA,* transverse cervical artery.

TABLE 40-1 Comparison between the TNM Atlas for Lymph Nodes in the Neck and the Guidelines of the Lymph Node Levels Modified from Robbins

TNM Atlas Terminology		Robbins–Modified Node Levels	
Group No.	**Terminology**	**Level**	**Terminology**
1	Submental nodes	Ia	Submental group
2	Submandibular nodes	Ib	Submandibular group
3	Cranial jugular nodes	II	Upper jugular group
4	Middle jugular nodes	III	Middle jugular group
5	Caudal jugular nodes	IVa IVb	Lower jugular group Medial supraclavicular group
6	Dorsal cervical nodes along spinal accessory nerve	V Va Vb	Posterior triangle group • upper posterior triangle nodes • lower posterior triangle nodes
7	Supraclavicular nodes	Vc	Lateral supraclavicular group
8	Prelaryngeal and paratracheal nodes	VI VIa VIb	Anterior compartment group: • anterior jugular nodes • prelaryngeal, pretracheal, and paratracheal nodes
9	Retropharyngeal nodes	VII VIIa VIIb	Prevertebral compartment group • retropharyngeal nodes • retrostyloid nodes
10	Parotid nodes	VIII	Parotid group
11	Buccal nodes	IX	Buccofacial group
12	Retroauricular and occipital nodes	X Xa Xb	Posterior skull group • retroauricular and subauricular nodes • occipital nodes

No., *Number.*

is less frequently involved in tumors of the oral cavity, larynx, or hypopharynx.

Level III contains the middle jugular lymph nodes located around the middle third of the IJV. It is the caudal extension of level II. It is limited cranially by the caudal border of the body of the hyoid bone and caudally by a plane in which the omohyoid muscle crosses the IJV (a surgical landmark) or by the caudal border of the cricoid cartilage (a clinical landmark). Level III contains a highly variable number of lymph nodes and receives efferent lymphatics from levels II and V and some efferent lymphatics from the retropharyngeal, pretracheal, and recurrent laryngeal nodes. It collects the lymphatics from the base of the tongue, tonsils, larynx, hypopharynx, and thyroid gland. Nodes in level III are at greatest risk for harboring metastases from cancers of the oral cavity, nasopharynx, oropharynx, hypopharynx, and larynx.

Level IVa contains the lower jugular lymph nodes located around the inferior third of the IJV from the caudal limit of level III to a limit set arbitrarily 2 cm cranial to the sternoclavicular joint, caudally. Level IVa receives efferent lymphatics primarily from levels III and V, some efferent lymphatics from the retropharyngeal, pretracheal, and recurrent laryngeal nodes, and collecting lymphatics from the hypopharynx, larynx, and thyroid gland. Level IVa nodes are at high risk for harboring metastases from cancers of the hypopharynx, larynx, thyroid, and cervical esophagus. Rarely metastases from the anterior oral cavity may manifest in this location with minimal or no proximal nodal disease. *Level IVb* contains the medial supraclavicular lymph nodes located in the continuation of level IVa down to the cranial edge of the sternal manubrium. Level IVb receives efferent lymphatics primarily from levels IVa and Vc, some efferent lymphatics from the pretracheal, and recurrent laryngeal nodes, and collecting lymphatics from the hypopharynx, esophagus, larynx, trachea, and thyroid gland. Level IVb nodes are at high risk for harboring metastases from cancers of the hypopharynx, subglottic larynx, trachea, thyroid, and cervical esophagus.

Level Va and Vb includes the lymph nodes of the posterior triangle group. This group includes the lymph nodes located along the lower part of the spinal accessory nerve and the transverse cervical vessels. It extends from a plane crossing the cranial edge of the body of the hyoid bone to a plane crossing the cervical transverse vessels caudally. The distinction between the upper posterior triangle (level Va) and the lower posterior triangle (level Vb) allows lymph node involvement of the lower two thirds of the spinal accessory nerve chain to be differentiated from that of the transverse cervical vessel chain.[8,9] A horizontal plane defined by the caudal edge of the cricoid cartilage separates these two compartments. The demarcation between the posterior end of level IIb and the uppermost part of level Va has still not been clearly defined. From an anatomic point of view, the uppermost part of level Va includes lymph nodes belonging to the occipital region (see level Xb).[10] Thus, it was proposed to use the hyoid bone as a radiological landmark to define the cranial limit of level Va. Level Va and Vb receives efferent lymphatics from the occipital and postauricular nodes and from the occipital and parietal scalp, skin of the lateral and posterior neck and shoulder, nasopharynx, oropharynx (tonsils and base of the tongue) and the thyroid gland. Level Vb lymph nodes are at high risk for harboring metastases from cancers of the nasopharynx, oropharynx, and thyroid gland. Nodes in level Va are more often associated with primary cancers of the nasopharynx, oropharynx, or cutaneous structures of the posterior scalp, whereas those in level Vb are more commonly associated with tumors arising in the thyroid gland.

Level Vc contains the lateral supraclavicular nodes located in the continuation of the posterior triangle nodes (level Va and Vb) from the cervical transverse vessels down to a limit set arbitrarily 2 cm cranial to the sternal manubrium, that is,

a similar limit than the caudal border of level IVa. It corresponds partly to the area known as the "the supraclavicular fossa" also called the *triangle of Ho*, which was clinically defined in the mid-1970s before the era of CT for the neck staging of nasopharyngeal carcinoma.[11] Level Vc receives efferent lymphatics from the posterior triangle nodes (level Va and Vb) and is more commonly associated with nasopharyngeal tumors.

Level VI lymph nodes contains the anterior compartment nodes including superficially, the anterior jugular nodes (level VIa), and in the deep previsceral space, the prelaryngeal, pretracheal and paratracheal (recurrent laryngeal nerve) nodes (level VIb). *Level VIa* is contained between the anterior edges of the sternocleidomastoid muscles. It is limited cranially by the caudal limit of level Ib, caudally by the cranial edge of the sternal manubrium, anteriorly by the platysma, and posteriorly by the anterior surface of the infrahyoid muscles. These nodes mostly drain the integuments of the lower face and anterior neck. Consequently, their treatment should only be addressed in lower lip tumors and in advanced gingivomandibular carcinomas invading the soft tissues of the chin. Level VIb is contained between the two common carotid arteries. Its most cranial part comprises two to three inconstant infrahyoid nodes, which rest on the thyrohyoid membrane and drain the anterior floor of mouth, tip of the tongue, and lower lip. Consequently, for all other primary tumor locations, it is proposed to set the cranial limit of level VIa at the caudal edge of the body of the thyroid cartilage. *Level VIb* is limited caudally by the cranial edge of the sternal manubrium. Level VIb receives efferent lymphatics from the anterior floor of mouth, the tip of the tongue, the lower lip, the thyroid gland, the glottic and subglottic larynx, the hypopharynx, and the cervical esophagus. These nodes are at high risk for harboring metastases from cancers of the lower lip, the oral cavity (floor of mouth and tip of the tongue), the thyroid gland, the glottic and subglottic larynx, the apex of the piriform sinus, and the cervical esophagus.

Level VIIa contains the retropharyngeal nodes, which lie within the retropharyngeal space, extending cranially from the upper edge of the first cervical vertebrae to the cranial edge of the body of the hyoid bone caudally. Typically, retropharyngeal nodes are divided into a medial and a lateral group. The lateral group lies medial to the internal carotid artery and lateral to a line parallel to the lateral edge of the longus capiti muscle. The medial group is an inconsistent group of one to two lymph nodes intercalated in or near the midline. Retropharyngeal node receives efferent lymphatics from the mucosa of the nasopharynx, the Eustachian tube, and the soft palate. These nodes are at risk of harboring metastases from cancers of the nasopharynx, the posterior pharyngeal wall, and the oropharynx (mainly the tonsillar fossa and the soft palate). *Level VIIb* contains the retrostyloid nodes, which are the cranial continuation of the level II nodes. They are located in the fatty space around the jugulo-carotid vessels up to the base of skull (jugular foramen). Retrostyloid nodes receive efferent lymphatics from the nasopharyngeal mucosa and are at risk of harboring metastases from cancers of the nasopharynx and from any other head and neck primary with massive infiltration of upper level II nodes through retrograde lymph flow.

Level VIII contains the parotid node group, which includes the subcutaneous preauricular nodes, the superficial and deep intraparotid nodes, and the subparotid nodes. These nodes extend from the zygomatic arch and the external auditory canal down to the mandible. The parotid group nodes receive efferent lymphatic from the frontal and temporal skin, the eyelids, the conjunctiva, the auricle, the external acoustic meatus, the tympanum, the nasal cavities, the root of the nose, the nasopharynx, and the Eustachian tube. They are at risk of harboring metastasis from cancers of these regions but especially from tumors of the frontal and temporal skin, the orbit, the external auditory canal, the nasal cavities, and the parotid gland.

Level IX contains the malar and buccofacial node group, which includes inconsistent superficial lymph nodes around the facial vessels on the external surface of the buccinator muscle. The buccofacial nodes receive efferent vessels from the nose, the eyelids, and the cheek. They are at risk of harboring metastases from cancers of the skin of the face, the nose, the maxillary sinus (infiltrating the soft tissue of the cheek), and the buccal mucosa.

Level Xa contains the retroauricular (also called *mastoid*) and subauricular nodes, which include superficial nodes lying on the mastoid process from the cranial edge of the external auditory canal cranially to the tip of the mastoid caudally. The retroauricular nodes receive efferent vessels from the posterior surface of the auricle, the external auditory canal, and the adjacent scalp. They are at risk of harboring metastases mainly from skin cancers of the retroauricular area. *Level Xb* contains the occipital lymph nodes, which are the cranial and superficial continuation of the level Va nodes up to the cranial protuberance. Level Xb nodes receive efferent vessels from the posterior part of the hair-bearing scalp and are at risk of metastases from skin cancers of the occipital area.

IMAGING OF THE NECK

The armamentarium available for the imaging workup of the metastatic cervical lymph nodes includes CT, magnetic resonance imaging (MRI), ultrasonography, and positron emission tomography (PET).[12] Nodal imaging is mandatory in a pretreatment workup because clinical assessment of the nodal status in patients with a thick or small neck has a low sensitivity and because deeply located nodes remain inaccessible in all patients.[13]

CT and MRI are standard cross-sectional imaging modalities through which anatomic "slices" of the entire neck depict the contours and internal structure of the nodes (Figures 40-2 and 40-3). MRI may have an advantage over CT scanning because of the higher spontaneous contrast it distinguishes between fatty and non-fatty tissues. The multiplanar capability of MRI has been an advantage of this technique since its introduction into clinical use in the early 1980s. However, the multirow detector technology and the spiral acquisition modality of newer-generation CT systems have boosted the multiplanar reformatting capabilities of CT scans, which now equal those of MR images. The major criteria for nodal malignancy using CT or MRI include the size of the nodes (a short axis longer than 10 mm) and the presence of a central necrosis (hypodensity on CT images; hypointensity on T1-weighted MR images and hyperintensity on T2-weighted MR images). Central necrosis is well highlighted by intravenous contrast agent perfusion, which enhances nodal areas with arterial blood supply on both CT and MR images (see Figures 40-2, *A*, and 40-3, *C*). However, the two techniques share common weaknesses: the inability to detect micrometastatic deposits within normal-sized nodes (false-negative results) and the risk for inappropriate classification of malignancy in nodes that are enlarged by benign reactive changes (false-positive results). Thus far, neither MRI nor CT can provide perfect diagnostic accuracy for nodal metastatic workup. It has been shown in a large series of patients that the two techniques have an almost similar and unsatisfactory performance.[14]

Ultrasonography has long been regarded as a low-cost, widely available, and innocuous alternative to CT/MRI, with the additional advantages of color Doppler flow–encoded

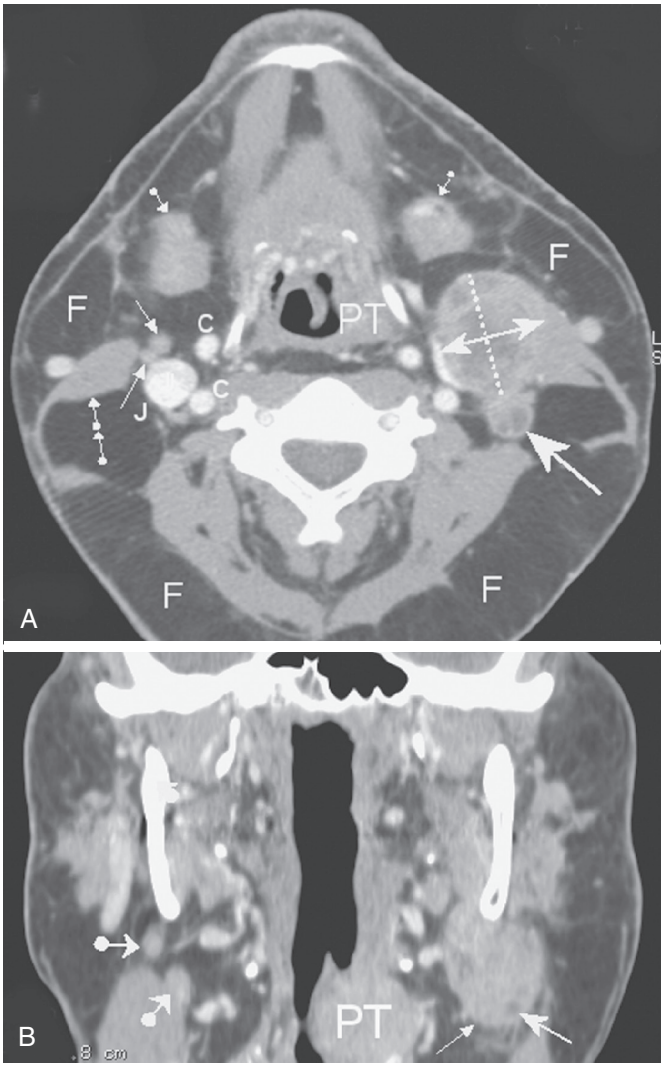


Figure 40-2 CT nodal display in a patient with left oropharyngeal squamous cell carcinoma (SCC). **A,** Native contrast-enhanced slice in the axial transverse plane using multislice multirow detector (MSMD) spiral acquisition technique. Hypodense fatty (F) environment allows clear delineation of the neck structures. Left oropharyngeal SCC (PT) is present. Abnormal nodes are seen within the left level II region, with anterior adenomegaly (long axis of 26 mm is shown as *dotted line*; short transverse axis of 18 mm is shown between the *double-ended arrow*) and a posterior, normal-sized node showing necrotic hypodensity *(thick arrow).* Normal-sized contralateral nodes are indicated *(thin arrows).* Observe the isodensity of the submandibular glands *(ball-arrowhead)* and of the muscles *(double ball-arrowhead).* Jugular veins (J) and carotid arteries (C) are strongly opacified at this early second phase of biphasic iodinated contrast agent perfusion. Notice the lamination of the left internal jugular vein by adenomegaly. **B,** Reformatted image in the coronal plane from the same three-dimensional data set shows the primary tumor (PT), left metastatic adenopathy, and contralateral, normal-sized nodes *(ball-arrowhead).* Observe the irregularities of the inferior aspect of the enlarged node, suggesting extranodal spread *(thin arrow)* and hypodense foci corresponding to necrotic areas within adenomegaly *(thick arrow).*
Courtesy E. Coche, MD, PhD.

vascular architecture depiction and fine-needle aspiration guidance. However, time demands and operator skill requirements are limiting factors, as well as the unresolved technical difficulties of fusing two-dimensional ultrasound data and three-dimensional CT/MRI data for radiotherapy planning. Ultrasound is also less efficient than CT and MRI at detecting nodal necrosis,[15] and deeply located nodes may be poorly accessible to the technique.

Research is under way to improve the diagnostic accuracy of MRI, including experimental lymphophilic contrast agents, magnetization transfer imaging (MTI), free water diffusion-weighted imaging (DWI), magnetic resonance spectroscopy (MRS), and bolus tracking perfusion-weighted imaging (PWI).[16-18] Currently, only the DWI MR technique has made a definite breakthrough in clinical routine by yielding fast-to-acquire and easy-to-process accurate quantitative data that significantly add to pretherapeutic nodal staging attempts,[19-21] early prediction of therapeutic response,[22] and posttreatment early detection of residual/recurrent tumor.[23] Many think that molecular imaging probes targeting either specific membrane antigens or metabolic pathways of tumor cells could be the definitive contributors to perfect diagnostic accuracy in nodal metastatic workup, in which case MRI and PET will be competitors.

PET using fluorodeoxyglucose (FDG) as a tracer has become the most available technique for "metabolic imaging" by enhancing foci of increased glucose uptake. However, PET alone provides only restricted diagnostic accuracy. The limitations of PET can be offset by coregistering the information on anatomic CT or MR images[24] (Figure 40-4). Integrated PET/CT combines the poor anatomic localization of PET with the accurate morphologic data provided by CT. The results of a recent large, prospective study showed that FDG-PET significantly improved the staging of HNSCC because of its detection of metastatic or additional disease.[25] However, a recent meta-analysis totaling 1236 patients demonstrated that the accuracy of FDG-PET was only marginally superior to that of CT or MRI. This study calls into question the routine value of FDG-PET for nodal staging.[26] In addition to research on dedicated tissue-specific MR contrast agents, research is under way on PET radiopharmaceutical tracers that would allow the assessment of hypoxia, angiogenesis, apoptosis, and receptor status. These studies make up the second main field of research in oncology imaging.[27] Using anatomic imaging studies to detect tumor recurrences in previously treated primary sites is unsatisfactory because extensive unspecific posttherapeutic changes may mask small foci of neoplastic recurrence.[28] On the other hand, promising data have been reported with the use of FDG-PET in this setting.[29] Similar concepts apply to nodal metastases, and it may be possible that molecular and metabolic imaging methods will also become standard in nodal relapse detection. The key imaging concept for the radiation oncologist's day-to-day practice is the capability of superimposing PET/MRI metabolic and molecular mapping onto CT/MRI anatomic images to improve the delineation of the irradiation target.[30] PET-CT and PET-MRI fusions are the founding paradigms that have now emerged into the clinical routine[31] (see Figures 40-3 and 40-4).

STAGING OF NECK NODE METASTASES

The seventh edition (2009) of the American Joint Committee on Cancer (AJCC) staging for neck node metastases[32] is presented in Table 40-2. This classification does not apply to nasopharyngeal, thyroid, or skin cancers. The classification for nodal staging applies whether the modality used for neck assessment is clinical examination or imaging. The routine use of CT or MRI and—in expert hands—ultrasound is recommended especially for assessing nodes not clinically identifiable (e.g., retropharyngeal, intraparotid, or superior mediastinal nodes) or for patients for whom clinical palpation of the neck is less sensitive (e.g., those who have a thick or small neck).[33] Last, it should be emphasized that the Nx

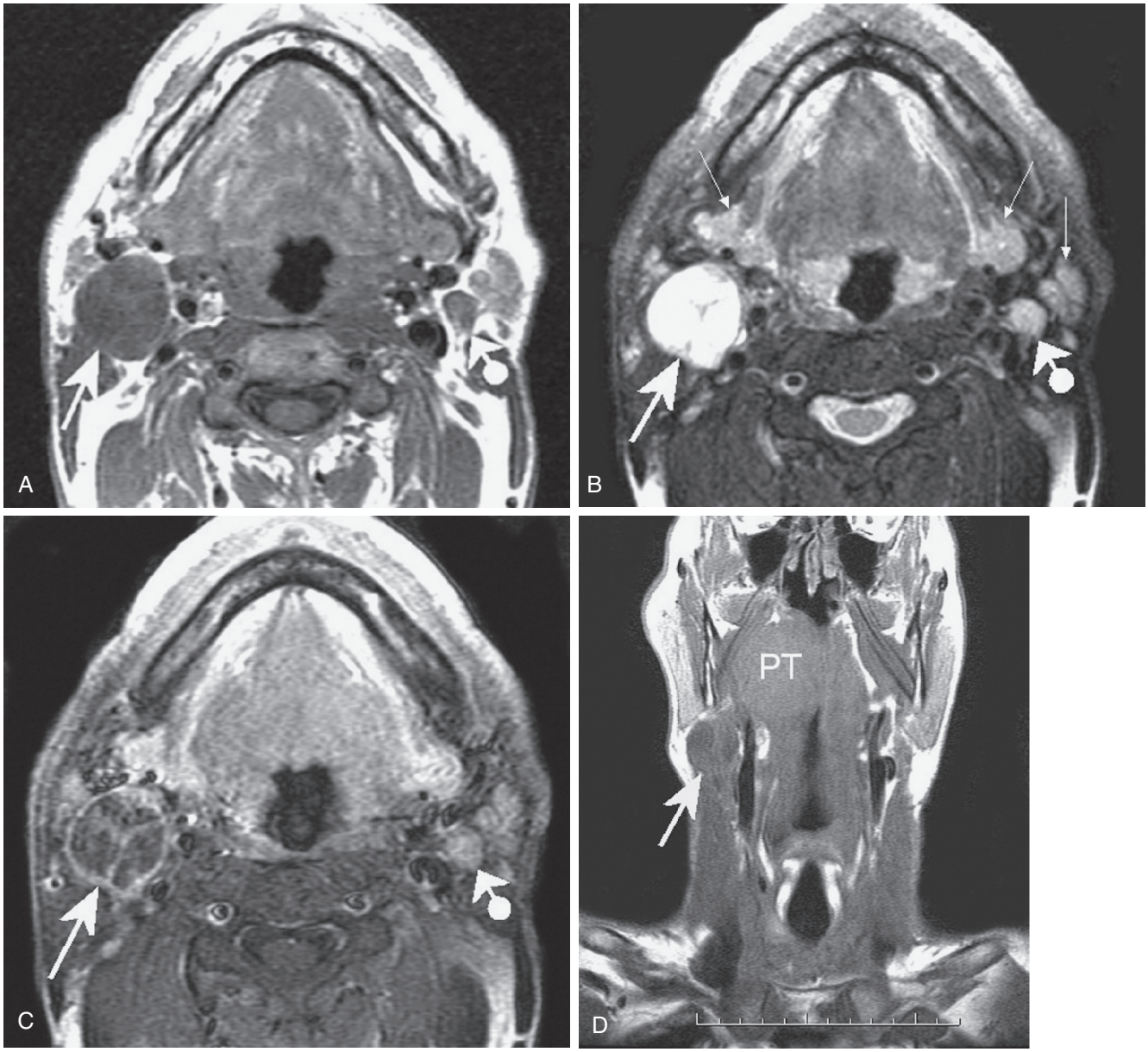


Figure 40-3 Magnetic resonance nodal display in a patient with right oropharyngeal squamous cell carcinoma (SCC). **A,** Transverse, unenhanced, T1-weighted spin-echo (SE) image showing a left level II hypointense necrotic adenopathy *(arrow)* with a normal contralateral node in level II *(ball-arrowhead).* **B,** Transverse, T2-weighted fast spin-echo (FSE) image with fat suppression option in a similar slice location discloses strong hyperintensity of the necrotic node due to fluid-like content *(arrow)* compared with the normal contralateral node, which displays the usual intermediate to high signal intensity *(ball-arrowhead).* Observe the almost similar signal intensity of the normal node and of the parotid and submandibular glands *(thin arrows).* **C,** Transverse, contrast-enhanced, T1-weighted SE image with fat suppression option in a similar slice location as in **A** and **B** shows only peripheral ring-like enhancement of the margin of the necrotic adenomegaly *(arrow).* The normal contralateral node enhances slightly and homogeneously *(ball-arrowhead).* **D,** Coronal view, precontrast, T1-weighted MR image shows a primary tumor *(PT)* and hypointense necrotic adenopathy *(arrow).*

classification applies only when the neck has not been assessed or could not be assessed.

INCIDENCE AND DISTRIBUTION OF NECK NODE METASTASES

Clinical and Radiologic Assessment

The metastatic spread of head and neck tumors into the cervical lymph nodes is rather consistent and follows predictable pathways, at least in the neck that has not been violated by previous surgery or radiotherapy. In Table 40-3, the frequency of metastatic lymph nodes is expressed as a percentage of patients who are node-positive.[34,35]

The frequency of neck node metastases and the distribution of clinically involved nodes depend to a major extent on the primary tumor site. Typically, hypopharyngeal tumors have the highest propensity for nodal involvement, which occurs in 70% of cases. Cranial and anterior tumors (e.g., oral cavity tumors) mainly drain into levels I, II, and III, whereas more caudally located tumors (e.g., laryngeal tumors) mainly drain into levels II and III and, to a lesser extent, levels IV and V.

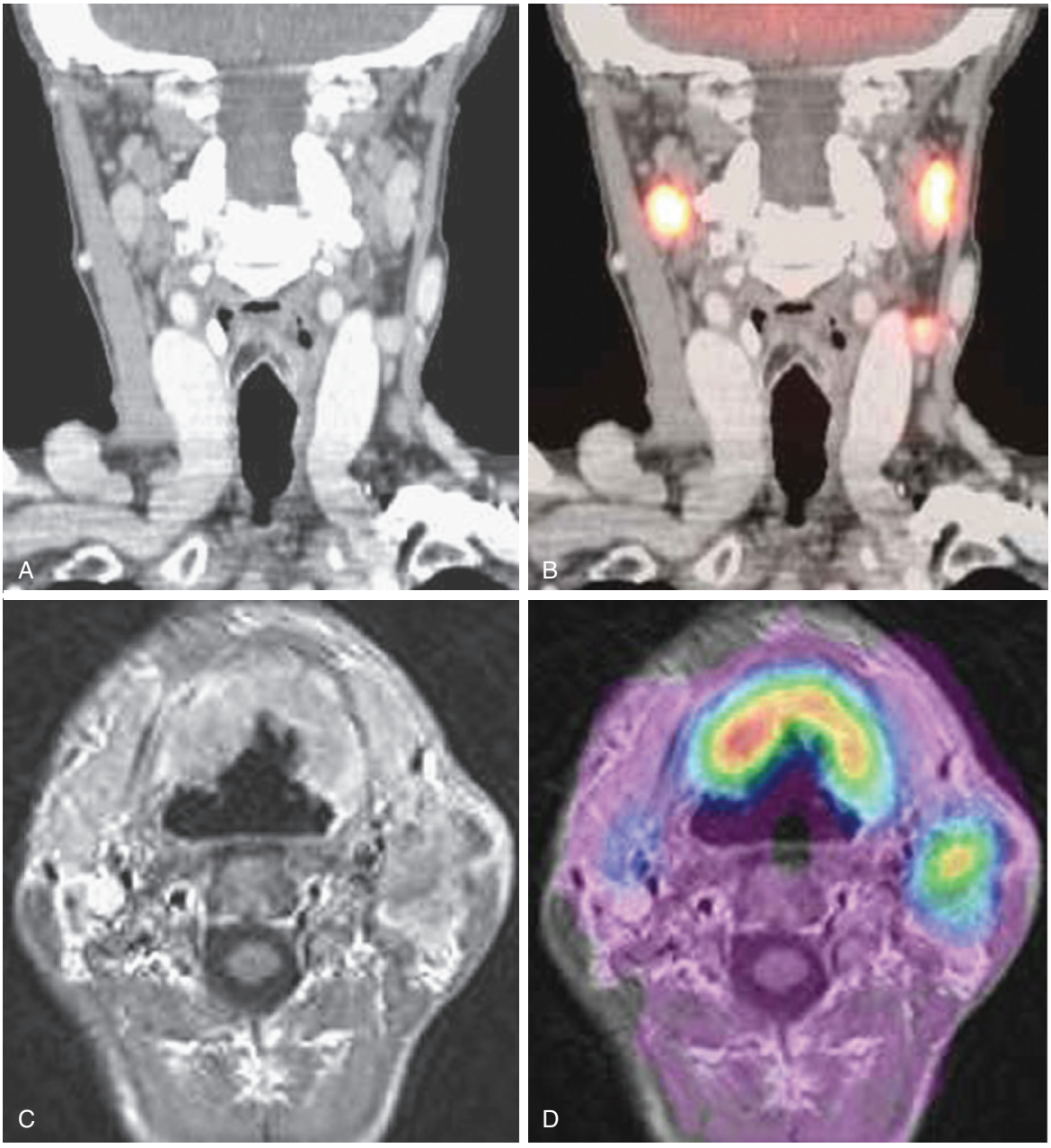


Figure 40-4 CT-MRI-PET image fusion. **A,** Postcontrast, reformatted CT image in the coronal plane shows bilateral, mildly enlarged metastatic nodes in the carotid-jugular chains. Tumoral involvement of the nodes remains speculative because of the borderline short-axis diameter and absence of obvious necrotic changes. **B,** Superimposition of ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET) data on a CT image demonstrates increased glucose uptake within the nodes. **C,** Postcontrast, T1-weighted, axial transverse MR image from three-dimensional gradient-echo acquisition using spoiled gradients (SPGR) shows bilateral anterior, horseshoe-sized oropharyngeal tumor and metastatic left-sided nodes in level II. **D,** Superimposition of FDG-PET data on an MR image demonstrates increased glucose uptake within the primary tumor and metastatic nodes. *Courtesy M. Lonneux, MD, PhD.*

Contralateral nodes are rarely involved except for midline tumors or tumors in sites where bilateral lymphatic drainage has been reported, such as the soft palate, base of the tongue, and pharyngeal wall. Even in these tumors, the incidence of contralateral involvement is much lower; in base-of-tongue tumors with clinically positive nodes, the rate is 31% in the contralateral level II nodes compared with 73% in the ipsilateral level II nodes (data not shown). Node distribution follows the same pattern in the contralateral neck as in the ipsilateral neck. Except for nasopharyngeal tumors, involvement of ipsilateral level V nodes is rather rare, occurring in less than 1% of oral cavity tumors, in less than 10% of oropharyngeal and laryngeal tumors, and in about 15% of hypopharyngeal tumors. It almost never occurs in contralateral level V nodes.

Metastatic lymph node involvement in the neck depends on the size of the primary tumor, increasing with the T category. In the series reported by Bataini et al,[34] 44% of patients with a T1 tumor had clinical lymph node involvement; this increased to 70% for patients with T4 lesions. There are, however, no data suggesting that the relative distribution of involved neck levels varies with the T category.

Retropharyngeal lymph nodes represent a special entity because they are usually not clinically detectable. The incidence of retropharyngeal lymph node involvement can be estimated only from series in which CT or MRI of the retropharynx has been systematically performed as part of the diagnostic procedure. Retropharyngeal node involvement occurs in primary tumors arising from (or invading) the mucosa of the occipital and cervical somites, such as the nasopharynx, pharyngeal wall, and soft palate (Table 40-4). The incidence of retropharyngeal lymph node involvement is higher in patients in whom involvement of other neck node levels has also been documented.[18,36,37] However, in patients with clinical stage N0 nasopharyngeal tumors and, to a lesser extent, in patients with pharyngeal wall tumors, the incidence of retropharyngeal node involvement is still significant—between 16% and 40%. Also, as already described for the other lymph node levels, involvement depends on the T category and is typically lower for T1 tumors.

TABLE 40-2 American Joint Committee on Cancer Staging for Neck Node Metastasis

Category	Definition
Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single ipsilateral node, ≤3 cm in greatest dimension
N2a	Metastasis in a single ipsilateral node, >3 cm but ≤6 cm in greatest dimension
N2b	Metastasis in multiple ipsilateral nodes, ≤6 cm in greatest dimension
N2c	Metastasis in bilateral or contralateral nodes, ≤6 cm in greatest dimension
N3	Metastasis in a lymph node >6 cm in greatest dimension

From Sobin L, Gospodarowicz M, Wittekind C: UICC/TNM classification of malignant tumors, ed 7, New York, 2009, Wiley-Blackwell.

Pathologic Lymph Node Metastases

The distribution of pathologic lymph node metastasis in patients with primary tumors of the oral cavity, oropharynx, hypopharynx, and larynx can be derived from retrospective series in which a systematic radical neck node dissection was proposed as part of the initial treatment procedures.[41-44] Retrospective series are essentially biased regarding patient and treatment selection, but these series from the Head and Neck Department at MSKCC are the largest and most consistent data ever published on that matter. The results of these retrospective studies are shown in Tables 40-5 and 40-6. The data are presented in terms of the number of neck dissections with positive lymph nodes divided by the total number of neck dissection procedures and expressed as a percentage. Most patients (>99% for patients with N0 tumors and 95% for patients with N+ tumors) had unilateral treatment only, and

TABLE 40-3 Distribution of Clinical Metastatic Neck Nodes from Oral Cavity and Pharyngolaryngeal Squamous Cell Carcinomas

Tumor Site	Patients with N+ Disease	Distribution* of Metastatic Lymph Nodes per Level (Percentage of Patients Who Were Node-Positive)					
		I	II	III	IV	V	Other†
Oral cavity (*n* = 787)	36%	42/3.5	79/8	18/3	5/1	1/0	1.4/0.3
Oropharynx (*n* = 1479)	64%	13/2	81/24	23/5	9/2.5	13/3	2/1
Hypopharynx (*n* = 847)	70%	2/0	80/13	51/4	20/3	24/2	3/1
Supraglottic larynx (*n* = 428)	55%	2/0	71/21	48/10	18/7	15/4	2/0

Modified from Lindberg R: Distribution of cervical lymph node metastases from squamous cell carcinoma of the upper respiratory and digestive tracts. Cancer 29:1446–1449, 1972; Bataini JP, Bernier J, Asselain B, et al: Primary radiotherapy of squamous cell carcinoma of the oropharynx and pharyngolarynx. Tentative multivariate modeling system to predict the radiocurability of neck nodes. Int J Radiat Oncol Biol Phys 14:635–642, 1988.

**Ipsilateral/contralateral nodes.*

†Parotid, buccal nodes.

TABLE 40-4 Incidence of Retropharyngeal Lymph Nodes in Oral Cavity and Pharyngolaryngeal Primary Tumors

Authors	Primary Site	Incidence of Retropharyngeal Lymph Nodes (Percentage of Total No. Patients)		
		Overall	N0 Neck Disease*	N+ Neck Disease†
McLaughlin[38]	Oropharynx			
	Pharyngeal wall	18/93 (19%)	6/37 (16%)	12/56 (21%)
	Soft palate	7/53 (13%)	1/21 (5%)	6/32 (19%)
	Tonsillar fossa	16/176 (9%)	2/56 (4%)	14/120 (12%)
	Base of tongue	5/121 (4%)	0/31 (0%)	5/90 (6%)
	Hypopharynx (piriform sinus, postcricoid area)	7/136 (5%)	0/55 (0%)	7/81 (9%)
	Supraglottic larynx	4/196 (2%)	0/87 (0%)	4/109 (4%)
	Nasopharynx	14/19 (74%)	2/5 (40%)	12/14 (86%)
Chua[39]	Nasopharynx	106/364 (29%)	21/134 (16%)	85/230 (37%)
Chong[40]	Nasopharynx	Not stated	Not stated	59/91 (65%)

**Clinically negative nodes in levels I to V.*

†Clinically positive nodes in levels I to V.

TABLE 40-5 Incidence of Pathologic Lymph Node Metastasis in Squamous Cell Carcinomas of the Oral Cavity

	Distribution of Metastatic Lymph Nodes per Level (Percentage of Neck Dissection Procedures)											
	Prophylactic RND*						Therapeutic RND (Immediate or Subsequent)*					
Tumor Site	No. RNDs	I (%)	II (%)	III (%)	IV (%)	V (%)	No. RNDs	I (%)	II (%)	III (%)	IV (%)	V (%)
Tongue	58	14	19	16	3	0	129	32	50	40	20	0
Floor of mouth	57	16	12	7	2	0	115	53	34	32	12	7
Gum	52	27	21	6	4	2	52	54	46	19	17	4
Retromolar trigone	16	19	12	6	6	0	10	50	60	40	20	0
Cheek	9	44	11	0	0	0	17	82	41	65	65	0
Total	192	20	17	9	3	1	323	46	44	32	16	3

Modified from Shah JP: Patterns of cervical lymph node metastasis from squamous carcinomas of the upper aerodigestive tract. Am J Surg 160:405–409, 1990.
RND, *Radical neck dissection.*
**Prophylactic RND—192 patients/procedures; Therapeutic RND—308 pts, 323 procedures.*

TABLE 40-6 Incidence of Pathologic Lymph Node Metastasis in Squamous Cell Carcinomas of the Oropharynx, Hypopharynx, and Larynx

	Distribution of Metastatic Lymph Nodes per Level (Percentage of Neck Dissection Procedures)											
	Prophylactic RND*						Therapeutic RND†					
Tumor Site	No. RNDs	I (%)	II (%)	III (%)	IV (%)	V (%)	No. RNDs	I (%)	II (%)	III (%)	IV (%)	V (%)
OROPHARYNX‡												
Base of tongue + vallecula	21	0	19	14	9	5	58	10	72	41	21	9
Tonsillar fossa	27	4	30	22	7	0	107	17	70	42	31	9
Total Oropharynx	48	2	25	19	8	2	165	15	71	42	27	9
HYPOPHARYNX‡												
Piriform sinus	13	0	15	8	0	0	79	6	72	72	47	8
Pharyngeal wall	11	0	9	18	0	0	25	20	84	72	40	20
Total Hypopharynx	24	0	12	12	0	0	104	10	75	72	45	11
LARYNX§												
Supraglottic larynx	65	6	18	18	9	2	138	6	62	55	32	5
Glottic larynx	14	0	21	29	7	7	45	9	42	71	24	2
Total Larynx	79	5	19	20	9	3	183	7	57	59	30	4

Pts, *Patients;* RND, *radical neck dissection.*
**Prophylactic RND: oropharynx 47 pts, 48 procedures; hypopharynx 24 pts/procedures; larynx 78 pts, 79 procedures.*
†Therapeutic RND: oropharynx 157 pts, 165 procedures; hypopharynx 102 pts, 104 procedures; larynx 169 pts, 183 procedures.
‡Modified from Candela FC, Kothari K, Shah JP: Patterns of cervical node metastases from squamous carcinoma of the oropharynx and hypopharynx. Head Neck 12:197–203, 1990.
§Modified from Candela FC, Shah J, Jaques DP, et al: Patterns of cervical node metastases from squamous carcinoma of the larynx. Arch Otolaryngol Head Neck Surg 116:432-435.

no distinction between the ipsilateral and contralateral neck was made.

Overall, metastatic disease was detected in 33% of the prophylactic neck dissections and in 82% of the therapeutic neck dissections. In these series, the overall sensitivity and specificity of the clinical examination reached 85% and 62%, respectively. As already observed with the pattern of clinical metastatic lymph nodes, the distribution of pathologically confirmed metastatic lymph nodes depended on the primary tumor site. Typically, in patients with clinical stage N0 oral cavity tumors, metastatic lymph nodes were observed in levels I to III, and in patients with clinical stage N0 oropharyngeal, hypopharyngeal, and laryngeal tumors, in levels II to IV. This pattern of node distribution is similar to that determined from the clinical palpation of the neck. It should be noted that the T-category distribution was different in the various groups. Of patients with laryngeal tumors, 54% (42 of 79) had stage T3 to T4 tumors (mainly, supraglottic lesions) compared with 27% of patients with oral cavity tumors (52 of 192), 25% of patients with hypopharyngeal tumors (6 of 24), and 17% of patients with oropharyngeal tumors (8 of 47). Such a difference in T category presumably explains the high incidence of microscopic node metastases in the group with laryngeal tumors.

The pattern of metastatic node distribution in patients who underwent therapeutic neck dissection was similar to that observed in patients with N0 tumors, with the difference that significant pathologic infiltration of an additional nodal level was typically observed—level IV for oral cavity tumors and levels I and V for oropharyngeal, hypopharyngeal, and, to a lesser extent, laryngeal tumors. Overall, this observation illustrates the gradual infiltration of node levels in the neck. This concept is well illustrated by the prevalence of metastases in level V. In the MSKCC series,[45] the prevalence of pathologic infiltration in level V was quite low, averaging 3% in 1277 neck dissections in patients with oral cavity, oropharyngeal, hypopharyngeal, and laryngeal tumors. The prevalence peaked at 11% for hypopharyngeal tumors with pathologically positive nodes (see Table 40-6). A thorough analysis of level V infiltration showed that for all tumor sites pooled together, infiltration of level V without metastases in levels I to IV was observed in only one patient (0.2%). This patient had a hypopharyngeal

tumor. Infiltration in level V remained below 1% when a single pathologically confirmed positive node was also observed in levels I to III, but reached 16% when a single pathologically confirmed positive node was also observed in level IV. When more than one level was infiltrated, the probability of level V involvement progressively increased, reaching 40% when levels I to IV were all involved. The pattern of involvement of level I is also a good illustration of the concept of gradual node infiltration. In the MSKCC series, pathologic involvement of level I was found in only 2% of patients with clinical N0 oropharyngeal tumors and was not observed in patients with clinical N0 hypopharyngeal tumors (see Table 40-6). On the other hand, in patients with clinically positive nodes, metastases in level I were reported in 15% and 10% of patients with oropharyngeal and hypopharyngeal tumors, respectively.

Incidence of Skip Metastases in the Neck

Skip metastases are metastases that do not progress in an orderly manner from one level to the next (e.g., from level I to level II). Depending on their frequency, skip metastases in patients with clinical stage N0 tumors may have a profound implication for the therapeutic management of the neck. In the series from the MSKCC,[44] 8 of 343 patients with clinical stage N0 tumors (2.5%) developed skip metastases. Seven of these patients had oral cavity tumors that metastasized in level IV or V only. One patient had a laryngeal tumor. These low figures are in good agreement with a rate of neck failure outside the dissected levels of 3% (2 of 64 lesions) observed in patients with pathologic N0 lesions treated at the same institution by supraomohyoid neck dissection.[46] Most of these patients had tumors of the oral cavity. None of them received postoperative radiation therapy because they were all free of metastases. Byers et al[47] carefully evaluated the frequency of skip metastases in 270 patients primarily treated by surgery at the M. D. Anderson Cancer Center (MDACC) from 1970 to 1990 for squamous cell carcinoma of the oral tongue. Of these patients, 12 had metastases in level III only, 9 had metastases in level IV only, and 2 had metastases in level IIb (i.e., nodes that are far enough posterior to the internal jugular vein). In addition, in 90 of the patients who had pathologic stage N0 tumors after selective neck dissection of levels I to III and who did not receive postoperative radiation therapy, 9 subsequently developed recurrence in level IV. Altogether (in levels IIb, III, and IV), the frequency of skip metastases reached 12% (32 of 270 lesions). If one excludes the skip metastases in level IIb and III, the frequency reached only 7% (18 of 270 lesions).

Incidence and Pattern of Node Distribution in the Contralateral Neck

There are few data available on the pattern of pathologic node distribution in the contralateral neck. Bilateral neck dissection was performed only when the surgeon thought there was a high risk of contralateral node involvement (e.g., with tumors of the oral cavity or oropharynx reaching the midline or extending beyond it or with hypopharyngeal and supraglottic tumors). Obviously, in such cases bilateral radical neck dissection was never performed, so an accurate estimate of the pattern of node involvement in levels I to V of the contralateral neck is not possible. Furthermore, in almost every study, data on both sides of the neck were pooled for presentation. Kowalski[48] presented data on 90 patients who underwent bilateral supraomohyoid neck dissection and in whom the pattern of node distribution in each side of the neck was reported separately. Most of these patients had squamous cell carcinoma of the lip or oral cavity. In the ipsilateral neck, pathologic infiltration in levels I, II, and III reached 20%, 15%, and 15%, respectively. In the contralateral neck, corresponding values reached 13%, 11%, and 0%, respectively. These figures are in good agreement with data on clinical node distribution showing that both sides of the neck exhibited a similar pattern of node distribution but with a lower incidence in the contralateral neck.

Foote et al[49] reported the rate of contralateral neck failure in a limited series of 46 patients with clinical stage N0 base of the tongue tumors treated by some form of glossectomy and ipsilateral neck dissection. None of these patients received postoperative radiation therapy. Ten patients (22%) had contralateral neck recurrence, and the most common sites were levels II, III, and IV. It appears that in two of these patients, recurrence was also observed at the primary site. The development of delayed contralateral neck metastases was not related to the clinical or pathologic extent of the base of the tongue tumor. O'Sullivan et al[50] reported a retrospective series of 228 patients with tonsillar carcinoma who were treated for the primary tumor and in the ipsilateral neck only with radiation therapy. The vast majority of these patients had T1 to T2 and N0 to N1 disease. Contralateral recurrence in the neck was observed in only 8 patients (2%), including 5 patients with local recurrence as well. No neck failures occurred in the 133 patients with N0 neck classification. Although not significant because of the small number of events, involvement of a midline structure (i.e., soft palate and base of the tongue) appeared to be a prognostic factor for contralateral neck recurrence. Similar results were reported in a series of 101 node-negative tonsil carcinoma (mainly, stage T1 to T3) cases treated unilaterally.[51] Only two neck recurrences were observed in the contralateral neck.

RECOMMENDATIONS FOR SELECTION OF TARGET VOLUMES IN THE NECK

Metastatic lymph node involvement of primary squamous cell carcinoma of the oral cavity, pharynx, and larynx typically follows a predictive pattern. Data on clinical and pathologic neck node distribution as well as on neck recurrence after selective dissection procedures support the concept that not all neck node levels should be treated as part of the initial management strategy of head and neck primaries of squamous cell origin.[52,53] However, the data on which such a concept is based have come from retrospective series and so may include possible biases (e.g., in patient selection, use of a series from the preimaging area, and so on) that could limit their validity.

Tables 40-7 and 40-8 present recommendations for the selection of clinical target volumes in the neck for pharyngolaryngeal squamous cell carcinomas. These guidelines can be applied whether the treatment modality is surgery or radiotherapy. A complete discussion on choosing between these two modalities is beyond the scope of this chapter, but factors to consider include the neck classification, the treatment option for the primary tumor, human papillomavirus (HPV) and Ebstein-Barr virus (EBV) status, the performance status of the patient, and the institutional policy agreed on by a multidisciplinary head and neck tumor board.

Selective treatment of the neck is appropriate for patients with clinical N0 HNSCC of the oral cavity, oropharynx, hypopharynx, and larynx.[46,53,54] Typically, levels Ia to III nodes should be treated for oral cavity tumors, and levels II to IV nodes should be treated for oropharyngeal, hypopharyngeal, and laryngeal tumors. Robbins[8] suggested that elective treatment of level IIb nodes is probably not necessary for patients with clinical N0 primary tumors of the oral cavity, larynx, or hypopharynx. Byers et al[47] suggested that level IV nodes be

TABLE 40-7 Recommendations for Selection of Clinical Target Volume in the Neck for Oral Cavity and Oropharyngeal Tumors

	Levels to Be Included in CTV	
Nodal Category (AJCC)	**Ipsilateral Neck**	**Contralateral Neck**
ORAL CAVITY		
N0-1 (in level I, II, or III)	I, II,* III, + IV‡	I, II,* III, + IV‡
N2a-b	I, II, III, IV, V†	I, II,* III, + IV for anterior tongue tumor
N2c	According to N category on each side of the neck	According to N category on each side of the neck
N3	I, II, III, IV, V ± adjacent structures according to clinical and radiologic data	I, II,* III, + IV for anterior tongue tumor
OROPHARYNGEAL		
N0-1 (in level II, III, or IV)	(Ib),§ II, III, IV, + RP for posterior pharyngeal wall tumor	II, III, IV, + RP for posterior pharyngeal wall tumor
N2a-b	Ib, II, III, IV, V, + RP	II, III, IV, + RP for posterior pharyngeal wall tumor
N2c	According to N category on each side of the neck	According to N category on each side of the neck
N3	I, II, III, IV, V, + RP ± adjacent structures according to clinical and radiologic data	II, III, IV, + RP for posterior pharyngeal wall tumor

AJCC, *American Joint Committee on Cancer;* CTV, *clinical target volume;* RP, *retropharyngeal nodes.*
**Level IIb could be omitted for N0 tumors.*
†Level V could be omitted if only levels I to III are involved.
‡For anterior tongue tumor and any tumor with extension to the oropharynx (e.g., anterior tonsillar pillar, tonsillar fossae, base of tongue).
§Any tumor with extension to the oral cavity (e.g., retromolar trigone, mobile tongue, inferior gum, oral side of anterior tonsillar pillar).

TABLE 40-8 Recommendations for Selection of Clinical Target Volume in the Neck for Hypopharyngeal and Laryngeal Tumors (T1N0 Glottic Tumors Excluded)

	Levels to Be Included in the CTV	
Nodal Category (AJCC)	**Ipsilateral Neck**	**Contralateral Neck**
HYPOPHARYNGEAL		
N0	II,* III, IV, + RP for posterior pharyngeal wall tumor + VI for apex of piriform sinus or esophageal extension	II,* III, IV, + RP for posterior pharyngeal wall tumor + VI for esophageal extension
N1N2a-b	Ib, II, III, IV, V, + RP + VI for piriform sinus or esophageal extension	II,* III, IV, + RP for posterior pharyngeal wall tumor + VI for esophageal extension
N2c	According to N category on each side of the neck	According to N category on each side of the neck
N3	I, II, III, IV, V, + RP + VI for piriform sinus or esophageal extension ± adjacent structures according to clinical and radiologic data	II,* III, IV, + RP for posterior pharyngeal wall tumor + VI for esophageal extension
LARYNGEAL		
N0-1 (in level II, III, or IV)	II,* III, IV, + VI for transglottic or subglottic extension	II,* III, IV, + VI for transglottic or subglottic extension
N2a-b	II, III, IV, V, + VI for transglottic or subglottic extension	II,* III, IV, + VI for transglottic or subglottic extension
N2c	According to N category on each side of the neck	According to N category on each side of the neck
N3	Ib, II, III, IV, V, + VI for transglottic or subglottic extension ± adjacent structures according to clinical and radiologic data	II,* III, IV, + VI for transglottic or subglottic extension

AJCC, *American Joint Committee on Cancer;* CTV, *clinical target volume;* RP, *retropharyngeal (nodes).*
**Level IIb could be omitted for N0 tumors.*

included in the treatment of the mobile tongue because of the high incidence (10%) of skip metastases. Retropharyngeal nodes should be treated in tumors of the posterior pharyngeal wall. For subglottic tumors, tumors with subglottic or transglottic extension, or hypopharyngeal tumors with esophageal extension, level VI nodes should also be included in the treatment volume.

As proposed by Byers,[54] similar guidelines could be recommended for patients who have N1 tumors without radiologic evidence of extracapsular infiltration. For hypopharyngeal tumors, however, because of their high lymphophilicity, comprehensive treatment of levels Ib to V may be advisable. When an involved lymph node is located at a boundary of a level that has not been selected for the target volume, it is recommended to extend the selection to include the adjacent level.[55] Typically, this applies only for oropharyngeal tumors with a single lymph node involved in level II at the boundary with level Ib or for an oral cavity tumor with an N1 node in level III at the boundary with level IV.

For patients with multiple nodes (N2b), the available data suggest that adequate treatment should include nodes in levels Ib (Ia for oral cavity) to V. Level Ib nodes could, however, be omitted for laryngeal tumors, and level V nodes omitted for oral cavity tumors with neck involvement limited to levels I to III. Prophylactic treatment of the retropharyngeal nodes should be systematically performed for oropharyngeal and hypopharyngeal tumors. Patients with N0 disease should have level VI nodes treated for subglottic tumors, tumors with subglottic or transglottic extension, or hypopharyngeal tumors with esophageal extension. It has been proposed that patients

with nodes in the upper neck (i.e., upper level II nodes) have the upper limit of the target volume extended to include the retrostyloid nodes (level VIIa).[55] Similarly, the supraclavicular nodes (level IVb) should be included in the target volume in cases of lower neck involvement (i.e., level IV or Vb nodes).[55]

There are no data available on the distribution of pathologic metastatic neck nodes in patients presenting with a single ipsilateral large node (N2a or N3) or with bilateral or contralateral nodes (N2c). For patients with a single large node—in the absence of data—it appears safe not to recommend selective treatment. For N3 disease, the type of treatment of the neck is also likely to be dictated by the local extension of the node into the adjacent structures (e.g., paraspinal muscles, parotid gland, blood vessels). For N2c tumors, one proposal is to consider each side of the neck separately, such as selective treatment on both sides for a small single node on each side, selective treatment for a small single node on one side, and more extensive treatment on the other side in the case of multiple nodes.

Prophylactic treatment of the contralateral neck for N0 disease lack consensus and is likely to be based on clinical judgment rather than on strong scientific evidence. Typically, patients with midline tumors or tumors originating from or extending to a site that has bilateral lymphatic drainage (e.g., the base of the tongue, vallecula, posterior pharyngeal wall) are thought to benefit from bilateral neck treatment, whereas well-lateralized tumors (e.g., the lateral border of the tongue, retromolar trigone, tonsillar fossa) can be spared contralateral treatment. It has also been reported that the risk of contralateral neck metastases increased with involvement of the ipsilateral neck in patients with tumors of the pharynx and larynx.[56] Putting all these data together, it would seem advisable to restrict treatment to the ipsilateral neck for tumors of the lower gum (not approaching the midline), lateral floor of the mouth, lateral border of the mobile tongue, upper gum, cheek, retromolar trigone, tonsillar fossa (without extension to the base of the tongue, soft palate, or posterior pillar), and lateral wall of the piriform sinus. In other situations in which prophylactic contralateral neck treatment is recommended, selection of the node levels to be treated should follow rules similar to those for the ipsilateral neck.

In principle, a similar approach should apply for the definition of the node levels to be irradiated postoperatively. However, if the selection criteria for postoperative radiotherapy are capsular rupture, a metastatic node more than 3 cm in diameter, or more than one metastatic node, then irradiation of levels I to V will typically be performed. As for primary irradiation, the retrostyloid space and supraclavicular fossae should be included in the target volume, depending on the location of the metastatic nodes.[55] For laryngeal tumors, level I nodes could be omitted. For oral cavity tumors with metastatic nodes located in level I or II only, postoperative irradiation of level V could be omitted. Retropharyngeal and paratracheal nodes should be treated as mentioned previously.

NECK NODE DISSECTION PROCEDURES AND SENTINEL NODE BIOPSY

In 1991, based on the definition of the neck level, the Committee for Head and Neck Surgery and Oncology of the American Academy for Otolaryngology–Head and Neck Surgery made several recommendations for neck dissection terminology. The main objective was to develop standardized terminology limited to the use of a few defined procedures in which the lymphatic and nonlymphatic structures removed were unambiguously described. Such recommendations had to correlate with the biology of neck metastases and meet the standards of oncologic principles. The goal of each type of neck dissection is to remove the lymphatic structures (nodes and vessels) that are poorly individualized in the fatty tissue of the neck. When it is oncologically sound, some or all nonlymphatic structures of the neck—such as the internal jugular vein, spinal accessory nerve, sternocleidomastoid muscles, and submandibular glands—may be preserved. Since the 1991 classification, revisions have been proposed; the current neck dissection terminology and definitions[8,9,57-59] are summarized in Table 40-9.

Radical neck dissection (RND), previously considered to be the standard basic procedure, is defined as the resection of lymph node levels I to V, including removal of the sternocleidomastoid muscles, IJV, and spinal accessory nerve.

Modified RND refers to the removal of all lymph nodes routinely resected by RND but sparing one or more nonlymphatic structures (i.e., spinal accessory nerve, IJV, sternocleidomastoid muscles) usually removed during RND (Figure 40-5). Medina[60] subclassified modified RND into three types: type I preserves the spinal accessory nerve only; type II preserves the spinal accessory nerve and sternocleidomastoid muscles; and type III preserves the spinal accessory nerve, sternocleidomastoid muscles, and IJV. Type III is also called by European authors "functional neck dissection," as first described by Suarez[61] and popularized by Bocca et al.[62,63] However, in their classic description, the submandibular gland was not removed.

Selective neck dissection (SND) is dissection with preservation of one or more lymph node levels routinely resected in RND (Figure 40-6). To avoid confusion in terminology for the different subtypes of SND, the 2002 revision of the node

TABLE 40-9 Classification of Neck Dissection: Definitions and Terminology

Type of Neck Dissection	Lymph Node Levels Resected	Nonlymphatic Structures Removed
Radical neck dissection	I, II, III, IV, V	SCM, IJV, SAN
Modified radical neck dissection	I, II, III, IV, V	Preservation of one or more of the following: SCM, IJV, SAN
Selective neck dissection	Preservation of one or more of the following: I, II, III, IV, V. Parentheses are used to denote levels or sublevels removed: SND (I-IV)	None
Extended neck dissection	Resection of one or more or additional lymph node group not routinely removed by radical neck dissection (e.g., parapharyngeal, paratracheal nodes)	Resection of one or more nonlymphatic structures not routinely removed by radical neck dissection (e.g., carotid artery, hypoglossal nerve, overlying skin)

Adapted from Robbins KT: Classification of neck dissection. Current concepts and future considerations. Otolaryngol Clin North Am 31:639–656, 1998.
IJV, *Internal jugular vein;* SAN, *spinal accessory nerve;* SCM, *sternocleidomastoid muscle.*

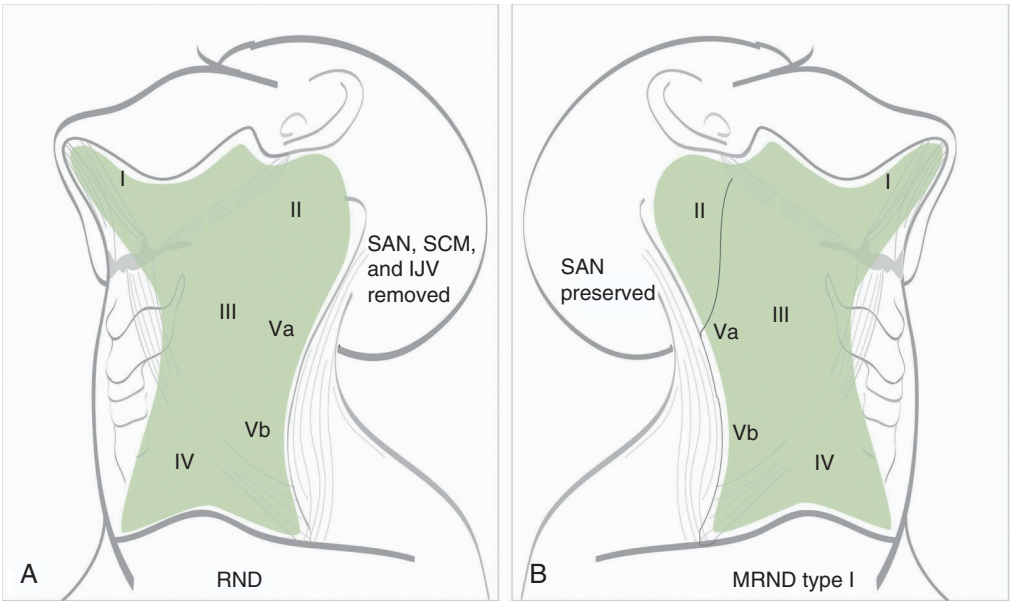


Figure 40-5 Lymph node levels and nonlymphatic structures removed in radical neck dissection **(A)** and modified radical neck dissection type I **(B).** In radical neck dissection for levels I to V, the spinal accessory nerve (SAN), sternocleidomastoid muscle (SCM), and internal jugular vein (IJV) are resected. In a modified radical neck dissection type I for levels I to V, the sternocleidomastoid muscle and internal jugular vein are resected. The spinal accessory nerve is preserved.

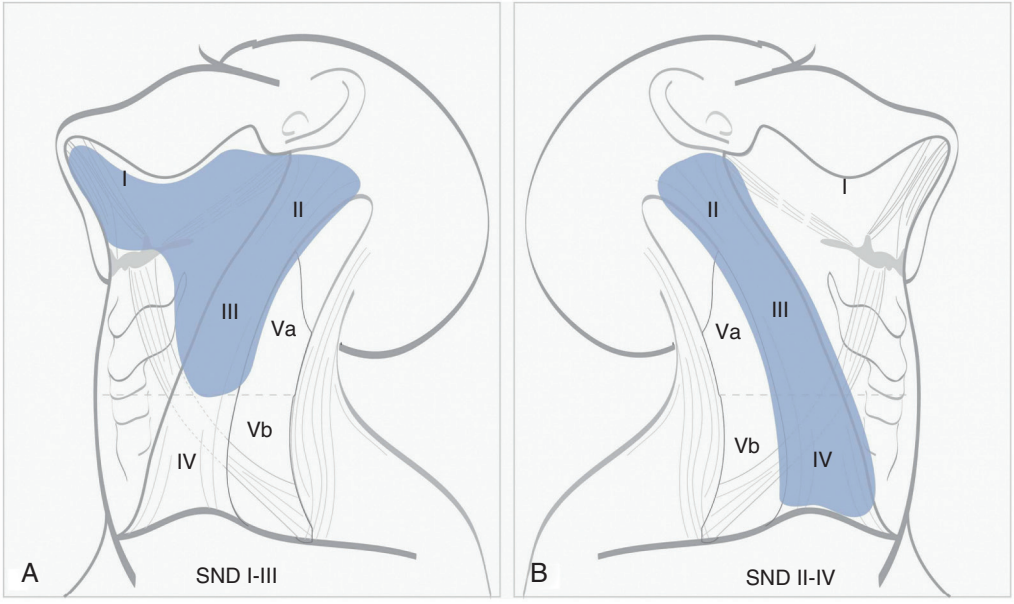


Figure 40-6 Examples of selective neck dissection (SND). In SND I to III or supraomohyoid neck dissection **(A)**, only levels I, II, and III are removed. In SND II to IV or lateral neck dissection **(B)**, only levels II, III, and IV are removed.

dissection classification excluded "named" node dissections (e.g., supraomohyoid node dissection, posterolateral node dissection) and proposed that the term *selective neck dissection* (SND) be followed in parentheses by the node levels or sublevels removed, for example, SND (I to III).[57] Super-selective neck dissection (SSND) is a SND limited to the dissection of two or fewer contiguous neck levels. The feasibility of SSND for residual lymph node disease after chemoradiation was first reported by Robbins et al.[64]

Extended RND is defined by the removal of one or more additional lymph node groups (e.g., parapharyngeal or paratracheal lymph nodes) or nonlymphatic structures (e.g., carotid artery, paraspinal muscles, vagus nerve), or both, nonroutinely resected during a RND. Any additional structures removed should be identified in parentheses.

A method recently introduced in HNSCC for detecting occult micrometastases in the neck is lymphoscintigraphy associated with sentinel lymph node biopsy (SLNB). The concept is based on identification of the primary echelon of lymphatic drainage followed by the harvest of the sentinel lymph node within this basin only, assuming that if the sentinel lymph node is negative, there is no need for a comprehensive neck dissection. The technique was initially proposed for the detection of lymph node invasion in cutaneous melanoma,

and thereafter in various sites.[65-67] SLNB of cervical lymph nodes was introduced as a minimally invasive diagnostic procedure, able to predict more accurately the nodal status in patients who are node-negative with oral and selected oropharyngeal squamous cell carcinoma.[68]

SLNB has been shown to improve staging of clinical N0 (cN0) tumors in patients with early squamous cell carcinoma of the oral cavity and oropharynx by identifying micrometastases.[70,71] Several centers have now adopted SLNB alone as a staging tool for early clinical N0, oral and selected oropharyngeal squamous cell carcinomas.[70] In experienced teams, it is now acknowledged that SLNB is a reliable diagnostic procedure for staging the cN0 neck and identifying patients with occult nodal metastatic disease.[71,72] A recent meta-analysis including 21 prospective studies and 847 patients showed a pooled estimate of sensitivity of 93% and the negative predictive value (NPV) ranged from 80% to 100%. The rate of detection of occult metastases ranged from 14% to 60% (median, 34%). The vast majority of the patients had early oral squamous cell carcinomas.[73] Moreover, it was recently reported in a study including a limited number of patients, that SLNB was associated with significantly less postoperative morbidity as compared to elective neck dissection.[74]

There is evidence supporting further treatment to the neck in patients with micrometastases in sentinel lymph nodes.[77] Regarding isolated tumor cells only, a watchful waiting policy could be warranted, although there is a low risk for metastases in nonsentinel lymph nodes. Larger series are required to establish the importance or significance of micrometastases and isolated tumor cells and to define an acceptable level of incorrectly downstaged isolated tumor cell disease in patients who have other metastases in the neck.

NECK NODE DELINEATION AND IRRADIATION TECHNIQUES

Delineation of the Clinical Target Volume

Several authors have proposed recommendations for the delineation of the neck node levels.[59,78-81] Detailed comparison of these guidelines revealed a few important discrepancies, preventing uniform target volume delineation in the neck among radiation oncologists. A critical review of the two proposals was undertaken in the early 2000s in collaboration with representatives of the major European and North American clinical cooperative groups to generate an international set of guidelines for the delineation of the neck node levels in a node-negative neck.[82] The correspondence between these guidelines and neck dissection procedures was further validated.[83] In the late 2000s, a few amendments were proposed to take into account the specific situation of a node-positive and postoperative neck.[55,84] Most recently, in 2013, a task force comprising opinion leaders in the field of head and neck radiation oncology from European, Asian, Australian/New Zealand, and North American clinical research organizations (DAHANCA, EORTC, HKNPCSG, NCIC CTG, NCRI, RTOG, TROG) was formed to review and update the previously published guidelines on nodal level delineation.[7]

The updated 2014 consensus guidelines for neck node delineation are presented in Table 40-10 and Figure 40-7. The volumes delineated in Figure 40-7 correspond to the clinical target volume (CTV) and do not include margins for organ motion or setup inaccuracy. The boundaries are based on a patient lying supine with the head in a "neutral" position. The terms *cranial* and *caudal* refer to structures closer to the cephalic and pedal ends, respectively. The terms *anterior* and *posterior* were chosen to be less confusing than the terms *ventral* and dorsal, respectively.

It is beyond the scope of this chapter to discuss in depth these recommendations. The reader is referred to the original publication.[7] A few specific issues, however, merit attention.

The proposal for the node level delineation is valid irrespective of the nodal status of the patient, that is, node-negative or node-positive. However the translation from the node levels to CTV delineation may need some adjustments as a function of the nodal status setting. In patients who are node-negative and in patients with a single small lymph node or with several small lymph nodes not abutting one of the surrounding structures (e.g., muscle, salivary gland), the CTV will be defined by the association of one or several of the node levels.

For larger lymph nodes abutting or infiltrating one of the surrounding structures (e.g., sternocleidomastoid muscle, the paraspinal muscles, or the parotid gland), CTV delineation may need to take account of macroscopic and microscopic tumor infiltration outside of the node. Based on experts' opinion, an isotropic expansion by 10 mm to 20 mm into these structures from the visible edge of the node (i.e., the nodal GTV) appears reasonable, excluding bone and airway.[84]

Last, the proposal for the node level delineation still holds for the postoperative situation, at least from a conceptual point of view.

Irradiation Techniques

With the use of three-dimensional conformal radiotherapy (3D-CRT) and intensity-modulated radiotherapy (IMRT), there is no longer a standard recipe for setting up field sizes and borders according to bony landmarks. Instead, the irradiation technique should be selected and adapted so that the entire planning target volume (PTV) receives the prescribed dose within the adopted dose-volume constraints and in full consideration of the International Commission on Radiation Units and Measurements (ICRU) recommendations.[85]

The dose prescription depends on various factors, such as prophylactic versus therapeutic irradiation, or the use of combined-modality treatment, planned neck node dissection, and postoperative irradiation, and so on, which are beyond the scope of this chapter for comprehensive review. For primary radiotherapy, a typical prophylactic dose of about 50 Gy, 54 Gy, or 56 Gy in 2, 1.8, or 1.6 Gy per fraction is given over 5 to 7 weeks, and a therapeutic dose of about 70 Gy in 2 Gy per fraction is given over 7 weeks. For postoperative irradiation, depending on the risk factors, doses usually range from 60 Gy to 66 Gy in 2-Gy fractions over 6 to 6.5 weeks.

CONTROL OF THE N0 NECK

Guidelines generally recommend performing prophylactic treatment of the neck in patients with primary HNSCC clinically staged at N0 but having a probability of 20% or more of occult lymph node metastases.[86] Elective neck dissection and elective neck irradiation are equally effective in preventing disease occurrence in the cN0 neck. The choice between these two procedures generally depends on the treatment modality chosen for the primary tumor and many other factors. However, the basic rule that should govern the choice between surgery and radiotherapy (RT) is to favor a single-modality treatment if possible, avoiding overtreatment. For example, supraglottic laryngectomy with selective neck node dissection is just as effective as primary radiation therapy of the larynx and neck for treating a T1 or T2N0 supraglottic laryngeal tumor. For such a disease stage, the need for postoperative RT quite low. Conversely, for a T3N0 supraglottic laryngeal tumor, a conservative treatment approach with primary RT or concomitant chemoradiation should be favored because of the

The sentinel lymph node can be identified by peritumoral injection of a radioactive tracer. The tracer mimics lymph spread and accumulates in the first-echelon node. With the help of lymphoscintigraphy and a gamma probe, the sentinel lymph node is localized and selectively excised. Histologic evaluation of the sentinel lymph node allows for pathologic staging of the neck. Additionally, lymphoscintigraphy and SLNB provide information on the presence of atypical basins or lymphatic flow that is not predictable and would typically not be addressed by a selective node dissection.[69]

Because sentinel lymph nodes are worked up thoroughly, a high number of occult metastases are revealed. Occult metastases are, by definition, clinical stage N0 neck metastases detected by histologic testing. They are further divided into macrometastases (>2 mm in largest dimension), micrometastases (<2 mm in greatest dimension), and isolated tumor cells.[75-77] Isolated tumor cells are recognized as a separate entity and are single tumor cells or small clusters of tumor cells not more than 0.2 mm in greatest dimension. Such cells are typically detected after immunohistochemical or molecular biologic testing only, and they do not show evidence of metastatic activity (e.g., proliferation or stromal reaction) or penetration of vascular or lymphatic sinus walls.[76] The debate continues whether patients with micrometastases or isolated tumor cells in sentinel lymph nodes have a risk similar to that for patients with metastases in the neck who have clinically invaded lymph nodes.

In conclusion, with a high detection rate and a high sensitivity, SLNB seems clearly an accurate and safe diagnostic modality to detect occult lymph node metastases in early oral cavity squamous cell carcinoma clinically N0. The conclusions of the meta-analysis gathering many studies with a small number of patients need to be validated by large multicenter studies with long-term follow-up. Also, prospective studies are needed to determine whether the implementation of SLNB alone would reduce patient morbidity but still be as effective as SND. In particular, the effect of SLNB on at least one third of patients with a positive SLNB remains an issue because the pathologic status of the SLN is only known a few days after the surgical procedure. Those patients require two surgical interventions instead of one to complete the neck dissection.[72] Some of those patients could have some delay before starting postoperative radiotherapy, when indicated. Furthermore, the morbidity in those patients should be compared with the morbidity in a group of patients who underwent SND electively. Development of rapid analysis of the SLN using molecular biology techniques could solve this issue.

TABLE 40-10 Consensus Boundaries, Node Levels I-X

Level	Boundaries					
	Cranial	**Caudal**	**Anterior**	**Posterior**	**Lateral**	**Medial**
Ia, submental	Mylohyoid m.	Platysma m. (caudal edge of ant belly digastric m.)	Symphysis menti	Body of hyoid bone/ mylohyoid m.	Medial edge of ant. belly, digastric m.	n.a.
Ib, submandibular	Cranial edge, submandibular gland; ant, mylohyoid m.	Plane through caudal edge hyoid bone and mandible; alternatively caudal edge submandibular gland (most caudal); platysma m.	Symphysis menti	Post edge submandibular gland (caudal)/post belly digastric m. (cranial)	Medial aspect mandible (inner side) down to caudal edge; platysma m. (caudal); medial pterygoid m. (posterior)	Lat edge of ant belly of digastric m (caudally); post belly of digastric m (cranially)
II, upper jugular	Caudal edge lateral process of C1	Caudal edge body of hyoid bone	Post edge submandibular gland/post edge of post belly of digastric m.	Post edge sternocleidomastoid m.	Deep (medial) surface of sternocleidomastoid m./platysma m./parotid gland/posterior belly of digastric m.	Medial edge of internal carotid artery; scalenius m.
III, middle jugular	Caudal edge body of hyoid bone	Caudal edge cricoid cartilage	Ant edge sternocleido-mastoid m.; post third thyrohyoid m.	Post edge sternocleidomastoid m.	Deep (medial) surface sternocleidomastoid m.	Medial edge common carotid artery; scalenus m.
IVa, lower jugular	Caudal edge cricoid cartilage	2 cm cranial to sternal manubrium	Ant edge of sternocleido-mastoid m. (cranial); body of sternocleido-mastoid m. (caudal)	Post edge sternocleidomastoid m. (cranial); scalenus mm. (caudal)	Deep (medial) surface of sternocleidomastoid m. (cranial); lat edge sternocleidomastoid m. (caudal)	Med. edge common carotid art; lat edge thyroid gland; scalenus m. (cranial); medial edge sternocleidomastoid m. (caudal)
IVb, medial supraclavicular	Caudal border of level IVa (2 cm cranial to sternal manubrium)	Cranial edge of sternal manubrium	Deep surface sternocleidomastoid m.; deep aspect of clavicle	Ant edge scalenius m. (cranial); lung apex, brachiocephalic vein, brachiocephalic trunk (R side), common carotid and sub-clavian arteries on the L side (caudal)	Lateral edge of scalenius m.	Lateral border of level VI (pretracheal component); medial edge common carotid artery
Va-b, posterior triangle*	Cranial edge of body of hyoid bone	Plane just below transv cervical vessels	Post edge sterocleido-mastoid m	Ant border trapezius m.	Platysma m.; skin	Levator scapulae m.; scalenus m (caudal)
Vc, lateral supra-clavicular	Plane just below transv cervical vessels (caudal border level V)	2 cm cranial to sternal manubrium (caudal border level IVa)	Skin	Ant border trapezius m. (cranial); ±1 cm ant to serratus ant m. (caudal)	Trapezius m. (cranial); clavicle (caudal)	Scalenus m.; lat edge sternocleidomastoid m, lat edge level IVa

VIa, ant jugular	Caudal edge hyoid bone or submandibular gland (most caudal)	Cranial edge sternal manubrium	Skin; platysma m.	Ant aspect infrahyoid (strap) m.	Ant edge both sternocleidomastoid m.	n.a.
VIb, prelaryneal, pretracheal, paratracheal, rec. laryngeal nerve	Caudal edge thyroid cartilage	Cranial edge sternal manubrium	Post aspect infrahyoid (strap) m	Ant aspect larynx, thyroid gland and trachea (prelaryngeal and pretracheal LN; prevertebral m (R) ; esophagus (L)	Common carotid artery, both sides	Lat aspect trachea and esophagus (caudally)
VIIa, retro-pharyngeal	Upper edge C1 body; hard palate	Cranial edge body of hyoid bone	Post edge sup or middle pharyngeal constrictor m.	Longus capitis m., longus colli m.	Medial edge int carotid artery	Line parallel to lat edge of longus capiti m.
VIIb, retrostyloid	Base of skull (jugular foramen)	Caudal edge lat process of C1(upper limit, level II)	Post edge prestyloid parapharyngeal space	C1 vertebral body, base of skull	Styloid process; deep parotid gland	Medial edge int carotid artery
VIII, parotid node	Zygomatic arch, ext auditory canal	Angle of mandible	Post edge mandibular ramus and masseter m. (lat); medial pterygoid m. (med)	Ant edge sternocleidomastroid m. (lat); post belly digastric m. (med)	SMAS layer subcutaneous tissue	Styloid process and styloid m.
IX, buccofacial	Caudal edge of orbit	Caudal edge mandible	SMAS layer subcutaneous tissue	Ant edge masseter m. & corpus adiposum buccae (Bichat's fat pad)	SMAS layer subcutaneous tissue	Buccinator m.
Xa, retroauricular nodes	Cranial edge ext auditory canal	Tip of mastoid	Ant edge mastoid (caudal) Post edge ext auditory canal (cranial)	Ant border occipital LN, post edge sternocleidomastroi m.	Subcutaneous tissue	Splenius capitis m. (caudal); temporal bone (cranial)
Xb, occipital nodes	Ext occipital protuberance	Cranial border level V	Post edge sternocleido-mastoid m.	Ant (lat.) edge trapezius m.	Subcutaneous tissue	Splenius capitis m.

Ant, *Anterior;* art, *artery;* ext, *external;* int, *internal;* lat, *lateral;* L, *left;* LN, *lymph nodes;* med, *medial;* m., *muscle;* mm., *muscles;* n.a., *not applicable;* post, *posterior;* sup, *superior;* R, *right;* transv, *transverse;*
**Surgically, level V is subdivided in two groups of upper (Va) and lower (Vb) nodes according to their respective relationships with the cricoid cartilage.*

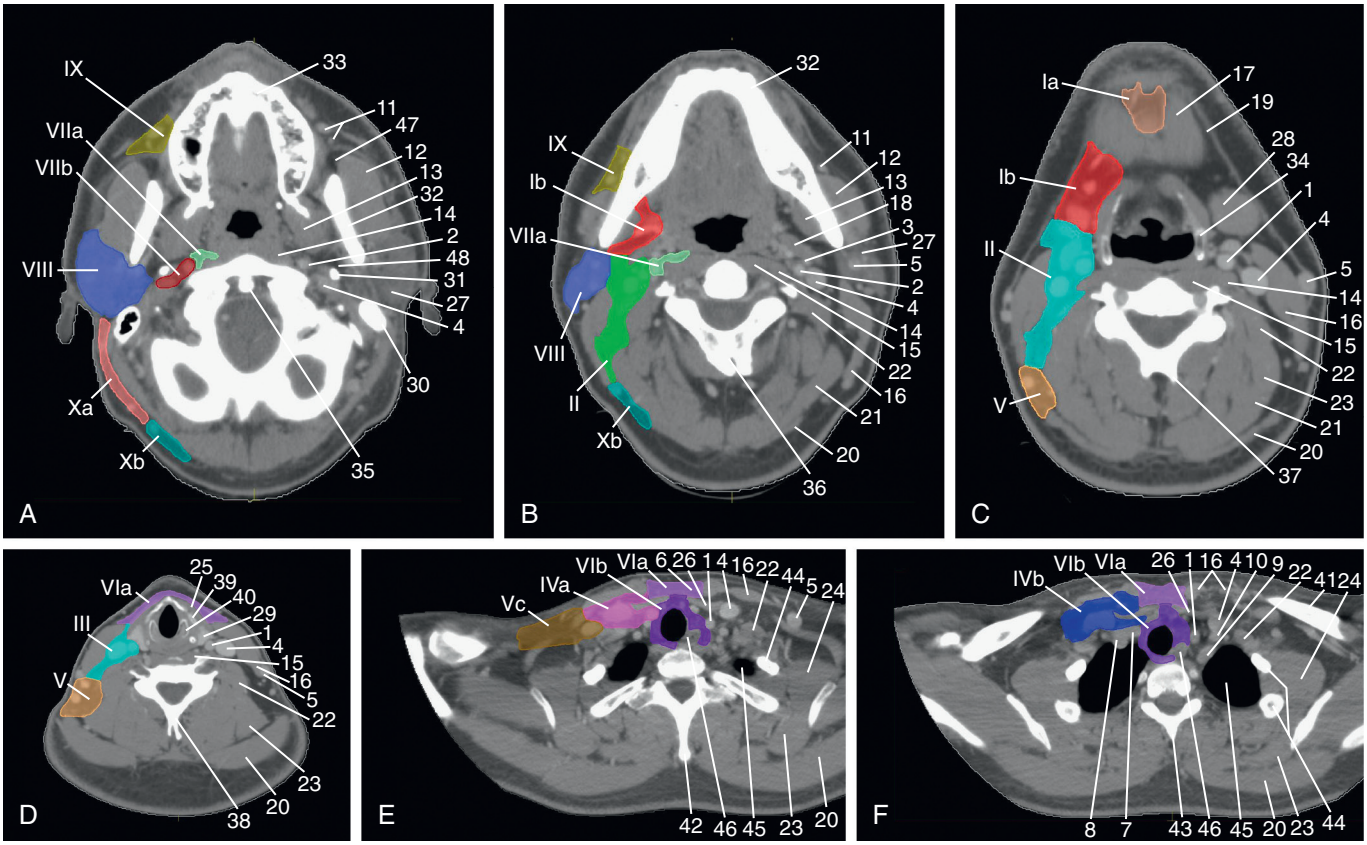


Figure 40-7 Head and neck CT sections performed on a 32 year-old volunteer immobilized with a head-neck-shoulder thermoplastic mask. The head was set in a "neutral" position. Sixty mL of iodinated contrast medium (Omnipaque 350, HealthCare, Diegem, Belgium) was injected intravenously at a rate of 1 mL/s, then after a 3-minute gap, another 50 mL were injected at a rate of 1.5 mL/s. The examination was performed on a Toshiba (Toshiba Aquilon LB, Toshiba Medical Systems Corporation, Japan) helicoidal CT (300 mAs and 120 keV) using a slice thickness of 2.0 mm, an interval reconstruction of 2.0 mm and a helicoidal pitch of 11. CT sections were reconstructed using a 512 × 512 matrix. Sections were taken at the level of the top edge of the first cervical vertebra (**A**), the bottom edge of the second cervical vertebra (**B**), midfourth cervical vertebra (**C**), the bottom edge of the sixth cervical vertebra (**D**), midfourth thoracic vertebra (**E**), and top edge of the second thoracic vertebra (**F**). Each node level corresponds to node groups, and thus does not include any security margin for organ motion, patient motion or set-up inaccuracy. 1: common carotid artery; 2: internal carotid artery; 3: external carotid artery; 4: internal jugular vein; 5: external jugular vein; 6: anterior jugular vein; 7: right brachiocephalic trunk; 8: right brachiocephalic vein; 9: left subclavian artery; 10: left subclavian vein; 11: facial vessels; 12: masseter muscle (m.); 13: pterygoid m.; 14: longus capitis m.; 15: longus colli m.; 16: sternocleidomastoid m.; 17: digastric (anterior belly) m.; 18: digastric (posterior belly) m.; 19: platysma m. 20: trapezius m.; 21: splenius capitis m.; 22: scalenus m.; 23: levator scapulae m.; 24: serratus anterior m.; 25: thyrohyoid m.; 26: sternohyoid m.; 27: parotid gland; 28: submandibular gland; 29: thyroid gland; 30: mastoid; 31: styloid process; 32: mandible; 33: maxilla; 34: hyoid bone; 35: odontoid process; 36: second cervical vertebra; 37: fourth cervical vertebra; 38: sixth cervical vertebra; 39: thyroid cartilage; 40: cricoid cartilage; 41: clavicle; 42: first thoracic vertebra; 43: second thoracic vertebra; 44: rib; 45: lung apex; 46: esophagus; 47: Bichat's fat pad; 48: prestyloid parapharyngeal space.

necessity of postlaryngectomy RT and the non-superiority of the surgical approach (Figure 40-8).

Neck Control after Neck Node Dissection

SND has become more widely used despite some concerns that it may not be as effective as a more comprehensive form of neck dissection, such as a modified RND. Anticipating the conclusions that could be drawn from the MSKCC data with regard to the extent of the neck dissection, several groups have been performing SND since the 1950s.[46,48,54,87-97] Such selective neck procedures were initially proposed for patients who were clinically node-negative and later extended to patients who were clinically node-positive. These studies are biased because the patients treated by a selective procedure were probably highly selected with regard to the tumor site, tumor stage, and nodal status. In addition, in most of these patients, postoperative RT was usually performed in the presence of high-risk features for primary tumor or neck recurrence, such as close or positive resection margins, multiple node involvement, large node infiltration, or extracapsular spread. It is likely that the irradiated field encompassed the node levels that were not dissected but that could be at risk for microscopic infiltration.

Originally, SND was typically considered a method for accurately staging neck disease but not one that could affect regional control and survival rates. A retrospective review of 359 patients with stage T1 to T2 N0 squamous cell carcinoma of the oral cavity and oropharynx treated at the University of Pittsburgh showed significant improvement in regional control, disease-free survival (DFS), and regional recurrence-free survival rates for the group of patients who underwent SND along with primary tumor excision as compared with another group of patients who underwent excision of the primary tumor only.[90] The patients who underwent SND were three times more likely to receive postoperative RT, most likely because of identification of adverse prognostic factors in the pathologic specimen. In a prospective randomized trial comparing modified RND and SND (I to III) (supraomohyoid

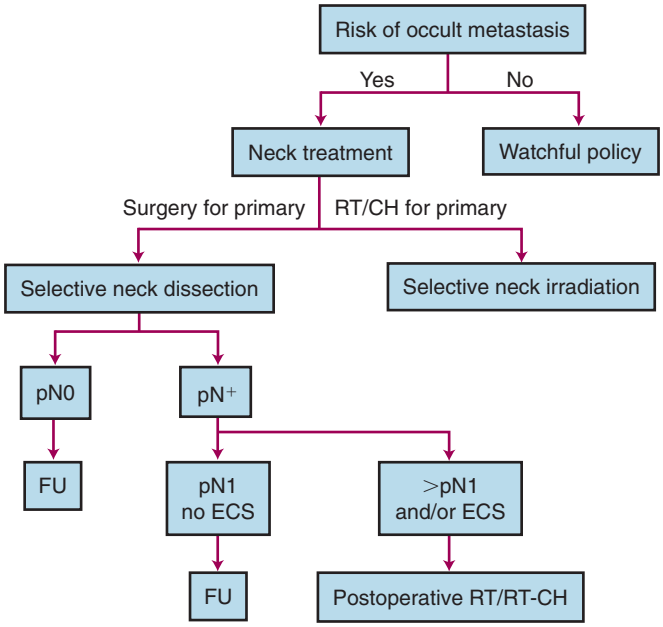


Figure 40-8 Treatment algorithm for clinically negative neck (N0) disease. *ECS,* Extracapsular spread; *FU,* follow-up; *RT,* radiotherapy; *RT-CH,* concomitant chemoradiation.

nodes) for patients who were clinically node-negative with T2 to T4 tumors of the oral cavity, the Brazilian Head and Neck Cancer Study Group was unable to show any difference either in 5-year actuarial overall survival (OS) or in the rate of neck failure.[87] Postoperative irradiation was delivered in cases with a positive margin of the primary tumor or positive lymph nodes. This study is however biased by the fact that patients included in the SND group and found to have a positive lymph node (on frozen section) during the neck dissection were offered a modified RND.

With these limitations in mind, in some of these studies the level of the neck recurrence was reported, allowing an estimate of the failure rate in the neck inside and outside the dissected levels (Table 40-11). In most of these studies, neck recurrence was reported only in patients in whom the primary tumor had been controlled, excluding neck recurrence as a result of reseeding from the recurrent primary tumor. After SND (I to III) or SND (II to IV), the rate of neck failure in nondissected levels was low, typically below 10%. Consequently, SND can be considered the optimal procedure for surgically managing N0 neck disease in patients with a high risk of occult lymph node metastasis.

Neck Control after Radiotherapy

Table 40-12 presents the percentage of neck recurrences in large retrospective series of pharyngolaryngeal squamous cell

TABLE 40-11 Neck Failure after Selective Neck Dissection for Squamous Cell Carcinomas of the Oral Cavity, Oropharynx, Hypopharynx, and Larynx

Author	Year	Site	Clinical Category (AJCC 1980)	Dissected Levels	Neck Failure (Percentage of Patients with Primary Tumor Controlled)		
					Total	Dissected Levels	Undissected Levels
Byers[81]	1988	Oral cavity, oropharynx, hypopharynx, larynx	T1-4 N0	I, I-III, II-IV, I-V	45/299 (15%)[a]	31/299 (10%)	14/299 (5%)[b]
Byers[52]	1985	Oral cavity, oropharynx	T1-4 N0-3	I-III	21/234 (9%)	16/234 (7%)	5/234 (2%)
Byers[82]	1999	Oral cavity, oropharynx, hypopharynx, larynx	T1-4 N0-1-2b	I, I-III, I-IV, II-IV	37/517 (7%)	26/517 (5%)	11/517 (2%)
Byers[82]	1999	Oral cavity, oropharynx	T1-4 N0-1-2b	I-III, I-IV	19/284 (6.5%)	13/284 (4.5%)	6/284 (2%)
Brazilian[80] HNCSG	1998	Oral cavity	T2-4 N0	I-III[c]	6/64 (9%)	3/64 (4.5%)	3/64 (4.5%)[d]
Duvvuri[83]	2004	Oral cavity, oropharynx	T1-2 N0	I-III	17/180 (9.5%)	12/180 (6.5%)[e]	5/180 (3%)
Pellitteri[87]	1997	Oral cavity + oropharynx Hypopharynx + larynx	T1-4 N0-3 T1-4 N0-3	I-III/I-IV II-IV	7/42 (17%) 1/25 (4%)	2/42 (5%) 1/25 (4%)	5/42 (12%)[f] 0/25 (0%)
Pitman[88]	1997	Oral cavity, orohypopharynx, larynx	T1-4 N0	I-III/I-IV II-IV	5/142 (3.5%)	5/142 (3.5%)	0/142 (0%)
Spiro[44]	1988	Oral cavity, oropharynx, larynx	T1-4 N0-1	I-III	12/107 (11%)	5/107 (4.5%)	7/107 (6.5%)
Spiro[89]	1996	Oral cavity, oropharynx (98%)	T1-4 N0-1-2a-2b	I-III	16/296 (5.5%)	8/296 (2.7%)	8/296 (2.7%)
Schmitz[90]	2009	Oral cavity, oropharynx, hypopharynx, larynx	T1-4 N0-3	I-III/I-IV II-IV/II-V	6/210 (2.9%)[g] 1/39 (2.6%)[h]	4/210 (1.9%) 0/39 (0%)	2/210 (0.9%) 1/39 (2.6%)

AJCC, *American Joint Committee on Cancer;* HNCSG, *Head and Neck Cancer Study Group.*

[a]*Patients treated by surgery alone.*

[b]*Six of these patients had failure on the contralateral undissected neck.*

[c]*Part of a randomized study comparing radical modified versus supraomohyoid neck dissection.*

[d]*One of these patients had failure on the contralateral undissected neck.*

[e]*Including one neck failure of unknown location.*

[f]*Three of these patients had failure on the contralateral undissected neck.*

[g]*One of these patients had failure on the contralateral undissected neck. Another patient presented with late neck recurrence, and a second primary tumor occurred 11 months later.*

[h]*One of these patients had failure on the contralateral undissected neck.*

carcinomas treated with conventional fractionated RT.[98-100] Some of the patients reported in these series were treated in the late 1950s, so the data must be interpreted with caution because of the likelihood of large uncertainties about the absolute dose calculation and dose distribution. Altogether, the neck control rates reached more than 92% after radiotherapy. After salvage surgery, the ultimate neck control rate reached a range of 94% to 100%. As expected, because of the high probability of regional control obtained with standard fractionation regimens, altered fractionation regimens or combined chemoradiation regimens did not improve the neck control rates.[101,102] All of these studies were performed using two-dimensional irradiation techniques, that is, with target volumes extending typically from the base of the skull to the clavicles.

With the introduction of 3D-CRT, IMRT, and selective neck irradiation, one important issue is the potential risk of geographic miss outside of the irradiated volumes. Eisbruch et al[103] reported a series of 135 patients treated bilaterally from 1994 to 2002 with 3D-CRT or IMRT for primary tumors located mainly in the oropharynx ($n = 80$) and without node metastasis in the contralateral neck. Of these, 73 patients received postoperative RT, but none had neck node dissection on the contralateral neck. In the contralateral neck, the CTV typically included the levels II to IV and retropharyngeal nodes. For the contralateral level II nodes, the upper limit was set at the junction between the posterior belly of the digastric muscle and the jugular vein. The median prophylactic dose was 50.4 Gy or 50 Gy in fractions of 1.8 Gy or 2 Gy. With a median follow-up of 30 months (range, 6 to 105 months), 15 patients had a regional recurrence (of these, 6 also had a primary tumor recurrence), 11 on the ipsilateral side and 4 on the contralateral side. Only 1 of the 15 patients presented a retropharyngeal node recurrence marginal to the CTV. Using a similar treatment philosophy, Bussels et al[104] did not report any recurrence on the ipsilateral side of the neck with N0 disease treated with parotid-sparing 3D-CRT in a series of 72 patients with oral cavity and pharyngolaryngeal squamous cell carcinoma. Chao et al[105] also looked at the pattern of recurrence in a series of 126 patients treated postoperatively ($n = 74$) or primarily ($n = 52$) for HNSCC by IMRT from 1997 to 2000. In this series, the lower neck (below the thyroid notch) was treated with a "traditional" anterior field. With a median follow-up of 26 months, 17 recurrences (13%) were observed. Six of these patients had recurrence outside of the target volumes, of which only one was in the lower neck of a patient with N0 disease.

CONTROL OF THE N1 TO N3 NECK

Neck Control after Surgery Alone

The surgical management of N1 neck tumors is more controversial (Figure 40-9). Traditionally, a comprehensive neck

TABLE 40-12 Neck Failure after Primary Radiotherapy for Patients Who Are Node-Negative

Authors	Years	Primary Tumor Site	No. Patients	Dose/Overall Treatment Time	Control of Neck after Radiotherapy	After Salvage Surgery
Bernier and Bataini[91]	1958-1974	Oropharynx, hypopharynx, larynx	611	45 Gy-55 Gy/4.5-5.5 wk	93%	Not stated
Johansen[93]	1963-1991	Oropharynx, hypopharynx, larynx	1324	57 Gy-72 Gy/6-9 wk*	92% at 10 years	94% at 10 years
Alpert[92]	1971-1998	Supraglottic larynx	98	50 Gy/5 wk	96.7%	100%

Including 28% of patients with a split course.

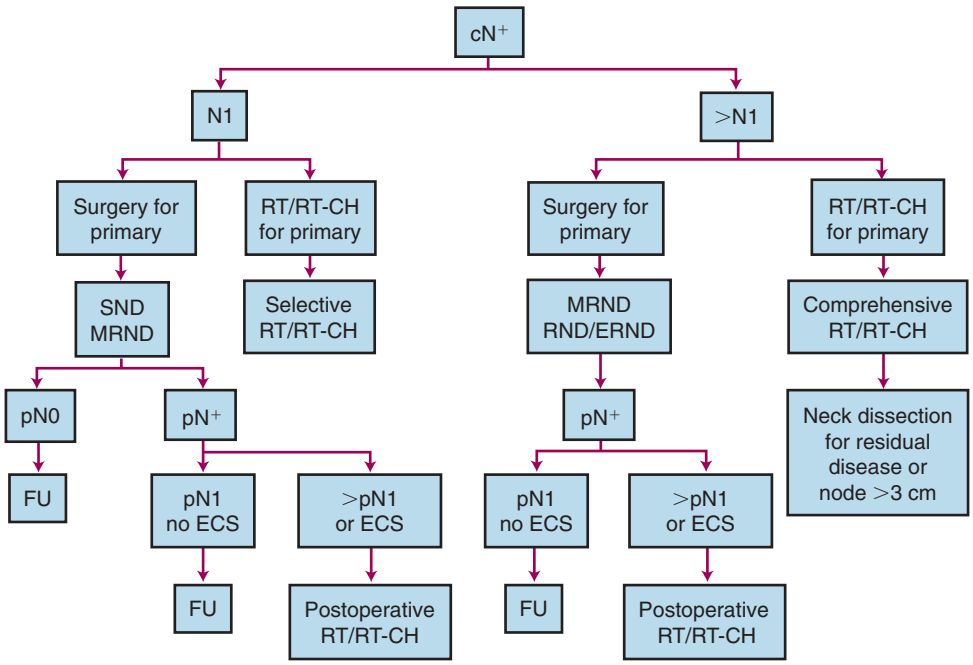


Figure 40-9 Treatment algorithm for clinically positive neck disease. *ECS,* Extracapsular spread; *ERND,* extended radical neck dissection; *FU,* follow-up; *MRND,* modified radical neck dissection; *RND,* radical neck dissection; *RT,* radiotherapy; *RT-CH,* concomitant chemoradiation; *SND,* selective neck dissection.

dissection (RND and modified RND) has been the surgical standard for patients presenting with neck disease. Andersen et al[106] reported that the rates of regional recurrences in the dissected neck following RND or modified RND type I for N1 or N2 disease were similar. Selective procedures have, however, gained popularity. In the retrospective study by Byers et al,[89] including 517 SND procedures mainly for patients with N0 or N1 neck disease, 50 patients had pathologic N1 disease. Of these patients, 36 received postoperative RT for the presence of risk factors associated either with the primary tumor or the nodal site and only 1 (3%) presented with a regional recurrence. In patients who did not receive irradiation despite the presence of risk factors, 5 of 14 (36%) had neck failure. In a large retrospective review of 296 selective node dissections in levels I to III, Spiro et al[96] reported a rate of regional failure of 6.5% in patients staged with a pathologically positive neck. Most patients with pathologically invaded lymph nodes had postoperative RT. Recently, Schmitz et al[97] reported a regional failure rate of 8% in neck disease of pathologic N1 without better regional control in the necks treated with postoperative irradiation, suggesting that postoperative irradiation is not justified in pathologic N1 neck disease without extracapsular spread. With the inherent limitation of retrospective studies, it appears that SND for patients with limited neck disease is a safe procedure, providing that postoperative irradiation is given in the presence of risk factors for regional relapse.

Despite the use of aggressive single and combined treatment protocols, patients with locally advanced metastatic neck disease still have a poor prognosis because of the high risk of regional failure and distant metastases.[107,108] However, the concept of using a less than radical procedure has gained acceptance even for advanced regional disease. Khafif et al[109] reported the results of 118 patients with N2 to N3 disease treated with RND or modified RND and was not able to find any difference in OS between the two groups. The recurrence rate in the modified RND group increased significantly in comparison with the group of patients treated with standard RND (52% versus 33%), but some modified RND procedures were not really comprehensive. In a study comparing RND and modified RND (type I) in 212 patients with N2 and N3 lesions, the MSKCC group reported an overall 5-year neck control rate of 86% and a 5-year actuarial survival rate of 61%.[106] No difference was found between the two groups. Adjuvant postoperative RT enhances regional control but does not seem to significantly improve survival rates.[110] Investigators of the Royal Prince Alfred Hospital in Sydney, Australia, reported the outcome of 181 patients who had 233 neck dissections for N2 to N3 disease (163 extended RND, RND, or modified RND and 70 SND).[111] Postoperative RT to the neck was given in 82% of the patients. At 5 years, control of disease in the treated neck was achieved in 86%. Adjuvant RT significantly improved neck control rates ($p = 0.004$) but did not alter survival rates.

The utility of extended RND depends on whether acceptable control rates are attainable without prohibitive morbidity. Shaha[112] described the results in 40 patients with N2 to N3 tumors treated by extended RND combined with postoperative RT. The regional control rate reached 70% at 2 years, with one perioperative death. The morbidity of extended RND depends on the additional structure or structures removed. If a common carotid artery is removed, the perioperative mortality rate ranges from 6% to 58%.[113,114] However, when the structures sacrificed are of no major neurovascular significance (e.g., parotid gland lymph nodes, paraspinal muscles), the additional morbidity is minimal.

Neck Control after Primary Radiotherapy

The lower probability of regional control of the positive neck with RT has been documented by several retrospective series performed in the pre-HPV era.[98,100,115] In a series from the Institut Curie in Paris,[98] 1646 patients with squamous cell carcinoma of the oropharynx and pharyngolarynx had a 3-year regional control probability of 98%, 90%, 88%, and 71% for N0, N1, N2, and N3 lesions (AJCC 1976 classification), respectively. The nodal size was an even more discriminating factor, with nodal failure rates of 6%, 14%, and 39% for nodes below 3 cm, between 4 cm and 7 cm, and more than 7 cm, respectively.[115] In this series, 75% of the neck nodes were treated by a form of concomitant boost approach with total doses in the range of 70 Gy to 85 Gy in 5 to 6 weeks. In the series of 458 patients who were node-positive with squamous cell carcinoma of the larynx and pharynx treated at Aarhus University Hospital from 1963 to 1991, the 5-year neck node control rate reached 68%, 68%, and 56% for N1, N2, and N3 lesions (UICC 1982 stage), respectively.[100]

An important issue in the management of positive neck disease by RT is whether these results can be improved by hyperfractionated or accelerated regimens, or concomitant chemoradiation. In randomized studies comparing a standard fractionated regimen with an altered fractionated regimen, no improvement was observed between the two arms[116-118] (Table 40-13). In the European Organization for Research and

TABLE 40-13 Probability of Neck Node Control after Altered Fractionated Regimens

Author	Primary Tumor Site	Stage	Treatment Schedule	Control of Neck	
				Standard Arm	Experimental Arm
Horiot[109] EORTC 22791 (n = 325)	Oropharynx	T2-3N0-1M0	Standard: 70 Gy/35 f/7 wk Experimental: 80.5 Gy/70 f/7 wk	N0: 93% at 5 years N1: 90% at 5 years	N0: 93% at 5 years N1: 90% at 5 years
Overgaard[110] DAHANCA 6 and 7 (n = 1476)	Oral cavity, pharynx, supraglottic larynx	Stages I-IV	Standard: 62 Gy-68 Gy/6-7 wk Experimental: 62-68 Gy/5-6 wk	N^-: 68% N^+: 44%	N^-: 77%*† N^+: 52%*‡
Cummings[111] (n = 331)	Oropharynx, hypopharynx, larynx	Stages III-IV	Standard: 51 Gy/20 f/4 wk Experimental: 58 Gy/40 f/4 wk	All stages: 71% at 5 years	All stages: 68%§ at 5 years

DAHANCA, *Danish Head and Neck Cancer Group;* EORTC, *European Organization for Research and Treatment of Cancer;* f, *fraction.*

**Locoregional control.*

†*Odds ratio (95% CI): 0.65 (0.50 to 0.85).*

‡*Odds ratio (95% CI): 0.72 (0.49 to 1.05).*

§$p = 0.80$.

TABLE 40-14 Probability of Neck Node Control after Concomitant Chemoradiation

Authors	Primary Tumor Site	Stage	Treatment Schedule	Control of Neck	
				Standard Arm	Experimental Arm
Calais[112] (*n* = 222)	Oropharynx	Stages III-IV*	Standard: 70 Gy/7 wk Experimental: 70 Gy/7 wk + carboplatin and 5-FU × 3	All stages: 69%	All stages: 81%
Lavertu[113] (*n* = 100)	Oral cavity, pharynx, larynx	Stages III-IV†	Standard: 65-72 Gy/7 wk Experimental: 65-72 Gy/7 wk + cisplatin and 5-FU × 2	N1: 6/10 (60%) N2-3: 13/27 (48%)	N1: 8/8 (100%) N2-3: 17/26 (65%)

5-FU, *5-fluorouracil.*
**75% of patients were node positive.*
†*71% of patients were node positive.*

Treatment of Cancer (EORTC) 22791 study, only patients with N0 or N1 neck disease were included, and because of the good control of neck disease in the standard arm, it was not surprising that the hyperfractionated regimen did not bring any benefit.[116] In the Danish Head and Neck Cancer Group (DAHANCA) 6 and 7 trials, no significant regional improvement was observed with the accelerated regimen in patients who were node-positive.[117] Similarly, despite a benefit in OS, the Toronto trial did not observe any increase in the control of the neck with an accelerated hyperfractionated regimen.[118] Contrary to results achieved with altered fractionation regimens, concomitant chemoradiation regimens appear to have an impact on the control of disease in the neck[119,120] (Table 40-14). In the study by Calais et al,[119] all neck stages were analyzed together. However, because 75% of the patients were node positive, it is unlikely that the 12% improvement rate resulted only from a beneficial effect in the patients with N0 lesions. In the study by Lavertu et al,[120] which included fewer patients, the improvement in node control was observed for all positive neck categories.

Indications for Postoperative Irradiation or Chemoradiation

The benefit of postoperative RT in HNSCC progressively emerged in the 1970s and 1980s as a standard of care for patients at high risk of locoregional relapse after surgery.[121-124] Prognostic indicators for locoregional relapse after surgery include the primary disease site, surgical margins at the primary site, presence of perineural invasion, number of metastatic lymph nodes, and presence of extracapsular rupture.[125,126] Based on the clustering of these pathologic factors, MDACC proposed to stratify patients into three risk categories, conditioning the need for postoperative RT[127] (Table 40-15). In the absence of any risk factor, the need for postoperative RT could not be shown. Patients with extracapsular rupture or a combination of two or more risk factors were identified as being at high risk of locoregional relapse, and for these patients a randomized study showed the benefit of a radiation dose of 63 Gy (in 35 fractions) as compared with 57.6 Gy (in 32 fractions). For patients with only one risk factor other than extracapsular rupture, a dose of 57.6 Gy was shown to be optimal. A subsequent study from the same group further validated the use of these categories of risk factors and also documented the time between surgery and the start of postoperative RT and the total treatment time (from surgery to the end of RT) as additional risk factors.[128] In this study, it was also shown that patients with a high risk of relapse benefited from accelerated treatment (63 Gy in 5 weeks versus 63 Gy in 7 weeks) in terms of both locoregional control and survival.

With the need to further improve locoregional control rates after surgery and postoperative RT, a few trials combining

TABLE 40-15 Prognostic Factors for Locoregional Relapse after Surgery

Moderate Risk	High Risk
Positive margin at the primary (R1) or close margin (<5 mm)	Extracapsular spread (ECS)
Primary tumor in the oral cavity	A combination of two or more of the moderate risk factors
Perineural invasion	
Two or more invaded lymph nodes	
Two or more invaded node levels	
Invaded node(s) >3 cm in diameter	
More than 6 wk between surgery and start of radiotherapy	

From Peters LJ, Goepfert H, Ang KK, et al: Evaluation of the dose for postoperative radiation therapy of head and neck cancer: first report of a prospective randomized trial. Int J Radiat Oncol Biol Phys 26:3–11, 1993.

postoperative concomitant chemotherapy and RT were reported in the 1990s.[129,130] Although the results favored the combined approach, these studies did not really influence the pattern of care of patients primarily treated with surgery. The European Organization for Research and Treatment of Cancer (EORTC) and the Radiation Therapy Oncology Group (RTOG) conducted similarly designed studies aimed at assessing the benefit of postoperative RT (60 Gy to 66 Gy) combined with cisplatin (100 mg/m^2) given on days 1, 22, and 43 for patients with a variety of risk factors that were slightly different between the two trials.[131,132] In the EORTC study, a highly statistically significant benefit in favor of the combined treatment was observed for both locoregional control and OS (Table 40-16). In the RTOG study, the benefit in locoregional control probability did not translate into a statistically significant difference in survival rates. Combined-modality treatment did not decrease the incidence of distant metastasis in either of these studies. In both studies, the concomitant use of chemotherapy significantly enhanced the acute local toxicity of radiotherapy, and only half the patients could actually receive the full treatment as planned. A meta-analysis of these two studies demonstrated a statistically significant benefit of combined chemoradiation but only in patients who had positive surgical margins or extracapsular spread, that is, patients with the highest risk of relapse after surgery.[133] For the other patients, RT alone can still be considered as a standard of care.

Indications for Postradiotherapy Neck Node Dissection

Advances in chemoradiation for advanced head and neck carcinoma have shown that organ preservation is feasible without compromising DFS and OS.[134,135] This strategy has led to

TABLE 40-16 Efficacy of Concomitant Chemotherapy and Postoperative Radiotherapy

Authors	Site	Regimen	Locoregional Control Rate		Overall Survival Rate	
			Radiotherapy	Chemoradiation	Radiotherapy	Chemoradiation
Bernier[124] (n = 334)	Oral cavity, oropharynx, hypopharynx, larynx	66 Gy (6.5 wk) vs. 66 Gy (6.5 wk) + cisplatin (100 mg/m^2) on days 1, 22, 43	69% at 5 years	82% at 5 yr p = 0.007 (Gray's test)	40% at 5 years	53% at 5 yr p = 0.02 (log-rank)
Cooper[125] (n = 416)	Oral cavity, oropharynx, hypopharynx, larynx	60 Gy-66 Gy (6-6.5 wk) vs. 60 Gy-66 Gy (6-6.5 wk) + cisplatin (100 mg/m^2) on days 1, 22, 43	72% at 2 years	82% at 2 years p = 0.01 (Gray's test)	56% at 2 years	64% at 2 years p = 0.19 (log-rank)

controversial issues concerning the role of node dissection after RT or chemoradiation for patients with N2 to N3 disease at initial diagnosis. A residual neck mass may be present in as many as 30% to 60% of patients after completion of chemoradiation. For these patients, irrespective of the neck category, there was a consensus in the literature favoring an immediate neck node dissection because of the low probability of achieving neck control with salvage surgery when recurrence develops.[136]

Whether a neck dissection should be proposed for all patients with N2 to N3 disease at diagnosis or only for those without a complete response is still a matter of debate.[137-147] That neck dissection could be avoided following complete nodal response to irradiation is a consequence of a better response assessment using imaging,[148] and improved regional control with chemoradiation[119,134,149,150] and with hyperfractionated or accelerated RT.[151,152] There are currently many arguments supporting the position that systematic planned neck dissection is no longer justified in patients without clinically residual disease in the neck,[153] and many institutions have switched to neck dissection for residual disease in the neck only.[137,144,147,154] Improvement in assessing the neck status with imaging (CT, MRI, FDG-PET) has contributed enormously to this change in paradigm.[155-164]

Optimum timing of PET after chemoradiation is crucial and could explain discordant results between series.[163,164] A prospective study conducted by the Ontario Clinical Oncology Group assessing the use of FDG PET-CT at 9 weeks post-RT to detect recurrence following treatment showed that PET-CT yielded high rates of false-negative results.[165] Conversely, studies on postchemoradiation PET performed at 12 to 13 weeks posttreatment showed NPV values of 97% to 100%, and PPV values of 62.5% to 71%, respectively.[166,167] Investigators from the MSKCC confirmed that after chemoradiation, FDG PET-CT reached an NPV of 94% for clinically residual enlarged lymph nodes (≥1 cm), and an NPV of 98% in clinically negative necks.[168] Based on these findings, patients with residual lymphadenopathy and absence of abnormal FDG uptake have a low probability of residual viable tumor cells.

Last, a cost-effectiveness analysis on the use of CT and PET/CT for assessing the need for adjuvant neck dissection was reported comparing three strategies: dissection in all patients, dissection in patients with residual disease on CT scanning, and dissection in patients with residual disease on PET/CT scanning.[169] Probabilistic sensitivity analyses confirmed that the PET/CT strategy was more cost-effective than the other two options. A definite answer on the issue of post-RT neck dissection should come from ongoing prospective studies.

To summarize, balancing the benefit with the increased morbidity of postchemoradiation surgery, current evidence suggests that neck node dissection be restricted to those patients with a noncomplete response after organ-preservation protocol.[153] In this situation, there is a growing evidence to support the approach of using SND even in patients with initial advanced nodal disease and with clinically persistent disease, with less than 5% of subsequent neck failure.[38-40,170,171] More, it has been recently demonstrated that SSND was a reliable surgical option for patients with residual disease confined to a single neck level.[172] In all studies reporting on postconcomitant chemoradiation SND, the rate of major postoperative complications was less than 10% and comparable to the rate of complications observed after primary surgery.[38,141,173-175] Despite the absence of a prospective study comparing SND and SSND with comprehensive node dissection after organ preservation protocols, one would intuitively expect less fibrosis, shoulder dysfunction and neck deformity in patients who underwent limited surgery.

LATE COMPLICATIONS AFTER NECK TREATMENT

Complications of Neck Node Dissection

In addition to the medical complications inherent in any surgical procedure, neck dissection may potentially be associated with some specific perioperative complications and late complications or sequelae. The description of perioperative complications is beyond the scope of this chapter. Readers interested in such topics will find detailed information in a textbook dedicated to head and neck surgery.[176]

Recognized complications after neck dissection include numbness or burning of the neck and ear, neck pain, shoulder discomfort, neck tightness, lower lip weakness, decreased range of motion of the head, neck, and shoulder, lymph edema, cramping and spasms of the neck musculature, and cosmetic disfigurement. In 2001, Shah et al[177] proposed a neck dissection–specific quality-of-life questionnaire used in a series of patients who had undergone neck dissection as part of their treatment.[177] Some of these patients had been previously treated by chemotherapy (25%) or RT (50%). Neck tightness and shoulder discomfort had the greatest effect on quality of life. Advanced tumor stage, often requiring more radical surgery and use of chemotherapy or RT, was associated with a worse quality of life after neck dissection. Overall, the quality of life after neck dissection tends to improve with time.[177]

The most noticeable sequela induced by spinal accessory nerve resection is the decreased ability to abduct the shoulder above 90 degrees. However, any type of neck dissection may result in impairment of shoulder function.[178] Studies reported that preservation of the spinal accessory nerve in modified RND and SND was associated with a better quality of life and fewer shoulder disorders in both the short and long term.[177] Using the University of Washington quality-of-life questionnaire, the Liverpool group reported that little morbidity associated with shoulder dysfunction was observed in patients

Investigators from the University of Florida reported negative predictive value (NPV) of CT scan of 94% to 97% for the detection of residual or recurrent neck metastasis, providing that strict criteria were used.[155-157] In a large Canadian study (n = 363), a NPV of 100% was reported for CT scan using a regression of the initial diameter equal or more than 80% at 6 to 8 weeks postconcomitant chemoradiation.[158] In a previously reported study, the same group has showed that CT assessment of patients with N3 nodes was not adequate.[159] Also, in the studies mentioned previously, the specificity (thus, the positive predictive value) of CT scan was found to be low, around 28%. In this framework, could MRI outperform CT examinations? A meta-analysis showed that CT and MRI were equivalent for the detection of pretreatment lymph node metastases in HNSCC.[160] Diffusion-weighted MRI was recently reported as a better tool than conventional MRI for initial regional staging and for assessment of treatment response early after the end of chemoradiation.[161,162]

The use of FDG-PET scanning has gained growing interest in this setting. In a 2004 study including 41 patients treated with definite RT (with or without concomitant chemotherapy), a negative PET scan after RT was highly correlated with a negative pathologic finding after neck node dissection or fine-needle aspiration, or with the absence of neck relapse (NPV of 100% for maximum standardized uptake values <3.0).[163] In another study including 24 patients staged with FDG-PET after induction chemotherapy followed by chemoradiation, the NPV of a PET scan reached only 73%.[164]

following a unilateral levels I to III or I to IV neck dissection in comparison with patients undergoing primary surgery without neck dissection.[179] However, unilateral neck dissection extending to level V and bilateral SND (I-III or I- IV) were associated with statistically significantly worse shoulder dysfunction. Adjuvant RT seemed to have a detrimental effect on shoulder dysfunction, whether or not the patient had a unilateral SND.

In another series, assessment of patients who underwent neck dissection with or without RT at least 1 year previously revealed that neck pain was present in one third of patients, shoulder pain in 37%, and loss of sensation in 65% (related to the number of dissected levels and to RT).[180] A prospective study on objective assessment after treatment concluded that adjuvant RT had no effect on shoulder joint function and that shoulder disability was inevitable in all types of neck dissections, whether or not the spinal accessory nerve was spared. However, shoulder function was better after SND and modified RND than after RND, although electromyographic findings were similar after either RND or modified RND and SND.[181] The benefit of postoperative physical therapy has been stressed, and it should be started in the early postoperative period after all types of neck dissections.[182]

Complications of Neck Irradiation

Late complications after head and neck irradiation were discussed in the previous chapters. In the following section, only specific complications arising in the soft tissues of the neck will be reviewed. They mainly concern subcutaneous fibrosis, thyroid dysfunction, and carotid artery stenosis. Typically, late complication probability depends on the total dose, dose per fraction, time interval between fractions, volume of normal tissue receiving a high dose, and use of concomitant chemotherapy or a biologic modifier.

The probability of grades-3 to -4 (RTOG late morbidity scale) subcutaneous fibrosis in the neck is rather low after standard RT. From randomized studies performed in the 1990s, it can be estimated at around 3%.[119,152,183,184] After accelerated or hyperfractionated treatments, no increase in grades-3 to -4 subcutaneous toxicity was observed, providing that enough time was allowed between fractions.[152] In an EORTC trial with only a 4-hour interfraction time, a 50% risk of fibrosis was documented at 5 years after treatment.[185] After concomitant chemoradiation, randomized trials reported a substantial increase in late skin morbidity, reaching figures of around 10%.[119]

Clinically indolent hypothyroidism in patients with lower neck irradiation has been reported at rates of up to 24%.[186,187] Most patients usually develop hypothyroidism within 1 year after treatment. Postoperative RT—especially after laryngeal surgery—including partial thyroidectomy, has been shown to be a risk factor. Yearly thyroid function testing (i.e., thyroid-stimulating–hormone level) is advised in the follow-up of patients with irradiation to the neck.

Carotid artery stenosis after neck irradiation has been reported by several authors, but few studies have investigated the incidence, disease patterns, and risk factors including tobacco use, hypertension, hyperlipidemia, diabetes, etc. Matched control Doppler ultrasound examinations have reported significant carotid stenosis in 30% to 50% of patients with previous irradiation to the neck.[188] Compared with the general population, a relative risk of stroke of 5.6 has been reported in patients with previous irradiation to the neck.[189] This relative risk was further increased for patients older than 60 years and with follow-up longer than 10 years. Increased attention to the clinical signs of carotid stenosis together with proper management of the other risk factors (e.g., diabetes, hypertension, hypercholesterolemia, smoking, obesity) should contribute to a decreased incidence of stroke and neurologic sequelae in this patient population.

All of the published data on late complications are from the era before IMRT was available. With the use of modern RT techniques (IMRT), a major reduction in late complications is anticipated, mainly through a reduction in the volume of normal tissue irradiated at a high dose and a reduction of the "uncontrolled" hot spot within or outside of the PTV. More fatigue, headache, and nausea and vomiting have also been reported with IMRT, likely resulting from the irradiation of the posterior fossa.[190] The introduction of IMRT has, however, raised the controversial concern of an increased risk of radiation-induced secondary neoplasms because a larger volume of normal tissue might be irradiated at a lower dose in comparison with standard two-dimensional techniques. Also, depending on the radiation technique used, the delivery of a specified dose to the isocenter from modulated fields may require a longer beam time compared with the same dose delivered to a nonmodulated field. The IMRT treatment plan then results in an increase in the number of monitor units by a factor of two to three, thus increasing the dose outside the boundary of the primary collimator caused by leakage and scattered radiation.[191] As a consequence, the total body dose received may be substantially increased. It is estimated that an additional 0.5% of surviving patients will develop a secondary malignancy as a result of an increased volume of normal tissue receiving a small radiation dose. This number needs to be added to the 0.25% of surviving patients who subsequently develop a radiation-induced malignancy. In all, it is estimated that about 0.75% of surviving patients may develop a secondary malignancy as a result of the switch to IMRT, which is approximately twofold greater than the incidence observed after more conventional RT.[192] Whatever the contribution of IMRT in the induction of secondary cancers may be, we should bear in mind that even if IMRT increases the probability of locoregional control and the potential for increased cause-specific survival, this group of patients experiences comorbidities and increased risk for a second primary tumor associated with their lifestyle. This may decrease the relative importance of radiation-induced secondary malignancies.

MANAGEMENT OF RECURRENT NECK DISEASE

Whether treated by RT, surgery, chemotherapy, or a combination of all three, the prognosis of patients with recurrence of disease in the neck remains abysmal. Recurrent neck disease is quite invariably associated with unfavorable prognostic factors. Extracapsular spread is almost always reported and multiple lymph node levels are frequently involved.[193] Neck disease recurrences are often unresectable because of involvement of the wall of the common carotid artery or the internal carotid artery, the paraspinal muscles, and the cranial nerves. Even when salvage surgery is attempted, the inability to achieve a complete resection with clear margins is generally the rule.

Few studies have specifically addressed the problem of recurrent neck disease following curative treatment in HNSCC. Godden et al[193] retrospectively reviewed the charts of 35 patients with recurrent neck disease after either primary surgery (80% of patients; 50% had postoperative RT and 18 had neck dissection) or primary RT. Recurrence in the neck was managed by neck dissection in 25 patients of whom 18 had postoperative RT. Ten patients (29%) were considered inoperable. Nine of the 18 patients with an initial neck dissection recurred in previously dissected level II. This high rate of level-II recurrence stresses the necessity of adequate training

for surgeons performing neck dissection procedures. In this series, ultimate control of neck disease was obtained in only 5 of the 35 patients and 4-year OS did not exceed 20%.

The likelihood of successful salvage treatment in patients with neck recurrence after primary RT is low. Bernier et al[98] reviewed 116 patients with isolated nodal failure after RT alone for oropharyngeal, hypopharyngeal, and laryngeal carcinoma. Fourteen patients had salvage neck dissection and 18 were reirradiated. Only one patient (1%) was successfully salvaged. In 1999, the University of Florida reviewed the medical records of 51 patients who experienced recurrent disease in the neck only.[194] Of the 18 patients (35%) who underwent salvage treatment, all had subsequent relapse of disease (locally, regionally, or distantly). Control of the neck at 5 years was only 9% for the patients who underwent salvage treatment, which was similar to the rate of neck control for the whole population. For the whole group of patients, absolute and cause-specific survival rates reached 10% at 5 years for both endpoints. However, at 3 years, patients who received salvage treatment had absolute and cause-specific survival rates of 44%. In comparison, none of the 33 remaining patients was alive at 3 years.

More recently, in a series of 540 patients, investigators from two institutions in the Netherlands reviewed the effectiveness of salvage neck dissection for regional pathologic lymphadenopathy after chemoradiation.[195] Patients with neck dissection for residual (persistent lymph node metastases diagnosed within 3 months after treatment) and recurrent regional disease (recurrent lymph node metastases diagnosed at least 3 months after treatment) were included. Sixty-eight patients were considered as unresectable. Salvage neck dissection was performed in 61 patients, 45 for regional residual disease and 16 for recurrent regional disease. In the group of patients who had salvage neck dissection, the 5-year regional control and OS rates were 79% and 36%, respectively. Interestingly, patients with recurrent disease had a better outcome than patients with residual disease. The 5-year regional control was 77% for residual disease and 86% for recurrent disease, but the difference was not statistically significant. In multivariate analysis, recurrent disease and negative surgical margins were shown as significant independent predictors for a better OS. Of note, only 8 of 16 patients who had salvage neck dissection for recurrent disease had histologically positive tumor in the specimen. These results confirm that salvage neck dissection may benefit selected patients with limited recurrence in the neck.

In 2010, the Institut Gustave Roussy reported a series of 93 patients who had recurrence after chemoradiation.[196] Salvage surgery was performed in 40% of these patients, and in this group 2-year OS was 43.4%. Univariate analysis demonstrated that initial stage IV disease and concurrent local and regional failure were significant prognostic factors for poor OS. In the group of patients without initial stage IV disease who had either an isolated regional or tumor recurrence, the 2-year OS reached 83%, whereas it was 0% in the group of patients with initial stage IV and concurrent local and regional failure. These results confirm that salvage surgery should only be proposed to selected patients with isolated resectable treatment failure in the neck.

Few institutions have evaluated salvage treatment with aggressive combined modality approaches that include low-dose reirradiation (preoperative or postoperative with or without concurrent chemoradiation) combined with an attempt at gross resection plus intraoperative radiotherapy (IORT) with either electrons (IOERT) or high-dose-rate brachytherapy (HDR-IORT).[197] Although the series involve small numbers of patients, early results suggest potential improvements in both locoregional control and survival rates compared with those of standard salvage approaches, and further evaluation is warranted.

In summary, most of the patients with regional recurrence are unable to undergo salvage treatment, and when salvage treatment with standard approaches (surgical resection, external beam radiation therapy) is attempted, control of neck disease remains poor. Salvage neck dissection alone should be restricted to patients with limited recurrence of disease in the neck.

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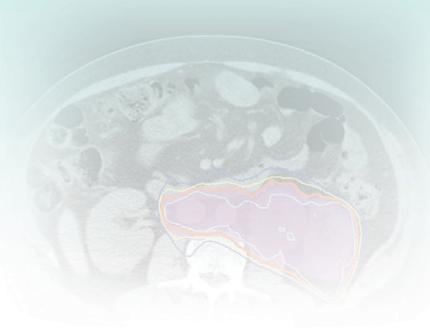
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CHAPTER

41 Cutaneous Carcinoma



Michael J. Veness and Julie Howle

INCIDENCE

Cutaneous basal cell carcinomas (BCCs) and squamous cell carcinomas (SCCs) are the most frequent cancers worldwide. White populations residing in locations with high level exposure to ultraviolet (UV) radiation, such as Australia and New Zealand and the southern United States, have a particularly high lifetime risk for developing skin cancer.

BIOLOGIC CHARACTERISTICS

The natural history of skin cancers varies widely with the histologic type ranging from tumors with an indolent course and a high cure rate of 90% to 95% (e.g., BCC) to aggressive tumors with high (30% to 50%) mortality rates (e.g., Merkel cell carcinoma [MCC]).

STAGING EVALUATION

After biopsy confirmation, patients should be staged with history and physical examination and, when indicated, blood chemistry, chest radiographs, contrast-enhanced computed tomography (CT), magnetic resonance imaging (MRI), or positron emission tomography (PET)/CT scans.

PRIMARY TREATMENT

Surgery is the primary treatment for most skin cancers. Nonsurgical treatment such as radiotherapy (RT) may be preferable for treating select BCCs and SCCs, particularly on and around the midface (e.g., nose, lower eyelids), lips, and ears because it may result in better functional and cosmetic results than surgery. Topical and locally destructive treatments may also be effective in cases of superficial (1 mm to 2 mm) skin cancer.

ADJUVANT TREATMENT

In patients with BCCs and SCCs, the indications for postoperative (or adjuvant) RT include the presence of close or positive surgical margins, perineural invasion, invasion of bone or cartilage, and extensive skeletal muscle infiltration. Most patients with MCC should be considered for wide-field adjuvant RT. Patients with a high incidence of occult nodal spread may benefit from elective nodal treatment, often wide-field RT that may also encompass the primary site (e.g., high-risk SCC, MCC).

No effective systemic adjuvant therapy is currently available for nonmelanoma skin cancers (NMSCs). The addition of concurrent chemotherapy with RT in select high-risk cases may be considered but is not supported by high-level evidence.

LOCALLY ADVANCED DISEASE AND PALLIATION

Surgery with adjuvant RT is the standard treatment for locally advanced and operable tumors. In certain patients, definitive RT can still offer a reasonable possibility of achieving local control in patients with locally advanced carcinomas who are either medically unable to undergo surgery or whose tumor is technically unresectable.

In patients unsuitable for an extended course of definitive RT, a short course of palliative RT can reduce symptoms for most patients with advanced inoperable cancer or with metastatic masses (e.g., pain, discharge, bleeding).

Cutaneous BCC and SCC are the most common malignancies in the world and occur at epidemic rates in countries such as Australia.[1] Collectively, these two carcinomas account for most (95%) patients with NMSC and are far more common than malignant melanomas (MM), which account for only 5% of all skin malignancies. BCC is the most common type of NMSC, with an incidence of more than twice that of SCC. Other NMSCs that are infrequently encountered include MCC, also known as primary cutaneous neuroendocrine carcinoma, a rare small cell carcinoma originally described by Toker in 1972,[2] adnexal carcinomas such as sebaceous gland carcinomas accounting for less than 1% of all skin cancers,[3] and eccrine carcinomas accounting for less than 0.01% of malignancies of the skin. NMSCs may be disfiguring and associated with local morbidity, and excluding MCC, are rarely lethal.

ETIOLOGY AND EPIDEMIOLOGY

Sun exposure is the main etiologic factor for NMSC particularly in Caucasians, whose skin is susceptible to the chronic carcinogenic effect of UV light.[4] Other, less common etiologic factors include exposure to chemical carcinogens (e.g., arsenic, tar, anthracene, and crude paraffin oil), chronic irritation or inflammation, and ionizing radiation.

The incidence and aggressiveness of SCC and MCC (both immunogenic carcinomas) are markedly increased in individuals with compromised immune function, including patients with non-Hodgkin's lymphoma, chronic lymphocytic leukemia,[5] and organ transplant recipients with iatrogenic immunosuppression.[6] In contrast, the incidence of BCC is not markedly increased and the outcome is similar as for patients who are immunocompetent.

Some genetic syndromes are also associated with a higher risk of developing skin carcinoma. Individuals with xeroderma pigmentosum are prone to developing BCC and SCC at a young age because of defective repair of UV light-induced DNA damage.[7] These patients usually die in their early 20s from disseminated SCC or melanoma. The basal cell nevus syndrome (or Gorlin's syndrome) is a genetic form of BCC inherited through an autosomal dominant gene.[8] Individuals with epidermodysplasia verruciformis tend to develop nodules of SCC within large verrucous plaques in the third and fourth decades of life.

PREVENTION AND SCREENING

Unprotected sun exposure, especially during the summer, is the main determinant for the subsequent development of skin cancer. Children and adolescents should be especially educated in regard to sun protection. The damage of excessive UV exposure is irreversible, but despite this, adults can still reduce their risk by avoiding further excessive UV exposure. Preventive measures to reduce skin cancer include avoidance of sunlight exposure—particularly limiting time spent outdoors between 10 AM and 3 PM—and wearing protective physical barriers, such as hats and clothing. If sun exposure cannot be limited because of occupational, cultural, or other factors, the use of sunscreens that are either opaque or that block UVA and UVB radiation is recommended. The use of tanning booths is also a factor in the risk of developing skin cancer, and guidelines regarding their appropriate use should be followed.

There is limited evidence that screening in the general population reduces the morbidity and mortality of skin cancers.[9] The American College of Preventive Medicine recommends periodic screening, consisting of a total cutaneous examination and a 2-minute to 3-minute visual inspection of the entire integument by an adequately trained physician for high-risk individuals. The risk factors include family history of skin cancer, fair skin, multiple nevi, immunosuppression, and a history of other skin cancers.

CLINICAL MANIFESTATIONS, PATHOBIOLOGY, AND PATHWAYS OF SPREAD

Basal Cell Carcinoma

Clinical Presentation and Pathology

BCC constitutes approximately 80% of all NMSC and is the most common malignancy worldwide. Most BCCs arise on the sun-exposed head and neck (80% to 85%); lesions occur less frequently on the trunk or extremities. Lesions may manifest as an asymptomatic nodule, a pruritic plaque, or a bleeding ulcer that characteristically waxes and wanes.[10,11] Many (up to 40% to 50%) patients treated for BCC develop at least one or more further BCC within 5 years.[12] Careful evaluation of sun-exposed skin should therefore be part of any follow-up examination.

BCC has numerous variants, each of which has distinctive clinical and histologic features and natural history. The characteristics of commonly occurring types are briefly summarized.

Nodular BCC, colloquially referred to as rodent ulcer, is the most frequently observed variant and accounts for approximately 50% of all lesions (Figure 41-1). It arises as a distinct papule that may develop central umbilication, progressing to central ulceration. The margins of this lesion appear pearly (pale and translucent) and contain enlarged capillaries (telangiectasia). Histologic features include the presence of large islands of monomorphous basaloid cells, varying in size and shape, embedded in a fibroblastic stroma in the dermis. The basaloid cells have large, oval hyperchromatic nuclei, scant cytoplasm, and no intercellular bridges. The peripheral cell layer of the aggregate frequently shows palisading, whereas central cells are less organized. Nodular BCC may show a varying degree of pigmentation (blue, brown, or black), depending on the number of melanocytes present in the lesion, and may be difficult to differentiate clinically from MM.[13]

Superficial BCC manifests as red, scaly macules with indistinct margins, usually located on the trunk. It enlarges into a crusted, erythematous patch without induration that may be difficult to differentiate clinically from solar keratosis, psoriasis, SCC in situ, or extramammary Paget's disease. Histologic examination shows multiple foci of buds of neoplastic cells with peripheral palisading originating from the undersurface of the epidermis.[10]



Figure 41-1 A 75-year-old white male with a long-standing nodular basal cell carcinoma occupying the left side of the lower nose with associated destruction and nostril retraction. The margins have a pearly appearance, and there are scattered telangiectasia. He was treated with definitive RT with the understanding that further retraction was likely to follow as the tumor regressed.

Morpheic (sclerosing) BCCs appear as single, flat, indurated, ill-defined macules. The lesions generally have a smooth, shiny surface that becomes depressed as it grows into a plaque. It is characterized histologically by the presence of small groups and narrow strands of basaloid cells embedded in a dense, fibrous connective tissue; there is little peripheral palisading.[14] Perineural invasion (PNI) is often reported to be present.

Infiltrative BCC has an opaque yellowish appearance and blends subtly with the surrounding skin.[14] Histologically, the lesion is characterized by poorly circumscribed spiky cell aggregates in the superficial portion and the main bulk, consisting of strands of neoplastic cells infiltrating the reticular dermis and subcutis.

Biology and Pattern of Spread

The biologic behavior of BCC varies with the histologic type. A superficial BCC may remain stable for a long time or enlarge gradually over many years to become a nodulo-ulcerative variant. Nodular BCC grow slowly over many years by peripheral and deep invasion, particularly along embryonal fusion planes, and PNI. Morpheic and infiltrative BCCs are more aggressive variants that may infiltrate deeper structures. The finding of PNI in BCC is uncommon (2% to 3% of patients), and generally occurs in the setting of recurrent disease or in morpheic histology.[15] Lesions located around the orbit with PNI present may gain access to the orbit via the first or second division of the trigeminal nerve.

High-risk BCC occur in the midface, or so-called H zone (Figure 41-2), which includes the periauricular region,

glabella, medial canthus, nose, nasolabial region, and columella, and contains embryonal fusion planes.[16] The depth of invasion of tumors in this region is frequently underestimated, leading to inadequate surgical excision, especially deep, and a higher rate of local recurrence. Histologic examination often reveals extensive infiltration of deeper structures by small nests of undifferentiated basal cells. This type of lesion may invade the orbit, nose, and maxilla, resulting in significant deformity (Figure 41-3). It should be readily recognized and treated promptly often necessitating extensive surgery with or without adjuvant RT.

BCCs rarely spread to the regional lymph nodes or distant organs with an overall incidence of metastasis less than 0.01%.[17] Most metastases occur in the regional lymph nodes with distant spread usually preceded by regional metastasis. Regional disease typically develops in association with large, ulcerated lesions in the head and neck that have recurred despite treatment.

Squamous Cell Carcinoma

Clinical Presentation and Pathology

SCC arises from epidermal keratinocytes and most commonly develops from skin exhibiting solar (or UV) damage. Actinic (or solar) keratosis (AK) is generally a precursor or premalignant lesion and at least 50% to 60% of all invasive SCCs arise from AK. Despite this, only a few (<5%) AK actually progress to invasive SCC. In a large study of 169 patients with 7784 documented AK, the risk of malignant progression was reported in 2.6% at 4 years.[18] Less frequently, SCC occurs from other preexisting skin lesions, such as arsenic keratosis, a thermal burn scar, or a chronic ulcer. Rarely, it arises from normal-appearing skin.[13]

Clinically, SCC in situ (Bowen's disease) manifests as a soft, erythematous, scaly, well-circumscribed red patch (Figure 41-4). Superficial SCC manifests as a scaly, crusted plaque or ulcer with a verrucous or papillate border, but invasive SCC can manifest as a firm, ulcerated mass with an elevated nodular border. Lesions can often be deeply invasive and progress rapidly in some patients (Figure 41-5).

Microscopically, SCC is composed of strands and sheets of atypical keratinocytes and referred to as SCC in situ when atypical keratinocytes are confined to the epidermis. Superficial SCC represents atypical keratinocyte proliferation

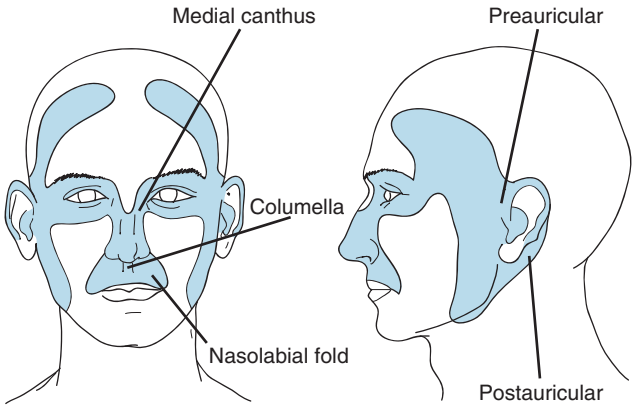


Figure 41-2 Diagram of H zone. Especially problematic areas are the medial canthus, glabella, nasolabial folds, and periauricular region.



Figure 41-4 A 75-year-old male with a large patch of biopsy proven in situ squamous cell carcinoma treated with local RT. Note the dashed green line delineating the RT treatment field with ~1.5-cm margins. The patient received 40 Gy in 10 fractions using superficial energy photons.



Figure 41-3 **A,** A 53-year-old male with a longstanding large and deeply invasive right temple basal cell carcinoma. **B,** He underwent wide local excision and free flap reconstruction and also required adjuvant RT because of a close deep margin.



Figure 41-5 **A,** A 68-year-old bed bound patient presenting with a rapidly enlarging left preauricular invasive squamous cell carcinoma that was poorly mobile over underlying structures. The patient was deemed medically inoperable and treated with wide field definitive RT (55 Gy in 25 fractions using high-energy electrons). Note the wide RT field margins to electively treat clinically uninvolved parotid and upper cervical nodes. **B,** Two months following RT the patient has experienced a complete clinical response to treatment.

confined to the upper reticular dermis, whereas infiltrating SCC denotes disease extension into and beyond the lower reticular epidermis.

Histologically, SCC is graded as well, moderately, or poorly differentiated, based on the degree of cellular polymorphism, keratinization, and mitosis. The spindle cell variant mimics other skin tumors, such as amelanotic melanoma, and may require a panel of immunohistochemical studies for complete characterization.

Biology and Pattern of Spread

SCC generally has a more aggressive course than BCC. SCC in situ (Bowen's disease) may evolve gradually into superficial (microinvasive) carcinoma in ~5% of cases.[19] Untreated, it may progress further into an infiltrating type that invades the surrounding and underlying structures. The rate of progression depends on the degree of cellular differentiation.

The risk of developing metastases, usually nodal, is markedly higher in SCC than in BCC. However, most patients who are immunocompetent with small (<2 cm), thin (<4 mm to 5 mm thick), nonrecurrent lesions are at low (<5%) risk of developing nodal metastases. Patients not meeting these criteria can be considered high-risk patients (>10% risk), and appropriate awareness and management are required.[20] Recurrent lesions in close proximity (forehead, temple, ear, cheek) to the parotid gland increase this risk. Data suggest that tumor thickness greater than 6 mm is a powerful, independent predictor of patients at risk for developing regional metastases.[21]

The most frequent sites for the development of metastatic cutaneous SCC are the parotid gland, the cervical lymph nodes, or both,[22] reflecting the high incidence of primary SCC in the head and neck region. In 20% to 25% of cases, an obvious index lesion is not identified. Invariably, these patients have a long-standing history of actinopathy and NMSC (Figure 41-6). The development of distant metastases (e.g., lung, liver) rarely occurs as a first site of relapse and is more often encountered after treatment for nodal relapse.

Metastatic SCC occurs less frequently in other nodal regions, such as the axilla and groin. Although difficult to quantify, the ratio of metastatic head and neck SCC to non–head and neck SCC is approximately 9:1. There are much fewer published data on the management of these patients, but analogous generalizations from the evidence on parotid and neck nodal metastases suggest operable patients should have surgical resection. Many will have unfavorable features, such as extranodal spread and incomplete margins, and should be recommended adjuvant RT.[23]



Figure 41-6 Elderly white male with a large metastatic lymph node containing metastatic squamous cell carcinoma located in his right upper neck in a parotid tail node. The patient had a long past history of skin cancers of the head and neck but did not have an obvious index lesion present or previously treated. He proceeded to surgery and adjuvant RT.

Merkel Cell Carcinoma

Clinical Presentation and Pathology

MCC is an aggressive cutaneous malignancy that often manifests as a rapidly enlarging firm, painless, pink-red, dermal-based nodule, frequently on the head and neck (50% to 60%) or extremities/trunk in older (>60 to 70 years old) individuals. In contrast to other types of NMSC, MCCs frequently occur in women (Figure 41-7). It is often misdiagnosed because it may resemble BCC or amelanotic melanoma. The median size of the primary lesion at diagnosis is approximately 2 cm, and the incidence of clinical nodal involvement at presentation is approximately 20% to 25%, although the risk of harboring occult nodal disease is high (30% to 40%).[24] Based on the U.S. Surveillance, Epidemiology, and End Results (SEER) database, the annual incidence in men is 0.34 per 100,000 with most patients older than 65 years and white (94%). In this study, slightly less than half (46%) of all lesions occurred in the head and neck, and at diagnosis, half of all patients had localized disease with nodal metastases present in approximately 25%.[25]

The cell of origin is thought to be the dermal neurotactile cell arising from the neural crest first described by Merkel.[26] Lesions usually involve the reticular dermis and subcutaneous tissues, with minimal extension to the papillary dermis and sparing of the epidermis. Vascular and lymphatic permeation is common, and clinically such permeation often manifests as in-transit metastasis. The neoplastic cells exhibit cytoplasmic extensions and small, uniform, membrane-bound neurosecretory granules on ultramicroscopic examination.[27] Several immunohistochemical markers have been identified in MCC. The neoplastic cells stain most consistently with polyclonal antisera to neuron-specific enolase and calcitonin, monoclonal antibody to neurofilament, and cytokeratin (CK 20 positive).[28]

Recent evidence suggests a possible viral association in the development of MCC. The Merkel cell polyomavirus (MCV) was first identified in 2008 and in some studies has been identified in around 80% of MCC tumors.[29] It is postulated that MCV in certain populations (e.g., Australians) may play less of a role compared to the mutagenic consequences of chronic UVB exposure, although this is controversial. The virus is considered part of normal human flora and is also present in healthy tissue from the general population. The prognosis of patients in the presence of MCV is also unclear with separate studies suggesting no difference, better or a worse outcome, respectively. In part this may explain some of the variation in outcome between different populations treated with MCC. Clinical management is currently unaltered whether a patient's tumor contains MCV or not.



Figure 41-7 Left cheek Merkel cell carcinoma (MCC) in an elderly white female. The lesion was asymptomatic, exophytic, rapidly growing with a reddish appearance all characteristics of a MCC. The patient underwent local excision followed by wide-field RT but subsequently developed liver metastases.

Biology and Pattern of Spread

MCC can exhibit an aggressive course characterized by a propensity for local recurrence even after wide surgical excision and a high incidence of nodal involvement (20% to 30% clinically present at diagnosis) with hematogenous dissemination a frequent site of relapse and death. Most series document a cancer-specific death rate of around 30%.[30] Patients may also present with metastatic nodal disease without an obvious index lesion. Such patients make up 10% to 20% of many series and have a better prognosis compared to patients with concomitant nodes and an index lesion.[31] MCC is a highly immunogenic carcinoma, and patients who are immunosuppressed (organ transplant recipients) and patients diagnosed with non-Hodgkin's lymphoma and chronic lymphocytic leukemia are at higher risk of developing MCC and having a poor outcome.[32] The role that the MCV plays in the pathogenesis of MCC may account for its higher incidence inpatients who are immunosuppressed.

Adnexal Carcinoma

Sebaceous Carcinoma

Clinical Presentation and Pathology

Sebaceous carcinomas are rare (approximately 400 reported) and arise most commonly (75% of cases) from the sebaceous glands of the ocular adnexa, the meibomian glands in the tarsus or glands of Zeis at the lid margin, and the caruncle. Extraocular locations, in decreasing frequency, are head and neck region, trunk and extremities, and external genitalia.[3]

For malignant neoplasms of the eyelids, sebaceous carcinomas are second only to BCC in frequency and second only to MM in lethality. The most common location of ocular sebaceous carcinomas is the upper eyelid, followed by the lower eyelid and caruncle. Sebaceous carcinomas predominantly affect individuals older than 60 years, and there is a slight preponderance for women. These lesions manifest clinically as slow-growing, nontender, deep-seated, firm nodules. They often produce a chalazion or manifestations suggestive of inflammatory processes, such as conjunctivitis, blepharitis, or tarsitis. Small primaries may be overlooked until orbital invasion or spread to preauricular or cervical nodes occurs.

The differential diagnosis includes sebaceous adenoma and BCC with sebaceous differentiation (basosebaceous epithelioma). Histologically, these carcinomas are composed of dermal-based lobules and cords of tumor cells, with varying

degrees of sebaceous differentiation and infiltration into the surrounding tissues. Differentiated cells contain foamy or vacuolated, slightly basophilic cytoplasm, whereas less differentiated cells contain more deeply basophilic cytoplasm. Clinical and pathologic features that indicate a poor prognosis include size of the primary lesion (>1 cm is associated with 50% mortality rate), vascular and lymphatic invasion, poor sebaceous differentiation, highly infiltrative growth pattern, and intraepithelial carcinomatous changes in the overlying epithelia.[33]

Biology and Pattern of Spread

Sebaceous carcinoma behaves more aggressively than SCC, with a propensity for nodal and hematogenous spread.[34] Of the 104 patients registered by the Ophthalmic Pathology of the Armed Forces Institute of Pathology, 23 patients (22%) experienced local recurrence once, and 11 patients experienced local recurrence two or more times. Metastatic disease was the cause of death in 23 patients.[33]

Eccrine Carcinoma

Clinical Presentation and Pathology

Sweat gland (eccrine, apocrine, apoeccrine) carcinomas are exceedingly rare, arise most frequently in the skin of the head and neck or the extremities, and manifest as painless papules or nodules that grow slowly. This type of neoplasm is usually diagnosed in individuals 50 to 70 years of age.

Histologically, eccrine or sweat gland carcinomas may resemble carcinomas of the breast, bronchus, and kidney and are difficult to differentiate from cutaneous metastases. Many histologic variants are reported and include ductal eccrine carcinoma, mucinous eccrine carcinoma, porocarcinoma, syringoid eccrine carcinoma, clear cell carcinoma, and microcystic adnexal carcinoma (MAC).[35]

Biology and Pattern of Spread

Eccrine carcinoma has a more aggressive behavior than BCC and SCC. In a series of 14 patients who underwent surgical excision with negative excision margins, 11 developed at least one local recurrence, and 5 relapsed at regional nodes or distant sites. One patient died of uncontrolled local relapse, and 4 died of distant metastasis 2 months to 10 years after diagnosis.[35] Apocrine carcinoma arises most commonly from apocrine glands of the axilla, but it can originate from apocrine glands of the vulva and eyelids and from ceruminal glands of the external auditory canal. It manifests clinically as a red-purple single or multinodular, firm or cystic dermal mass in elderly individuals. The natural history of apocrine carcinoma is not well documented but nodal and distant metastases have been reported.[36,37]

Microcystic Adnexal Carcinoma

Clinical Presentation and Pathology

MAC is a rare (~700 documented cases in the literature) locally aggressive carcinoma that belongs to the spectrum of adnexal carcinomas and most often arises on the mid face.[38] It usually grows slowly over years and often is deeply invasive when diagnosed. It arises equally in males and females and tends to occur in adults 55 to 60 years old and occasionally in children.

Histologically, the tumor is composed of keratin horn cysts, nests, or cords of basaloid cells that are usually more prominent in the superficial dermis. Tumor strands and cystically dilated tubules are arranged in sold islands and embedded in deeper desmoplastic stroma. The cells usually show no atypia or mitoses, and the differential diagnosis may include trichoadenoma, syringoma, desmoplastic trichoepithelioma, or morpheaform BCC.[39]

Biology and Pattern of Spread

Patients with MAC often present with advanced and deeply invasive lesions after years of slow growth and misdiagnosis. PNI is reported to be present in many cases particularly in the recurrent setting. Lymph node metastases rarely occur. MAC tends to be a locally recurrent tumor with morbidity related to local invasion and destruction.

PATIENT EVALUATION AND STAGING

Most patients with NMSC present with an asymptomatic skin lesion, and often have a history of other NMSCs. Symptoms suggestive of PNI, such as pain, tingling, and hypesthesia, should be specifically sought from the patient. Up to 60% of patients with PNI may be clinically asymptomatic (microscopic PNI), and a crawling sensation on the skin termed *formication* is suggestive for sensory nerve involvement.[40] The most common primary sites associated with PNI are the frontozygomatic (supraorbital nerve) and infraorbital (infraorbital nerve) regions. Patients occasionally present with cranial nerve palsy as the first sign of PNI. Facial nerve involvement is usually preceded by muscle fasciculations followed by frank paralysis.[41] Clinical evaluation of patients with NMSC should consist of inspection and palpation of the involved area and the draining lymph nodes.

Imaging studies (chest radiography, CT, or MRI) generally are not required in most patients with NMSC but should be obtained as indicated (e.g., clinically suspicious lymph nodes). Lymph node metastasis and bone involvement are best assessed with contrast-enhanced CT scan acquired with soft tissue and bone windows (Figure 41-8). MRI, with and without contrast enhancement and fat suppression, should be obtained for all patients in whom PNI is suspected, with the findings of an enlarged or abnormally enhancing nerve raising the possibility of PNI.[42] Patients may need to undergo biopsy of the suspected nerve to confirm the diagnosis.[43] PET-CT is generally not required to stage patients with NMSC.

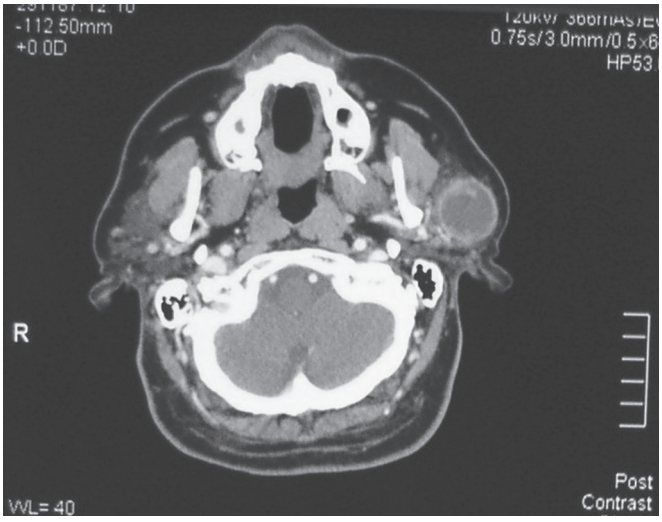


Figure 41-8 Axial CT scan showing metastatic cancer in the left parotid. There is concentric nodal enlargement, contrast enhancement of the rim, and central necrosis, all features consistent with a metastatic node from squamous cell carcinoma.

Staging of Basal and Squamous Cell Carcinoma

Previous staging systems have been criticized for lacking clinical and prognostic relevance, especially for patients with SCC.[44] More recent changes now include reporting of important pathologic high-risk features, such as tumor depth and the presence of PNI. The previous American Joint Committee on Cancer (AJCC) TNM (primary tumor, regional nodes, metastases) staging systems were based primarily on clinical findings and were of limited usefulness. The newer staging system (AJCC seventh edition) incorporates important clinicopathologic factors and does not rely purely on size as a T-category determinant.[45] High-risk features can now upstage a tumor, for example from T1 to T2, even if horizontal size is unchanged.

Similar to flaws in staging patients with the primary, or T-category, patients with nodal metastases from SCC were assigned an N-category via a flawed previous staging system with all patients indiscriminately assigned as N1 category regardless of metastatic nodal size, number, or presence of extranodal spread.[46] O'Brien et al[47] proposed a staging system for metastatic SCC to the parotid or neck that categorizes N (neck) and P (parotid) category based on the aforementioned variables. The new AJCC system now describes three nodal categories (N1-N3) based on the number and size of involved nodes.

Staging of Merkel Cell Carcinoma

A staging system developed by the Memorial Sloan Kettering Cancer Center separated patients with lesions less than, or greater than, 2 cm (stage I/II), with stage III representing those with nodal disease and stage IV those with distant disease.[48] In the current AJCC TNM seventh edition staging system, primary size and clinical and pathologic nodal status are incorporated into new group staging.[45] Of the stages documenting nondistant spread, stages I and II are classified by tumor size >2 cm and within each stage further categorized (A, B) depending on whether draining nodes have been evaluated as being uninvolved clinically (IA or IIA), or pathologically (IB, IIB) (e.g., by sentinel lymph node biopsy [SLNB]). Patients with stage III disease have pathologically confirmed nodal metastases and are further divided into those with micrometastases (i.e., occult) or macrometastases (clinically detectable).

PRIMARY TREATMENT AND RESULTS

Basal and Squamous Cell Carcinoma

Primary Tumor

The general strategy for managing most early NMSC is similar for either BCC or SCC. Various surgical and medical approaches are available, including curettage and electrodesiccation, Mohs's micrographic surgery, cryotherapy, surgical resection, and definitive RT. Numerous topical (e.g., 5FU, imiquimod) and intralesional (e.g., methotrexate, interferon) options as well as other modalities (e.g., photodynamic therapy [PDT]) are also available, often with ill-defined criteria for using them. Additionally the evidence to support topical or intralesional treatment is predominantly low level with long-term follow-up (up to 5 years) lacking and therefore clinicians need to consider various issues prior to any recommendation. Such treatments are essentially limited to select superficial NMSC and premalignant conditions (e.g., AK).[49]

With correct case selection the various surgical and medical approaches are similarly effective in curing most NMSC. The choice of treatment for individual patients is determined by factors such as the site and size of a lesion, anticipated functional and cosmetic results, treatment time and cost, patient age, occupation, and general condition. Carcinomas in the H zone or embryonic fusion planes may have extensive local spread, so treatment that ensures wide marginal (especially deep) coverage should be selected.

Overall, surgery is preferred for most patients. Simple procedures can yield high local control rates for patients with small lesions. Younger patients who have years of future exposure to sunlight are often better managed by surgery than by RT, although in certain cases RT may still be considered a better option. In numerous settings, especially in the setting of a close or positive margins or the presence of PNI, postoperative RT may be beneficial to reduce the risk of local recurrence. Other factors such high-grade histology, invasion of bone and cartilage and extensive skeletal muscle infiltration may also contribute to a decision to recommend adjuvant RT.

Local RT is an effective option when excision is incomplete and reexcision is not considered possible. In a study of 315 patients with primary cutaneous SCC of the head and neck undergoing wide local excision, patients undergoing surgery followed by adjuvant RT ($n = 52$) had a 92% reduced risk of recurrence (hazard ratio, 0.08; 95% CI 0.0 to 0.26; $p < 0.001$) compared to those treated with surgery alone.[50]

Primary (or definitive) RT is often recommended for lesions on and around the nose, lower eyelids, medial canthus, and ears, where it may yield better functional and cosmetic results than surgery[51] (Figure 41-9). Extensive lesions of the cheek, lip, and oral commissures that would require full-thickness resection may also be better irradiated. RT avoids the need for an operation and the surgical morbidity, scarring and requirement for reconstruction and has the benefit of being able to treat both wide (5 mm to 30+ mm) and deep margins, tissue that would otherwise require excision (with or without reconstruction). This particular advantage may result in improved cosmesis in situations in which a flap or graft is required. RT is particularly useful in areas of the midface, such as the periorbital region (especially the medial canthus), lower eyelid, nose (particularly the ala and tip), nasolabial fold, lip and chin, where excision and reconstruction could have a greater impact on form and function. Elderly patients with comorbid conditions are also often better approached with RT.

The lower lip is especially suited for RT when surgery may result in microstomia or require complex reconstruction for lesions occupying more than one third of the lips, and patients can be easily treated with orthovoltage RT after insertion of a lead oral cavity shield with expected cure rates similar to surgery. Patients may also benefit from postoperative RT if excision is incomplete and reexcision is not considered possible. In an Australian study of 217 patients with early lower lip SCC (considered as a sun-induced skin cancer), patients undergoing local adjuvant RT (50 Gy to 55 Gy in 20 to 25 fractions) in the setting of close (<2 mm) or positive margins had a significantly improved relapse free survival compared with similar patients not receiving RT (hazard ratio 0.36; 95% CI 0.17 to –0.77; $p = 0.008$). Of note, 57% of patients treated with excision alone developed a recurrence compared with 9% treated with surgery and RT, in the setting of close or positive margins.[52]

The overall local control rate of all sizes and types of cutaneous carcinoma treated with various modalities is 80% to 95%. RT is an excellent treatment option for patients in whom other modalities may have failed or are considered less optimal. In a series from M. D. Anderson Cancer Center of patients with SCC of the eyelid treated with definitive RT, an excellent 5-year local control of 89% was achieved.[53]



Figure 41-9 **A,** A 55-year-old white female with a 2.5-cm nodular basal cell carcinoma located on the right medial canthus. An internal eye shield has been inserted in preparation for RT markup. **B,** At markup, an RT field margin of approximately 1 cm *(solid line)* was applied. **C,** At completion of RT (55 Gy in 25 fractions using superficial energy photons), the tumor has almost completely regressed. At 3-year follow-up, she remained disease-free.

Patients with recurrent lesions (compared with de novo lesions) and with SCC (compared with BCC) have lower rates of local control. Similarly, as lesions increase in size, rates of local control decrease. In one study of patients with locally advanced (>T2) SCC and BCC, 4-year locoregional control rates were 86% and 58% for SCC and BCC, respectively.[54] Despite this, RT may still remain the best option.

One of the disadvantages of RT compared to surgery is the time required to undergo a course of treatment. The typical course of fractionated RT ranges from 10 to 25 daily 10-minute outpatient treatments (or fractions). However, fewer fractions (3 to 5) may be used in older patients with comorbid illnesses. Another disadvantage is that RT cannot be delivered a second time to the same site because of the risk of potential late complications such as soft-tissue and cartilage necrosis. Reirradiation is rarely ever considered an option but may be considered if surgical salvage is not possible. Although the initial cosmetic result after RT is excellent, fibrosis, soft-tissue or epidermal atrophy, and in-field pigmentation changes may become apparent over time (Figure 41-10). Unprotected sun exposure to irradiated sites is likely to exacerbate these changes, and patients should be warned to take appropriate measures. When RT is delivered to younger patients, daily fraction sizes of 2 Gy to 2.5 Gy are recommended (e.g., 55 Gy in 25 fractions) to minimize late changes. This should apply whether treatment is delivered in the definitive or adjuvant setting. The risk of developing a late in-field radiation-induced malignancy after RT is rare and poorly documented in the literature. Alternative treatments should be considered for younger patients, however, because many develop further skin cancers as they



Figure 41-10 Elderly male having 2 years previously received definitive RT (40 Gy in 10 fractions) to the tip of his nose in the setting of a nodular basal cell carcinoma. Note the well demarcated in-field hypopigmentation, scattered telangiectasia (small blood vessels), and epidermal atrophy.

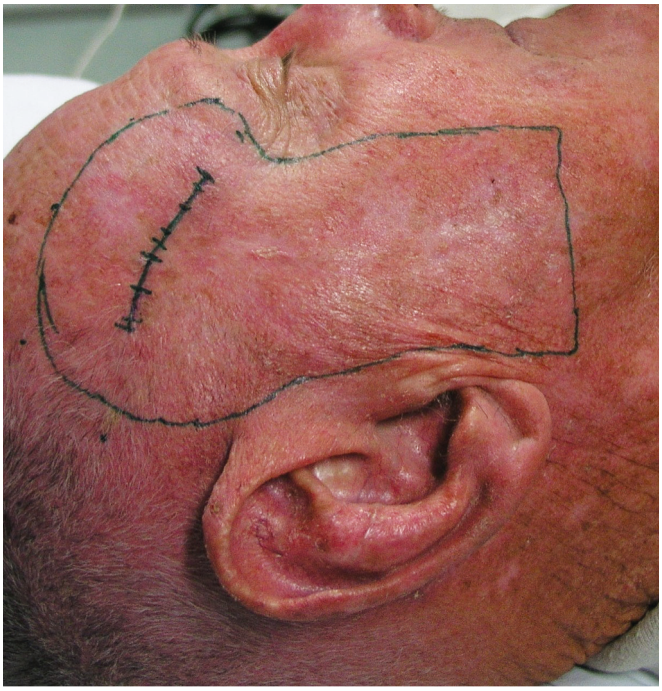


Figure 41-11 A 73-year-old white male had wide-field adjuvant RT to a high-risk squamous cell carcinoma (recurrent and positive deep margin) with the field electively encompassing his parotid lymph nodes. The patient received 50 Gy in 20 fractions using orthovoltage energy photons.

age. There is, however, no absolute contraindication for offering RT to younger patients if the patient and clinician agree this is the optimal modality.

Regional Nodes

Elective nodal treatment is not indicated for BCC or low-risk SCC because of the low incidence of lymphatic spread. However, select patients with high-risk SCC of the head and neck may warrant elective treatment (surgery or RT) of clinically node-negative regional nodes in conjunction with treatment of the primary, although consensus is lacking for this approach.[20,55] For example, a patient with a recurrent temple SCC in whom adjuvant RT is recommended in the setting of a positive deep margin may also be considered for the parotid nodes to be included electively en bloc in the RT field (Figure 41-11).

Patients who develop metastatic cutaneous SCC to the parotid or neck are optimally treated with surgery and adjuvant RT with few exceptions.[56] The aim of adjuvant RT is to reduce the risk of regional relapse because most patients have unfavorable features, such as multiple metastatic nodes, extranodal spread, close margins, or the presence of PNI. Despite combined treatment, 10% to 15% develop in-field recurrence, often in the parotid bed or skull-base region. Most will be inoperable and incurable. An ongoing study (Trans Tasman Radiation Oncology Group [TROG] 05.01) is evaluating the role of concurrent carboplatinum to adjuvant RT in improving regional control. With surgery and adjuvant RT, 5-year overall survival (OS) is 70% to 75%. Patients considered medically or technically inoperable can still be treated with RT alone, although the likelihood of cure is reduced. Patients of good performance status may also be considered suitable to receive concurrent platinum chemotherapy although this approach may also increase the toxicity of treatment and is experimental.

Perineural Invasion

The role of surgery and RT in patients with PNI is unclear. Patients with asymptomatic PNI, detected postoperatively, may benefit from wide field local RT without the need to treat neural pathways. Patients with symptomatic PNI may, however, require more extensive volumes irradiated to encompass involved neural pathways, including intracranial extension. Doses of 50 Gy to 60 Gy may be required and attention paid to the tolerance of structures such as the orbital contents and optic chiasm. Whether patients benefit from excision of involved nerves in addition to RT is controversial but recommended by some skull-base surgeons.[57]

Sentinel Lymph Node Biopsy

The role of SLNB in NMSC is unclear because the overall incidence of metastatic nodal disease is low. In contrast to patients with MM, there is limited evidence to guide clinicians with a meta-analysis (13 studies) reporting positive selective lymph nodes in 12.3% of high-risk patients.[58] In certain patients considered to have high-risk SCC, however, SLNB may be useful in guiding clinicians, provided that expertise in undertaking this investigation is available.

Merkel Cell Carcinoma

The initial treatment for MCC is usually surgery to establish tissue diagnosis. The role of RT in the management of MCC has been evaluated since the early 1980s because of the high rate of locoregional relapse in this radiosensitive disease.

With few exceptions, most studies report a marked benefit to locoregional control and survival with the addition of adjuvant RT. In the largest study ($n = 1665$) of its type, the addition of adjuvant RT significantly improved median survival in patients with lesions greater than 2 cm from 21 months to 50 months ($p = 0.0003$).[59] In a meta-analysis of 1254 patients, Lewis et al[60] reported a significant reduction in local (hazard ratio 0.27, $p < 0.001$) and regional (hazard ratio 0.34, $p < 0.001$) relapse and a benefit in overall survival (hazard ratio 0.63, $p = 0.04$) in patients treated with surgery and adjuvant RT compared with patients treated with surgery alone.

The routine use of adjuvant chemotherapy is unclear. In a Phase II single-arm study from Australia, 53 patients received concurrent and adjuvant chemotherapy (carboplatin and etoposide) with RT with 3-year OS, locoregional control, and distant control rates of 76%, 75%, and 76%, respectively.[61] These results add support for a randomized controlled trial to confirm the hypothesis that chemotherapy may benefit these patients.

With few exceptions, most patients with MCC should proceed to wide-field adjuvant RT when a diagnosis has been confirmed. Given the high risk of local recurrence, RT margins around a primary lesion (or excision site) of at least 3 cm to 4 cm are recommended, if possible, and as a guide treatment fields should encompass, as a minimum, the primary site, in-transit tissue, and first-echelon nodes (Figure 41-12).[61,62] RT should not be delayed by the need for further surgery if excision margins are involved. The risk of occult nodal metastases at presentation is 30% to 50%, and if left untreated, patients may develop clinical nodal metastases, which carries a poor prognosis.[62] Thus, all patients should have the draining lymph nodes either investigated with SLNB, or treated electively usually with RT in association with RT to the primary site. Patients who may be considered for close observation because of the relatively low risk of recurrence include those with small lesions (<10 mm) widely excised (5-mm to 10-mm margins), without the presence of lymphovascular invasion and SLNB negative.



Figure 41-12 A 49-year-old male undergoing wide-field adjuvant RT after excision of a 12-mm Merkel cell carcinoma from the right upper face. The large field encompasses the excision site, in-transit tissue, and parotid and upper neck lymph nodes. A dose of 55 Gy in 25 fractions using 9-MeV electrons was prescribed. The patient developed confluent brisk in-field erythema by the end of treatment.

Patients with small volume (<3 cm to 4 cm) nodal metastases can be treated adequately with RT without the need to undergo nodal resection. In the setting of inoperable disease, definitive RT to doses of 50 Gy to 55 Gy in 20 to 25 daily fractions still offers the likelihood of excellent in-field control (75%) and cure in a few patients.[63]

Adnexal Carcinoma

The standard treatment of sebaceous carcinoma is wide local excision and therapeutic nodal dissection if lymphadenopathy is present. Consideration may be given to excision with Mohs's micrographic surgery. The role of adjunctive modalities has not been explored systematically, but there is evidence that RT may be an effective modality in MAC in both the adjuvant and definitive setting and should therefore be considered in select patients.[64,65] Generally, postoperative irradiation is indicated when the surgical margins are positive or close, multiple lymph nodes are involved, or extracapsular nodal extension is present.

For eccrine and apocrine carcinomas, wide excision of the primary lesion is accepted as the standard treatment in patients with no lymphadenopathy at diagnosis. Postoperative RT to the surgical bed with 2-cm to 3-cm margins may be indicated.

The role of elective treatment of regional lymphatics is controversial in this rare disease. As most malignant skin adnexal neoplasms have a low rate of nodal metastasis, and there is little evidence in the literature regarding the use of SLNB, we do not generally recommend the routine use of SLNB in patients with malignant skin adnexal tumors. However, in select patients with high-risk eccrine porocarcinoma (tumor thickness >7 mm, lymphovascular invasion present) it may be of benefit.[66]

LOCALLY ADVANCED DISEASE AND PALLIATION

Patients with locally advanced (T4) primary skin cancers involving bone and cartilage, muscle, or nerves can still be treated and cured with definitive RT. In many cases, surgical salvage is an option if RT is unsuccessful. Al-Othman et al[67] documented an initial local control rate of 53% and an ultimate local control rate of 90% with surgical salvage in 85 patients with previously untreated (n = 43) and recurrent (n = 45) T4 skin carcinomas given RT to doses of 60 Gy to 75 Gy over 6 to 8 weeks. Bone invasion or PNI was found to reduce the likelihood of local control in this small series. Cause-specific survival at 5 years was 76%, and 15% developed severe late complications in the form of soft-tissue or bone and cartilage necrosis. In a study of 21 patients with T4 NMSC treated with megavoltage RT almost 60% achieved disease control with many treated with intensity-modulated RT (IMRT).[68] The utilization of newer technology such as IMRT in select patients with advanced NMSC may allow the delivery of higher doses of RT, yet minimize the side effects of treatment. Similarly, in 25 patients with an advanced NMSC and treated with helical tomotherapy (a form of IMRT) delivering doses between 50 Gy and 70 Gy, the authors documented complete clinical remission in 88%.[69]

Radiation can reduce symptoms (pain, bleeding, fungation, infection, and drainage) for most patients with advanced inoperable cancer or metastatic disease. Recommended dose-fractionation schedules depend on the tumor location and patient's life expectancy. The most frequently used regimens include the following:

- 20 Gy to 30 Gy in 5 to 10 fractions over 1 to 2 weeks for skeletal or cerebral metastasis or even a single fraction of 8 Gy, especially for skeletal metastases.
- 45 Gy to 50 Gy in 18 to 25 fractions over 4 to 5 weeks for patients with tumor deposits in the proximity of critical structures (e.g., parotid, axillary, or ilioinguinal region) but otherwise having a reasonable life expectancy. Alternative approaches include a QUAD SHOT schedule in which patients receive 4 fractions delivered over 2 days and repeated every 3 weeks to a total dose of approximately 42 Gy to 44 Gy (Figure 41-13).

In a study of 28 patients treated palliatively in the setting of advanced NMSC (5 cm median size) 24 Gy was delivered over 3 weeks. The authors report an alleviation of symptoms in 83% of assessable sites and a complete response recorded in 36% of patients.[70] Alternatively, large single fractions of 10 Gy to 15 Gy may also be appropriate in patients who are debilitated and in a nursing home with large neglected lesions that are often painful, bleeding, and infected.

Many SCCs express epidermal growth factor receptor and targeted treatment using monoclonal antibodies is an emerging option in select advanced cases. In some cases, dramatic results have been obtained using this relatively nontoxic treatment.[71] Similarly, a recent finding in patients with BCC has been genetic alterations resulting in up-regulation in the hedgehog signaling pathway. A new oral drug, Vismodegib, inhibits this pathway and may offer a potentially new treatment for patients with advanced (inoperable or previously treated) and metastatic BCC, and patients with Gorlin's syndrome (basal cell nevus syndrome). A recent study reported a complete response of 21% in eligible patients although the median duration of response was short (7.6 months) and serious adverse events and even death were reported. With further research it is likely that the outcome for these patients will improve with molecular inhibition of this and other pathways.[72]



Figure 41-13 **A,** Patient, 85 years old, unwell, with a rapidly growing left facial squamous cell carcinoma deemed inoperable. **B,** The patient underwent palliative RT (35 Gy in 10 fractions using orthovoltage photons) to the lesion and experienced an excellent regression in her cancer and an improved quality of life.

IRRADIATION TECHNIQUES

Carcinoma

As previously documented, definitive RT yields an excellent disease control rate with good functional and cosmetic results for lesions around the nostril, lower eyelids, ears, and lips. Patients who are poor surgical risks and patients with large lesions are also sometimes best treated with RT. Proper planning and execution of RT are essential to achieve the best outcome.

Target Volume

The RT target volume (or RT field) for a localized NMSC is determined by the size of the lesion, lesion location, and type of growth (infiltrative lesions require more generous field margins). The treatment field typically encompasses the visible or palpable tumor and 1 cm to 2 cm of surrounding normal-appearing skin. Margins may be tighter (1 cm) when treating areas close to the eye or when the primary lesion is 1 cm or smaller. More generous margins are appropriate for lesions with ill-defined borders to adequately encompass subclinical (i.e., microscopic) extension. In a study involving 159 NMSC in 150 patients the authors pathologically determined microscopic spread beyond gross lesions and made recommendations on RT field margins to achieve 95% coverage of subclinical spread. For BCC the margins ranged from 10 mm to 13 mm, and for SCC, from 11 mm to 14 mm. Clinicians should be aware that inadequate margins place a patient at risk of recurrence.[73]

Occasionally, in patients with SCC presenting with either low-volume lymphadenopathy and concomitant primary disease or high-risk primary lesions and a clinically negative nodal basin, the initial field may encompass the primary lesion and the regional lymphatics with the treatment field subsequently reduced to cover the areas of gross disease with adequate margins. A typical site is a temple primary with parotid metastases in which the initial RT field should receive a prescribed dose of 50 Gy, or equivalent, followed by an extra 10 Gy to 20 Gy to a reduced field (1 cm to 2 cm around macroscopic disease). In many cases, small treatment fields can be safely treated with hypofractionated schedules using 2.5-Gy to 4-Gy fractions, which reduces the overall duration of treatment.

In patients receiving postoperative RT in the setting of lymph node metastasis or PNI, the initial portal also may need to encompass the primary tumor bed, if technically feasible. However, if the time interval from primary site treatment exceeds 12 months, and there is no evidence of local recurrence, this may be omitted. Some clinicians may choose a longer period of time such as 24 months before omitting treatment of the primary site.

The clinical target volume in the setting of PNI depends on the primary site and the relevant cranial nerves involved and in many cases includes the skull base, cavernous sinus, and intracranial routes back to the brainstem.[74] IMRT may allow for the accurate treatment of neural pathways while limiting the dose to critical structures. Electively treating regional lymph nodes in patients with PNI is an option but probably unnecessary.

Setup, Field Arrangement, and Dose Fractionation Schedule

Patients are best immobilized in a position that gives optimal access to irradiate the tumor to ensure daily reproducibility. Preferably, the position is such that the plane of the skin to be treated is horizontal to facilitate the placement of a lead shield for skin collimation. Irradiation is delivered through a single appositional field, in most cases using superficial or orthovoltage energy photons (usually 75 kVp to 300 kVp) or electrons (usually 6 MeV to 9 MeV). Low-energy photons are preferable to using small field electrons when treating skin cancers. However, NMSC can still be treated effectively with electrons, provided that clinicians are aware of certain aspects of using electrons (e.g., skin sparing, dose constriction at depth, wide penumbra). In a large study of 434 NMSC in 333 patients all were treated with electrons (4 MeV to 12 MeV) receiving either 54 Gy in 18 fractions or 44 Gy in 11 fractions. With a median follow up of 43 months local control rates varied between 94% and 97% without a significant difference in outcome between BCC and SCC. Cosmetic outcome was also assessed in a small group without any significant difference between the two treatment schedules. These results suggest electrons are an effective treatment in departments that lack a superficial or orthovoltage machine.[75]

An alternative to external beam RT in select patients with superficial (<4 mm thick) well-circumscribed NMSC is brachytherapy (or contact therapy). In an Australian center 236



Figure 41-14 A patient undergoing RT to the left side of the nose. A lead mask is cut out to define the RT field receiving treatment. There is an extra layer of lead covering the eyes to reduce further any scattered dose.

NMSC (in 200 patients) were treated with high-dose rate brachytherapy using a surface applicator (max diameter 30 mm) and prescribed a dose of 36 Gy in 12 daily fractions taking ~10 minutes for each daily treatment. The outcome of these patients was excellent with local control achieved in 98% and a reported good or excellent cosmesis obtained in 88%. Centers with expertise in brachytherapy may consider this alternative in select patients, especially if the department lacks a superficial or orthovoltage machine.[76]

The energy of x-rays or electrons is chosen based on the thickness of the lesion to be treated. This decision is critical when using electrons, the energy of which should be selected such that the 90% isodose line including surface bolus is a few millimeters deeper than the base of the lesion. The treatment distance for x-rays also depends on the thickness of the lesion. A shorter 20-cm to 30-cm focus skin distance cone is appropriate for superficial tumors, but a 50-cm focus skin distance open field with skin collimation is preferable for thicker lesions to avoid a large dose gradient across the lesion. The focus skin distance for electrons is usually 100 cm.

Several techniques and devices are helpful in minimizing radiation exposure to the surrounding normal tissues and obtaining the desired dose distribution. A 3- to 4-mm-thick lead cutout is used for field shaping, conforming to the geometry of the lesion by skin collimation (Figure 41-14). The overall size of the cutout should be large enough so that the cone or collimator setting for electron beams is at least 4 × 4 cm in size for reliable dosimetry. Skin bolus or a scatter plate is used when treatment is given with electrons to ensure full surface dose. Additional shielding can be applied to protect tissues from "exit radiation." An internal eye shield is inserted when treating an eyelid lesion with orthovoltage x-rays or electrons of 8 MeV or less (see Figure 41-9, *B*). It is important to calibrate commercially available eye shields individually



Figure 41-15 A 45-year-old white male undergoing definitive RT for a T2 N0 lower lip squamous cell carcinoma. The patient received 55 Gy in 25 fractions using orthovoltage energy photons with the daily insertion of an oral cavity lead shield to limit exit dose to the mandible, teeth, and oral cavity.

with respect to their electron-attenuating properties because transmission through these shields can be considerable, even for a nominal 6-MeV beam. Similarly, lead oral cavity shields are used to shield the mandible, teeth, and oral cavity when treating a lip cancer (Figure 41-15).

Several fractionation schedules can be used and are effective in curing NMSC. Generally, more protracted fractionation schedules using lower dose (2 Gy to 2.5 Gy) per fraction give the best cosmetic results. The recommended radiation regimen for individual patients depends on patient age, lesion size, and site. For most skin cancers in older patients, a dose of 40 Gy in 10 fractions, 45 Gy in 15 fractions, or 50 Gy in 20 fractions is an appropriate and effective regimen. If the patient is in poor general condition, hypofractionation (e.g., 32 Gy in 4 fractions, 21 Gy in 3 fractions, 35 Gy in 5 fractions, or a single dose of 15 to 20 Gy) may be used. Delivering large fractions using superficial energy photons or orthovoltage energy photons can take 20 to 30 minutes, and an uncooperative patient may need to be lightly sedated.

The dose for treatment with x rays is specified at D_{max}. The dose for irradiation with electrons is prescribed at 90%. Prescription of electron doses at 90% versus D_{max} for superficial x-rays allows for the difference in relative biologic effectiveness between the two beam qualities.

After resection of a nodal basin (e.g., parotid or neck), patients with positive nodes (or a single node with extranodal spread) usually receive radiation in 2 Gy fractions to a dose of 60 Gy because of the large treatment volume. Similarly, for patients with inoperable nodal disease treated with RT alone, 2 Gy to 2.5 Gy fractions to a total dose of 60 Gy to 70 Gy with a shrinking field are used unless the intent is palliative.

Merkel Cell Carcinoma and Adnexal Carcinoma

Target Volume

The target volume for MCC consists of the excision site (with 3-cm to 4-cm margins), in-transit tissue, and at least the first echelon nodes (may consider next level as well). When a lesion is close to critical structures (e.g., orbit) narrower margins and appropriate shielding need to be considered.

The target volume for adnexal carcinoma consists of the surgical bed with margins of 2 cm to 3 cm and, depending on the site and size of the primary tumor, the draining lymphatics.



Figure 41-16 **A,** Multinodular Merkel cell carcinoma located on the distal foot of a 90-year-old male. **B,** The patient received 25 Gy in five fractions to the distal foot and experienced rapid disease regression by the end of treatment. **C,** At 2 months after RT, there was no evidence of disease; at 18-month follow-up, he remained disease free.

Setup, Field Arrangement, and Dose Fractionation Schedule

The general principles of patient setup and portal arrangement are as outlined for BCC and SCC. As primary treatment, RT is administered, preferably with electrons, in 2 to 2.5-Gy fractions to a cumulative dose of 45 to 55 Gy for elective irradiation, plus a boost dose of 10 Gy in 5 fractions to the gross disease. A cumulative dose of 60 to 66 Gy may be recommended for the treatment of bulky, inoperable primary tumors. Elderly patients of poor performance status who are unsuitable for an extended course of RT may still benefit from shorter palliative schedules, such as 25 Gy in 5 fractions (Figure 41-16).

Radiation regimens used for adnexal carcinoma are 60 Gy to 70 Gy in 30 to 35 fractions, depending on the site and target volume. The portal is generally reduced to encompass areas of known gross disease after 50 Gy to 54 Gy.

Patient Care During and after Radiotherapy

A tumoricidal dose of RT produces moist desquamation of the irradiated skin by the end of, and shortly after, treatment. The irradiated skin area should be protected from heat, cold, sunlight, friction, disinfectants, and other sources of irritation to avoid additional tissue injury. During RT, the daily application of a bland emollient is recommended. When moist desquamation occurs, the area should be kept clean to prevent secondary infection and may require the application of a burn-type dressing (e.g., silver sulfadiazine cream) for at least 2 to 3 weeks. Patients are instructed to use sunscreen over the irradiated area after completion of treatment.

Patients should also be informed about the specific acute and late side effects of treatment, such as mucositis of the nasal passages and upper lip, nasal dryness, synechiae (when treating nostril lesions), and conjunctivitis and loss of eyelashes (when treating eyelid cancers). After treatment involving the lacrimal canaliculi, irrigation of the ducts during the healing phase helps to prevent synechiae.

Regular follow-up examinations should include evaluation of the treated area for late complications and search for new lesions. The latter develop in up to 50% of treated patients occasionally in proximity to a previous treatment field. Late side effects include hypopigmentation, hyperpigmentation, telangiectasia, and skin atrophy. Skin retraction at the lower eyelid may result in ectropion. These are rarely serious after properly administered RT.

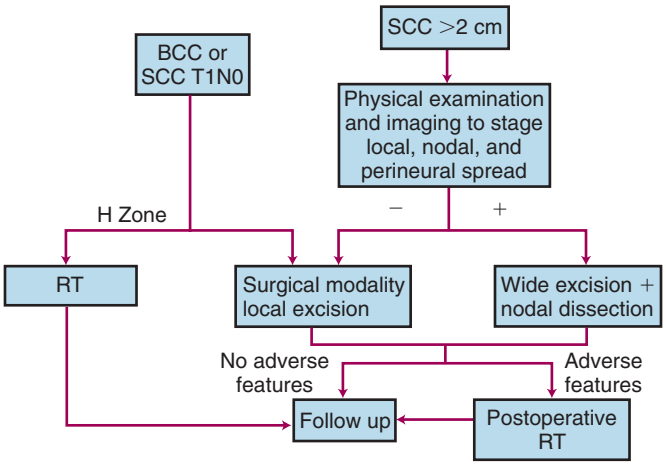


Figure 41-17 **Diagnostic and treatment algorithm for cutaneous basal cell carcinoma (BCC) and squamous cell carcinoma (SCC).** *RT,* Radiotherapy.

DIAGNOSTIC AND TREATMENT ALGORITHMS

Basal Cell Carcinoma and Squamous Cell Carcinoma

Figure 41-17 illustrates the diagnostic and treatment algorithm for BCC and SCC. The choice of treatment for individual patients is determined by factors such as the lesion site and size, anticipated functional and cosmetic results, treatment

time, treatment cost, and patient preference. Surgical approaches are preferred for most patients with resectable tumors, but RT may yield better functional and cosmetic results for lesions of the nose, lower eyelids, and ears. A combination of surgery and adjuvant RT is indicated in larger tumors or tumors with inadequate excision, PNI, invasion of bone or cartilage, extensive skeletal muscle infiltration, or nodal metastasis.

Merkel Cell Carcinoma and Adnexal Carcinoma

A combination of surgery (respecting form and function) and wide-field elective or adjuvant RT is recommended for most patients with MCC and adnexal carcinoma. In most situations, there should be elective treatment, usually RT, of first echelon lymph nodes. The role of adjuvant chemotherapy for the treatment of MCC is unclear without high-level supportive evidence to support a benefit. RT alone still offers a potential cure for inoperable patients or patients refusing surgery. More recent evidence suggests that PET/CT scanning in patients with MCC may alter management or prognosis, or both, in 30% to 40% of patients.[77]

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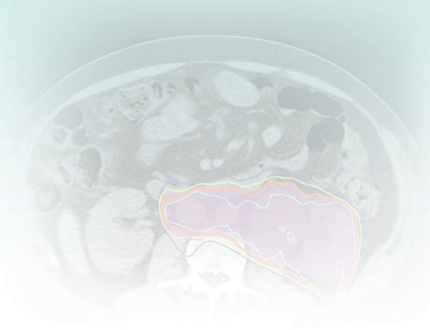
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CHAPTER

42 Malignant Melanoma



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INCIDENCE

The incidence of melanoma continues to rise faster than that of any other cancer. It is estimated in 2015 that there will be 73,870 new cases of melanoma diagnosed and 9940 deaths in the United States.

BIOLOGIC CHARACTERISTICS

Sun exposure is clearly associated with the development of cutaneous melanoma. Inherited mutations may also play a role in some cases.

The natural history of melanoma is usually characterized by early, stepwise dissemination from a primary tumor to regional lymph node lesions and then to lesions at distant sites.

The main determinants of survival are the thickness of the primary tumor (measured in millimeters), the presence or absence of primary ulceration, the status of regional lymph nodes, and the sites of distant disease.

STAGING EVALUATION

For evaluating localized disease, a thorough history and physical examination including dermoscopy can suffice. For patients with nodal spread, the staging evaluation should include serum level measurement of lactate dehydrogenase and imaging with contrast-enhanced computed tomography (CT) and positron emission tomography (PET). Magnetic resonance imaging (MRI) of the brain should be considered, and it should be routine for patients with distant metastases.

PRIMARY THERAPY

Treatment of a primary melanoma lesion that is less than 0.75 mm thick is wide local excision alone. Sentinel lymph node biopsy is generally recommended for any lesion that is 1 mm or thicker or if ulceration or Clark level IV or V invasion exists in a lesion that is ≥0.75 mm and <1 mm. If the sentinel node is not involved, the patient may be observed, but if it is involved, complete lymph node dissection should be considered because it does offer a survival benefit in patients who are node positive.

If complete lymph node dissection is not possible because of medical comorbidities, elective radiation therapy to the involved nodal basin is preferred to observation.

ADJUVANT THERAPY

For patients at risk of nodal spread in whom sentinel lymph node biopsy will not alter subsequent management because of medical comorbidities, regional irradiation (i.e., elective irradiation) is preferred compared to observation.

Indications for postdissection nodal radiation therapy are high-risk pathological features including nodal extracapsular extension, lymph nodes measuring 3 cm or more in the widest diameter, at least two involved lymph nodes, and recurrent nodal disease after previous dissection for pathologically involved lymph nodes.

Adjuvant systemic interferon alpha-2b improves relapse-free survival for patients with thick, localized melanoma lesions and those with nodal metastases. It is however associated with significant toxicity.

LOCALLY ADVANCED DISEASE AND METASTASES

Palliative radiation therapy reduces symptoms in more than 80% of patients with inoperable disease or metastatic masses. Significant improvements in overall survival are seen in patients receiving systemic CTLA-4 blockers and BRAF inhibitors.

Malignant melanoma remains a predominantly surgically treated disease, and most patients with early-stage disease are cured by simple excision of the primary lesion. By the time growth of the primary tumor reaches a few millimeters, however, the risk of nodal and distant spread increases rapidly, and the role of adjuvant radiation therapy and systemic therapy takes on increasing importance. As for many diseases, radiation therapy is often recommended as an adjuvant to surgical dissection of locally advanced disease or as a palliative treatment of distant metastases. Until recently, the acceptance of radiation therapy as part of a standard treatment algorithm for patients with melanoma has been marred by controversy.

In the early 1930s, melanoma was considered to be categorically radioresistant. This belief was perpetuated by popular textbooks of the time until laboratory data showed that the reputed radioresistance of melanoma might reflect a broad shoulder in the low-dose portion of the cell survival curve. The data suggested that melanoma cells might be more sensitive to radiation delivered as a large dose per fraction (i.e., hypofractionation regimen). Although a randomized trial performed by the Radiation Therapy Oncology Group (RTOG) did not confirm clinical superiority for hypofractionation in a heterogeneous group of patients receiving palliative radiation therapy, these types of regimens are favored by clinicians specializing in melanoma radiation therapy.[1] Retrospective reviews of clinical experiences have suggested that the hypofractionated regimens are effective and can be safely delivered in a short period of time to a group of patients for whom survival is ultimately dictated by the risk of distant metastasis.[2,3]

Although hypofractionated radiation therapy has been shown to be effective in several clinical settings, the perceived risk of distant metastatic disease and concern over the rate of long-term radiation-related toxicity often precludes its use, regardless of effectiveness. In this chapter, we present the rates

of local failure, regional failure, distant failure, and long-term treatment-related toxicity for patients with melanoma and provide data supporting the use of radiation therapy in a defined group of patients. Only by balancing the competing risks of failure and treatment-related toxicity can physicians appropriately integrate radiation therapy into the management of patients with malignant melanoma.

ETIOLOGY AND EPIDEMIOLOGY

For 2015, 73,870 new cases of cutaneous malignant melanoma are estimated to occur in the United States, or 4.5% of all newly diagnosed cancers.[4] Although the incidence of malignant melanoma more than doubled between 1975 and 2000, new cases of melanoma are being diagnosed earlier in the course of the disease because of increased public awareness, and the mortality rate has steadily decreased.[4] The reason for the rise in incidence has not been explained. The number of deaths resulting from melanoma in 2013 was estimated to be 9480.

Several lines of evidence link sun or ultraviolet (UV) radiation exposure to the development of cutaneous melanoma.[5,6] There is a higher incidence of melanoma in populations with high levels of sun exposure, among sun-sensitive people, on sun-exposed body sites, in populations with high sun exposure, among people with other sun-related skin conditions,[7,8] and in those using artificial sources of UV radiation such as sunbeds. The development of melanoma may also be reduced by protection of the skin against sun exposure.[7]

Analysis of patients with familial clustering of melanoma has identified two genes, *CDKN2A* and *CDK4*, that confer increased susceptibility to melanoma development.[9] Although only a small percentage of patients with melanoma has a mutation in *CDKN2A*, carriers of this mutation have an almost 70% chance of developing melanoma by the age of 80 years.[10,11]

The presence of an increasing number of nevi also represents a well-accepted risk factor for the development of melanoma.[12] Whether the type of nevi (i.e., common, atypical, or dysplastic) is also important or merely reflects the degree of previous sun-related damage remains controversial.

PREVENTION AND EARLY DETECTION

Advocates of early detection and screening programs generally assume that early detection and treatment will significantly affect the mortality rate and the quality of life, particularly in melanoma, for which the association between tumor thickness and survival is well documented. Unfortunately, there are no randomized clinical trials to support routine screening of the general population. In the United States, routine screening of high-risk populations is still generally recommended, and educational efforts have been directed to clinicians and the public to promote early recognition of suspicious skin lesions. Periodic separate or mass screening for high-risk individuals consists of a total cutaneous examination and a 2- to 3-minute visual inspection of the entire integument by adequately trained physicians. Risk factors include a family history of skin cancer, fair skin, multiple nevi, and a history of melanoma or other skin cancers. Recognized signs of melanoma include the ABCDs of early diagnosis: A, asymmetry; B, border irregularity; C, color variation; and D, a diameter greater than 6 mm.

The U.S. Preventive Services Task Force (USPSTF)[13] performed a thorough review of the medical literature and issued a practice policy statement regarding skin cancer prevention counseling. Recommended preventive measures include avoidance of sunlight exposure—particularly limiting time spent outdoors between 10 AM and 3 PM—and wearing protective physical barriers such as hats and clothing and sunscreens that are opaque or that block UV A and B radiation.

CLINICAL MANIFESTATIONS, PATHOBIOLOGY, AND PATHWAYS OF SPREAD

Clinical Presentation and Pathology

Primary cutaneous melanoma may develop in or adjacent to one of the precursor lesions (e.g., lentigo maligna, dysplastic nevus) or in normal skin, and it can manifest clinically in four major growth patterns.[14] The most prevalent variant is *superficial spreading melanoma,* which constitutes approximately 70% of cases.[15,16] Superficial spreading melanoma often arises in a junctional nevus, where it first appears as a deeply pigmented area, progressing gradually to a flat induration, generally over several years. As the lesion grows, the surface and perimeter may become irregular with amelanotic patches. On histologic examination, it is characterized by a prominent intraepidermal proliferation of malignant melanocytes similar to Paget's disease; hence, this pattern is called *pagetoid melanoma*.[17] The malignant cell may be confined to the lower portion of the epidermis or may spread up into the granular cell layer of the epidermis, which is frequently hyperplastic. As the lesion enlarges, clusters of malignant cells invade the dermis and subcutaneous tissues.

Nodular melanoma is the second-most common variant (15% to 25% of melanoma lesions).[15,16] Nodular melanoma develops more frequently de novo on the trunk, head, or neck of middle-aged individuals. In contrast to superficial spreading melanoma, the nodular variant affects men more than women. It manifests as a raised or dome-shaped, blue-black lesion, which is usually darker than superficial spreading melanoma. Approximately 5% of nodular variants manifest as nonpigmented, fleshy nodules, and therefore, this type of lesion is called *amelanotic melanoma*. Histologic testing shows that nodular melanoma is characterized by an expansile nodule centered at the papillary dermis, with little or no epidermal component, composed of epithelioid cells. Spindle cells, small epithelioid cells, and mixtures of cells may be present. Deeper invasion of the dermis and subcutis occurs as the lesion grows.

Lentigo maligna melanoma is seen in less than 10% of malignant melanoma lesions.[16,18] This variant occurs most frequently on the face or neck of Caucasians older than 50 years, and it arises from a precursor lesion of melanoma in situ called *lentigo maligna* (i.e., *Hutchinson's melanotic freckle*).[19] It manifests as a relatively large (>3 cm), flat, tan-colored (with different shades of brown) lesion that often has been present for more than 5 years. The border becomes irregular as the lesion enlarges. On histologic examination, an invasive tumor is usually composed of spindle-like cells. These cells may be embedded in a fibrous stroma (i.e., desmoplastic pattern) or may form fascicles displaying neural features and infiltrating endoneural and perineural structures of the cutaneous nerves.[19,20]

Acral lentiginous melanoma occurs characteristically on the palms or soles or beneath nail beds.[21-23] The relative frequency of acral lentiginous melanoma varies substantially with race. It represents about 5% of melanomas in Caucasians and 35% to 60% in dark-skinned individuals.[24,25] Most acral lentiginous melanomas occur on the foot sole in individuals older than 60 years. They generally start as tan or brown stains and evolve over a period of years to reach an average diameter of 3 cm before a diagnosis is established.[22,23] Histologic testing reveals that early-stage acral lentiginous melanoma is composed of large, highly atypical, pigmented cells along the dermoepidermal junction in an area of hyperplastic epidermis. At the

invasive stage, infiltrating cells may be epithelioid or spindle shaped.[20] Sometimes, infiltration to deeper structures occurs, predominantly through the eccrine ducts.[17]

Biology and Patterns of Spread

Superficial spreading and lentigo maligna melanomas generally grow slowly over many years (i.e., radial growth phase). Left untreated, however, these lesions gradually invade the dermis and subcutis (i.e., vertical growth phase) and acquire metastatic potential. Acral lentiginous melanomas and, particularly, nodular melanomas have a shorter natural history, with rapid progression to the vertical growth pattern.

Previously, two microstaging systems were used. The Breslow system classifies lesions by the vertical thickness between the granular layer of the epidermis and the deepest part of invasion, measured with an ocular micrometer. In ulcerated lesions, measurements are made from the surface to the deepest part.[26] The Clark method categorizes lesions into five groups by the level of dermal or subcutis invasion: level I, confined to the epidermis; level II, invasion to the papillary dermis; level III, invasion to the papillary-reticular dermal interface; level IV, invasion to the reticular dermis; and level V, invasion to the subcutaneous tissue.[15] Of the two systems, tumor thickness is more accurate in predicting outcome, although level of invasion remains prognostic for patients with lesions less than 1 mm thick.[27]

In an analysis of 17,600 patients with melanoma, several clinical and histologic variables were found to be of prognostic value, and they formed the basis for an updated American Joint Committee on Cancer (AJCC) staging system[27,28] (Table 42-1). For patients without clinical evidence of nodal spread, primary thickness and ulceration were the most important prognostic features. The 10-year melanoma-specific mortality increased proportionally as the thickness of the primary tumor increased (Figure 42-1), and the survival of patients with ulcerated primary lesions diminished to a level equivalent to that of patients with thicker primary lesions that were not ulcerated[27] (Figure 42-2). There was significantly inferior 10-year disease-specific survival (DSS) according to site of the primary lesion (i.e., worse for trunk, head, and neck lesions than extremity lesions), gender (i.e., worse for patients who were male than for those who were female), and age (i.e., worse for patients who were older than for those patients who were younger).[27]

For patients with documented nodal metastases, the most important prognostic feature was the number of involved lymph nodes, but primary tumor ulceration and burden of nodal disease (microscopic compared to macroscopic) remained of prognostic significance on multivariate analysis[27] (Table 42-2). Patients with skin, subcutaneous, and distant lymph node metastases fared better than those with visceral metastases.[27]

PATIENT EVALUATION AND STAGING

Suggested staging guidelines for patients with melanoma are shown in Table 42-3. Clinical evaluation of patients with melanoma consists of inspection and palpation of the involved area of skin and the regional lymph nodes. Patients with primary lesions 1 mm thick or larger are generally staged at the time of wide local excision with sentinel lymph node biopsy. Patients with thinner lesions may still be at risk of nodal disease and may benefit from sentinel lymph node biopsy if the primary lesion is ulcerated, is associated with satellitosis, or is Clark level IV or V. If the sentinel node is involved, CT scanning of the lungs, abdomen, and pelvis is warranted as a baseline evaluation.[29]

Chest radiography plays little or no role in the initial management of patients with localized disease. PET scans and MRI

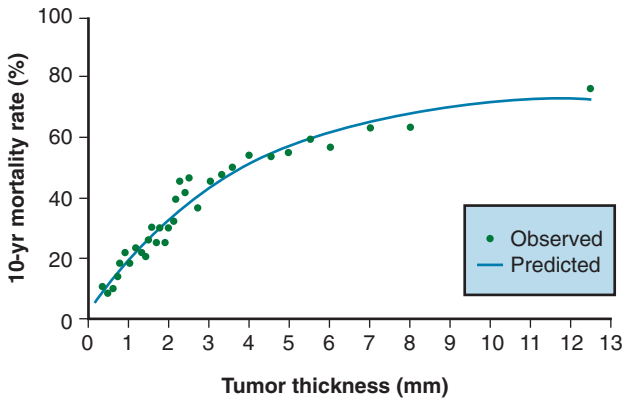
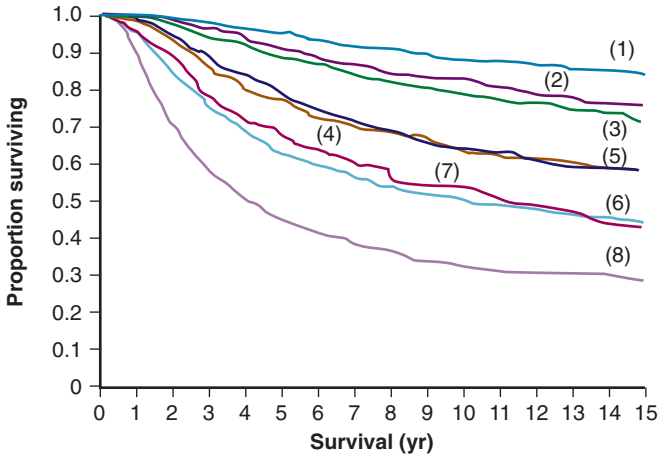


Figure 42-1 Observed and predicted 10-year mortality rate of 15,320 patients with clinically localized melanoma based on the mathematical model $f(t) = 1 - 0.998e(-211t = 0.009\ t_2)$, which is derived from the melanoma database of the American Joint Committee on Cancer (AJCC). t is the measured thickness (mm), and $f(t)$ is the 10-year melanoma-specific mortality rate ($p < 0.0001$).
From Balch CM, Soong S, Gershenwald JE, et al: Prognostic factors analysis of 17,600 melanoma patients. Validation of the American Joint Committee on Cancer melanoma staging system. J Clin Oncol 19:3622–3634, 2001.



	Thickness (mm)	Ulceration	No. Patients
(1)	= <1.0	No	4510
(2)	= <1.0	Yes	1380
(3)	1.1–2.0	No	3285
(4)	1.1–2.0	Yes	958
(5)	2.1–4.0	No	1717
(6)	2.1–4.0	Yes	1523
(7)	>4.0	No	563
(8)	>4.0	Yes	978

Figure 42-2 Survival curves for 14,914 patients with localized melanoma stratified by melanoma thickness and presence or absence of ulceration. The correlation of the subgroups used for defining melanoma TNM staging with melanoma-specific survival is significant ($p < 0.0001$).
From Balch CM, Soong S, Gershenwald JE, et al: Prognostic factors analysis of 17,600 melanoma patients. Validation of the American Joint Committee on Cancer melanoma staging system. J Clin Oncol 19:3622–3634, 2001.

TABLE 42-1 American Joint Committee on Cancer Staging System for Melanoma of the Skin

Primary Tumor (T)		Clinical Stage Grouping	
TX	Primary tumor cannot be assessed (e.g., shave biopsy, regressed melanoma)	Stage 0	TisN0M0
		Stage IA	T1aN0M0
T0	No evidence of primary tumor	Stage IB	T1bN0M0
Tis	Melanoma in situ		T2aN0M0
T1	Melanoma ≤1 mm thick, with or without ulceration	Stage IIA	T2bN0M0
T1a	Melanoma ≤1 mm thick, and mitosis <1/mm^2, no ulceration		T3aN0M0
		Stage IIB	T3bN0M0
T1b	Melanoma ≤1 mm thick, and mitosis >1/mm^2, or with ulceration		T4aN0M0
		Stage IIC	T4bN0M0
T2	Melanoma 1.01-2 mm thick, with or without ulceration	Stage III	TanyN1M0
			TanyN2M0
T2a	Melanoma 1.01-2 mm thick, no ulceration		TanyN3M0
T2b	Melanoma 1.01-2 mm thick, with ulceration	Stage IV	TanyNanyM1
T3	Melanoma 2.01-4 mm thick, with or without ulceration		
T3a	Melanoma 2.01-4 mm thick, no ulceration		
T3b	Melanoma 2.01-4 mm thick, with ulceration		
T4	Melanoma >4 mm thick, with or without ulceration		
T4a	Melanoma >4 mm thick, no ulceration		
T4b	Melanoma >4 mm thick, with ulceration		
Regional Lymph Nodes (N)		**Pathologic Stage Grouping**	
NX	Regional lymph nodes cannot be assessed	Stage IA	T1aN0M0
N0	No regional lymph node metastasis	Stage IB	T1bN0M0
N1	Metastasis in one lymph node		T2aN0M0
N1a	Clinically occult (microscopic) metastasis	Stage IIA	T2bN0M0
N1b	Clinically apparent (macroscopic) metastasis		T3aN0M0
N2	Metastasis in two or three regional nodes or intralymphatic regional metastasis without nodal metastases	Stage IIB	T3bN0M0
			T4aN0M0
		Stage IIC	T4bN0M0
N2a	Clinically occult (microscopic) metastasis	Stage IIIA	T1-4aN1aM0
N2b	Clinically apparent (macroscopic) metastasis		T1-4aN2aM0
N2c	Satellite or in-transit metastasis without nodal metastasis	Stage IIIB	T1-4bN1aM0
			T1-4bN2aM0
N3	Metastasis in four or more regional nodes, or matted metastatic nodes, or in-transit metastasis, or satellite(s) with metastasis in regional nodes(s)		T1-4aN1bM0
			T1-4aN2bM0
			T1-4aN2cM0
Distant Metastasis (M)		Stage IIIC	T1-4bN1bM0
MX	Distant metastasis cannot be assessed		T1-4bN2bM0
M0	No distant metastasis		T1-4bN2cM0
M1	Distant metastasis		TanyN3M0
M1a	Metastasis to skin, subcutaneous tissues, or distant lymph nodes	Stage IV	TanyNanyM1
M1b	Metastasis to lung		
M1c	Metastasis to all other visceral sites or distant metastasis at any site associated with elevated lactic dehydrogenase		

From Edge SB, Byrd DR, Compton CC, et al: AJCC cancer staging manual, ed 7, New York, 2010, Springer.

TABLE 42-2 Five-Year Survival Rates for Patients with Stage III (Nodal Metastases) Disease Stratified by Number of Metastatic Nodes, Ulceration, and Tumor Burden

	Microscopic Nodal Disease (No. Involved)						Macroscopic Nodal Disease (No. Involved)					
Melanoma Ulceration	**1 Node % ± SE**	**No.**	**2-3 Nodes % ± SE**	**No.**	**>3 Nodes % ± SE**	**No.**	**1 Node % ± SE**	**No.**	**2-3 Nodes % ± SE**	**No.**	**>3 Nodes % ± SE**	**No.**
Absent	69 ± 3.7	252	63 ± 5.6	130	27 ± 9.3	57	59 ± 4.7	122	46 ± 5.5	93	27 ± 4.6	109
Present	52 ± 4.1	217	50 ± 5.7	111	37 ± 8.8	46	29 ± 5.0	98	25 ± 4.4	109	13 ± 3.5	104

From Balch CM, Soong SJ, Gershenwald JE, et al: Prognostic factors analysis of 17,600 melanoma patients. Validation of the American Joint Committee on Cancer melanoma staging system. J Clin Oncol 19:3622-3634, 2001.
SE, standard error.

of the brain are indicated for patients with multiple or clinically palpable nodal metastases and for all patients with documented distant disease.

PRIMARY THERAPY AND RESULTS

Primary Tumor

Standard treatment for localized melanoma (stages I and II) is wide local excision. Wide local excision is a therapeutic intervention, but it also establishes tissue diagnosis and provides accurate microstaging. Six randomized trials have examined the appropriate width of excision for primary melanoma.[30-34] The recommended skin margins vary from 1 cm to 2 cm depending on lesion thickness and location.[34,35]

Sentinel lymph node biopsy is recommended according to the aforementioned criteria (see "Patient Evaluation and Staging" section). This diagnostic procedure involves injection of the primary site with a dye and radiotracer-tagged colloid that localizes to the first draining lymph node or nodes after a short period of time. These nodes are then removed, serially sectioned, and examined with immunohistochemical staining techniques. Patients without involved lymph nodes are spared a comprehensive lymph node dissection. The procedure provides accurate nodal staging, but it should be followed by complete lymph node dissection or nodal radiation therapy if the sentinel node is involved. The rate of nodal spread according to primary thickness is shown in Table 42-4; it is less than 5% for lesions 0.75 mm or smaller, 10% for lesions 0.76 mm to 1.5 mm, 20% for lesions 1.51 mm to 4 mm, and 30% to 50% for lesions larger than 4 mm.[36-47]

Radiation therapy is not indicated as definitive management of primary malignant melanoma. An exception to this rule is large facial lentigo maligna melanomas for which wide surgical resection may require extensive reconstruction. In a series of 25 patients treated at the Princess Margaret Hospital with primary radiation therapy using orthovoltage x-rays (100 KeV to 250 KeV) and followed for a period of 6 months to 8 years (median, 2 years), local control was achieved in 23 patients (92%).[48] Regimens used were 35 Gy in 5 fractions over 1 week for lesions smaller than 3 cm, 45 Gy in 10 fractions over 2 weeks for primary tumors of 3 cm to 4.9 cm, and 50 Gy in 15 to 20 fractions over 3 to 4 weeks for tumors 5 cm or larger.

Radiation therapy is rarely recommended as an adjuvant to wide local excision as local recurrence rates are generally low (<10%). High-risk features such as primary thickness greater than 4 mm, head or neck primary site, and primary ulceration or satellitosis have been reported to significantly increase the risk of local recurrence, but few series report recurrence rates much higher than 15%[32,49-60] (Table 42-5).

One variant of melanoma, the desmoplastic subtype with neurotropism, has historically been associated with recurrence rates as high as 50% after wide local excision alone.[61-68] In a nonrandomized series specifically examining the role of radiation therapy in 150 patients with desmoplastic melanoma, a

TABLE 42-3 Staging Guidelines and Diagnostic Algorithm

Disease Presentation	Workup
Primary lesion <1 mm, and Clark levels II-III, and not ulcerated	History and physical examination*
Primary lesion ≥1 mm, or Clark levels IV-V, or ulcerated	History and physical examination* Sentinel lymph node biopsy
Microscopic nodal metastases	History and physical examination* Chest radiograph and serum LDH level Further imaging if warranted
Macroscopic nodal metastases	History and physical examination* Serum LDH level CT imaging of chest, abdomen, pelvis CT imaging of head and neck if primary tumor above clavicles Consider brain MRI Further imaging if warranted
Distant metastases	History and physical examination* Chest radiograph and serum LDH level CT imaging of chest, abdomen, pelvis CT imaging of head and neck if primary tumor above clavicles Brain MRI Further imaging if warranted

CT, *Computed tomography;* LDH, *lactate dehydrogenase;* MRI, *magnetic resonance imaging.*
**Attention to comprehensive skin and nodal basin examination.*

TABLE 42-4 Percentage of Patients with Positive Sentinel Lymph Nodes by Primary Melanoma Thickness

	Patients (%) by Tumor Thickness (mm)							
Study	**≤0.75**	**0.76-1.5**	**1.51-4**	**>4**	**≤1**	**1.01-2**	**2.01-4**	**>4**
Krag et al[36]	4	3	22	27	—	—	—	—
Joseph et al[37]	0	7	18	30	—	—	—	—
Mraz-Gernhard et al[38]	—	—	22	28	—	—	—	—
Haddad et al[39]	0	15	19	29	—	—	—	—
Gershenwald et al[40]	5	5	19	34	—	—	—	—
Statius Muller et al[41]	0	15	26	57	—	—	—	—
Bachter et al[42]	—	7	21	44	—	—	—	—
Blumenthal et al[43]	—	9	64	27	—	—	—	—
Caprio et al[44]	2	4	17	39	—	—	—	—
Vuylsteke et al[45]	—	—	—	—	6	16	34	55
McMasters et al[46]	—	—	—	—	—	15	30	45
Rousseau et al[47]	—	—	—	—	4	12	28	44
Weighted average (%)	1	7	21	33	4	14	29	45

From Bonnen MD, Ballo MT, Myers JN, et al: Elective radiotherapy provides regional control for patients with cutaneous melanoma of the head and neck. Cancer 100:383-389, 2003.

TABLE 42-5 Local Recurrence after Surgery Alone for Primary Tumor According to High-Risk Pathologic Characteristics

Characteristic	%	References
Breslow thickness ≥4 mm	6 to 14	35,49-53
Head and neck location	5 to 17	32,49,50,52,54-58
Ulceration	10 to 17	32,35,50,52
Satellitosis	14 to 16	59,60

Adapted from Ballo MT, Ang KK: Radiotherapy for cutaneous malignant melanoma. Rationale and indications, Oncology 18:99–107, 2004.

recurrence rate of 24% (14 of 59 patients) was reported without irradiation and 7% (5 of 71 patients) with irradiation.[67]

Regional Nodes

Elective Nodal Treatment

The role of elective nodal therapy at the time of wide local excision of the primary tumor has been disputed extensively. Advocates of elective lymph node dissection argued that melanoma progresses in a stepwise fashion from the primary lesion to regional nodes and then to distant sites, whereas opponents suggested that positive regional lymph nodes are only indicators of systemic spread. Results of an early nonrandomized study by the Sydney Melanoma Unit[69] involving 1319 patients suggested that elective lymph node dissection improved the survival rates of patients with intermediately thick melanomas (0.76 mm to 4 mm), however, four prospective Phase III trials did not confirm these results.[70-73]

The surgical community has embraced sentinel lymph node biopsy with selective lymph node dissection as a replacement to elective lymph node dissection, despite no reported therapeutic benefits in terms of overall survival (OS). This choice depends on several lines of reasoning.[74,75] The status of the sentinel lymph node is a powerful determinant of subsequent survival and provides prognostic information to the patient; it identifies patients with early regional lymph node metastases that might benefit from nodal dissection as a way of avoiding advanced regional recurrence; and it identifies patients who may be candidates for investigational systemic therapy trials.

Morton et al[76] randomly assigned 1269 patients with intermediate-thickness primary melanoma to wide excision and postoperative observation of regional lymph nodes with lymphadenectomy if nodal relapse occurred, or to wide excision and sentinel lymph node biopsy with immediate lymphadenectomy if nodal micrometastases were detected on biopsy. This trial, known as the Multicenter Selective Lymphadenectomy Trial (MSLT-I), reported improved 5-year disease-free survival (DFS) when patients undergoing sentinel lymph node biopsy with selective lymph node dissection were compared with patients who were observed. There were no differences in melanoma-specific survival. In a subgroup analysis confined to patients with nodal metastases, there was improved melanoma-specific survival in patients undergoing immediate lymphadenectomy compared with those in whom delayed lymphadenectomy was required for recurrent disease. Although the validity of this postrandomization analysis has been questioned by many,[77] the prognostic information provided by sentinel lymph node biopsy was confirmed. A second Multicenter Selective Lymphadenectomy Trial (MSLT-II) is currently examining the role of ultrasound in the staging of patients who are clinically node negative and randomizing patients with involved sentinel lymph nodes to completion lymph node dissection or observation with periodic ultrasonography.

Although sentinel lymph node biopsy remains the standard approach to patients with early-stage melanoma, there are some patients with significant medical comorbidities for whom detailed prognostic information is of little relevance and enrollment in a clinical trial is unlikely. For these patients, elective nodal irradiation is superior to observation, which places the patients at unnecessary risk of regional recurrence.[78] In a retrospective analysis from the M. D. Anderson Cancer Center, Bonnen e al[79] reviewed 157 patients with stage I or II cutaneous melanoma of the head and neck who received elective regional irradiation instead of lymph node dissection after wide local excision of the primary site. Indications for regional irradiation included primary thickness of 1.5 mm or greater or Clark level IV or V disease. There were 15 regional failures (89% regional control at 10 years) despite estimation that 33 to 40 patients had microscopically involved regional nodes (based on data from Table 42-4). Six percent of patients required medical care for a clinically significant complication, with moderate hearing loss being the most common complaint (5 patients). Although elective nodal irradiation has the same limitations as elective lymph node dissection, it can effectively provide regional control for patients at risk for regional recurrence while avoiding surgical dissection.

Therapeutic Nodal Approaches

For most patients, nodal dissection results in more than an 80% likelihood of regional control. For patients with certain clinicopathologic features, however, the surgical literature suggests regional recurrence rates as high as 80% and, therefore, a need for additional regional therapy. Although nodal extracapsular extension remains the strongest predictor of subsequent regional recurrence after surgery alone, several series have reported elevated recurrence rates if at least four lymph nodes are involved, the lymph nodes measure at least 3 cm in diameter, they are located in the cervical basin, or they are detected during a therapeutic dissection (as opposed to elective dissection or at the time of sentinel lymph node biopsy).[80-85] Although less well described in the literature, nodal recurrence after previous dissection for involved regional nodes also places the patient at increased risk of subsequent relapse. Patients with one of these six clinicopathologic features have a 30% to 50% rate of subsequent regional recurrence after nodal dissection alone (Table 42-6).

There are substantial retrospective data supporting the effectiveness of regional radiation therapy for patients with one of the aforementioned high-risk features. Relapse rates after adjuvant radiation therapy range from 5% to 20%, compared with the much higher range seen without adjuvant irradiation.[83,86-96] The Trans-Tasman Radiation Oncology Group and the Australia and New Zealand Melanoma Trials (TROG/ANZMTG) group completed a randomized trial comparing nodal observation with radiation therapy after lymphadenectomy in patients with palpable nodal disease and high-risk features.[97] High risk features included one or more involved parotid nodes, two or more involved cervical or axillary nodes, or three or more involved inguinal nodes; presence of extranodal tumor spread; or the maximum diameter of the largest metastatic lymph node was 3 cm or more (for a cervical node) or 4 cm or more (for an axillary or inguinal node). Patients received 48 Gy in 20 fractions over 4 weeks to standard conventional fields. Although there was no improvement in overall survival, this trial reports acceptable acute toxicity and 5-year regional control of 77% with radiation therapy compared with 60% without it ($p = 0.023$).

Tolerance to adjuvant radiation therapy is generally excellent and early toxic effects are infrequent and minor. Most patients receiving comprehensive neck irradiation experience transient parotid swelling after the first radiation fraction that

typically lasts 1 day. For most sites, brisk erythema with patches of moist skin desquamation, particularly within the axilla and the groin, are common. In the TROG/ANZMTG randomized trial, late radiation-related complications were distinctly uncommon, except for an increase in subcutaneous fibrosis in the adjuvant radiation therapy arm. Clinically significant extremity lymphedema (requiring some form of medical management such as a compressive sleeve or physical therapy) occurs in a minority of patients. It is more common after groin dissection than after cervical or axillary dissection, and it appears to moderately increase further in the setting of adjuvant irradiation, particularly for patients with locally advanced groin metastases[85,93-102] (Table 42-7). In one series examining the timing of lymphedema, however, half of the patients had developed lymphedema before starting adjuvant groin irradiation.[95] This suggested that the higher rate of lymphedema was to some extent a consequence of locally advanced disease and its surgical treatment and not solely the result of the radiation therapy. In this same series, there was a correlation between body mass index and the development of chronic lymphedema, suggesting that patient factors need to be incorporated into rational treatment guidelines.[95] In the randomized trial there were no differences in quality of life, although regional symptoms were worse in those patients receiving radiation therapy.

TABLE 42-6 Regional Relapse Rates after Surgery Alone for Nodal Disease According to High-Risk Pathologic Characteristics

Nodal Characteristic	Study	Year	Relapse Rate (%)
Extracapsular extension	Calabro et al[80]	1989	28*
	Lee et al[81]	2000	63*
	Monsour et al[82]	1993	54
	Shen et al[83]	2000	31*
≥4 Involved lymph nodes	Calabro et al[80]	1989	17 to 33*
	Lee et al[81]	2000	46 to 63
	Miller et al[84]	1992	53*
Lymph node ≥3 cm	Lee et al[81]	2000	42 to 80
	Shen et al[83]	2000	14
Cervical lymph node location	Bowsher et al[85]	1986	33
	Lee et al[81]	2000	43*
	Monsour et al[82]	1993	50
Therapeutic dissection	Byers[55]	1986	50
	O'Brien et al[57]	1991	34
	Lee et al[81]	2000	36
	Shen et al[83]	2000	20

Significant on multivariate analysis.

Distant Disease and Adjuvant Systemic Therapy

A great amount of resources has been directed toward developing effective systemic therapy for patients with melanoma. Although surgical resection with selective use of adjuvant radiation therapy results in satisfactory local and regional control for most patients, even thin melanomas have significant metastatic potential. Most research initiatives have focused on interferon alpha-2b (IFN) or vaccines, or combinations of both. European investigators have examined the role of low-dose IFN therapy, and U.S. investigators have focused primarily on high-dose regimens. Three randomized Eastern Cooperative Oncology Group (ECOG) trials are used to support the use of adjuvant IFN for patients with a high risk of recurrence.[103-105]

The first trial (ECOG 1684) enrolled 287 patients with primary melanomas thicker than 4 mm without palpable nodes, lymph node metastasis detected at elective lymph node dissection, a clinically palpable regional lymph node with primary melanoma of any stage, or regional lymph node recurrence at any interval after appropriate surgery for primary melanoma of any depth.[103] This prospective study revealed a significant prolongation of relapse-free survival (RFS) (5-year actuarial, 37% versus 26%; $p = 0.002$) and OS (5-year, 46% versus 37%; $p = 0.02$) associated with high-dose IFN therapy (i.e., intravenous administration five times per week for 4 weeks, then subcutaneous administration three times per week for 48 weeks). The overall benefit of treatment in this trial was correlated with the tumor burden and the presence of microscopic nonpalpable and palpable regional lymph node metastases. The benefit of therapy with IFN was greatest among recipients with palpable regional nodal metastases or nodal recurrences.

The second trial (ECOG 1690) compared high-dose IFN for 1 year or low-dose IFN for 2 years versus observation.[104] Intent-to-treat analysis revealed 5-year RFS of 44% and 40% for the high-dose and low-dose IFN arms, respectively, compared with 35% in the observation arm ($p = 0.05$ for high-dose IFN versus observation, and $p = 0.17$ for low-dose IFN versus observation). Most of the benefit was observed for patients with two to three involved lymph nodes. For OS, there was no difference demonstrated for the three treatment arms (52%, 53%, and 55% for high-dose IFN, low-dose IFN, and observation, respectively).

TABLE 42-7 Clinically Significant Lymphedema According to Site of Regional Disease and Treatment

	Surgery Alone*			Surgery and Radiation*		
Nodal Basin	Study	Year	%	Study	Year	%
Cervical	Urist et al[98]	1983	0	Ballo et al[93]	2002	0
	Wrightson et al[99]	2003	0	Burmeister et al[102]	2002	0
				Burmeister et al[96]	2006	0
Axilla	Urist et al[98]	1983	1	Ballo et al[94]	2003	16
	Wrightson et al[99]	2003	5	Burmeister et al[102]	2002	7
	Bowsher et al[85]	1986	3	Burmeister et al[96]	2006	9
Groin	Bowsher et al[85]	1986	18	Burmeister et al[102]	2002	45
	Karakousis et al[100]	1994	10	Ballo et al[95]	2004	27
	Hughes et al[101]	2000	19	Burmeister et al[96]	2006	19
	Wrightson et al[99]	2003	32			

Clinically significant lymphedema required some form of medical management (e.g., compressive device or physical therapy).

The third trial (ECOG 1694) compared high-dose IFN with a ganglioside GM2 melanoma vaccine.[105] After 880 patients were randomized to one of the treatment arms, an interim analysis indicated inferiority of the ganglioside vaccine with respect to RFS and OS. In a subgroup analysis, however, the beneficial effects of IFN were seen only in the patients with stage T4N0 disease and not those with nodal disease.

Debate over the merits of routine IFN therapy has focused on the inconsistent subgroup analysis findings and concerns about the toxicity of IFN, but it is not unreasonable to recommend one year of IFN for patients with thick tumors (>4 mm thick), ulceration, a high mitotic rate (≥1 per mm^2), or nodal metastases.[106]

Frequently observed regression of primary melanoma and even occasionally metastatic disease has suggested an important role for the immune system. This has fueled a long-standing search for active immunotherapies against melanoma. Interleukin-2 has shown durable response rates in 15% of patients and is considered a reasonable first option for patients with metastatic disease with sufficient performance status to tolerate its significant toxicity.

Until recently, none of the immunologic approaches had demonstrated clinical efficacy in terms of OS. However, the U.S. Food and Drug Administration recently approved new drugs as treatment for metastatic melanoma based on Phase III trial data reporting improvement in OS.

The BRAF kinase inhibitor vemurafenib blocks the mitogen-activated protein kinase (MAPK) signaling pathway that normally promotes cell proliferation and contains BRAF kinase as one of its components. Oncogenic (i.e., abnormal) BRAF kinase has been reported in almost 50% of cutaneous melanomas resulting in uncontrolled activation of the MAPK pathway. In 675 patients randomized to either vemurafenib or dacarbazine there was an improvement in the 6 month OS (84% versus 64%, $p < 0.001$) with vemurafenib and a response rate of 48%.[107] Vemurafenib should be considered in patients with untreated metastatic disease, but genetic mutation analysis is essential to verify the appropriate BRAF mutation (V600E) is present. A second BRAF inhibitor, dabrafenib, was also tested against dacarbazine in 250 patients with the V600E mutation and resulted in improved progression-free survival.[108]

The human monoclonal antibody Ipilimumab blocks cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4) and stimulates an antitumor T-cell response. In 676 patients with stage III or IV disease ipilimumab was given either alone or with gp100 vaccine and compared to a third group receiving gp100 vaccine alone. The median survival was improved in both groups receiving the ipilimumab when compared to the gp100 group (10 months versus 6.4 months, $p < 0.001$).[109] In a second trial of 502 patients with untreated metastatic melanoma ipilimumab was given with dacabazine and compared to dacarbazine plus placebo and resulted in significantly improved OS at 3 years (20.7% versus 12.2%, $p < 0.001$).[110] Ipilimumab should be considered in patients with untreated receptor negative (e.g. BRAF, cKit) metastatic disease. When temporally combined with radiation ipilimumab has been reported to result in regression of disease distant from the irradiated site suggesting the possibility of an immunologically mediated abscopal effect.[111] Trials involving combinations of targeted therapy and radiation therapy are under way to determine if responses can be improved.

LOCALLY ADVANCED DISEASE AND PALLIATION

Radiation therapy can reduce symptoms for more than 80% of patients with advanced inoperable or metastatic disease. The recommended dose-fractionation schedule for external beam therapy depends on the tumor's location and the patient's life expectancy. The most frequently used regimens are 30 Gy given in 10 fractions over 2 weeks for skeletal or multiple cerebral metastasis, 36 Gy in 12 fractions for pathologic fracture of extremity bones (after internal fixation), 50 Gy in 25 fractions for solitary metastases after resection or radiosurgery (brain), and 36 Gy in 6 fractions over 3 weeks (twice each week) for dermal or subcutaneous melanoma masses or for neck node metastasis. Conventional fractionation schedules may always be considered if tumor lies near critical structures. The use of stereotactic ablative radiation therapy has gained considerable attention recently for the management of oligometastases from melanoma in the brain, lung, bones, spine, and liver. Dose schedules vary according to the tumor volume and site of disease but are generally well tolerated.

RADIATION THERAPY TECHNIQUES

Target Volume

Adjuvant radiation therapy for primary melanoma should encompass the primary site scar with a 3-cm to 4-cm margin, depending on the anatomic site and surrounding critical structures.

The target volume for patients receiving *elective nodal irradiation* for *head and neck primary sites* includes the primary lesion, the preauricular and postauricular lymph nodes (for high facial and scalp primary tumors), and the ipsilateral lymph nodes from levels I through V, including the ipsilateral supraclavicular fossa (Figure 42-3). For patients receiving therapeutic nodal irradiation for one of the aforementioned high-risk nodal features, the target volume is essentially the same, including the dissection scar, except that the primary tumor bed is irradiated only if regional relapse occurred less than 1 year after excision of the primary disease.

For *axillary nodal metastases,* radiation fields include the axillary lymph nodes from levels I through III (Figure 42-4). The supraclavicular fossa and low cervical lymph nodes may be included if there is bulky high axillary disease but otherwise do not need to be treated.

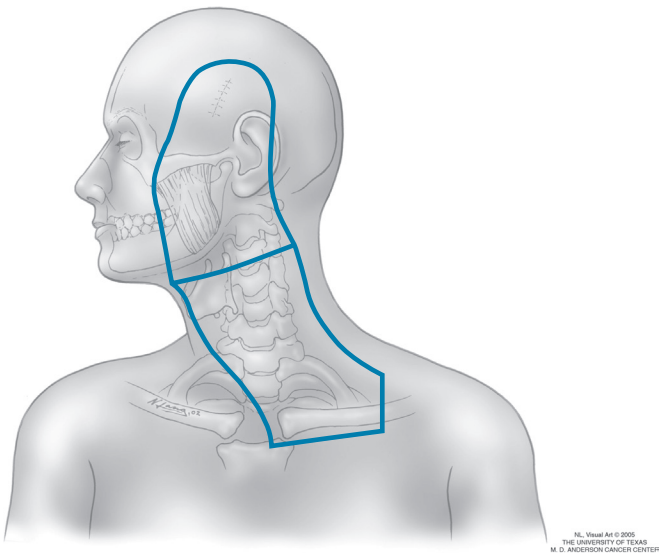


Figure 42-3 Typical external beam radiation treatment field for a patient with cervical lymph node metastases. A similar field is used for a patient requiring elective irradiation.
Courtesy NL Visual Art © 2005, The University of Texas M. D. Anderson Cancer Center, Houston, Texas.

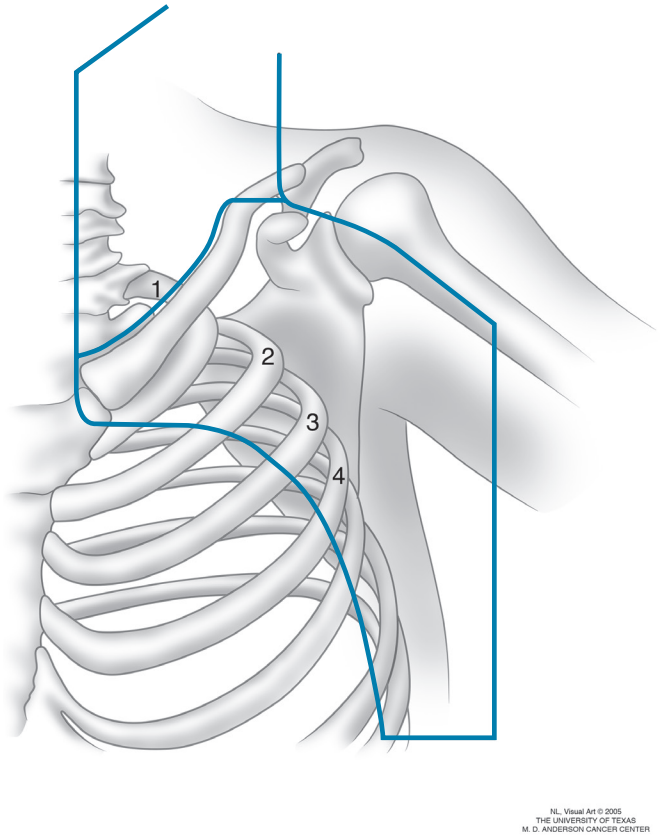


Figure 42-4 Typical external beam radiation treatment field for a patient with axillary lymph node metastases. Numbers correspond to the ribs. The upper border of the field typically ends at the superior aspect of the clavicle, but the supraclavicular and cervical lymph nodes may be irradiated if clinically involved.
Courtesy NL Visual Art © 2005, University of Texas M. D. Anderson Cancer Center, Houston, Texas.

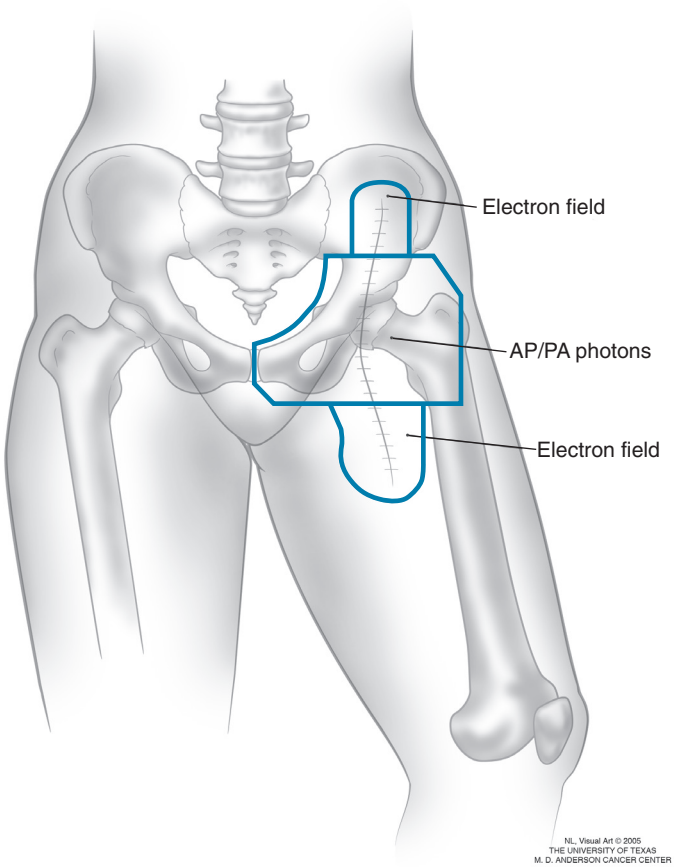


Figure 42-5 Typical external beam radiation field for a patient with groin lymph node metastases.
Courtesy NL Visual Art © 2005, University of Texas M. D. Anderson Cancer Center, Houston, Texas.

At a minimum, a field for groin lymph node metastases covers the nodal regions that have pathologically confirmed nodal disease and usually includes the entire surgical scar (Figure 42-5). Judgment must be used regarding elective irradiation of adjacent nodal regions (i.e., external iliac coverage in the setting of confirmed inguinal disease) because of concern about the increased toxicity associated with groin irradiation, particularly for patients who are obese. Unlike the cervical or axillary regions, where electrons and flashing photon fields, respectively, generally deliver a full dose to the skin, special attention must be paid to delivering a full dose to the groin scar.

Setup, Field Arrangement, and Dose-Fractionation Schedule

For patients with cervical disease, an open neck position provides access to the primary site and parotid and cervical lymphatics, and it allows treatment delivery with electrons of appropriate energy. Lesions of frontal, temporal, and preauricular areas; the auricle; and the cheek are usually treated with two or three fields, depending on the distance between the primary tumor and the parotid nodes. Matching electron fields are used to treat the primary site, the parotid and lower neck nodes. The junctions between the fields are moved (0.5 cm to 1 cm) after the second and fourth treatments to improve dose homogeneity. A tissue-equivalent bolus is placed over a line connecting the lateral canthus and the mastoid tip to spare the temporal lobe, and an additional piece of bolus may be placed over the larynx. The thickness of this bolus depends on the electron energy used. Elective or adjuvant radiation treatment is administered to a total dose of 48 Gy in 20 daily fractions (Monday through Friday) or 30 Gy at 6 Gy per fraction, twice each week (Monday and Thursday or Tuesday and Friday) over 2.5 weeks. Electron doses are specified at D_{max} (maximal depth dose) and care is always taken to ensure that the dose to the spinal cord does not exceed 40 Gy at 2.4 Gy per fraction or 24 Gy at 6 Gy per fraction.

For axillary treatment, the patient is immobilized in a supine position with the treatment arm akimbo. Laser lines that include the upper and lower torso ensure a reproducible treatment setup. Typically, anterior and posterior photon fields are used to deliver the dose to the levels I, II, and III axillary lymph nodes. Dose homogeneity is ensured using a field-within-a-field technique (using multileaf collimators). The radiation dose is 48 Gy in 20 daily fractions or 30 Gy at 6 Gy per fraction, twice each week over 2.5 weeks. If necessary the dose may be prescribed to a volume such that the isocenter dose is 3% to 6% lower than the prescribed dose as dose heterogeneity can result in unacceptable toxicity at these doses per fraction.

To irradiate the groin, patients are immobilized in a unilateral frog-leg position, eliminating any inguinal skin folds.

Photons or electrons can be used depending on the patient's contour, extent of surgical bed and whether the pelvic nodes are included as part of the target volume. Lower-energy electron fields can be used superiorly and inferiorly to cover the full extension of the scar. If a photon technique is selected, a tissue-equivalent bolus is used over the scar, and the dose is weighted anteriorly. Doses are either 48 Gy in 20 daily fractions or 30 Gy at 6 Gy per fraction, twice each week over 2.5 weeks. Appropriate reductions are made to limit the small bowel dose to 40 Gy at 2.4 Gy per fraction or 24 Gy at 6 Gy per fraction.

For all sites of regional disease, intensity-modulated radiotherapy (IMRT) may also be used to cover the aforementioned regions. IMRT is currently under investigation as an alternative technique aimed at reducing toxicity.

Radiation Therapy for Bulky or Inoperable Nodal Disease

Radiation therapy can be considered for bulky or inoperable nodal disease in which surgery is likely to be incomplete or the extent of the nodal disease would predict a poor OS. Similar techniques used in the postoperative setting can be used with surgery to follow 10 to 12 weeks later if the patient continues to have localized disease.

Patient Care during and after Radiation Therapy

Patients are informed of the specific acute side effects of treatment, such as mucositis and parotiditis after irradiation of the cervical basin and moist desquamation after irradiation of the axilla or groin. After moist desquamation occurs, cleaning the area with mild soap and water to prevent secondary infection is recommended.

Regular follow-up examinations include evaluation of the treated area for late complications and a search for potential relapse. The most common late side effects include hypopigmentation, hyperpigmentation, telangiectasia, and skin and subcutaneous tissue atrophy. After cervical irradiation, monitoring for subclinical hypothyroidism and the signs and symptoms of hearing loss, although relatively uncommon, is essential. Acute lymphedema is managed early and aggressively with physical therapy and compressive devices to avoid chronic lymphedema.

TREATMENT ALGORITHMS AND CLINICAL TRIALS

Elective Nodal Treatment

Sentinel lymph node biopsy has obviated routine elective treatment of the draining lymphatics of patients with thick primary melanomas. Although retrospective studies of elective irradiation have verified the effectiveness of this approach, sentinel lymph node biopsy with complete lymph node dissection has become accepted as the standard of care. For patients whose medical comorbidities preclude sentinel lymph node biopsy (and the required comprehensive dissection if the sentinel node is involved), elective nodal irradiation is favored over observation, which reduces the risk of regional recurrence with its associated morbidity. Although this approach is still investigational, it is suggested that patients with a positive sentinel lymph node biopsy result who refuse subsequent dissection be referred for regional irradiation. Observation in the setting of an involved sentinel lymph node is not appropriate, and systemic therapy is not a substitute for completing regional therapy.

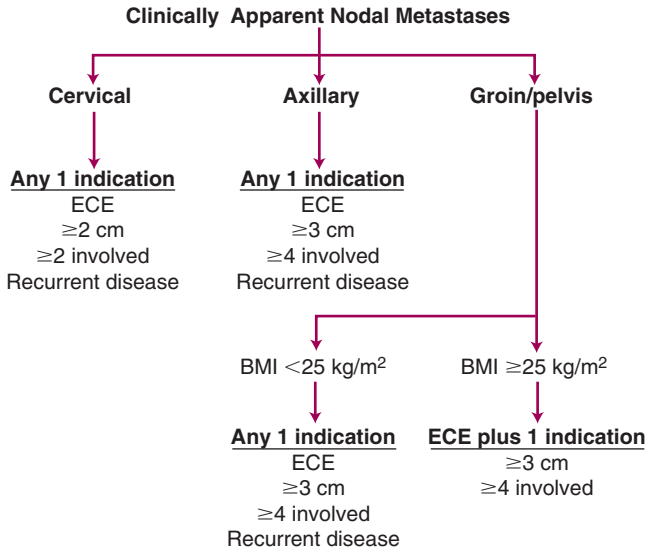


Figure 42-6 Treatment algorithm for patients with nodal metastases from melanoma. Typically, the threshold for irradiating patients with cervical lymph node metastases is lower than for those with inguinal lymph node metastases, for which the risk of long-term lymphedema is higher. *BMI*, Body mass index; *ECE*, extracapsular extension.

Therapeutic Nodal Approaches

Therapeutic nodal dissection is the standard treatment for patients with lymph node metastases, and available data support the use of systemic, high-dose adjuvant IFN. Adjuvant postoperative irradiation is also indicated to reduce the regional recurrence rate in patients with high-risk clinicopathologic features. Although some of the same features that predict regional failure, such as extracapsular extension and number of involved lymph nodes, also predict distant failure, the importance of regional control should not be underestimated, and radiation therapy should not be systematically avoided because the risk of distant metastasis is perceived to be too high.

We have developed radiation treatment guidelines that account for the complex clinical interaction between the risk of regional recurrence, the risk of regional toxicity, and the risk of distant metastatic disease (Figure 42-6). For patients with cervical disease, the threshold for irradiation may be lowered to include those with at least two involved lymph nodes or those with tumors measuring at least 2 cm in diameter. For patients with groin metastases, the threshold may be raised so that combinations (two or more) of the high-risk features must be present before adjuvant irradiation is given.

ACKNOWLEDGMENTS

To K. Kian Ang for demanding excellence.

CRITICAL REFERENCES

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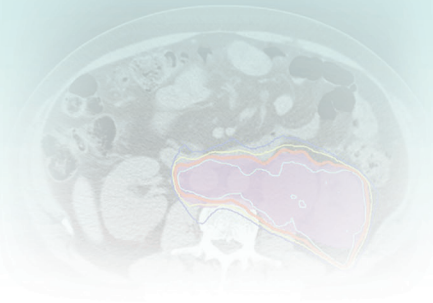
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Overview



Jeffrey A. Bogart

Primary thoracic neoplasms are reviewed in detail in the chapters of this section. In this overview, we consider developments and controversies in the diagnosis and treatment of non–small cell lung cancer (NSCLC), small cell lung cancer (SCLC), esophageal cancer, thymic tumors, pulmonary carcinoid, and mesothelioma.

EPIDEMIOLOGY

Lung Cancer

Lung cancer is the most common and deadliest thoracic malignancy, accounting for approximately 3000 deaths each week in the United States.[1] Exposure to tobacco smoke is the most common cause of lung cancer, with 85% to 90% of cases directly linked to active or passive tobacco exposure.[2] Lung cancer mortality rates have been trending downward in men because of reductions in smoking prevalence dating back to the mid-1960s, whereas mortality rates in women started to stabilize only in 2003. There is substantial geographic variation in the United States, with California the only state with decreasing lung cancer incidence and death rates in women.[3] Exposures to several occupational respiratory carcinogens have been controlled in developed nations, but environmental exposure to radon, the second-leading cause of lung cancer death, remains problematic.[4] Lung cancer in never-smokers is increasingly recognized as a distinct entity, described in greater detail in Chapter 44, and is the seventh-most common cause of cancer worldwide. Most of these cancers occur in women, and geographic, cultural, and genetic differences and hormonal factors have been implicated.[5]

The median age of patients who present with lung cancer is 70 years.[6] Lung cancer is broadly separated into SCLC and NSCLC types, and NSCLC accounts for approximately 80% to 85% of cases. Less than 50% of patients with NSCLC have resectable disease on initial presentation, and 25% of patients present with locally advanced (regional lymph node involvement without distant metastases) disease. Approximately 30% of patients with SCLC have limited-stage disease on presentation.[7]

Esophageal Cancer

In 2013, an estimated 17,990 patients Americans were diagnosed with esophageal cancer, and the incidence of esophageal cancer has increased approximately 15% during the past two decades.[8] Patients with esophageal cancers often present with advanced-stage disease, and most eventually die of their disease. Approximately 50% of patients present with locally advanced disease, and another 30% to 40% present with systemic metastases.[9]

Esophageal carcinomas are divided into squamous cell carcinoma and adenocarcinoma, each of which has a distinct epidemiology. Adenocarcinoma is associated with gastroesophageal reflux disease, Barrett's esophagus, obesity, and male gender. Squamous cell carcinoma is associated with alcohol and tobacco exposure, nutritional deficits, and lower socioeconomic status.[10] Although the incidence of squamous cell carcinoma has remained stable in the United States, the incidence of esophageal adenocarcinoma has increased dramatically over the past several decades, surpassing squamous cell carcinoma as the most common esophageal cancer in the United States.

Thymic Neoplasms

Thymoma is the most common tumor in the anterior mediastinum. Most thymic neoplasms arise in the epithelial cells of the thymus. The incidence of thymoma in the United States is estimated to be 0.13 to 0.15 per 100,000 people.[11] The median age of patients with thymoma is older than 50 years, and thymomas are diagnosed equally in men and women.[12] Thymic carcinomas account for a minority of all thymic neoplasms,[13] and they are more aggressive than thymomas.[14] Thymic carcinoids represent less than 5% of anterior mediastinal tumors, but they have a higher rate of regional lymph node metastases on presentation compared with carcinoids found in other locations in the body.[15]

Pulmonary Carcinoid

Pulmonary or bronchial carcinoid tumors are often low-grade neoplasms that arise from bronchial mucosal cells known as enterochromaffin cells or Kulchitsky cells.[16] These specialized cells are capable of producing bioactive amines, which cause carcinoid syndrome if released into the blood stream by the tumor. The respiratory tract is the second-most common site for carcinoids (after the gastrointestinal tract). Pulmonary carcinoid tumors are often centrally located and confined to the main or lobar bronchi.[17]

The incidence of bronchopulmonary carcinoids in the United States is estimated to be 0.6 per 100,000 people.[17] Carcinoid tumors tend to occur at a younger age than other lung cancers, with a median age ranging from 50 to 56 at diagnosis. In contrast to NSCLC and SCLC, bronchial carcinoids are more common in women.

Mesothelioma

The incidence of mesothelioma in the United States is estimated to be 10 per 1 million people,[18] or approximately 3000 patients per year, and the rate is expected to increase to about 4000 cases per year by 2025. Approximately 90% of mesotheliomas can be attributed to prior occupational asbestos exposure, and a lag of 20 to 40 years between asbestos exposure and diagnosis is typical.[19] Mesothelioma occurs predominantly in men, but secondary asbestos exposure from a spouse or parent can be as significant as environmental exposure. Major histologic subtypes of mesothelioma include epithelioid, biphasic, and sarcomatoid. Although epithelioid tumors are most common and have a better prognosis than other histologic types, the prognosis for most patients with mesothelioma remains poor.[20]

BIOLOGY

Lung Cancer

Lung cancers have a propensity to disseminate early and have a high rate of relapse despite aggressive treatment with surgery, chemotherapy, radiotherapy (RT), or combinations of these modalities. Molecular characteristic of NSCLC and SCLC are described in Chapters 43 and 44. Although NSCLC has traditionally been treated as a single disease, there is increasing recognition that histologic and molecular characteristics may help direct therapy, and targeted drugs are now considered first-line therapy for advanced NSCLC with specific epidermal growth factor receptor (EGFR) mutations or anaplastic lymphoma kinase (ALK) gene rearrangements.[21,22] Efforts to take advantage of molecular abnormalities in small cell lung cancer in developing more effective treatment have been less successful.

Esophageal Cancer

Esophageal cancer is characterized by early locoregional and distant spread of disease. Although the biologic characteristics of squamous cell carcinoma and adenocarcinoma of the esophagus differ, implications for therapeutic approach are unclear at this time. Molecular targets of interest identified in carcinoma of the esophagus include EGFR, Her2-neu, vascular endothelial growth factor (VEGF), cyclin D1, and cyclooxygenase-2.[23] Alterations in p53 may be important in the development of esophageal cancer, although mutations for squamous cell carcinoma differ from adenocarcinoma, and p15 and p16 have been found to be involved in the pathogenesis of esophageal cancer.[24]

Thymus Tumors

The cause of thymic neoplasms is unclear. Environmental factors that contribute to the development of thymic neoplasms may include Epstein-Barr virus infection[25] and exposure to ionizing irradiation.[26] The translocation of chromosomes 15 and 19 has been observed in thymic carcinoma.[27] Benign thymoma has been associated with deletion of the short arm of chromosome 6. Abnormalities in TP53, epidermal growth factor, and EGFR may contribute to the development of thymoma.[28,29]

Thymic carcinoma displays features that are similar to features of carcinoma arising in other body sites. It has a higher rate of capsular invasion, involvement of the regional lymph nodes, and systemic metastases compared with invasive thymomas.[30] Features of thymic carcinomas may include expression of high levels of EGFR, VEGF, and basic fibroblast growth factor.[31,32] CD70 positivity may serve as a marker for thymic carcinoma.[33] In contrast to lung cancer, thymic carcinomas usually do not express transcription termination factor-1.[34]

Pulmonary Carcinoid

Although most pulmonary carcinoids are nonfunctional, some can secrete various substances, which can lead to paraneoplastic syndromes, including carcinoid and Cushing's syndrome.[35] Serotonin is the most common substance released by carcinoid tumors, but corticotropin, histamine, dopamine, substance P, neurotensin, prostaglandins, and kallikrein may also be involved.[36]

Typical carcinoids usually display an indolent clinical course, but atypical carcinoids have a higher rate of regional and systemic involvement on presentation.[37] Most familial pulmonary carcinoids have been reported in patients with multiple endocrine neoplasia type I.[38] In atypical carcinoids, there seems to be a higher rate of inactivation of TP53.[39] Other genetic alterations in lung carcinoids include losses of 3p, 5p, 9p, 10q, and 13q.[40]

STAGING AND WORKUP

Lung Cancer

As with other medical conditions, the workup begins with a careful history and physical examination. There should be an emphasis on the duration of symptoms and signs related to the thoracic neoplasm and the overall baseline medical condition of the patient.

Diagnosis and staging should be accomplished in an orderly and cost-effective manner. Although sputum cytology reveals a diagnosis in only a small percentage of patients, it is a simple and noninvasive evaluation that should be considered for patients with respiratory symptoms and a suspicious lung mass. Traditionally, bronchoscopy has been employed for biopsy of central lesions, whereas transthoracic needle biopsy is often the first consideration for peripheral lesions. Endobronchial ultrasound is increasingly used to obtain tissue from mediastinal lymph nodes or parenchymal lung lesions; esophageal ultrasound may be used for biopsy of paraesophageal lymph nodes.

Staging evaluation is often initiated before a definitive pathologic diagnosis has been established. Positron emission tomography with ^{18}F-fluorodeoxyglucose positron emission tomography (^{18}F-FDG-PET) combined with computed tomography (CT) imaging is indicated in most patients with localized NSCLC and SCLC and can replace the traditional workup that included CT imaging of the chest and abdomen plus a bone scan. The use of ^{18}F-FDG-PET imaging has been shown to reduce the number of futile thoracotomies for patients with NSCLC and has a substantial impact on the radiation treatment plan for NSCLC and SCLC, particularly when an approach of involved field RT is used.[41-43] Generally, biopsy of suspected distant metastatic sites should be considered in lieu of biopsy of the primary lung lesion because this would confirm both histology and stage. ^{18}F-FDG-PET imaging is typically not warranted in patients presenting with evidence of distant metastases (on other imaging studies) because treatment would not likely be altered by the PET results. Magnetic resonance imaging (MRI) of the brain should be obtained in patients with localized SCLC and patients with clinical stage III NSCLC, in addition to patients presenting with neurologic symptoms.

The TNM (primary tumor, regional nodes, metastases) staging system for bronchogenic cancer has undergone substantial revision to correlate stage better with clinical outcome

(see Tables 44-2 and 44-3). Changes in T stage include subclassifying T1 into T1a and T1b and T2 into T2a and T2b, reclassifying T2c and additional nodules in the same lobe as T3, and reclassifying nodules in the ipsilateral nonprimary lobe as T4. Malignant pleural or pericardial effusions have been reclassified from T4 to M1.[44] Although the American Joint Committee on Cancer (AJCC) system has been proposed for use in staging patients with both SCLC and NSCLC, it is more common to use the 1973 Staging System of the Veterans Administration Lung Cancer Study Group for staging SCLC. It distinguishes disease extent as limited versus extensive,[45] with limited-stage SCLC often described as one that can be treated with a "reasonable" RT portal to encompass the known disease.

Mediastinal staging is indicated for most patients with early-stage clinical node-negative NSCLC because CT and ^{18}F-FDG-PET imaging have a false-negative rate (in the mediastinum) ranging from 10% to greater than 25%.[46] Combined anatomic and functional imaging is generally sufficient to assess mediastinal lymph node involvement for the subset of patients with peripheral stage I NSCLC.[47] Whether comprehensive mediastinal lymph node sampling with endobronchial ultrasound can replace mediastinoscopy is an area of active investigation.

Esophageal Cancer

The staging of esophageal cancer underwent substantial revision in the most recent version (seventh edition) of the AJCC Staging Manual (see Box 45-1). Staging groups are now divided according to histology, acknowledging the difference in biology between squamous cell carcinoma and adenocarcinoma. The staging system has also been amended to account for the influence of tumor grade on prognosis. Regional lymph nodes have been redefined, and N has been subdivided according to the number of lymph nodes involved. In addition, the previous division between M1a and M1b has been abandoned because it was not found to be useful.

Clinical staging is typically based on findings of endoscopy with biopsy, endoscopic esophageal ultrasound, and anatomic CT imaging. Endoscopic ultrasound can assess the depth of invasion with up to 90% accuracy once the tumor has gone through the submucosa and can detect abnormal or enlarged lymph nodes.[48] Assessment with ^{18}F-FDG-PET/CT has become commonplace in the workup of esophageal carcinoma and is particularly helpful in detection of unsuspected distant or regional disease, although the sensitivity of ^{18}F-FDG-PET imaging in defining regional lymph node metastases seems to be improved with integrated ^{18}F-FDG-PET/CT imaging.[49-51] A randomized prospective trial from the American College of Surgeons Oncology Group showed that ^{18}F-FDG-PET after conventional staging evaluation identified confirmed metastatic disease in approximately 5% of patients. This study was performed before routine availability of integrated ^{18}F-FDG-PET/CT.[52] Thoracoscopic or laparoscopic assessment may be helpful in certain cases to help determine disease extent and resectability.

Thymic Tumors

Approximately 10% to 15% of patients with myasthenia gravis have thymoma, and 30% to 45% of patients with thymomas have myasthenia gravis.[53] Serum alpha-fetoprotein and beta-human chorionic gonadotropin levels should be obtained in young men to exclude nonseminomatous germ cell tumors.[54] Thymic carcinoids may also be associated with Cushing's syndrome, Eaton-Lambert syndrome, syndrome of inappropriate secretion of antidiuretic hormone, and hypercalcemia.[55]

TABLE C-1 Masaoka Staging System for Thymoma

Stage	Criteria
I	Completely encapsulated macroscopically and no microscopic capsular invasion
II-1	Macroscopic invasion into surrounding fatty tissue or mediastinal pleura
II-2	Microscopic invasion into capsule
III	Microscopic invasion into adjacent organs
IVA	Pleural or pericardial implants
IVB	Lymphatogenous or hematogenous metastasis

Symptoms of classic carcinoid syndrome are rare in patients with thymic carcinoids.

A routine chest x-ray examination can detect 30% to 40% of patients with thymic neoplasms.[56] CT is the most valuable radiologic study in the workup of thymic tumors.[57] It can establish the initial clinical staging and response to treatment. MRI has not been shown to be more accurate than CT in assessing anterior mediastinal tumors.[58] ^{18}F-FDG-PET has not been established as routine in the workup of thymic neoplasms. The risk of tumor spillage and pleural seeding during biopsy of thymoma is uncertain, although current guidelines suggest biopsy may be avoided for resectable tumors if thymoma is strongly suspected by clinical and radiographic features.

Thymomas histologically display epithelial and lymphatic cell types. They can be classified according to the degree of the epithelial and lymphatic cell combination. The neoplastic cells are the epithelial cells, but there is no consistent correlation between the histology of thymomas and their malignant potential or systemic syndromes. The degree of invasion of the capsule and adjacent tissues defines malignancy.[59] The Masaoka staging system[60] is used widely and is based on the anatomic extent of disease at the time of surgery (Table C-1). Thymic carcinoma histology is cytologically not different from carcinomas in other sites. Thymic carcinomas often involve the pleura and locoregional lymph nodes. Distant metastases to the lungs, liver, brain, and bone can also develop.[61]

Pulmonary Carcinoid

Pulmonary carcinoids are often located centrally within the tracheobronchial tree, and approximately 10% to 20% are in the peripheral lung parenchyma.[62] The AJCC lung staging system (TNM) is commonly used for lung carcinoids. Most patients with typical carcinoid present with early-stage disease, and less than 5% have evidence of distant spread. Approximately 20% of patients with atypical carcinoids have stage IV disease at presentation.

Functioning carcinoids may be diagnosed by showing an increase in urinary excretion of the serotonin metabolite, 5-hydroxyindoleacetic acid. In addition to anatomic CT imaging, targeted radioactive octreotide or pentetreotide has been used to stage carcinoids.[63] Such targeted imaging against type 2 somatostatin receptors may be useful in 80% of carcinoids. The utility of ^{18}F-FDG-PET imaging is controversial, although PET imaging using alternative tracers seems promising.[64,65]

Mesothelioma

A detailed history of asbestos exposure should be investigated for any patient with mesothelioma. Thoracentesis and percutaneous fine-needle aspiration biopsy have a low diagnostic

sensitivity because mesothelioma can be difficult to differentiate from benign pleural disease and other malignancies.[66] Video-assisted thoracoscopic biopsy seems to be the most accurate means to establish a pathologic diagnosis.[67]

Contrast-enhanced CT imaging of the chest is indicated as part of initial staging but can underestimate the extent of the disease. MRI may be more accurate in predicting the extent of chest wall and diaphragm invasion. Additional invasive studies such as laparoscopy and peritoneal lavage may be indicated to document resectability. The AJCC staging system, which is based on the International Mesothelioma Interest Group staging system, is commonly used, and the most common sites of metastatic disease are the peritoneum, contralateral pleura, and lung.[68]

NORMAL TISSUE TOXICITY CONSIDERATIONS

The spinal cord, lung, esophagus, and heart are the dose-limiting structures in RT for thoracic malignancy. Generally, functioning subunits of an organ may be arranged as an in-series or in-parallel structure. Normal tissue such as the lung is an example of an in-parallel structure in which critical numbers of functioning units must be damaged before the organ is impaired.[69] Organ failure occurs when functional subunits are damaged beyond a critical level. The gastrointestinal tract and spinal cord represent in-series structures in which a loss of a single functioning subunit may lead to organ impairment or development of clinical symptoms. Current grading systems for toxicities include Common Terminology Criteria for Adverse Events version 4.0 (CTCAEv4) from the National Cancer Institute.

Although many reports suggest limited toxic effects after stereotactic body radiotherapy (SBRT) for early-stage NSCLC, mature prospective results are just starting to appear in the literature.[70] Phase II data from Indiana University initially showed an increased risk of toxic deaths after SBRT for centrally located lesions, although a statistically significant difference in severe toxicity was not seen between central and peripheral lesions with longer follow-up.[71,72] Nevertheless, central tumors were excluded from the subsequent multiinstitutional RTOG Phase II study (RTOG 0236), and caution should be used in treating central lesions with SBRT outside of a clinical study.[73] No treatment-related deaths were reported on RTOG 0236, which was reported with 34-month median follow-up, although 14% grade 3 and 4% grade 4 *protocol-specified* toxicity was observed, and six additional patients had severe toxicity that was not classified prospectively as protocol specified. Rigorous quality assurance was mandated. In addition to tumor location, size of the gross tumor volume was a significant predictor of severe toxicity in the Indiana University trial.[74] In other experience, fatalities have been observed secondary to fistula (tracheoesophageal or bronchopulmonary), pneumonitis, pleural effusion, and hemoptysis.[75] Several more recent SBRT reports have also shown higher than expected skin, rib, soft-tissue, and brachial plexus toxicity.[76-78] Specific dose constraints for SBRT regimens have been suggested by the RTOG and National Comprehensive Cancer Network (NCCN).

The following sections are generally based on data derived with conventionally fractionated RT and may not apply when large doses per fractions are used, such as in SBRT. Routine integration of conformal RT planning has facilitated the assessment of dose-volume relationships for conventionally fractionated RT. A systematic review of the literature found that an ideal dose-volume parameter predicting for pulmonary toxicity has not been identified,[79] although the most widely used measures are the total lung volume receiving at least 20 Gy (i.e., V20) and the mean lung dose.[80-82] Other metrics, including baseline pulmonary function and perfusion abnormalities, have also been used, and it is likely that multiple physical and biologic factors are important in predicting the risk of pulmonary toxicity.[83,84] Barriers to describing accurately the relationship between treatment and its resultant toxicity include the use of imperfect metrics and the inaccurate reporting of toxic effects. The latter may be particularly relevant for patients with underlying pulmonary toxicity, where it may be difficult to determine whether a functional decline is attributable to the effects of therapy.

The dose-volume relationship may also be affected by the integration of systemic chemotherapy, and the sequencing of therapies may have a significant impact on the toxic effects of therapy.[85] Most current prospective combined modality trials have adopted V20 as a treatment planning parameter and limit V20 to a maximum 30% to 40% of the total lung volume. Current NCCN guidelines recommend limiting the V20 lung to less than 37% and the mean lung dose to less than 20 Gy. There is increasing recognition of the potential impact of exposing relatively large volumes of lung to low doses of 5 Gy or 7 Gy, which is particularly relevant when intensity-modulated radiotherapy (IMRT) techniques are employed for lung cancer, esophageal cancer, or mesothelioma.[86]

Esophageal toxicity is generally the major clinically relevant acute toxicity during thoracic RT. The implementation of conformal techniques may affect esophageal toxicity by reducing the volume of esophagus irradiated, particularly for patients without extensive mediastinal adenopathy. The risk of radiation-induced acute esophageal toxicity varies according to fractionation, and increased acute toxicity has been observed with hyperfractionated and accelerated RT regimens.[87] The integration of concurrent chemotherapy with thoracic RT results in significantly increased severe esophagitis compared with primary RT or sequential therapy. Dosimetric parameters that may correlate with esophageal toxicity include the length of esophagus treated to greater than 40 Gy to 50 Gy, the volume of esophagus receiving greater than 50 Gy, and the mean esophageal dose.[88-90] Current NCCN guidelines recommend keeping the mean esophageal dose less than 34 Gy if possible, but esophageal dose guidelines are not absolute, and acute esophagitis should be managed aggressively with measures including pain management and nutritional support.

It is crucial that the patient's treatment plan not be compromised because of a (generally) temporary toxic effect of therapy. The role of "radioprotective" agents is unclear; the RTOG conducted a randomized trial to test the ability of amifostine to reduce esophagitis in locally advanced NSCLC treated with concurrent RT and chemotherapy.[91] The rate of grade 3 esophagitis did not differ between arms (34% versus 30%), although subjective swallowing function was apparently better with the addition of amifostine. Amifostine was associated with higher rates of acute nausea, vomiting, cardiovascular toxicity, and infection or febrile neutropenia. Amifostine is not recommended in combination with thoracic RT outside of a clinical trial.

Spinal cord radiation injury, covered in detail in Chapter 30, is a serious but rare complication of thoracic RT. Most contemporary clinical trials of concurrent fractionated RT and chemotherapy for thoracic malignancies limit the maximum point dose to the spinal cord to 45 Gy to 50 Gy.

The risk of radiation-induced cardiovascular disease is difficult to define for patients treated for locally advanced lung cancer and esophageal cancer as there are relatively few long-term survivors, though a recent analysis of RTOG 0617 demonstrated a negative impact of increasing heart dose (V50) on overall survival in patients with locally advanced NSCLC

(ASCO 2013).[92] Most data relating to cardiovascular toxicity is derived from patients with Hodgkin's disease and breast cancer. Multiple studies have shown that patients with Hodgkin's disease are at higher risk for the development of cardiovascular disease after mediastinal irradiation, and fatal myocardial infarction is the leading cause of noncancer death in this population.[93] Although the total dose used to treat Hodgkin's disease has been reduced over the years, it is not yet clear whether this results in a reduced risk of myocardial infarctions.

The increased risk of cardiac mortality for patients treated with RT for breast cancer has been defined by the Early Breast Cancer Trialists' Collaborative Group meta-analyses of randomized clinical trials, which showed patients treated with RT have a 1.27 relative risk of mortality from cardiac disease compared with patients not receiving RT.[94] The treatment of left-sided breast cancer and the treatment of internal mammary lymph nodes seem to increase the risk of cardiac morbidity further.[95] There seems to be a decline in RT-induced cardiac disease with modern RT planning. The implementation of advanced treatment techniques including conformal therapy, IMRT, image guidance, and respiratory gating should reduce the risk of cardiac toxicity, through improved sparing of cardiac structures, in treating thoracic cancers. Current NCCN guidelines suggest that no more than 50% of the heart should receive 4000 cGy when combined RT and chemotherapy is given.

TREATMENT CONSIDERATIONS

Non–Small Cell Lung Cancer

The standard of care for fit patients with early-stage I NSCLC is anatomic resection (lobectomy). Patients with borderline cardiopulmonary function should be assessed for rehabilitation and smoking cessation before being deemed to be medically inoperable. In a Phase III trial conducted during the 1980s for fit patients with peripheral stage I (<3 cm) NSCLC, limited resection was associated with a substantially higher risk of local tumor relapse and increased risk of death from cancer compared with lobectomy.[96] Evidence has emerged supporting the use of limited resection for peripheral NSCLC smaller than 2 cm, although most experience comes from Asia where the biology of small peripheral lesions may differ from the biology in North America and Europe.[97] An ongoing North American Phase III trial studying limited resection for lesions less than 2 cm should soon complete accrual.[98] Alternatively, provocative results with SBRT have been reported in certain *fit* patients with early-stage NSCLC. Prospective Phase II trials of SBRT in operable patients have been completed in North America and Japan and mature outcomes are pending. Phase III trials comparing SBRT and surgery in this population have not successfully met accrual goals.[99-101]

Treatment of patients with early-stage NSCLC and cardiopulmonary dysfunction has rapidly evolved during the past decade. Fractionated RT has been the most frequent treatment, but approaches including sublobar resection, SBRT, and radiofrequency ablation are increasingly used.[102,103] Local tumor control approaching 90% has been reported in several trials of SBRT for stage I NSCLC, although some trials with aggressive SBRT regimens restrict entry to lesions in the lung periphery owing to concerns about severe toxicity.[75] Accelerated hypofractionated RT regimens, with daily fractions given over 3 to 4 weeks, also seem promising.[104,105] Although traditional dose escalation is feasible with modern treatment planning, protracted regimens do not seem to be as effective as accelerated regimens and are more burdensome for patients.[106-108] Although pilot experience suggested the addition of I-125 brachytherapy might reduce local relapse for high-risk patients treated with sublobar resection for stage I NSCLC, an initial report of a Phase III American College of Surgeons Oncology Group (ACOSOG) trial failed to show a benefit with intraoperative I-125.[109] The relative merit of SBRT and sublobar resection in high-risk early stage NSCLC remains unclear. A randomized Phase III trial comparing SBRT and sublobar resection for high-risk peripheral stage I NSCLC was closed prematurely because of poor accrual, and it is not likely that level 1 evidence will emerge in the foreseeable future. Large randomized studies show that adjuvant chemotherapy improves survival for patients with resected NSCLC, although the benefit diminishes over time.[110] The role of adjuvant chemotherapy for early-stage node-negative NSCLC is controversial. A Cancer and Leukemia Group B (CALGB) trial did not show a benefit for adjuvant chemotherapy for T2 NSCLC, although there was a suggestion of improved survival for tumors larger than 4 cm.[111] Whether chemotherapy should be given to patients treated with primary RT for node-negative NSCLC has not been well studied.

The role of surgery for patients with stage IIIA NSCLC is unclear despite the reporting of mature results of a Phase III trial comparing concurrent chemotherapy and definitive RT (61 Gy) with induction concurrent chemotherapy and RT (45 Gy) followed by surgical resection.[112] Improved relapse-free survival, but not overall survival, was observed for patients assigned to receive surgery. Nevertheless, surgical resection is currently used in certain patients with stage IIIA NSCLC, although it is recognized that induction therapy should be administered. Whether induction therapy should consist of chemotherapy or combined chemotherapy and RT is controversial, and a randomized trial assessing the question closed prematurely because of poor accrual.

The cornerstone of treatment for patients with "unresectable" locally advanced NSCLC is concurrent systemic doublet chemotherapy and thoracic RT as described in Chapter 42. There are several controversies regarding the optimal treatment of this population, as described next.

Chemotherapy Regimen and Schedule During Radiotherapy

The landmark Phase III studies supporting concurrent chemotherapy and RT over a sequential approach used cisplatin-based chemotherapy in a schedule similar to that administered when chemotherapy is given for systemic disease.[113] Nevertheless, several Phase III trials have adopted a regimen of weekly paclitaxel and carboplatin as standard of care despite a lack of level 1 evidence.[114] Whether the weekly chemotherapy schedule or the substitution of carboplatin for cisplatin affects outcomes is unknown, though the excellent results from the standard (60 Gy) arm of RTOG 0617 lend support to the considering weekly concurrent paclitaxel and carboplatin as an acceptable standard therapy.[92]

Sequencing and Timing of RT and Chemotherapy

Trials conducted in the 1980s first showed that giving cisplatin-based chemotherapy before thoracic RT improved overall survival compared with RT alone, and subsequent trials showed that concurrent administration of chemotherapy and RT was better than sequential treatment.[115] Additional chemotherapy is frequently given in clinical practice either before or after concurrent therapy, although more recent Phase III randomized trials failed to show benefit for either induction chemotherapy or consolidation chemotherapy.[116,117] Toxicity was enhanced in the cohorts receiving longer duration chemotherapy. Further research assessing consolidation chemotherapy is likely given more recent reports favoring "maintenance" chemotherapy for patients with metastatic NSCLC treated with primary chemotherapy.[118]

Radiation Dose Escalation and Fractionation

The standard RT regimen for NSCLC, 60 Gy in daily 2-Gy fractions, was defined by an RTOG trial conducted in the 1970s.[119] The emergence of conformal RT planning ushered in several dose escalation studies, and encouraging outcomes of Phases I-II studies led to development of a Phase III trial, RTOG 0617, testing 74 Gy compared with 60 Gy with weekly carboplatin and paclitaxel chemotherapy.[120,121] Unexpectedly, results of this seminal trial demonstrate that higher doses of RT result in significantly worse survival and provides strong evidence against dose-escalated RT outside of a clinical trial.[92]

Altered fractionation has been tested in several Phase III trials of locally advanced NSCLC. Regimens that accelerate the time to complete therapy by giving multiple daily treatments have shown promise, although the utility of these regimens is limited by difficulty in integrating concurrent chemotherapy and the logistic challenge for many centers to treat patients up to three times a day.[122,123] The use of hyperfractionated RT seems to have no benefit if the time to complete treatment is not shortened.[124-126] The emergence of advanced treatment technologies, which facilitate limiting radiation dose to critical normal tissue, has resulted in increased interest in studying accelerated hypofractionted regimens, and ongoing cooperative group studies are assessing hypofractionated RT concurrent with chemotherapy.

Although there is limited experience treating locally advanced NSCLC with proton therapy, the increase in proton facilities in the United States and worldwide has resulted in the development of a Phase III RTOG trial comparing photon and proton radiotherapy concurrent with chemotherapy. A planned total dose of 7000 cGy is recommended in both arms, although there is allowance for dose reduction if normal tissue constraints cannot be met.[127]

Radiation Target Volumes

The role of elective nodal irradiation (ENI) is controversial; current practice has generally evolved such that clinically uninvolved lymph node regions are not intentionally targeted.[128,129] Studying the impact of ENI and accurately documenting sites of relapse in locally advanced NSCLC is challenging, although a modest-sized Chinese study showed less toxicity without a detriment in survival with involved field treatment compared with ENI.[130]

The potential influence of ENI may be lessened in the era of routine ^{18}F-FDG-PET staging, and most ongoing prospective trials do not include ENI.

Integration of Molecular Targeted Agents

A Phase III trial conducted by SWOG from 2001 to 2005 demonstrated worse survival with maintenance EGFR inhibitor gefitinib after chemoradiotherapy in locally advanced NSCLC,[131] curbing enthusiasm for large-scale study of targeted agents in potentially curable populations. Pilot data from CALGB showed gefitinib concurrent with chemoradiotherapy results in poor outcomes, although encouraging results were observed with concurrent administration of gefitinib with RT if concurrent chemotherapy was not given.[132] A subsequent Phase II trial assessing erlotinib and RT for patients who were a poor risk with stage III NSCLC failed to reach the primary survival endpoint although the median survival of 17 months was reasonable for a poor-risk population.[133] Additionally, although Phase II studies showed that combining cetuximab (a monoclonal antibody against EGFR) with concurrent chemotherapy and RT yielded encouraging outcomes,[134,135] cetuximab did not improve survival in the recently reported Phase III RTOG 0617 trial.[92] Routine administration of targeted agents do not appear to have a role in the treatment of unselected patients, but a recently activated randomized RTOG study is assessing the role of induction targeted therapy in patients with locally advanced NSCLC harboring either an EGFR mutation or an ALK gene rearrangement.

The addition of the VEGF inhibitor bevacizumab to doublet chemotherapy improves survival for patients with advanced non–squamous cell carcinoma.[136] Although there was initial enthusiasm for studying bevacizumab in locally advanced disease, an increased risk of tracheoesophageal fistula has been shown when bevacizumab is given with chemoradiotherapy for both NSCLC and SCLC. Administration of bevacizumab months to years after completion of thoracic RT has been linked to fistula formation.[137] These agents should not be used in combination with RT outside of a clinical trial.

Prophylactic Cranial Irradiation

The role of prophylactic cranial irradiation was assessed in four early trials for locally advanced NSCLC,[138-141] with the general conclusion that prophylactic cranial irradiation reduces brain metastases but does not improve overall survival. Results of an RTOG-led an intergroup study confirm this observation, although the trial was terminated prematurely because poor accrual.[142]

Postoperative Radiotherapy

Meta-analyses of postoperative RT has been roundly criticized on many counts, including the use of outdated technology, inclusion of patients with early-stage disease, and administration of excessive RT doses.[143] Nevertheless, a survival detriment was shown for postoperative RT in early-stage node-negative NSCLC, with an unclear benefit in patients who are node positive. Current efforts have generally focused on assessing postoperative RT for resected N2 disease, and a more recent Surveillance, Epidemiology, and End Results (SEER) analysis supports the contention that postoperative RT may be beneficial in N2 disease when delivered with modern technology in appropriate doses (e.g., 50 Gy in 2-Gy fractions).[144] A Phase III European study assessing postoperative RT is ongoing.[145]

Small Cell Lung Cancer

Treatment of limited stage SCLC includes the concurrent administration of RT and chemotherapy. Standard practice includes delivery of full dose cisplatin-based systemic chemotherapy during accelerated hyperfractionated thoracic RT (1.5 Gy twice daily to 45 Gy over 3 weeks). Prophylactic cranial irradiation is indicated after completion of thoracic RT and chemotherapy in patients with a good tumor response. Several issues that remain unresolved in the standard treatment of limited SCLC are described next.

Thoracic Radiotherapy Dose and Fractionation

Although high clinical response rates are expected with combined-modality therapy, durable local tumor control is poor when modest dose, conventionally fractionated thoracic RT is employed. Intensifying the RT course by accelerating the time to complete treatment seems to be an effective strategy in limited stage SCLC. Intergroup trial 0096 randomly assigned patients to receive 4500 cGy in either conventional (180 cGy daily fractions) or hyperfractionated, accelerated (150 cGy twice daily fractions) regimens.[146] Thoracic RT was initiated with the first cycle of etoposide and cisplatin chemotherapy. Mature results favored accelerated RT. With accelerated RT, 5-year survival was 26% compared with 16% for patients receiving conventional RT. The major increased toxicity of the accelerated regimen was a doubling of the grades 3 to 4 acute esophagitis rate (e.g., 16% versus 32%). Despite this result, the

regimen of 45 Gy twice daily has not been well accepted in clinical practice. The Patterns of Care Study published in 2003 noted that less than 10% of patients with limited stage SCLC received this regimen, whereas more than 80% were treated with daily RT.[147] Reluctance to accept accelerated RT may be in part as a result of the increased acute toxicity and practical issues involved with treating patients twice each day. However, the results of the study have also been questioned because of the inclusion of relatively low dose (45 Gy) daily RT as the standard treatment.

The CALGB studied high dose daily thoracic RT. CALGB 8837,[148] a Phase I study, assessed the maximum tolerated dose of RT given in standard daily and accelerated twice daily schedules. The maximum tolerated dose of twice daily RT was determined to be 45 Gy in 30 fractions over 3 weeks, whereas it was judged to be at least 70 Gy in 35 fractions for daily RT. The median survival for patients receiving daily RT was 29.8 months compared with 24 months for patients receiving twice daily RT. A subsequent Phase II study suggested encouraging survival with less apparent toxicity than was observed on studies using twice-daily fractions to 45 Gy.[149] Alternatively, the RTOG studied a concomitant boost strategy in limited stage SCLC. A Phase II study, RTOG 0239, employing a 61.2-Gy concomitant boost regimen demonstrated excellent local tumor control although 2-year overall survival fell well short of expectations.[150] An ongoing Phase III trial, CALGB 30610/RTOG 0538, initially compared standard thoracic RT (1.5 Gy twice daily) with the CALGB 70-Gy once daily and the RTOG 61.2-Gy concomitant boost regimens, but the 61.2-Gy cohort was discontinued in 2013 after an interim analysis of acute toxicity.[151] A Phase III study in Europe for limited small cell lung cancer, assessing 45-Gy twice-daily RT compared with 66-Gy once-daily RT, recently completed accrual and results should be reported in the next few years.[152]

Timing of Radiotherapy

The optimal timing of thoracic RT relative to chemotherapy is controversial. CALGB 8083 randomly assigned patients to receive initial RT plus chemotherapy, delayed RT plus chemotherapy, or chemotherapy alone. Mature results showed that survival with chemotherapy alone was inferior to both thoracic RT arms. A significant difference was not observed between early and delayed RT, although there was a trend favoring delayed thoracic RT ($p = 0.14$).[153] Conversely, a Phase III trial from the National Cancer Institute of Canada showed a benefit for initiating RT, 40 Gy in 3 weeks, with the second chemotherapy cycle compared with the sixth cycle of chemotherapy.[154] In the early thoracic RT cohort, 5-year survival was 20% compared with 11% in the late thoracic RT arm; the difference was ascribed to a reduction in brain metastases because local tumor control did not differ between arms. Additional studies have attempted to address the timing of thoracic RT. Meta-analyses have been published addressing this issue.[155,156] Although definitive conclusions cannot be reached, there is general consensus that the early initiation of thoracic RT (e.g., first through third cycle) may be beneficial, particularly in the context of intensive thoracic RT.

Treatment Volume

The issue of optimal thoracic RT volume in limited stage SCLC therapy has not been well studied in comparative trials. Investigators from the Southwest Oncology Group found that targeting the postchemotherapy tumor volume instead of the tumor volume on presentation did not result in increased failure rates.[157] More recent prospective trials using delayed (e.g., third or fourth cycle) chemotherapy incorporated reduced volume thoracic RT for all patients.[158,159] Mature patterns of failure data from the North Central Cancer Treatment Group, showing that only 2 of 90 local relapses may have occurred outside the postinduction volume but inside the preinduction volume, indicate that reduced field thoracic RT may be an acceptable strategy.[159]

Data attesting to the role of ENI for limited stage SCLC are lacking. Most prospective trials have included selected bilateral mediastinal stations as part of the initial target volume, although elective inclusion of the supraclavicular regions and the contralateral hilum is not indicated. Whether implementation of ^{18}F-FDG-PET imaging can reduce the role of ENI for SCLC has not been well studied, though small trials from the Netherlands suggest that promising results can be obtained with FDG-PET–guided involved field radiotherapy.[160]

Prophylactic Cranial Irradiation

The meta-analysis by the Prophylactic Cranial Irradiation Overview Collaborative Group[161] showed a convincing survival benefit (5.4% at 3 years) for the addition of prophylactic cranial irradiation following a complete response to therapy. A Phase III trial compared standard dose (25 Gy in 10 fractions) and high dose (36 Gy in either once-daily or twice-daily fractions) in limited stage SCLC. Higher doses of prophylactic cranial irradiation did not further reduce brain metastases, but increased mortality was observed on the patients receiving high doses.[162]

Chemotherapy Regimen

SCLC is exquisitely sensitive to systemic chemotherapy. The combination of cisplatin and etoposide became standard frontline therapy in the 1980s because of its clinical activity and tolerability in combination with concurrent thoracic irradiation. Efforts to improve outcomes by adding a third chemotherapy agent have been disappointing. A Phase III trial showed increased severe toxicity without a survival benefit when paclitaxel was added to etoposide and cisplatin for first-line therapy in extensive SCLC.[163] The RTOG conducted a Phase II study of paclitaxel, etoposide, and cisplatin chemotherapy with 45-Gy twice-daily RT in limited stage SCLC. Although the regimen was active, the authors of the study concluded that the addition of paclitaxel was unlikely to improve survival in patients with limited stage SCLC.[164] Topotecan and irinotecan, topoisomerase I inhibitors, are active agents against SCLC. Topotecan has been studied in combination with paclitaxel in both extensive and limited SCLC, but Phase II results did not warrant study in a Phase III setting.[165] In contrast, chemotherapy with irinotecan and cisplatin was superior to cisplatin and etoposide in a Phase III study for extensive SCLC conducted by the Japanese Cooperative Oncology Group.[166] Nevertheless, confirmatory trials conducted in North America failed to show improved survival for irinotecan and cisplatin chemotherapy over cisplatin and etoposide chemotherapy.[167,168]

Esophageal Cancer

There is no universally agreed on standard treatment for many patients with esophageal cancer, due in large part to the difficulty conducting large-scale randomized trials. Surgical resection alone is considered curative therapy for the few patients with early stage disease, with the potential for a minimally invasive approach (endoscopic mucosal resection) in certain patients.[169]

Treatment of locally advanced disease with primary RT is inappropriate for patients able to receive combined-modality therapy. This point is best illustrated by the results of RTOG 85-01, which showed a statistically and clinically significant survival benefit for concurrent chemotherapy[170] and RT compared with primary RT. In that experience, none of the patients

assigned to receive primary RT survived at least 5 years compared with a 5-year survival of 27% of patients receiving chemoradiotherapy.

Whether induction therapy improves outcomes for surgically treated patients has been debated extensively, and recently reported studies contribute substantially to evidence supporting multimodality therapy. The Phase III Chemoradiotherapy for Oesophageal Cancer followed by Surgery Study (CROSS) included 366 patients, and overall survival was significantly improved with preoperative radiotherapy (41.4 Gy) with concurrent weekly paclitaxel and carboplatin. Median survival was 24 months for patients assigned to surgery and 49.4 months in the preoperative chemoradiotherapy group.[171] A North American Intergroup trial also demonstrated improved survival with the addition of neoadjuvant chemoradiotherapy to surgery, even though the study was closed because of poor accrual after only 56 patients were randomized.[172] The impact of induction chemotherapy (without RT) on survival for surgically treated esophageal cancer is likewise controversial, and the two largest studies addressing the question reached different conclusions.[173,174]

The role of surgical resection after concurrent RT and chemotherapy remains unclear. Two European Phase III trials, the French FFCD 9102 trial[175] and the German Esophageal Cancer Study Group trial,[176] did not find a significant difference in survival between patients who received preoperative chemoradiotherapy or chemoradiotherapy alone, although the local recurrence rate was higher without surgery. On the other hand, locoregional tumor relapse was only 14% with trimodality therapy in the recently reported CROSS study, which is far less than would be expected with either definitive chemoradiotherapy or surgery alone, suggesting trimodality therapy should be considered for fit patients with locally advanced disease.[177] Additional studies suggest reduced local relapse with the addition of surgery. The possible benefit of surgical resection needs to be weighed against the risk of perioperative morbidity and mortality.

The standard RT dose regimen for patients treated with definitive RT and concurrent chemotherapy is 5040 cGy in 180-cGy fractions, and prospective studies have demonstrated that higher doses of radiotherapy result in increased toxicity without improving outcomes.[178] When neoadjuvant chemoradiotherapy is used, radiation doses typically range between 4500 cGy and 5040 cGy, similar to nonsurgical treatment, although a slightly reduced dose of 4140 cGy was used in the CROSS trial. Whether the integration of advanced technology, including ^{18}F-FDG-PET imaging, image-guided RT, and motion management, might alter the therapeutic radio of delivering more intense doses of RT remains open to study.

The combination of cisplatin and 5-fluorouracil, which had been considered standard chemotherapy for esophageal cancer in the United States (before the CROSS trial was reported), has resulted in pathologic complete response rates of approximately 20% to 30%. Although no chemotherapy regimen has proven superior to cisplatin and 5-fluorouracil in combination with RT, the regimen of weekly paclitaxel and carboplatin resulted in encouraging outcomes in the CROSS study and is increasingly used in clinical practice and clinical trials. An active CALGB Phase II trial is assessing the role of FDG-PET response directed chemotherapy and should complete accrual in the near future.[179] Despite overexpression of EGFR in esophageal cancer, several trials assessing agents that inhibit the EGFR pathway have reported disappointing results.[180] An active RTOG Phase III trial specific to Her2-overexpressing esophageal adenocarcinoma is evaluating trastuzumab in patients treated with trimodality therapy.[181]

RT guidelines have been published for gastroesophageal junction adenocarcinoma, and these tumors are sometimes managed similarly to gastric adenocarcinoma with initial surgical resection followed by adjuvant chemotherapy and RT as pathologically indicated.[182-185]

Thymoma

The initial treatment of choice for thymic tumors is surgery. Adjuvant RT or chemotherapy should be considered for patients at high risk for recurrence. Complete en bloc surgical resection is the standard of care for resectable thymomas. The primary determinants of clinical outcome are surgical-pathologic staging, tumor size, histology, and extent of surgical resection.

Complete resection of thymoma can lead to low recurrence and excellent survival rates.[186] Although prospective, randomized data on the value of adjuvant RT after resection of invasive thymoma are lacking, certain retrospective studies have shown improvements in local tumor control and survival in patients receiving RT for invasive disease.[187-189] However, conflicting results regarding the utility of adjuvant RT have been reported from analyses of large multiinstitutional series, including the SEER database. A more recent analysis of SEER data showed postoperative RT had no advantage in patients with localized thymoma (Masaoka stage I), but a possible survival benefit was suggested in patients with regional disease (Masaoka stage II-III).[190] The strongest data supporting postoperative RT were in the population of patients with non-extirpative surgery. In contrast, Kondo and Monden[13] reported a large multiinstitutional, retrospective study of 1320 patients with stage II or III thymic epithelial tumors for whom no significant benefit of adjuvant irradiation after surgery was found.

Primary RT has been administered to certain patients with unresectable thymoma with reasonable results, including approximately 65% local control and 5-year survival rate of 40% to 50%.[191] Likewise, salvage RT for patients with recurrent thymoma may achieve a 7-year survival rate of approximately 70%.[192]

Similar to the treatment for thymomas, surgery remains the predominant treatment for patients with thymic carcinomas, which are treated similarly to carcinomas found in other body sites. Adjuvant RT is commonly administered after surgery.[193] There may be a trend toward improved survival and local control with adjuvant therapy, but it is difficult to show.[194] There are reports of promising 5-year overall survival rates of more than 50% for patients who received irradiation after surgery.[195]

Pulmonary Carcinoid

Surgery is the primary treatment for typical and atypical pulmonary carcinoids, and long-term results after complete resection are excellent.[196] Clinical symptoms such as flushing can be relieved with ondansetron, a serotonin 5-HT$_3$ antagonist. Somatostatin analogs, inhibitors of neuropeptide release, relieve the symptoms of carcinoids by binding to somatostatin receptors.[197] Long-acting analogs of somatostatin, such as octreotide and lanreotide, are used to control diarrhea and flushing, and they have an approximately 70% chance of improving symptoms.

Typical carcinoids do not require adjuvant therapy after curative resection.[198] Patients with a tumor greater than 3 cm in diameter, lymph node metastasis, atypical histology, or residual disease may benefit from RT.[199]

Tumor targeting with radioactive somatostatin analogs has been used in patients with carcinoids with inconclusive results.[200] Interferon-α, alone or in combination with octreotide, has resulted in symptomatic relief in some patients.[201]

Chemotherapy results have been inconclusive, with a possible role for cisplatin and etoposide in patients with atypical carcinoids.[202] RT may palliate symptoms in patients with locally advanced or metastatic disease.[203]

Mesothelioma

Because mesothelioma usually involves the visceral and parietal pleural surfaces of the lung and extends into the pleural-lined pulmonary fissures, it can be difficult to perform a complete resection without an extrapleural pneumonectomy (EPP). EPP includes en bloc removal of tissues in the hemithorax, including the parietal and visceral pleura, involved lung, mediastinal lymph nodes, diaphragm, and pericardium. Given the aggressive nature of the surgery, EPP is considered only for patients with localized disease who have minimal comorbid medical problems. Even with EPP, R0 resections cannot be accomplished, and the relative value of EPP compared with lesser resection has been questioned.[204]

The value of RT in patients with unresectable mesothelioma is controversial. A report from Cancer Care Ontario's Program in Evidence-based Care suggested there was little evidence in the published literature to support a role for RT in the management of mesothelioma.[205] A more recent review of the SEER database identified epithelioid histology, pneumonectomy, and RT as predictive of increased survival.[206] Median survival for patients treated with pneumonectomy with and without RT was 19 months and 13 months ($p = 0.01$). Additional studies have suggested improved local tumor control when RT is administered after EPP.

The combination of pemetrexed and cisplatin is considered standard of care for patients with advanced (unresectable) mesothelioma,[207] and the expected median survival in patients treated with the regimen approaches 12 months. Carboplatin is frequently substituted for cisplatin, often owing to medical comorbidity, without an apparent decrease in efficacy. Chemotherapy has now routinely been integrated as part of trimodality therapy for patients with resectable mesothelioma based primarily on promising results in select series.[208]

Treatment of the ipsilateral hemithorax with IMRT after EPP has been associated with a high rate of toxic deaths in several single-institution experiences.[209,210] Fatal pneumonitis has been related to radiation exposure of the contralateral lung, and NCCN guidelines suggest that the mean lung dose be limited to 8.5 Gy and the V5 lung be kept as low as possible. Recent series suggest IMRT can be used with acceptable toxicity if normal tissue dose constraints are strictly followed.

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CHAPTER

43 Small Cell Lung Cancer

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INCIDENCE

Approximately 30,000 Americans are diagnosed with small cell lung cancer (SCLC) each year. This represents 13% to 15% of all cases of bronchogenic carcinoma.

BIOLOGIC CHARACTERISTICS

The 2004 World Health Organization (WHO) classification system describes two variants: small cell carcinoma and combined small cell carcinoma. The latter includes SCLC cells with any of the histologic types of non–small cell lung cancer (NSCLC).

STAGING EVALUATION

The International Association for the Study of Lung Cancer (IASLC) TNM Staging System is recommended for use in staging SCLC, but the 1973 Veterans Administration (VA) distinction of extensive stage (E-SCLC) compared to limited stage (L-SCLC) is commonly employed. Imaging studies including whole body 2-[18F] fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET)/computed tomography (CT) and brain magnetic resonance imaging (MRI) should be routinely obtained if possible.

PRIMARY THERAPY, ADJUVANT THERAPY, AND LOCALLY ADVANCED DISEASE AND PALLIATION

Chemotherapy is standard therapy for all patients with SCLC who are fit enough to tolerate its use and etoposide with cisplatin (EP) are the most commonly used agents in the United States. The standard management of L-SCLC disease is EP given concurrently with thoracic radiation therapy (TRT). A Phase III trial demonstrated a survival advantage for twice-daily TRT over standard once-daily TRT. Fit patients with L-SCLC should undergo combined-modality therapy including twice-daily TRT to 45 Gy with concurrent EP for four cycles. Most current clinical protocols for L-SCLC employ the involved-field technique of TRT, in which the target volume includes the known extent of the primary tumor and malignant lymphadenopathy (as defined with CT and FDG-PET imaging). Elective radiotherapy (RT) of the supraclavicular and contralateral hilum is discouraged. If a patient achieves any degree of favorable response on restaging, prophylactic cranial irradiation (PCI) should be recommended. For patients with E-SCLC, primary therapy consists of EP and irradiation for symptomatic or nonresponding sites. Carefully selected patients with E-SCLC (with complete responses outside of the chest) should receive TRT. Following chemotherapy, PCI should be offered to all patients having any degree of response. Although long-term survival with E-SCLC is quite uncommon, about one fourth of patients with L-SCLC will survive 5 years or longer.

INTRODUCTION

During 2013, lung cancer was diagnosed in an estimated 246,210 patients and caused an estimated 163,890 deaths in the United States.[1] Between 13% and 15% of patients with lung cancer have SCLC, and of these, about 30% have L-SCLC.[2] Few patients with SCLC have stage I disease. Lung cancer occurs quite frequently in the elderly with a median age of 71 years at diagnosis.[3]

The natural history of untreated SCLC included rapid tumor progression with a median survival of only 2 to 4 months.[4] Until the late 1960s, physicians did not differentiate the management of SCLC from non-SCLC (NSCLC), and clinical trials in the 1970s continued to include both major histological types. It was recognized that most patients with SCLC had poor survival following resection or TRT with little apparent survival benefit from either. A major change in management occurred in the late 1960s and was linked to the recognition that SCLC was more responsive to chemotherapy than NSCLC.[5]

ETIOLOGY AND EPIDEMIOLOGY

The most common cause of SCLC is tobacco smoking. Additionally, secondary exposures to tobacco smoke and inhalation of asbestos or radon have also been associated with the development of this disease. Radon gas is the daughter product of decay of uranium and is most commonly found in areas with uranium within the soil.

Prevention and Early Detection

Prevention of SCLC is possible by addressing the causes of this disease mentioned previously. Smoking prevention and cessation are the chief methods of prevention. Radon can be removed from homes where it is present through proper ventilation. Asbestos exposure has been dramatically decreased recently by removing it from buildings and work environments.

BIOLOGIC CHARACTERISTICS AND MOLECULAR BIOLOGY

Cigarette smoke is a powerful mutagen that is strongly associated with the development of SCLC. Acquired hypermethylation of the promoter region of key genes is a common mechanism to inactivate tumor suppressor genes (TSGs) in tumor formation. The common molecular abnormalities in

TABLE 43-1 Molecular Anomalies Frequent in Small Cell Lung Cancer

Chromosomal Anomalies	Roles
Deletions or epigenetic inactivation of 3p, 5q, 13q, and 17p 3p21 (*RASSF1*, *FUS1*, *SEMA3B*, and *SEMA3* genes) 3p14.2 (*FHIT* gene) 3p24 (*RARβ* gene) 13q14 (*RB* gene) 17p13.1 (*p53* gene)	Disabled tumor suppressor genes
Amplifications of 1p, 2p, 3q, 5p, 8q, and 19p Telomerase *Bcl-2* genes Myc	Contain oncogenes promote survival and growth
Intracellular signal pathways Phosphoinositide 3-kinase/AKT/mTOR pathway P13K = mutated, overactive PTEN = mutated mTOR, S6K1, and 4EBT1 = active	Defective and lead to growth and survival
Receptor tyrosine kinases cKit and ligand (SCF) C-Met and ligand (HGF/SF) IGF-1R and ligand (IGF-1&2) FGFR 1-4 and ligand (FGF &2) VEGFR 1-3 and ligand (VEGF(A-E))	Overexpressed stimulating growth and survival
Molecular chaperones Heat shock protein (HSP)-90	Alters confirmation of client proteins Activates and inactivates proteins including AKT, MET, bcl-2, telomerase, survivin, and Apaf-1 Antiapoptotic
Cell surface proteins that are overexpressed NCAM (CD65) Gangliosides: FucGM1	Modulate growth, differentiation, and cell adhesion
Developmental pathways Hedgehog (Hh): Sonic hedgehog (SHh) Indian hedgehog (IHh) Desert hedgehog (DHh) Notch: Notch receptors 1-4 ligands: delta-1, Jagged 1 Jagged 2 WNT: multiple molecules SOX2	Cell proliferation Cell proliferation and neuroendocrine differentiation Leads to neuroendocrine differentiation Proliferative, differentiation, survival, and motility Proliferation of stem cells
Neuroendocrine marker proteins Synaptophysin Chromogranin A CD-56	
Histone modifying gene mutations Alters enzymes CREBBP, EP300, and MLL	

AKT, *V-akt murine thymoma viral oncogene;* Bcl-2, *B-cell lymphoma 2;* CD-56, *neural cell adhesion molecule;* cKit, *v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene;* C-Met, *met proto-oncogene;* CREBBP, *CREB binding protein;* EP300, *E1A binding protein p300;* FGFR1, *fibroblast growth factor receptor 1;* FHIT, *fragile histidine triad protein;* FucGM1, *ganglioside fucosyl-GM1;* FUS1, *cell FUSion1;* IGF-1R, *insulin-like growth factor 1 receptor;* MLL, *methyltransferase gene;* mTOR, *mammalian target of rapamycin;* Myc, *v-myc avian myelocytomatosis viral oncogene;* NCAM, *neural cell adhesion molecule;* P13K, *phosphoinositide 3-kinase;* P53, *tumor protein 53;* PTEN, *phosphatase and tensin;* RARβ, *retinoic acid receptor beta gene;* RASSF1, *ras association domain family member 1;* RB, *retinoblastoma;* SEMA, *sema domain;* SOX2, *SRY (sex determining region Y)-box 2;* VEGFR, *vascular endothelial growth factor receptor;* WNT, *wingless-type MMTV integration site family.*

SCLC are shown in Table 43-1.[6-8] A large number of genetic mutations are frequently observed in SCLC tumors, especially common in TSGs. The mutations lead to dysfunction of these suppressor molecules resulting in unrestricted tumor growth. It is common to find deletions or epigenetic inactivation of 3p, 5q, 13q, and 17p that contain a number of TSGs (Table 43-1). The chromosome 3 genetic deletions, observed in almost all cases, are found in both dysplastic and preneoplastic cells and have been demonstrated as the genetic mutations associated with the transformation of precancerous lesions into carcinoma. There has been substantial progress in understanding the molecular abnormalities leading normal bronchial epithelium to become carcinoma. However, there has not yet been much progress in preventing these events or reversing them once they have taken place.

Amplification or overexpression of 1p, 2p, 3q, 5p, 8q, and 19p are common. These contain oncogenes (Bcl-genes, myc and telomerase genes) that promote survival and growth of SCLC. Telomerase is unique in that it functions in the maintenance of telomeres, which are repeated nucleotide sequences at the ends of DNA molecules. Telomeres shrink over time leading eventually to cell death. The enzyme telomerase adds more nucleotides to the DNA ends and can confer immortality to tumor cells.

Intracellular signal pathways become defective leading to increased tumor growth and survival. These have been focus of much research in an attempt to develop effective targeted therapies. None of these are used in standard practice today. Molecular chaperones are large proteins that alter the conformation of client proteins leading to both activation and deactivation of pathways that can result in disregulation of normal cellular growth and development. Receptor tyrosine kinases are overexpressed stimulating growth and survival of SCLC through many pathways. Cell surface proteins are overexpressed modulating growth, differentiation, and cell adhesion.

Another biologic feature that distinguishes SCLC from NSCLC is the more frequent expression of neuroendocrine markers in SCLC. These neuroendocrine markers include enzymes (neuron-specific enolase and L-dopa decarboxylase), peptide hormones (gastrin-releasing peptide, arginine vasopressin), and surface markers such as neural cell adhesion molecule (NCAM). There are also peptide hormones that meet the criteria of autocrine growth factors, which require the production of a growth-promoting protein for which the producing cell has functional receptors. In the case of gastrin-releasing peptide, there is clear evidence that it is produced and secreted by many SCLC cells and then attaches to its cellular membrane receptors stimulating tumor growth.[9]

PATHOLOGY AND PATHWAYS OF SPREAD

The 2004 WHO classification defined SCLC as "a malignant epithelial tumor consisting of small cells with scant cytoplasm, ill-defined cell borders, finely granular nuclear chromatin, and absent or inconspicuous nucleoli." The cells are round, oval, and spindle shaped. Nuclear molding is prominent. Necrosis is extensive, and the mitotic count is high. SCLC occurs in two variant forms: small cell carcinoma and combined small cell carcinoma. The latter type includes SCLC cells and any of the histologic types of NSCLC.[10]

CLINICAL MANIFESTATIONS, PATIENT EVALUATION, AND STAGING

The signs and symptoms of lung cancer depend on the location and bulk of the primary tumor, adenopathy, and metastatic disease. Because of the high frequency of extensive mediastinal and hilar nodal involvement in SCLC cases, patients frequently present with symptoms such as dyspnea, dysphagia, hoarseness, and superior vena cava (SVC) syndrome. Many patients with SCLC present with other thoracic symptoms including cough, hemoptysis, chest pain, and weight loss.

SCLC is the most common solid tumor associated with paraneoplastic syndromes. Several of these are endocrinologic or neurologic. The most common endocrinologic abnormality is the syndrome of inappropriate secretion of antidiuretic hormone (SIADH). This condition results from the excessive secretion of ADH from tumor cells, leading to severe hyponatremia with resultant hypoosmolality. SIADH occurs in about 11% of patients with SCLC and typically resolves after response to anticancer therapy. Restriction of free water intake is critical to maintaining proper sodium concentrations before SIADH improves secondary to cancer therapy.[11] Atrial natriuretic peptides (ANP) or arginine vasopressin (AVP) syndromes also result in hyponatremia. Paraneoplastic syndromes associated with SCLC are found in Table 43-2.[12]

The neurologic syndromes associated with SCLC (Table 43-2) include Lambert-Eaton syndrome, cerebellar degeneration syndrome, encephalomyelitis, sensory neuropathy, and cancer-associated retinopathy. Each of these is observed in well under 5% of all patients with SCLC. Lambert-Eaton syndrome is an autoimmune disorder that affects calcium channels of the neuromuscular junction. Antibodies are directed against the calcium channels responsible for the presynaptic release of acetylcholine. These antibodies prevent the opening of calcium channels, which presents the release of acetylcholine. Patients with Lambert-Eaton syndrome present with myasthenia gravis–like symptoms of proximal myopathy, autonomic dysfunction, and hyporeflexia. Like many paraneoplastic syndromes, this condition is generally improved with response to anticancer therapy, although there can also be symptomatic responses to anti-myasthenia therapies.[13] The other neurologic syndromes are believed to be primarily autoimmune phenomena, which usually respond poorly to cancer therapy.[14,15]

SCLC can be diagnosed with histologic or cytologic sampling. In most cases, a diagnosis can be obtained via sputum expectoration, bronchoscopic sampling, or CT-guided transthoracic needle aspiration.

The VA Lung Cancer Study Group's Staging System, which distinguishes between limited and extensive SCLC, is most commonly used.[16] The initial definition of limited disease was an extent of intrathoracic disease encompassable within a "reasonable" radiation field. Investigators in recent years have recognized the dangers of variable interpretations and recent cooperative group trials require staging of patients with SCLC with the standard TNM system. However, the categorization of patients with SCLC into limited versus extensive stage disease has been extremely helpful for making rational treatment choices and designing trials.

Approximately two thirds of patients with SCLC have extensive-stage or stage IV disease at presentation. Staging evaluation would traditionally include a history and physical

TABLE 43-2 Paraneoplastic Syndromes Associated with Small Cell Lung Cancer

Syndrome	Manifestation(s)	Frequency (%)	Correctable with Therapy
SIADH	Hyponatremia	11	Yes
ANP or AVP syndrome	Hyponatremia	15	Yes
Ectopic ACTH or CRH production	Ectopic Cushing's syndrome	5	Rarely
Lambert-Eaton syndrome (antibodies to VGCC)	Myasthenia gravis–like symptoms	1-3	Yes
Other neurologic syndromes*	Other neurologic symptoms	<5	Rarely
Cancer-associated retinopathy	Visual loss	<1	Rarely

ACTH, *Adrenocorticotropic hormone;* ANP, *atrial natriureticpeptides;* AVP, *arginine vasopressin;* CRH, *corticotropin-releasing hormone;* SIADH, *syndrome of inappropriate antidiuretic hormone;* VGCC, *P/Q-type voltage gated calcium channels.*

**Other neurologic syndromes are often related to Hu antibody and include cerebellar degeneration, encephalopathy, sensory neuropathy, or opsoclonus/myoclonus.*

examination, complete blood cell count, chemistry panel, contrast-enhanced CT scan of the thorax and upper abdomen, pulmonary function testing, and CT or MRI scan of the brain. PET scans are quite accurate for the staging of this SCLC. PET scan can aid with the choice of appropriate therapy and radiotherapy (RT) planning by better identifying tumor extent.[17] PET/CT scanning can replace the traditional radiographic staging studies for SCLC with the exception of CT or MRI of the brain. Because of the high uptake of the tracer (radioactive glucose) within the normal brain, metastases are difficult to distinguish from the brain itself.

Investigators need to be cautioned regarding the influence of ever improving staging techniques on the interpretation of survival results. Many patients previously believed to have limited disease are currently "upstaged" to the extensive-disease category because of more sensitive staging studies. It is likely that their inclusion in the extensive-disease group and their exclusion from the limited disease category will improve survival rates of both groups. This effect is known as the *Will Rogers phenomenon*, which was first used in oncology regarding patients with SCLC and is based on Rogers's quote, "When the Okies left Oklahoma and moved to California, they raised the average IQ in both states." The best method of minimizing this potential bias is to perform properly stratified randomized trials.

There have been several efforts to identify prognostic factors other than staging as a means to better select patients for specific therapies. As with many malignancies, good performance status, young age, and female gender are associated with better prognosis, and these have been verified in large multivariate analyses.[18-21] The Mayo Clinic/North Central Cancer Treatment Group (NCCTG) evaluated 1598 patients with SCLC to determine prognostic factors. Multivariate analysis revealed that performance status, age, gender, number of metastatic sites, and baseline creatinine levels were all associated with survival of patients with E-SCLC. Among patients with L-SCLC, only age and gender were associated with survival.[20] One critical reason for determining prognostic factors is for use in the proper patient stratification and selection when designing trials.

One must consider a patient's pulmonary and cardiac fitness, ability to tolerate specific chemotherapeutic agents, prior malignancies, patient age, and performance status when making decisions regarding optimal therapy for patients with SCLC.

PRIMARY THERAPY LOCALLY ADVANCED DISEASE AND PALLIATION

Thoracic Radiotherapy in LSCLC

In the 1960s it was recognized that chemotherapy was quite active against SCLC and that patients treated with surgery or radiation alone did quite poorly. Therefore, chemotherapy became the primary therapy for SCLC.[22,23] Unfortunately, recurrence inevitably followed the response to chemotherapy and these relapses were most frequently in areas of previous disease. This pattern of failure led investigators to reexamine the use of TRT for L-SCLC. Today, both RT and chemotherapy have central roles in the treatment of SCLC.[24,25] A series of randomized trials were performed comparing chemotherapy alone to chemotherapy with TRT for patients with L-SCLC.[26-29] In 1992, two meta-analyses were published regarding the role of TRT in addition to chemotherapy.[2,29] Pignon et al reported a 3-year survival rate of 14.3% with combined-modality therapy compared to 8.9% with chemotherapy alone ($p = 0.001$). This 5.4% absolute difference in 3-year survival rates was identical to the 5.4% difference in 2-year survival ($p < 0.001$) in a similar meta-analysis reported by Warde and Payne. Although this 5.4% difference appears rather small, it represented a 61% increase in the 3-year survival of 8.9% achieved with chemotherapy alone.[29] In addition, the intrathoracic tumor control was improved by 25% with TRT.[2]

Sequencing and Timing of TRT and Chemotherapy

Chemotherapy and TRT can be delivered concurrently, sequentially, or in an alternating manner. Potential advantages of concurrent delivery include a shorter overall treatment time, increase in treatment intensity, and potential anticancer synergism between the various therapies. Disadvantages include the heightened toxicity and the inability to assess the antitumor response of the chemotherapy alone. The Japanese Clinical Oncology Group performed a Phase III trial in which patients with L-SCLC were randomized to sequential or concurrent therapy. All 231 patients received four cycles of EP every 3 weeks (sequential arm) or 4 weeks (concurrent arm) and were randomized to receive TRT during the first cycle of chemotherapy in the concurrent arm or after the fourth cycle in the sequential arm. TRT included 45 Gy (1.5 Gy twice daily) over 3 weeks. The median survival time was 19.7 months in the sequential arm compared with 27.2 months in the concurrent arm ($p = 0.097$). The 5-year survival rate for patients treated sequentially was 18.3% compared to 23.7% for those treated concurrently. Hematologic toxicity was more severe in the concurrent arm as was severe esophagitis which occurred in 9% in the concurrent arm and 4% in the sequential arm. The authors concluded that the findings strongly suggested that concurrent therapy was more effective for L-SCLC.[30] Although the p value was not significant, the trend favors concurrent therapy. The interpretation of this result is confounded by the difference in timing of TRT because TRT was initiated several months earlier in patients receiving concurrent therapy.

There have been conflicting results from the randomized trials that have addressed the issue of timing of TRT during chemotherapy. However, recent meta-analyses do help make sense of the contradictory data. One study analyzed randomized trials published after 1985 addressing the timing of TRT relative to chemotherapy in L-SCLC. Early TRT was initiated before 9 weeks after starting of chemotherapy and late TRT after 9 weeks. Seven trials ($n = 1524$ patients) met the inclusion criteria and were included. The relative risk of survival for early TRT compared to late TRT for all studies was 1.17 ($p = 0.03$), indicating an increased 2-year survival for patients undergoing early TRT. This translated to a 5.2% ($p = 0.03$) improvement in the 2-year survival for early TRT. This small but significant improvement in 2-year survival for early TRT was similar in magnitude to the benefit of adding TRT or PCI to chemotherapy.[31]

A subsequent meta-analysis investigated the influence of the time interval between the start of any treatment until the end of TRT (SER) on local tumor control, survival, and esophagitis. There was a significantly higher 5-year survival rate in the shorter SER arms (relative risk [RR] = 0.62; $p = 0.0003$), which was more than 20% when the SER was less than 30 days. A low SER was also associated with a higher incidence of severe esophagitis (RR = 0.55; $p < 0.0001$). Each week of extension of the SER beyond that of the study arm with the shortest SER resulted in an overall absolute decrease in the 5-year survival rate of 1.83%. Thus, earlier, shorter, more intense TRT programs improved survival.[32] The current Phase III trial, CALGB 30610/RTOG 0538, allows TRT to start with either the first or second cycle of chemotherapy. Given the complexity of modern RT planning and the urgency to initiate therapy in patients with SCLC, the majority of patients treated in the United States and Europe appear to receive TRT starting with the second cycle of chemotherapy.

Thoracic Radiation Therapy Dose

SCLC is considered a radioresponsive malignancy because the low doses of TRT previously used produced encouraging responses. Total TRT doses for L-SCLC have ranged from 25 Gy to 30 Gy in 10 fractions in the 1970s to up to 70 Gy in 35 fractions in recent years. Doses in the lower end of this range may have been acceptable when chemotherapy was less effective and disseminated disease occurred earlier in the disease course. Improvements in systemic therapy have increased the need for aggressive TRT regimens that produce more durable responses. It was estimated by Choi and Carey that the risk of intrathoracic tumor failure at total doses of 40 Gy or less was 80%,[33] which was confirmed in a National Cancer Institute of Canada (NCIC) L-SCLC trial in which patients were randomized between 25 Gy over 10 fractions versus 37.5 Gy over 15 fractions.[34] The 2-year actuarial rates of local failure were 80% and 69%, respectively.

The most commonly administered doses of TRT range from 45 Gy to 70 Gy in 1.8 Gy to 2.0 Gy daily fractions. Most trials estimated the local control rates in this dose range between 58% and 85%.[35] Cancer and Leukemia Group B (CALGB) investigators have explored high-dose conventionally fractionated TRT in detail. A Phase I trial suggested 70 Gy was feasible given with the fourth cycle of chemotherapy with provocative 5-year survival of 36%, albeit in a select cohort of patients.[36] Subsequent Phase II trials, where TRT was given with the third cycle of (carboplatin based) chemotherapy have reported mixed results. Pooled data from these prospective studies include 200 patients assigned to receive TRT of 70 Gy (35 daily fractions of 2.0 Gy) with median follow-up of 78 months. Treatment was relatively well tolerated (grade 3 or greater esophagitis was 23%), and median survival was similar to reports with 45 Gy (1.5 Gy twice daily). The median survival for the entire cohort assigned to 70 Gy TRT was 19.9 months and 5-year survival rate was 20%. This experience may aid practitioners decide whether high-dosage daily RT with platinum-based chemotherapy is appropriate outside of a clinical trial.[37,38]

The feasibility of high-dose daily TRT coupled with the fact that the majority of patients are treated with daily TRT in clinical practice has resulted in a Phase III trial (CALGB 30610/RTOG 0538) comparing EP and concurrent TRT with either 45 Gy in 30 twice-daily fractions or 70 Gy in 35 daily fractions.[37] A Phase III trial conducted in Europe has also directly addressed the question of high-dose once-daily TRT. The CONVERT Trial randomized more than 500 patients to receive 66 Gy in 2 Gy daily fractions or 45 Gy in 1.5 Gy twice-daily fractions starting with the second cycle of chemotherapy. The trial recently completed accrual and results should be reported in the next few years.[39]

TRT and Altered Fractionation

In addition to increasing the number of daily treatments, another means of intensifying TRT is the use of altered radiation fractionation. For patients with L-SCLC, most altered fractionation strategies have employed twice-daily fractionation with fraction sizes varying from 1.1 Gy to 1.8 Gy and total doses ranging from 40 Gy to 54 Gy. Most regimens have tested the principle of accelerated hyperfractionation in which a twice-daily regimen allows the delivery of a standard total TRT dose over a shortened duration. These regimens should provide an improved therapeutic index for patients with rapidly growing tumors such as SCLC with a small shoulder and a steep slope on their in vitro cell survival curves.

Several encouraging pilot studies led to the development of Intergroup Trial 0096, a Phase III trial testing the concept that accelerated hyperfractionation would improve the outcome for patients with L-SCLC (Table 43-3). The experimental regimen was 45.0 Gy in 1.5 Gy twice-daily fractions beginning on day 1 of a four-cycle regimen of EP. The interfraction interval was 6 to 8 hours and the elapsed treatment time was 19 to 21 days. A total of 419 patients were randomized between the TRT regimens of 45.0 Gy in 1.8 Gy daily fractions compared to 45.0 Gy in 30 to 1.5 Gy twice-daily fractions. Of these, 10 treatments were often given with off cord oblique fields (afternoon session of the final 2 weeks) and dose to the spinal cord was limited to 36 Gy. In both arms the TRT began on day 1 of a four-cycle course of EP. There was a significant survival advantage for the patients with twice-daily TRT s compared to the patients with daily TRT with 5-year survival rates of 26% and 16%, respectively ($p = 0.04$). The median survival time was 19 months for the daily TRT group and 23 months for the twice-daily TRT. The intrathoracic tumor failure rate was 36% for the twice-daily TRT arm and 52% for the daily TRT arm ($p = 0.06$). The principal difference in toxicity was a higher rate of grade 3 esophagitis in the twice-daily TRT arm: 27% versus 11% ($p < 0.001$).[40] This study confirms the principle that an intensification of TRT beyond the relatively low dose daily TRT can improve both local control and survival. This trial has altered the standard of care of patients with L-SCLC because this twice-daily fractionation program is considered to be the standard by which all other programs are compared.

TABLE 43-3 Intergroup 0096 Study Comparing Once- with Twice-Daily Thoracic RT for Patients with L-SCLC Treated with Concurrent Cisplatin and Etoposide

Characteristic	Arm 1 (Once Daily)	Arm 2 (Twice Daily)	*p* Value
Number of patients	206	211	—
Median survival time (mo)	19	23	—
2-year survival rate	41%	47%	—
5-year survival rate	16%	26%	0.04
Failure-free survival rate	24%	29%	0.10
Local failure rate	52%	36%	0.06
Simultaneous local and distant failure rate	23%	6%	0.005
Grade 3 esophagitis rate	11%	27%	<0.001

L-SCLC, *Limited-stage small cell lung cancer;* RT, *radiation therapy.*

The North Central Cancer Treatment Group (NCCTG) performed a trial (89-20-52) that has been misinterpreted as contradicting the findings of the Intergroup Trial 0096. This trial included 310 patients with L-SCLC initially treated with three cycles of EP.[41] Subsequently, the 261 patients without progression were randomized to two cycles of EP plus either daily TRT (50.4 Gy in 28 fractions) or split-course twice-daily TRT (24 Gy in 16 fractions, 2.5 week break and 24 Gy in 16 fractions). Patients then received a sixth cycle of EP followed by PCI. The median and 5-year survival rates were 20.6 months and 21% with daily TRT compared with 20.6 months and 22% for twice-daily TRT($p = 0.68$). The findings of these two Phase III studies comparing daily to twice-daily TRT for L-SCLC led to the conclusion that continuous course of twice-daily TRT is better than daily TRT, but split course twice-daily RT is not.

There has also been investigation of higher doses of twice-daily RT in an attempt to further improve outcome. NCCTG

95-20-53 was a Phase II trial that included six cycles of EP.[42] PCI (25 Gy over 10 fractions) was delivered during cycle three. Cycles four and five included concurrent EP and TRT (30 Gy over 20 twice-daily fractions, a 2-week break, and 30 Gy over 20 twice-daily fractions). The 5-year survival rate of the 76 evaluable patients was 24% (median, 20 months). The 5-year survival rate of the 64 patients who received TRT was 29% (median, 22 months). The 5-year cumulative incidence of in-field failure was 34%. This high-dose twice-daily TRT regimen resulted in a favorable 5-year survival rate. Local failure remains a problem that will require further investigation. Newer technology should allow the safe administration of greater doses of TRT that should improve outcome. Schild et al evaluated data from this trial and others to demonstrate a positive correlation between biologically effective dose (BED) and 5-year survival.[42]

A hybrid approach of concomitant boost TRT has been investigated by the RTOG in both a Phase I and a Phase II setting.[43,44] A dose of 61.2 Gy was given with the first cycle of EP in the Phase II study with twice-daily TRT given during the final 9 days of therapy. Although encouraging local tumor control was reported, overall survival was less than predicted. This regimen was initially included as one of the experimental treatment arms on the CALGB 30160/RTOG 0538 trial, though the concomitant boost arm was discontinued after a planned interim analysis of toxicity between the two experimental arms. As noted previously, the CALGB 30160/RTOG 0538 trial continues as a direct comparison of 45 Gy twice-daily TRT with 70 Gy daily TRT, testing the hypothesis that the higher BED twice-daily regimen will improve survival.

Chemotherapy

The selection of chemotherapeutic agents to combine with TRT for patients with L-SCLC is largely based on trials of multiagent regimens used for E-SCLC. The currently accepted standard chemotherapy regimen for both E-SCLC and L-SCLC in the United States is the two-drug regimen of EP. SWOG was the first group to report a completed trial of concurrent TRT with EP for L-SCLC. They reported a median survival time of 17.5 months and 4-year survival rate of 30%, which appeared superior to the previously reported results with TRT combined with other non–platinum-containing regimens.[45] Additionally, promising results were subsequently reported with TRT and EP and were confirmed in the Intergroup Trial 0096.[46-48] No randomized trial has demonstrated the superiority of TRT and EP over any other regimen for L-SCLC.

New Agents

A recent Japanese Trial compared irinotecan and cisplatin compared with EP for E-SCLC. The median survival was 12.8 months with irinotecan and cisplatin compared to 9.4 months with EP ($p = 0.002$).[48] A similarly designed SWOG Trial S0124 was unable to confirm a survival advantage obtained by irinotecan and cisplatin.[49] Hanna et al reported similarly negative findings from a third similar Phase III trial.[50] Paclitaxel has also been studied extensively in SCLC. A Phase III study in extensive stage disease showed increased fatal toxicity without an improvement in survival with the addition of paclitaxel to EP.[51] A Phase II RTOG trial in LSCLC demonstrated that paclitaxel could be given together with EP during twice-daily TRT, though overall survival did not appear to be better than prior studies using only two chemotherapy drugs.[52] In this age of targeted biological therapy, many compounds have been tested, with a particular interest in antiangiogenic agents, including bevacizumab, in extensive stage disease. These agents have generally demonstrated improved progression-free survival but not overall survival, though results of a completed Phase III trial assessing bevacizumab in extensive disease[53] are pending. The integration of targeted agents in L-SCLC should be undertaken with caution and not done outside of a clinical trial, given that severe tracheoesophageal fistula has been reported in pilot studies using bevacizumab with TRT.[54]

Role of Surgery

The use of resection as primary management of SCLC was largely abandoned by the 1970s when poor survival rates were reported and few complete resections were achieved.[55] In a report by the VA Surgical Oncology Group published in 1982, 5-year survival rates for patients with resected T1N0, T1N1, and T2N0 SCLC were 60%, 31%, and 28%, respectively.[56] All of these patients received chemotherapy. A SWOG protocol enrolled 15 patients with L-SCLC who underwent resection followed by chemoradiation and found this group to have a better 2-year survival rate than a cohort of matched patients treated nonoperatively in other SWOG trials (45% versus 14%).[57] Ichinose et al reported on 112 patients with SCLC who underwent surgical resection and were then randomized between two chemotherapy regimens.[58] Although the chemotherapy regimens produced comparable outcomes, the 3-year survival rates were encouraging: 65% for N0 disease, 52% for N1 disease, and 29% for N2 disease. Chandra et al also found a favorable 5-year survival of 38% in patients with stages I and II SCLC who had resections performed.[59] Each of these three reports suggests that for patients with the rare N0 or N1 L-SCLC, resection followed by chemotherapy produced survival results that may be superior to nonoperative approaches. The role of TRT in this setting remains unclear. A pattern-of-failure study of patients with resected SCLC receiving postoperative chemotherapy alone would help clarify this issue.

A randomized trial was conducted by the Lung Cancer Study Group in which patients with L-SCLC achieving a partial response (PR) or complete response (CR) to chemotherapy received either resection or none.[60] There was no survival difference between the arms, with a 2-year survival rate of 20% in both arms ($p = 0.55$). Based on this trial and on the proven survival benefit of concurrent chemotherapy and TRT, adjuvant surgery following chemotherapy is not recommended.

There are limited data regarding the role of resection of intrathoracic recurrences. Shepherd et al reported on 28 patients with L-SCLC who underwent salvage surgery following either a PR to chemotherapy or subsequent progressive disease.[61] Ten of these 28 patients had NSCLC elements in their specimen. Their 5-year survival rate was 23%. There are only anecdotal data regarding surgical salvage of patients initially treated with both chemotherapy and TRT. Although there may be a role for resection in patients with stages I or II SCLC, it is unclear that surgical intervention would provide a benefit when compared to TRT for similar volumes or stages of disease. While it appears that some patients may be salvaged after a PR or local failure, resection has not been widely employed. This may be as a result in part of the propensity of SCLC to metastasize.

Prophylactic Cranial Irradiation for Both L-SCLC and E-SCLC

PCI was initially introduced into practice in the 1960s for patients with acute lymphoblastic leukemia who had a high risk of failure in the central nervous system (CNS).[62] It was first tested for patients with SCLC in the 1970s following the recognition that brain metastases were frequent. The blood-brain barrier prevents the penetration of most chemotherapeutic agents leaving the brain as a sanctuary site for relapse.

PCI has been shown to improve survival of patients who achieve a CR. Auperin et al published a meta-analysis that included data from seven Phase III studies that compared PCI to no PCI after a CR was achieved.[63] As in the TRT meta-analyses, the 3-year survival rate was 5.4% better for those who received PCI at 20.7% compared with 15.3% for those with no PCI ($p = 0.01$). Although 5.4% appears small, it does reflect a 35% increase in 3-year survivors.

PCI is important for the majority patients with E-SCLC. Slotman et al conducted a randomized trial (EORTC 08993-22993) of PCI in patients with E-SCLC who had had any degree of response to chemotherapy.[64] Patients received either PCI or no further therapy (control group). The PCI included 20 Gy in 5 to 8 fractions, 24 Gy over 12 fractions, 25 Gy in 10 fractions, or 30 Gy over 10 or 12 fractions. The cumulative risk of brain metastases within 1 year was 14.6% in the PCI group and 40.4% in the control group (hazard ratio, 0.27; $p < 0.001$). PCI was associated with an increase in median survival from 5.4 months to 6.7 months. The 1-year survival rate was 27.1% in the PCI group and 13.3% in the control group ($p = 0.003$). PCI had side effects but did not have a significant effect on global health status. The largest mean difference between the two arms was observed for fatigue and hair loss, which were greater with PCI.[65] PCI reduced brain metastases and prolonged survival.[64] PCI should be standard care for all patients with SCLC who have any degree of favorable response to initial chemotherapy. This trial did not evaluate which dose-fractionation regimen was best.

The optimal PCI regimen would include the following desirable characteristics: decreases brain metastases, increases survival, takes the least time from the patients' remaining life, decreases cost, and causes the least toxicity. An international consortium studied dose-fractionation in a Phase III trial. Le Pechoux reported the results of this study that compared standard to higher doses of PCI. This trial included 720 patients with L-SCLC in CR after chemotherapy and TRT. Patients were assigned to either standard ($n = 360$, 25 Gy over 10 fractions) or high-dose PCI ($n = 360$, 36 Gy). The high-dose PCI was either conventional (18 daily fractions of 2 Gy) or accelerated hyperfractionated (24 twice-daily fractions of 1.5 Gy) regimens. There was no significant difference in the 2-year incidence of brain metastases between the standard PCI group and the higher-dose group at 29% and 23%, respectively ($p = 0.18$). The 2-year overall survival was 42% in the standard-dose group and 37% in the higher-dose group ($p = 0.05$). The most common acute toxic events were fatigue, 30% in the standard-dose group compared to 34% in the higher-dose group, headache 24% compared to 28%, and nausea or vomiting 23compared to 28%. They concluded that although there was not a significant decrease in brain metastases after higher-dose PCI, there was a significant increase in mortality. Therefore, they concluded that PCI at 25 Gy over 10 fractions should be the standard of care for SCLC.[66] Although this trial did not address the effects of dose-fractionation for patients with E-SCLC, it is still the most compelling data available regarding the regimen used for PCI for patients with SCLC. While the 25 Gy in a 10-fraction regimen did not meet all the characteristics for the optimal regimen, it was associated with better survival, decreased patient time required, and decreased healthcare costs.[66]

Based on the currently available data, it is recommended that patients with SCLC achieving any degree of response to initial therapy should be offered PCI.[67] The current standard dose-fractionation pattern is 25 Gy over 10 fractions.[67,68] There are also data from a pooled retrospective NCCTG analysis that found that PCI benefits patients who have stable disease after initial therapy. Thus, it appears likely this group of patients benefits from PCI as do those with a favorable response.[67]

MANAGEMENT OF METASTATIC AND RECURRENT DISEASE

Approximately two thirds of all patients with SCLC have extensive-stage disease.[2] The most common sites of extrathoracic metastases are the liver, bone, brain, and adrenal glands.

Initial management of most patients with newly diagnosed ESCLC is four or more cycles of EP. Novel targeted agents are the focus of much research and it is hoped that newer agents will improve outcomes. Second-line chemotherapy often includes topotecan because this was proven superior to best supportive care in patients failing initial therapy.[69]

The Role of Non-CNS Radiotherapy for E-SCLC

RT also has important use for E-SCLC. One role for RT is to palliate bulky intrathoracic disease causing airway compromise, cough, hemoptysis, postobstructive pneumonia, or SVC syndrome. This is often accomplished with a short regimen such as 30 Gy over 10 fractions (or shorter), which will improve symptoms in the majority of patients.

Although the role of TRT is less clear in patients with E-SCLC, there appears a distinct survival benefit to delivering TRT to carefully selected patients. Jeremic et al performed a Phase III study that evaluated chemotherapy with or without TRT in patients with E-SCLC. Patients initially received three cycles of carboplatin and etoposide. Those patients with a CR at distant sites and a PR or better in the chest were randomly assigned to receive either twice-daily TRT (54 Gy in 36 fractions) plus concurrent carboplatin and etoposide followed by two cycles of the same chemotherapy or four cycles of the same chemotherapy without TRT. All patients with a CR at the distant sites also received PCI. Patients who received TRT had significantly better survival than those who did not (median survival time, 17 versus 11 months; 5-year survival rate, 9.1% versus 3.7%; $p = 0.041$).[70] This study revealed improved survival from TRT in carefully selected patients with E-SCLC. It appears that patients who benefit are those for whom the RT encompassed all known residual disease within the body.

The hypothesis that RT can be added to chemotherapy to more effectively treat E-SCLC was evaluated further in a Mayo Clinic Trial. Bonner et al performed a trial that explored the use of RT for both the thoracic and metastatic lesions. This study included an aggressive regimen of seven cycles of an alternating six-drug combination. The first cycle consisted of cyclophosphamide, doxorubicin, etoposide, vincristine, and lomustine. Subsequent cycles used a regimen of doxorubicin alternating with cisplatin.[71] PCI and TRT were given during the chemotherapy. PCI was delivered during the first week of chemotherapy cycles two and three (17 Gy in 5 fractions, each of 3.4 Gy, during each week for a total of 34 Gy in 10 fractions). The TRT was delivered in a split-course fashion during the first week of chemotherapy cycles five and six (20 Gy over 5 fractions, each of 4 Gy, during each week for a total of 40 Gy in 10 fractions). After the seven cycles, patients received 6 Gy in 1 fraction upper hemibody RT followed by 8 Gy in 1 fraction lower hemibody RT. Thirteen patients completed the initial seven cycles. Two of the 20 (10%) patients had fatal hematologic complications after lower hemibody RT. Three (15%) patients had severe peripheral neurologic toxicity, two (10%) had severe central nervous system toxicity, and one (5%) had severe cardiac toxicity. The median survival time was 11.5 months and 5-year survival rate was 16%.

There are valuable lessons to be learned from these data. First, this therapy was toxic. The collective hematologic toxicity from six drugs combined with the TRT, PCI, and sequential

upper and lower hemibody RT resulted in 10% (2 of 20 patients) mortality. Irradiating the entire marrow led to excessive marrow suppression, toxicity, and mortality. Additionally, the PCI regimen (34 Gy in 10 fractions) given during chemotherapy was associated with an unacceptably high risk of leukoencephalopathy.[72] It appears best to administer the PCI after all other therapy because concurrent chemotherapy plus PCI further increases the risk of leukoencephalopathy. Despite the toxicity issues, the finding that the 5-year survival of 16% was much better than other trials for patients with E-SCLC. It is quite possible that RT to the sites of initial disease or areas of residual disease that persist after chemotherapy could be helpful, because failures following chemotherapy alone frequently occur in the sites of original disease and RT lowers the risk of such recurrences. This is the basis of a currently opened RTOG trial 0937, a Phase II trial for patients with E-SCLC and four or fewer distant metastases. This randomized trial compares chemotherapy followed by either PCI (standard arm) or PCI plus TRT and involved field RT to all sites of remaining disease after chemotherapy. The primary endpoint is survival.

The Treatment of Metastases

Patients with brain metastases at diagnosis require cranial RT in their initial management, usually concurrently with the first or second cycle of chemotherapy. The whole-brain RT doses most commonly used for brain metastases range from 20 Gy in 5 fractions to 37.5 Gy in 15 fractions. The majority of patients receive effective palliation as a result.

Patients with a few or solitary primary or recurrent brain metastases can be considered for more aggressive treatment options such as radiosurgery. There is little data addressing specialized therapy such as radiosurgery for patients with SCLC. Sheehan performed a retrospective review of 27 patients with 47 recurrent SCLC brain metastases who underwent radiosurgery.[73] The overall median survival was 18 months after the diagnosis of brain metastases. They concluded that radiosurgery for recurrent SCLC metastases provided effective local tumor control in the majority of patients.

One particular subgroup of patients with E-SCLC included those with disease limited to the chest and the brain only. This group may benefit from the use of chemotherapy, whole-brain RT, and TRT. Kochhar et al identified 30 such patients who initially received cisplatin-based chemotherapy and concomitant whole-brain RT consisting of 36 Gy to 48 Gy.[74] Subsequently, 22 patients also received TRT. The median survival was 14 months. The outcome of patients with E-SCLC with the brain as the sole site of metastases at diagnosis was similar to patients with L-SCLC. Of this cohort, patients who received TRT tended to have a longer median survival (16 months) than those who did not receive TRT or who received it at the time of local disease progression (12 months; $p = 0.3$). This concept of treating E-SCLC with chemotherapy and irradiating all known gross disease probably explains the favorable results in the study of Kochhar et al and the extraordinary 5-year survival rate of 16% achieved in the Mayo Trial reported by Bonner et al.[71] Currently, the RTOG is performing RTOG 0937, previously described, to more fully evaluate the role of RT for carefully selected patients with E-SCLC.

Sites of metastatic involvement may also require palliative RT for effective symptom management. These include painful or weight-bearing bony lesions, symptomatic adrenal metastases, or soft-tissue masses. Lesions causing any debilitating symptoms can be considered for palliative RT.

SVC syndrome may also develop in patients with SCLC. This appears more frequent with this histology than others as a result of a propensity to develop bulky mediastinal adenopathy. Chan et al reported on 76 consecutive patients with SCLC with SVC syndrome,[75] and 93% had improvement in SVC symptoms after chemotherapy compared with 94% after TRT. Additionally, a favorable response was obtained with a wide range of RT fractionation patterns and total doses administered. Those who received chemotherapy and TRT had a longer time to recurrence of SVC syndrome ($p = 0.018$) compared to those who received chemotherapy alone. The early mortality from SVC syndrome was 2%. Chemotherapy or TRT was effective initial treatment in patients with SCLC with SVC syndrome. They also concluded that there is no need to use large radiation fraction sizes for the first few treatments. TRT resulted in more durable palliation than achieved with chemotherapy alone. This study debunked the myth that RT needs to begin emergently within hours. It is preferable to begin chemotherapy quickly and take adequate time for optimal RT treatment planning. This will decrease the normal tissue volumes within the fields and insure that the entire tumor is irradiated.

Management of Recurrent SCLC

The prognosis of any patient with recurrent SCLC is grave, regardless of the site of relapse. Although there are responses noted to second-line chemotherapy, these responses are usually short-lived and often precede rapid tumor progression. Palliative or salvage RT or re-RT (including reirradiating brain metastases) can be of substantial benefit to such patients.

TECHNIQUES OF IRRADIATION

Treatment is dependent on accurate identification of the disease and a clear understanding of its exact distribution with relationship to normal structures. The combination of PET scans and CT imaging are helpful in defining the extent of disease except within the brain. Within the chest, functional imaging (PET) allows better detection of viable tumor within a structure and the CT is better to define the exact extent and location of these structures. Incorporating both PET and CT scans into RT planning can be used to generate smaller, more precise tumor fields that may further decrease toxicity while treating all gross disease with RT. Over time, improvements in imaging allow physicians to more precisely locate and irradiate all sites of disease.

Treatment Volumes and Normal Tissue Considerations

The ability of a patient with L-SCLC to tolerate increasingly aggressive RT regimens and higher total doses during concurrent chemotherapy is in part related to improved TRT target volume selection.[35] There emerged evidence in the 1980s and 1990s that the use of smaller radiation fields did not adversely influence tumor control in patients receiving concurrent cisplatin-based chemotherapy. The fields employed in Intergroup Trial 0096 confined the high-dose volume to the tumor with a 1.5-cm margin, the ipsilateral hilum, and the mediastinum from the thoracic inlet to the subcarinal region. The contralateral hilum and supraclavicular regions were excluded. These treatment volumes have been widely adopted in subsequent clinical trials.

Smaller volumes have the advantage of further sparing of the surrounding normal tissues: lung, esophagus, heart, spinal cord, and bone marrow (Figure 43-1). Optimal sparing is important to decrease the high risk of severe morbidity from therapy. We compiled the toxicity experienced by patients treated on NCCTG 89-20-52, which included concurrent chemotherapy plus either daily or twice-daily TRT. The most common toxicity was hematologic; 90% of patients had grade

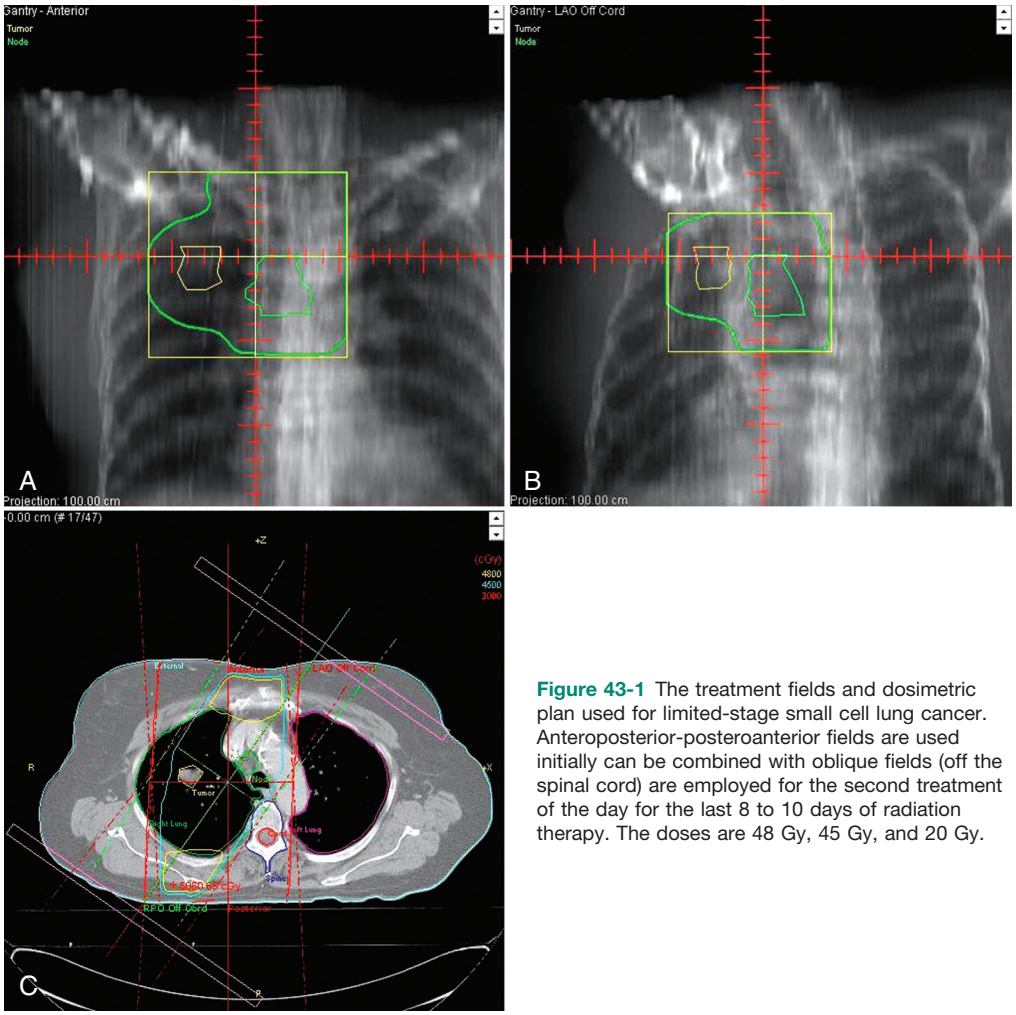


Figure 43-1 The treatment fields and dosimetric plan used for limited-stage small cell lung cancer. Anteroposterior-posteroanterior fields are used initially can be combined with oblique fields (off the spinal cord) are employed for the second treatment of the day for the last 8 to 10 days of radiation therapy. The doses are 48 Gy, 45 Gy, and 20 Gy.

3 or greater (3+) hematologic toxicity and 43% had grade 4+ hematologic toxicity. Forty-seven percent of patients had grade 3+ nonhematologic toxicity and 11% had grade 4+ nonhematologic toxicity. Nausea, vomiting, and esophagitis were the most common nonhematologic toxicities. Fatal toxicity occurred in four patients (2%) of patients.[41] Thus, smaller, more precise fields are needed to deliver therapy more safely. Prospective trials in Europe have evaluated an approach of "involved field" radiotherapy in LSCLC. An initial trial using CT directed radiotherapy fields reported an 11% isolated nodal relapse, whereas isolated nodal relapse was only 3% in a follow-up study that included both CT– and FDG-PET–based disease.[76-78] The current Phase III trial, CALGB 30610, does not employ elective mediastinal radiotherapy, though level 1 evidence regarding elective nodal irradiation is lacking.

RT-induced toxicity is related to dose-volume parameters. In a classic study, Graham et al reported that the risk of grade 2+ pneumonitis was 0% when the V20 (total lung volume that received ≥20 Gy) was <22%, 7% when the V20 was 22% to 31%, 13% when the V20 was 32% to 40%, and 36% when V20 was >40%.[79] The ongoing Phase III study (CALGB 30610) recommends limiting the V20 lung to <40%, although this can be difficult to achieve when bulky disease is present. It is generally accepted that the spinal cord can safely receive 45 Gy to 50 Gy in 1.8 Gy to 2.0 Gy fractions. In most twice-daily TRT regimens employing 1.5 Gy fractions, the spinal cord is limited to 36 Gy to 37 Gy without incident.[41] In the Intergroup 0096 regimen, the oblique off cord fields were used for the second daily treatment for the last 8 to 10 treatments. The TD5/5 (toxic dose to 5% of patients in 5 years) was estimated at 60 Gy for one third of the heart, 45 Gy for two-thirds of the heart, and 40 Gy for the entire heart.[80] Esophagitis is related to the dose of radiation, volume of esophagus irradiated the fractionation schema, and the timing of chemotherapy. Of the patients in the Intergroup Trial 0096 who received twice-daily TRT, 32% had grade 3+ esophagitis compared with 16% for those who received twice-daily TRT ($p = 0.001$).[40] Although esophagitis is uncomfortable, can lead to dehydration, and the need for intravenous hydration or hospitalization, this should not be used as reasons to deny fit patients twice-daily TRT.

Watkins described the factors associated with development of severe acute esophagitis during twice-daily TRT with concurrent chemotherapy in patients with L-SCLC. Twice-daily chemoradiotherapy included 45 Gy at 1.5 Gy twice daily with concurrent platinum-based chemotherapy. The most strongly associated dosimetric variable was the V15 (grade 3 esophagitis rates of 15% versus 64% for V15 <60% versus >60%, respectively).

TREATMENT ALGORITHM, CONTROVERSIES, PROBLEMS, CHALLENGES, FUTURE POSSIBILITIES, AND CLINICAL TRIALS

A proposed treatment algorithm for patients with SCLC is shown in Figure 43-2.

L-SCLC with Good Performance Status and TRT

The management of SCLC is dependent on stage and medical fitness. For patients with good performance status and L-SCLC, the recommended therapy would include concurrent TRT with EP chemotherapy. Specifically, the treatment with the best evidence justifying its use is four cycles of EP chemotherapy with twice-daily TRT beginning early.[31,32] The twice-daily TRT is delivered in 1.5 Gy fractions with an interfraction interval of more than 6 hours to a total dose of 45.0 Gy. This recommendation is based on the Intergroup Trial 0096.[40] The Cancer and Leukemia Group B/Radiation Therapy Oncology Group trial (CALGB 30610/RTOG 0538) and CONVERT trial will help determine which of two TRT regimens is best.

For patients with huge tumors, postobstructive pneumonia, or atelectasis, there may be value in delaying initiation of TRT until a later cycle of chemotherapy. This may be necessary in some cases if the initial tumor volume would require an excessive volume of normal lung to be irradiated. It is unknown if adding TRT improves the outcome of the rare patient with resected L-SCLC. However, chemotherapy is generally administered after resection.

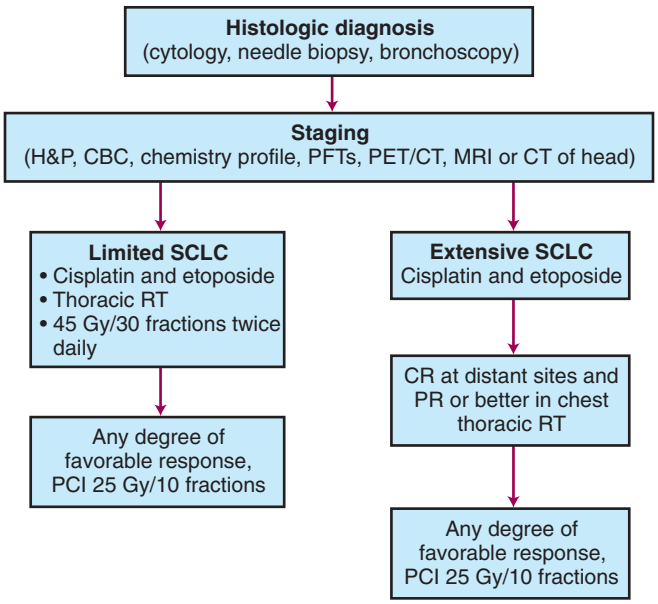


Figure 43-2 Treatment algorithm for small cell lung cancer. *CBC,* Complete blood counts; *CR,* complete response; *CT,* computed tomography; *MRI,* magnetic resonance imaging; *PCI,* prophylactic cranial irradiation; *PET,* positron emission tomography; *PFT,* pulmonary function test; *PR,* partial response; *RT,* radiotherapy; *SCLC,* small cell lung cancer.

L-SCLC in Special Populations: The Elderly and Those with a Lower Performance Status

Treatment in fit elderly patients (>70 years of age) can be carried out in a manner similar to fit younger individuals. NCCTG 89-20-52 included 263 patients with L-SCLC and an ECOG performance status of <2 who were randomized to daily TRT or split course twice-daily TRT. The outcomes of the younger patients (<70 years old) were compared to the elderly patients (>70 years old). The overall incidence of grade >3 (3+) or grade >4 (4+) toxicity was not significantly greater in elderly patients. One specific toxicity, grade 4+ pneumonitis occurred in 0% of those <70 years compared to 6% of older patients ($p = 0.008$). Grade 5 toxicity occurred in 3 of 54 (5.6%) patients >70 years old compared with 1 of 209 (0.5%) younger individuals ($p = 0.03$). Overall survival was not significantly worse in older individuals; the 5-year survival rates were 22% in younger patients compared with 17% in older patients ($p = 0.14$). Fit elderly patients with L-SCLC can receive combined-modality therapy, if carefully monitored, with a reasonable expectation of 5-year survival.[81]

Patients with lower performance status tolerate the aggressive twice-daily TRT and EP more poorly. However, there is still a likely benefit to concurrent chemoradiation for these patients, particularly if their reduced functional status is as a result of tumor. One alternative would be to deliver daily TRT in 1.8 Gy 2.0 Gy fractions to 50 Gy to 70 Gy, while sparing the spinal cord above 45 Gy to 50 Gy. This could be delivered beginning with the first or second cycle of chemotherapy. Judgment and flexibility are critical when treating very old (≥80 years) or patients who are have poor performance status. It is also reasonable to administer sequential therapy to patients who can not tolerate the rigors of concurrent therapy.

E-SCLC and TRT

Initial management of E-SCLC involves primary chemotherapy (EP), with RT being reserved for brain metastases, bulky and symptomatic intrathoracic disease, and symptomatic bony or visceral metastatic sites. In addition, patients with a good performance status, a CR of metastatic disease, and at least stable disease in the chest following chemotherapy may benefit from the addition of TRT.[70]

Prophylactic Cranial Irradiation for Both E-SCLC and L-SCLC

PCI should be considered for all patients with SCLC who have achieved any degree of favorable response following initial management with chemotherapy or chemoradiation; 25 Gy in 10 fractions is considered the most standard regimen.[66]

Controversies and Clinical Trials

Issues addressed in current clinical trials include the potential benefits of higher dose daily TRT regimens in the management of L-SCLC. In E-SCLC, most research focuses on systemic therapy. However, there is a trial open examining whether patients benefit from the administration of RT to the chest and sites of residual disease plus PCI compared to PCI alone following systemic chemotherapy.

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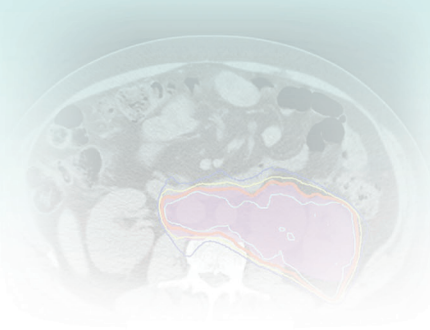
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CHAPTER

44 Non–Small Cell Lung Cancer



Henry Wagner, Jr. and Corey Jay Langer

EPIDEMIOLOGY AND PATHOLOGY

An estimated 228,190 new cases and 144,570 deaths from lung cancer occurred in the United States in 2013. Fifteen percent of patients will be alive at 5 years. Because of a decline in smoking rates over the past 40 years, the incidence and death rates in the United States have begun to decline for white men, but they remain stable or are rising in other demographic groups. An increasing percentage of patients with newly diagnosed lung cancer are ex-smokers. In clinical trials, this demographic often constitutes more than half of those enrolled. Although the majority of lung cancers are associated with current or prior tobacco use, lung cancer in persons who have never smoked is often a distinct molecular and clinical entity and accounts for close to 20% of all cases. Lung cancer is an increasing cause of illness and death worldwide, where smoking rates are often much higher than in the United States.

Three histologic types—squamous cell carcinoma, adenocarcinoma (including bronchioalveolar), and large cell undifferentiated carcinoma—comprise non–small cell lung cancer (NSCLC).[1]

BIOLOGIC CHARACTERISTICS

Genetic or epigenetic alterations have been described in NSCLC and in premalignant lung tissues exposed to tobacco smoke. Distinct patterns of genetic and epigenetic modifications have been described for squamous cell and adenocarcinoma. Genomic profiling of lung cancer complements anatomic staging in predicting prognosis and dictating treatment. The biologic subtypes of NSCLC have clinical implications in terms of chemotherapy regimens and targeted therapeutic strategies. Diagnostic biopsies should include sufficient material to allow molecular characterization of the tumor.

STAGING

The TNM system underwent major revisions in 2009. Combined positron emission tomography (PET) using ^{18}fluorodeoxyglucose (^{18}FDG) and computed tomography (CT) is the preferred study for evaluation of the primary tumor and metastatic disease. False-positive rates of 20% to 30% dictate that patients not be denied potentially curative treatment solely on the basis of radiographic findings without histologic confirmation.

PRIMARY THERAPY FOR EARLY-STAGE DISEASE

Anatomic resection, either lobectomy or pneumonectomy, with thorough sampling or formal dissection of hilar and mediastinal nodes remains the preferred treatment in patients with clinical stage IA to IIB NSCLC. Patients with medical contraindications to surgery should be offered radiation therapy (RT), with or without chemotherapy, with curative intent. Hypofractionated stereotactic beam radiotherapy (SBRT) shows promise for lesions up to 5 cm in the absence of nodal spread, with local control and survival rates rivaling those of surgery.

ADJUVANT AND NEOADJUVANT THERAPY

Postoperative RT (PORT) of ipsilateral hilar and mediastinal lymph node reduces the risk of local recurrence in patients with resected node-positive NSCLC. A small survival benefit for patients with N2 disease has been suggested in retrospective analyses, but this remains controversial and has not been adequately tested in prospective trials. PORT is not indicated for patients with N0 or N1 disease. There is a significant survival benefit for adjuvant chemotherapy using platinum-containing regimens (North America and Europe) or tegafur and uracil (Japan), and such therapy should be offered after resection to patients with good performance status with resected stage N1 and N2 disease and strongly considered for those with N0 tumors whose size exceeds 4 cm. For patients with resectable but poor-prognosis disease (stages IIB to IIIA), neoadjuvant chemotherapy or chemoradiation has been investigated. For patients with more advanced mediastinal disease (N2 or N3, selected T4, N0 to N1 with direct mediastinal invasion), either definitive chemoradiation or surgery after induction chemotherapy or chemoradiation are acceptable options with similar overall survival (OS) but differing patterns of failure and morbidity. Brain metastases are common in patients with NSCLC; however prophylactic cranial irradiation (PCI)—although decreasing central nervous system (CNS) failure—has not been shown to improve OS and is not standard therapy.

LOCALLY ADVANCED DISEASE

Most patients with stage IIIB or unresectable stage IIIA disease are treated nonsurgically with irradiation and chemotherapy, with a 10% to 20% long-term survival rate for patients with good performance status and no significant weight loss. Combinations of RT and sequential or concurrent chemotherapy are superior to RT alone. Concurrent chemoradiation yields superior median and long-term survival than sequential therapy.

PALLIATION

External beam irradiation (EBRT) effectively palliates local symptoms or metastases to bone or brain. Hypofractionated regimens are effective and well tolerated. Endobronchial irradiation or photodynamic therapy can relieve obstruction or hemoptysis. Chemotherapy with a platinum-based doublet can extend survival and relieve symptoms and improve quality of life. Molecularly targeted agents are highly active in appropriate patients. Epidermal growth factor receptor–tyrosine kinase inhibition (EGFR–TKI) are the therapy of choice for patients whose tumors harbor EGRF-activating mutations. Likewise, crizotinib has become the standard approach for patients whose tumors harbor ELM4/ALK or ROS1 translocations.

INTRODUCTION

Lung cancer killed an estimated 144,570 men and women in the United States in 2013, more than colon, breast, prostate, and pancreatic cancer combined.[1] More than 80% of these cases were caused by habitual or environmental exposure to tobacco smoke.[2] This common origin makes lung cancer a disease better suited to prevention than treatment. However, non–tobacco-associated lung cancer (NTLC) is not a rare disease; these include about 40,000 cases per year in the United States and an even greater percentage of total lung cancer cases in Asia. NTLC frequently differs at a molecular level from tobacco-associated NSCLC, and these differences have clinical and therapeutic implications.

The reduction of lung cancer deaths in white American men over the past two decades has resulted more from the decrease in cigarette smoking after the publication of the U.S. Surgeon General's report in 1964 than from major advances in the efficacy of therapy or early detection, although this may be changing. Recent data from the National Lung Screening Trial (NLST) have shown reduction of lung cancer deaths with low-dose CT screening of high-risk populations.[3]

Although the results of current therapy are frustrating, they must not be viewed nihilistically. Adjuvant treatment in resected NSCLC has resulted in a modest but statistically significant and clinically meaningful improvement in survival, especially those with nodal involvement. In locally advanced NSCLC, concurrent chemoradiation has led to a substantive increase in long-term survival, particularly in patients with good prognosis with intact performance status (PS) and minimal weight loss. Finally, in advanced or recurrent NSCLC, modern systemic therapy has both prolonged life and enhanced quality of life. These incremental improvements in therapy have helped many individuals diagnosed with NSCLC. Although avoiding tobacco use is the most efficient strategy for reducing lung cancer deaths, it is clearly worthwhile to optimize current therapeutic modalities of surgery, irradiation, and chemotherapy. Even if all current smokers quit smoking this instant, their previous carcinogen exposure would lead to another million or more cases of lung cancer over the next 30 to 50 years. Thus, the need for more effective treatment will continue into the foreseeable future.

Advances in multiple disciplines include tumor biology techniques that enable both identification and selective treatment of particular molecular entities within the broad spectrum of diseases termed lung cancer, imaging and treatment delivery technologies that better identify where to put the dose and deliver it accurately and reproducibly (or adaptively to a target size and shape that is changing over time), and a growing willingness of specialists of all modalities to work collaboratively for their patients' benefit. The development of interventions to facilitate such continuity of care and communication to patients and with other care providers is gaining attention.[4] The key to improving treatment is the integration of diagnostic and treatment modalities by a team whose members are interested in lung cancer and its treatment, well versed in the application of the appropriate modalities, and able to combine them without undue bias.[5,6] This interdisciplinary approach and the expertise, dedication, and collaboration it mandates is the vital to optimizing therapy for our patients. The development of advocacy groups such as the Lung Cancer Alliance and their endorsement by other groups such as the American Academy of Chest Physicians should hasten this becoming the standard of practice, as is already the case for patients with breast and prostate cancers.

ETIOLOGY AND EPIDEMIOLOGY

More than 80% of lung cancer can be attributed to carcinogens in tobacco smoke. Habitual and environmental exposures are clearly linked to lung cancer at levels ranging from descriptive epidemiology, characteristic patterns of oncogene and tumor suppressor gene mutations, and measurement of tobacco-associated carcinogens in the urine of individuals exposed to second-hand smoke.[7-10] It has been speculated that up to a third of lung cancers in those who never smoked may be attributable to secondary exposure.[11] Hecht et al showed that nonsmokers, when exposed to side-stream smoke in concentrations comparable to those found in a smoky room, excreted metabolites of tobacco-specific carcinogens in their urine.[12] Pipe and cigar smokers have lower lung cancer rates than cigarette smokers, but these habits are far from innocuous, particularly in former cigarette smokers, who often continue to inhale.

The risk of lung cancer is related to the amount smoked daily and the duration of smoking, leading to the term *pack-years* as a measure of smoking exposure. When individuals quit smoking, their risk of lung cancer declines over at least a decade but remains higher than that observed in those who never smoked.[13-15] Lung cancer incidence and death rates typically reflect smoking behavior from two to three decades previously. Examination of the respiratory epithelium of former smokers years after quitting shows persistence of telltale patterns of genetic and epigenetic change.[16,17] Once initiated, the process of lung carcinogenesis can proceed without continued smoke exposure. This has led to the ironic observation in the new millennium that the majority of cases of lung cancer are diagnosed in former smokers rather than current smokers.

Current epidemiologic efforts are devoted to better understanding the molecular determinants of risk distal to smoke exposure, including metabolic activation of procarcinogens, degradation and excretion of carcinogens, accurate repair of damaged DNA (or apoptotic execution of cells harboring DNA damage), and other less-well-understood mechanisms that result in the development of lung cancer in some but not all heavy smokers.[18-20] Although no single genetic abnormality has been clearly implicated in causing lung cancer, there is considerable epidemiologic evidence for an inherited component of risk, particularly for cases of lung cancer diagnosed in younger individuals.[21] Polymorphisms in a variety of enzymes involved in the metabolism of potential carcinogens, their detoxification, and in DNA repair enzymes have been associated with risk of lung cancer in a number of small studies of both smokers and nonsmokers but no clear risk pattern has been replicated in large populations.

Smokers with chronic obstructive pulmonary disorder (COPD) are at significantly higher risk for lung cancer than individuals with similar smoke exposure without COPD.[22] It is not known whether this reflects a common behavioral cause (e.g., deeper smoke inhalation, longer smoke retention) in these individuals or if there are differences in metabolism of components of tobacco smoke that increase the risk for both COPD and lung cancer.

Several recent studies have shown that a polymorphism in the nicotinic receptor gene cluster in the chromosome 15q24-25 region is strongly associated both with nicotine dependence and the development of both COPD and lung cancer.[23] Such associations have been seen in European, African, and Asian populations. Whether this locus is directly involved in tobacco carcinogenesis or indirectly mediated through strength of nicotine dependence is not yet clear and both direct and indirect mechanisms may be involved.[24]

In addition to tobacco smoke, many other substances have been implicated in causing lung cancer. Several industrial

chemicals, particularly the chloromethyl ethers, have been associated with lung cancer. Exposure to both asbestos and tobacco smoke produces lung cancer more frequently than either exposure alone. Exposure to inhaled radioactive substances by uranium miners or by individuals living in areas with high endogenous radon levels also increases risk.

Lung cancer has been reported in a number of patients with human immunodeficiency virus (HIV) infection, but there is no strong evidence for a direct causative role. Lung cancer is not particularly common in individuals otherwise immunosuppressed, such as after organ transplantation. Individuals who are HIV positive with lung cancer tend to be younger than other patients, almost always have a history of heavy tobacco use, tend to present with advanced-stage disease (80% stages III and IV), show a predominance of adenocarcinomas, and have a poorer prognosis, even for the minority who present with early-stage disease. The tolerance of these patients to treatment, particularly to aggressive chemoradiation may be compromised by limited hematologic reserve and development of severe mucositis during and after RT.[25]

Although lung cancer was formerly a predominately male disease, its incidence and death rates in women began to rise in the United States in the 1960s, and since 1987, the death rate from lung cancer in women has exceeded that of breast cancer.[26] In the United States, the incidence of lung cancer in men increased through much of the 20th century until leveling off and then starting to decline in the 1980s. In women, the incidence rose steadily through the latter part of the past century but appears to be plateauing in the United States and Europe.

Although most cases of lung cancer occur in individuals with a history of tobacco use, lung cancer in those who have never smoked or in minimal smokers is far from a rare disease. It represents 15% to 20% of lung cancer seen in North America and Europe and up to 40% in parts of Asia. In the United States, 20,000 individuals each year die from non–tobacco-associated lung cancer, which, based on this simple math would make this entity the fifth-most common cause of cancer death. The clinical and molecular characteristics of lung cancer arising in persons who have never smoked or in minimal smokers are generally distinct from those of tobacco-associated lung cancer and warrant separate therapeutic strategies.[27-29]

MOLECULAR BIOLOGY OF LUNG CANCER

The past decade has seen dramatic changes in our understanding of the molecular genetics of lung cancers. Multiple genetic changes have been identified in lung cancers and cell lines derived from them and several distinct pathways of oncogenic development, both for squamous cell and adenocarcinoma, have been proposed.[30-32] The morphologic and clinical differences between the various types of NSCLC are reflected in decidedly different patterns of oncogene and tumor suppressor genes modifications in these disease families, and we are moving to a reclassification of NSCLC along patterns of genomic expression rather than light microscopic appearance. The old category of "large cell undifferentiated" NSCLC is now becoming increasingly infrequent as molecular characteristics of these tumors classify them as squamous or adenocarcinoma.[29-31] To an increasing extent we are moving from an early emphasis on identifying abnormalities in single genes to genomewide analysis and targeting of pathways rather than single enzyme or receptor targets. Although there are no absolute differences or characteristic mutations for either type, in the way that the *BCR-ABL* translocation is relatively pathognomonic of chronic myeloid leukemia, some molecular abnormalities frequent in one histologic type are rare in another.[33-35]

Molecular Changes

RAS

The *RAS* oncogene family contains three members, *HRAS*, *KRAS*, and *NRAS*, which encode membrane-associated proteins involved in mediation of signals arising from binding of ligands to cell membrane receptors such as epidermal growth factor receptors (EGFRs) to nuclear transcription factors.[36] Mutation in several specific sites, including codons 12, 13, and 61, lead to constitutive activation of these signaling pathways. In lung cancer, mutations are most commonly seen in *KRAS*.[37] They are most frequently seen in adenocarcinoma but are also seen in other NSCLC histologies. They are seen almost exclusively in smokers and rarely if ever in those who have never smoked whose tumors contain EGFR mutations. Patients whose lung cancers contain mutated *KRAS* almost never respond to EGFR-TKI, but it is not clear that they are resistant to cetuximab as is the situation in colorectal cancer.[38] The presence of mutated *RAS* genes has been an adverse prognostic factor in resected and advanced lung cancer in most series in which this has been assessed.[39] *RAS* mutations are rare in small cell lung cancer (SCLC), and when detected, they may represent an admixture of NSCLC elements or the development of an intermediate SCLC line.[40]

TP53

Abnormalities in *TP53* function through deletion or mutation of the gene or overexpression of *MDM2* leading to aberrant *TP53* inactivation are among the most common genetically induced changes in human malignancies.[41] Mutations are reported in a high frequency in lung cancer, about 50% of NSCLCs, and 90% of SCLCs.[42] Different patterns of mutation (e.g., ratio of transitions to transversions) are seen in smokers and in persons who have never smoked, suggesting different mutagens. Normal *TP53* plays several key roles in determining cellular response to genetic damage, particularly whether cells enter growth arrest or apoptosis. There have been conflicting reports about the prognostic implications of abnormal *TP53* function in lung cancer. For a number of chemotherapeutic agents and ionizing radiation, cells lacking normal *TP53* function are resistant to apoptotic cell death, although the effect on overall cell survival is controversial.[43-45]

RB1

The *RB1* gene–encoded product (RB) is a nuclear protein that undergoes cyclic phosphorylation and dephosphorylation during the cell cycle under the control of G_1 cyclins.[46,47] RB regulates E2F1 transcription factor activation. Absence of normal function occurs in most SCLCs but only in about 10% of NSCLC lines examined.[48-50]

CDKN2A

Normally, *CDKN2A* (previously designated *p16*) regulates transcription through phosphorylation of the RB1 protein. Abnormalities of *CDKN2A* function are reported in a reciprocal fashion to those of RB1; they are common in NSCLC and rare in SCLC. Because either of these abnormalities can allow uncontrolled transcriptional activation through E2F, it is not surprising that they are not commonly found together.[51] Although mutations in either are common in lung cancer, these mutations have not been correlated with prognosis.

Growth Factors

Abnormalities in normal growth factor signaling pathways have been proposed as a common mechanism for the dysregulated cell growth in cancer. In lung cancer, several clear

examples of this have been demonstrated to exist and have become targets for possible therapeutic intervention.

Epidermal Growth Factor Receptor

EGFR mediates a number of signaling pathways critical for cell growth, survival, and response to cytotoxins, including ionizing radiation and several chemotherapeutic agents. It is overexpressed in a variety of malignancies, and overexpression has been correlated with poorer clinical outcome and resistance to radiation. Clinical attempts to target this pathway have included monoclonal antibodies targeted to the extracellular domain of the receptor (C225, ABX) and low-molecular-weight compounds that bind the adenosine triphosphate (ATP) site and inhibit the tyrosine kinase activity of the receptor. About 10% of patients with NSCLC have mutations involving the ATP-binding pocket of the EGFR, which gives rise to more prolonged signaling activity in response to ligands such as epidermal growth factor (EGF) or transforming growth factor–beta and causes them to bind these inhibitors more tightly.[52-54] Such activation mutations are seen primarily in individuals with no or minimal smoking history and in Asian women and are more common in adenocarcinomas than squamous cell carcinoma. Patients whose tumors have these mutations are likely to have significant objective responses to treatment with compounds that target this pathway, but it is postulated that patients with wild-type, overexpressed EGFR are more likely to show a response of growth restraint but not regression. The presence of specific activating mutations in the tyrosine kinase domain of EGFR, particularly in-frame deletions in exon 19 and single-nucleotide substitutions in exon 21, rather than overexpression of wild-type EGFR, is a better correlate of response to treatment with EGFR-TKI such as gefitinib, erlotinib, or afatinib.[55-57]

ERBB2

Overexpression of *ERBB2* (formally *HER2*) is reported in NSCLC, particularly adenocarcinoma, and it is correlated with decreased survival of patients with resected disease.[58,59] The degree of overexpression is typically much less than seen in cancer of the breast, with few lung cancer patients showing 3+ staining. Trials of monoclonal antibodies directed against *ERBB2* in patients with unselected NSCLC have shown relatively little activity whether used alone or in combination with cytotoxic chemotherapy.[60]

In addition to overexpression of wild-type *ERBB2*, activating point mutations have been described in a number of patients with NSCLC.[61] These patients, about 5% of all with NSCLC or 15% of those with adenocarcinoma, may be more sensitive to therapies directed against ERBB2-mediated signaling and warrant further study with these agents.[56]

EML4-ALK

Recently, fusion genes that produce atypically activated transcription factors or kinases, long known in leukemias and sarcomas, have been described in a number of solid tumors.[62] Fusion of *EML4* and *ALK* has been described in a subset of patients with NSCLC.[63] Patients with *EML4-ALK* are typically young and light smokers or persons who have never smoked with adenocarcinoma. Because these clinical features also are more commonly seen in patients with *EGFR* mutations but patients with *EML4-ALK* mutations are not sensitive to TKIs targeting EGFRs such as gefitinib or erlotinib, it becomes increasingly important to select targeted therapies on the basis of molecular profiling of individual tumors rather than population statistics.[64] Inhibitors of the ALK kinase have shown significant activity both in vitro and in clinical trials and have shown significant improvements in overall response rates and progression-free survival (PFS) in patients with *EML4-ALK* translocations.[65-67]

EARLY DETECTION AND PREVENTION

Fewer than 20% of lung cancer patients in the United States are diagnosed with localized (stage I) disease. The poor survival of patients with symptomatic lung cancer prompted efforts to diagnose the disease in asymptomatic individuals. Until recently these had not shown a significant reduction in lung cancer deaths, but this has changed with reports of the recently completed National Lung Screening Trial.

The U.S. National Cancer Institute (NCI) had sponsored several trials in the 1970s comparing active screening using annual chest radiography and sputum cytology with "routine" medical care.[68,69] These studies showed increased detection of localized disease in the screened populations, with higher rates of resectability, but no decrease in mortality. This led to recommendations from the American Cancer Society to abandon routine screening for lung cancer by the methods used and in the populations studied.

Since the report of these trials, important demographic and technologic changes have occurred. Lung cancer is increasingly a disease of women.[70] Lung cancer has also increasingly become a disease of former smokers. Multiple large centers have reported that more than one half of their patients with lung cancer are former (i.e., more than 1 year since cessation) rather than current smokers.[71] Similar demographics have been observed on clinical trials. This change has had key implications for therapeutic interventions and in the possibility of enlisting this population, which has already demonstrated a high degree of motivation by quitting smoking, in studies of early detection and chemoprevention.

Silvestri et al[72] reviewed the current status of screening for lung cancer in light of this changing demography and proposed 10 essential criteria for a successful screening program: "The disease must have serious consequences and be readily detectable in the preclinical phase. The test should have a high accuracy, detect the disease before a critical point, cause little morbidity, be available and affordable, and result in little overdiagnosis. Finally, treatment for the disease must exist, and it must be effective before symptoms occur, with little risk or morbidity."

Computed Tomography–Based Screening Studies

The availability of fast high-resolution CT has prompted a new round of screening trials.[73] CT is more sensitive in detecting pulmonary nodules in asymptomatic individuals than chest radiography. The percentage of detected nodules ultimately proved to be cancerous has varied considerably in different series, in part because of the background frequency of conditions such as endemic fungal infections that may give rise to benign pulmonary nodules. Most series have shown a shift to earlier stage at diagnosis for screened patients compared with historical controls, which is potentially a marker for improved survival. However, others have argued that tumors detected through screening are likely to have a different and more indolent biology than tumors that present clinically and that only prospective trials can determine whether CT screening reduces overall or tumor-specific mortality. Several large trials of screening CT have been completed in recent years to determine if there is a reduction in overall mortality.

The NLST, which enrolled individuals at risk for lung cancer (30 pack-years or more of smoking history; ages 55 to 75) demonstrated a significant reduction in lung cancer mortality for low dose spiral CT imaging compared to chest x-ray.[74] From August 2002 through April 2004, investigators evaluated

53,454 persons at high risk for lung cancer in 33 separate U.S. medical centers. Participants were randomly assigned to undergo three annual screenings with either low-dose CT (26,722 participants) or single view posteroanterior chest x-ray (26,732). The rate of adherence to screening was more than 90%. The rate of positive screening tests was 24.2% with low dose CT and 6.9% with radiography over all three rounds. A total of 96.4% of the positive screening results in the low-dose CT group and 94.5% in the radiography group were false-positive results. The incidence of lung cancer was 645 cases per 100,000 person-years (1060 cancers) in the low dose CT group compared with 572 cases per 100,000 person-years (941 cancers) in the chest x-ray group (rate ratio, 1.13; 95% confidence intervals [CI], 1.03 to 1.23). There were 247 deaths from lung cancer per 100,000 person-years in the low-dose CT group and 309 deaths per 100,000 person-years in the chest x-ray group, corresponding to a relative reduction in mortality from lung cancer with low-dose CT screening of 20% (95% CI, 6.8 to 26.7; $p = 0.004$). The rate of death from any cause was reduced in the low-dose CT group compared to the radiography group by 6.7% (95% CI, 1.2 to 13.6; $p = 0.02$).

Screening is not innocuous. In addition to the small but finite radiation hazard from CT scans, patients undergoing screening are at risk for complications of further testing and intervention associated with false-positive screen findings. Patients should be made aware of these potential downsides of screening before making decisions to be screened outside the context of a clinical trial. Despite these encouraging results from the NLST trial, there remains concern about the high false-positive rate of initial screen abnormalities and the possibility that some of the screen-detected cancers are indolent and would not have led to clinically evident disease.[75] Patz et al have estimated that about one in five cancers detected by low-dose CT screening in the NLST trial was biologically indolent, rising to 78.9% for bronchoalveolar carcinomas.[76] Because only 1 in 320 screen-detected abnormalities turns out to be a cancer, issues of cost, anxiety, and the rare morbidity and mortality associated with efforts to obtain diagnostic tissue remain of concern and should be part of the discussion with individuals who are considering being screened. Based on current data, a decision to screen individuals in high-risk populations is reasonable so long as the individual understands the benefits and risks of screening, and organizations such as the American Academy of Chest Physicians, the American Lung association, and the U.S. Preventive Services Task Force have endorsed screening programs for the NLST population.

Cytologic and Molecular Screening

Advances in molecular technology offer the promise of detecting malignant changes in exfoliated cells well before morphologic changes appear. Tockman et al have shown that with monoclonal antibody staining using sera developed against SCLC and NSCLC lines, sputum cells showing atypia could predict which patients were going to develop frank malignancy with a lead time of about 2 years.[77] This technique is being studied further in a prospective trial of patients who have undergone resection of a stage I NSCLC and are at high risk for local recurrence and development of a second primary lung cancer. Mao et al reported similar findings using probes for mutations of KRAS and TP53 genes.[78] Mills et al also reported detection of KRAS mutations in fluid obtained at bronchioalveolar lavage.[79] Others have reported the ability to detect EGFR mutations in circulating tumor cells or DNA fragments and the increasing potential of such "liquid biopsies" may greatly enhance our abilities for early detection (or detection of early recurrence) of a variety of solid tumors.[80-82] Sozzi et al have reported on the utility of a microRNA signature in conjunction with CT screening to reduce number of false-positives.[83]

Autofluorescence bronchoscopy has been used to examine the tracheobronchial tree and look for early neoplastic or preneoplastic lesions.[84] This approach complements CT screening, which primarily detects peripheral lesions and has poor sensitivity for small endobronchial lesions.[85]

Chemoprevention

Several classes of compounds have been investigated as candidate agents for lung cancer prevention.[86] Epidemiologic data show a higher incidence of lung cancer in populations with low dietary intake of retinoids and carotenoids. Deficiencies of these agents can lead to squamous metaplasia in animal models. Provision of exogenous vitamin A to animals that have developed metaplasia or atypia can lead to morphologic normalization of the epithelium.

Initial trials of retinoids in patients at high risk for lung cancer suggested reduced second primary lung tumors.[87-89] However, larger, prospective, confirmatory trials testing isotretinoin or retinyl palmitate and *N*-acetylcysteine have failed to confirm the initial promise of earlier trials.[90,91] To further complicate matters, several trials of β-carotene as a chemopreventive agent have observed increased rates of cancer in individuals who continue to smoke.[92]

The epidemiologic correlation between reduced consumption of foods rich in carotenoids and an increased risk of lung cancer in smokers and the laboratory data showing a protective effect of β-carotene against lung carcinogenesis led to two large chemoprevention trials.[93-96] In Finland, a trial of placebo versus β-carotene or α-tocopherol (i.e., vitamin E), or both, showed increased rates of and death from lung cancer in subjects receiving β-carotene. Participants in this trial were predominantly actively smoking males.[97] In the United States, a trial of β-carotene (CARET) was closed early when an interim analysis also showed an increased incidence of lung cancer in the treated arm of the study.[98] The increased risk of lung cancer and death of from cancer persisted even after further administration of β-carotene was discontinued.[99,100]

Selenium is a trace mineral whose presence in the soil varies considerably with geography. Selenium deficiency in animals can produce premalignant changes. Epidemiologic studies have suggested correlation between low dietary intake and cancer of a number of sites. A trial of selenium supplementation versus placebo in subjects with a history of multiple skin cancers did not show reduction in subsequent skin cancers (the primary endpoint), but fewer lung cancer cases were observed in patients randomized to receive selenium.[101] Unfortunately, a confirmatory North American trial in patients with resected stage I NSCLC failed to show any benefit for selenium compared with placebo.[102]

At present, no agent or combination of agents has been proven to delay or prevent the development of lung cancer of any histology in an at-risk population of current or former smokers. The surprising result of increased lung cancer incidence in some retinoid trials as well as the increased risk of diabetes in patients taking selenium in a prostate cancer chemoprevention trial suggest caution rather than therapeutic adventurism.[103] The American College of Clinical Pharmacy (ACCP) currently recommends that no agent be used for lung cancer chemoprevention outside of a clinical trial.[104]

PATHOLOGY AND PATHWAYS OF SPREAD

The respiratory epithelium has a total surface area about the size of a tennis court. It may be divided functionally and pathologically into three zones. From the trachea through the major bronchi the normal lining is made of squamous cells

with interspersed neuroendocrine cells, which appear most commonly at airway bifurcations. Terminal alveoli are lined predominantly with type I and type II pneumocytes. Intermediate bronchi and bronchioles show a transition between squamous and adenomatous lining cells and a corresponding mixture of tumor types. The exposure of this large organ to a common set of inhaled toxins sets in process a widespread set of molecular and subsequent morphologic changes. Slaughter et al, who first observed this phenomenon in patients with multiple primary tumors of the head and neck, referred to this phenomenon as *field cancerization*.[105] Auerbach et al described similar widespread changes in the lungs of smokers with lung cancer, and Saccomano et al described a pattern of progressive degrees of cytologic atypia leading to frankly invasive carcinoma.[106,107] The practical consequence of this is that patients who develop one neoplasm of the upper aerodigestive tract (i.e., head, neck, lung, and esophagus), if treated successfully, remain at substantial risk for developing a second or subsequent primary tumor. For patients with resected stage I NSCLC, this risk is on the order of 2% to 3% per year for at least 10 years after treatment of the first cancer.[90,108,109] It can sometimes be difficult to distinguish second primary tumors from local recurrences or metastases; differences in histology, location, and presence of adjacent mucosal abnormalities have been proposed as criteria. Molecular markers may allow for fingerprinting by characteristic mutations at such sites as *KRAS* or *TP53* (which are known to have different mutational spectra in different parts of the aerodigestive tract), although it still sometimes may be difficult to distinguish between separate primary tumors and clonal variation of a metastasis and most cells in its primary tumor. Recent data have suggested, however, that multifocal lung cancers may share a common clonal origin.[110,111]

In addition to cell type and anatomic stage, a variety of molecular prognostic factors have been proposed to provide further prognostic or predictive information in lung cancer (Table 44-1). These include measures of cell proliferation (e.g., S-phase fraction, proliferating-cell nuclear antigen [PCNA], Ki-67, potential doubling time [T_{pot}]), mutated or overexpressed oncogenes or tumor suppressor genes (e.g., *KRAS, TP53, ERBB2, BCL2*), cell surface antigens (i.e., blood type antigens and their precursors), and induction of angiogenesis. Most of these have been proposed on the basis of small series of patients treated in a nonuniform fashion, and they often are based on univariate rather than multivariate analysis. Proper validation of these will require prospective study in large series of patients staged, treated, and observed in a uniform fashion.[112] It is likely that patterns of expression of multiple markers as assessed by genomic or proteomic analysis will more successfully predict prognosis, as has been shown for breast cancer and intermediate-grade lymphomas.[113,114] Small series have reported the success of such profiling in lung adenocarcinomas, but large validation series in uniformly treated patient groups are awaited.[115] Such profiling may also be useful in determining those patients at greatest risk for specific patterns of metastatic spread, such as to the brain, for whom particular targeted adjuvant therapies such as prophylactic cranial irradiation may have a better risk-to-benefit ratio.

Lung cancer spreads through regional lymphatic vessels within the lung to the hilar and paratracheal nodes, which drain to the supraclavicular fossae and, to a lesser degree, the upper abdomen (Figure 44-1). The patterns of nodal spread are partially predictable on the basis of tumor size, histology, and proximity to central airways. Involvement most often begins with intrapulmonary nodes, extends centrally to the hilum, and then to the mediastinum. However, noncontiguous "skip" metastases are well described. Although nodal involvement can usually be detected by preoperative CT or CT/PET, even for T1 primary tumors, the incidence of clinically undetected nodal metastases can be as high as 15% to 20% for peripheral adenocarcinomas.[116,117]

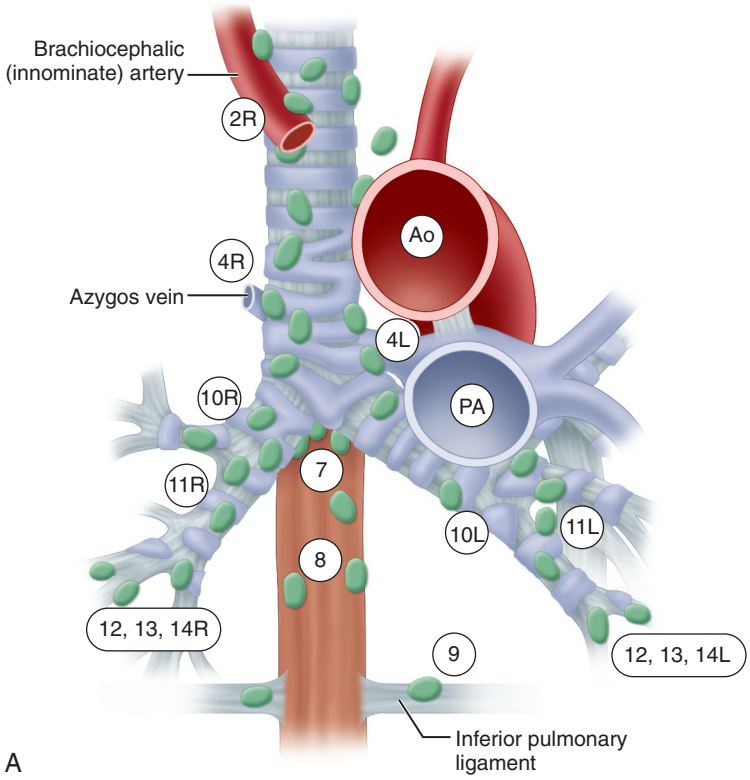
Hematogenous dissemination is common and is usually associated with nodal involvement, although about 20% of patients with resected T1N0 lesions will experience relapse in distant sites. Nodes that appear normal on routine histology, when examined by immunohistochemical staining for epithelial antigens, contain tumor cells in 15% to 25% of cases.[118] Occult bone marrow metastases in rib resected at the time of thoracotomy are also found by this method, including patients without any evidence of nodal disease.[119] It appears that nodal and hematogenous spread, which usually are associated, may occur independently.

Although nodal drainage is primarily to the ipsilateral hilum and mediastinum, the left upper lobe drains commonly to contralateral paratracheal nodes as well as to nodes in the anterior mediastinum.[120] Direct involvement of visceral and parietal pleura by peripheral tumors puts the entire ipsilateral

TABLE 44-1 Proposed Prognostic and Predictive Factors for Non–Small Cell Lung Cancer

Factor	Comment
Tumor volume	Partially incorporated into new TNM classification
Number of nodal sites	—
Clinically evident nodal involvement	Identified preoperatively as distinct from microscopic nodal involvement
Extranodal extension	May be prognostic for local recurrence and predictive of impact of postoperative radiation therapy on survival
IHC detection of nodal metastases	Nodes negative by H&E but positive by IHC
Histology	Predictive of response and toxicity with some agents
Ploidy	—
Proliferative rate (labeling index, Ki-67, T_{POT})	—
KRAS mutation	Predictive of resistance to EGFR-TKI
3p deletion	—
TP53 mutation or overexpression	—
Angiogenesis (microvessel density)	—
Vascular endothelial growth factor (VEGF) overexpression	—
Epidermal growth factor receptor (EGFR) overexpression and/or mutation	Mutation predictive for response to EGFR-TKI
ERBB2 (HER/neu) oncogene expression and/or mutation	Possibly predictive for response to trastuzumab
EML4-ALK	Predictive for response to ALK-TKI

Adapted from Wagner H, Bonomi P: Preoperative and postoperative therapy for non–small cell lung cancer. In Roth JA, Ruckdeschel JC, Weisenburger TH, editors: Thoracic oncology, Philadelphia, 1995, WB Saunders, pp 147–163.
H&E, *Hematoxylin-eosin;* IHC, *immunohistochemical;* TKI, *tyrosine kinase inhibition;* T_{POT}, *potential doubling time.*



Superior mediastinal nodes

1 Highest mediastinal
2 Upper paratracheal
3 Prevascular and retrotracheal
4 Lower paratracheal (including azygos nodes)

Aortic nodes

5 Subaortic (A-P window)
6 Paraaortic (ascending aorta or phrenic)

Inferior mediastinal nodes

7 Subcarinal
8 Paraesophageal (below carina)
9 Pulmonary ligament

N1 nodes

10 Hilar
11 Interlobar
12 Lobar
13 Segmental
14 Subsegmental

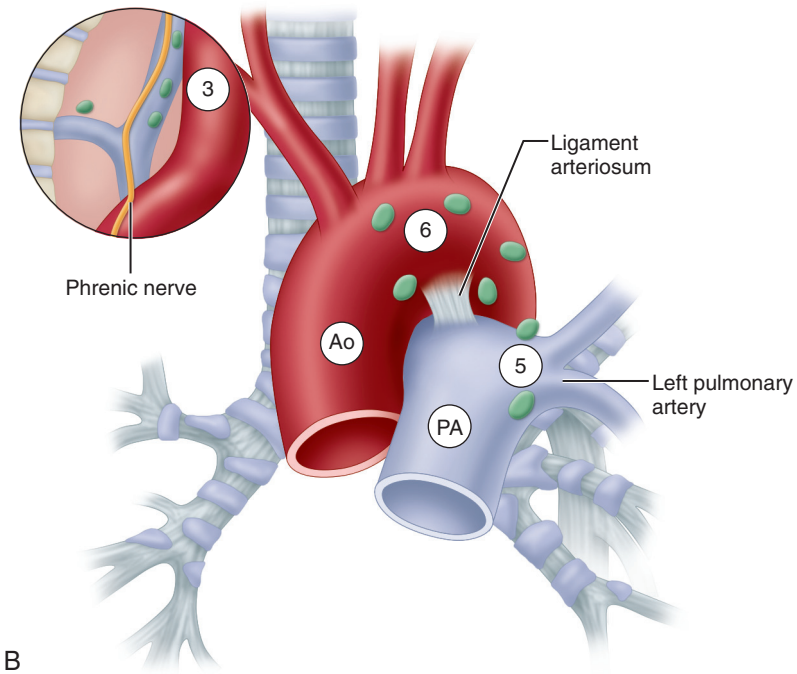


Figure 44-1 Map of intrathoracic lymph node stations. Single-digit stations (1 to 9) are N2 nodes; double-digit stations (10 to 14) are N1 nodes.

pleural space at risk for involvement. The true frequency of this is not well known, nor is its clinical significance or appropriate therapeutic response. Several series have reported that intraoperative pleural lavage detects tumor cells in about 10% of patients and that their survival is markedly worse than that of patients with tumors of otherwise similar stage with cytologically negative lavage.[121-123]

Extrathoracic spread differs somewhat among the major histologic types of NSCLC. Early extrathoracic dissemination, particularly to the CNS, is seen more frequently with adenocarcinoma and large cell carcinoma than with squamous cell carcinoma.[124] However, all histologic types are prone to early and widespread extrathoracic metastases, with brain, bone, liver, adrenal, and lung the most commonly involved sites.

CLINICAL MANIFESTATIONS, PATIENT EVALUATION, AND STAGING

Most patients diagnosed with lung cancer present with symptoms that may be as a result of the primary tumor, its nodal and systemic metastases, or to paraneoplastic syndromes.

Central endobronchial tumors may cause partial or complete airway obstructions, with cough, hemoptysis, postobstructive pneumonia, or dyspnea. Peripheral tumors are often asymptomatic unless they involve the chest wall and produce pain from involvement of intercostal nerves. Tumors that involve the superior pulmonary sulcus may directly involve branches of the brachial plexus with pain and weakness in the shoulder and arm or involve the sympathetic trunk, producing Horner's syndrome with ipsilateral ptosis, miosis, and anhidrosis.

Regional lymph node metastases may compress adjacent structures. Although complete obstruction of main bronchi by extrinsic compression is uncommon, this occurs more readily in distal airways. The superior vena cava is a relatively thin-walled, low-pressure system, and it is vulnerable to compression with significant clinical consequences. The intrathoracic course of the recurrent laryngeal and phrenic nerves is vulnerable to compression by nodal metastases. Patients presenting with hoarseness or who have a fixed elevated hemidiaphragm should be suspected of having such nodal involvement.

Lung cancer can metastasize to a wide variety of extrathoracic sites and produce diverse symptoms. The most frequent symptoms of distant metastatic disease are bone pain and neurologic symptoms from brain metastases. These are not, however, absolute indicators of metastatic disease. Pulmonary hypertrophic osteoarthropathy typically presents with bilateral pain and tenderness in the legs, which are often most tender over the tibias. Bone scintigraphy or CT/PET will show diffuse uptake in these areas, and plain films usually show a characteristic elevation of the periosteum without involvement of cortical bone.

Although focal neurologic symptoms most commonly result from brain metastases, CNS symptoms may also be caused by paraneoplastic cerebellar degeneration or by metabolic disturbances such as hyponatremia resulting from syndrome of inappropriate antidiuretic hormone (most commonly seen in SCLC) or hypercalcemia resulting from secretion of parathyroid-like hormone (most commonly seen in squamous cell carcinoma). Nonspecific decreases in cognitive function compared with age- and gender-matched controls have also been reported in patients with lung cancer before any treatment, particularly in SCLC.[125]

Liver metastases are common but usually asymptomatic unless advanced. Abnormalities in liver function studies are uncommon unless there has been extensive destruction of liver parenchyma, although alkaline phosphatase and bilirubin levels may be elevated by small-volume hepatic or nodal disease blocking the common hepatic or common bile duct. Elevation of the lactate dehydrogenase level is a poor prognostic sign, but it probably reflects overall tumor burden rather than solely the extent of hepatic disease. Adrenal metastases are common, particularly at autopsy, but rarely symptomatic unless large and painful. Symptomatic adrenal hypofunction has been described, but it is infrequent unless both adrenals are involved.

Radiographic Procedures in Staging

As with any other medical test, radiographic staging procedures should be used primarily when their results will lead to a change in choice of therapy. A secondary role is in defining homogeneous groups of patients for clinical research. When used in this manner, the possibility of differences between groups so staged and the more general population of patients must be kept in mind.

Appropriate radiographic procedures for patients with suspected or newly diagnosed lung cancer depend in part on the histologic type of cancer and on the therapeutic options. The otherwise healthy individual who presents for an elective orthopedic procedure and is found to have an incidental 2-cm peripheral lung nodule without any other abnormalities on chest radiography, combined PET/CT of the chest, and routine laboratory studies (e.g., complete blood cell count, chemistry profile including electrolytes, renal, and hepatic function) is unlikely to have any useful information found with further testing. At the other end of the spectrum, the patient who presents with limiting cardiopulmonary disease, substantial recent weight loss, poor performance status, new bone pain, and a large hilar mass requires only an efficient choice of the least invasive means of obtaining a tissue diagnosis and choice of appropriate palliative therapy. Delineation of all sites of metastatic disease in such a setting is an expensive and wasteful application of resources that does not often lead to changes in care or outcome.

Evaluation of the primary tumor is generally best accomplished by CT enhanced with intravenous contrast.[126] The parameters of contrast enhancement (dose, infusion rate, and site of infusion [left side preferred to visualize vessels crossing in the anterior mediastinum]) can make a great difference in the quality of information obtained. It is important to examine the chest using both lung and mediastinal window settings.

Staging of the Mediastinum

Combined PET/CT is the radiographic method of choice for evaluation of the mediastinum.[127,128] The false-positive and false-negative rates are about 20%, however, and this should be considered when planning therapy. In most cases, histologic confirmation of suspected nodal involvement should be obtained before making decisions regarding potentially curative treatment. The accessibility of mediastinal nodes to biopsy under guidance of CT or of endoesophageal or endobronchial ultrasonography makes this a simple, minimally invasive procedure for most patients, with the use of more invasive procedures such as mediastinoscopy or anterior sternotomy (i.e., Chamberlain procedure) reserved for a minority of patients.[129,130] It is critical to personally review diagnostic imaging and not simply rely on written reports. In some cases, a patient is said to have "mediastinal adenopathy" with the implication of unresectable N2 disease, although CT demonstrates the presence of several benign 1-cm nodes. The distribution of size of mediastinal nodes in normal individuals easily includes this range; and of nodes 1.5 cm in the greatest dimension, about 20% will be histologically benign. The percentage of such false-positive results is even higher among patients with obstructing endobronchial lesions or extrinsic bronchial obstruction from hilar nodes and postobstructive infection.

Although there was initially hope that magnetic resonance imaging (MRI) might be superior to CT in differentiating benignly enlarged from malignant mediastinal nodes, this has not been the case. CT, with its better spatial resolution and greater freedom from motion artifact, is the superior modality for imaging the mediastinum. MRI does have a role in evaluation of lesions that involve the lung apex (and possibly the brachial plexus) and medial lesions that abut the vertebrae and may invade the neural foramina. Such involvement may preclude resection and poses a risk for spinal cord compression, and its delineation has important implications for planning radiation therapy.

FDG-PET has good sensitivity and specificity in detecting mediastinal nodal involvement and diseases in extrathoracic metastatic sites.[131-137] PET has greater sensitivity and specificity than CT, but is still imperfect. Nodes that appear involved by PET or CT should be sampled for confirmation of their status when such information will lead to alterations in clinical management, particularly when deciding whether to consider resection. If a negative PET scan is being considered adequate to avoid performing pathologic evaluation of mediastinal nodes, it is important to require that the primary tumor show measurable uptake (often not the case for bronchioalveolar carcinoma), that there not be a central primary tumor whose uptake could obscure small nodes, and that a dedicated PET/CT scanner be used.[138] FDG-PET has also been studied for evaluating the response to preoperative chemotherapy or chemoradiation and for distinguishing between viable tumor and fibrosis in patients who have received RT or chemotherapy, or both, in assessing local disease control in patients treated nonoperatively.[139-146] Regardless, in equivocal situations, mediastinoscopy is still considered the gold standard for evaluation of mediastinal nodes.

Evaluation for Extrathoracic Metastases

The liver and adrenals are common sites of metastasis for NSCLC and are well imaged by CT and PET. Although metastases to the adrenals are common, so are adenomas, and the distinction between these may require biopsy in patients who are otherwise good candidates for curative treatment. Routine bone scintiscans are of limited value. Many patients have abnormal results of bone scintigraphy because of benign degenerative diseases or prior trauma. The likelihood of detecting occult metastatic disease in patients without focal symptoms or elevation in alkaline phosphatase levels is low. PET scan, at this point, has largely replaced bone scans in the evaluation of bone involvement.

The use of total-body PET has been advocated as a cost-effective replacement for CT of the liver and adrenals and radionuclide bone scanning.[127] The typical PET scan does not image the brain, and the high glucose uptake of normal brain tissue will obscure small metastases. It will not replace MRI for this purpose. The typical PET or fused PET/CT does not image the entire skeleton, typically omitting the calvarium and the distal extremities.

Clinically occult involvement of the CNS is common, especially in patients with involvement of mediastinal nodes or other sites of extrathoracic involvement. Scanning of the brain is not indicated for patients with stage IA disease, for which the probability of CNS involvement is about 5%; however, that risk goes up to 15% to 20% for patients with N2 disease.[127] In patients being considered for aggressive chemoradiation with or without surgery, the finding of CNS metastases will lead to major changes in therapy, and scanning is warranted in this situation. Although historically routine brain scanning has not been obtained in patients with extrathoracic metastatic disease in the absence of CNS symptoms, increasingly specific treatments (e.g., bevacizumab) and protocols require brain imaging at the outset before therapy can begin.

The role of CNS imaging in the patient with stage IB to II disease is controversial. Although the false-positive rate of CT and MRI is low and few patients would wrongly be excluded from surgery, the true-positive rate is also low. However, in some series, 10% of patients with stage IB to II NSCLC without neurologic symptoms had metastases demonstrated on enhanced CT.[147] Such a frequency of involvement probably warrants more common CNS imaging as part of routine staging, considering the cost and morbidity of a thoracotomy, which would most likely be futile in the presence of brain metastases.

Tumor-Node-Metastasis Stage Grouping

NSCLC is staged according to the principles of the tumor-node-metastasis (TNM) system. The International Staging System outlined by Mountain in 1986[148] has been the standard for reporting treatment results since that time. The broad outlines of this system are clearly valid. However, several areas emerged that indicated the need for modification of this system, and revisions were implemented in 1997 and again in 2009.[149] The current version is reasonably predictive of outcome, particularly for patients treated surgically (Tables 44-2 and 44-3). This system may not deal so well with anatomic prognostic factors that may be important for nonsurgical treatment.

Tumor volume is not considered an independent prognostic factor except by the proxy of unidimensional measurements. A 1-cm lesion involving the visceral pleura is T2, and a 2.9-cm lesion surrounded by lung parenchyma is T1. It might be expected that the smaller T2 lesion would be more readily controlled by RT than the larger T1 lesion, and available data are in agreement with this expectation. Data from several institutions support the hypothesis that tumor volume, independent of stage, is prognostic for local control and survival of patients with NSCLC treated with RT or chemoradiation.[150-154] Such volumetric measurements can be performed using commercially available RT planning software, although standardization of technique is important to reduce interobserver variability.[155]

There are several reports that size is an important predictor of prognosis in the clinical T1N0 group and directly correlates with the likelihood of microscopic involvement of hilar and mediastinal lymph nodes.[156] This is relevant to treatment strategies that try to reduce the extent of resection or limit the radiation target volume by eliminating elective nodal irradiation (ENI) in these patients and for patients treated with SBRT. Data suggest that only patients with lesions smaller than 1 cm in diameter have a risk of nodal involvement below 10%.

Several of the old TNM stage groups have considerable heterogeneity in outcome.[157] This is true to some degree for patients with stage I disease, where the survival of patients with T1N0M0 disease (~80%) is strikingly better than that of patients with T2N0M0 disease (~60%). It is in the current stage group III that the heterogeneity and need for subgrouping is greatest. This was partially recognized by Mountain,[148] who divided the grouping into IIIA (i.e., no direct tumor invasion of the mediastinum or involvement of contralateral mediastinal or supraclavicular nodes, no pleural effusion) and IIIB (i.e., with one or more of the previous characteristics). This distinction separated a group of patients (IIIA), some of whom could undergo complete resection and have a reasonably favorable prognosis (e.g., T3N1M0), from those with unresectable disease who are often treated palliatively. In patients with stage IIIA or IIIB NSCLC who are treated nonsurgically with radical RT or chemoradiation, the survival differences based on stage are much less striking.[158]

Several other groups have proposed different revisions to the staging system. Based on the European Lung Cancer Working Party data on patients receiving chemoradiation, Berghmans et al proposed separating patients with stage T3 or 4, N3, M0 disease from other factors that predicted better survival than the usual stage IIIA versus IIIB distinction.[159] Andre evaluated patients with resected stage III NSCLC, some of whom had received induction chemotherapy, and found that the number of lymph node levels and clinically detectable nodal metastases (cN2) were adverse prognostic factors.[157]

Although the 2009 modifications introduced to the TNM staging system for lung cancer constitute a clear improvement, they do not deal adequately with a number of the issues that

TABLE 44-2 International Staging System: TNM Classification (2009)

Category	Definition
Tx	Primary tumor cannot be assessed, or tumor proven by the presence of malignant cells in sputum or bronchial washings but not visualized by imaging or bronchoscopy
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	A tumor 3 cm or less in greatest dimension, surrounded by lung or visceral pleura, without radiographic or bronchoscopic evidence of invasion more proximal than the lobar bronchus (i.e., not in the main bronchus)
T1a	Tumor 2 cm or less in greatest dimension*
T1b	Tumor more than 2 cm but not more than 3 cm in greatest dimension
T2	Tumor more than 3 cm but not more than 7 cm; or tumor with any of the following features†: • Involves main bronchus, 2 cm or more distal to the carina • Invades visceral pleura Associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung
T2a	Tumor more than 3 cm but not more than 5 cm in greatest dimension
T2b	Tumor more than 5 cm but not more than 7 cm in greatest dimension
T3	Tumor more than 7 cm or one that directly invades any of the following: chest wall (including superior sulcus tumors), diaphragm, phrenic nerve, mediastinal pleura, parietal pericardium; or tumor in the main bronchus less than 2 cm distal to the carina but without involvement of the carina; or associated atelectasis or obstructive pneumonitis of the entire lung or separate tumor nodule(s) in the same lobe as the primary tumor
T4	Tumor of any size that invades any of the following: mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, carina; separate tumor nodule(s) in a different ipsilateral lobe to that of the primary tumor
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastases in ipsilateral peribronchial or hilar lymph nodes and intrapulmonary nodes, including involvement by direct extension
N2	Metastases in ipsilateral mediastinal or subcarinal lymph node(s)
N3	Metastases in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s)
M0	No distant metastases
M1	Distant metastasis
M1a	Separate tumor nodule(s) in a contralateral lobe; tumor with pleural nodules or malignant pleural or pericardial effusion‡
M1b	Distant metastasis

From Goldstraw P: Staging manual in thoracic oncology, Orange Park, FL, 2009, Editorial Rx Press.
**The uncommon superficial spreading tumor of any size with its invasive component limited to the bronchial wall, which may extend proximal to the main bronchus, is also classified T1a.*
†T2 tumors with these features are classified T2a if 5 cm or less or if size cannot be determined and T2b if greater than 5 cm but not larger than 7 cm.
‡Most pleural (pericardial) effusions with lung cancer are the result of tumor. In a few patients, however, multiple microscopic examinations of pleural (pericardial) fluid are negative for tumor and the fluid is nonbloody and is not an exudate. When these elements and clinical judgment dictate that the effusion is not related to the tumor, the effusion should be excluded as a staging element and the patient's disease should be classified as M0.

TABLE 44-3 Stage Grouping and TNM Categories

Stage	TNM Categories
Occult carcinoma	TXN0M0
Stage 0	TisN0M0
Stage IA	T1a,bN0M0
Stage IB	T2aN0M0
Stage IIA	T1N1M0
Stage IIB	T2bN1M0 T3N0M0
Stage IIIA	T1a,bT2a,bN2M0 T3N1-2M0 T4N0-1M0
Stage IIIB	T4N0-2M0 Any T, N3M0
Stage IV	Any T, any N, M1

From Goldstraw P: Staging manual in thoracic oncology, Orange Park, FL, 2009, Editorial Rx Press.

pertain to surgical and nonsurgical therapy. The number of lymph node stations involved, as well as whether involvement is microscopic or macroscopic, has also been found to be of prognostic significance in patients with resected stage IIIA disease, though this assessment may be inconsistent from institution to institution.

Practical treatment decisions for patients with stage IIIA and IIIB NSCLC are often made along the following lines.[160]

GROUP A (old T1-3N2aM0): Involvement of a single mediastinal nodal station found at mediastinoscopy or mediastinotomy or at thoracotomy. The nodal capsule is not breached. In some institutions, patients undergo definitive resection and then are given adjuvant postoperative therapy, whereas others are given preoperative therapy.

GROUP B (old T1-3N2bM0): Involvement of multiple mediastinal nodal stations with potentially resectable disease. Recent trials have compared chemoradiation or chemotherapy as preoperative regimens without providing a definitive answer.

GROUP C (old T1-3N2cM0): Bulky involvement of mediastinal nodes (e.g., seen on a chest radiograph), possibly with superior vena caval compression. Disease is unlikely to be resectable, even with preoperative therapy, but the patient is a candidate for definitive chemoradiation.

GROUP D (old T4aNXM0): Central T4 or N3 disease that can all be encompassed within a reasonable RT portal, limited by lung and spinal cord dose. These patients should be considered for definitive chemoradiation.

GROUP E (old T4bNXM0, now stage IVa): Disease includes malignant pleural or pericardial effusion. Because all known disease cannot be irradiated to a tumoricidal dose, these patients should be treated as other stage IV disease using primary chemotherapy, with irradiation reserved to treat or prevent local symptoms.

Medical Considerations for Surgical Resection: Cardiopulmonary Evaluation

Before undergoing surgery, patients must undergo appropriate cardiopulmonary evaluation to determine their ability to tolerate the operative procedure and the expected reduction in lung function after resection.[161,162] Patients with a history of coronary artery disease should be assessed carefully. Appropriate testing may include a stress test as well as stress radionuclide angiography. Patients in whom coronary artery calcification can be seen on CT should be similarly evaluated.

Pulmonary function evaluation should include determination of lung volumes and flow rates, diffusing capacity, and arterial blood gas analysis. A recommended preoperative workup is outlined in Table 44-4. Some patients with poor baseline pulmonary function the result of extensive bullous disease and poor lung compliance may have improvement in function after combined resection of the tumor and pulmonary dead space.

Patients not meeting criteria for lobectomy should be considered for lesser resections (i.e., wedge or segmental resection) if these appear capable of obtaining negative margins. The Lung Cancer Study Group (LCSG) trial,[163] which randomized patients with stage T1N0M0 NSCLC between lobectomy and more conservative resection, showed significantly better local control for lobectomy and an emergent difference in survival. The role of sublobar resection followed by RT to the tumor bed using intraoperatively placed brachytherapy mesh, was studied by the American College of Surgeons Oncology Group (ACOSOG). Local failure rates were 12.8% and 12.5% with and without brachytherapy, respectively, and staple line failure rates 6.4% and 4.8%, with no benefits seen for brachytherapy in this trial.[164]

PRIMARY THERAPY

Early-Stage Disease

Surgery is the most effective treatment for patients with technically resectable NSCLC, stage IA through IIB. The role of surgery for patients with IIIA (N2) disease is controversial. Several points arise from consideration of the survival of patients with surgically resected disease and the patterns of failure for those with disease that recurs:

- Five-year OS for the most favorable patients, those with small stage T1N0M0 lesions, approaches 80%, not too different from that seen in women with early-stage breast cancer.[165] This refutes the common impression of lung cancer as an intrinsically incurable disease and more correctly focuses attention on early detection.
- Most treatment failures are systemic rather than local (Table 44-5).
- Many patients with compromised pulmonary function can be managed surgically, if they undergo careful perioperative care.[175]
- Complication rates depend on patient (age, physiologic status), disease (e.g., extent of required resection), and technical (e.g., surgical expertise) factors.[176]

Definitive Radiation Therapy

Single-institution reports of results of definitive RT for patients with stage I or II NSCLC who refuse surgery or are deemed inoperable for medical reasons vary in patient selection, RT technique, and outcome (Table 44-6). Some of this variation comes from differing definitions of "medical unresectability," with institutions that consider borderline disease to be unresectable, improving the apparent results of both their surgical and RT series by the Will Rogers effect (i.e., stage migration).[197] However, several general conclusions may be drawn from these series:

1. Some patients with locally confined disease are cured with definitive RT. "Unresectable" is not synonymous with "incurable."
2. Survival of clinically staged patients treated with radical RT is inferior to that of surgically staged patients treated surgically.
3. Survival of these patients decreases with increasing T stage, tumor size (within T stage), and clinical involvement of hilar lymph nodes.

TABLE 44-4 Preoperative Evaluation of Pulmonary Function

Test	Desirable Value	Comment
FEV_1	>1.5 L lobectomy >2 L pneumonectomy >80% predicted	Should obtain regional ventilation and perfusion scans and calculate predicted postoperative FEV_1 in borderline cases
PCO_2	<45 mm Hg	Recent studies suggest that this may not be an independent risk factor
SaO_2	>90%	Further testing indicated if <90%
DLCO	>80% of predicted	Further testing indicated if <80%
VO_2max	>15 mL/kg/min	Values ≥15 mL/kg/min predict low surgical morbidity. Those >10 but <15 are borderline, and the patient's overall clinical status needs to be considered carefully

Data from Colice GL, Shafazand S, Griffin R, et al: Physiologic evaluation of the patients with lung cancer being considered for resectional surgery. Chest 132(Suppl):e166S–e190S, 2007.

See also Brunelli A, Kim AW, Berger KI, et al: Physiologic evaluation of the patients with lung cancer being considered for resectional surgery. Chest 143(Suppl):161S–177S, 2007.

DLCO, *Diffusing capacity of the lung for carbon dioxide;* FEV_1, *forced expiratory volume in 1 second;* PCO_2, *partial pressure of carbon dioxide;* VO_2max, *maximum oxygen consumption.*

TABLE 44-5 Selected Reports of Stereotactic Radioablation of Lung Tumors: Primary Lung Cancers and Metastatic Lesions

Study*	No. Patients	Stage	Dose/ Fractions/ Time	Localization and Immobilization	Local Control	Survival	Comments
Timmerman[166]	44	T1-2N0	24 Gy-60 Gy 3 fractions 2 wk	Stereotactic body frame	NS	NS	Phase I dose escalation trial; six local failures seen at lower dose range; no clinical MTD reached, although G2 pneumonitis seen for patients with larger (T2) tumors
Nagata[167]	55	T1-3N0	48 Gy 4 fractions 12 days	Stereotactic body frame	100% for T1-T2 tumors	1-year: 95 T1, 95 T2 2-year: 92 T1, 82 T2	Worst toxicity: G2 pneumonitis
Onishi[168]	40	T1-2N0	60 Gy 10 fractions 5 days (twice daily)	Breath-hold	2-year: 94%	2-year: 63% 2-year cause specific: 75%	Single-institution study using combined CT-Linac gantry; no toxicity >G2
Onishi[169]	241	153 T1N0 88 T2N0	18 Gy-75 Gy 1-22 fractions	Varies among institutions	Local recurrence in 10.4%	3-year: 56% 3-year cause specific: 71.8%	Multiinstitution study using a variety of treatment techniques and dose schedules; may include some patients from other series listed here; pneumonitis ≥G3 in 2.1%
Harada[170]	25	T1-2N0	35 Gy-48 Gy 4 fractions 1 wk	Real-time tumor tracking and machine gating	1-year: 77%	1-year: 83%	G2 pneumonitis in 24%
Niibe[171]	22	T1-2 (≤5 cm)	59.5 Gy-75 Gy 3-4 Gy/fraction 25-38 days	NS	1-year: 92.3% 2-year: 8 3.1% 3-year: 83.1%	1-year: 100% 2-year: 83.3% 3-year: 55.6%	G2 pneumonitis in 10%
Hof[172]	10	T1-2N0	19 Gy-26 Gy Single fraction	Stereotactic body frame	1-year: 88.9% 2-year: 71.1%	1-year: 80% 2-year: 64%	Five patients with DM, 1 with NM; 3 patients developed pneumothoraces requiring chest tube placement after placement of fiducial marker in tumor
Whyte[173]	23	T1-2N0 or metastatic	15 Gy Single fraction	Breath-holding for 9 patients; real-time tumor tracking and machine gating for 14 patients	NS	NS	
Fukumoto[174]	22	T1-2N0M0	48 Gy-60 Gy 8 fractions 2 wk	Free breathing PTV based on CT at full inspiration and full expiration in addition to free breathing	94% for 17 patients with minimum 24-mo follow-up	Lung cancer-specific survivals: 1-year: 94% 2-year: 73%	No clinical radiation-related side effects or significant changes in VC, FEV_1, TLC, or DLCO; radiographic fibrosis in all; 5 patients have died with DM and 6 of intercurrent disease; 3 had regional node disease (also DM)

DLCO, *Diffusing capacity of the lung for carbon dioxide;* DM, *distant metastases;* FEV_1, *forced expiratory volume in 1 second;* G2, *grade 2;* G3, *grade 3;* MTD, *maximum tolerated dose;* NM, *nodal metastases;* NS, *not stated;* PTV, *planning target volume;* TLC, *total lung capacity;* VC, *vital capacity.*

**When series have included patients with primary lung cancer and pulmonary metastases, data are reported for primary tumors only when they were available separately.*

TABLE 44-6 Radical Radiation Therapy for Patients with Medically Inoperable Non–Small Cell Lung Cancer

Study	No. Patients	Clinical Stage	2-year Survival (%)	5-year Survival (%)	Local Failure (%)
Morrison[177]*	28	Operable	14	6 (4 yr)	NA
Smart[178]	40	Operable	≈50	22	NA
Coy[179]†	141	T1-3NX	31	11	45‡
Cooper[180]†	72	T1-3N0-1	N/A	6	NA
Haffty[181]	43	T1-2N0-1	60	21	39
Noordijk[182]	50	T1-2N0	56	16	70
Zhang[183]	44	T1-2N0-2	≈55	32	27
Talton[184]†	77	T1-3N0	36	17	NA
Sandler[185]	77	T1-2NX	30	≈10	56
Ono[186]	38	T1N0	68	42	NA
Dosoretz[187,188]†	152	T1-3N0-1	40	10	70
	44§	T1N0-1	≈60	≈60	30
Hayakawa[189]	17	Stage I	75	31	NA
	47	Stage II	44	22	NA
Rosenzweig[190]	62	T1-2N1	33	12	60
Kaskowitz[191]	53	T1-2N0	43	6	55
Graham[192]	103	T1-2N0-1	35	14	NA
	35§	T1N0-1	NA	29	NA
Gauden[193]	347	T1-2N0	NA	27	NA
Sibley[194]	141	Stage I	39	13	42
Furuta[195]	32	Stage I-II	40	16	NA
Bogart[196]	39	T1-2N0 (<4 cm)	64	NA	8

**Includes some patients with small cell carcinoma.*
†Includes some patients with proximal unresectable T3 lesions.
‡Data from autopsies of 31 patients (22% of series), of whom 14 had locoregional disease, 17 had disseminated disease, and 6 had no evidence of disease.
§Subset of entire series.

4. Even for patients with the most favorable disease status, local control has historically been inferior to that seen with surgery.
5. Even for patients with favorable disease status, distant metastases are a common cause of death.

These observations suggest several strategies to improve treatment outcome. Combining RT with systemic chemotherapy in an attempt to reduce distant relapse and to improve local control is a logical approach to explore, particularly as the toxicity of current chemotherapeutic regimens has decreased. RT time-dose parameters are another fertile ground for clinical trials. Sibley reviewed 10 reports of definitive RT for patients with medically inoperable stage I NSCLC.[194] About 15% of patients were long-term survivors, 25% died of intercurrent disease, 30% died of distant metastases, and 30% died of local failure. Neither time to local failure nor OS correlated with the treatment volume (i.e., primary tumor volume alone or inclusion of elective nodal irradiation), whereas the total tumor dose, in the range of 55 Gy to 70 Gy, did correlate with outcome. This suggested that escalation of the biologic effective dose was a logical approach to improve the RT management of these patients. There is limited experience combining systemic therapy with radiotherapy and potential toxicities need to be considered in patients who are medically inoperable.[198,199]

Stereotactic Body Radiation Therapy

A number of investigators have explored the use of hypofractionated SBRT (also referred to as stereotactic ablative radiotherapy [SABR]) for these patients (see Table 44-5). Both frame-based and frameless systems have been used, with daily tumor localization by orthogonal images, cone-beam CT, and real-time tracking of implanted fiducial markers. Motion resulting from respiration presents a complicating factor not encountered in intracranial stereotactic treatment. Such motion is present in conventional large-field RT, where it is often accommodated by increasing field margins at the expense of treating increasing volumes of normal lung tissue. This is unacceptable for stereotactic large-fraction treatment. A number of approaches have been developed for minimizing respiratory motion through breath-hold and abdominal compression techniques, gating the beam-on time to a particular phase of the respiratory cycle, or tracking the tumor or radiopaque fiducial markers implanted in it and adapting the target volume to the real-time position of the tumor. These approaches continue to evolve, but the results to date are highly promising and suggest that, at least for T1 tumors, the results of SBRT rival those of surgery for local control and survival (see Table 44-5).

The Radiation Therapy Oncology Group (RTOG) has conducted a Phase I/II trial of fractionated SBRT for patients with medically inoperable stage I NSCLC using a regimen consisting of three treatment fractions. Results from this and multiinstitutional trials in Japan and Europe indicate local control rates of about 90% when tumors are treated to a biologically effective dose of 100 biologically effective dose (BED) or greater.[200] A number of different fractionation schemes have been employed, ranging from a single fraction of 34 Gy to three- to five-fraction regimens over 1 to 2 weeks. At present, the optimal dose and fractionation, as well as the optimal dose homogeneity in the target volume remain to be clarified. Dose calculations for the multiple small fields used and tissue heterogeneities are also highly dependent on the calculation model used.[201] There also have been reports of substantial toxicity, particularly with regimens using smaller numbers of fractions, when the high-dose volume includes central

vascular or airway structures or the chest wall.[202,203] Implementation of a program of SBRT requires careful attention to details of patient positioning, treatment planning, and dose calculation to be safe and effective, but this approach, when properly executed, appears to challenge the primacy of surgery in potentially curative treatment of patients with early-stage lung cancer.[204]

There have been at least three attempts to conduct prospective Phase III trials comparing SBRT with surgery for patients with early stage (T1-2N0M) NSCLC; these include an RTOG trial, the ROSEL trial in the Netherlands, and a trial sponsored by Accuray comparing SBRT using the Cyberknife platform with resection.[205] All of these trials failed to meet accrual goals and were closed prematurely. It would appear that despite strong Phase II data supporting the use of SBRT for patients with marginally resectable NSCLC, neither patients nor physicians are at equipoise and willing to randomize patients between surgical and nonsurgical treatments at the present time.

Another therapeutic option that has been explored for medically inoperable patients with early stage NSCLC is radiofrequency ablation (RFA). Local control rates of 50% or more are reported for tumors less than 3 cm. Prospective trials are being conducted to better define the role of this therapy.[206]

Adjuvant Therapy for Early-Stage Disease

Multiple trials since 2000 (IALT, BR10, and ANITA) have demonstrated a survival benefit for adjuvant chemotherapy. Discussing the risks and benefits of adjuvant treatment with patients is difficult. Telling a patient who is recovering from a major surgical procedure that he or she is at high risk for recurrence despite having had a complete resection with no obvious viable tumor remaining is a challenge. Adjuvant treatment with platinum-based chemotherapy is designed to reduce this risk of distant relapse, but the added benefit in long-term survival of roughly 5% overall, although statistically significant, is relatively modest. Moreover, the statistical nuances of disease-free and OS curves escape many patients (Table 44-7). The format in which data are presented (i.e., whether the effect of an adjuvant treatment is expressed as a hazard ratio, a relative survival difference, or an absolute survival difference) can greatly affect a patient's willingness to proceed with adjuvant therapy.[210,211]

Postoperative Radiation Therapy

Several retrospective series published in the 1960s claimed that PORT improved survival of patients with resected NSCLC, particularly if they had nodal metastases.[212-215] This issue has been investigated in several prospective trials that, although methodologically flawed, provide a consensus answer that survival is minimally if at all improved, but local failure is probably reduced with such treatment.

A meta-analysis of 2128 patients treated in nine randomized trials of PORT versus observation concluded that this treatment was associated with a highly significant increase in the risk of death[216] (Figure 44-2). Overall, the risk ratio was 1.21 ($p = 0.001$). The authors concluded that PORT as used in these studies was detrimental and should not be used, at least for the time being. There are several significant differences between the treatment administered in several of the trials included in this meta-analysis and current practice. One fourth of the patients had stage I disease and given patterns of failure PORT would not be expected to be beneficial (see Table 44-7). Details of treatment, including preoperative staging, surgical technique, and radiation dose and dose delivery, differed substantially from current practice. Several of the trials required or allowed daily fraction sizes in excess of 2.0 Gy, with the Medical Research Council (MRC) trial using 2.6 Gy/day and the Slovenian trial using 3.0 Gy/day. Larger fraction sizes would be expected to produce an increase in acute and late complications compared with smaller fractions. Seven of the nine trials also allowed the use of cobalt-60 (^{60}Co) treatment beams, with their poorer depth-dose characteristics than higher energy accelerator beams, and only one study included CT-based treatment planning. Compared with current practice, PORT as used in these trials was outmoded and probably caused excess deaths from cardiac and pulmonary damage. It is notable that in this meta-analysis the increase in risk of death was most marked in those patients with stage I disease and was not significant for patients with N2 disease.

The PORT Meta-analysis Group updated their analysis with the inclusion of one additional trial.[217] The overall conclusions that PORT was detrimental for patients with stage I or II NSCLC and that there was no clear evidence for benefit or detriment for patients with stage III N2 disease were not altered. However, results and updates of several other recent trials were not included in this analysis.[218-220]

TABLE 44-7 Rates and Patterns of Relapse after Resection of Non–Small Cell Lung Cancer

Study	Stage	Histology	No. Patients	Survival	Chest Only (%)	Distant Only (%)
Feld*[207]	T1N0	NSCLC	162	NS	9	17
	T2N0	NSCLC	196	NS	11	30
	T1N1	NSCLC	32	NS	9	22
Pairolero[208]	T1N0	NSCLC	170	71% (5-year)	6	15
	T2N0	NSCLC	158	59% (5-year)	6	23
	T1N1	NSCLC	18	33% (5-year)	28	39
Thomas*†[187]	T1N0	Squamous cell	226	≈85%	5	7
	T1N0	Nonsquamous	346	≈65%	9	17
Martini†‡[209]	T1-2, N1	Squamous cell	93	44%	16	31
	T1-2, N1	Adenocarcinoma	114	34%	8	54
	T2-3, N2	Squamous cell	46	≈30% (5-year)	13	52
	T2-3, N2	Nonsquamous	103	≈30% (5-year)	17	61

From Wagner H, Bonomi P: Preoperative and postoperative therapy for non–small cell lung cancer. In Roth JA, Ruckdeschel JC, Weisenburger TH, editors: Thoracic oncology, Philadelphia, 1995, WB Saunders, pp 147–163.

NSCLC, *Non–small cell lung cancer;* NS, *not specified.*

**First site of relapse only.*

†Relapse rates include patients with relapse in multiple sites.

‡Some patients received postoperative irradiation and/or chemotherapy.

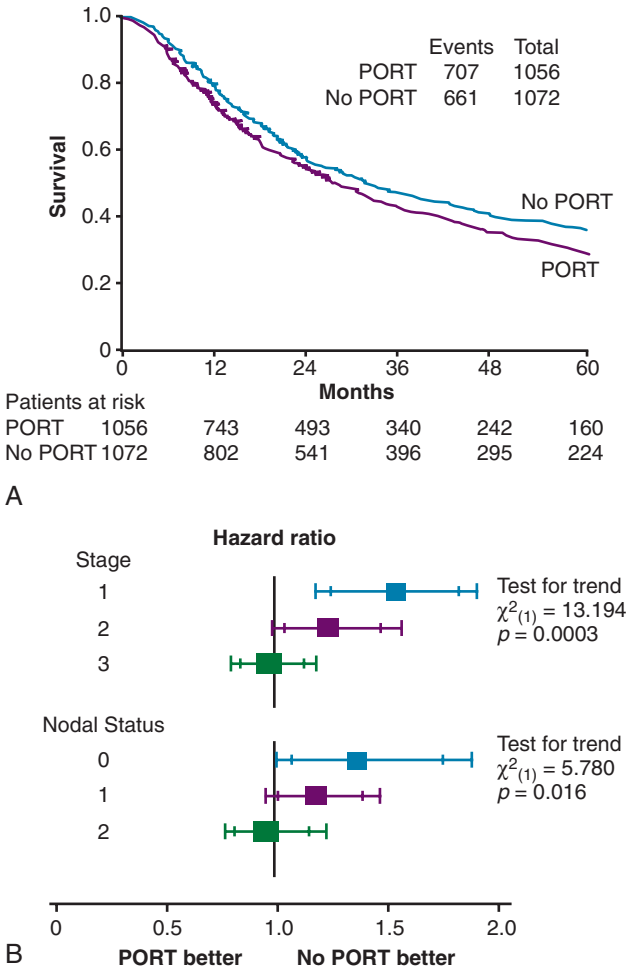


Figure 44-2 **A,** The overall survival curves for all patients analyzed show a significant deleterious effect of postoperative radiation therapy (PORT) on survival. **B,** This deleterious effect varies strongly with extent of local disease (expressed as stage group or N stage), with the hazard function not overlapping with unity for patients with stage groups 1 or N0 disease.
From Burdett S, Stewart L: Postoperative radiotherapy in non–small-cell lung cancer. Update of an individual patient data meta-analysis. Lung Cancer 47:81–83, 2005.

Several studies suggest an improved therapeutic ratio when PORT is delivered with modern techniques. Philips et al[221] reported improved survival and less cardiac and pulmonary toxicity associated with linear accelerator treatment and CT-based treatment planning compared with ^{60}Co therapy. A recent meta-analysis of PORT in N2 disease also suggested linear accelerator-based therapy was associated with the greatest benefit[222] Schraube et al reported calculated complication probabilities for patients receiving postpneumonectomy RT delivered using two-dimensional (2D) or three-dimensional (3D) treatment planning.[223] For equivalent physical doses to the mediastinal nodal target volume, the biologic mean dose to lung and heart and the associated normal tissue complication probabilities were considerably lower with 3D treatment planning. Machtay et al compared the rates of death from intercurrent disease (DID) for patients who had received adjuvant PORT.[224] They observed a 4-year actuarial risk of 13.5%, which was minimally, but not significantly greater than the 10% expected. The total radiation dose was strongly associated with the risk of DID: 2% for doses less than 54 Gy and 17% for 54 Gy and higher doses. Wakelee et al performed a retrospective analysis of DID in the INT 0115 trial, which compared PORT (50.4 Gy if no extracapsular extension, 59.4 Gy if this was documented) to concurrent PORT and chemotherapy with cisplatin and etoposide against that expected based on U.S. vital statistics.[225] The actuarial rates of DID at 4 years were 12.3% for irradiation and 13.7% for irradiation plus chemotherapy (not significant) and no higher than expected given the age and smoking status of the treated patients.

Selection of patients at highest risk for mediastinal recurrence after R0 resection cannot at present be done as accurately as desired. Although the presence of metastases in resected N2 nodes clearly predicts for disease in unresected nodes, the role of extracapsular extension has not been well investigated. One surgical study reported that it predicted for overall relapse in patients treated with surgery alone, whereas in another retrospective review it was found that postoperative mediastinal irradiation appeared to improve OS in patients with resected N2 disease without but not with extracapsular extension.[226,227] Evidence from several institutions indicates that locoregional failure is increasingly common with a higher number of involved N2 nodes and that induction chemotherapy followed by surgery often yields inadequate control of mediastinal disease.[228-231]

The CALGB initiated a Phase III trial of PORT in patients with resected N2 disease in the late 1990s, but only 40 patients accrued before the trial was closed leaving the issue unresolved.[232] Subsequent retrospective data with modern PORT include a review of the U.S. Surveillance, Epidemiology, and End Results (SEER) database indicating that although survival for patients with resected NSCLC was not generally improved by the addition of PORT, it was significantly improved for patients with N2 disease (hazard ratio, 0.855; 95% CI, 0.76 to 0.959).[233] Douillard et al reviewed the results of the ANITA trial in which patients with resected NSCLC, stages I through IIIA, were randomized to either adjuvant chemotherapy (cisplatin/vinorelbine) or observation. The use of PORT was left to individual investigator discretion, based on institutional preference. Although the numbers were small and not protected by randomization to PORT, the results were provocative. PORT was not beneficial for patients with N0 or N1 disease. But for patients with N2 disease, PORT improved both local control and survival whether or not patients received adjuvant chemotherapy, and did not significantly increase the risk of death from intercurrent disease.

If the PORT meta-analysis failed to demonstrate a survival benefit for patients with N2 disease because this benefit was counterbalanced by excess deaths resulting from complications of the RT as given and modern RT is less toxic as the described studies suggest, a trial conducted now might well show a survival benefit. The Institute Gustave-Roussey has coordinated a Phase III Trial of PORT compared to observation for patients with resected N2 NSCLC (the Lung ART trial). Patients may receive preoperative or postoperative chemotherapy. This trial has recently been joined by the EORTC and is scheduled to accrue 700 patients. Its primary endpoint is relapse-free survival (RFS), not overall survival, which allows for a smaller sample size than were overall survival the primary endpoint. As of December 2013 this trial had accrued 226 of the required 700 patients. A Phase III trial is also currently active in China for resected N2 disease, supported by data reported by Dai et al.[234]

A difficult clinical situation is the question of PORT for a patient without proven mediastinal lymph node involvement but whose surgery did not adequately sample or dissect the mediastinum. CT scans done postoperatively may show one or more somewhat enlarged mediastinal nodes, but this may reflect tumor or postoperative infection or inflammation. The use of PET in this setting has been explored by Roberts et al,

TABLE 44-8 Central Nervous System Relapse in Patients with Locally Advanced Non–Small Cell Lung Cancer

Study	Stage	No. Patients	CNS Failure (Crude Risk)	Median Survival (mo)
Choi[239]	T1-3, pN2		30%	25
Stuschke[238]	T1-4, pN2	28	46%	20
Albain[240]	pN2-3 or T4		21%	15
Andre[241]	cN2		22%	NA
Law[242]	IIIA/B or IV	32	28%	20

c, *Clinical;* mo, *month; NA*, *no data available;* p, *pathologic.*

who suggested that it might be helpful in directing when to give and when to withhold further therapy.[144] However positive nodes in this setting are not specific and should be considered for biopsy by endoesophageal or endobronchial ultrasonography.

At present adjuvant PORT cannot be recommended on the basis of improved survival but should be considered in selected patients at high risk of local recurrence, particularly when there is involvement of multiple nodal stations in the mediastinum or extracapsular tumor spread. Its use in conjunction with adjuvant chemotherapy is discussed in the next section. For patients with microscopically positive margins after resection the situation is quite different, and concurrent chemoradiation should be considered for residual microscopic disease.

Prophylactic cranial irradiation has been less well evaluated in patients with NSCLC than in SCLC. Three older reported randomized trials of prophylactic cranial irradiation in patients with NSCLC failed to show any survival benefit, but none of them included patients with early-stage, resected disease or even patients thought to be in complete remission after definitive RT (with or without chemotherapy).[235-237] One retrospective series reported benefit in CNS failure rates for prophylactic cranial irradiation in patients with stage III NSCLC treated with an aggressive chemoradiation regimen. The earlier group of patients who did not receive prophylactic cranial irradiation had a CNS failure rate of 46% (13 of 28) compared with 9% (4 of 47) in a subsequent group who received prophylactic cranial irradiation.[238] Others have also reported high CNS relapse rates for patients with stage IIIA/B NSCLC who were aggressively treated (Table 44-8). The RTOG more recently conducted a Phase III trial of prophylactic cranial irradiation in patients with stage IIIA/B NSCLC who had completed all other planned therapy, which included various combinations of surgery, RT, and chemotherapy, and had stable disease or better.[243] The trial had planned to accrue 1058 patients to evaluate a potential relative 20% improvement in OS as its primary endpoint but was closed after enrollment of 356 patients because of slow accrual. Neither overall nor disease-free survival was significantly different between the two arms, but the incidence of brain relapse at 1 year was 7.7% in the prophylactic cranial irradiation arm and 18% in the observation arm. The neurologic effects of PCI in this trial were reported by Sun et al, who noted no change in overall cognitive functioning but a significant decline in memory at 1 year for the PCI group.[244] As control of local and extrathoracic metastatic tumor improves, the potential benefit of PCI may increase, but it cannot be considered standard at this time.

Postoperative Chemotherapy

Early trials of postoperative chemotherapy for patients with resected NSCLC failed to show significant benefit. Many of these were conducted with agents with minimal antitumor activity in this disease, and all were underpowered to detect a modest but clinically worthwhile improvement in survival on the order of 5%. A meta-analysis of all published randomized trials comparing observation with adjuvant chemotherapy showed no overall benefit, but the results differed by type of chemotherapy regimen.[245] Older alkylating agent–based regimens significantly worsened survival by 5%, whereas cisplatin-based regimens gave a 5-year survival improvement of 5%, which approached statistical significance ($p = 0.08$). Although there was considerable heterogeneity of stage, surgical procedure, and planned and delivered chemotherapy, this result suggested that chemotherapy with modest activity for metastatic disease could improve survival in the adjuvant setting, as had been previously demonstrated in breast and colorectal cancers.

Several large trials of adjuvant chemotherapy have been reported since publication of the meta-analysis (Table 44-9). The North American Intergroup conducted a large trial designed to test the efficacy of postoperative chemotherapy in patients with completely resected N1 and N2 NSCLC.[246] PORT was included in both arms to optimize local control, potentially increasing the ability to detect an effect of chemotherapy on systemic metastases. This trial (INT 0115), which enrolled 488 patients, showed no trend or significant difference in survival for the two arms, regardless of whether all 488 entered patients or 368 eligible and evaluable patients were considered. Multivariate analysis showed no benefit for the chemotherapy used in this study (i.e., four cycles of cisplatin and etoposide beginning concurrently with the start of irradiation) for any clinical subset of patients. Concurrent chemoradiation also failed to improve local mediastinal control, compared with RT alone.

The Adjuvant Lung Project Italy (ALPI) accrued 1209 patients with resected stage IA-IIIA NSCLC and randomized them to either observation or to chemotherapy with mitomycin, vindesine, and cisplatin.[247] Forty-three percent of patients also received PORT (after chemotherapy if this was given). There was a survival trend favoring the chemotherapy study arm that did not reach statistical significance.

The International Adjuvant Lung Cancer Trial (IALT) is the largest trial of adjuvant chemotherapy in lung cancer ever conducted.[249] The trial was designed to study 3000 patients, but it closed after enrolling 1867 patients because of declining accrual and evidence of a significant difference between the arms of the trial on interim analysis. Patients were randomized between observation and adjuvant chemotherapy that used cisplatin and an institutional choice of second agents (i.e., etoposide, vindesine, vinblastine, or vinorelbine). RT could be given (by institutional policy) after chemotherapy. There was an overall absolute improvement in the 5-year survival rate of 4% (44.4% versus 40.4%), which was highly significant, was present for all stage groups, and was observed whether patients also received postoperative mediastinal irradiation (not a randomized variable in this trial but done according to institutional preference). Although this trial showed a clear benefit in survival for adjuvant chemotherapy, it did not provide information on patterns of failure.

TABLE 44-9 Adjuvant Chemotherapy Trials

Study	No. Patients	Stage	Regimen	5-year Survival	*p* Value
Keller[246]	488	IIA-IIIA (N1-2)	RT/DDP/VP16 RT		NS
Scagliotti[247]	1209	IA-IIIA	MMC/VNB/DDP OBS	HR 0.96	NS
Douillard[248]	840	I-IIIA	DDP/VNB	HR 0.80*	
Arriagada[249]	1867	IA-IIIB	DDP/X OBS	44.4	<0.03
Strauss[250]	344	IB	CBP/PTX OBS	71 (4-year) 59	0.028
Winton[251]	482	IB-II (T3 N0)	DDP/VNB OBS	69 (3-year) 54	0.011
Kato[252]	716	IA	Oral UFT OBS	89 90	NS
	263	IB	Oral UFT OBS OBS	85 74	0.005

CBP, *Carboplatin;* DDP, *cisplatin;* HR, *hazard ratio;* MMC, *mitomycin C;* NS, *not significant;* OBS, *observation;* UFT, *tegafur and uracil;* VNB, *vinorelbine;* VP16, *etoposide;* X, *etoposide, vinblastine, vindesine, or vinorelbine.*
**8.4% absolute survival advantage at 7 years.*

Two other trials have demonstrated the strong, positive effects of adjuvant chemotherapy. The National Cancer Institute of Canada Cancer Treatment Group (NCIC-CTG) randomized patients with resected stage IB and stage II NSCLC to observation or to adjuvant chemotherapy with cisplatin and vinorelbine.[251] They found a large and significant improvement in OS: 69% versus 54% at 5 years. Despite the availability of effective antiemetic regimens, compliance with this adjuvant chemotherapy regimen was not very good; only about 50% of patients completed all four cycles of this regimen, with variations by age, gender, extent of surgery, and nationality.[253] The CALGB randomized patients with resected stage T2N0M0 NSCLC to observation or to adjuvant therapy with carboplatin plus paclitaxel. The result of this trial was initially positive, with 71% versus 59% survival at 4 years, but the difference became nonsignificant with longer follow-up and the *p* value rose from 0.028 to 0.10.[250]

Douillard et al in the ANITA trial compared a combination of vinorelbine and cisplatin to observation in patients with resected NSCLC and demonstrated a statistically significant survival advantage that has stood the test of time.[248] Eight hundred and forty patients with stage IB-IIIA NSCLC from 101 centers in 14 countries were randomly assigned to observation ($n = 433$) or to 30 mg/m^2 vinorelbine plus 100 mg/m^2 cisplatin ($n = 407$). Postoperative radiotherapy was not mandatory and was undertaken according to individual institution policy. 367 patients in the chemotherapy group and 431 in the control group received their assigned treatment. 301 (36%) patients had stage IB disease, 203 (24%) had stage II disease, and 325 (39%) had stage IIIA disease. Side effects of chemotherapy mainly included neutropenia in 335 (92%) of patients and febrile neutropenia in 34 (9%); seven (2%) toxic deaths were also recorded. After a median follow-up of 76 months (range 43 to 116 months) median survival was 65.7 months (95% CI, 47.9 to 88.5) in the chemotherapy group and 43.7 (35.7 to 52.3) months in the observation group. Adjusted risk for death was significantly reduced in patients assigned chemotherapy compared with controls (hazard ratio, 0.80; 95% CI, 0.66 to 0.96); $p = 0.017$. Overall survival at 5 years with chemotherapy improved by 8.6%, which was maintained at 7 years (8.4%) in follow-up.

Hotta et al[254] published a meta-analysis of trials of adjuvant chemotherapy limited to those trials reported after the Collaborative Group meta-analysis published in 1995. Eleven trials and 5716 patients were analyzed. Trials mandating PORT in both arms (e.g., INT 0115) were excluded. With the exception of several Japanese trials using only tegafur and uracil (UFT), the chemotherapy incorporated was cisplatin plus a variety of other agents, mostly *vinca* alkaloids or etoposide. A significant survival improvement (hazard ratio, 0.872; $p = 0.001$) was seen overall, and in subset analysis this held for the cisplatin-containing chemotherapy and for UFT. The latter results are surprising in view of the rather low response rates (6.3%) seen with UFT in the setting of metastatic disease.[255] Hamada et al also analyzed six published Japanese trials of UFT adjuvant chemotherapy with a highly significant improvement in 5-year OS (absolute magnitude of 5%; $p = 0.01$).[256] Despite the success in Japan, the use of UFT or other fluorinated pyrimidines has not gained wide acceptance in North America or Europe.

A meta-analysis of these recent trials, the Lung Adjuvant Cisplatin Evaluation (LACE) has confirmed an OS benefit for cisplatin-containing adjuvant chemotherapy for patients who are node-positive.[257] There is no clear signal for patients with node-negative tumors, but there is a suggestion of benefit for patients with lesions greater than 4 cm in diameter. Several recent publications with longer follow-up of some of the adjuvant trials have reported conflicting results as to the durability of the benefit of adjuvant chemotherapy. The IALT trial showed survival benefit for the first 5 years but not with longer follow-up, similar to results seen by the CALGB using carboplatin and paclitaxel for earlier stage disease. But the Canadian trial using cisplatin/vinorelbine reported continued benefit beyond 5 years, as did the ANITA trial led by Douillard et al.

Off-study clinical policy currently should recognize the following:

1. Cisplatin-containing doublets have shown modest but statistically significant survival benefit in a number of trials of patients with resected NSCLC and should be considered for all fit patients with resected stage II or IIIA NSCLC and in selected patients with stage IB NSCLC.
2. The benefits are most clearly seen in patients with node-positive tumors and possibly with larger (>4 cm) node-negative tumors.
3. Substitution of carboplatin for cisplatin is not supported by the available data but may be considered for patients with contraindications to cisplatin.

4. Age is not an impediment to treatment or therapeutic benefit, but minimal data exist for patients 75 years of age or older.
5. The role of molecular selection of patients for adjuvant therapy, for example by *ERCC1* expression, is suggested in some retrospective analyses but awaits wider confirmation and the availability of reliable and readily reproducible assays.
6. The role of molecular targeted agents (including cetuximab and bevacizumab), EGFR-TKI (e.g., gefitinib, erlotinib, afatinib) for patients with activating EGFR mutations, crizotinib for patients with EML4/ALK translocations as well as vaccines and other immunomodulators is currently under active investigation but is not established.

Although there are sufficient data to establish adjuvant chemotherapy as standard for most patients with resected NSCLC, with the exception of patients with stage T1N0M0 disease, there are few data on the ability of this therapy to reduce the high rates of local recurrence seen in some patient subgroups. With the failure of CALGB 9734 to accrue adequate numbers of patients, the question of adjuvant RT in combination with or after adjuvant chemotherapy for patients with N2 disease remains unresolved and as noted previously is being addressed in active Phase III trials in Europe and China.

Potentially Resectable Disease: Stages IIIA and IIIB

Preoperative Treatment for Patients with Resectable Non–Small Cell Lung Cancer

Several trials conducted in the 1960s showed that for patients with initially resectable lung cancers, preoperative RT did not improve survival, and for those with initially unresectable disease, it improved resectability, but had no subsequent effect on survival.[258-260] Surgical complications, particularly bronchopleural fistulas, were increased. The approach was largely discarded until recently, when a flurry of trials of preoperative chemotherapy or chemoradiation prompted renewed interest in preoperative RT. Unlike the trials of the 1960s, these trials have used strict criteria for resectability, surgical staging of the mediastinal nodes, and modern attention to RT planning.

Two small, randomized, Phase II trials have been reported from the CALGB and the Lung Cancer Study Group (LCSG).[261,262] Both studies randomized patients with unresectable stage IIIA/B NSCLC to either preoperative RT followed by surgery or preoperative chemotherapy followed by surgery. Postoperative treatment was not specified in the LCSG trial but included RT to varying doses depending on tumor status at time of resection in the CALGB trial. Table 44-10 shows the results of these two trials, as well as those of several other randomized trials that compared immediate resection to induction chemotherapy followed by surgery for patients with stage IIIA NSCLC.[263-266] Results of the trials reported by Roth and Rosell, though quite small, were significantly positive, and the trials were closed early because of survival differences seen on interim analysis, but the LCSG, Japan Clinical Oncology Group (JCOG), and CALGB trials failed to show any difference in survival or resectability between preoperative RT, a strategy that might improve local but not systemic control, and preoperative chemotherapy. The trial by Depierre included patients with stages IB through IIIB; and although it demonstrated a survival benefit for patients with stage IB and IIA/B disease, it did not show a significant difference for patients with stage IIIA disease. Because all of these studies were small, there is no consensus on the optimal management of patients with operable stage IIIA NSCLC. In the United States, many centers advocate the use of preoperative treatment with chemotherapy or chemoradiation, but whether this is superior to resection and postoperative therapy or definitive chemoradiation without surgical resection remains unclear, although a number of theoretical considerations ranging from better patient tolerance to earlier treatment of occult systemic disease favor the preoperative approach.

The Bimodality Lung Oncology Team (BLOT) investigated preoperative therapy in patients with clearly resectable stage IB and II NSCLC using carboplatin and paclitaxel for two or three cycles. Despite a low overall pathologic complete response rate of only 5%, 2- and 3-year survival rates

TABLE 44-10 Randomized Phase II and Phase III Trials of Neoadjuvant Therapy in Patients with Stages IIIA/IIIB Non–Small Cell Lung Cancer

Study	Therapy	No. Patients	Median Survival (mo)	2- to 3-year Survival
Pass[263]	ST	14	15.6	23*
	PE→ST	12	28.7	50
Rosell[264]	ST	30	8	0*
	MIP→ST	29	26	29
Roth[265,266]	ST	32	11	15*
	CEP→ST	28	64	56
Wagner[267]	MVP→ST	24	12	≈30†
	RT→ST	25	12	≈30
Elias[261]	PE→ST→PE→RT	23	23	NA
	RT→ST	24	19	NA
Depierre[268]	ST	(167)	NR	21‡
	MIP→ST			28
Ichinose[269]	ST	(62)	16	25‡
	PE→ST		18	8
Pisters[270]	ST	168	41	38
	CP→ST	169	62	48

CEP, *Cyclophosphamide, etoposide, and cisplatin;* MIP, *mitomycin C, ifosfamide, and cisplatin;* mo, *months;* MVP, *mitomycin C, vinblastine, and cisplatin;* NA, *data not available;* NR, *not reported;* PE, *cisplatin and etoposide;* RT, *radiation therapy;* ST, *surgery.*

**Three-year survival.*

†Two-year survival.

‡Five-year survival.

compared favorably with those of historical controls.[271] The data were sufficiently encouraging to warrant a prospective trial coordinated by the Southwest Oncology Group (SWOG, S9900) comparing surgery alone to induction chemotherapy for patients with stage IB through IIIA disease.[270] Unlike the original BLOT trial, pathologic assessment of the mediastinum was not required. The accrual goal of this trial was over 600 patients, but it was closed early in 2004 because of declining accrual when the positive results of the Depierre trial for preoperative chemotherapy (at least for patients with stage IB and II disease) and the positive IALT trial for adjuvant postoperative chemotherapy for all stages made randomization to the surgery only arm unappealing. Results on the 365 patients entered showed modest benefits in PFS and OS for the induction chemotherapy arm, but these did not reach statistical significance.

A Spanish trial that compared surgery alone to either preoperative or postoperative chemotherapy (the NATCH trial) failed to show a PFS benefit for either timing of chemotherapy, and a meta-analysis of trials of preoperative or postoperative chemotherapy for patients with resectable NSCLC did not find any difference between these strategies with respect to OS.[272] In addition, an indirect comparison meta-analysis of trials of either preoperative or postoperative chemotherapy compared with surgery alone failed to show differences in the hazard ratios for either disease-free or OS between the preoperative and postoperative approaches.[273] However, a more recent meta-analysis performed by the NSCLC Meta-Analysis Collaborative Group, which examined 2385 patients (Stage IB-3A) entered in 15 randomized trials, did show a survival benefit of 5% at 5 years for preoperative chemotherapy.[274]

The role of surgery in patients with stages IIIA and IIIB disease remains controversial. A small RTOG/Eastern Cooperative Oncology Group (ECOG) trial of induction chemotherapy followed by RT or surgery found no difference in outcome but was inadequately powered.[275] The North American Intergroup Trial INT 0139 that randomized patients with pathologic N2 disease to definitive chemoradiation (cisplatin/etoposide concurrent with 61 Gy) or concurrent preoperative chemoradiation to 45 Gy showed better PFS but no OS benefit with the inclusion of surgery; however, an unplanned subset analysis of patients who underwent lobectomy compared with carefully matched patients who were thought to be candidates for lobectomy had they been randomized to the trimodality arm did show a survival benefit.[276] Of note, the surgical mortality rate in this trial was much higher for patients undergoing pneumonectomy, on the order of 23%, which may have nullified any chance of observing an OS benefit. Advocates of surgery argue that better exclusion of patients at poor risk for surgery would have shown an OS benefit, whereas partisans of nonsurgical treatment will point out that there have been significant improvements in radiographic staging (e.g., PET/CT) and RT planning and delivery since this trial was conducted (1994-2001), and that the trial overall failed to show an OS advantage.

In the European Organization for Research in Cancer Therapy (EORTC) trial 08941 patients with stage IIIA (N2) NSCLC received induction chemotherapy with cisplatin/etoposide and responders were randomized between RT and surgery. There was no difference in median or 5-year survival between these approaches.[277]

Neither of these trials, which are the largest published to address the role of surgery for patients with stage IIIA (N2) disease, showed a clear benefit. They do differ considerably in design, and neither meets current standards for staging or treatment delivery. Strong advocates of either surgical or nonsurgical approaches to these patients are unlikely to be convinced by the results.

A German Lung Cancer Group trial of preoperative CT alone or CT plus RT showed no PFS or OS benefit to the irradiation-containing arm of this study.[278] However, PORT was given to the patients in the study arm not receiving preoperative RT. The overall resectability rate in the trial was low, only about 50%, in a population that was composed of about two thirds of patients with stage IIIB disease. By including RT in both arms of the trial, the issue becomes one of timing rather than amount of treatment, and the similarity in overall outcome is perhaps not surprising.

Betticher et al reported on 90 patients with stage IIIA N2 NSCLC given induction chemotherapy with cisplatin and docetaxel, of whom 75 underwent resection, with 59 R0 resections (i.e., microscopically negative margins).[279] The overall median survival was 27.6 months and 33 months for patients who were resected. Among patients with resected disease, 50% experienced relapse (10 local, 10 local plus distant, and 18 distant only). The pathologic complete response (CR) rate in this trial was 19% of patients who underwent resection. An RTOG neoadjuvant (RTOG 0412) trial took the Betticher regimen and added RT in one arm to determine whether preoperative RT in this setting could improve local control, but this trial closed prematurely because of low accrual.

Several trials have shown that those patients faring best after preoperative treatment with chemotherapy or chemoradiation were those with pathologic sterilization of mediastinal nodes but not necessarily of the primary tumor. This has prompted trials evaluating higher preoperative radiation doses. The RTOG (RTOG 0229) has demonstrated that 60 Gy concurrent with weekly carboplatin and paclitaxel in carefully selected patients could be delivered with acceptable toxicity, a high resectability rate and more than 50% mediastinal nodal clearance.[280]

If sterilization of mediastinal lymph nodes is a useful criterion in selecting patients for surgery, how can this best be assessed preoperatively? CT is not particularly helpful, and it is not clear that early PET, done to allow resection within 4 to 6 weeks after neoadjuvant therapy, can discriminate between dead or dying cells or radiation-induced inflammatory changes at this early point. Biopsy by either endobronchial ultrasound (EBUS) or mediastinoscopy ultimately may be the gold standard, but using the presence or absence of residual nodal involvement after definitive chemoradiation to make therapeutic decisions is hazardous: to begin, results may be unreliable in the setting of radiation therapy (XRT) induced inflammation or fibrosis; secondly, a subset of patients with viable nodes after chemoradiation may still be cured by surgical resection.

Unresectable Stages IIIA and IIIB Disease

There are few good prospective data exploring the role of radiation dose on local control and survival in patients with NSCLC. In the 1980s it was believed by many authorities that local control could be achieved in about one half of patients treated to doses to 60 Gy given in 30 fractions over 6 weeks. However, the data on which that assumption was based (RTOG 73-01) indicated failure of local progression at time of systemic progression or death, which almost certainly overestimates long-term local control rates in an era when neither CT nor CT/PET was used to assess local control.[281] Patients were randomized to 40 Gy, 50 Gy, or 60 Gy given as a continuous course at a dose of 2 Gy/day and to a fourth arm of 40 Gy given by split course (i.e., 20 Gy in five fractions, a 2-week break, repeated dosage). The 50-Gy and 60-Gy arms showed modest improvement in local control and survival compared with the 40-Gy split or continuous arms, but this advantage was lost after 2 years. The lack of durable benefit for the higher doses may be the result of a number of factors: (1) poor local control even at higher doses, (2) the lack of CT treatment

planning, and (3) the use of posterior spinal cord blocks that shielded mediastinal lymph nodes. Patterns of failure in this trial were reported in terms of crude risk of clinically detected local failure: 33% with 60 Gy and 44% to 49% with 40 Gy.

It is incorrect to assume that local control is achieved in 67% of patients with 60 Gy. Le Chevalier et al[282-284] reported actuarial local control of only 17% to 20% at 1 year, in patients assessed radiographically and bronchoscopically after definitive RT to a dose of 65 Gy in 26 fractions in 6.5 weeks either alone or preceded or followed by chemotherapy with cyclophosphamide, cisplatin, lomustine, and vindesine. This percentage fell to about 10% at 4 years. In addition to its necessity for cure, local control is also important for quality of life because even patients dying of systemic disease are benefited if they can avoid the complications of local disease progression, such as airway obstruction with dyspnea or postobstructive infection, hemoptysis, compression of mediastinal structures such as the superior vena cava and phrenic or recurrent laryngeal nerves, or pain from chest wall invasion.

Several strategies have been investigated to improve local control. One approach uses chemotherapeutic agents or biologic response modifiers in conjunction with irradiation, and several of these appear to be effective. Another involves surgery after induction therapy with chemotherapy, RT, or both, a strategy that is undergoing investigation in the Phase III trials discussed in the preceding section. Strategies involving modification of radiation time dose and fractionation have also been explored, falling into the general categories of accelerated hyperfractionation and classic hyperfractionation.

COMBINING RADIATION THERAPY AND CHEMOTHERAPY

One risk of multimodality therapy of lung cancer is the potential for extending the time from initial presentation to the start of definitive local treatment. Several reports have shown inconsistent effects of time to treatment on average and long-term survival of lung cancer patients. This may stem in part from starting patients with a disease with a poor prognosis on simple palliative treatment quickly, with more delay for both thorough staging and planning of more complex treatment for patients treated with curative intent. In the study by Wang et al, no benefit in average survival was seen, but there was a significant association between shortened time to treatment and survival for patients who lived more than 5 years, about 10% of the entire population.[285]

Chemotherapy and RT can be combined in several ways. One can try to achieve additive cytotoxicity by treating the known local disease with RT and the local and systemic disease with chemotherapy. Such an approach is epitomized by the use of induction chemotherapy before local treatment with RT or surgery. This strategy may allow greater sparing of normal tissue by virtue of smaller RT target volumes or lesser resections performed on the postchemotherapy tumor volume. Another approach is to administer RT and chemotherapy concurrently in the hope of shortening the overall time of treatment and avoiding delay of starting either modality, in effect, turning off the "metastatic engine." Both approaches have proven superior to RT alone in prospective trials conducted in the 1980s and 1990s. Concurrent therapy has more acute toxicity (myelosuppression and esophagitis), but its superiority to sequential therapy has been demonstrated in additional trials. At least six randomized trials comparing the sequential and concurrent use of chemotherapy and RT for patients with stage IIIA/B NSCLC have been reported (Table 44-11). Although all trials addressed the same general question of sequencing, they differed in many details. Different chemotherapy regimens with different toxicity profiles were used. The number of cycles of induction chemotherapy administered before RT varied from two to four. It is not clear in these trials whether the prechemotherapy or postchemotherapy tumor volume was taken as the gross tumor volume or whether treatment planning was completed before the start of chemotherapy.

Some of these trials demonstrated a clear-cut advantage for concurrent chemoradiation; others did not. However, meta-analysis of individual patient data, confirmed the superiority of concurrent rather than sequential irradiation and chemotherapy.[291] An alternate interpretation is that the overall treatment time is key and that this is intrinsically shorter for concurrent regimens. With protraction of the overall treatment time, accelerated repopulation of the tumor, which may have begun during chemotherapy, may outpace the ability of daily fractionated radiation to kill remaining tumor clonogens. Data from the U.K. Continuous Hyperfractionated Accelerated Radiation Therapy (CHART) trial and ECOG 2597 are consistent with this hypothesis. The median survival for the ECOG sequential chemotherapy followed by accelerated irradiation arm was 20.3 months compared with 14 months for patients receiving conventional irradiation after chemotherapy.[292]

Similarly, the CHART trial showed a clear-cut survival advantage for continuous hyperfractionated XRT given three times a day compared to conventional once-daily XRT over a

TABLE 44-11 Chemoradiation Sequencing in Non–Small Cell Lung Cancer: Randomized Trials

Study	No. Patients	Chemotherapy Regimen	Radiation Dose (Gy)	Median Survival (mo)	Actuarial Survival (%)	Statistics	Comments
Furuse[286]	314	MVP	56 SEQ 56 CON	13 17	9 19 (2-year)	$p = 0.04$	Improved local control in concurrent arm despite split-course RT
Curran[287]	400	VP	63 SEQ 63 CON	14.6 17.1	18 26 (3-year)	$p = 0.04$	Third arm with concurrent twice-daily RT and DDP/VP16 was not statistically superior to sequential arm
Pierre[288]	212	NP EP/NP	66 SEQ 66 CON	13.9 15.6	24 36 (2-year)	NS	Different chemotherapy regimens in the two arms
Zatoukal[289]	102	NP	60 SEQ 60 CON	13 20.4		$p = 0.02$	RT delayed until after four cycles of chemotherapy in sequential arm
Choy[290]	178	TC	63 SEQ 63 CON	13 17.2	31 35 (2-yr)	NS	Randomized Phase II trial without planned comparison between arms

CON, *Concurrent;* DDP, *cisplatin;* MVP, *mitomycin C/vindesine/cisplatin;* NP, *vinorelbine/cisplatin;* NS, *not specified;* PE/NP, *cisplatin and etoposide during RT/navelbine and cisplatin after RT;* RT, *radiation therapy;* SEQ, *sequential;* TC, *paclitaxel/carboplatin;* VP, *vinblastine/cisplatin.*

longer period. The CALGB has reported a trial comparing induction chemotherapy with carboplatin and paclitaxel followed by concurrent chemoradiation with initial concurrent therapy. Unlike the Locally Advanced Multimodality Protocol (LAMP) trial, this was planned as a Phase III comparison. This large cooperative group trial failed to confirm the earlier Phase II results, with somewhat disappointing median survival times of 11.4 months for the initial concurrent regimen and 14 months for induction followed by concurrent therapy (p = 0.154) though it should be noted that this trial allowed enrollment of patients with more than 5% weight loss.[293]

The SWOG conducted a Phase II trial employing consolidation with docetaxel rather than additional cycles of cisplatin plus etoposide after concurrent irradiation with cisplatin plus etoposide (EP/XRT) in patients with stage III unresectable NSCLC. Median survival was 26 months, and the 3-year survival rate was 37%. In a prior SWOG trial exploring continued cisplatin plus etoposide as consolidation, the median survival time was 15 months and 3-year survival was 17%.[294] This is a striking difference, but it should be noted that these two studies were conducted in different treatment eras, with potentially different staging, patient allocation, and treatment planning. The Hoosier Oncology Group (HOG) attempted to confirm the SWOG results in a Phase III trial comparing EP/XRT alone to EP/XRT followed by three cycles of consolidation with docetaxel, but this study showed no survival benefit for consolidation therapy with docetaxel despite a significant increase in toxicity and hospitalization.[295]

Before the results of the HOG trial the SWOG incorporated consolidation docetaxel as part of their standard treatment regimen in a trial testing the role of maintenance gefitinib in unselected patients whose EGFR mutation status was not already identified. This trial showed significantly poorer disease specific and OS in the patients receiving gefitinib compared to placebo, for reasons that are not fully understood.[296] One possible explanations includes the development of more aggressive phenotypes (e.g., *MET* mutation) because of the selective pressure of gefitinib. In addition, molecular testing was not routinely performed on tumor specimens, so an unappreciated negative selection bias might have prevailed. For this reason, a recently initiated Intergroup trial (RTOG 1306) will test induction therapy for 3 months with either erlotinib followed by definitive chemoradiation in patients with documented activating mutations of EGFR or crizotinib followed by definitive chemoradiation in patients with documented ALK translocations.

At present, however, there is no established role for additional chemotherapy or targeted therapy after concurrent radiation and systemically dosed chemotherapy for patients with stages IIIA and IIIB NSCLC. In patients who receive radiosensitizing doses of chemotherapy during XRT, it is common to deliver one or two cycles of full-dose chemotherapy after completion of concurrent RT, but this is a strategy that has never been prospectively compared to observation alone after completing chemotherapy and concurrent XRT.

INTEGRATION OF MOLECULAR TARGETED AGENTS WITH RADIATION THERAPY

Identification of radioresistant cells in human tumors has led to several approaches to sensitize them while not altering the radiation response of normal tissues. Tumor cells may be resistant because of the local environment (e.g., hypoxia) or because of genetic changes (e.g., mutations in *TP53* or *KRAS*). Past strategies have attempted to reverse environmental hypoxia without great success, but some newer agents show promise. Several approaches that exploit specific tumor genetic changes are also being explored.[297,298]

Epidermal Growth Factor Receptor Inhibitors

Exposure of cells to ionizing radiation induces phosphorylation of EGFR and activation of its kinase activity in much the same fashion as binding of ligands such as EGF or transforming growth factor-α. This leads to activation of several signaling cascades with resultant increased cellular proliferation, decreased apoptosis, and stimulatory effects on neoangiogenesis and DNA repair.[299-302] Inhibition of these processes through anti-EGFR monoclonal antibodies, expression of a dominant-negative truncated version of EGFR, or low-molecular-weight compounds that bind to the ATP site of EGFR and block its kinase activity can result in significant radiosensitization of a number of cell lines in vitro and in vivo.[303,304] A Phase III trial comparing RT with or without the anti-EGFR antibody C225 in patients with squamous cell carcinoma of the head and neck, which commonly overexpresses EGFR, has demonstrated clinically significant improvements in local control and survival.[305] Similar trials in NSCLC using monoclonal antibodies (e.g., C225) and the low-molecular-weight tyrosine kinase inhibitors (TKIs) erlotinib and gefitinib have been conducted.

The RTOG conducted a Phase II trial investigating the combination of cetuximab with concurrent weekly carboplatin and paclitaxel and radiation to 63 Gy that showed acceptable toxicity and an encouraging median survival of about 22 months. Unfortunately, RTOG 0617, one of the largest studies ever conducted in LA-NSCLC, failed to demonstrate a survival benefit for the addition of C225 to standard chemoradiation compared with radiation alone, although a post-hoc analysis suggested that patients with heightened EGFR expression (H scores exceeding 200) might enjoy a survival advantage with the addition of C225.[306] To date, there are no mature Phase III trials showing a survival benefit for EGFR TKIs in combination with XRT or chemoradiation. Several groups have shown that objective regressions of NSCLC in response to treatment with EGFR TKIs occur almost exclusively in patients with specific point mutations in the ATP-binding region, which are present in only a minority of patients, though relatively more common in women, never smokers, East Asians, and those with adenocarcinoma.

The incremental activity of bevacizumab in combination with chemotherapy in patients with metastatic NSCLC and theoretical considerations and demonstration in colorectal cancer of increased tumor perfusion after bevacizumab treatment prompted interest in its combination with chemoradiation for patients with stage III NSCLC and limited SCLC. Several small trials were conducted using concurrent treatment, with disturbing reports of life-threatening hemoptysis as well as formation of tracheobronchial fistulas, prompting early trial closure.[307] Such combinations, and by extrapolation other strategies combining RT or chemoradiation with antivascular agents, should be approached with caution and only in the context of a clinical trial.

Radiation Dose and Fractionation

In North America, dose and fractionation for curative treatment of patients with unresectable NSCLC has generally been 1.8 Gy to 2.0 Gy per fraction, one fraction per day, 5 days per week, to a total dose of 60 Gy to 65 Gy. Such a low total dose has been recognized as unlikely to achieve a high rate of local control, but simple dose escalation using conventional radiation techniques was limited by acute and late toxicity to normal tissues. Several series have challenged this assumption by using conformal treatment planning and quantitative evaluation of doses to various normal tissues. Retrospective data

from the University of Michigan found a relationship between radiation dose and survival for patients with stage III NSCLC, which was seen both for patients receiving irradiation as a single modality as well as those undergoing concurrent or sequential chemoradiation.[308] Some of these trials have also limited the target volume by eliminating ENI.[152,190] Others have treated more traditional elective volumes, at least to doses of 50 Gy or so for possible microscopic disease.[309] These trials have clearly demonstrated the feasibility of dose escalation substantially above what had been previously believed limiting, to at least 74 Gy to 78 Gy. Retrospective review suggests improvement in clinical outcome, particularly in patients with bulky disease, with higher doses of XRT.[310] Whether these doses truly result in better local control and survival when used as a component of combined-modality therapy remains to be demonstrated in prospective trials.

The RTOG recently completed a randomized Phase III trial (RTOG 0617) in patients with stages IIIA/B NSCLC comparing 60 Gy to 74 Gy in combination with concurrent and consolidation chemotherapy (with or without cetuximab in a second randomization) to address the dose question.[311] In both trial arms only gross disease was targeted; there was no ENI. Unfortunately, the high dose arm unexpectedly and paradoxically sustained inferior survival and impaired control compared to the standard dose. The reasons for this remain unclear and an assessment of possible differences in treatment planning between the two arms is ongoing.

The use of altered fractionation schedules is an attempt to exploit differences between tumor and normal tissues in the fraction-size dependence of their radiation sensitivity.[312] Several variations on standard fractionation have been proposed and evaluated:

- *Hyperfractionation:* The use of small fractions (e.g., 100 cGy to 120 cGy) given two or more times each day to allow a higher total dose to be delivered within the tolerance of late effects to normal tissues.
- *Accelerated fractionation:* Reduction of the overall treatment time to decrease tumor cell proliferation during RT, increasing the probability of local control for a given dose. This may reduce the effects of repopulation and acquired resistance.
- *Concomitant boost:* Another approach to reduce proliferation during treatment is to begin with conventional fractionation but accelerate with twice-daily treatment during the last 2 or 3 weeks of treatment when accelerated repopulation increases.
- *Continuous hyperfractionated accelerated RT:* In a combination of the previous two methods, fraction size is decreased but overall time significantly shortened, typically by treating with three fractions per day.

In addition to these strategies, many other approaches have been proposed and tested. Some regimens feature accelerated fractionation in two courses with an intervening treatment break. Although the dose rate during the weeks of treatment is increased, when the break is taken into account, the overall rate of dose delivery is often only minimally greater than with conventional fractionation.

Hyperfractionation

The RTOG conducted a series of trials exploring the use of altered fractionation in NSCLC.[313,314] The first groupwide trial (RTOG 81-08) evaluated acute toxicity of several radiation dose levels using fractions of 1.2 Gy given 4 to 6 hours apart. Dose to the initial large volume encompassing known and electively treated tissues was always 50.4 Gy, whereas the dose to known disease was increased from 50.4 Gy to 60 Gy, 69.6 Gy, and 74.4 Gy. This was a dose-seeking and toxicity study, but comparison of the group of patients treated to 69.6 Gy with contemporaneous controls from other trials (RTOG 78-11 and 79-17) suggested a late survival benefit (8.3 ± 4.0% versus 5.6 ± 1.5% survival at 5 years). After this, in RTOG 83-11 the total dose was increased in two sequential randomizations from 60 Gy to 79.2 Gy.[315] Late toxicities were similar in all trial arms, and OS did not differ between arms. However, when a favorable subset of patients was analyzed, identified retrospectively by the CALGB criteria of good performance status and minimal weight loss, the 69.6-Gy arm appeared superior to other arms and to 60 Gy in 6 weeks as featured in other RTOG trials (13 months on median survival time [MST], and 1- and 2-year survival rates of 56% and 29%, compared with 9 months on RTOG 83-21, and 1- and 2- year survival rates of 35% and 10%, respectively). The higher-dose arms did not show this benefit, although they were not associated with greater reported toxicity, which might have offset a better therapeutic effect.

An Intergroup RTOG/ECOG trial made two comparisons: conventional RT alone or preceded by induction chemotherapy (as in CALGB 8433) and, as a third arm, the 69.6-Gy, twice-daily regimen, which seemed to have had the best therapeutic index of various dose levels tested in prior RTOG trials. This study confirmed the benefit for induction chemotherapy, previously observed by the CALGB trial using an identical regimen, with a statistically significant survival advantage for induction vinblastine and cisplatin compared to standard RT alone.[316,317] The twice-daily arm was numerically superior to daily fractionation, but the differences did not reach statistical significance.

The North Central Cancer Treatment Group (NCCTG) conducted a trial of similar design. Instead of using a continuous twice-daily regimen, they employed a split-course regimen of 1.5 Gy given twice daily for 20 fractions over 2 weeks, a 2-week break, and another 1.5 Gy given in 20 fractions.[318] The total dose was 60 Gy in 20 fractions, but the overall time was no shorter than with conventional fractionation. This was compared with standard fractionation of 60 Gy in 30 fractions over 6 weeks. A third arm combined the twice-daily split-course regimen with concomitant cisplatin plus etoposide chemotherapy. Accrual to this trial was slow, and it was closed short of the planned sample size. The results trended in favor of the twice-daily arm (with or without chemotherapy) for freedom from progression and survival. For patients with nonsquamous histology, survival was significantly improved ($p = 0.02$). In the NCCTG trial, freedom from local progression was better for the twice-daily regimen with or without concomitant chemotherapy, although this did not quite reach statistical significance ($p = 0.06$).

In RTOG 83-01, 11% of patients experienced significant treatment interruptions.[319] Compared with those completing treatment in the planned timeframe, survival at 2 and 5 years was significantly lower for those with treatment interruption (24% versus 13% at 2 years; 10% versus 3% at 5 years). Similar detrimental effects of treatment protraction have been reported for other trials of XRT alone as well as concurrent chemoradiation.[319,320] However, the length of treatment was not determined randomly and may reflect other prognostic factors. Survival differences, like the benefit for hyperfractionation, were seen only for the subset of patients with good performance status and minimal weight loss.

Accelerated Fractionation: CHART, HART, and CHARTWEL Regimens

Saunders et al compared an accelerated regimen called continuous hyperfractionated accelerated radiation therapy (CHART) to a conventional regimen of 60 Gy in 30 fractions in a mixed group of patients who had locally advanced (stages IIIA/IIIB) or medically unresectable (stage I or II) disease.[321,322]

The CHART regimen consisted of 54 Gy given in 36 fractions (three times daily) over 12 consecutive days (weekends included). The interfraction interval was 6 hours. Results showed a survival advantage (30% versus 20% at 2 years; $p < 0.001$) for the CHART regimen, with local control also significantly improved. Modifications of this regimen that increased total dose, shortened interfraction interval to 4 hours, and omitted weekend treatments (HART in the United States[323] and CHARTWEL in the United Kingdom[324]) have reported similar encouraging results in Phase II trials.

ECOG conducted a trial of HART compared with standard daily fractionation in patients with stages IIIA and IIIB NSCLC (E2597).[292] Patients received two cycles of induction chemotherapy with carboplatin and paclitaxel and were then randomized to conventional RT or to HART. The study was powered to show an improvement in median survival from 14 to 21 months, but it was closed early because of slow patient entry. The results, a median survival of 21 months on the HART arm and 13 months on the standard arm, are provocative, and seem to mirror those observed in the RT only trials, but the difference did not reach statistical significance in this underpowered trial. One recent meta-analysis comparing hyperfractionated and accelerated trials to conventional fractionation has shows benefit but at the expense of increased esophageal toxicity.[325]

Physical Considerations in Fractionation Trials

Many of the previously discussed trials evaluating radiation dose and fractionation were performed before the routine use of CT, PET/CT and 3D planning, let alone intensity-modulated radiation therapy (IMRT) in lung cancer treatment. Given the limitations of the imaging of that era, there was considerable uncertainty about the extent of disease and the adequacy of its coverage, particularly with the use of lateral and oblique beams. If a different proportion of the total dose is administered through anterior-posterior/posterior-anterior and oblique beam arrangements in the two fractionation regimens and the rate of tumor miss was greater for oblique than for anterior-posterior/posterior-anterior beams, it was reasonable to expect a difference in local control based on technique independent of any difference because of fractionation. Even in trials incorporating fairly straightforward patient eligibility criteria and irradiation technique requirements, errors in staging and field size or placement were roughly 15%. Because more complex techniques were typically used in the hyperfractionated regimens that gave a higher total dose, the net effect might have been to mask a possible biologic benefit of the higher-dose regimen. The use of large fields and ENI also increased acute toxicity. The role of accelerated fractionation to smaller target volumes in patients with CT/PET staging (PET was not performed in the majority of patients in CALGB 39904) is worthy of further study and has given promising results in some early trials.[196]

Evaluation of Local Control

Most trials of altered fractionation have attempted to evaluate patterns of failure. Assessing local control in irradiated NSCLC is difficult for several reasons:

- Difficulty in distinguishing between recurrence from fibrosis
- Variable assessment of local control after relapse in other sites
- High rate of early death from systemic relapse and intercurrent disease

Some of these difficulties can be dealt with statistically through methods such as reporting failures in terms of competing risks. In addition, PET is helpful, though not foolproof, in distinguishing scar from tumor. Current estimates of postirradiation local control, short of resection, should be considered approximations at best.

RADIATION THERAPY TECHNIQUE

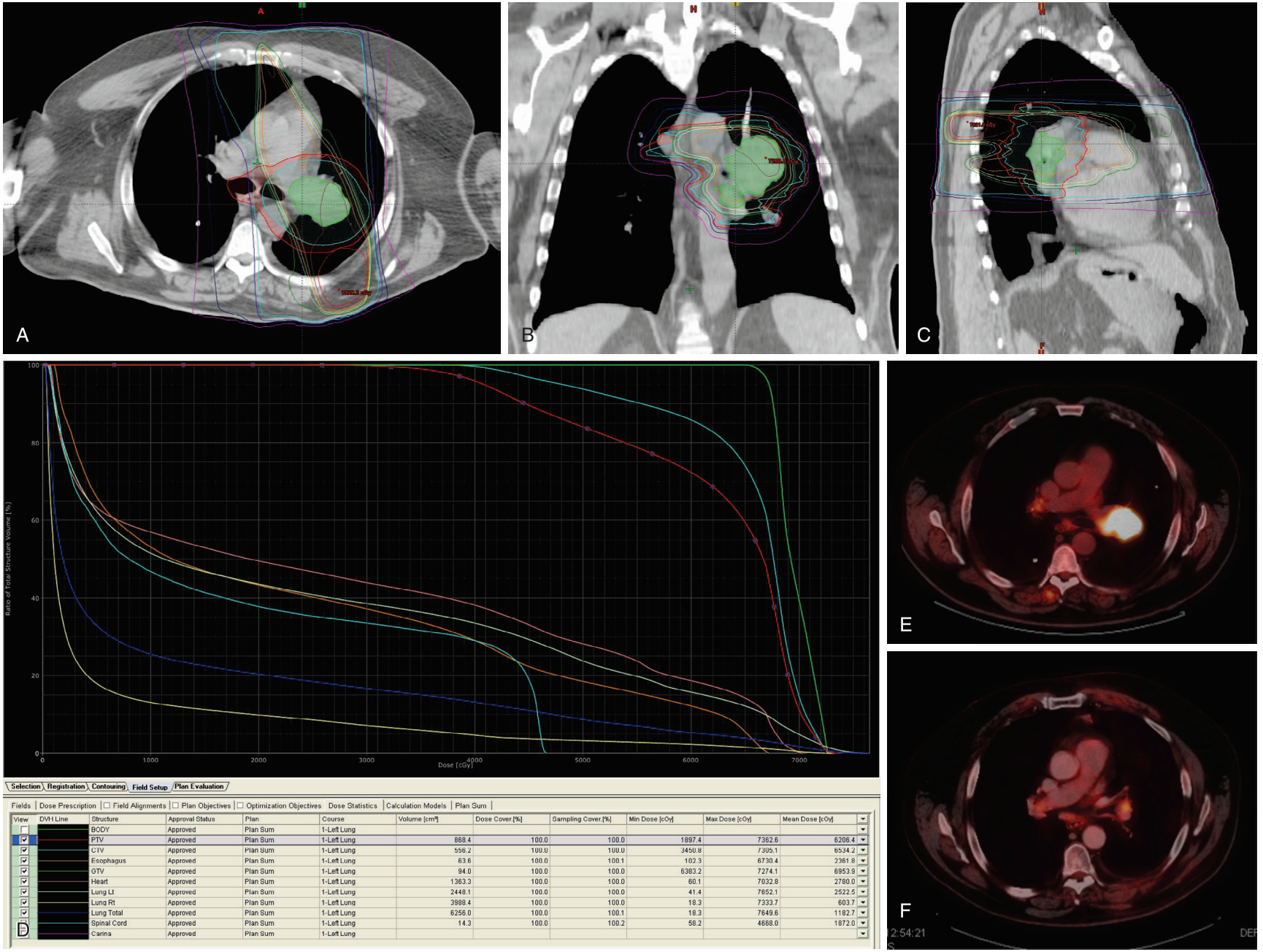
Positioning and Immobilization

Patients are generally positioned supine during treatment, with the torso supported and partially immobilized using custom devices such as Alpha Cradles or VacLoc bags or using adjustable wingboards. Positioning the arms above the head allows for more options using lateral or oblique beam angles, but care must be taken to allow the arms to fit in the gantry (typically 70 cm or 80 cm) of CT scanners used for image acquisition. Prone positioning may seem appealing for patients with tumors located posteriorly in the chest, but it may result in greater motion of intrathoracic structures with respiration. In the absence of more formal respiratory arrest (deep breathing and breath-hold) or respiratory gating techniques, patients should be instructed in quiet, steady respiration during treatment and planning. Wu et al found that the predominate effect of respiration was on translation of the tumor position rather than rotation or deformation of the tumor volume.[326] Others have reached similar conclusions.[327,328]

When cone-beam CT scans are used for positional matching there are often several organs that can be used for the primary match, whether this be done manually or automatically. Higgins et al have investigated image registration using matches made on the spine, carina, and tumor in a series of 30 patients with lung cancer with four different individuals performing the matches and found that reproducibility was greatest for automatic matching on the carina and worst for manual matching on the tumor.[329] Automated matches took an average of 1 minute, manual ones, 4 minutes. With this technique and their definition of target volumes (clinical target volume [CTV] = gross tumor volume [GTV] + 5 mm, ITV = CTV_{inhale} + CTV_{exhale}; planning target volume [PTV] = internal target volume [ITV] + 5 mm) they reported no geographic misses using any of the registration techniques. One way of improving direct matching on the tumor is the use of implanted fiducials. There remain limitations to this technique; peripheral lesions are often difficult to reach bronchoscopically, and percutaneous CT-guided placement poses a risk of pneumothorax.[173,330]

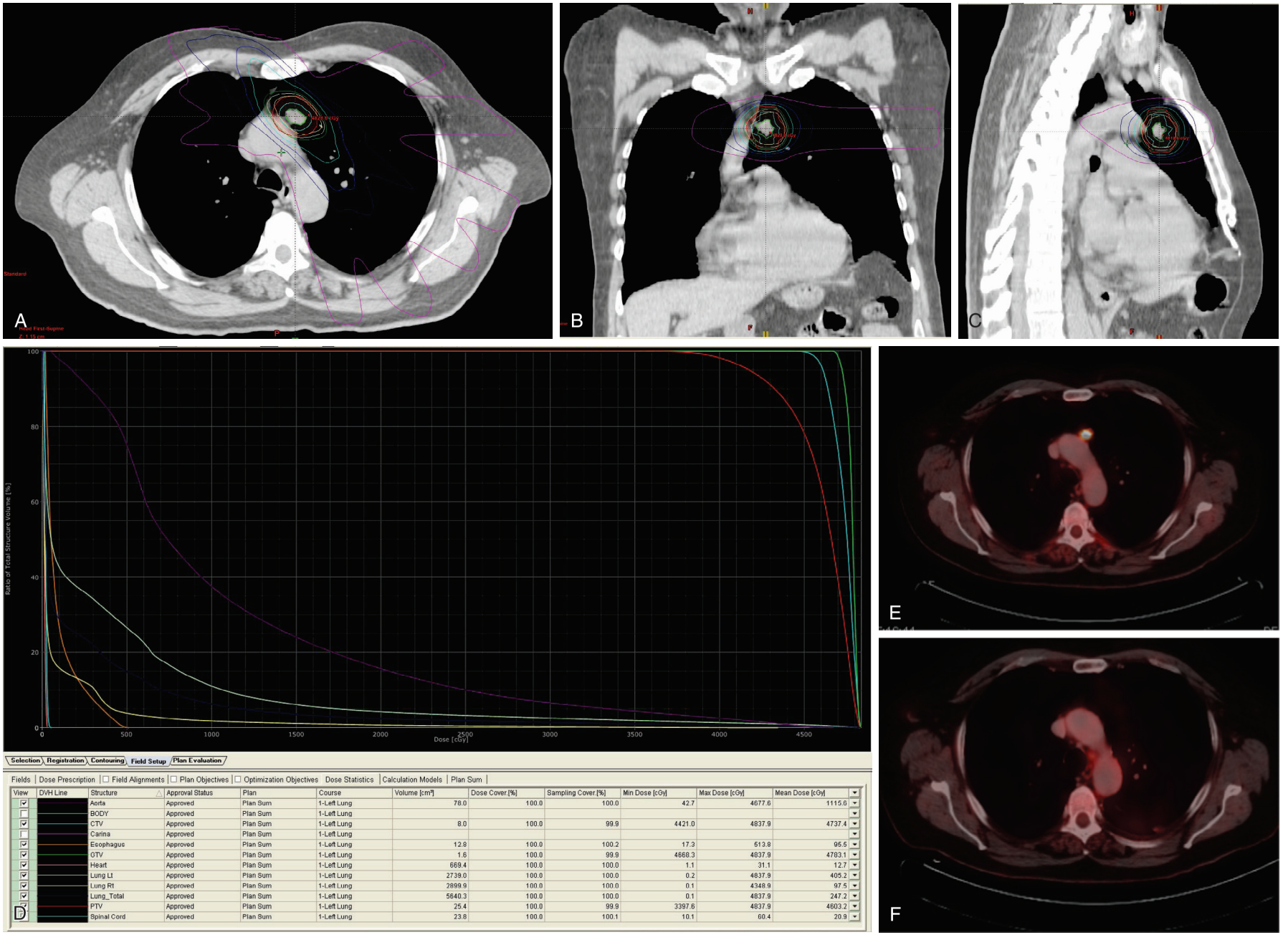
Definition of Target Volume

Traditional treatment volumes for patients with stages IIIA/B NSCLC have been based on principles of covering the known volume of the primary tumor and its nodal metastases and on the "elective" irradiation (ENI) of nodal echelons at risk for microscopic involvement.[331] This initial volume was treated to a dose appropriate for microscopic disease, usually in the range of 45 Gy to 50 Gy, and then areas of known disease were boosted to a total of 60 Gy to 65 Gy. Such an approach typically treated large amounts of normal tissue, including lung, heart, and spinal cord, to a high dose. Current approaches that restrict the target volume to known disease and try to avoid the transit of opposed beams through normal tissue can produce dose distributions that better conform to the target volume but may treat larger volumes of normal tissue, albeit to lower dose.[332-334] Figures 44-3 and 44-4 show isodose curves and dose-volume histograms for a patient with a stage T3N0M0 squamous cell carcinoma of the left lung for two different treatment plans, one with and the other without ENI. The development of appropriate dose-volume-effect nomograms, with and without chemotherapy, for clinically important normal tissues, including lung, esophagus, heart, and spinal cord, is an active area of clinical research.



View	DVH Line	Structure	Approval Status	Plan	Course	Volume [cm³]	Dose Cover.[%]	Sampling Cover.[%]	Min Dose [cGy]	Max Dose [cGy]	Mean Dose [cGy]
		BODY	Approved	Plan Sum	1-Left Lung						
✓		PTV	Approved	Plan Sum	1-Left Lung	868.4	100.0	100.0	1897.4	7362.6	6206.4
✓		CTV	Approved	Plan Sum	1-Left Lung	556.2	100.0	100.0	3450.8	7305.1	6534.2
✓		Esophagus	Approved	Plan Sum	1-Left Lung	63.6	100.0	100.1	102.3	6730.4	2361.8
✓		GTV	Approved	Plan Sum	1-Left Lung	94.0	100.0	100.0	6383.2	7274.1	6953.9
✓		Heart	Approved	Plan Sum	1-Left Lung	1363.3	100.0	100.0	60.1	7032.8	2780.0
✓		Lung Lt	Approved	Plan Sum	1-Left Lung	2448.1	100.0	100.0	41.4	7652.1	2522.5
✓		Lung Rt	Approved	Plan Sum	1-Left Lung	3988.4	100.0	100.0	18.3	7333.7	603.7
✓		Lung Total	Approved	Plan Sum	1-Left Lung	6256.0	100.0	100.1	18.3	7649.6	1182.7
✓		Spinal Cord	Approved	Plan Sum	1-Left Lung	14.3	100.0	100.2	58.2	4668.0	1872.0
✓		Carina	Approved	Plan Sum	1-Left Lung						

Figure 44-3 Isodose curves **(A, B, C)**, dose-volume histogram **(D)**, and pretreatment **(E)** and 3-month posttreatment **(F)** PET/CT scans for a patient with T3N2M0 NSCLC being treated with definitive chemoradiation. This plan was designed to deliver 74 Gy to areas of known disease and 50 Gy to possible sites of lymph node drainage in the mediastinum. The lung V20 was 27%, and the maximum cord dose was 46 Gy. The patient received concurrent chemotherapy with weekly carboplatin and paclitaxel during radiation therapy.



View	DVH Line	Structure	Approval Status	Plan	Course	Volume [cm³]	Dose Cover.[%]	Sampling Cover.[%]	Min Dose [cGy]	Max Dose [cGy]	Mean Dose [cGy]
		Aorta	Approved	Plan Sum	1-Left Lung	78.0	100.0	100.0	42.7	4677.6	1115.6
		BODY	Approved	Plan Sum	1-Left Lung						
		CTV	Approved	Plan Sum	1-Left Lung	8.0	100.0	99.9	4421.0	4837.9	4737.4
		Carina	Approved	Plan Sum	1-Left Lung						
		Esophagus	Approved	Plan Sum	1-Left Lung	12.9	100.0	100.2	17.3	513.8	95.5
		GTV	Approved	Plan Sum	1-Left Lung	1.6	100.0	99.9	4660.3	4837.9	4783.1
		Heart	Approved	Plan Sum	1-Left Lung	669.4	100.0	100.0	1.1	31.1	12.7
		Lung Lt	Approved	Plan Sum	1-Left Lung	2739.0	100.0	100.0	0.2	4837.9	405.2
		Lung Rt	Approved	Plan Sum	1-Left Lung	2899.9	100.0	100.0	0.1	4348.9	97.5
		Lung_Total	Approved	Plan Sum	1-Left Lung	5640.3	100.0	100.0	0.1	4837.9	247.2
		PTV	Approved	Plan Sum	1-Left Lung	25.4	100.0	99.9	3397.6	4837.9	4603.2
		Spinal Cord	Approved	Plan Sum	1-Left Lung	23.8	100.0	100.1	10.1	60.4	20.9

Figure 44-4 Isodose curves **(A, B, C)**, dose-volume histogram **(D)**, and pretreatment **(E)** and 3-month posttreatment **(F)** PET/CT scans of a patient with a T1N0 NSCLC treated by stereotactic radiation therapy. Treatment was prescribed to the 85% isodose line, and dose was 4800 cGy in five fractions over 2 weeks. Because of the proximity of the tumor to the aorta, the dose plan was intentionally made nonspherical to reduce the volume of aorta receiving a high dose, with more dose going into a clinically less critical volume of lung. At 3 months after treatment the patient had achieved a complete metabolic response, and at 6 months he continued without evidence of disease or toxicity.

As larger target volumes are treated, it becomes more difficult to limit doses to normal tissue tolerances, and there is a reciprocal relation between the volume of the target and the dose to which the target can be safely treated. The spinal cord, because of its intolerance of damage to even a short section, is probably an exception to this dose-volume relationship. Late esophageal stricture formation probably falls in this category as well, because even a short length of stricture can be quite symptomatic, but it is of less clinical importance because of the effectiveness of esophageal dilatation. If we wish to improve local control by increasing radiation dose, it follows that we need to consider reducing target volume. Several trials have demonstrated the feasibility of such an approach and the impossibility of major dose escalations when large target volumes are used.[335-338]

Modeling studies have suggested that meaningful improvements in local control and potentially in survival can be achieved by dose escalation within the range of what is achievable with present-day techniques so long as target volumes are limited, typically with the reduction or elimination of ENI. Even greater dose escalation is feasible with active breathing control or other respiratory gating techniques.[339] Unfortunately Phase III data from RTOG 0617, which found poorer local control and survival in patients treated to 74 Gy versus 60 Gy, indicate that this theoretical benefit is not yet presently achievable in the clinic.

The issue of ENI in NSCLC has been hotly debated in the past decade and is now beginning to be illuminated by data from Phase II and Phase III trials. Yet at the same time that we are retreating from routine ENI for patients receiving definitive chemoradiation many are also advocating postoperative mediastinal irradiation for patients with resected N2 disease. Is this inconsistent? Perhaps, but a reasonable argument can be made for both positions. In patients treated definitively without resection of the primary tumor, the greatest bulk of disease and the site at greatest risk of failure remains at the primary site. If this is not controlled, the benefit of eradicating microscopic disease in adjacent nodes is moot. Most of these patients will develop tumor progression either locally or distantly before microscopic regional nodal disease will grow sufficiently to be scored a regional failure, let alone become a clinical problem for the patient. But in the postoperative setting, where all macroscopic intrathoracic tumor has been resected, the implications of residual microscopic disease can become much greater and may warrant more extensive elective treatment.

A distinction between intentional and incidental ENI should also be considered. Several studies have shown that when clinically uninvolved hilar and mediastinal lymph node stations are not specifically targeted in the treatment plan, they may receive nonnegligible doses that may be significant for controlling small-volume metastatic disease.[320,340,341] Doses to the mediastinum adequate to control microscopic disease has also been recently reported for patients treated with SBRT for T1-2N0M0 tumors.[342]

One randomized trial reported by Yuan et al has attempted to address the issue of ENI directly, although its design was confounded in that the involved-field and ENI arms intentionally received different radiation doses of 68 Gy to 74 Gy and 60 Gy to 64 Gy.[343] Response and local control were better in the higher-dose involved-field arm. Survival was also better with a significant improvement at 2 years, though not at other time points. Unfortunately, the trial did not address the issue of whether ENI to 60 Gy, boosting macroscopic disease to 74 Gy, would have been superior to the 74 Gy involved-field arm. Further prospective studies of appropriate target volume are clearly indicated as both systemic therapy and the way in which we deliver RT can be improved.

Once the decision is made as to the volume that warrants treatment, it must be delineated in the treatment planning system. Several studies have addressed the correlation between tumor volume as measured from surgical specimens with that measured by imaging techniques such as CT or PET/CT. Pioneering studies by Giraud showed microscopic extension of tumor cells for several millimeters beyond the CT-demonstrated tumor border for resected lung tumors and that this differed for squamous and adenocarcinoma.[344] More recent studies are extending this approach to tumor volumes obtained by PET/CT in an attempt to determine optimal standard uptake value cutoffs so that the GTV_{PET} and the GTV_{PATH} match more closely.[345] General issues concerning the benefits and challenges of incorporating PET/CT in RT treatment planning have been reviewed by Ford et al.[346]

One attempt to reduce the individual variability in target volume contouring has been the addition of FDG-PET/CT information to the usual CT-based contouring process, with either manual incorporation of this information or direct registration of the PET data with the planning CT scan. Several studies have shown that the contoured volume changes in about one third to half of cases, both by inclusion of nodes not significantly enlarged but FDG avid and by exclusion of non–FDG-avid regions in the lung thought to represent atelectasis rather than tumor. However, not all of these changes have been verified histologically, and there is particular uncertainty in knowing where to draw discontinuous tumor/nontumor contours in a region of continuously decreasing standard uptake value at the interface between tumor and atelectasis.[346-349] There are also reports that both interobserver and intraobserver variation in contouring of the GTV is reduced with the incorporation of data from PET/CT scans.[350-352] It is clear, however, that the greater sensitivity of PET/CT for the detection of distant metastases and the attendant stage migration of patients thought initially to have stages I to III disease, who, in fact, have stage IV NSCLC will artificially improve the apparent outcome of treatment of patients with localized NSCLC.

Bradley et al reported on an RTOG Phase II trial that compared radiation treatment plans derived with and without the use of PET/CT data, which showed a net reduction in target volumes, with an average reduction of 12.5 cm^3. This led to a reduction in mean lung dose from 19 Gy to 17.8 Gy ($p = 0.06$) and of V20 from 32% to 30.8%. With a median follow-up of 12.9 months the rate of failure in nontargeted nodal regions was 2%. These results are likely to be sensitive to the details of the contouring protocols used for both CT and PET/CT contouring. Several groups have shown that the contoured volumes and their correspondence to the pathologic tumor volume is highly dependent on the chosen threshold values.[353,354]

Individualized Radiation Dosing

Several groups have reported trials of adaptive radiation therapy for patients with NSCLC in which the target volume for the last portion of treatment is modified based on the response of the tumor to earlier fractions, as assessed by regression of the tumor on CT or CT/PET imaging.[355] This approach can allow increase in delivered dose while staying within normal tissue tolerances if there is substantial tumor regression in the first several weeks of treatment and early and promising results have been reported.[356,357] The RTOG 1106 is exploring this approach in LA-NSCLC after showing its feasibility in limited institution Phase I/II trials.

Another approach modifies the radiation prescription for each patient to achieve a predetermined probability of normal tissue toxicity. Thus, patients with smaller primaries and regional nodes could be treated to a higher dose than patients with larger target volumes while having the same risk of

complications. Such as approach, termed *individualized isotoxic accelerated radiotherapy* (INDAR) has been combined with concurrent chemotherapy with encouraging results in Phase I/II trials.[358,359]

Beam Energy

Careful dosimetry has indicated that in regions of electronic disequilibrium, as seen in going from low-density lung to higher-density tumor, the use of high-energy photons can lead to significant underdosing of tumor cells at such interfaces or of microscopic extensions of tumor into lung.[360,361] This problem is reduced but not eliminated, particularly for small fields, with lower photon energies (6 MV to 10 MV). With multiple-beam conformal and IMRT plans there is little reason to use higher energies.

Proton beam RT is just beginning to be explored in the treatment of lung cancer. Early clinical experience has been reported in treating patients with stage III disease, and both clinical reports and modeling studies for its use in SBRT for early-stage disease have been published.[362-364] Although the virtual dosimetric and early clinical reports are encouraging, caution should be exercised in adopting proton beam RT in the setting of a tumor when both uncertainty as to the extent of disease and interfraction and intrafraction motion may make overstrict definitions of the target volume hazardous. On the other hand, use of proton beams to limit the volume of lung receiving relatively low but still toxic doses (e.g., V5) may be advantageous so long as the PTV is not made excessively restricted. The RTOG will spearhead a Phase III trial comparing proton beam XRT to photon beam XRT in the context of chemoradiation for LA-NSCLC (ClinicalTrials.gov Identifier NCT01993810). In both arms the target volume will receive a dose of 70 Gy.

Choice of Beam Direction

Traditional 2D treatment-planning schemes typically treated the tumor and regional nodes with opposed anterior and posterior portals until spinal cord tolerance was approached and then used lateral or oblique beam angles, sparing the cord but treating substantial volumes of lung to a relatively high dose.[365] The general planning approach accepted these high doses but attempted to limit the volume of normal lung receiving them. An alternative approach is to avoid the use of opposed beams, increasing the total number of beams used, and in some cases, using noncoplanar beams. The net result of these strategies is to increase the volume of lung receiving some radiation dose but to keep this well below lung tolerance, except in the immediate vicinity of the tumor. Particularly when the target volume is small, a higher degree of heterogeneity of dose (e.g., hot spots) can be accepted within the target volume if this allows better sparing of normal tissue. These considerations, although valid for all patients with lung cancer, are particularly important for those who are unable to undergo resection because of poor pulmonary function. Low dose exposure (~V5) to large segments of the lung are of concern when using multiple fields for treatment of locally advanced disease. Some investigators are also exploring the possibility of optimizing beam placement through relatively nonfunctional portions of lung (e.g., those involved with extensive bullous disease or postobstructive atelectasis) and minimizing dose to functional lung parenchyma.[366,367]

TOXICITY OF THORACIC IRRADIATION AND COMBINED-MODALITY THERAPY

Treatment of patients with aggressive multimodality therapy requires attention to and management of a variety of acute and chronic toxicities.[368] These involve local toxicities such as esophagitis and pneumonitis and systemic considerations such as myelosuppression (Table 44-12). Acute toxicities during RT may compromise the ability of patients to complete treatment without interruption, and late effects limit the total dose that can be given.

TABLE 44-12 Common Toxicity Criteria of Particular Importance in Lung Cancer

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Cough	Mild symptoms; nonprescription intervention indicated	Moderate symptoms, medical intervention indicated; limiting instrumental ADL	Severe symptoms; limiting self-care ADL	—	—
Definition: A disorder characterized by sudden, often repetitive contraction of the thoracic cavity, resulting in violent release of air from the lungs and usually accompanied by a distinctive sound.					
Dyspnea	Shortness of breath with moderate exertion	Shortness of breath with minimal exertion; limiting instrumental ADL	Shortness of breath at rest; limiting self-care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an uncomfortable sensation of difficulty breathing.					
Pneumonitis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic: medical intervention indicated; limiting instrumental ADL	Severe symptoms; limiting self-care ADL; oxygen indicated	Life threatening respiratory compromise; urgent intervention indicated (e.g., tracheotomy or intubation)	Death
Definition: A disorder characterized by inflammation focally or diffusely affecting the lung parenchyma.					
Esophagitis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered eating/swallowing, oral supplements indicated	Severely altered eating/swallowing; tube feeding, TPN, or hospitalization indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by inflammation of the esophageal wall.					

Data from Common Toxicity Criteria: Cancer Therapy Evaluation Program, Version 4.03, 14 June 2010.
ADL, *Activities of daily living;* IV, *intravenous;* TPN, *total parenteral nutrition.*

Risk factors for radiation pneumonitis include radiation dose and lung volume treated and compromise in the patient's baseline pulmonary function.[369] Patients with lower lobe tumors are more likely to have pneumonitis, probably because of the greater lung volume treated. Although the effect of most chemotherapeutic agents on pneumonitis is not well defined, there is an increased risk associated with the use of mitomycin C, gemcitabine, irinotecan, and possibly taxanes. The etoposide/cisplatin regimen in combination with XRT features one of the lowest rates of pneumonitis. Newer immunologic strategies, such as monoclonal antibodies targeting PD1 and PDL1, are also associated with pneumonitis, though these agents have not yet been studied in the context of definitive chemoradiation.

Another approach to reducing lung toxicity is to take advantage of the regional and individual variations in lung function and preferentially place beams through lung parenchyma that is not particularly functional, sparing as much functional (as opposed to merely volumetric) lung parenchyma as possible. This approach was first proposed by Marks et al using simple ventilation-perfusion lung scans.[366,367] Although this approach has not yet made much clinical impact, further studies using both single-photon emission computed tomography (SPECT) and hyperpolarized ^{3}He-MRI to map regional lung function as well as the increasing availability of software to fuse such functional imaging with CT obtained for treatment planning suggest that the time may be right for wider evaluation of the true degree of lung function sparing that can be achieved with such techniques and whether it is of clinical benefit.[370]

The number and variety of dosimetric parameters that have been associated with pulmonary toxicity suggests that no single parameter is adequate to characterize treatment plans and the necessity of reviewing the entire dose-volume histogram in evaluating a plan for toxicity, just as we have appreciated the need to review the entire set of isodose curves in evaluating the adequacy of tumor coverage rather than simply relying on the dose-volume histogram.[371] To date, V_{20} and the mean lung dose are currently the best and most widely used predictors of lung tolerance. It should be kept in mind that the data on which these formalisms are based is largely with daily fractions in the 180 cGy to 200 cGy range in patients not receiving concurrent chemotherapy. Extrapolation beyond these conditions should be done with caution. It is well recognized that the radiation is not acting on a uniform biologic substrate, but efforts to identify genetic or phenotypic changes associated with increased sensitivity of normal tissues to radiation have, until recently, met with little success. With the ability to perform genomewide association studies as well as evaluate a wide variety of intermediate processes in the development of radiation toxicity it may be possible in the future to develop plans based not only on physical dose distributions but also on individual tumor and normal tissue radiosensitivity.[372,373]

Management of Toxicity

Management of patients with moderately severe radiation pneumonitis symptomatic with cough and dyspnea has generally included suppression of cough with codeine or benzonatate and the use of oral corticosteroids such as prednisone to reduce acute inflammation in the hope of decreasing late fibrosis. In patients with symptomatology or hypoxia, prednisone is generally dosed initially at 1 mg/kg with a taper based on symptom improvement.

Esophagitis is common in patients who receive concurrent RT and chemotherapy or accelerated fractionation regimens. Management with a soft diet, use of topical analgesics such as lidocaine or diphenhydramine, and systemic narcotics is helpful. Particularly in patients treated with curative intent, the presence of moderate to severe acute esophagitis should prompt aggressive supportive therapy, including enteral or parenteral feeding when indicated, rather than a treatment interruption, which can jeopardize local control.[374]

Amifostine, a thioester that is actively taken up by normal tissues but enters most tumor cells only by passive diffusion, can protect normal tissues to some degree against radiation mucositis and the renal and bone marrow toxicity of chemotherapeutic agents such as cisplatin.[375-377] Preliminary results of a Phase III trial enrolling patients with head and neck cancers demonstrated a delay in time of onset and reduction in maximal severity of oral mucositis, and Phase II data for lung cancer were promising.[378] However, in a Phase III trial in patients receiving induction chemotherapy followed by concurrent chemotherapy and twice-daily RT, statistically significant differences were not demonstrated in objective measures of esophagitis and only borderline differences were noted in patient self-assessment. Weight loss was significantly less common in the amifostine group, although the magnitude of the difference in average weight loss (3.4% versus 4.7%) is of questionable clinical relevance.[379]

Myelitis is the most feared complication of thoracic irradiation, but it is rare with current radiotherapeutic techniques. The tolerance dose (TD5/5) for the thoracic spinal cord has been estimated at about 50 Gy, but it may be higher than this. With the use of multiple fractions per day, however, repair of damage is not complete in 6 hours, and the total cord dose should be lowered for twice- or thrice-daily regimens.

Late normal tissue effects of radiation have until recently been thought to be irreversible. Changes in our understanding of fibrosis have indicated that this is a dynamic process, undergoing continued tissue remodeling long after irradiation and have raised hopes that fibrosis may be reversed after the fact by disruption of ongoing cytokine cascades.[380] Animal studies and limited human trials with amifostine and vitamin E have suggested some ability of these agents to modify fibrosis in lung and subcutaneous tissue but more definitive studies are needed.

Attempts to improve the therapeutic ratio of treatment for patients with stage III NSCLC must address treatment efficacy and toxicity. Efforts to adopt new uniform criteria for reporting acute and late toxicities, shown in Table 44-12, should facilitate these efforts. These considerations are of great importance as long as the clinical gains achieved with aggressive treatments are modest.

PALLIATION OF LOCAL AND SYSTEMIC DISEASE

Several recent publications have highlighted the limited understanding of many patients with stage IV cancer of the goals of their treatment, whether palliative radiation therapy or chemotherapy (Table 44-13).[381,382] The reasons for this range from patient hopefulness to physician hesitancy to be upfront about the reasonable expectations from therapy. Palliation is a worthy goal on its own, and early implementation of formal palliative management on a regular basis has been shown to improve not only quality of life but also actually extend survival in patients with advanced NSCLC.[383] Early involvement of the palliative care team is important for optimal patient care.

Chemotherapy

The introduction of cisplatin and carboplatin ushered in an era of modestly effective and clinically beneficial chemotherapy for NSCLC. Chemotherapy has demonstrated benefit in

TABLE 44-13 Palliative Management of Local Expressions of Systemic Metastatic Disease

Syndrome	Presentation	Management
Brain metastases	Headache; nausea or vomiting; altered mental status; focal motor, sensory, or cerebellar deficits; focal or generalized seizures	Corticosteroids; whole-brain irradiation. Consider resection or radiosurgery of oligometastatic disease in patients whose other sites of disease are controlled or indolent. Avoid prophylactic anticonvulsants that are ineffective and have their own potential toxicities. Caution patients about driving.
Spinal cord compression	Back pain (early); motor or sensory deficits, loss of sphincter control (late)	Emergency evaluation by contrast-enhanced MRI; high-dose corticosteroids; local radiation or surgical decompression
Pleural effusion	Dyspnea; chest pain	Thoracentesis and pleurodesis with doxycycline, bleomycin, or talc
Pericardial effusion	Dyspnea; syncope	Emergency evaluation by cardiac ultrasound to exclude atrial collapse; pericardiocentesis or pericardiectomy. Avoid diuretics.
Superior vena cava obstruction	Dyspnea; facial and neck swelling; distention of superficial chest wall veins	Corticosteroids; mediastinal irradiation Concurrent chemotherapy if good performance status
Bone metastases	Pain; may be asymptomatic	Analgesics, radiation therapy. Consider prophylactic orthopedic intervention for weight-bearing bones. Consider use of bisphosphonates or RANK ligand inhibitors.

patients with metastatic disease, in patients with locally advanced disease when given together with RT, and in the adjuvant and neoadjuvant treatment of patients with localized disease. For the past 30 years, chemotherapy combinations containing a platinating agent and a second drug have results in palliation of patients with metastatic disease and, in combination with RT or surgery, have increased cure rates for patients with locally advanced disease or early stage NSCLC. From literally hundreds of clinical trials,[384-386] several general conclusions may be drawn:

1. Doublet therapy with cisplatin or carboplatin and a second active agent is superior to single-agent therapy, and single agents are superior to best supportive care.
2. The addition of a third conventional cytotoxic agent increases toxicity without significantly improving response rates or survival.
3. A variety of second-generation (vinblastine, etoposide) and third-generation (vinorelbine, gemcitabine, paclitaxel, docetaxel, pemetrexed) drugs produce broadly similar response rates and survival, although each of the third-generation agents in combination with platinum have generated statistically significant albeit clinically modest improvements in OS compared to second-generation combinations. Among the third-generation agents, given the minimal differences in response rates and survival, the choice between regimens is generally based on the particular toxicity spectrum (hematologic, renal, neuropathy), the patients preexisting comorbidities, and scheduling convenience (weekly versus every 3 weeks). Several trials have compared various third-generation agents in combination with cisplatin or carboplatin and not found meaningful differences in outcome.[387]
4. In nonsquamous histology, in combination with cisplatin, pemetrexed has clearly demonstrated superior survival compared to gemcitabine in the first-line treatment of patients with advanced NSCLC,[388] and superior survival in the maintenance setting compared with intravenous (IV) placebo. Conversely, gemcitabine in combination with cisplatin proved superior to pemetrexed/cisplatin in patients with squamous cell histology. These histology-specific differences in outcome may well be as a result of differences in expressions of relevant target enzymes (e.g., thymidylate synthase for pemetrexed, ribonucleotide reductase for gemcitabine). Choosing a drug regimen based on histology is likely a temporary surrogate for a more sophisticated individualized therapy based on genomic, proteomic, and metabolomic profiling of individual tumors.[389-391]
5. When used at equivalent doses, cisplatin and carboplatin show similar activity. Cisplatin regimens may produce slightly higher response rates but minimal differences in OS. In the United States, there is a tendency to use carboplatin when treating patients for palliation and cisplatin in the adjuvant and neoadjuvant settings. In locally advanced NSCLC, at least one Japanese study showed little difference in long-term outcome for XRT in combination with cisplatin-based therapy (MVP) compared to XRT in combination with weekly carboplatin/paclitaxel or carboplatin/irinotecan.[392]
6. Virtually all patients who respond to first-line chemotherapy will experience relapse, and the role of second-line therapy for these patients is becoming increasingly well defined. Docetaxel, pemetrexed, and erlotinib are each approved by the Food and Drug Administration (FDA) for the second-line treatment of patients whose disease has progressed on first-line platinum-based regimens. In addition, several recent trials have suggested that switching to a different agent (e.g., pemetrexed, erlotinib) for maintenance after response or stabilization on initial chemotherapy may prolong remission and survival in selected patients, although the routine use of such maintenance chemotherapy is controversial.[393] One concern regarding the trials that claim benefit for immediate maintenance therapy is that patients in the control arm of these trials were not routinely crossed over to the maintenance agent at the time of disease progression. In the trial of pemetrexed reported by Ciuleanu et al, only 67% of the patients in the control arm received poststudy chemotherapy, and fewer than 20% received pemetrexed.[394] Therefore, this trial has not clearly shown that immediate maintenance with pemetrexed is superior to a policy of close observation after initial chemotherapy with routine delayed use of pemetrexed at the time of disease progression. Such a policy would require close follow-up but might be preferred by some patients, particularly if initial treatment was toxic.

The availability of agents with diverse mechanisms of action and the increasing feasibility of genomic and proteomic profiling of individual tumors is rapidly moving us to an era of personalized medicine in lung cancer as well as other malignancies. The molecular heterogeneity of NSCLC is giving rise to new clinical trial designs in which patients, particularly

those with adenocarcinoma histology, first undergo molecular analysis to determine which of several targeted therapies would be most appropriate.[395,396] In this regard, an EGFR TKI (erlotinib, gefinitib, afatinib) is indicated in the first-line treatment of patients with an EGFR mutation based on multiple prospective Phase III trials showing a major relative risk (RR) and PFS advantage compared with standard platinum-based chemotherapy. By the same token, patients whose tumors harbor EML4/ALK or ROS1 translocations warrant therapy with crizotinib. For now, these assays are based on tumor biopsies. The ability to identify and quantitate genomic changes in tumor by analysis of either circulating tumor cells or circulating cell-free DNA may greatly facilitate such analyses by reducing the need for invasive biopsy procedures.[80,81,397] Such "liquid biopsies" are being developed first in the treatment of patients with metastatic disease, in whom their sensitivity approaches 100%, but may yield even greater value when applied to patients with earlier-stage disease.[83] Such developments will require better characterization of the molecular determinants of radiosensitivity of tumor and normal tissues and their patient-specific modification by chemotherapeutic agents, which may or may not be the same as for these agents when used without RT.

Data from SWOG 0003 and the Japanese Four-Arm Cooperative Study showed clinically significant ethnic differences in chemotherapy tolerance. These trials had generally similar outcomes, except for 1-year survival, but despite a lower dose of paclitaxel in the Japanese trial (200 mg/m^2 versus 225 mg/m^2), Japanese patients had twice the incidence of neutropenia.[398] Data also were available for population variations in the rate of glucuronidation of irinotecan metabolites among racial and ethnic groups. What in the past had been puzzling differences between national trials may herald the development of metabolically individualized treatment regimens.[399] One example of this is a polymorphism in BIM, which confers resistance to EGFR TKI and is seen in about 15% of East Asians but is rare in European or North American patients.[400]

Management of the Patient with Oligometastatic Disease

Although the majority of patients with stage IV NSCLC have widespread metastatic disease and a poor survival, an occasional patient will present with only one or a small number of evident metastatic sites. Such oligometastatic disease presents in 5% to 10% of patients (depending in part on how carefully additional metastatic sites are sought after the first one is identified). Management of these patients is controversial. Most will do poorly, but a few will fare quite well with aggressive treatment to all known sites of disease. Khan et al reported long-term survival of 5 of 23 such patients and have argued that these patients may constitute about 6% of all new patients with NSCLC in the United States and that with aggressive treatment 1500 to 2000 patients per year could experience long-term disease-free survival.[401] Even in patients who will not be cured, the effective palliation or prevention of symptoms from bulky intrathoracic disease by local RT may improve both quality of life and survival. In this regard the difference between patients with stages III and IV disease is one of degree rather than kind.[402]

Treatment of the patient with otherwise early-stage NSCLC with a solitary brain metastasis is the best example of this phenomenon. With aggressive therapy, including surgical resection of the lung primary and the brain metastasis, these patients in some cases have a good outcome, far better than that typically observed in patients with stage IV disease.[403] Some are even cured.

Palliative Radiation Therapy

For patients with advanced NSCLC who are candidates for neither surgery nor chemoradiation with curative intent and who lack symptoms requiring immediate RT, it is not clear that there is benefit to early RT rather than waiting for symptoms and treating palliatively at that time. One randomized trial that compared these two approaches in 230 patients found no differences in OS, activity level, or psychological distress. Patients randomized to deferred RT started RT a median of 125 days from randomization.[404] This strategy allows for a window of opportunity in which to offer either a conventional or investigational chemotherapeutic regimen to patients with good performance status and with measurable or evaluable nonirradiated lesions.

The radiation dose required for effective palliation of symptoms has been the subject of several randomized trials and reviews (Table 44-14). For most patients there seems little

TABLE 44-14 Palliation of Symptoms of Non–Small Cell Lung Cancer with External Beam Irradiation or with Multiagent Chemotherapy

	Percentage of Patients with Symptom Palliated				
Symptom	**Standard RT (24 Gy-30 Gy in 6-10 Fractions)***	**17 Gy in 2 Fractions (First Trial/Second Trial)*†**	**1 Fraction of 10 Gy***	**EDAM/MMC/VBL‡**	**DDP/MMC/VBL§**
Cough	56	65/48	56	23/10	40
Hemoptysis	86	81/75	72	5/0.3	100
Chest pain	80	75/59	72	21/10	44
Anorexia	64	68/45	55	NA	NA
Depression	57	72/NA	NA	NA	NA
Anxiety	66	71/NA	NA	NA	NA
Breathlessness	57	66/41	43	22/15	66

DDP, *Cisplatin;* EDAM, *edatrexate;* MMC, *mitomycin C;* NA, *data not available;* RT, *radiation therapy;* VBL, *vinblastine.*

**Data from Bleehen N: Inoperable non–small cell lung cancer (NSCLC). A Medical Research Council randomized trial of palliative radiotherapy with two fractions or ten fractions. Br J Cancer 63:265–270, 1991; Bleehen N, Girling D, Machin D, et al: A Medical Research Council (MRC) randomised trial of palliative radiotherapy with two fractions or a single fraction in patients with inoperable non–small-cell lung cancer (NSCLC) and poor performance status. Br J Cancer 65:934–941, 1992.*

†Trial 1 compared standard RT with 17 Gy in 2 fractions; Trial 2 compared 17 Gy in 2 fractions with a single fraction.

‡Data from Kris M, Gralla R, Potanovich L, et al: Assessment of pretreatment symptoms and improvement after EDAM + mitomycin + vinblastine (EMV) in patients with inoperable non–small cell lung cancer (NSCLC) [abstract 883]. Proc Am Soc Clin Oncol 9:299, 1990. Scores are not percentage of patients improved but rather median symptom severity (0 = least, 100 = most) before and after chemotherapy.

§Data from Tummarello D, Graziano F, Isidori P, et al: Symptomatic, stage IV, non–small cell lung cancer (NSCLC). Response, toxicity, performance status change, and symptom relief in patients treated with cisplatin, vinblastine, and mitomycin C. Cancer Chemother Pharmacol 3:249–253, 1995.

benefit, in either survival or relief of specific symptoms, with increased doses; the typical 20 Gy in 5 fractions or 30 Gy in 10 fractions are quite reasonable. Shorter regimens of 1 or 2 fractions have also been used with success, especially in patients with end-stage disease where a longer course of treatment can constitute a substantial proportion of the patient's anticipated survival. For selected patients with good performance status, little metastatic disease burden or metastatic disease that has responded well to chemotherapy, there may be a modest benefit for higher doses of thoracic RT, although this is not clear from published data and higher doses may produce more acute toxicity, particularly esophagitis.[405,406]

Most patients with lung cancer have symptoms from their intrathoracic disease. RT has long been the mainstay of treatment for such patients, with relatively high rates of palliation for irritative or obstructive symptoms such as cough and for hemoptysis, but poorer results for symptoms of nerve compression such as recurrent laryngeal and phrenic paralysis (see Table 44-13). In the United States, common practice has been to treat such patients to doses of 30 Gy to 35 Gy in 10 to 15 fractions over 2 to 3 weeks. In the United Kingdom, several randomized trials conducted by the Medical Research Council (MRC) compared such schedules with shorter regimens of 17 Gy in 2 fractions 1 week apart or a single fraction of 10 Gy with equally good palliation of symptoms and survival and toxicity no greater than with more fractionated treatment (see Table 44-14). Such schedules are particularly attractive for patients who may otherwise have to travel substantial distances or remain hospitalized for the duration of their RT. They provide good symptom management while limiting the use of medical resources and reducing disruption of the schedules of the patients and their caregivers. For patients with better performance status, however, more fractionated schedules have resulted in modest improvements in survivals compared with 1- or 2-fraction schedules.[407,408]

The most common sites of locally symptomatic metastases of NSCLC are bone and brain. These can be palliated in most patients with relatively brief courses of RT, typically 2 weeks in the United States and two fractions in the United Kingdom (see Table 44-14). In appropriate situations, resection of solitary CNS metastases, particularly larger cystic ones unlikely to respond well to radiation therapy or radiosurgery, or orthopedic stabilization of metastases to weight-bearing bones should be considered. For patients with one to three CNS metastases, stereotactic radiosurgery in addition to whole-brain radiation therapy (WBRT) improves radiographic and clinical response and, for patients with a single metastatic lesion, improves survival.[409] It has been suggested that for these patients, WBRT can be omitted in their initial management and used only if needed subsequently, without a detrimental effect on survival.[410,411] A concern with this strategy is that the risk of subsequent CNS events is rather high in these patients (30% to 60%), and the psychological morbidity of multiple brain metastases and their treatment may be substantial. This issue has been addressed in several randomized trials.[412-415] The majority of data from both retrospective reviews and prospective trials have indicated that the addition of WBRT to local treatment (either resection or radiosurgery) reduces the rate of relapse in the brain (both at the site of the initially treated metastasis and other intracranial sites) without appreciably impacting survival. In the EORTC trial, the rate of death from intracranial progression was reduced. In the M. D. Anderson trial, however, survival was significantly shorter in the patients randomized to receive WBRT. This was attributed by the investigators to the significantly greater rate of neurocognitive deterioration. An alternative explanation is that in this small trial, with a total of just 58 patients, a potential imbalance in prognostic factors led to poorer survival in the patients randomized to WBRT and that their neurocognitive functioning deteriorated rapidly as they approached death. The optimal approach in this situation remains controversial and clearly needs to be individualized.

Bone metastases are common and are often painful and debilitating. A high index of suspicion, early imaging, and consultation between appropriate medical, radiation, and surgical oncologists is essential to reduce the adverse effects of skeletal-related events, such as pain, fracture, and spinal cord compression. For lesions without risk of fracture short-course palliative RT, such as 8 Gy in a single fraction, has been shown to be as effective and considerably less expensive and more convenient compared to longer fractionated courses such as 30 Gy in 10 fractions but it results in a higher frequency of retreatment.[416] The use of bisphosphonates (e.g., zoledronic acid) and RANK ligand inhibitors (e.g., denosumab) appears to reduce the incidence of skeletal-related effects as well as delay their onset.[417]

Reirradiation of thoracic tumors, either the primary site or vertebral metastases, may be appropriate in selected cases where there is no evidence of distant dissemination and pressing local symptoms. By using IMRT, it is possible to deliver doses on the order of 70 Gy while limiting reirradiation of the spinal cord to 20% to 25% of this.[418] SBRT has also been used for reirradiation of localized recurrence with acceptable toxicity and evidence of good early responses.[419]

In past years, chemotherapy for palliation of specific symptoms was thought to be inferior to irradiation. Trials of new chemotherapeutic regimens typically reported response rates and survival, but infrequently reported palliation of specific symptoms or effects of treatment on quality of life. More recent trials have addressed these issues and have shown that with a number of platinum-containing chemotherapy regimens, the rates of clinical improvement and symptomatic palliation were about twice as great as the rates of Response Evaluation Criteria in Solid Tumors (RECIST)-specified objective response (Table 44-15). This suggests that for patients with widely metastatic disease and good performance status, an initial trial of chemotherapy should be offered, with RT reserved for nonresponding lesions. RT should be employed early in patients with metastases to weight-bearing bones, impending spinal cord compression, or caval or major airway obstruction. Because of the increased risk of neutropenic sepsis in patients with lobar or main-stem bronchus obstruction, attempts to open such obstructed airways with external beam or endobronchial irradiation, laser excision, or stent placement are desirable before chemotherapy.

One shortcoming of clinical research has been the conduct of a large number of clinical trials of similar design. The power of these trials is limited, and to obtain statistical significance, it has been necessary (e.g., the role of PCI in SCLC, impact of platinum-containing chemotherapy on survival of patients with metastatic NSCLC) to combine data from multiple individual trials in meta-analyses. When done with care, this process can complement the results of large randomized trials as well as provide hypotheses for further testing.[420] But given the burgeoning number of new agents we are faced with the prospect of large numbers of promising but inconclusive small trials without clear direction for changing therapy. This will be further complicated by the individualization of therapy required to target distinct molecular lesions in individual tumors, unless the magnitude of effects in these cases is so dramatic (as in treatment of gastrointestinal stromal tumors with imatinib) that definitive trials will require few patients. Such individualized therapy holds the promise of treatments that are more effective and less toxic, but implementing them will require major changes in the way we fund and perform diagnostic procedures, molecular

TABLE 44-15 Recommended Therapy for Patients with Non–Small Cell Lung Cancer Who Are Good Risks

Clinical Stage	Primary Therapy*	Adjuvant Considerations
T1N0M0	Resection (usually lobectomy)	If pathologic N0, no adjuvant therapy is indicated. Should be considered for trials of early detection and chemoprevention
T2N0M0	Resection (usually lobectomy)	Postoperative adjuvant chemotherapy†
T1-2N1M0	Resection (consider preoperative chemotherapy)	Postoperative adjuvant chemotherapy†
T3N0-1M0	Resection (consider preoperative chemotherapy)	Postoperative adjuvant chemotherapy†
T1-3N2M0	Resection followed by adjuvant chemotherapy ± mediastinal irradiation‡	Single N2 node found at intraoperative mediastinoscopy
T1-3N2M0	Induction chemotherapy or chemoradiotherapy and resection or definitive chemoradiotherapy	Multiple N2 nodes or single node with extranodal extension identified before thoracotomy
T1-3N3M0	Definitive chemoradiotherapy	Chemoradiotherapy clearly superior to standard radiation therapy alone; local control remains poor. With conventional fractionation, use concurrent rather than sequential chemoradiation.
T4N1-3M0	Definitive chemoradiotherapy	Consider preoperative radiochemotherapy and resection for patients with T4N0M0 lesions, especially those of the superior sulcus.§
T1-4N0-3M1	Symptomatic palliative treatment with radiation and/or chemotherapy	Consider more aggressive therapy for primary and metastatic disease, including resection for patients with T1-3N0M1 lesions with a solitary lesion in the brain or adrenal, particularly if responsive to initial chemotherapy.

**Patients who are good risks are characterized by adequate cardiopulmonary function, ECOG PS ≤1, weight loss ≤5%. Patients not meeting these criteria may still be suitable for therapy but should be evaluated with particular care.*

†Regimens with demonstrated efficacy in this setting include cisplatin or carboplatin and a second agent such as etoposide, vinorelbine, paclitaxel, docetaxel, or gemcitabine.

‡Adjuvant postoperative radiation to the mediastinum, if given, should be carefully planned to avoid excessive cardiac and pulmonary treatment and limited to a dose of 45 Gy to 50 Gy (1.8 to 2.0 fractions) with a possible boost to a small field if there is known extracapsular extension or adherence of nodal metastases to adjacent unresected structures.

§For preoperative chemoradiation, radiation doses in the range of 45 Gy to 50 Gy are best established using concurrent chemotherapy with cisplatin/etoposide or carboplatin/paclitaxel.

analysis of tumors, as well as the ways in which we conduct clinical trials and develop new drugs. This may be particularly true in trials using multiple investigational agents being developed by different drug companies.[113] These will need to be balanced with societal needs to control healthcare expenditures by various means including limitation of reimbursement to evidence-based therapies. These goals, although not necessarily in conflict, will require careful codevelopment for successful implementation.[421,422]

Although there is great popular interest in and use of natural, holistic, complementary, and alternative methods of cancer therapy and prevention, it is our responsibility to present our patients with data, not merely hope often born of desperation, and to assess such approaches honestly, openly, and critically.[423-425] No such approach has been shown to impact lung cancer incidence or survival in unselected populations, and as previously noted, trials have shown that supplementation with β-carotene could increase the risk of lung cancer in smokers. Although there should be no prejudice against investigating therapies that arise from alternative sources or belief systems neither, should there be any hesitation to hold them to strict standards of clinical investigation in randomized clinical trials.[426]

CONTROVERSIES

The past several decades have witnessed a clear demonstration of modest survival improvements for patients with LA-NSCLC when they were treated with careful combinations of RT and chemotherapy. Also new tools for tumor imaging and radiation dose delivery may allow us to escalate tumor dose with manageable normal tissue toxicity and will enable us to determine whether this dose increase can result in improved local control and survival. Several reasonable guidelines for stage-specific therapy may be proposed based on good-quality evidence from prospective clinical trials (see Table 44-15). There remain a number of basic questions about the role of RT that have not been addressed or answered by current clinical research:

1. Should ENI be reduced or eliminated for patients in early-stage disease, in whom the probability of nodal disease is low, or in patients with bulky primary disease that is not likely to be controlled with current chemoradiation? Is there an intermediate subgroup of patients with a reasonable probability of primary tumor control and substantial risk of regional nodal metastases for whom elective nodal treatment improves survival? Would a strategy of fractionated RT to the elective nodal volume combined with SBRT to primary lesions with a reasonable probability of microscopic nodal metastases be of value?
2. Will adjuvant chemotherapy effective against occult M1 disease also eradicate microscopic nodal disease, or will there be an ongoing role for adjuvant mediastinal irradiation to improve both local control and survival, especially in those who undergo resection of N2 nodes?
3. Is the superiority of concurrent versus sequential combinations of RT and chemotherapy the result primarily of selective radiosensitization or of shortening the overall treatment time? If overall time rather than concurrency is the critical factor, alternate strategies to shorten time without exposing tissues to overlapping toxicities of concurrent treatment, such as induction chemotherapy followed by accelerated RT or rapidly interdigitated therapy (e.g., RT during the week with chemotherapy on the weekend), may warrant investigation.
4. What is the role of surgery in patients with advanced stages IIIA(N2) and IIIB disease? If sterilization of mediastinal lymph nodes is useful in selecting patients for surgery, how

can this best be assessed preoperatively? Will increasing radiation dose to the mediastinum to increase the rate of sterilization of mediastinal nodes translate to increased survival, even though it does not necessarily affect systemic disease?

5. Does close follow-up benefit patients with NSCLC after surgical or nonsurgical therapy, or does it merely shorten the measured disease-free survival without extending OS or improving quality of life? There is marked variation in current clinical practice after curative resection.[427] Most recurrences are detected clinically; asymptomatic recurrences are most commonly detected by routine chest radiographs or CT. OS does not seem significantly affected, and close follow-up does not clearly improve survival. However, many of these studies were conducted at a time when chemotherapy was less effective and active second-line and third-line agents had not been identified. The high rate of second primary lung cancers in these patients is a strong argument for close surveillance.
6. How is local tumor control best evaluated in patients not undergoing surgical resection? Several investigators have demonstrated that assessment based on CT measurement of tumor size, whether evaluated unidimensionally as in the RECIST, by traditional bidimensional measurements, or by volumetric assessment, does not correlate particularly well with clinical outcome. Assessment by ^{18}FDG-PET has correlated better with endpoints such as pathologic response at surgery or survival, but postirradiation inflammatory changes and infection may also cause persistently increased FDG uptake. There may be benefits in functional imaging with other agents that more directly detect image cell proliferation or apoptosis.[428]
7. How can we best assess the efficacy of SBRT in good performance status patients with stage I NSCLC when neither they not their physicians have been supportive of randomized trials?
8. To what degree will molecular profiling of individual tumors and the normal tissues in which they arise lead to individualization of dose and fractionation in radiation therapy, as it is starting to lead to individualized chemotherapy?[35,429,430]

CONCLUSIONS

The past several years have seen modest progress in the treatment of patients with NSCLC, particularly in the combination of local and systemic modalities of treatment. Staging has become more accurate with the introduction of FDG-PET; and although this does not improve treatment per se, it allows a better match between a patient's true extent of disease and the ideal treatment for the patient's tumor. Adjuvant chemotherapy for most resected patients (excluding those with stage T1N0M0 disease) has demonstrated a modest but statistically significant and clinically meaningful survival benefit of similar magnitude to those seen with other adult solid tumors such as breast or colorectal cancer.

Better imaging and treatment planning technologies for RT, including adaptation for tumor motion, herald a new era of treatment precision and the ability to explore dose escalation in a more meaningful fashion than previously. As more effective systemic treatment agents are introduced, we may reasonably expect modest gains in survival. This progress is real, can be achieved with acceptable cost, and should be made widely available to patients with unresectable disease. These gains should not blind us to the fact that prevention of this disease is far better than its treatment and that detection and treatment of early-stage disease is far better than the best chemoradiation for advanced disease. Basic research and clinical trials assessing smoking prevention and cessation, chemoprevention, and early detection in smokers and the growing population of former smokers who remain at high risk for lung cancer must remain high priorities to produce a major reduction in deaths from this disease. Funding for basic and clinical research in lung cancer, which currently is less than a fourth of that expended on other malignancies (expressed as dollars per death), must be increased if we are to continue to make progress against this devastating disease. (Table 44-16).

TABLE 44-16 U.S. Research Funding for Various Cancers (Dollars per Death/Year)

Year	Breast	Prostate	Colon	Lung
2005	25,635	16,329	5607	1871
2009	27,480	14,336	6590	1249

Data from the Lung Cancer Alliance (www.lungcanceralliance.org). Accessed April 20, 2014.

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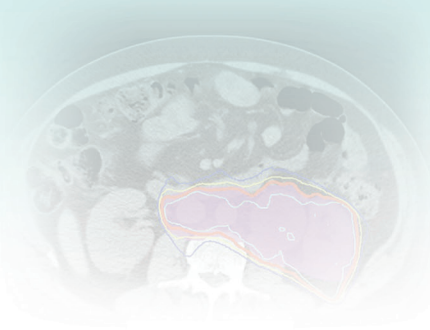
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CHAPTER

45 Cancer of the Esophagus



A. William Blackstock, Jr. and Suzanne Russo

INCIDENCE

Esophageal cancer is the eighth-most common cancer worldwide and is endemic in Asia, South and East Africa, and Northern France. Esophageal cancer accounts for approximately 1% of cancers in the United States and is associated with an 85% mortality rate. In 2012, 17,460 (13,950 men and 3,510 women) in the United States were diagnosed with esophageal cancer, resulting in approximately 15,000 deaths (12,040 men and 3030 women).

BIOLOGIC CHARACTERISTICS

The predominant histologic types are squamous cell carcinoma and adenocarcinoma. Major prognostic factors are local tumor extent, presence of nodal involvement or distant metastases, and pathologic response to therapy. Approximately 15% to 30% of adenocarcinomas and 5% to 13% of squamous cell carcinomas overexpress Her-2/neu.

STAGING EVALUATION

Staging evaluates the extent of primary tumor, involvement of lymph nodes, and presence or absence of metastases. Staging evaluations should include a history and physical examination, blood count and chemistries, endoscopy with biopsy, 18-fluorodeoxyglucose positron emission tomography (FDG-PET) with computed tomography (CT) imaging and endoscopic ultrasound (EUS).

DEFINITIVE THERAPY

Surgical resection is the primary therapy for resectable esophageal cancer. Cure rates of 60% to 80% are achieved in the rare patient found to have disease confined to the esophagus without nodal involvement. Preoperative chemoradiation (for resectable squamous and adenocarcinomas of the esophagus) and perioperative chemotherapy (for distal and esophagogastric adenocarcinomas) significantly improve survival in patients with more advanced locoregional disease amenable to surgical resection. Concurrent chemoradiation therapy provides a significant improvement in overall survival and local control over radiation alone for both squamous and adenocarcinomas. There is no demonstrated benefit to escalation of radiation dose in this setting.

Postoperative chemoradiation has demonstrated a survival benefit for patients with stage IB-IV, M0 resected gastroesophageal junction and gastric adenocarcinomas who have not received preoperative therapy compared to surgery alone. Chemotherapy alone in the preoperative setting has demonstrated a small survival advantage over surgery alone.

PALLIATION

Patients with unresectable esophageal cancer causing obstruction or bleeding may obtain palliation with concurrent chemotherapy and radiation. In patients with poor performance status who cannot tolerate systemic therapy, external beam radiation or brachytherapy is a reasonable option for palliation of dysphagia. Esophageal stenting should also be considered. Radiotherapy is also used for palliation of symptomatic distant disease such as bone or brain metastases. Intraluminal brachytherapy with or without the addition of external beam irradiation is occasionally used for palliation.

INTRODUCTION

The diagnosis and management of esophageal cancer continues to evolve. Advances in the operative and postoperative management and rational applications of multimodality therapy have produced modest improvements in survival rates over the last 25 years.[1] In this chapter, we review biologic and epidemiologic factors associated with esophageal cancer. We also discuss review the rationale for and results of combined-modality approaches, as well as the use of palliative therapies. We conclude with a summary of current treatment recommendations and a discussion of several important clinical trials in progress.

ETIOLOGY AND EPIDEMIOLOGY

Esophageal cancer is the eighth-most common cancer worldwide[1] and is endemic in developing nations with wide variations in prevalence between low- and high-incidence regions (Asia, South and East Africa, and Northern France).[2] In 2012, 17,460 patients (13,950 men and 3510 women) in the United States were diagnosed with esophageal cancer, resulting in approximately 15,000 deaths (12,040 men and 3030 women).[3] The incidence of esophageal cancer continues to rise and has increased 5% over the last 2 years in contrast to 2010, when 16,640 Americans were diagnosed with esophageal cancer, and there has been a 14.6% increase in incidence over the previous 5 years.[4,5] Esophageal cancer represents only approximately 1% of new cancers in the United States, but approximately 85% of patients die of their disease without significant overall improvement over the last 25 years.[3-5] In 2008, esophageal cancer was the fifth leading cause of death in males age 40 to 79.[3]

Esophageal cancers are histologically classified as either adenocarcinoma or squamous cell carcinoma. Both squamous cell and adenocarcinomas are more common in males, however the incidence of squamous cell carcinoma is declining in North America and Western Europe as the incidence of adenocarcinoma of the distal esophagus and gastroesophageal junction is increasing, currently representing approximately 70% of all esophageal carcinomas in the United States.[6] Squamous cell carcinoma remains dominant in endemic regions and underdeveloped parts of the world.[6-8]

TABLE 45-1 Incidence of Adenocarcinoma of the Esophagus

Investigator	Years	Adenocarcinoma (%)
Smithers[14]	1936-1951	7.3
Hesketh/Conn. Register[12]	1983-1986	22.9
Birgisson[15]	1987-1994	73.5
Steyerberg[16]	1991-1999	52.0
Brown[6]	2000-2004	61.1*

*White males and females only.

Data from the Surveillance Epidemiology and End Results (SEER) program of the National Cancer Institute demonstrated that the incidence of esophageal cancer in white males steadily increased by 45% in the United States between 1975 and 2004, with the incidence of adenocarcinoma increasing by 463%, and the incidence of squamous cell carcinoma declining by 50% during the same time period.[6] In contrast, the overall incidence of esophageal cancer has remained constant among white females, although there have been similar trends observed with a 335% increase in the incidence in adenocarcinomas and a 29% decline in the incidence of squamous cell carcinomas.[6,9] The incidence of squamous cell carcinoma has shown a significant decline in black males beginning in 1992,[10] but it remains the most common cell type among blacks in the United States,[11] despite the twofold to threefold increase in incidence of adenocarcinomas in black males and females. Interestingly, a review of the New England tumor registries[12] demonstrated that the incidence of adenocarcinoma has increased even when tumors located at the esophagogastric junction have been excluded, and data from the National Cancer Institute's SEER database (1973-2001) found no evidence of histologic reclassification of esophageal squamous cancers or anatomic reclassification of adenocarcinomas of the gastric cardia to explain this trend.[13] Table 45-1 reflects recent changes in the prevalence of adenocarcinoma of the esophagus over the span of several decades.

Racial disparities have been observed in the esophageal cancer population. Males who are black are more likely to present with advanced or metastatic disease, resulting in a survival rate that is 60% of that for males who are white.[3,4] In a multivariate regression analysis controlling for age, gender, marital status, tumor histologic type, and tumor location, black race was associated with worse survival rates. In this study analyzing SEER data, when the tumor status, surgical technique, and radiotherapeutic modality were added to the model, race was no longer significantly associated with survival rates.[11] Provocative data from Steyerberg[16] and others[17,18] also suggested that the underuse of potentially curative surgery may, in part, explain the poorer survival rates observed for patients who are black with locally advanced disease because a population-based analysis showed that once data had been corrected for treatment received, there was no difference in survival rates between patients regardless if they were white or black. It has been postulated that the increased incidence of disease and increased mortality rates observed in patients who are black are reflections of socioeconomic status and dietary risk factors but not ethnicity. Squamous cell carcinoma remains the most common histologic type among males who are black[11] and may be associated with worse outcomes, facts that could explain some of the observed racial disparities in survival rates.[12] In one population-based study there appeared to be a risk for developing esophageal cancer in patients who are black beyond what could be attributed to alcohol and tobacco use.[19] The reasons for the apparent racial difference in risk from the same level of alcohol and tobacco use could be associated, in part, with increased mutations in the *TP53* gene in esophageal cancers found in patients who are black, as reported by Baron et al.[20]

PREVENTION AND EARLY DETECTION

The use of tobacco is an established risk factor for squamous cell carcinoma of the esophagus and also for adenocarcinoma, but to a lesser extent[21]; smoking cessation reduces the risk of only squamous cell carcinoma, however.[22-24] In addition, patients with both squamous cell and adenocarcinomas of the esophagus are at increased risk of developing second primary cancers, including lung and head and neck malignancies, which are also correlated with tobacco use.[25,26] Alcohol consumption has been shown to be a risk factor for squamous cell carcinoma but not adenocarcinoma.[21,27] Other environmental factors associated with the development of squamous cell cancers include thermal injury and exposure to nitrates and potentially carcinogenic nitrosamines, asbestos fibers, or water contaminated with petroleum products.[28-30] In addition, the presence of human papillomaviruses (HPV-16 and HPV-18) may be risk factors for the development of cancers of the esophagus.[31]

Obesity and high body mass index (BMI) have been established as strong risk factors for development of esophageal adenocarcinoma but not squamous cell carcinomas.[27,32,33] Those individuals who are in the 75% highest BMI range have a 7.6-fold increased risk of developing adenocarcinoma of the esophagus compared to those with lower BMIs.[34,35] Obesity-related comorbid illnesses that contribute to the development of esophageal cancer include gastroesophageal reflux disease (GERD) and type 2 diabetes. One study demonstrated that the presence of type 2 diabetes was associated with an increased risk of developing esophageal, among other cancers, whereas treatment with metformin reduced the risk.[36] Diet affects both types of esophageal carcinomas, with increased intake of fruits and vegetables associated with a reduced incidence of cancer.[37] Lifestyle changes, including weight loss and exercise, postulated to reduce the risk of developing esophageal adenocarcinoma, are currently being investigated.

GERD predisposes to Barrett's esophagus and both are associated with an increased risk of adenocarcinoma of the esophagus, with severe long-standing disease.[22,38-41] The incidence of GERD appears to be increasing in the United States. Barrett's esophagus is known to be associated with GERD and is a precursor lesion for esophageal adenocarcinoma, although most Barrett's lesions do not proceed to carcinoma. The normal squamous mucosa is damaged by chronic GERD and is replaced by columnar metaplasia in Barrett's esophagus that predisposes to malignancy.[42] A 30% to 60% increased risk of development of esophageal adenocarcinoma has been demonstrated in patients with Barrett's esophagus.[40] Long-standing GERD, length of Barrett's esophagus, male gender, age, and hiatal hernia size are strongly associated with high-grade dysplasia[43-45] and are thought to be a predictor for development of adenocarcinoma in patients with Barrett's esophagus. The risk of development of esophageal malignancy increases from 4% in patients with Barrett's esophagus with low-grade dysplasia to 59% in patients with high-grade dysplasia.[46] Biomarkers such as aneuploidy and loss of heterozygosity of p53,[47-49] cyclin D1,[50] and P16[51] have been associated with increased risk of progression from high-grade dysplasia to adenocarcinoma, whereas p53 expression has been correlated with treatment response.[49]

Medical management of Barrett's esophagus is designed to control GERD symptoms using proton pump inhibitors (PPIs) and histamine receptor antagonists. Patients with Barrett's esophagus with high-grade dysplasia should undergo surgical

resection or alternative local strategies, such as endomucosal resection (EMR), cryoablation, radiofrequency ablation (RFA), or photodynamic therapy (PDT).[52] Some have postulated that the use of pharmaceutical agents for the treatment of GERD (i.e., antisecretory agents and therapies to relax the lower esophageal sphincter) have precluded necessary surveillance required for the detection and management of Barrett's esophagus and is therefore related to the recent increase in the incidence of Barrett's esophagus–associated adenocarcinomas.[53] Nonetheless, efforts continue to improve early detection of Barrett's esophagus. Endoscopy is performed on patients with severe symptomatic GERD, especially those with a family history of esophageal cancer or Barrett's esophagus, and can evaluate progression of metaplasia to dysplasia or carcinoma, but the rate of progression is fairly low.[54] Guidelines of the American College of Gastroenterology currently recommend surveillance every 3 years for patients without dysplasia until none is detected on two consecutive endoscopies, as confirmed by biopsy. If high-grade dysplasia is discovered, followup endoscopy should be performed at 3 months to rule out adenocarcinoma and repeated each 3 months thereafter.[55]

The use of chemopreventive agents are under investigation. Nguyen[56] reported the results of a retrospective observational study of 344 patients with Barrett's esophagus demonstrating that prescription use of PPIs is associated with a reduced risk of high-grade dysplasia or cancer with adjustment for gender, age, and the length of duration of Barrett's esophagus and the use of nonsteroidal antiinflammatory drugs (NSAIDs) or aspirin resulted in a nonsignificant trend toward a lower incidence of high-grade dysplasia and cancer.[56] A meta-analysis demonstrated that the use of NSAIDs decreases the risk of both squamous cell carcinoma and adenocarcinoma, with odds ratios of 0.58 and 0.67, respectively.[57] Similar results were reported in a prospective cohort study.[58] Currently, there is a large multicenter, randomized controlled clinical trial (AspECT) evaluating the long-term chemopreventive effect of esomeprazole with or without aspirin.[59]

Dysplastic lesions as well as carcinomas of the esophagus have been shown to overexpress the cyclooxygenase-2 (COX-2) enzyme.[60-62] COX-2 expression is correlated with the proliferative activity in dysplastic lesion and was found to be increased, in a stepwise fashion, with the transition from normal esophageal tissue to low-grade dysplasia to high-grade dysplasia, suggesting that COX-2 is involved in the early stages of carcinogenesis and that interruptions in the dysplasia-carcinoma sequence could be an important part of a chemoprevention strategy.[63] In a recent animal study, celecoxib was shown to significantly decrease the risk of Barrett's esophagus and prevent the development of esophageal adenocarcinoma in a rat surgical model with mixed reflux of acid and duodenal juice.[64] COX-2 may be an effective selective target of chemoprevention for adenocarcinoma of the esophagus in humans but requires further clinical evaluation.

The human epidermal growth factor receptor 2 (*HER-2*) gene or HER-2 protein expression has been associated with the development of esophagogastric and gastric adenocarcinomas.[65] The Her-2/neu oncogene is overexpressed or amplified in preneoplastic lesions and may indicate an increased risk of developing esophageal adenocarcinoma among patients with Barrett's esophagus.[66] Chemoprevention with targeted therapies, such as trastuzumab, are being investigated.[67]

BIOLOGIC CHARACTERISTICS AND MOLECULAR BIOLOGY

The HER2/neu oncogene is overexpressed in esophageal cancers (15% to 30% of adenocarcinomas and 5% to 13% of squamous cell carcinomas)[68-70] and has been associated with tumor invasion, lymph node metastases, and poor prognosis.[66,68,71] Her-2/neu positivity is identified in 21% of gastroesophageal tumors compared to 33% of gastric tumors.[72] Typically both immunohistochemistry and fluorescence in situ hybridization (FISH, which expresses the ratio between the number of copies of the Her-2 gene and the number of chromosome 17 centromeres) are used to test to identify HER-2 overexpression. However gastric cancer cells demonstrate incomplete HER-2 membrane staining in a basolateral pattern and increased tumor heterogeneity compared to breast cancer cells, which may lead to underestimation of HER-2 overexpression using standard techniques.[73,74] Hence, Hoffman et al developed a modified HER-2 scoring system using 10% stained area cut-off for resected specimens, and no cut-off for biopsies to better identify patients with gastroesophageal and gastric cancers that would be candidates for anti-HER-2 therapy.[75] This method was validated and subsequently used in the Trastuzumab for Gastric Cancer Trial (ToGA) trial.[73,76] HER-2 testing with immunohistochemistry using the modified scoring system is currently recommended for all patients with metastatic esophagogastric or gastric adenocarcinomas at the time of diagnosis. FISH is reserved for confirmation of equivocal immunohistochemistry results (2+), although some institutions routinely perform both tests on all patients.

Overexpression of the epidermal growth factor receptor (EGFR) is found in both esophageal squamous cell carcinomas and esophageal adenocarcinomas, as well as their precursor lesions, such as squamous dysplasia and Barrett's esophagus.[77-79] Overexpression of EGFR on immunohistochemical testing occurs in approximately 80% of patients with esophageal adenocarcinoma and squamous cell carcinoma.[80] Additionally, amplification of the *EGFR* gene has been detected by FISH analysis in 8% to 30% of esophageal adenocarcinomas.[81,82] Clinical studies have shown that increased EGFR expression is associated with an overall decrease in survival rates in patients with esophageal cancer.[83] Ongoing trials continue to evaluate the efficacy of EGFR inhibitors, erlotinib[84-86] and cetuximab,[87-91] in addition to chemotherapy in patients with advanced disease.

Vascular endothelial growth factor (VEGF) expression levels and microvessel density are significantly higher in cancerous tissues compared with normal tissues and Barrett's dysplastic tissues.[92,93] VEGF expression has been correlated with tumor differentiation, depth of invasion, and lymph node metastases.[94,95] VEGF is overexpressed in 30% to 60% of esophageal cancers, and studies have demonstrated a correlation between high levels of VEGF expression, advanced stage, and poor overall survival rates.[96-102] A meta-analysis of 1,453 patients from 19 studies has correlated VEGF overexpression in Asian patients with esophageal carcinoma with poor prognosis, especially for those with squamous cell histology; however no correlation was observed for non-Asian patients.[103] Ongoing clinical trials are evaluating the potential benefit of the addition of VEGF inhibitors to chemotherapy for patients with advanced tumors.[104-106]

COX-2 is another molecular target that has significance in cancer development and progression, and inhibition of COX-2 activity results in enhanced radiosensitization of tumor tissue but not normal tissue.[107,108] Selective COX-2 inhibition has been shown to directly inhibit tumor neovascularization.[109] The combination of these effects suggests potential enhancement of selective tumor targeting by COX-2 inhibition.

Mutations in the p*53* gene are present in up to 80% of esophageal cancers. Interestingly, the mutations for squamous tumors, which are in A-T base pairs, are different from the mutations usually seen in adenocarcinomas.[110] Data from Montesano[110] indicate that the mutations common to

squamous tumors are correlated with smoking. Mutations in the *p53* gene are an early event in the carcinogenic process. There is no concordance between *p53* gene mutations and the accumulation of the p53 protein nor are *p53* gene mutations independently predictive of clinical outcome.[111] In vitro data showed that wild-type p53 protein levels increased after chemotherapy.[111,112] Despite this correlation, p53 is not currently used in clinical practice.

Additional molecular abnormalities include cyclin D1, a cell cycle-regulating protein involved in the G_1 phase to S phase transition. Overexpression of cyclin D1 has been observed in approximately 30% to 40% of esophageal adenocarcinomas and squamous cell carcinomas.[113] Inactivation of the *p16* gene, a tumor suppressor gene, occurs in a significant number of esophageal cancers,[51] and restoring p16 expression appears to inhibit the proliferation and tumorgenicity of esophageal cancers.[112] These represent but a few of the potential molecular targets for directing therapies in future clinical studies.

PATHOLOGIC FINDINGS AND PATHWAYS OF SPREAD

The predominant histologic types of esophageal cancer are squamous cell carcinomas and adenocarcinomas and should be established by biopsy for staging and treatment purposes. Approximately 20% of esophageal squamous tumors involve the upper "cervical" esophagus, although the majority is found in the middle esophagus, defined as the segment of esophagus from the aortic arch to the inferior pulmonary vein and usually representing the segment at 25 cm to 32 cm from the incisors. The remaining 30% of squamous tumors are found in the distal esophagus (at 33 cm to 42 cm from the incisors). In contrast, more than 90% of adenocarcinomas are found in the distal esophagus and gastroesophageal junction. Other malignant histologic types are unusual but include adenosquamous, mucoepidermoid, and adenoid cystic tumors and malignant tumors with endocrine differentiation (small cell cancers). Histologic review of esophagectomy specimens with early-stage disease revealed little difference between the rate of submucosal spread and the rate of lymph node metastasis for squamous cell carcinomas and adenocarcinomas.[114]

The esophagus is a hollow tube approximately 25 cm in length that extends from the pharynx to the stomach and consists of three parts: the cervical, thoracic, and distal esophagus. The cervical esophagus lies just left of the midline behind the larynx and trachea. The upper portion of the thoracic esophagus passes behind the tracheal bifurcation and left main stem bronchus, and the lower thoracic esophagus runs behind the left atrium. The distal esophagus is an area approximately 6 to 8 cm in length merging into the gastroesophageal junction. Adenocarcinomas of the esophagogastric junction are classified into three types based anatomic location and the epicenter of the tumor.[115] The current classification system identifies tumors 1 cm to 5 cm above the esophagogastric junction as distal esophageal tumors (Siewert Type 1), those tumors with the epicenter or mass located within 1 cm proximal and 2 cm distal to the esophagogastric junction are classified as true carcinomas of the cardia (Siewert Type 2), and subcardial tumors with epicenter located 2 cm to 5 cm distal to the esophagogastric junction (but may be infiltrating the esophagogastric junction) are classified as Siewert Type 3.[115] In addition to the Siewert classification, the revised American Joint Committee on Cancer (AJCC) staging system specifies that tumors that meet the criteria for Siewert Types 1 and 2 are classified as adenocarcinomas of the esophagus for the purposes of staging.[116] Those meeting criteria for Siewert Type 3 are classified as gastric cancers.[116]

In the esophagus, mucosal lymphatics merge with a submucosal plexus, which then merges with lymphatic channels in the muscularis. These channels communicate with an extensive network of cooperating lymphatics that extend longitudinally throughout the esophagus and eventually drain into nodal groups as cephalad as the internal jugular lymph nodes and as caudal as the celiac lymph nodes. The nodal groups at risk for involvement in cancers of the cervical esophagus include the supraclavicular and upper paratracheal nodes. The nodes at risk for gastroesophageal tumors include the pulmonary ligament, paracardial, left gastric, common hepatic, splenic, and celiac nodes. The esophagus lacks a serosal surface and is only separated from adjacent structures by a loose connective tissue, the adventitia. The adventitia provides little barrier to local spread, and as a consequence, tracheoesophageal and esophagobronchial fistulas develop in 5% to 10% of patients with cancer of the esophagus.

CLINICAL MANIFESTATIONS, PATIENT EVALUATION, AND STAGING

More than 90% of patients present with progressive and worsening dysphagia often resulting in significant weight loss. Other findings include odynophagia, chest pain, cough, and fever associated with possible respiratory fistulas, hoarseness associated with tumor involvement of the recurrent laryngeal nerve, and melena resulting from intraluminal bleeding.

Patients with newly diagnosed esophageal cancer should undergo a complete history and physical, physical examination, upper endoscopy with biopsy, complete blood count, serum chemistries, coagulation studies, and a contrasted CT scan of the chest and abdomen. An endoscopic ultrasound (EUS) with or without fine-needle aspiration (FNA) and 18-FDG–positron emission tomography (PET; FDG–PET) or PET/CT are also recommended. Her-2/neu testing is also recommended. The initial workup identifies patients with locoregional cancer and those with metastatic (M1) disease. In patients with locoregional disease who are deemed fit for surgery, cardiac and pulmonary function as well as nutritional status should be evaluated. Jejunostomy or nasogastric feeding tubes may be considered for those patients in need of nutritional support. A gastric feeding tube is not recommended. Laparoscopic staging of the peritoneum with washing can be considered for adenocarcinomas, if there is no other evidence of distant metastases.

The TNM staging system for esophageal cancer according to the AJCC is based on the pathologic review of pathologic specimens of patient undergoing primary surgical treatment for esophageal cancer without adjuvant therapy.[116] The AJCC staging manual, seventh edition, is shown in Box 45-1. This staging system incorporates a risk-adjusted analysis of the data generated by the Worldwide Esophageal Cancer Collaboration (WECC) for more than 4,500 patients, which correlates decreased survival with squamous histology, increasing depth of invasion, involvement of regional nodes, and presence of distant metastases.[117] Esophageal cancers are staged according to the histologic subtype, depth of invasion, presence of regional lymph nodes or distant metastatic disease, and grade and location of tumor. Some difficulties have arisen because this is a surgical staging system and many patients are now treated initially without resection, making accurate pathologic staging impossible. Patient outcomes are correlated with surgical pathologic stage and do not take into account the impact of adjuvant therapy. Other limitations of this staging system include inclusion of the proximal 5 cm of the stomach,

BOX 45-1 TNM Staging of Esophageal Cancer[15]

Histologic Grade

G1	Well differentiated
G2	Moderately differentiated
G3	Poorly differentiated
G4	Undifferentiated

Cancer Location

Upper thoracic	20 cm-25 cm from incisors
Middle thoracic	>25 cm to 30 cm from incisors
Lower thoracic	>30 cm to 40 cm from incisors
Esophagogastric junction	Includes cancers whose epicenter is in the distal thoracic esophagus, esophagogastric junction, or within the proximal 5 cm of the stomach (cardia) that extends into the esophagogastric junction or distal thoracic esophagus (Siewert III). These stomach cancers are stage grouped similarly to adenocarcinoma of the esophagus

Primary Tumor

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	High-grade dysplasia
T1	Tumor invades lamina propria, muscularis mucosae, or submucosa
T1a	Tumor invades lamina propria or muscularis mucosae
T1b	Tumor invades submucosa
T2	Tumor invades muscularis propria
T3	Tumor invades adventitia
T4	Tumor invades adjacent structures
T4a	Resectable tumor invading pleura, pericardium, or diaphragm
T4b	Unresectable tumor invading other adjacent structures, such as aorta, vertebral body, trachea

Regional Lymph Nodes

Nx	Regional nodes not assessed
N0	No regional lymph node metastasis
N1	Metastasis in one to two regional lymphnodes*
N2	Metastasis in three to six regional lymphnodes*
N3	Metastasis in seven or more regional lymph nodes*

Distant Metastasis

MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

STAGE AND PROGNOSTIC GROUPINGS FOR ESOPHAGEAL CANCER

Adenocarcinoma

Stage 0	Tis, N0, M0, grade 1 or X
Stage I A	T1, N0, M0, grades 1-2 or X
Stage I B	T1, N0, M0, grade 3
	T2, N0, M0, grades 1-2 or X
Stage IIA	T2, N0, M0, grade 3
Stage IIB	T3, N0, M0, any grade
	T1-2, N1, M0, any grade
Stage IIIA	T1-2, N2, M0, any grade
	T3, N1, M0, any grade
	T4a, N0, M0, any grade
Stage IIIB	T3, N2, M0, any grade
Stage IIIC	T4a, N1-2, M0, any grade
	T4b, any N, M0, any grade
	Any T, N3, M0, any grade
Stage IV	Any T, any N, M1, any grade

Squamous Cell Carcinoma

Stage 0	Tis, N0, M0, grade 1 or X, any location
Stage I A	T1, N0, M0, grade 1 or X, any location
Stage I B	T1, N0, M0, grades 2 or 3, any location
	T2-3, N0, M0, grade 1 or X, lower esophagus or X
Stage IIA	T2-3, N0, M0, grade 1 or X, upper and middle esophagus
	T2-3, N0, M0, grade 2 or 3, lower esophagus or X
Stage IIB	T2-3, N0, M0, grade 2 or 3, upper and middle esophagus
	T1-2, N1, M0, any grade, any location
Stage IIIA	T1-2, N2, M0, any grade, any location
	T3, N1, M0, any grade, any location
	T4a, N0, M0, any grade, any location
Stage IIIB	T3, N2, M0, any grade, any location
Stage IIIC	T4a, N1-2, M0, any grade, any location
	T4b, any N, M0, any grade, any location
	Any T, N3, M0, any grade, any location
Stage IV	Any T, any N, M1, any grade, any location

**Regional lymph nodes include any paraesophageal node extending from cervical nodes to celiac nodes.*

emphasis on number of involved nodes, rather than size or location relative to the primary tumor, and failure to discern between resectable and unresectable disease.[116] Diagnostic tools are used to evaluate local extent of primary tumor (EUS, endoscopy), identify and quantify lymph node involvement (EUS), and identify metastatic disease (FDG-PET).

EUS performed before therapy evaluates the depth of tumor invasion (T) and presence of enlarged or abnormal regional (mediastinal and perigastric) lymph nodes (N).[118,119] Preoperative EUS results in accurate T stage in 59% of patients and 82% accuracy in patients with transmural tumor extension.[120] EUS has been reported to be 87% accurate for detecting mediastinal nodal disease,[121] which is improved when confirmed by EUS-guided FNA[122-125]; however EUS is inadequate for objective pathologic response evaluation after neoadjuvant chemoradiation.[126,127] Combining diagnostic studies improves staging accuracy. One study compared CT, EUS, and EUS-FNA for preoperative lymph node staging and found EUS-FNA to be more sensitive than CT (83% versus 29%) and more accurate than both CT and EUS (87% versus 51% and 74%, respectively).[125] Review of CT or PET-CT imaging before EUS staging is recommended to identify obstructing tumors that may increase the risk of perforation and identify areas concerning for nodal involvement before the procedure. In addition thoracoscopic staging can be used to further increase the accuracy of tumor penetration and lymph node staging to 88%, as demonstrated in a cooperative group trial of patients undergoing subsequent surgery.[128]

The importance of staging for the selection of surgical candidates cannot be overstated. Cancers confined to the epithelium and muscularis mucosa and without nodal involvement are defined as stages I and II. In a clinicopathologic review of

165 patients with esophageal cancer treated with resection only, Holscher et al[129] observed 0% lymph node metastases in patients with disease confined to the mucosa compared with 18% for tumors with submucosal spread. The 5-year overall survival rate reported for patients with node-negative disease was 63%. Lymph node involvement was shown to be a strong independent predictor of poor survival following surgery alone. Tumors invading the adventitia or surrounding structures have a worse outcome, and there is almost always associated nodal involvement.

The addition of FDG-PET to standard staging techniques has improved the detection of occult metastatic disease[130-134] and can result in up to 15% upstaging from M0 to M1 compared with CT and EUS.[131] In a meta-analysis reported by van Westreenen, FDG-PET showed limited sensitivity (0.51) and reasonable specificity (0.81) for the detection of locoregional metastases.[135] This study also demonstrated detection of distant lymphatic and hematogenous metastasis with a sensitivity and specificity of 0.67 and 0.97, respectively.[135] Taken in total, these data are compelling and have resulted in an increasing use of FDG-PET for the routine staging of patients with esophageal cancer.

Investigation of gene profiling[136] and biomarkers[137] to improve patient selection for surgical therapy is currently being investigated and may improve prognostic stratification in the future.

PRIMARY THERAPY

The management of patients with esophageal and esophagogastric junction cancers requires the expertise of several disciplines and support infrastructure. Treatment decisions should be made in an environment that fosters a multidisciplinary collaboration.

Single-Modality Therapy

Surgery

In 1913, Dr. Franz Torek[138] used a transpleural approach to perform the first successful resection of an esophageal carcinoma reconstructed with an external rubber esophagus. With improvements in anesthesia, subsequent surgeons used mainly a transthoracic approach with primary esophagogastric anastomosis, and in 1933, Ohsawa[139] reported extended survival rates in 8 of 20 patients who had a resection. In 1938, Adams and Phernister[140] were the first Western surgeons to successfully adopt the Japanese transthoracic technique. The results of these studies, however, revealed a discouraging 5-year survival rate of 5% to 10%.

Esophagectomy should be performed in high-volume centers by experienced surgeons for best results.[141] One standard option includes a transthoracic resection, or Ivor-Lewis procedure,[142] which allows better access to lesions in the upper two thirds of the esophagus and complete visualization of the esophagus. For distal tumors, this approach allows for resecting a substantial proximal margin and placing the anastomosis high in the chest (above the azygos vein), a technique that is thought to result in fewer anastomotic leaks and less postoperative reflux. The initial laparotomy is for exploring the abdomen for distant disease and mobilization of the stomach. The second incision is a thoracotomy incision for exposure and dissection of the esophagus. After tumor resection, the stomach is pulled through the hiatus for an intrathoracic anastomosis. An alternative transthoracic approach is the McKeown esophagogastrectomy (right thoracotomy followed by laparotomy and cervical anastomosis).[143]

The transhiatal procedure is an alternative to the transthoracic approach that uses abdominal and left cervical incisions, where the procedure is performed through the abdominal incision and the gastric conduit is drawn through the posterior mediastinum and the esophagogastric anastomosis is exteriorized in the cervical incision.[144] The esophagus is removed via blunt dissection and continuity is reestablished with a cervical esophagogastric anastomosis, which eliminates an anastomosis in the chest and the risk of a leak producing mediastinitis. The advantages for this technique include eliminating the morbidity associated with a thoracotomy.

Another acceptable approach is the left transthoracic or thoracoabdominal esophagastrectomy, which is a technique sometimes used for distal esophageal cancers that uses a contiguous left thoracic and abdominal incision through the eighth intercostal space.[145] The esophagogastric anastomosis is performed in the left chest superior to the pulmonary vein.

At present, there are no definitive data to suggest that one technique is superior to the others and long-term survival is not different between the two approaches.[146] In one review of 210 patients treated with either a transthoracic resection (n = 172) versus a transhiatal resection (n = 38), an increased incidence of tumor perforation (18%) and injuries to the recurrent laryngeal nerve (13%) following the transhiatal approach was observed.[147] Another retrospective study of 238 patients observed increased rates of wound infections, pneumothorax, and hospital mortality for patients treated with transthoracic resection.[148] In contrast, Stark et al[149] observed increased rates of respiratory complications and hospital mortality following transhiatal resection. Others have identified little or no difference in overall complication rates or operative mortality rates between the two surgical approaches.[150,151] These findings are consistent with a meta-analysis reported by Hulscher et al[152] who observed that the 5-year survival rate with surgery alone was approximately 20% after both transthoracic and transhiatal resections.

Surgery remains a major component of treatment for resectable disease and is usually performed with curative intent following adequate staging and pretreatment nutritional support. There has been a marked reduction in surgical morbidity and mortality with improvements in staging techniques, patient selection,[153] perioperative care and surgical experience, but improvements in cancer control have been modest. Moertel[154] reviewed 18 older surgical series involving 4109 patients treated with resection and found a 5-year overall survival rate of 9.6% (range, 3% to 20%).

Regional lymph node involvement results in a worse outcome following esophagectomy.[155,156] One study demonstrated a 31% overall survival rate for all patients undergoing resection; only 13% of patients with nodal disease were alive at 5 years versus 44% for patients who were node-negative.[157] Another study demonstrated similar results with 5-year survival rates after surgery alone at 57% for patients who were node negative and 15% for node-positive disease.[158] Other investigators found that no patient with more than 30% regional nodal tumor involvement was alive at 5 years, whereas 45% of patients with less than 30% nodal disease were alive at 5 years.[129] These data indicate that in the limited cohort of patients who present without regional nodal involvement, many will do well with surgery alone, but patients found to have nodal disease are rarely treated successfully with surgery alone.

The optimum number of lymph nodes to be removed and examined at the time of resection is unclear. One retrospective analysis demonstrated that the number of lymph nodes removed at the time of surgery was an independent predictor of survival time and that the optimal threshold for this survival benefit was removal of 23 nodes.[159] Another study suggested at least 18 lymph nodes should be removed.[160] The largest retrospective analysis analyzed the SEER database for

29,656 patients with esophageal cancer and found that patients with more than 12 lymph nodes examined had a significant reduction in mortality compared to those without examination of lymph nodes. Those with 30 or more lymph nodes examined demonstrated the lowest mortality.[161] A report from the WECC database evaluating 4627 patients undergoing esophagectomy alone demonstrated increased survival with greater extent of lymphadenectomy in patients with pathologic pN0M0 staging.[156] However, extent of lymphadenectomy may only be prognostic because one study demonstrated that extent of lymphadenectomy did not predict survival in patients undergoing surgery alone for esophageal cancer.[162]

Esophagectomy remains the standard of care for high-grade dysplasia and superficial cancers; however, surgical morbidity and mortality may be substantial for patients who are medically unfit. More recently, minimally invasive esophagectomy (MIE) and endoscopic treatments have become treatment options for selected patients with early-stage localized esophageal cancer. MIE strategies include laparoscopic-assisted, thoracoscopic, or limited thoracotomy Ivor-Lewis or McKeown esophagectomies. A recent meta-analysis using data from 10 studies to evaluate the effects of MIE versus open esophagectomy on outcome demonstrated trends in favor of MIE, with reductions in morbidity, pulmonary complications, anastomotic leakage, mortality, length of hospital stay, operating time, and blood loss compared to open esophagectomies.[78,163-166] MIE is useful in older patients who are at increased risk for operative morbidity.[167] However, not all patients are candidates for minimally invasive procedures, especially those who have undergone prior abdominal surgery or who have bulky tumors or lymph nodes difficult to resect. No randomized trials have assessed whether MIE improves outcome compared with open esophagectomy. However, in the absence of prospective trials with adequate followup MIE remains investigational.[168,169]

The goal of EMR and ablative therapies is eradication of Barrett's esophagus and removal of the associated dysplasia (Tis) or early malignancy (well to moderately differentiated T1a tumors without evidence of lymphovascular invasion). EMR of Barrett's esophagus and high-grade dysplasia occasionally results in a diagnosis of esophageal cancer. Although EMR of visible lesions can be effective, there is a high rate of recurrence. EUS staging before EMR is recommended in the setting of high-grade dysplasia or early carcinoma.[170] All focal nodules should be resected rather than ablated and Tis and high grade dysplasia should be fully characterized for presence of nodularity, lateral spread, and multifocal disease. Patients with Tis or selected T1a tumors are candidates for curative therapy with EMR. EMR is considered therapeutic for completely excised moderately differentiated tumors <2 cm in diameter without evidence of invasion beyond the muscularis mucosa or lymphovascular spread. For patients with tumors in the submucosa or deeper, or evidence of lymph node involvement, esophagectomy remains the standard surgical treatment.

Data regarding the role of surgery in patients treated with definitive concurrent radiation and chemotherapy is presented in the section regarding combined modality therapy.

Ablative Therapies

Endoscopic ablative procedures (cryoablation, RFA, and PDT) are mainly used for Barrett's esophagus or dysplasia. Balloon-based RFA results in complete remissions in the majority of patients with Barrett's esophagus or high-grade dysplasia.[171] Endoscopic cryoablation is also an effective therapy in this setting.[172] PDT has been reported to provide local control in early esophageal cancers arising from Barrett's esophagus, ranging from 17% to 100%, and high-grade dysplasia, ranging from 75% to 100%.[173-175] There are no randomized studies that compare ablative therapies to EMR. Recurrence rates using ablative treatments are higher than with esophagectomy and require close endoscopic surveillance and retreatment in some patients. Ablative therapies may also be useful in achieving long-tem palliation of dysphagia, anorexia, or malnutrition.[176,177]

Chemotherapy

Esophageal cancer has a distant failure rate of more than 70%. A large number of chemotherapy agents have been evaluated for response (Table 45-2), but the response rates remain low, with only about 20% of patients having an objective response to a variety of single agents. Combination chemotherapeutic regimens have shown a higher response rate, the best responses being seen in patients receiving multiagent chemotherapy regimens (Table 45-3). Despite increased response rates, the duration of response is typically short and comparable to that seen with single-agent chemotherapy. New agents including targeted therapies remain under investigation.

Targeted Biologic Therapies

HER-2/NEU

Overexpression of HER-2/neu has been reported to range from 0% to 52% in squamous cell carcinomas of the esophagus

TABLE 45-2 Single-Agent Activity in Chemotherapy of Esophageal Cancer*

Drug	No. Patients	Complete Response Rate or Partial Response Rate (%)	Median Duration of Response (mo)
Cisplatin[178]	47	38	2-3
5-Fluorouracil[179]	26	15	1-5
Vindesine[180]	71	36	4
Vinorelbine[181]	29	7	2
Mitomycin C[178]	51	27	3-4
Paclitaxel[182]	52	32	4
Etoposide[183]	26	19	4
Irinotecan[184]	43	14	6
Tarceva[185]	20	15	NR
Gefitinib[186]	34	9	NR
Cetuximab[87]	35	3	NR

NR, *Not reported.*
**Response as determined by radiographic or endoscopic methods.*

TABLE 45-3 Combination-Agent Activity in Chemotherapy of Esophageal Cancer*

Combination	No. Patients	Overall Response Rate (%)
Cisplatin + bleomycin[187]	61	15
Cisplatin + vindesine + bleomycin[188]	68	53
Paclitaxel + cisplatin[189]	20	40
5-Fluorouracil + cisplatin + doxorubicin[190]	21	33
Cisplatin + etoposide[191]	73	48
5-Fluorouracil + cisplatin[192]	88	35
Bleomycin + doxorubicin[193]	16	19
Irinotecan + cisplatin[194]	35	57
Gemcitabine + cisplatin[195]	36	41
Gemcitabine + irinotecan[196]	61	NR
Bevacizumab + irinotecan + cisplatin[105]	47	65
Bevacizumab + docetaxel + cisplatin + 5-fluorouracil[105]	44	67
Bevacizumab + capecitabine/5-fluorouracil + cisplatin[197]	372	38
Sorafenib + docetaxel + cisplatin[198]	44	41
Cetuximab + epirubicin + cisplatin + 5-fluorouracil	90	58
Cetuximab + cisplatin + irinotecan	90	38
Cetuximab + leucovorin + 5-fluorouracil + oxaliplatin[199]	90	51
Cetuximab + leucovorin + 5-fluorouracil + irinotecan[91]	38	44
Panitumumab + epirubicin + oxaliplatin + capecitabine[200]	278	46
Trastuzumab + 5-fluorouracil + cisplatin[73]	594	47.3

NR, *Not reported.*
**Response as determined by radiographic or endoscopic methods.*

and 0% to 73% in adenocarcinomas.[201] The ToGa trial screened tumors from 3807 patients with advanced gastric (80%) or esophagogastric (20%) cancer, and 22.1% were found to be Her-2/neu-positive. In this trial 594 patients with Her2/neu positive cancers were randomized to receive either chemotherapy (5-fluorouracil or capecitabine and cisplatin) alone or the same chemotherapy with trastuzumab resulting in improved survival for those patients with Her-2/neu positive (IHC 2-3+ or FISH+) tumors treated with trastuzumab. Median overall survival was 16 months for those patients receiving trastuzumab with IHC 2-positive and FISH-positive or IHC 3-positive tumors compared to 11.8 months for those who did not.[73] Trastuzumab emtansine (T-DM1) is a conjugated antibody to a potent microtubule inhibitor. T-DM1 has demonstrated efficacy in esophagogastric cancer cells and xenograft models.[202] A Phase II/III trial is planned using a taxane with or without T-DM1 in patients with refractory esophagogastric cancer.

EGFR

Up to 80% of esophageal adenocarcinomas and squamous cell carcinomas demonstrate increased EGFR expression, which is associated with decreased overall survival.[82] Multiple trials with tyrosine kinase inhibitors of anti-EGFR antibodies have failed to suggest utility for these agents in advanced disease for either adenocarcinoma or squamous cell carcinoma. The potential application of these agents combined with radiotherapy is discussed in the section on combined modality therapy.

VEGF

High levels of VEGF expression have been correlated with poor overall survival rates in patients with esophageal cancer.[94,96-100] The impact of VEGF inhibition in combination with chemotherapy in patients with esophageal cancer is under evaluation, but impact on survival remains unclear. Recently reported results from Phase III studies in advanced gastric (including gastroesophageal junction) cancers have not demonstrated a survival benefit for the addition of bevacizumab to systemic chemotherapy, although improved progression-free survival was observed.[203,204]

Sorafenib is a tyrosine kinase inhibitor of VEGFR1-3, Raf-1, Braf, and PDGFR1. It has been studied in combination with docetaxel and cisplatin in advanced gastric and esophagogastric junction cancer demonstrating a 41% response rate and 13.6 month median survival.[198]

COX-2

COX-2 is another molecular target that has been shown to have significance in cancer development and progression in dysplastic lesions of the esophagus, with COX-2 level increasing in the early stages of carcinogenesis of esophageal adenocarcinoma.[63] Selective inhibition of COX-2 has been shown to alter the development and progression of cancer in clinical trials.[205] In addition, inhibition of COX-2 activity results in enhanced radiosensitization of tumor tissue but not normal tissue.[107,206] Selective COX-2 inhibition has also been shown to directly inhibit tumor neovascularization.[107,108,206,207] The combination of these effects suggests potential enhancement of selective tumor targeting by COX-2 inhibition. Studies combining COX-2 inhibition with neoadjuvant chemotherapy and radiation have demonstrated tolerability but failed to demonstrate an improvement in the pathologic response over standard neoadjuvant combined-modality treatment.[208-210]

New Targets

Hepatocyte Growth Factor/Mesenchymal Epithelial Transition Factor (Hgf/Met). cMET (mesenchymal–epithelial transition factor) and its ligand, HGF are potential therapeutic targets in esophagogastric cancer. MET tyrosine kinase activation is mediated by HGF binding and multiple downstream signal transduction pathways (Ras, mTOR, STAT3, PI3K and

NF-κB)[211,212] and can promote angiogenesis.[213,214] MET signaling is altered by receptor or ligand overexpression as well as gene amplification in some gastric and esophagogastric tumors.[213-217] MET gene mutations may be sporadic or hereditary.[213,218,219] Only 2% of esophagogastric adenocarcinomas contain the MET amplification, which is associated with advanced stage disease.[220] Crizotinib is an orally available small molecule inhibitor of MET and ALK. In a small study of patients with esophagogastric with MET amplification treated with crizotinib, a 30% response rate was observed.[220] Another strategy to target the MET pathway is Rilotumumab, a human monoclonal antibody to HGF. A randomized Phase II study has demonstrated an improved median survival with the addition of rilotumumab to epirubicin, cisplatin and capecitabine (ECX) in patients with gastric/esophagogastric disease with greater than 50% of cells staining positive for MET by immunohistochemistry.[221] MET expression is predictive of both poor overall prognosis and response to anti-HGF antibody therapy.[221] A Phase III study is planned for first-line therapy in patients with esophagogastric adenocarcinoma with high MET expressing tumors using rilotumumab.

Heat Shock Protein 90 (Hsp90). HSP90 binds to nucleotide binding sites as a chaperone protein resulting in the release of important client proteins, which include wild-type and activated signaling proteins of B-RAF, KIT, EGFR, HER-2, PDGFR, and KIT. Hsp90 inhibition results in alterations in the structure of these proteins and subsequent ubiquitination and degradation.[222] In a study of human esophageal cell lines, inhibition of Hsp90 with 17-allylamino-17-demethozygeldanamycin (17-AAG) resulted in decreased proliferation and survival, and synergistic effect with radiation.[223] A Phase II study of a small molecule inhibitor of Hsp90, STA9090, in patients with metastatic esophagogastric cancer is completed and results are pending (NCT01167114).

Radiation Therapy

Historical series reported results using external beam radiation alone for the treatment of patients with esophageal cancer, mostly those who refuse surgery or those with unresectable tumors (T4). The outcome following primary radiation therapy alone in the treatment of clinically localized esophageal cancer remains poor, with a 2-year survival rate of approximately 10% to 20% and a 5-year survival rate of approximately 5%[224-226] (Table 45-4). Several autopsy studies demonstrate that 50% to 89% of patients harbor both local and undetected distant disease.[227] Review of the literature examining patterns of failure following irradiation alone demonstrate local failure rates of 50% to 91% following doses greater than 50 Gy.[228,229] Attempts to increase total radiation dose have failed to improve outcome for these patients. In the Radiation Therapy Oncology Group (RTOG) 85-01 trial, all patients in the radiation alone arm who received 64 Gy at 2 Gy per fraction delivered with conventional techniques died of cancer within 3 years following treatment.[230,231]

Twice-a-Day Radiation

Building on the encouraging data of twice-daily radiotherapy in other tumor sites, a number of researchers have investigated its usefulness in esophageal cancer. Kikuchi et al observed an encouraging 5-year cause-specific survival rate of 31.5% for 60 patients receiving twice-a-day concomitant boost radiation therapy alone,[239] while Zhao et al reported on the feasibility of late-course accelerated hyperfractionated radiotherapy for early-stage esophageal carcinoma (41.4 Gy in 5 weeks, followed by a 2-week course of twice-daily irradiation at 1.5 Gy per fraction; cumulative dose of 67 Gy to 70 Gy). The investigators observed an encouraging 5-year local control rate of 85%.[240] Another study reported a 5-year survival rate of 33% for patients treated with definitive late-course accelerated radiotherapy alone to 68.4 Gy.[237] The addition of chemotherapy appears to improve outcome for patients treated with hyperfractionated radiation as demonstrated by Girvin et al who treated patients with twice-a-day preoperative irradiation plus concurrent 5-fluorouracil, cisplatin, and vinblastine and observed a remarkable complete response rate of 79%.[241] Data from a larger series using a similar concurrent regimen of 5-fluorouracil plus cisplatin and twice-daily irradiation did not confirm the findings of Girvin, however. In the series reported by Yu et al, a local tumor control rate of 94% was reported with an alternating schedule of cisplatin and 5-fluorouracil with twice-daily irradiation on alternating weeks (1.8 Gy to 2 Gy to 60 Gy), but the regimen was associated with significant grade-5 acute toxicity.[242] The use of twice-daily irradiation is currently restricted to clinical trials.

TABLE 45-4 Results with Irradiation Alone for Definitive Treatment of Esophageal Cancer

Investigator	Years	No. Patients	5-year Survival (%)
Hussey[232]	1945-1975	69	10
Newaishy[224]	1956-1974	444	9
Van Houtte[233]	1962-1972	81	3
Appelqvist[234]	1965-1974	50	4
Lewinsky[235]	1966-1971	85	4
Petrovich[236]	1963-1986	137	2
Herskovic[230]	1986-1990	53 evaluable†	10 at 2 years
Shi[237]	1988-1990	42‡	33
Girinsky[238]	1986-1993	88*	6 at 3 years

**Some patients received chemotherapy.*
†Escalated total dose: 64 Gy in 32 fractions per fraction
‡Late course accelerated fractionation: 41.4 Gy in 23 fractions over 4 to 5 weeks then 1.8 Gy/day to 64.8 Gy total.

Combined-Modality Therapies

Combined-modality therapy has been adopted for the treatment of esophageal cancer because of the poor survival rates associated with patients treated with surgery or radiation alone and has now become standard for the treatment of non-metastatic disease, except for the earliest lesions.[243]

Surgery with Neoadjuvant or Adjuvant Chemotherapy (without Radiation)

The rationale for the use of chemotherapy before either surgery or chemoradiation includes the early treatment of subclinical distant disease while the primary tumor is also being treated, administering the drug when the patient can best tolerate the toxicities. In addition to the hope that both local and distant control rates might improve, there is also hope that this approach might identify patients who would respond to additional chemotherapy for control of minimal residual disease.

Although a number of studies evaluating preoperative chemotherapy have demonstrated good response rates, only a few randomized studies have been reported. The most robust experience comes from the Medical Research Council Oesophageal Cancer Working Group.[244] In this study, 802 previously untreated patients with resectable esophageal cancer were randomized to receive either two cycles of cisplatin plus 5-fluorouracil followed by surgery or surgery alone. The

median survival time was 16.8 months for patients randomized to chemotherapy compared with 13.3 months for patients who underwent surgery alone. The 2-year survival rate was also improved for patients randomized to chemotherapy (43%) versus surgery alone (34%) and at a median followup of 6 years, survival remained higher for those patients treated with preoperative chemotherapy (23% versus 17%).[245] Lesser improvements in median survival times have been demonstrated in other randomized studies.[191,246-248]

In striking contrast are the data from Kelsen et al from the Intergroup trial (INT 0113).[249,250] Four hundred sixty-seven patients were randomized to surgery alone versus induction chemotherapy (three cycles of cisplatin/5-fluorouracil chemotherapy) followed by surgery. With a median follow-up time of 55.4 months preoperative chemotherapy decreased the incidence of R1 resections, but produced no significant differences in survival.[250] An individual patient databased meta-analysis has demonstrated a small but significant difference (4%) in overall and disease-free survival favoring preoperative chemotherapy over surgery alone.[251] A larger meta-analysis of 1981 patients from nine randomized trial also showed a survival benefit for patients treated with preoperative chemotherapy.[252]

The utility of postoperative chemotherapy alone has also been studied in a limited fashion. A multicenter Phase II trial evaluated four cycles of adjuvant paclitaxel and cisplatin chemotherapy; the 3-year survival rate was encouraging at 42%, but most patients (76%) had failure at distant sites.[253] The Japan Clinical Oncology Group reported the results from 242 patients with squamous cell carcinoma of the esophagus who underwent transthoracic esophagectomy with lymphadenectomy and were then randomized to either observation or two courses of cisplatin plus 5-fluorouracil chemotherapy. Although an improvement in the 5-year disease-free survival rate was seen for patients receiving the adjuvant chemotherapy (55% versus 45%), a slight improvement in overall survival rate was observed (61% versus 52%).[254] These results were not different from those observed in a 205-patient Phase III trial showing no benefit with the addition of adjuvant cisplatin and vindesine chemotherapy to surgery.[255] We currently recommend that patients receive adjuvant chemotherapy only as part of a clinical trial.

There is a growing interest in perioperative chemotherapy for the treatment of resectable esophagogastric cancer. The MAGIC trial randomized 503 patients with esophageal (25%; 14% lower esophagus, and 11% esophagogastric junction) or gastric (75%) adenocarcinomas to receive pre- and postoperative chemotherapy (epirubicin, cisplatin, and 5-fluorouracil). The perioperative chemotherapy group was found to have less advanced nodal involvement (84% versus 70.5%) and a greater proportion of early stage (T1-T2) tumors (51.7% versus 36.8%) than the surgery alone group, and chemotherapy improved 5-year survival rates (36% versus 23%, respectively).[256] A similar approach was taken by the FNCLCC/FCCD trial in which patients with adenocarcinoma of the lower esophagus or esophagogastric junction (75%) or proximal stomach (25%) were treated with perioperative 5-fluorouracill and cisplatin. The 5-year disease-free (34% versus 19%) and overall survival (38% versus 24%) rates were improved for patient receiving perioperative chemotherapy.[257] These studies have established perioperative chemotherapy as a viable option for patients with resectable adenocarcinoma of the distal esophagus or esophagogastric junction.

Neoadjuvant Radiation Followed by Surgery (without Chemotherapy)

Early attempts to improve local control and survival rates combined radiation and surgery. At the Memorial Sloan Kettering Cancer Center from 1956 to 1966, 85 patients were treated with preoperative radiation and surgery, with 47 patients ultimately going on to resection. The overall crude 5-year survival rate was 6% and the median survival rate was 14 months. No tumor was seen in the surgical specimen in 7 (14%) of the tumors resected.[228] One study compared the outcomes for patients who underwent staging laparotomy, gastrostomy, and nutritional supplementation before preoperative radiation (20 Gy to 25 Gy in four to five fractions) followed by a total esophagectomy with the outcomes for patients who underwent either irradiation or surgery alone. The 3-year survival rate was 27% for patients treated with combined therapy versus 22% for those treated with surgery alone and 6% with irradiation alone,[258] but updated data showed a 5-year survival rate of 13% for the combined-modality cohort.[259] Others report a 5-year survival rate of 25% for patients receiving 50 Gy preoperatively versus 14% for patients treated with surgery alone.[260]

These studies, however, were all retrospective reviews that did not allow direct comparisons of treatments. Prospective randomized trials evaluating outcomes for patients treated with either surgery alone or preoperative irradiation demonstrated no benefit to the addition of preoperative radiotherapy; reported 5-year survival rates ranged from 9.5% to 45% for the preoperative radiation and surgery group and from 11.5% to 25% for patients treated with surgery alone.[261-264] To date, randomized trials have not demonstrated a survival advantage for either preoperative or postoperative radiation alone.[264-266] Table 45-5 summarizes the results of randomized trials comparing radiation alone followed by surgical resection to surgery alone.

Primary radiotherapy or preoperative radiation therapy should be restricted to palliation for patients who are medically unable to receive chemotherapy as part of their treatment course.

Chemoradiotherapy

Numerous single institutions and cooperative groups have investigated the use of concurrent chemotherapy and radiotherapy in the management of patients with localized esophageal cancer, either as definitive treatment or as preoperative therapy. A significant body of information suggests that chemotherapeutic agents such as 5-fluorouracil, cisplatin, mitomycin C, gemcitabine, irinotecan, oxaliplatin, and paclitaxel

TABLE 45-5 Results of Randomized Trials of Surgery Alone ± Preoperative Irradiation (No Chemotherapy)

Investigator	Year	No. Patients	Radiation Dose	5-year Survival (%)
Launois[263]	1981	67	40 Gy	9.5
		57	Control	11.5
Huang[262]	1986	83	40 Gy	45.5
		77	Control	25
Gignoux[261]	1987	102	33 Gy	16
		106	Control	10
Wang[264]	1989	104	40 Gy	35
		102	Control	30
Nygaard[267*]	1992	108	35 Gy	21
			Control	9
Arnott[268]	1992	176	20 Gy	9
			Control	17

Gy, *Gray.*
**3-year survival data.*

have a greater than additive effect when used in combination with radiation therapy. In addition, there is a growing body of evidence that incorporation of targeted therapies in to treatment regimens may enhance radiosensitization. Therefore, most studies testing multimodality therapy have used these agents in a concurrent schedule. The mechanism of the interaction between irradiation and chemotherapeutic agents is complex and not entirely understood.

Definitive Concurrent Chemotherapy and Irradiation

Table 45-6 reports the results of several nonrandomized trials employing concomitant chemotherapy and radiation therapy for the definitive treatment of esophageal cancer. Generally, the most successful treatment regimens have combined infusional 5-fluorouracil with either mitomycin C or cisplatin.

Randomized data have shown benefit in patients treated with definitive concurrent chemoradiation (Table 45-7), resulting in local control rates ranging from 24% to 67% (Tables 45-8 and 45-9).

The most important contemporary trial is that of Herskovic et al (RTOG 85-01).[230] One hundred and twenty-one patients were randomized to either 50 Gy with concurrent chemotherapy with 5-fluorouracil (1000 mg/m^2 for 4 days) and cisplatin (75 mg/m^2) versus 64 Gy alone. At 5 years, 27% of the combined-modality patients were alive versus none of the patients in the irradiation-only group.[280] The median survival time for the combined-modality arm was 14.1 months versus 9.3 months for the irradiation-alone arm.[280] These results are important because they not only demonstrate a survival advantage with combined-modality therapy but also show that the survival advantage cannot be obtained by simply substituting a higher radiation dose in place of chemotherapy.

There was a suggestion of a radiotherapy dose-response relationship from early (nonrandomized) studies at Wayne State University, as patients treated to 5000 cGy (concurrent with a 5-fluorouracil plus cisplatin regimen) appeared to have longer median survival than patients treated to 3000 cGy with the same chemotherapy (see Table 45-6).[274] INT 0123,

TABLE 45-6 Results from Definitive Chemoradiotherapy for Esophageal Cancer

Investigator	No. Patients	Irradiation Dose	Chemotherapy Agents	Median Survival Time (mo)	2-year Survival (%)
Kavanagh[269]	45	60 Gy-64 Gy	5-FU or etoposide, cisplatin or carboplatin	18	27
Seitz[270]	35	40 Gy	5-FU, cisplatin	17	45
Keane[271]	35	45 Gy-50 Gy	5-FU, mitomycin C	NR	28
Hukku[272]	34	30 Gy	5-FU, cisplatin	NR	38
John[229]	30	41 Gy-50 Gy	5-FU, cisplatin, mitomycin C	11	29
Herskovic[273]	22	50 Gy	5-FU, cisplatin	19.5	36
	39	30 Gy	5-FU, cisplatin	9.8	20
Minsky[274]	109	64.8 Gy	5-FU, cisplatin	13 NS	31 NS
	109	50.4 Gy	5-FU, cisplatin	18 NS	40 NS

5-FU, *5-Fluorouracil;* Gy, *Gray;* NR, *not reported;* NS, *not significant.*

TABLE 45-7 Randomized Studies Comparing Definitive Irradiation Alone with Chemoradiotherapy

Investigator	No. Patients	Irradiation Dose	Chemotherapy Agents	2-year Survival (%)
Araujo[275]	28	50 Gy	Control	22
	31	50 Gy	5-FU, mitomycin C, bleomycin	38
Sischy[276*]	62	60 Gy	Control	12
	65	60 Gy	Mitomycin C, 5-FU	30
Roussel[277]	69	45 Gy	Control	31 at 1 year
	75	56 Gy	Methotrexate	35 at 1 year
Herskovic[230]	60	64 Gy	Control	10
	61	50 Gy	5-FU, cisplatin	38

5-FU, *5-Fluorouracil;* Gy, *Gray.*
**Some patients went to resection.*

TABLE 45-8 Patterns of Failure Following Definitive Concurrent Chemoradiotherapy

Investigator	No. Patients	Local Control Rate (%)	Local Plus Distant Control Rate (%)	Distant Control Rate (%)
Kavanagh[269]	45	24	20	18
Chan[278]	21	24	18	43
Coia[279]	57	25	23	16
Herskovic[273]	22	32 (50 Gy)	18	23
	39	67 (30 Gy)	18	3
Minsky[274]	109	44 (64.8 Gy)	50	91
	109	48 (50.4 Gy)	45	84

Gy, *Gray.*

TABLE 45-9 Patterns of Failure from Randomized Studies of Definitive Chemoradiotherapy versus Radiation Alone

Investigator	No. Patients	Therapy	Local Control Rate (%)	Distant Control Rate (%)
Herskovic[230]	121	Radiation therapy	64	70
		Radiation therapy + chemotherapy	44	25
Araujo[275]	59	Radiation therapy	74	13
		Radiation therapy + chemotherapy	46.5	18
Minsky[274]	218	50.4 Gy + chemotherapy	52	16
		64.8 Gy + chemotherapy	56	9

Gy, *Gray*.

randomized patients with unresectable esophageal cancer to receive the same chemotherapy (5-fluorouracil and cisplatin) with either 64.8 Gy or 50.4 Gy. In this study there was no significant difference in median survival times (13 months versus 18.1 months), 2-year survival rate (31% versus 40%), or locoregional failure rate (56% versus 52%) between the high-dose and standard-dose treatment arms, respectively; however there was a higher treatment-related mortality rate (10% versus 3%) in the patients assigned to the high-dose radiation arm, which did not seem to be related to the higher radiation dose.[274] The trial was stopped after an interim analysis. The reason for the lack of benefit in the high-dose arm is unclear, but there was a significant prolongation of the treatment time because of toxicity breaks when correcting for the number of radiation treatments as well as a significantly lower 5-fluorouracil dose delivered when compared with the low-dose arm.[274] Results of these studies have established 50.4 Gy as the standard dose for definitive chemoradiation in esophageal cancer.

The improvement in survival rates in the combination trials seems related at least in part to an improvement in local control rates. Tables 45-8 and 45-9 show the crude patterns of failure from several definitive chemoradiation trials. These data suggest that combined-modality therapy produced a shift in the pattern of failure, from a local failure rate of 50% to 90% for irradiation alone to 20% to 50% with combined-modality therapy. RTOG 85-01 reported a crude local persistence or recurrence rate of 44% for patients treated with chemoradiation versus 64% for the irradiation alone group. The 2-year actuarial local failure rate was reduced from 68% to 43% and the rate of distant metastases was reduced from 70% to 25% with combined-modality therapy.[230]

Many chemotherapy agents have been investigated in an attempt to improve outcomes. RTOG 0113 was a randomized Phase II study for patients who were unwilling to have surgery or were medically unfit for surgery, who were randomly assigned to receive either induction treatment with 5-fluorouracil, cisplatin, and paclitaxel and then 5-fluorouracil plus paclitaxel with 50.4 Gy of irradiation or induction with paclitaxel plus cisplatin and then the same chemotherapy with 50.4 Gy of irradiation. Unfortunately, both arms were associated with high morbidity rates, and the study did not meet its 1-year survival end point.[281] Others have demonstrated efficacy of carboplatin and paclitaxel with concurrent definitive chemoradiation in esophageal cancer.[282,283] Definitive chemoradiation with cisplatin and docetaxel has been shown to result in a high response (98%), local control (60%), and 3-year survival (37%) rates in patients with squamous cell carcinoma.[204] A recent Phase II trial randomized patients to either FOLFOX (leucovorin, 5-fluorouracil, oxaliplatin) or 5-fluorouracil and cisplatin with concurrent definitive radiation resulting in improved outcome for those treated with FOLFOX (3-year OS 18.2 months versus 17.4 months; median OS 20.2 months versus 17.5 months, respectively).[284] An optimum regimen for concurrent chemoradiation has not been established, though active cooperative group prospective trials have adopted paclitaxel and carboplatin or FOLFOX-based regimens as standard therapy concurrent with radiotherapy.

A number of targeted agents have been incorporated into chemoradiation trials with attempt to improve outcome. Trastuzumab in addition to cisplatin, paclitaxel, and concurrent radiation followed by maintenance trastuzumab has demonstrated safety and a promising 3-year survival rate of 47% for patients with esophageal adenocarcinomas that overexpress HER-2.[285] Based on this encouraging safety and efficacy data, RTOG 1010 (NCT01196390) is studying the addition of trastuzumab to chemoradiation in patients with HER2-positive operable locally advanced adenocarcinoma of the esophagus and esophagogastric junction. Results of a randomized Phase III trial (RTOG 0436; NCT00655876) of cisplatin, paclitaxel, and radiation therapy with or without cetuximab in locally advanced, nonsurgically treated esophageal cancer were recently presented, and the addition of cetuximab did not improve OS regardless of histology.[286] A smaller prospective study (SWOG 0414) evaluating cetuximab with concurrent cisplatin, irinotecan, and radiation demonstrated poor tolerability of the regimen with treatment-related mortality approaching 10% resulting in early study closure.[287] The SCOPE1 study (NCT00509561) randomized Phase II/III study showed the addition of cetuximab to chemoradiotherapy resulted in both greater toxicity and worse survival.[288] These results give caution to the use of targeted agents outside of a clinical trial.

An important concern regarding the use of combined-modality therapy is treatment toxicity. In the Wayne State University series, 5 of 20 patients required hospitalization for intravenous hydration and nutritional support, and 38% developed pulmonary compromise (thought to be secondary to receiving bleomycin plus irradiation) that required corticosteroids.[273] The overall irradiation dose appears to be important, as has been reflected in data from Sauter et al.[289] In a study of 30 patients receiving concurrent chemotherapy and irradiation (60 Gy), only 67% of patients were able to complete the irradiation schedule as planned and only 18 of the 30 patients were able to proceed to resection.[289] Coia et al[279,290] reported a 56% incidence of moderate to severe acute toxicities, whereas the researchers of RTOG 85-01 found that side effects were severe in 44% of patients and life-threatening in 20% of patients in the combined-modality arm versus 25% and 3% in the radiation only group, respectively.[230] Most of the toxicity was hematologic, along with significant esophagitis and stomatitis. Although only 1 of 61 patients in the combined-modality group died of acute toxicity, only 50% of patients completed all four cycles of chemotherapy.[230]

Definitive Sequential Chemotherapy and Irradiation

The usefulness of sequential chemotherapy followed by a course of definitive radiation therapy alone has been

evaluated on a limited scale. One study evaluated patients treated with sequential cisplatin/bleomycin chemotherapy for three courses followed by definitive thoracic irradiation and resulting in a partial response rate of 52% and a complete response rate of 16% as determined by CT scanning and endoscopy, with 1-year and 4-year survival rates disappointing at 20% and 8%, respectively.[291] Similarly, patients treated with two cycles of induction cisplatin-vindesine-bleomycin chemotherapy followed by definitive radiotherapy results in a discouraging 15% OS rate at 5 years.[292] A more recent Phase II sequential study reported by Sharma et al,[293] testing multiple cycles of 5-fluorouracil plus cisplatin followed by a definitive course of irradiation (60 Gy), was equally disappointing, with a median survival time of 39 weeks. This approach has generated relatively little interest as it does not take advantage of the probable benefit of concurrent chemoradiotherapy.

Definitive Induction and Concurrent Chemotherapy and Irradiation

A number of investigators have tested induction chemotherapy followed by definitive irradiation and concurrent chemotherapy, mostly in the preoperative setting.[294-301] One report in the nonoperative setting evaluated 45 patients with locally advanced disease treated with three cycles of induction 5-fluorouracil and cisplatin followed by two additional cycles of chemotherapy delivered concurrently with irradiation to 64.8 Gy. Although the median survival time was an encouraging 20 months, six patients died from treatment-related toxicity.[302,303] The impact of induction chemotherapy on the therapeutic ratio for patients receiving definitive concurrent chemoradiotherapy has not been well studied.

Preoperative Chemoradiation

Preoperative chemoradiation followed by surgery is the most commonly used treatment approach for patients with esophageal carcinoma. The Southwestern Oncology Group (SWOG) and the Radiation Therapy Oncology Group (RTOG), based on pilot data from Wayne State University, performed two similar Phase II trials using concurrent chemotherapy and irradiation followed by planned resection in patients with squamous cell carcinoma of the esophagus. In the SWOG study, 113 patients with initially resectable tumors received treatment with infusional 5-fluorouracil plus cisplatin with concurrent irradiation to a dose of 30 Gy. The overall operability rate was 63%, and the overall resectability rate was 49%. The median survival time was 12 months, with 16% of patients alive at 3 years.[304] Of the 41 patients entered in the RTOG preoperative trial of concurrent irradiation plus 5-fluorouracil and cisplatin, 7.5% were alive at 3 years.[305] For patients with esophageal adenocarcinoma, preoperative chemoradiation followed by surgery has been the subject of numerous clinical trials. Data from the University of Michigan and Duke University report 5-year survival rates of 34% and 27%, respectively.[269,306]

Although chemotherapy before preoperative chemoradiation has been included in several regimens, there are no randomized clinical trials at this time that demonstrate benefit over concurrent chemoradiation without induction chemotherapy. A renewed interest in this approach has come about recently with exploration of early PET scans to assess the response.[307,308] Currently, the CALGB is evaluating a response-adapted strategy using induction chemotherapy with early FDG-PET imaging followed by chemoradiation, with concurrent chemotherapy selection based on the response to initial chemotherapy (CALGB 80803—NCT01333033). In this study patients receive either modified FOLFOX (leucovorin, 5-fluorouracil and oxaliplatin) for three 14-day courses or carboplatin and paclitaxel for two 21-day courses. Patients then undergo PET/CT scan. Patients with responsive disease (tumor metabolic activity decreased by ≥35%) receive three additional courses of FOLFOX and concurrent radiotherapy or weekly radiosensitizing doses of concurrent carboplatin/paclitaxel with concurrent radiotherapy. The primary endpoint of this study is pathologic complete response rate of PET/CT nonresponders within each treatment group.

The next generations of chemoradiation trials attempted to incorporate more novel chemotherapeutic agents. The results of a 46-patient Phase II study of irradiation and concurrent cisplatin, 5-fluorouracil, and paclitaxel demonstrated a pathologic complete response rate of 45% for the 40 patients able to undergo resection. The overall median survival time was 34 months, with 37% of patients alive at 5 years.[309] Urba et al reported results from a Phase II trial using preoperative cisplatin, paclitaxel, and twice-daily irradiation, with 90% of patients able to undergo surgery and a 19% complete pathologic response rate. Survival data compared favorably with other previously reported combinations, with a median survival time of 24 months.[310] Oxaliplatin has also been evaluated in combination with 5-fluorouracil–based chemotherapy with or without irradiation in the neoadjuvant setting. Data suggest that a course of preoperative oxaliplatin and concurrent chemotherapy with protracted venous infusion of 5-fluorouracil with irradiation (50.4 Gy) is an active regimen in locally advanced esophageal cancer, resulting in rates of 81% for complete radiologic response and 38% for complete pathologic response.[311] More recent studies demonstrated promising complete pathologic response rates of up to 63%,[312] but excessive treatment-related deaths were encountered. Currently, it is thought that concurrent irradiation and containing-containing regimens are not acceptable because of excess toxicity.[312,313]

The addition of targeted agents to chemoradiation in the neoadjuvant setting is under investigation. One treatment strategy evaluated the benefit of the addition of bevacizumab to preoperative chemoradiation using carboplatin, paclitaxel, and 5-flurouracil in stages I to III esophageal or esophagogastric junction cancer (95% adenocarcinomas). A pathologic complete response rate of 29% was observed, similar to regimens not containing bevacizumab.[314] Ilson et al evaluated the efficacy chemoradiation with bevacizumab in patients with Siewert I/II adenocarcinoma of the esophagus. The treatment regimen consisted of induction chemotherapy with cisplatin, irinotecan, and bevacizumab followed by concurrent chemotherapy with cisplatin, irinotecan, and bevacizumab concurrent with radiation therapy. Surgery was followed by adjuvant bevacizumab. A pathologic complete response was observed in only 12% and progression-free and OS were 14 and 30 months, respectively.[315] Given the lack of improvement in the pathologic complete response rate in these Phase II compared with historical controls, there is no role for bevacizumab with chemoradiation for esophageal cancer outside of clinical trials.

Chemoradiation with cetuximab has been extensively studied in the Phase II setting. The Swiss Group for Clinical Cancer Research (SAKK) 75/06 trial evaluated treatment with induction cisplatin, docetaxel, and cetuximab followed by radiation therapy with concurrent cisplatin and cetuximab in 28 patients with operable esophageal cancer resulting in a pathologic complete response rate of 32%.[316] Another study evaluated cetuximab, paclitaxel, and cisplatin in combination with radiation therapy in 60 patients and a pathologic complete response rate of 27% was observed.[317] These studies were not associated with unacceptable toxicity. In contrast, ECOG 2205 evaluated a neoadjuvant regimen of cetuximab combined with 5-fluorouracil, oxaliplatin, and radiation but because of an excess of acute respiratory deaths (ARDS), the study was closed.[318]

TABLE 45-10 Results from Preoperative Chemoradiotherapy and Chemoradiotherapy with Targeted Agents Followed by Surgery

Investigator	No. Patients	Irradiation Dose	Chemotherapy Agents	2-year Survival (%)	Median Survival
Bates[319]	35	45 Gy	5-FU, cisplatin	47	22 mo
Forastiere[320]	47	44 Gy	5-FU, cisplatin	58	31.3 mo
Kavanagh[269]	58	45 Gy	5-FU or etoposide, cisplatin or carboplatin	37	18 mo
Gignoux[261]	119	37.5 Gy	Cisplatin	56.5 (18 mo)	NR
Bidolo[321]	34	30 Gy	5-FU, cisplatin	38	NR
Seydel[305]	41	30 Gy	5-FU, cisplatin	15	13 mo
Poplin[304]	71	30 Gy	5-FU, cisplatin	28	NR
Stewart[322]	68	30 Gy	5-FU, cisplatin, etoposide, leucovorin	76	26 mo
Urba[310]	69	45 Gy twice daily	Paclitaxel, cisplatin	50	24 mo
Meluch[323]	129	44 Gy	Paclitaxel, 5-FU, carboplatin	47	22 mo
Choi[309]	46	58.5 Gy concomitant boost	Paclitaxel, 5-FU, cisplatin	57	34 mo
Ruhstaller[299]	66	45 Gy	Cisplatin, docetaxel	66	NR
Ajani[295]	43	45 Gy	Irinotecan, cisplatin	42	22.1 mo
Ilson[308]	19	50.4 Gy	Irinotecan, cisplatin	NR	31.7 mo
Khushalani[311]	38	50.4 Gy	Oxaliplatin, 5-FU	NR	NR
Ruhstaller[324]	28	45 Gy	Cisplatin, docetaxel, cetuximab	NR	16 mo
Kleinberg[318]	22	45 Gy	Oxaliplatin, 5-FU, cetuximab	NR	NR*
Suntharalingam[286]	344	50.4 Gy	Cisplatin, paclitaxel, cetuximab Cisplatin, paclitaxel	41 42	NR
Ilson[315]	33	50.4 Gy	Irinotecan, cisplatin, bevacizumab	NR	30 mo
Bendell[314]	62	45 Gy	Paclitaxel, carboplatin, bevacizumab	NR	NR†

5-FU, *5-Fluorouracil;* Gy, *Gray;* mo, *months;* NR, *not reported.*
**Closed early because of unacceptable pulmonary toxicity resulting in early deaths.*
†*Pathologic complete response 30%.*

Results from several nonrandomized trials employing using various chemotherapeutic and targeted therapies in the setting of preoperative chemoradiation are shown in Table 45-10.

The question of whether combined preoperative radiotherapy and chemotherapy is superior to preoperative chemotherapy was addressed in a Phase III study in patients with locally advanced esophagogastric junction adenocarcinomas. A higher pathological complete response rate and uninvolved lymph node rate was observed in those patients treated with combined modality therapy compared to those receiving only chemotherapy (15% versus 2% and 64% versus 37%, respectively). Although the study was closed early because of poor accrual, there was a trend for 3-year survival rate in favor of the combined-modality group (47% versus 27%, $p = 0.7$).[300]

Preoperative Chemoradiation versus Surgery Alone

Preoperative chemoradiation is the most common treatment approach for patients with esophageal carcinoma and is currently considered standard of care. Although earlier randomized trials comparing surgery alone with chemoradiation followed by surgery for the treatment of resectable esophageal cancer have shown conflicting results[325-330] four meta-analyses have demonstrated that chemoradiation results in improved survival[252,331-333] and decreased local recurrence compared to surgery alone.[331,333] In addition, preoperative chemoradiation has been reported to result in increased pathologic response rates compared with preoperative chemotherapy without radiation (28% versus 4%, respectively) in patients with locally advanced esophageal cancer,[334] while pathologic complete response to neoadjuvant therapy has been associated with an improvement in overall survival in some series[334] but not in others.[335]

In a nonrandomized study of preoperative chemoradiation and surgery versus surgery alone, Vogel et al[336] reported an OS advantage for patients receiving multimodality therapy, with 36% alive at 5 years versus 11% for surgery alone. Urba et al also reported a 3-year survival advantage for those patients receiving preoperative concurrent chemoradiation compared with surgery alone (30% versus 16%, respectively), although not nonstatistically significant.[208] Walsh et al conducted a randomized study of patients treated with two 5-day courses of 5-fluorouracil given on weeks 1 and 6 and cisplatin with concurrent (40 Gy) irradiation, delivered before surgery compared with patients who underwent surgery alone. The reported (actuarial) survival rates favored patients receiving combined-modality therapy, with 32% alive at 3 years versus 6% who underwent surgery only[330]; however, this trial has been criticized for the unusually low survival rate in the surgical arm. In contrast, no survival advantage was observed for patients receiving preoperative chemoradiation versus surgery alone in a randomized study reported by Bosset.[325] This study, however, used a unique irradiation and chemotherapy schedule: irradiation was delivered via a split course, and over the span of 2 weeks, a total dose of 37 Gy in 3.7-Gy daily fractions was delivered. The chemotherapy consisted of cisplatin given prior to each week of irradiation. Patients were taken to surgery 2 to 4 weeks after completing the preoperative regimen.[325] The lack of benefit and increased toxicity observed for the combined-modality arm may have been predicted with the application of large radiation fractions, the inclusion of a planned treatment break, an inadequate recovery period between the preoperative therapy and surgery, and the use of single-agent chemotherapy.

The U.S. Gastrointestinal Intergroup trial attempted to further evaluate the role of preoperative chemoradiation therapy compared to surgery alone but was stopped before completion because of poor accrual. Nonetheless, Tepper et al[327] reported the results from this trial (CALGB 9781) for the 56 patients who were enrolled before the trial closed. A median survival time of 4.48 years versus 1.79 years in favor of trimodality therapy and a 5-year survival rate of 39% versus 16% in favor of trimodality therapy were demonstrated on an intent-to-treat analysis.[327] Despite the low accrual rate, the observed difference supportive trimodality therapy as an appropriate standard for resectable esophageal cancer.

The Phase III CROSS trial randomized patients with resectable esophageal cancer (75% adenocarcinomas) to preoperative weekly radiosensitizing carboplatin and paclitaxel with concurrent radiation (41.4 Gy at 1.8 Gy per fraction) or surgery alone and demonstrated improved median and 5-year survival in the chemoradiation arm compared to the surgery arm (49 months versus 24 months, and 47% versus 34%, respectively). The pathologic complete response rate was higher for squamous cell carcinomas compared to adenocarcinomas, but histology was not prognostic for survival. The study included 368 patients (23% squamous cell; 75% adenocarcinoma; and 2% undifferentiated) with 178 patients randomized to neoadjuvant chemoradiation. R0 resection was achieved in 92% of the patients receiving neoadjuvant chemoradiation compared with 69% of those who proceeded directly to surgery. A pathological complete response was achieved in 47 of 161 patients (29%) who underwent resection after preoperative therapy. The results of this trial were statistically significant and present convincing data supporting trimodality therapy for patients with resectable esophageal cancer.[329]

A recently reported meta-analysis of more than 1000 patients enrolled in nine randomized trials evaluating preoperative chemoradiation versus surgery alone revealed a 0.66 survival odds ratio at 3 years in favor of patients receiving preoperative therapy.[333] Three other meta-analysis also demonstrate a similar survival advantage to trimodality therapy compared to surgery alone.[252,331,332] Table 45-11 summarizes the randomized trials comparing the results of preoperative chemoradiation followed by surgery to surgery alone.

Preoperative Chemoradiation versus Definitive Chemoradiation

Bedenne et al[337] have reported the results of a study comparing preoperative chemoradiation followed by surgery versus definitive chemoradiation. In this randomized Phase III trial, patients with locally advanced esophageal cancer received two cycles of induction 5-fluorouracil plus cisplatin with radiotherapy, either delivered via standard fractionation (46 Gy in 4.5 weeks) or over a split course. Patients were then randomized between surgical resection versus completion of definitive chemoradiation to 61 Gy. The 2-year survival rates and median survival times were not different, at 34% and 17.7 months for patients in the preoperative arm versus 40% and 19.3 months for patients randomized to definitive chemoradiation ($p = 0.56$).[337] In a related German study, patients with locally advanced squamous carcinoma of the esophagus received induction chemotherapy followed by a randomization to either chemoradiotherapy (40 Gy) followed by surgery or definitive chemoradiotherapy. The analysis of the 172 randomized patients showed the overall survival rates to be equivalent; the survival rate at 3 years was 31% for patients randomized to combined-modality therapy versus 24% for patients treated with definitive chemoradiation.[338]

A study from the Minnie Pearl Cancer Research Network reflects the difficulties associated with studies that randomize patients away from a surgical intervention. In this study, patients with locally advanced esophageal cancer were to receive a course of preoperative chemoradiation followed either by surgery or by completion of the definitive chemoradiation regimen. One-hundred and ninety-four patients were entered, but only 57 patients actually proceeded with the treatment to which they were randomized. When all patients were considered, the survival rates were similar; the 3-year survival rate for patients undergoing resection was 35% versus 31% for patients receiving definitive chemoradiation.[323]

The data, taken in aggregate, suggest that the results with definitive chemoradiation are comparable to those observed with treatment strategies that incorporate preoperative chemoradiation and surgery. However, compared to data from historical control patients undergoing planned esophagectomy 4 to 6 weeks after completion of chemoradiation, patients undergoing salvage esophagectomy following definitive chemoradiation experienced increased rates of operative death and complications, including the need for prolonged intubation or longer stays in the intensive care unit and hospital and increased anastomotic leaks. Salvage esophagectomy, nonetheless, has demonstrated a 25% 5-year survival rate in a subset of patients with stage T1-T2, N0 tumors, who undergo R0 resection, and those with a prolonged time to recurrence.[339]

TABLE 45-11 Randomized Trials of Chemoradiotherapy Plus Surgery versus Surgery Alone

Investigator	No. Patients	Treatment	Median Survival Time (mo)	3-year Survival Rate (%)	*p* Value
Urba[328]	50	Surgery	NR	16	0.15
	50	Chemoradiation plus surgery	NR	30	
Walsh[330]	55	Surgery	NR	6	0.01
	58	Chemoradiation plus surgery	NR	32	
Bosset[325]	139	Surgery	NR	37*	0.78
	143	Chemoradiation plus surgery	NR	39*	
Burmeister[326]	256	Surgery	19	NR	0.38
		Chemoradiation plus surgery	22	NR	
Tepper[327]	475	Surgery	21	NR	0.002
		Chemoradiation plus surgery	54	NR	
Van Hagen[329]	366	Surgery	24	44	0.003
		Chemoradiation plus surgery	49	58	

Mo, *Months;* NR, *not reported.*

**Approximate 3-year survival rate or time determined from survival curve.*

Postoperative Chemoradiation

Prospective and retrospective analyses have demonstrated a survival benefit to the addition of postoperative chemoradiation in patients with node-positive esophageal cancer who have undergone esophagectomy.[340-342] SWOG 9008/INT-0116[341] reported a 3-year disease-free survival of 37% for patients with node-positive disease receiving postoperative chemoradiation compared to 24% for patient who did not. SWOG 9008/INT-0116 investigated the benefit of postoperative chemoradiation following surgery in patients with stage Ib-IV, M0 resectable adenocarcinoma of the esophagogastric junction or stomach in a prospective randomized trial. In this trial 556 patients (20% esophagogastric junction) were randomized to receive surgery alone or surgery followed by postoperative chemoradiation (5-fluorouracil plus leucovorin for one cycle followed by concurrent chemoradiation during cycles two and three, followed adjuvant 5-fluorouracil plus leucovorin following completion of chemoradiation). Patients treated on the postoperative chemoradiation arm experienced improved 3-year overall survival (50% versus 41%) and relapse-free survival (48% versus 31%) rates compared to those treated with surgery alone. There was also a decrease in local failure observed in this group (19% versus 29%). However, high rates of hematologic and gastrointestinal toxicities were associated with this treatment regimen resulting in 17% discontinuation of treatment. Despite the significant number of patients who did not complete the treatment, survival benefits have persisted after more than 10 years of followup and the results of INT-0116 have established postoperative chemoradiation as a standard of care for patients with completely resected adenocarcinoma of the esophagogastric junction or stomach.[341] Based on these results, postoperative chemoradiation is considered an acceptable treatment strategy for patients with stage Ib-IV, M0 distal esophageal and esophagogastric junction tumors who undergo resection.

The Significance of Pathologic Complete Response to Neoadjuvant Chemoradiation

Compared with historical unimodality series, failures locally and distantly have markedly decreased with the advent of multimodality therapy (Table 45-12). In general, preoperative irradiation and chemotherapy produce complete pathologic response rates of 20% to 50% (an average of approximately 30%) (Table 45-13). Pathologic complete response to neoadjuvant therapy has been associated with an improvement in OS in some series,[334] but not in others.[335] In the SWOG study, patients who had no evidence of disease at the time of surgery, when compared with all patients who had resection, had a projected 3-year survival rate of 45% versus 14%, and a median survival time of 32 months versus 14 months, respectively.[304]

TABLE 45-12 Patterns of Failure for Concurrent Chemoradiotherapy Followed by Surgical Resection

Investigator	No. Patients	Local Control Rate (%)	Local Plus Distant Control Rate (%)	Distant Control Rate (%)
Herskovic[273]	50	36	38	16
MacFarlane[345]	22	0	38	16
Forastiere[343]	43	2	5	28
Kavanagh[269]	57	14	10	29

TABLE 45-13 Pathologic Findings after Preoperative Chemoradiotherapy

Investigator	No. Patients	Pathologic Complete Response Rate (%)	Radiation Therapy Dose	Chemotherapy Agents
Parker[346]	33	33	30 Gy	5-FU, mitomycin C
Seydel[305]	41	19.6	30 Gy	5-FU, cisplatin
Herskovic[273]	50	24	30 Gy	5-FU, cisplatin
Gignoux[261]	101	24	37.5 Gy	Cisplatin
Forastiere[343]	43	24	37.5 Gy-45 Gy	5-FU, cisplatin, vinblastine
Bates[319]	32	50	45 Gy	5-FU, cisplatin
Kavanagh[269]	72	42	45 Gy	5-FU or etoposide, cisplatin or carboplatin
Hoff[347]	51	21	30 Gy	5-FU, cisplatin, etoposide, leucovorin
Van Hagen[329]	178	29	41.4 Gy	Paclitaxel, carboplatin
Urba[310]	69	19	45 Gy twice daily	Paclitaxel, cisplatin
Bains[348]	41	26	50.4 Gy	Paclitaxel, cisplatin
Meluch[323]	129	46	44 Gy	Paclitaxel, 5-FU, carboplatin
Choi[309]	46	45	58.5 Gy concomitant boost	Paclitaxel, 5-FU, cisplatin
Ruhstaller[299]	66	23	45 Gy	Cisplatin, docetaxel
Ajani[295]	43	41	45 Gy	Irinotecan, cisplatin
Ilson[308]	19	16	50.4 Gy	Irinotecan, cisplatin
Khushalani[311]	38	38	50.4 Gy	Oxaliplatin, 5-FU
Ruhstaller[324]	28	68	45 Gy	Cisplatin, docetaxel, cetuximab
Ilson[315]	33	15	50.4 Gy	Irinotecan, cisplatin, bevacizumab
Bendell[314]	62	30	45 Gy	Paclitaxel, carboplatin, bevacizumab

5-FU, *5-fluorouracil;* Gy, *Gray.*

A similar survival advantage was demonstrated by investigators from the University of North Carolina where median survival time for patients with no evidence of disease at resection was 37 months compared to 13 months for patients with residual tumor.[319] Similarly, in the University of Michigan series, the median survival time was improved for patients without evidence of residual disease at the time of surgery compared to the entire cohort (70 versus 29 months, respectively).[343] Although survival rates were higher in patients who had no disease in the surgical specimen in the University of Michigan and University of North Carolina series, there were long-term survivors among patients with residual disease, suggesting that the addition of surgery, at least in a subset of patients, can produce additional cures after chemoradiation therapy. A retrospective review was performed using a recursive partitioning analysis for 276 patients who received chemoradiation before esophagectomy. These results supported the idea that a pathologic complete response predicted for improved survival rates compared with patients with residual disease, but was less prognostic than the presence of nodal disease and metastases.[344]

Nodal status following neoadjuvant chemoradiation has also been demonstrated to be a predictive factor for survival rates. Gaca et al[349] performed a retrospective analysis of 28 patients with a complete pathologic response and found that patients who were node-negative, regardless of T stage, experienced improved median disease-free survival rates compared with patients with stage N1 nodes. They also found that preoperative tumor stage, patient age, tumor location, or the presence of Barrett's esophagus did not independently predict OS on univariate analysis. Multivariate analysis showed that only posttreatment nodal status, and not posttreatment tumor status, predicted disease-free survival.[349]

Assessing Residual Disease Following Neoadjuvant Chemoradiation

There are no reliable methods to predict pathologic complete responders following neoadjuvant. The use of preresection endoscopy was not useful for determining the tumor response; although 77% of patients were reported to have had a clinical complete response (by endoscopy) preoperatively, 41% of these patients had residual tumor in the pathologic specimen.[319] The inaccuracy of endoscopy in discerning the response after preoperative chemoradiation has been further confirmed in a study from Roswell Park and is important because it suggests that a strategy of initial chemotherapy plus radiation therapy with surgery saved for patients with incomplete clinical response may not be successful.[350]

FDG-PET as an indicator of complete response has also been evaluated.[297,351-353] Tumors with low pretreatment standard uptake unit values, defined as less than 4.5, are less likely to show evidence of treatment response after chemoradiation. A higher likelihood of nodal and pathologic complete response has been demonstrated in tumors with pretreatment SUV_{max} values greater than 4.5. Patients with tumors in both low and high pretreatment SUV_{max} groups demonstrate similar survival rates.[353]

PALLIATION

Oncologists can produce palliation with irradiation alone by using external beam radiation doses ranging from 30 Gy in 2 weeks to 50 Gy to 60 Gy over 6 weeks (Table 45-14). Wara et al[354] reported on 103 patients who completed therapy with 50 Gy to 60 Gy, with 89% having symptomatic improvement and 66% maintaining relief for 2 months or more. The average duration of palliation was 6 months. The dysphagia usually improved near the end of therapy, and almost all patients reported an arrest of their previous symptom progression.[354] Similar data report a 60% to 88% improvement in dysphagia with radiation doses of 50 Gy or higher.[355,356] Concurrent chemoradiation may also be used for palliation of dysphagia (Table 45-14). Studies demonstrate a rate of up to 88% improvement in swallowing, with the median time to improvement being 2 weeks with durable relief of symptoms.[290] Aggressive concurrent irradiation potentially increases complications in patients with incurable disease and a limited life span, but it may offer a more effective means of palliation.

When considering brachytherapy in esophageal cancer, one must keep in mind both the biologic characteristics of the disease and the physics of brachytherapy. Esophageal tumors are rarely confined to the mucosa or the muscular wall, and they generally extend outside the walls of the esophagus and have a high incidence of nodal spread. The physics of brachytherapy are such that the dose is primarily delivered within a radius of approximately 1 cm from the applicator. Therefore, it is quite unlikely that this approach will be effective for curative therapy of most esophageal carcinomas because of inadequate therapy to much of the tumor. It may, however, be useful for palliation where the central disease is producing the symptoms and can be effectively treated with brachytherapy. Several small series have demonstrated that intracavitary irradiation in the appropriately selected patient is a safe and

TABLE 45-14 Palliative Impact of Radiation Therapy with and without Chemotherapy

Investigator	No. Patients	Radiation Therapy Dose	Chemotherapy Agents	Palliation of Dysphagia (%)
Albertsson[357]	67	<45 Gy	None	55
	43	>45 Gy	None	65
Wara[354]	169	50 Gy-60 Gy	None	67
Petrovich[236]	133	55 Gy	None	52
Whittington[358]	165	50 Gy-60 Gy	5-FU, mitomycin C	87
Kavanagh[269]	143	44 Gy-60 Gy	Cisplatin, carboplatin, etoposide, 5-FU	71
RANDOMIZED TRIALS				
Herskovic[230]	121	64 Gy	None	66
		50 Gy	5-FU, cisplatin	58
Roussel[277]	170	56.2 Gy	None	78
		56.2 Gy	Methotrexate	71

5-FU, *5-fluorouracil;* Gy, *Gray.*

effective method of palliation resulting in local control rates of 25% to 35%. Harvey et al reviewed 22 patients treated with either 20 Gy in three fractions of low-dose-rate brachytherapy versus 12.5 Gy in one fraction of high-dose-rate brachytherapy and found that both modalities resulted in equally effective palliation of dysphagia.[359] Accelerated treatments are especially suitable for patients in poor physical condition or with a short life expectancy; however, the incidence of stricture and fistula formation increased with the brachytherapy fraction size (9.5% for fractions <500 cGy, 20% for fractions between 500 cGy and 800 cGy, and 38% for fractions >800 cGy). In a randomized trial by Sur et al, there was no reported difference in local control or survival between palliative external beam radiotherapy or high-dose rate brachytherapy.[360] Brachytherapy as an intraluminal boost has also been evaluated in RTOG 85-01 in which patients with unresectable esophageal cancer received 50 Gy with concurrent cisplatin and 5-fluorouracil followed by a brachytherapy intraluminal boost. Although the local failure rate was 27%, there were a significant number of grade-3 to grade-5 toxicities, and the cumulative incidence of fistulas was 18% per year.[361] The benefit of brachytherapy added to chemoradiation or external beam radiation alone remains unclear.

TOXICITY FROM IRRADIATION

Benign Strictures Resulting from Irradiation

Unfortunately, benign strictures can result from irradiation of esophageal cancers, causing a worsening of symptoms. The incidence of benign stricture is estimated at 12% to 30% in patients treated with irradiation alone. Strictures usually develop 4 to 6 weeks after therapy.[290,362,363] In 25 patients treated with concurrent irradiation and chemotherapy, Coia et al observed a 12% incidence of benign strictures that responded to one or two dilations.[290]

Tracheoesophageal Fistula

The development of a malignant fistulous tract between the esophagus and airway (trachea or bronchus) is not uncommon in midesophageal lesions because of the anatomic location of the two structures. Most fistulae involve the trachea, but they can also involve either a main stem, lobar, or segmental bronchus. Involvement of the trachea with tumor can lead to fistula formation during irradiation because of necrosis of the tumor or the natural progression of the disease. It is estimated that the incidence of this complication is 5% to 10% of patients with esophageal cancer. In general, excision, bypass, or intubation has been recommended in an attempt to prevent further contamination of the airway. The median survival time following these limited measures can be as brief as 6 to 10 weeks, with the procedures themselves resulting in a mortality rate of 10% to 32%.[364]

Many oncologists accept the fact that irradiation of a fistula worsens the condition because healing may be compromised by irradiation. However, Burt et al found that the survival rate for patients with an untreated fistulous tract was 4% at 6 months and 1% at 1 year compared to 15% and 5% in patients treated with irradiation, respectively.[365] Treatment of radiation-induced fistulae can be challenging. Yamado et al reported on 14 patients with fistulae secondary to esophageal cancer who were treated with primary irradiation. Closure of the fistula occurred in 5 of 8 patients whose fistulae developed before or during irradiation. In two of these cases, the closure lasted over the long term, but for patients who developed fistulae during irradiation, resolution was less likely.[366] Gschossmann reported on a 10-patient series from the Mayo Clinic with fistulae developing during treatment and observed that the severity of the fistulae did not increase with therapy and the median survival time was 4.8 months.[367]

Although it has been speculated that development of radiation-induced fistulae may impact patient outcome, there is also a growing body of evidence supporting the safe use of chemotherapy with or without irradiation in managing patients with a tracheoesophageal fistula. Malik et al observed an objective response and closure of the fistulae in two patients treated with chemoradiation and concluded that the presence of a fistula should not exclude a patient from receiving combined-modality therapy.[368] At present, it is difficult to determine whether aggressive combined-modality therapy will increase treatment-related morbidity in patients who present with airway or esophageal fistulae or develop them shortly after starting therapy. Once the diagnosis of a fistulous tract into the airway is documented and the process is stabilized, planned curative therapy for selected patients with localized disease is recommended, especially if the fistula is relatively small.

IRRADIATION TECHNIQUES

The recommended dose for preoperative therapy is 41.4 Gy to 50.4 Gy delivered over 4 to 5 weeks, using 1.8-Gy to 2-Gy daily fractions. The recommended dose for postoperative radiation 45 Gy to 50.4 Gy is recommended. When definitive irradiation is used concurrently with sensitizing chemotherapy without surgery, a total dose of approximately 50 Gy to 54 Gy is recommended as lower doses may not be adequate. For inoperable tumors of the cervical esophagus, 60 Gy to 66 Gy may be appropriate.

The irradiation of esophageal cancer presents a challenge to radiation oncologists because these tumors are situated deeply in the mediastinum and are surrounded by several vital structures. The mucosa of the esophagus is mostly squamous epithelium, and the acute mucosal reaction can be substantial. Acute odynophagia and dysphagia are common, usually developing 10 to 14 days after the initiation of therapy. The esophagitis is self-limiting, but without nutritional support, the acute mucosal reaction may force a delay in completing treatment. Patients should be closely monitored and aggressive supportive care should be provided for the management of radiation-induced acute toxicities to avoid unnecessary treatment interruptions. Consideration of feeding jejunostomy, nasogastric feeding tube, or intravenous hydration should occur in case of inadequate caloric intake or dehydration.

Portions of the upper airway, trachea, bronchi, lung parenchyma, and pleura are unavoidably irradiated during therapy. The pulmonary parenchyma is highly susceptible to radiation injury, with clinical lung damage reported at total fractionated doses in the range of 20 Gy. However, the likelihood of clinical injury relates strongly to the baseline pulmonary status of the patient, as well as the amount of lung in the irradiation field. It is not uncommon for patients with esophageal cancer to have chronic obstructive lung disease, which affects the amount of normal lung that can be safely irradiated. The risks of permanent lung injury and late pneumonitis are also volume-related.

If the heart is irradiated, complications involving the pericardium and myocardium can result. Irradiation of the pericardium can result in both acute and chronic pericarditis. The former is an uncommon complication of thoracic irradiation that usually develops within the first posttreatment year. It is often associated with viral infections, which makes diagnosis difficult. Although it has been reported at doses in the range of 20 Gy to 40 Gy, acute pericarditis generally occurs with

substantially higher doses. Chronic pericarditis typically develops more than 1 year after treatment and is related to volume treated.

Irradiation of the myocardium can result in an interstitial fibrosis that decreases cardiac function. This phenomenon is also related to the volume of irradiated heart and a total dose that exceeds 40 Gy. Data have associated irradiation of the myocardium with an acceleration of coronary arteriosclerosis and sudden cardiac death in young persons. Because the vast majority of patients with esophageal cancer are older and have a limited prognosis, myocardial injury is not a significant clinical problem at present time.

Other rare complications of esophageal irradiation include the risk of rib fractures, damage to the brachial plexus, and spinal cord injury, which is potentially the most devastating side effect. In general, it is safe to treat the spinal cord with irradiation alone to a cumulative dose of 45 Gy to 50 Gy delivered in standard single daily fractions of 180 cGy to 200 cGy.

The difficulty in controlling esophageal tumors with irradiation relates to the frequent extension of tumor through the thin esophageal wall, the involvement of vital mediastinal structures, including large vessels and the trachea, and the threat of perforation; the frequent spread of tumor through submucosal lymphatics, ultimately involving long segments of the esophagus; the spread of tumor to regional lymph nodes; the presence of metastatic disease in a high percentage of patients (either occult or clinically apparent disease); and the generally poor nutritional status of patients at presentation. Esophageal tumors can extend submucosally in the cephalo-caudad direction for a significant distance from the primary tumor. In 1962, Miller[369] reported a 15% incidence of longitudinal microscopic tumor spread at greater than 6 cm from the primary lesion and an incidence of regional nodal involvement of 40% to 70%.

For lesions of the cervical esophagus, irradiation fields must take into account tumor spread into mediastinal, supraclavicular, and low anterior cervical lymph nodes. The supraclavicular nodes are generally electively treated in patients with high thoracic tumors but not in those with middle or distal thoracic tumors. Although there is a significant incidence of involvement of the celiac axis lymph nodes, little information supports routine treatment of this nodal group for patients without evidence of tumor involvement, especially if this necessitates a substantial extension of the irradiation field.

The typical irradiation field extends approximately 4 cm to 5 cm above and below gross tumor, with a field width of approximately 8 cm. The size of the tumor dictates the exact field width needed to obtain adequate mediastinal nodal coverage and to adequately cover the primary tumor mass. CT simulation and three-dimensional treatment planning techniques are recommended. When four-dimensional CT planning or other motion management is available, margins may be reduced to account for motion control. Intravenous or oral contrast should be used to facilitate target and normal tissue localization. The gross tumor volume (GTV) includes the primary tumor and the involved regional nodes as identified by CT, PET/CT, barium swallow, or EUS. The clinical tumor volume (CTV) includes areas at risk for microscopic spread and elective node regions depending on the location of the primary tumor. The planning target volume (PTV) includes the tumor plus a cephalo-caudad margin of 4 cm to 5 cm and a radial margin of 2 cm. Efforts to reduce radiation dose to surrounding normal tissue should be made.

If conventional two-dimensional radiation planning is used, patients are initially treated with anterior-posterior treatment fields to 36 Gy to 40 Gy in 1.8 Gy to 2 Gy daily fractions to limit the dose to the heart and spinal cord. The treatments then continue, avoiding the spinal cord, with either oblique or lateral fields, to a total dose of 45 Gy to 50 Gy. An alternative approach is to treat through the entire course with multiple fields that limit the dose to the spinal cord to a total dose of 45 Gy to 50 Gy.

The use of three-dimensional conformal radiation is recommended and dose volume histograms (DVH) should be generated and used as predictors of normal tissue complications. Custom blocking may be used to limit the volume of normal tissue receiving radiation. Recommended normal tissue constraints for treatment planning purposes included liver (no greater than 60% volume should receive more than 30 Gy), kidneys (no greater than 60% of one kidney should receive more than 20 Gy), spinal cord (maximum dose 45 Gy), heart (efforts to keep minimal dose to the left ventricle), and lungs (no greater than 20% volume should receive more than 20 Gy and 40% volume greater than 10 Gy). Figure 45-1 represents a three-dimensional CT-based plan demonstrating radiation treatment for a distal esophageal tumor.

Intensity-modulated radiation therapy (IMRT) may be appropriate in selected cases and has the potential of reducing the amount of radiation delivered to surrounding normal tissues. Wu et al[370] compared IMRT plans with forward and inverse three-dimensional conformal irradiation plans for 15 patients with midesophageal cancers and demonstrated that the IMRT plans generated the most conformal high-dose distribution around the planning target volume while delivering a lower mean lung dose and mean heart dose. Others have demonstrated similar findings comparing the ability of three-dimensional therapy and IMRT to deliver simultaneous integrated boost, dose-escalation in upper esophageal locations. Lower V20 and V30 volumes in the lung were consistently demonstrated in the IMRT plans.[371] An additional study explored the potential advantage of IMRT in distal esophageal cancers, resulting in a significant reduction in the mean lung dose, V10, and V20, without a significant reduction in the cardiac dose from the three-dimensional conformal plans.[372] Because the actual use of IMRT plans has not been well studied, care needs to be taken to avoid the risk of unexpected normal tissue toxicities resulting from the low-dose regions, especially in the lungs, being widely spread into normal tissue. Figure 45-2 represents an IMRT CT-based plan demonstrating radiation treatment for a distal esophageal tumor. Figure 45-3 is a dose-volume histogram showing the dose distribution differences for surrounding normal structures between a three-dimensional treatment plan and an IMRT treatment plan for the same patient. Considerations of tumor/target motion are of particular importance when IMRT is used. A full discussion of motion management considerations is found in the chapter on non–small cell lung cancer.

Proton beam therapy (PBT) is a promising modality for the management of thoracic malignancies, including esophageal cancer. A series of 62 patients treated with PBT and concurrent chemotherapy either definitively or preoperatively at M. D. Anderson Cancer Center from 2006 to 2010 evaluated toxicity associated with this treatment approach. With a median radiation dose of 50.4 Gy (range 36 Gy to 57.6 Gy), few toxicities were observed. The most common acute toxicities encountered were grade-2 to grade-3 esophagitis (46.8%), fatigue (43.6%), nausea (33.9%), anorexia (30.1%), and radiation dermatitis (16.1%). Two cases of grade-2 and grade-3 radiation pneumonitis occurred. There was no apparent impact on subsequent surgery in the preoperative cohort. There were significantly fewer local regional recurrences in the preoperative group (3 of 29) than in the definitive group but there were no differences in distant metastases or OS between the two groups.[373] Although the clinical outcomes are encouraging, a prospective comparison with traditional radiation techniques is warranted.

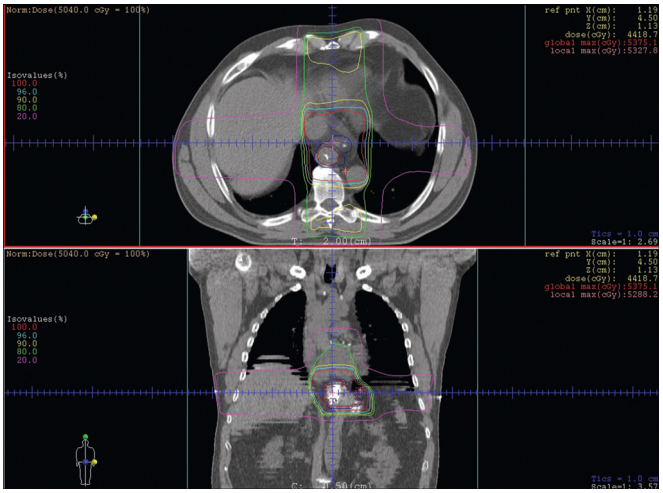


Figure 45-1 Three-dimensional treatment planning for a patient with distal gastroesophageal junction cancer. Axial and sagittal representations illustrate the dose distribution when the initial clinical target volume encompassing 5 cm of esophagus proximal to the tumor and 2 cm distal into the stomach is treated to 45 Gy using an AP/PA technique. An opposed lateral technique is used to boost the tumor and 2-cm margins to 50.4 Gy.

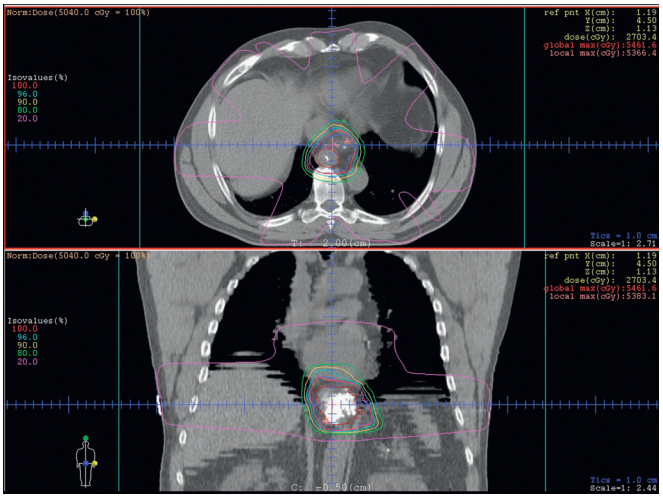


Figure 45-2 Intensity-modulated radiation treatment planning for a patient with distal gastroesophageal junction cancer. Axial and sagittal representations illustrate the dose distribution when the initial clinical target volume encompassing 5 cm of esophagus proximal to the tumor and 2 cm distal into the stomach is treated to 45 Gy to initial clinical target volume, followed by a boost to the tumor plus 2 cm to 50.4 Gy.

Other changes in treatment planning are being pursued with improved tumor localization. One study compared CT-based tumor volumes to PET/CT-based tumor volumes and demonstrated a change in target volumes for 84% of patients, with 48% with minor differences and 36% with major differences. These discrepancies were mostly in celiac or distant mediastinal lymph node involvement, resulting in a change in length of the tumor volume in 56% percent of patients.[374] It should be recognized that significant changes in treatment volumes may also increase treatment-related toxicity. Caution should be exercised in determining the exact size of a tumor from a PET/CT scan because the apparent size is determined heavily by the settings on the computer. FDG-PET

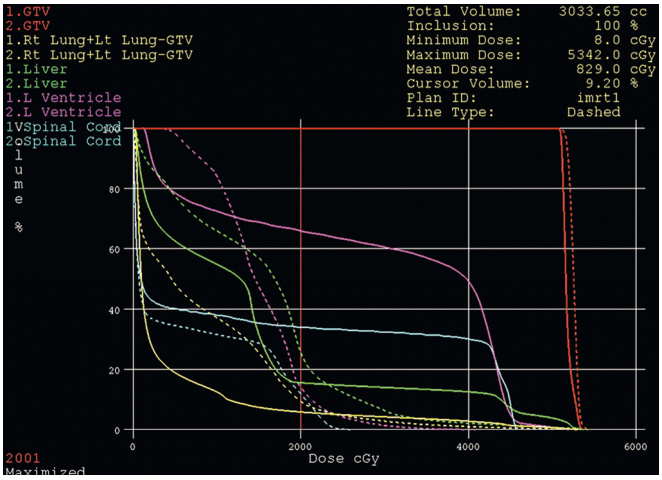


Figure 45-3 Dose-volume histograms compare dose delivered to surrounding normal tissues resulting from the three-dimensional treatment plan illustrated in Figure 45-1 *(solid lines)* and a seven-field intensity-modulated radiation therapy (IMRT) treatment plan *(dashed lines)* designed to treat the same volumes to the same dose (45 Gy to the initial clinical target volume, followed by a boost to the tumor plus 2 cm to 50.4 Gy). Note that mean doses of normal tissue are reduced, whereas the volumes of normal tissue receiving lower radiation doses (V10) increase for the IMRT plan compared with the three-dimensional conformal plan for all structures.

is perhaps most useful in finding areas of unexpected disease and determining the precise location of known lesions.

TREATMENT ALGORITHM, CONTROVERSIES, AND FUTURE POSSIBILITIES

Although surgery alone remains the standard of care in the management of early-stage localized esophageal cancer, combined-modality approaches have an important role for the typical patient with a locally advanced tumor. Figure 45-4 describes an algorithm for the treatment of esophageal cancer.

Today, the treatment of this disease requires a multimodality approach by the surgeon, radiation oncologist, and medical oncologist and a clear understanding of the interactions and toxicities associated with these modalities. Combined chemoradiation either as definitive therapy or in the preoperative setting is considered standard of care. The complications associated with multimodality therapy are significant and must be considered. Data supporting alternative treatment strategies including perioperative chemotherapy and preoperative chemotherapy followed by selective use of chemoradiation are emerging. Minimally invasive surgical techniques are promising options in selected patients. IMRT and improved tumor targeting may assist in reducing treatment-related morbidity. The use of FDG-PET response to direct therapy may be further explored depending on the results of the ongoing CALGB 80803 trial (NCT01333033) evaluating a response-adapted strategy using early FDG-PET imaging for treatment selection. We continue to evaluate novel treatment strategies using new systemic therapies, targeted agents, and radiation techniques to improve patient outcomes. We await the results of RTOG 1010 evaluating the addition of trastuzumab to chemoradiation in patients with operable, locally advanced adenocarcinoma of the esophagus and esophagogastric junction with HER2 positivity (NCT01196390).

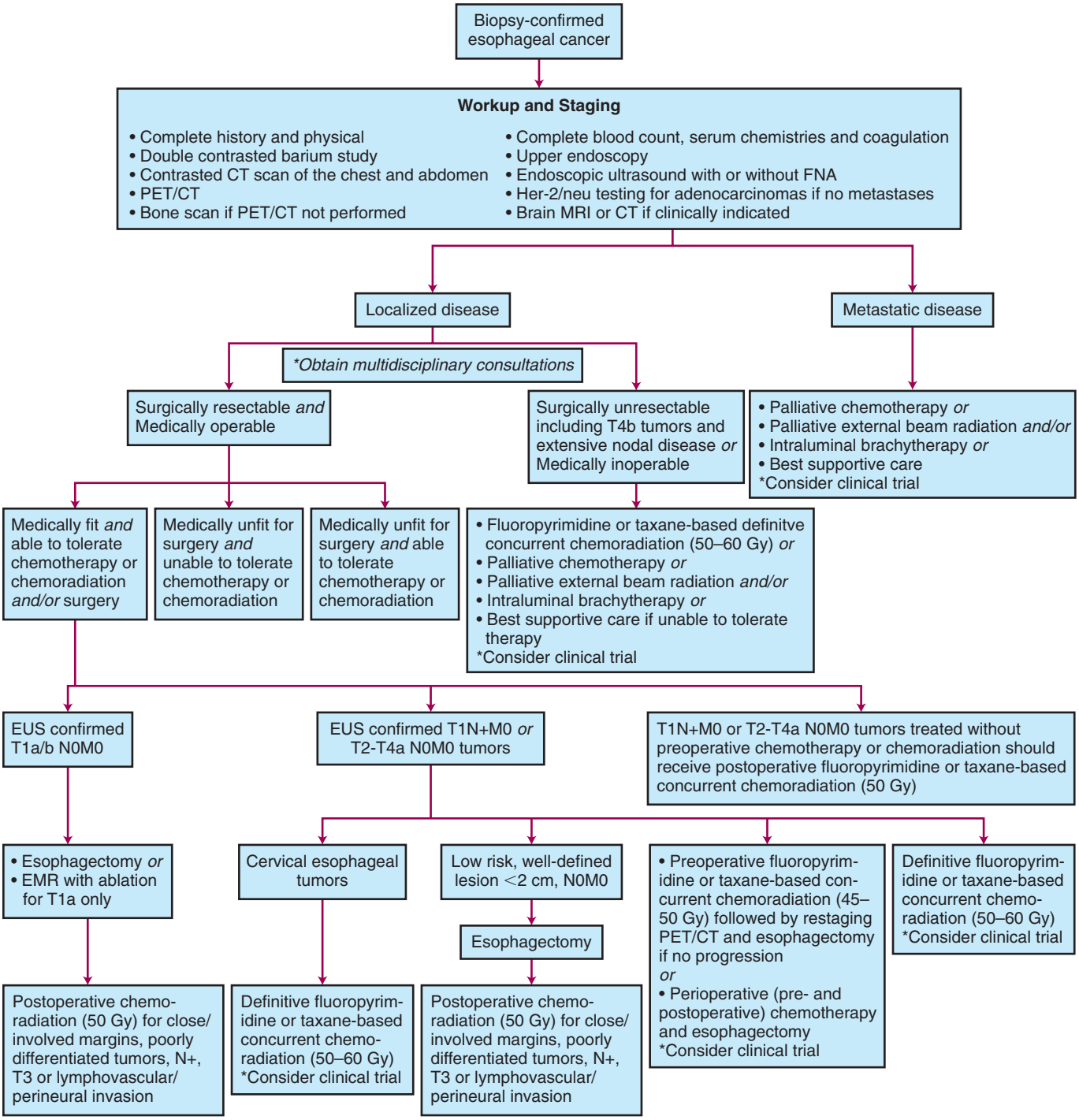


Figure 45-4 Treatment algorithm for newly diagnosed esophageal cancer. Treatment options for esophageal cancer are based in location and stage of the tumor, as well as surgical resectability and medical fitness of the patient. A multidisciplinary approach to the treatment of cancer usually includes combination therapy consisting of surgery and perioperative chemotherapy or chemoradiation, except in early stage, node-negative disease. Standard of care chemotherapy consists of fluoropyrimidine-or taxane- based regimens. Other chemotherapeutic regimens and/or targeted therapies should be considered on clinical trial. *CT,* Computed tomography; *EMR,* endomucosal resection; *EUS,* endoscopic ultrasound; *FNA,* fine-needle aspiration; *MRI,* magnetic resonance imaging; *PET,* positron emission tomography.

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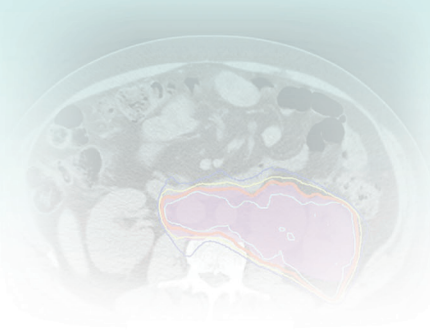
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CHAPTER

46 Uncommon Thoracic Tumors



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INCIDENCE

The overall incidence of thymoma in the Unites States is 0.15 cases per 100,000 persons.[1] Thymoma is the most common tumor of the anterior mediastinum, accounting for 30% of anterior mediastinal lesions and 20% of all mediastinal tumors in adults.

Between one and two cases of carcinoid tumor of any site occur per 100,000 people in the United States. The rate for bronchopulmonary carcinoids is 0.6 per 100,000 persons.[2] Pulmonary carcinoids make up almost 30% of all neuroendocrine tumors.[3]

The incidence of malignant pleural mesothelioma (MPM) is 10 cases per million people. The incidence is increasing, and the disease is classically seen in patients exposed to asbestos.[4] Based on the predicted 30-year to 40-year lag in presentation from the time of exposure to asbestos, it is expected that mesothelioma rates will continue to rise in the United States until approximately 2020.

BIOLOGIC CHARACTERISTICS

Thymomas tend to be slow-growing tumors with an indolent natural history. Histologically benign, they are capable of local and regional invasion and have a marked tendency for local recurrence. The two most important prognostic factors are invasiveness and completeness of surgical resection.

Pulmonary carcinoids generally are nonfunctional, but they can secrete physiologically active substances, leading to paraneoplastic syndromes. Biologic behavior ranges from indolent to aggressive. Prognostic factors are atypical histologic findings, nodal involvement, and the presence of symptoms at presentation.

MPM is aggressive, and local disease progression is the main cause of symptoms and death. It spreads by direct extension and seeding in the pleural space. Local recurrence is the predominant pattern of failure.

STAGING EVALUATION

Patients with suspected thymoma require routine screening blood work and chemistry testing, but diagnosis is usually based on clinical radiographic findings. Historically, biopsy confirmation of an anterior mediastinal mass was avoided because of concerns about needle tract seeding.[5,6] Treatment without biopsy confirmation remains controversial. The value of neoadjuvant therapy cannot be properly assessed without a pretreatment biopsy.[7] Image guided fine-needle aspiration biopsy is useful, though a core biopsy increases accuracy.[8] Bronchoscopy, video-assisted thoracoscopic surgery, mediastinoscopy, or anterior thoracoscopy also may help to yield a diagnosis before resection.

Pulmonary carcinoid requires a similar workup. Transbronchial biopsy or computed tomography (CT)- or ultrasound-guided fine-needle aspiration biopsy may establish the diagnosis preoperatively. The role of positron emission tomography (PET) scans remains controversial because of the relatively low glucose uptake of carcinoid tumors.[9,10]

Patients with suspected mesothelioma should be asked about a history of asbestos exposure. CT of the chest is needed. Although thoracentesis, percutaneous fine-needle aspiration, or ultrasound-guided core biopsy may yield the diagnosis, the most accurate method is video-assisted thoracoscopic biopsy.

PRIMARY THERAPY

Complete en bloc surgical resection is the treatment of choice for all thymomas, except in rare advanced cases with extensive intrathoracic or extrathoracic metastasis.

Curative resection of localized primary lung carcinoids is the treatment of choice. Endoscopic laser ablation may be used to palliate tumor obstruction, improve atelectasis, and reduce inflammation before resection.

Pleurectomy and extrapleural pneumonectomy (EPP) are extensive surgical procedures for mesothelioma. Patients require careful assessment to ensure that the operation will be tolerated physiologically. More recently, the role of EPP in mesothelioma has been called into question, and some advocate for pleurectomy as the primary surgical treatment.[11]

ADJUVANT THERAPY

Encapsulated, noninvasive, stage I thymomas do not require adjuvant postoperative radiation therapy. Radiation therapy can be an effective adjuvant therapy for invasive thymomas. It is unclear whether all stage II thymomas benefit from adjuvant radiotherapy (RT).[12-14]

Typical carcinoids usually do not require adjuvant therapy after resection. Certain symptoms, including flushing, can be relieved by pharmacologic agents such as octreotide.[15] Adjuvant RT has been used in patients with large tumors (>3 cm), positive nodes, positive margins, atypical histologic findings, residual disease, and inoperable disease.

For mesothelioma, high-dose postoperative RT can dramatically reduce ipsilateral thoracic failures. Postoperative irradiation should include the entire volume immediately adjacent to the pleural space, but it is technically difficult to deliver.

LOCALLY ADVANCED DISEASE

Preoperative RT and primary RT alone have each been advocated in patients with thymoma with unresectable advanced disease. Chemotherapy may produce an improvement in overall survival (OS) rates. Chemoradiation may be appropriate for some patients with locally advanced unresectable malignant thymoma.

RT has been used adjuvantly or to palliate symptoms from locally advanced or metastatic carcinoids.

EPP followed by irradiation or systemic chemotherapy may reduce the risk of relapse and provide better local control of mesothelioma than surgery alone.

PALLIATION

RT can provide effective palliation in patients with symptomatic metastatic or unresectable disease.

THYMIC TUMORS

The thymus gland is a bilobed lymphoepithelial organ located in the anterior mediastinum, behind the sternum and in front of the great vessels. In early life, the thymus functions in T-lymphocyte differentiation and maturation and releases T lymphocytes into the circulation. It weighs 12 g to 15 g at birth and 40 g at puberty, and during adulthood, it slowly involutes and is largely replaced by adipose tissue. The thymus is composed of an outer cortex consisting primarily of epithelial cells, degenerated keratinized epithelial cells (Hassall's corpuscles), myoid cells, thymic lymphocytes ("thymocytes"), and B lymphocytes, which form rare germinal centers.[16]

Although various tumors and cysts can arise in the thymus, tumors of the thymus are uncommon. Most thymic tumors arise in the epithelial cells of the thymus. They account for approximately 50% of anterior mediastinal masses.[17,18] The most common thymic tumors are thymoma, thymic carcinoma, and thymic carcinoids. Thymomas, 90% of which are found in the anterosuperior mediastinum, are commonly associated with myriad paraneoplastic syndromes. They are the most common tumor found in the anterior mediastinum.[18,19] Thymomas are associated with an exuberant lymphoid component composed of immature cortical thymocytes. Although they appear benign histologically, they may exhibit invasive behavior clinically.

Thymic carcinomas (i.e., type C thymomas) also arise in the thymic epithelium, but they have a higher propensity for capsular invasion and widespread metastases, especially those with features of high-grade malignancy. The histologic subtypes include clear cell, sarcomatoid, and anaplastic carcinoma. Low-grade thymic carcinomas (well-differentiated squamous cell carcinomas, basaloid carcinomas, and mucoepidermoid carcinomas) are characterized by a relatively more favorable clinical course, with a lower incidence of local recurrence and metastasis.[20,21]

Neuroendocrine tumors of the thymus are rare, accounting for less than 5% of all neoplasms of the anterior mediastinum. Like carcinoids at other sites, they are thought to originate from endodermal cell (or foregut cellular) precursors. Unlike carcinoids in other locations, most thymic carcinoids behave aggressively, often invade locally and commonly metastasize to regional lymph nodes.[22] Approximately 50% of patients may develop endocrine abnormalities.[23]

Etiology and Epidemiology

The etiology of thymic tumors is largely unknown. There is a reported association between Epstein-Barr virus (EBV) infection and tumors of the thymus. For instance, thymic diseases are more common in far Eastern countries, where the incidence of EBV infection is high.[24,25] Defective viral genomes have been isolated in patients with lymphoepithelioma-like thymic carcinoma.[24,26-28] Childhood thymus irradiation has been linked to the development of thymic tumors,[29] and familial cases have been reported, suggesting a possible relationship with cytogenetic abnormalities.[30,31] In an analysis of secondary or concomitant neoplasms in 1495 patients with acute lymphoblastic leukemia enrolled in two consecutive multicenter protocols, an increased risk of solid tumors was identified.[32] Although the histologic characteristics of these second malignant tumors varied, thymoma was among the solid tumors identified in adult survivors of acute lymphoblastic leukemia. Among patients with primary thymic carcinoid tumors, up to 30% had multiple endocrine neoplasia type 1 or 2.[33,34] Other studies have reported a distinctive chromosome abnormality involving translocation of fragments of chromosomes 15 and 19 [t(15:19)(q15:p13)] in thymic carcinoma, particularly in young adults and pediatric patients with high-grade thymic carcinoma.[35-37] Deletion of the short arm of chromosome 6 is associated with benign thymomas.[38] Aberrations involving chromosome 6 suggest that several putative tumor suppressor genes may contribute to the pathogenesis of thymoma.[39]

TABLE 46-1 World Health Organization Classification of Thymic Epithelial Tumors

Type	Pathologic Classification	Prognosis
A	Medullary thymoma Spindle cell thymoma	Benign clinical course
AB	Mixed thymoma	
B1	Lymphocyte-rich thymoma Lymphocytic thymoma Predominately cortical thymoma Organoid thymoma	Moderately malignant clinical course
B2	Cortical thymoma	
B3	Epithelial thymoma Atypical thymoma Squamoid thymoma Well-differentiated thymic carcinoma	
C	Thymic carcinoma	Highly malignant clinical course

In a small study of 37 cases, most World Health Organization (WHO) type A thymomas (Table 46-1) did not show any chromosomal aberration, whereas type B3 thymomas and thymic carcinoma (i.e., type C thymoma) shared some genetic aberrations, including the loss of chromosome 6 and the gain of chromosome 1q.[40] The loss of chromosome 6, on which the human leukocyte antigen locus and some of the tumor suppressor genes have been identified, and the gain of chromosome 1q, to which growth promoter genes have been mapped,[40-42] may play a role in tumorigenesis and pathogenesis of the paraneoplastic autoimmunity characteristics of thymoma. Such chromosomal aberrations have been implicated in a variety of human neoplasms.[43,44]

The true incidence of thymoma is unknown, and the annual incidence in the United States has not been well defined. The SEER program reported a thymoma incidence of 0.13 to 0.15 per 100,000 people.[1] Although thymomas are uncommon, they are the most frequently diagnosed mediastinal masses, representing approximately 30% of anterior mediastinal lesions and 20% of all mediastinal tumors in adults.[17-19,45-47] Most patients with thymoma are between the ages of 40 and 60 years, with a median age of 52 years and an equal overall gender ratio.[48-51] Thymomas are less common in children, accounting for approximately 15% of anterior mediastinal masses.[19,48-51]

Thymic carcinomas are distinct from invasive thymomas both pathologically and clinically.[52] They account for 5% to 36% of all thymic neoplasms.[53-56] The wide range in incidences reflects differences and changes in the pathologic classification of this rare tumor. Patients with thymic carcinoma are typically middle-aged or elderly, and there is a slight male predominance. Thymic carcinoids represent less than 5% of anterior mediastinum lesions[57,58] and typically affect middle-aged men.[21]

Prevention and Early Detection

A small subgroup of cases are associated with thymic irradiation during childhood, EBV infection (associated with

lymphoepithelioid thymic carcinoma), or familial cytogenetic abnormalities; the etiologic factors for most thymic tumors are unknown, however, and there is no known mechanism for prevention. Thymomas are characterized by an indolent growth pattern with a tendency toward local invasion. Thymomas are associated with autoimmune disorders, particularly myasthenia gravis, in 30% to 45% of cases.[59,60] Most thymic tumors are discovered incidentally because of abnormalities observed on routine radiographs or during evaluation for myasthenia gravis. Approximately 10% to 15% of patients with myasthenia gravis have benign or malignant thymomas.[61-65] Thymic carcinomas and carcinoids are commonly detected incidentally. They are locally invasive and are found to have metastasized to regional lymph nodes and distant sites in up to 30% of patients at diagnosis.[22,54,66]

Biologic Characteristics and Molecular Biology

Patients with thymoma may have dysregulation of the lymphocyte selection process associated with abnormal proliferation, autoimmunity, and immunodeficiency. Thymoma-associated autoimmune disease involves an alteration in circulating T-cell subsets.[67-69] Up to 70% of thymomas may be associated with paraneoplastic syndromes.[55] Various autoantibodies have been described.[70,71] In addition to T-cell defects, B-cell lymphopenia has been observed in thymoma-related immunodeficiency along with hypogammaglobulinemia (i.e., Good's syndrome).[72,73]

Factors influencing the different biologic behaviors of thymoma subtypes are poorly understood. Some pathologic features, such as altered expression of TP53 and BCL2,[74,75] counts of argyrophilic nucleolar organizer regions,[76,77] proliferating cell nuclear antigen, matrix metalloproteinases, and Ki-67 index,[77,78] are associated with biologic behavior, clinical stage, and prognosis.[79] There is a tendency for up-regulation of adhesion and costimulatory molecules.[80-83] Altered TP53 expression may be implicated in the initial stages of tumorigenesis, and increased expression of epidermal growth factor (EGF) and epidermal growth factor receptor (EGFR) may play a role in thymoma genesis.[84] A decreased OS time is predicted by Src kinase and TP53 co-expression.[85] It has been proposed that a deficiency in the autoimmune regulator *(AIRE)* gene has an oncogenic effect on thymomas. AIRE expression is lacking in approximately 95% of thymomas; therefore loss of AIRE expression may provide a potential mechanistic link for the well-recognized association of autoimmunity with thymoma.[86,87]

Thymic carcinomas possess overt features of malignancy similar to those of carcinoma arising in any other organ, with a higher propensity for capsular invasion and metastases than invasive thymomas. Paraneoplastic syndromes occasionally exist with well-differentiated lesions.[88,89] Most variants of thymic carcinoma are highly lethal, producing frequent metastases to regional lymph nodes, bone, liver, and lung.[90-92] Thymic carcinomas may express high levels of EGFR,[84,93,94] but *EGFR* gene mutations are rare.[95] Tumor and serum levels of vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF) can be elevated,[96,97] and correlations among such growth factors, angiogenesis, and invasiveness have been observed.[97-99] Thymic carcinoma has been associated with increased expression of epithelial membrane antigen, cytokeratin subtypes, and TP53 protein.[75,100-104] Somatic *KIT* gene mutations are present in some thymic carcinomas but not in thymomas.[105,106] Increased expression of CD70 may serve as a marker for thymic carcinoma.[107] Other surface antigenic molecules, such as CD5 and CD99, have aberrant expression in thymic carcinoma.[108-110] Cytoplasmic phosphorylated AKT serine 473 and insulin-like growth factor-1 receptor (IGF-1R) are expressed in a higher proportion of recurrent tumors and more aggressive subtypes according to the WHO staging system. IGF-1R was associated with a worse progression-free survival time.[111,112] Thymic carcinomas can be distinguished from lung carcinomas by negative expression of thyroid transcription factor-1[100] and a distinctly different cytokeratin profile.[113] Additionally, although mutations in the *TP53* gene are common in lung carcinoma, *TP53* gene mutation was not found in any of seven examined thymic carcinomas.[105] The combination of c-KIT, CD5, and cells such as β5t thymic cortical environmental marker cells, cortical thymocytes, and thymic cortical dendritic macrophages can be used to distinguish thymic carcinoma from Type B3 thymoma or lung squamous cell cancers.[114]

Thymic carcinoids have a malignant clinical course with a poor prognosis, frequently worse than carcinoids of the gastrointestinal tract. They may secrete peptides, amines, kinins, prostaglandins, or other substances. In a study of 80 patients with thymic carcinoids, 74% were male, 72% had related symptoms, 6% had Cushing's syndrome, and 16% had other endocrine abnormalities.[115] Even after complete resection, recurrence is common (36% to 87%).[22,115,116] OS rates were only 28% and 10% at 5 and 10 years, respectively.

Pathology and Pathways of Spread

There is no direct correlation between the histopathology of thymomas and their malignant potential.[48,117,118] However, an accurate histologic diagnosis is still crucial in patient management.

The histologic diagnosis of thymoma can be difficult, and a variety of systems have been proposed. The WHO classification, developed in 1999 and revised in 2004, is the most widely accepted. Tumors with true malignant cytologic characteristics are considered to be thymic carcinomas rather than thymomas. Invasive thymomas invade the capsule macroscopically or microscopically, with typically "bland" cytologic characteristics of thymic epithelial cells admixed with mature lymphocytes. The term *invasive thymoma* should be used instead of malignant thymoma to denote the tumor's predilection for capsular invasion.

Grossly, thymomas are nodular, multilobulated, and firm. They may contain cystic spaces, calcification, or hemorrhage and may be neatly encapsulated, adherent to surrounding structures, or invasive. Thymomas generally have epithelial and lymphatic cells. They are classified as predominantly epithelial, predominantly lymphocytic, mixed lymphoepithelial, or spindle cell type. Morphologically, thymoma cells are rather large and may be round, oval, or spindle shaped with vesicular nuclei and small nucleoli. The cytoplasm is often eosinophilic or amphophilic. Thymic neoplasms arise from epithelial cells (Figure 46-1). The lymphocytic component is mostly normal-appearing mature lymphocytes. Some of the other microscopic features that may be seen in thymomas include Hassall's corpuscles, keratinizing squamous epithelium, rosettes, glands, cysts, papillary structures, and germinal centers. Immunohistochemistry is often helpful in making the diagnosis. Thymomas typically stain positive for thymic epithelial markers, including cytokeratin, thymosin β3 and α1, and epithelial membrane antigen.

Thymic carcinoma histologic characteristics are more diverse. The tumor is cytologically malignant, and most commonly have squamous cell histologic findings. Other subtypes include lymphoepithelioma-like carcinomas, clear cell carcinomas, sarcomatoid carcinomas, adenosquamous carcinomas, mucoepidermoid carcinomas, adenocarcinomas, and basaloid squamous cell carcinomas.[21] Their histologic appearances are not different from carcinomas in other sites.[119]

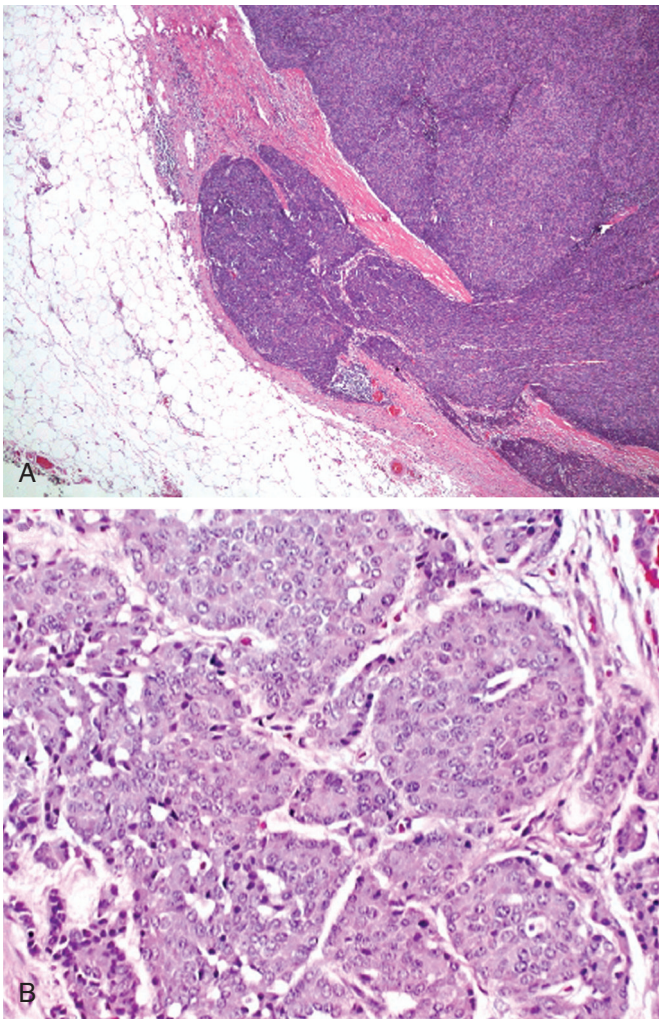


Figure 46-1 Lymphocyte-rich thymoma with dense lymphocytic cell population containing scattered larger epithelial cells with pale cytoplasm surrounding perivascular spaces. **A,** Low power (×100). **B,** High power (×400).

BOX 46-1 Paraneoplastic Diseases Associated with Thymoma

- Addison's disease
- Carcinoid syndrome
- Chronic mucocutaneous candidiasis
- Cushing's syndrome
- DiGeorge syndrome
- Erythroid and neutrophil hypoplasia
- Hashimoto's thyroiditis
- Hyperparathyroidism
- Hyperthyroidism
- Hypertrophic osteoarthropathy
- Hypogammaglobulinemia
- Lambert-Eaton syndrome
- Lupus erythematosus
- Myasthenia gravis
- Myocarditis polyarthropathy
- Myotonic dystrophy
- Myotonic dystrophy scleroderma
- Nephrotic syndrome
- Pancytopenia
- Panhypopituitarism
- Pemphigus
- Pernicious anemia
- Polymyositis
- Polyneuritis
- Red cell aplasia
- Rheumatoid arthritis
- Sarcoidosis
- Sjögren's syndrome
- Syndrome of inappropriate secretion of antidiuretic hormone (SIADH)
- Ulcerative colitis
- Whipple's disease

The histologic features of thymic carcinoids are identical to carcinoid tumors in other organs. Unlike thymomas, they are rarely encapsulated. Immunohistochemically, they may stain positively with CAM 5.2, low-molecular-weight cytokeratins, chromogranins, synaptophysin, and leucine-7.[115]

The predominant pattern of spread of thymomas is by direct invasion into adjacent organs. The degree of encapsulation and the invasion of adjacent tissues define malignancy for these tumors rather than the histologic appearance.[120] Approximately 50% of cases in surgical series are noninvasive.[18,48-50,121,122] Thymomas may metastasize as implants on pleural surfaces or pulmonary nodules, but they rarely metastasize to extrathoracic areas.[123] When thymomas metastasize, the most common site is the pleural cavity, where they form plaques, malignant pleural effusions, and diaphragmatic masses. Invasion into the superior vena cava, brachiocephalic vein, lung, and pericardium may be observed.[124]

Thymic carcinomas invade locally, often involve the pleura and mediastinal nodes, and sometimes spread regionally to the cervical and axillary lymph nodes.[125] Distant metastases to the lungs, liver, brain, and bone also occur. Distant metastases to bone, liver, or skin occur in 30% to 40% of cases of thymic carcinoids,[23] and they may be seen in 70% of patients within 8 years from initial diagnosis.[126]

Clinical Manifestations and Patient Evaluation

Approximately 30% to 40% of patients with thymic neoplasms are asymptomatic and the tumors are discovered incidentally.[51,59,123,127] Clinical symptoms vary greatly, depending on the size of the tumor and effect on adjacent structures, but they are usually those of a mediastinal mass producing cough, chest pain, dyspnea, hoarseness, superior vena cava syndrome, and symptoms related to tumor hemorrhage.[21,128,129] Patients may also have dysphagia, fever, weight loss, and anorexia.

Some thymomas present with symptomatic paraneoplastic syndromes; the most common is myasthenia gravis, which is seen in approximately 45% of patients.[59] Box 46-1 lists other syndromes.[19,59,61,120,130] Thymic carcinoids may also be associated with Cushing's syndrome, Eaton-Lambert syndrome, syndrome of inappropriate secretion of antidiuretic hormone (SIADH), and hypercalcemia,[23] but the classic carcinoid syndrome is rare. The causes of these syndromes remain obscure, although autoantibodies have been demonstrated, mostly in thymoma patients.[70,71,131]

Myasthenia gravis is an autoimmune neuromuscular junction disorder characterized by the presence of anti-acetylcholine receptor antibodies, which cause an acetylcholine receptor deficiency at the motor end plate. The disease is characterized by rapid exhaustion of voluntary muscular contractions, with a slow return to the normal state.[130,132] Myasthenia gravis is

common with thymoma but rare in thymic carcinoma. Patients with thymoma and myasthenia gravis may have an increased operative mortality rate, and most surgical deaths are attributed to myasthenic crisis. Death of patients with thymoma and myasthenia gravis is commonly caused by complications of myasthenia gravis, whereas in patients without myasthenia gravis, death often is attributed to local progression of tumor.[122]

Prognostic Factors

The two most important prognostic factors for thymoma are invasiveness (stage) and completeness of surgical resection.[49,51,133-135] Capsular invasion is commonly used as the basis for designation as benign or malignant. Tumor size (>10 cm) and the presence of symptoms also have prognostic value.[46,136,137] Patients with complete or radical excision have significantly improved survival times over those with subtotal resection or biopsy only.[133,138] Although almost all noninvasive thymomas can be totally resected, the ability to achieve a complete resection in invasive cases varies from 58% to 73%.[62,133,139] Older series reported a poor prognosis associated with myasthenia gravis,[6,49,50] but several modern series have failed to confirm this observation.[134,135,140-142] Myasthenia gravis may even confer a survival advantage because neuromuscular symptoms may lead to earlier discovery of a small thymoma.[136,143,144] After thymectomy, patients with myasthenia gravis have attenuation of the severity of symptoms over time but not necessarily complete resolution of them.[145-147] About 50% of patients with pure red cell aplasia have thymoma, and about 10% of patients with hypogammaglobulinemia have thymoma. Patients with red cell aplasia, hypogammaglobulinemia, and lupus erythematosus appear to have a poorer prognosis.[122,136,142,143]

Although the degree of tumor invasiveness is strongly related to stage and prognosis, there are data to support the prognostic significance of the histologic findings, independent of tumor stage.[141,148,149] The historical classification proposed by Marino and Muller-Hermelink categorized thymoma as cortical, mixed, and medullary types.[150] Thymomas arising from the epithelial cells of the cortex were classified as cortical thymomas, and those arising from the medullary spindle cells were classified as medullary thymomas. According to the Marino and Muller-Hermelink data, cortical thymomas have a more aggressive course than medullary thymomas and are more likely to be associated with myasthenia gravis. Of note, thymic carcinomas were categorized as a separate entity.

In 1999, the WHO published a classification including six subtypes of thymic tumor, based on the relative proportion of epithelial and lymphocytic cells (see Table 46-1). This is the most widely accepted histologic classification system, and the WHO cell type is an independent prognostic factor.[149,151-153] A retrospective study of 324 patients found that patients with WHO types A, AB, and B1 had a 100% disease-specific survival rate without RT and therefore did not benefit from adjuvant RT.[154] There was no survival difference for cell types B2 and B3 with or without adjuvant RT. Reiker et al,[155] noted that survival rates of patients with types A, AB, B1, and B2 were better than for type B3, and that type C had the lowest OS. The prognostic value of the subtype of type B thymomas has been examined in one series that found no differences in recurrence or survival rates among the three subtypes of type B, but all patients who recurred had stage III disease, indicating that the Masaoka stage was predictive.[156] The risk of myasthenia gravis increases progressively with WHO type from A (~20%) to B3 (~60%).[87]

Paraneoplastic syndromes occasionally exist with well-differentiated thymic carcinomas.[88,89] However, clinical features have not proved useful as prognostic indicators.[149] As with thymomas, total resection and stage at presentation are important prognostic factors for thymic carcinoma.[22] Extensive lymph node dissection (>10 nodes) is needed to accurately stage patients, and disease-free survival (DFS) can be as high as 90% in N0 patient with extensive nodal dissection, whereas patients with node-positive disease can have DFS on the order of 33%.[157]

Recently, a nine-gene assay has been developed that divides thymomas into high and low risk of metastasis, with 10-year metastasis-free survival of 77% and 26%, respectively.[158] This product is available commercially.[159]

Diagnostic Workup for Thymic Tumors

The diagnostic workup of a patient with an anterior mediastinal mass begins with a thorough history and physical examination. Particular focus should be given to detect signs and symptoms that may suggest myasthenia gravis, such as fatigue, diplopia, ptosis, and dysarthria. Constitutional symptoms such as fever, chills, and weight loss are more suggestive of lymphoma. Routine screening blood work and chemistry testing may give clues to the presence of associated syndromes. In the case of suspected Cushing's syndrome, seen in 1% to 2% of patients, a dexamethasone suppression test and urinary cortisol level should be obtained, although some carcinoids can be suppressed, making diagnosis difficult. The differential diagnosis, in addition to thymic lesions, includes germ cell tumors, lymphomas, and thyroid proliferative disorders. Serum alpha-fetoprotein and beta-human chorionic gonadotropin levels should be obtained in young men if a non-seminomatous germ cell tumor is suspected.[160-162] Exclusion of metastases from extrathymic primary tumors is important.

The chest radiograph often demonstrates a hilar mass (Figure 46-2). CT scan with contrast defines the characteristics of a mediastinal lesion, as well as its relation to or invasion of other mediastinal structures.[163,164] Thymic tumors are usually homogeneous, well-demarcated lesions with a round or lobulated shape, and occasionally have calcification (Figure 46-3).[165,166] The presence of fat planes between the tumor and adjacent structures suggests localized disease. Pleural involvement may be seen in advanced disease. The radiographic presence of both an anterior compartment mass as well as "drop" metastases to the pleura is highly suggestive of the diagnosis. Thymic carcinomas often contain calcifications, cysts, or necrosis on imaging.[167] A nomogram has been developed by Marom et al,[168] using CT characteristics to predict the Masaoka stage (Figure 46-4). In the absence of symptoms and signs, extensive radiographic imaging is unnecessary. Magnetic resonance imaging (MRI) has not been superior to CT scanning.[169,170]

The role of PET has not been well established as FDG (fludeoxyglucose) uptake in thymomas is variable. However, PET/CT can help distinguish thymomas from thymic carcinomas, as well as help predict WHO grade.[171-174] A report of 51 patients found that FDG uptake was higher in patients with thymic carcinoma than thymoma, and type B3 thymomas had higher uptake than lower histologies (A through B2).[173] Similar results were seen in 47 patients from Italy, where SUV max and ratio of SUV max to tumor size correlated with WHO grade and Masaoka stage.[174] However, a series of 58 patients from Japan found that while SUV max can differentiate between thymic carcinoma and thymoma, there was no difference between the low- and high-risk thymoma groups.[171] High uptake of FDG also appears to correlate with the degree of tumor invasiveness,[175-177] and may be helpful in identifying nodal and distant metastasis.[172]

Patients presenting with a thymic mass need a histologic diagnosis before definitive therapy. CT- or ultrasound-guided fine-needle aspiration biopsy can establish the diagnosis

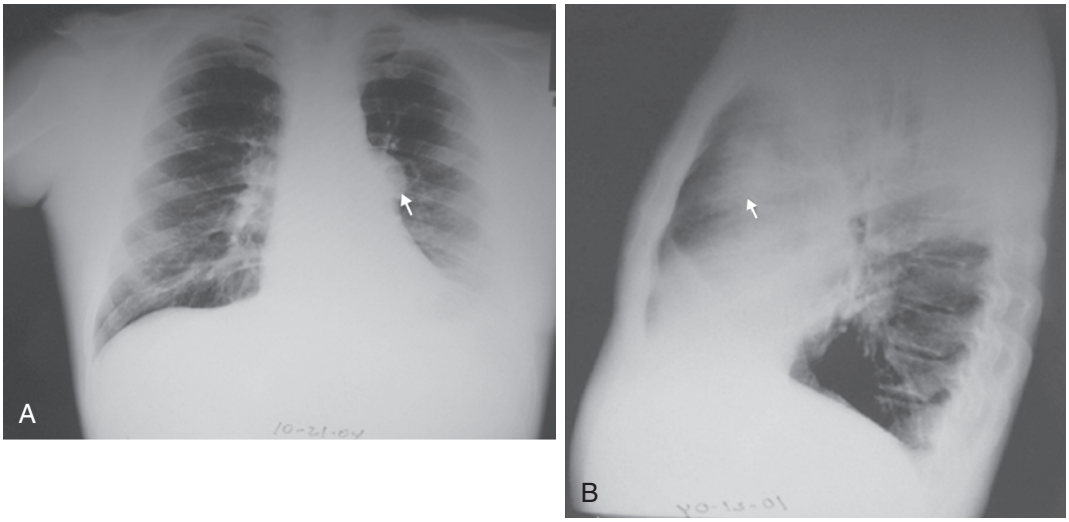


Figure 46-2 **A,** Anteroposterior chest radiograph demonstrates a mass *(arrow)* projecting over the left hilum. **B,** Lateral chest radiograph confirms the location of the mass in the anterior mediastinum.

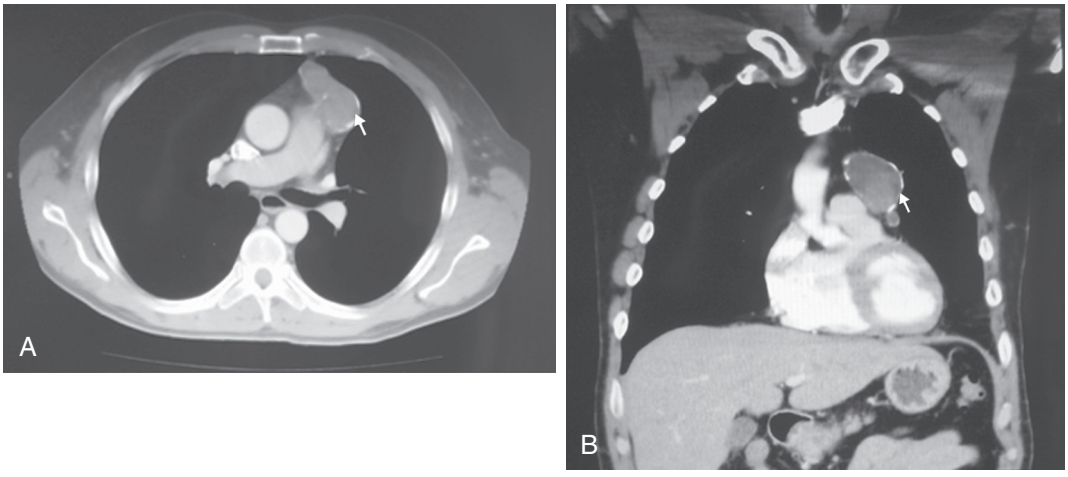


Figure 46-3 Computed tomography (CT) demonstrates a mass *(arrow)* with calcification in the anterior mediastinum. **A,** Axial view. **B,** Coronal view.

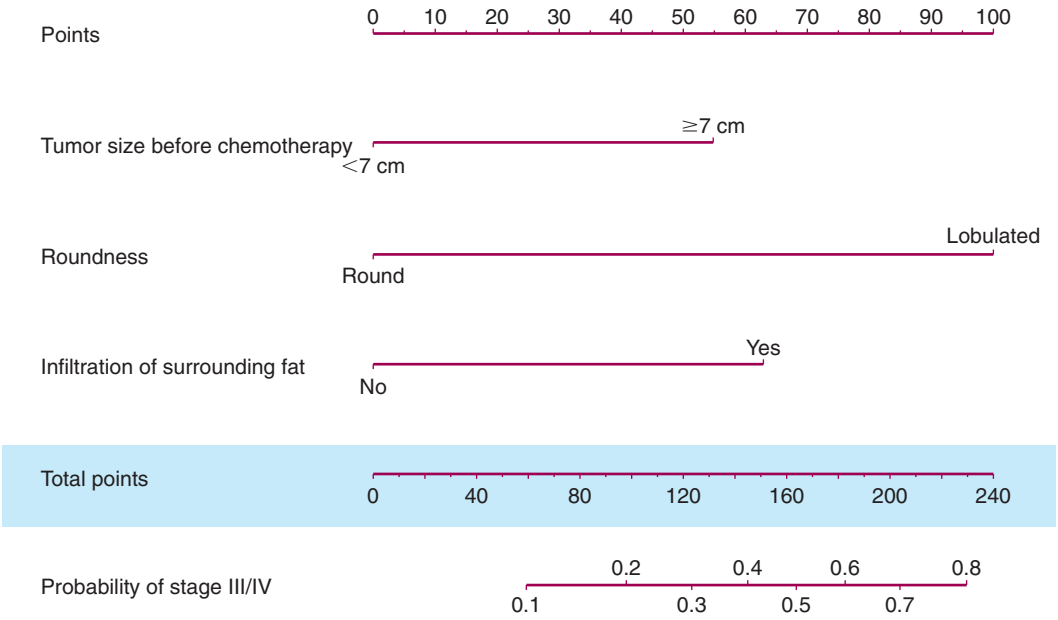


Figure 46-4 Nomogram to predict stages III/IV thymoma using computed tomography findings at presentation.
(Used with permission from Marom EM, Milito MA, Moran CA, et al: Computed tomography findings predicting invasiveness of thymoma. J Thorac Oncol 6(7):1274–1281, 2011.)

TABLE 46-2 Masaoka Staging System for Thymoma

Stage	Description
I	Macroscopically completely encapsulated with no microscopic detectable capsular invasion
II	Macroscopic invasion into surrounding mediastinal fatty tissue or mediastinal pleura or microscopic invasion into the capsule
III	Macroscopic invasion into surrounding organs (e.g., pericardium, great vessels, lung) or intrathoracic metastases, or both
IVA	Pleural or pericardial implants or dissemination
IVB	Lymphogenous or hematogenous metastases

Adapted from Masaoka A, Monden Y, Nakahara K, et al: Follow-up study of thymomas with special reference to their clinical stages. Cancer 48:2485–2492, 1981.

preoperatively[178] with a sensitivity and specificity of 87% to 90% and 88% to 100%, respectively, for thoracic neoplasms.[179] When larger tumor samples are required to distinguish between lymphoma and lymphoid-predominant thymoma, core-needle biopsy provides sufficient specimens with an overall sensitivity of 96% and specificity of 100%.[179] Bronchoscopy, video-assisted thoracoscopic surgery, mediastinoscopy, or anterior thoracoscopy may help yield the diagnosis before resection, especially if enlarged lymph nodes are present.[160,180,181] The potential risk of breaching the capsule, leading to spillage and seeding of tumor cells during biopsy, has been debated and remains unsettled.[6,182,183]

Staging

Bergh et al introduced the first clinical staging system for thymoma in 1978.[184] Their staging system was subsequently modified by Masaoka in 1981 and is the most widely accepted (Table 46-2).[133] It is based on pathologic findings at time of surgery.

A separate, simplified staging paradigm was proposed by Suster and Moran.[185] Stage I lesions are localized and encapsulated; stage II lesions are locally invasive; and stage III lesions have nodal, visceral, or distant metastasis. A tumor-node-metastasis (TNM) staging system was proposed by Tsuchiya[186] but is not widely accepted. There is no formal American Joint Committee on Cancer (AJCC) staging system for thymoma.

Treatment

Surgery for Thymoma

Surgery is the mainstay of therapy in resectable cases. However, adjuvant or neoadjuvant radiation therapy plays an important role in subtotally resected or unresectable cases. Many patients who present with symptoms of myasthenia gravis benefit from a thymectomy.[134] Consequently, surgical resection alone for stage II thymomas is a reasonable approach.[12,13] In general, surgical resection for thymoma carries low risks of morbidity and mortality; most surgical deaths can be attributed to a myasthenia gravis crisis, but the risk can be minimized with appropriate perioperative management, including plasmapheresis, in selected situations.[122,187] After an encapsulated thymoma without associated myasthenia gravis is removed without disturbing the integrity of the capsule, recurrences are rare.[49,62,188,189]

Successful surgical treatment of locally invasive thymoma depends on the completeness of resection.[190] Consequently, the surgeon should remove as much of the lesion as possible, including surrounding mediastinal fat, possibly to include an extended thymectomy.[191] However, resection of an involved phrenic nerve is controversial, and surgeons advocate debulking alone, leaving both phrenic nerves intact if there is bilateral phrenic nerve involvement because of the respiratory morbidity from resection. When complete resection is not possible, a debulking operation should be considered, because good long-term results can be achieved when such surgery is followed by postoperative radiation therapy.[122] Only about one fourth of patients with stage IVA disease have resectable disease.[59] Surgical approaches have varied from discrete resection of pleural metastases to en bloc mediastinal dissection with EPP.[192] A few small single-institution series have suggested that EPP may improve local control rates.[192-194] The conventional surgical approach for thymoma resection uses an open sternotomy. There has been recent interest in using a VATS thymectomy, with encouraging results, especially for smaller and noncystic tumors.[195-198] The surgeon should delineate the extent of the tumor, specify the areas of invasion, and identify the areas of positive or questionable margins and residual disease with metallic clips to assist future radiation therapy planning.

Radiation Therapy for Thymoma

Although the role of adjuvant irradiation for invasive thymomas has never been tested in a prospective, randomized fashion, there is general agreement that RT is an effective adjuvant therapy for invasive thymomas,[199] and most retrospective studies have reported improvements in local tumor control and survival rates after adjuvant irradiation.[65,116,137,138,144,146] However, patients with encapsulated, noninvasive stage I thymoma should not receive postoperative RT after complete resection because the recurrence rate is approximately 0% to 2%.[65,115,193-195]

There is controversy about whether postoperative RT should be used for completely resected invasive thymomas. A meta-analysis of 22 studies with 592 patients with completely resected stage II or III thymoma found no reduction in recurrence after adjuvant RT,[200] but it is difficult to draw firm conclusions, given the selection bias in retrospective series. Berman et al reported a single-institution retrospective cohort comparison of 74 patients with stage II thymoma after complete surgical resection.[14] Patients who were thought to be at high risk for local recurrence were referred for adjuvant RT. The rate of locoregional recurrence was 8% in patients who were observed versus 0% in the RT group ($p = 0.15$). The researchers concluded that no benefit of postoperative RT was observed in patients with stage II thymoma as a group; however, a higher-risk subset of these patients may benefit from adjuvant therapy.[14] Kondo and Monden reported a multiinstitutional, retrospective study of 1320 patients with thymic epithelial tumors and found no significant difference in the recurrence rates between two groups with stage II or III thymoma,[22] one of which underwent surgery alone and the other surgery plus adjuvant irradiation. This observation may reflect the fact that most of the patients underwent complete resection (100% with stage II disease and 85% with stage III disease); as has been pointed out by the study authors, the recurrence rates they found were lower than in previous reports.

Although some studies showed no benefit from adjuvant RT,[12,13,154,201] the recurrence rates of surgery alone, even with complete resection, may approach 30%.[121,136] A SEER study of 901 patients showed a 10% absolute improvement in 5-year OS rates but no statistical difference in cause-specific survival rates in patients with stages II to III disease.[201] Conversely, another SEER study of 476 patients with stage III disease saw

improved DFS but not OS in patients receiving adjuvant RT.[202] In a study of 141 patients with thymoma, Nakahara et al reported a 5-year survival rate of 92% for patients with stage II disease and 88% for patients with stage III disease who were treated with postoperative irradiation.[139]

Histology may impact the role of adjuvant irradiation. A series of 188 patients with type B3 thymoma found that Masaoka stage and adjuvant radiation were independent prognostic factors for OS in patients with stages III and IV.[203] After complete resection, invasive thymomas still carry a poorer prognosis than noninvasive tumors.[50,204,205] Survival rates continue to fall with long-term follow-up.[140] The 5-year and 10-year survival rates for well-encapsulated thymomas without invasion are more than 90%, and for invasive thymomas, the rates range from 30% to 70%.[6,121,133,139] The 5-year survival rates according to Masaoka stage are 83% to 100% for stage I disease, 86% to 98% for stage II disease, 68% to 89% for stage III disease, and 50% to 71% for stage IV disease.[22,133,206,207] The approximate 10-year survival rates are 80%, 78%, 47%, and 30%, and the 15-year rates are 78%, 73%, 30%, and 8% for stages I to IV, respectively.[207] Table 46-3 provides a summary of treatment results.

In cases with gross fibrous adhesions of the tumor to the pleura at the time of surgery or microscopic invasion of the pleura on histologic studies, there is an increased risk for recurrence. Haniuda found that patients with fibrous adhesion to the mediastinal pleura without microscopic invasion benefited most from postoperative radiation therapy.[210,217] The recurrence rates, with and without adhesion to the mediastinal pleura, were 36% and 0%, respectively. In another study,[218] patients with resected stage II thymoma had recurrence rates of 8% and 29%, respectively, with and without adjuvant radiation therapy. Although postoperative radiation therapy may decrease local recurrence, it does not appear to decrease the incidence of subsequent pleural dissemination that may occur outside of radiation fields; in fact, the pleura is the most common site of failure after radiation.[214] This may be a reflection of the natural pattern of spread of this disease. Extended radiation fields to include the entire pleura significantly increases the normal tissue toxicity and is not routinely employed.

Anecdotal studies have demonstrated good local control of thymomas treated with primary irradiation. Of 23 patients treated with irradiation alone, 8 had complete regression, 10 had partial regression, and 5 had no regression of disease.[49] In a report by Marks et al, tumor was controlled in all nine cases treated with megavoltage irradiation.[219] The average follow-up was 5.5 years (minimum, 30 months). Ariaratnam et al observed tumor control in 8 of 11 patients with malignant thymoma with a minimum follow-up of 2 years.[220] Two of the three patients who died had received only 30 Gy in 3 weeks to the mediastinum. Overall, irradiation as monotherapy may result in local control rates of approximately 65% and 5-year survival rates of 40% to 50%.[205,211,221]

With the increasing availability of proton radiation therapy, there is a potential for an improved therapeutic ratio in radiation therapy for thymomas by taking advantage of the proton dose distribution. Figura et al present a case of stage III thymoma treated with adjuvant radiation, showing that compared with intensity-modulated radiation therapy (IMRT), proton radiation lowered esophageal dose by 55%, heart dose by 28%, lung dose by 37%, and generalized normal tissue dose by 59%.[222] However, there was a 27% (1.9 Gy) increase in breast dose. Although dedicated studies of thymoma are lacking, multiple studies evaluating tumors in the mediastinum have found lower doses to normal structures, including heart, spinal cord, esophagus, and whole-body radiation dose with the use of protons.[223-225]

Locally Advanced Thymoma and Palliation

For patients with stage III to IV disease, the evidence supporting the use of postoperative radiation therapy is robust. Urgesi et al reported no in-field recurrences in a study of 33 patients with completely resected stage III thymoma treated with postoperative irradiation.[135] Curran et al reported a 53% 5-year actuarial mediastinal relapse rate in patients with stages II and III disease after surgery alone, compared with 0% after total resection and irradiation and 21% after subtotal resection or biopsy and irradiation.[226] Similarly, in a study of 70 patients with Masaoka stages III to IV thymoma, the relapse rate for patients receiving postoperative radiation therapy was reduced from 50% to 20%, and most disease (80%) recurred outside of the irradiated field.[227]

Preoperative radiation therapy has been advocated for unresectable or marginally resectable thymomas.[49,228-230] Several small studies assessing preoperative radiation therapy for extensive disease found a decrease in tumor burden at the time of surgery, with response rates as high as 80%, and described a theoretical decrease in the potential for tumor seeding during surgery.[121,122,209,231] Onuki et al found that a dose of 12 Gy to 20 Gy given to 21 patients with stage III thymomas resulted in a 76% response rate, with more aggressive WHO histologic subtypes having a less robust volume reduction.[231] Preoperative chemoradiation has also been tested in locally advanced thymic tumors with favorable results. Korst et al found that in a group of 22 patients with 71% Masaoka stage III or IV disease with aggressive histology (62% B3 thymoma or thymic carcinoma), two cycles of cisplatin and etoposide concurrent with 45 Gy led to a 77% R0 resection rate and 14% R1 resection rate.[232] These series demonstrated that preoperative irradiation facilitated total or subtotal resection of the invasive thymoma mass by reducing the tumor volume.[228]

Primary radiation therapy as the definitive treatment has been advocated in nonsurgical candidates or patients with unresectable advanced disease. In a study of 12 patients who presented with unresectable tumors and were treated with primary radiation therapy, 7 patients were alive 1 year 8 months to 5 years 1 month later.[233] Similar outcomes were reported for 31 patients with unresectable stage III or IV disease.[234] Five-year survival rates of 53% to 87% and 10-year survival rates of 44% were reported for patients with advanced thymoma receiving irradiation after biopsy only or incomplete resection.[211,221] Urgesi reported the use of radiation therapy alone in 21 patients with intrathoracic recurrences of thymoma.[235] The 7-year survival rate of 70% was similar for those treated with irradiation alone and those treated with surgery and adjuvant therapy. However, the retrospective nature of these studies, small number of patients, differing amounts of clinical disease, and variations in radiation doses and techniques are significant confounding variables.

Preoperative and primary radiation therapy alone has fallen out of favor. Because of the improved response rates to chemotherapy, most patients with advanced disease are treated with a combined-modality approach. Other therapies, such as cryotherapy, have been attempted, and could have efficacy.[236]

Chemotherapy for Thymoma

In general, thymomas are chemosensitive tumors, but chemotherapy is reserved for locally advanced or metastatic disease. However, there are no prospective, randomized trials comparing different chemotherapeutic agents.[205] Platinum-based regimens have commonly been used, with response rates of more than 50% with the application of cisplatin-based combination chemotherapy.[237] Some of the commonly employed combinations are cisplatin, doxorubicin, and cyclophosphamide (PAC),

TABLE 46-3 Summary of Adjuvant Therapy Results of Thymoma

Study	Year	No. Patients (Stage)	Irradiation Regimen	Radiation Dose	Local Control Rate (%)	5-year Survival	Comments
Bretti et al[208]	2004	43 (III) 20 (IVa)	Preoperative/ postoperative ± chemotherapy	24 Gy-30 Gy preoperative 45 Gy-55 Gy postoperative	—	Median PFS 59% (III) 21% (IVA)	Preoperative radiation therapy improved resection rate
Cowen et al[209]	1995	13(I) 46 (II) 58 (III) 32 (IVa)	Preoperative/ postoperative ± chemotherapy	22 Gy-50 Gy preoperative 30 Gy-70 Gy postoperative (median, 40 Gy-55 Gy)	78.5% (overall rate) 100% (I) 98% (II) 69% (III) 59% (IVA)	59.5% (DFS) (49.5% at 10 yr)	Stage and extent of resection influenced local control and survival rates
Curran et al[121]	1988	43 (I) 21 (II) 36 (III) 3 (IV)	Postoperative for stages II-IV	32 Gy-60 Gy	100% (II-III, total resection) 79% (II-III, subtotal resection or biopsy)	100% (I) (DFS) 58% (II) 53% (III)	No recurrence for stage I after surgery only; radiation therapy improved local control rates for stages II-III
Haniuda et al[210]	1992	70 (II/III)	Postoperative	40 Gy-50 Gy	100% (IIp1)* 70% (III)	74% (II) 69% (III)	Radiation therapy benefited patients with pleural adhesion, without microinvasion
Jackson and Ball[211]	1991	28 (II/III)	Postoperative (after biopsy or subtotal resection)	32 Gy-60 Gy (mean, 42 Gy)	61%	53% (OS) (44% at 10 years)	High rate of radiation therapy complications (11%), with two deaths
Kondo and Monden[22]	2003	522 (I) 247 (II) 201 (III) 101 (IV)	Postoperative ± chemotherapy	— 43.7 Gy ± 7.7 Gy (II) 45.4 Gy ± 8.4 Gy (III)	99.1% (I) 95.9% (II) 71.6% (III) 65.7% (IV)	100% (I) 98% (II) 89% (III) 71% (IV)	Largest study; no difference in recurrence rates ± radiation therapy in stages II and III patients; high complete resection rates
Latz et al[212]	1997	10 (II) 14 (III) 19 (IV)	Postoperative ± chemotherapy	10 Gy-72 Gy (median, 50 Gy)	81%	90% (II) 67% (III) 30% (IV)	Uncertain radiation therapy benefit for completely resected stage II tumors
Mornex et al[213]	1995	21 (IIIa) 37 (IIIb) 32 (IVa)	Preoperative and postoperative ± chemotherapy	30 Gy-70 Gy (median, 50 Gy)	86% (IIIA) 59% (IIIB-IVA)	64% (IIIA) 39% (IIIB)	Great impact of radiation therapy on local control rates; >50 Gy recommended for incompletely resected tumors

Continued

TABLE 46-3 Summary of Adjuvant Therapy Results of Thymoma—cont'd

Study	Year	No. Patients (Stage)	Irradiation Regimen	Radiation Dose	Local Control Rate (%)	5-year Survival	Comments
Nakahara et al[139]	1988	45 (I) 33 (II) 48 (III) 12 (IVA) 3 (IVB)	Postoperative (73% received radiation therapy)	30 Gy-50 Gy	—	100% (I) 91.5% (II) 87.8% (III) 46.6% (IV) 97.6% (complete resection) 68.2% (subtotal) 25% (biopsy)	Complete resection plus radiation therapy resulted in best survival rates
Ogawa et al[214]	2002	13 (I) 61 (II) 25 (III)	Postoperative	30 Gy-61 Gy (median, 40 Gy)	RFS 100% (I) 90% (II) 56% (III)	100% (I) 90% (II) 48% (III)	8% mediastinal failure in involved-field group versus 0% for mediastinal field; however, pleural failure is dominant in both
Pollack et al[138]	1992	11 (I) 8 (II) 10 (III) 7 (IV)	Postoperative; primary RT (22 patients)	50 Gy (median)	59% (OS)	74% (I) 71% (II) 50% (III) 29% (IV)	Patients with incomplete resections did worse; multimodality treatment recommended for these patients
Singhal et al[12]	2003	30 (I) 40 (II)	Postoperative vs. surgery alone	45 Gy-54 Gy	98.6% (OS)	94% (I) 90% (II)	One recurrence for all stages I-II patients treated with surgery alone and one recurrence for all treated with adjuvant radiation therapy
Urgesi et al[135]	1990	59 (III) 18 (IVA)	Preoperative and postoperative	39.6 Gy-60 Gy	85%-90%	78% (III) (58% at 10 years)	Most relapses were out of radiation therapy fields
Zhu et al[215]	2004	47 (I) 41 (II) 41 (III) 32 (IVa) 9 (IVb)	Postoperative and definitive	50 Gy-55 Gy 60 Gy-65 Gy	96% (II) 56% (III) 43% (IVa) 22% (IVb)	86.4% (OS) 96% (II) 78% (III) 57% (Iva) 36% (IVb)	No local control or survival benefit for extended-field versus involved-field radiation therapy
Shen et al[216]	2013	21 (I) 30 (II) 15 (III) 6 (IV)	Postoperative	45 Gy-64 Gy		94% WHO Type A + AB 87% WHO Type B1-3	Adjuvant RT showed no obvious survival benefit

DFS, *Disease-free survival rate;* Gy, *gray;* OS, *overall survival rate;* PFS, *progression-free survival rate;* RFS, *recurrence-free survival rate;* ±, *with or without.*
**Fibrous adhesion to the mediastinal pleura without microscopic invasion.*

with reported overall responses in excess of 70%,[238-240] and cisplatin, doxorubicin, vincristine, and cyclophosphamide (ADOC).[241] In a study by Fornasiero,[242] 37 patients with stage III or IV thymoma were treated with ADOC, with an overall response rate of 92% and a 43% complete response rate. Loehrer studied 23 patients with localized but unresectable thymomas treated with PAC followed by radiation therapy.[238] The overall objective response rate was 70%, with five complete responders. The estimated 5-year DFS rate was 54%, with a median survival time of 93 months. Multivariate analysis demonstrated that chemotherapy was associated with an improvement in OS rates for patients with stages III and IV disease. Similar results with combination PAC have been reported in Taiwan; all responders had overexpression of the topoisomerase 2α gene, but patients with no detectable expression progressed with treatment.[243]

Targeted Agents for Thymoma

Because thymic tumors harbor a number of molecular aberrations, this has encouraged the use of targeted agents.[244,245] Although EGFR overexpression is common in thymic tumors,[246] patient exhibit limited partial and complete response.[247,248] Patients with thymic carcinomas also have higher serum VEGF and bFGF than controls,[96] although patients with thymoma and controls show no difference. However, low response rates have been seen with bevacizumab and erlotinib.[248] Similarly, KIT overexpression has led to testing imatinib, which shows no substantial activity.[249,250] Early case reports with sorafenib and sunitinib show some activity, although this remains to be validated,[251,252] A retrospective series of mTOR inhibitors showed 60% stable disease or partial response, but this remains to be validated prospectively.[253]

Combined-Modality Therapy for Thymoma

The role of chemotherapy as an adjuvant therapy after resection has not been established, but there is anecdotal evidence that combining chemotherapy with irradiation with or without surgery can be effective with acceptable toxicity in selected cases.[254-257] It has also been shown that neoadjuvant chemotherapy and then surgery, followed by additional chemotherapy and irradiation, may improve the resectability and survival rates of patients with locally advanced disease.[257,258]

In a Phase II study of 22 patients with unresectable thymoma treated with induction PAC resection, adjuvant irradiation, and consolidative chemotherapy, there was a 77% response rate to chemotherapy, a 95% 5-year OS rate, and a 79% 7-year OS rate.[240] A trial from the Japanese Clinical Oncology Group reported on 23 patients with unresectable stage III thymoma treated with weekly dose-dense cisplatin, vincristine, doxorubicin, and etoposide and found no deaths from toxicity, but only 57% were able to complete chemotherapy as planned.[259] Thirteen of the patients were able to undergo resection, with nine R0 resections. With a 62% response rate, efficacy of the dose-dense regimen was no better than with conventional chemotherapy.[238,240]

In a study by Macchiarini, all 7 patients with stage III invasive thymoma treated with neoadjuvant cisplatin, epirubicin, and etoposide were able to undergo surgical resection.[256] Four had complete resections, and three had incomplete resections. Shin reported that 9 of 11 patients with unresectable stages III and IV thymoma were able to undergo complete resection after induction chemotherapy consisting of cyclophosphamide, doxorubicin, and cisplatin.[255] All 9 patients were given additional postoperative radiation therapy and chemotherapy. Of these patients, 7 were disease free at a median follow-up time of 43 months. Wright reported on 10 patients with stages III to IVA thymoma treated neoadjuvantly with two cycles of cisplatin and etoposide and concurrent irradiation followed by surgery.[260] Eight patients had R0 resections, and the 5-year survival rate was 69%.

Treatment of Thymic Carcinoma

Although the optimal treatment of thymic carcinoma is unclear, surgical extirpation remains the cornerstone of therapy, and in most published studies, surgery has been followed by adjuvant radiation therapy.[20,66,261-263] Because many series are gathered over decades, it has been difficult or impossible to control for the changes in pretreatment tumor imaging, surgical techniques, and thoracic radiation therapy planning and delivery, all of which may contribute to the inconsistent results in the literature. A prescriptive dose range has yet to be identified, with most studies using 40 Gy to 70 Gy at 1.8 Gy to 2 Gy per fraction, but in general, doses of 45 Gy to 55 Gy are used in the adjuvant setting, whereas 60 Gy or more is used for definitive irradiation. Although a survival benefit has not been seen, there is a trend toward improved survival and local control rates with adjuvant therapy.[20,262] No dose-related survival advantage has been established, although a relationship between dose and local control rates has been demonstrated.[264]

In a series of 26 patients treated with surgery and postoperative irradiation, Hsu et al observed a 77% 5-year OS rate,[262] with respective 82% and 66% survival rates for completely resected and subtotally resected cohorts. With a median dose of 60 Gy (range, 40 Gy to 70 Gy), an excellent 5-year local control rate of 91% was observed. For a cohort of 40 patients receiving definitive or adjuvant radiation therapy, Ogawa et al reported an absence of local recurrence for those with complete resection and radiation doses greater than 50 Gy.[20] Kondo and Monden reported the largest retrospective,[22] comparative study and found no statistically significant survival benefit from the addition of adjuvant irradiation to surgical resection, although no definitive conclusions could be made because of subgroup sample size limitations and the retrospective nature of the study.

Although local control rates are increased with irradiation, a survival benefit remains to be demonstrated. For patients with any question of clinical resectability, neoadjuvant platinum-based chemotherapy is a reasonable treatment consideration.[265] For patients with early stage cancer with completed resected disease, there is some thought that adjuvant radiation is not indicated.[266] Table 46-4 summarizes some of the treatment results of thymic carcinoma.

Treatment of Thymic Carcinoid

Complete surgical resection is the preferred method of treatment, although recurrence and distant metastases are common.[22,272,273] A SEER analysis of 160 patients found that the median survival time was 79 months in patients who had surgical resection compared with 26 months in those who did not have surgery.[273] Patients who received irradiation had a worse OS rate, but patients who received irradiation were more likely to have advanced disease. In a study of 40 patients, the recurrence rate was 64%, even though 35 of the 40 patients had a complete resection,[22] and the 5-year survival rate was 84%. Despite a lack of conclusive evidence, incomplete resections followed by irradiation or chemotherapy, or both, may improve local control rates without significantly increased morbidity and mortality rates.[58,126,274,275] However, distant metastases occur in approximately 30% of patients.[276] The long-term prognosis is poor, with an overall 5-year survival rate of 0% to 31%.[272,277]

Techniques of Irradiation

High-energy (>10-MV) x-rays usually are preferred for irradiation. A CT scan is indispensable for adequate treatment planning. Clips placed at the time of surgery denoting the extent

TABLE 46-4 Summary of Thymic Carcinoma Treatment Results

Study	Year	No. Patients	Treatment	Radiation Therapy Dose	Local Control Rate (%)	5-year OS	Comments
Blumberg et al[66]	1998	43	TR/SR ± Ch/RT	—	52 (CR)	65% (35% at 10 years) 68% (TR) 62% (SR)	Masaoka stage was not prognostic, but invasion of innominate vessel was prognostic
Chang et al[261]	1992	16	TR/SR/BX ± Ch/RT		77	31% (median, 30 mo)	Better survival rate was seen with squamous type
Hsu et al[262]	2002	26	TR/SR ± RT	40 Gy-70 Gy	91 (OS)	77% (OS) 82% (TR) 66% (SR)	Masaoka stage was prognostic; very good local control rate observed with surgery + RT
Kondo and Monden[22]	2003	186	TR/ST/BX ± Ch/RT	—	49 (TR)	50.5% (OS) 66.9% (TR) 30.1% (SR) 24.2% (BX) *Subgroups:* 72.2% (TR alone) 73.6% (TR + RT) 46.6% (TR + Ch/RT) 81.5% (TR + Ch)	Largest number of patients gathered from multiple institutions in Japan; total resection was the most important factor in survival rate; RT did not improve results for completely resected tumors
Liu et al[267]	2002	38	TR/SR/BX ± Ch/RT	—		27% (MS, 24 mo)	Grade, stage, and resectability were predictors of survival rates
Lucchi et al[265]	2001	13	TR/SR ± Ch/RT	45 Gy-60 Gy	46 (OS)	61% (MS, 38 mo)	100% objective tumor response with induction chemotherapy but small study
Nakamura et al[268]	2000	10	BX + Ch ± RT	6 Gy-56 Gy	0	0% (MS, 11 mo)	Poor survival rate for unresectable disease; median chemotherapy response was only 6 mo
Ogawa et al[20]	2002	40	TR/SR/BX ± Ch/RT	10 Gy-70 Gy (mean, 50 Gy)	100 (TR + RT)	38% (28% at 10 years)	Long-term study; better survival and local control rates with complete resection + RT (12 of 16 patients versus 1 of 24 patients)
Shen et al[216]	2013	43	TR/SR ± Ch/RT	45 Gy-64 Gy (mean, 51.4 Gy)		61% at 7 years	Thymic carcinomas are more likely to present with advanced Masaoka stage than thymoma
Roden et al[269]	2013	29	TR/SR/BX ± Ch/RT	—		36%	Weight loss is associated with worse survival
Okereke et al[270]	2012	16	TR/SR ± Ch/RT	—	88	63% (MS, 57 mo)	Long-term survival can be achieved with R0 resection
De Montpreville et al[271]	2013	37	TR/SR/BX ± Ch/RT	—		67% at 3 years (MS, 94 mo)	Lymph node dissection should be systematic when resection is performed

Adapted from Eng TY, Fuller CD, Jagirdar J, et al: Thymic carcinoma. State of the art review. Int J Radiat Oncol Biol Phys 59:654–664, 2004.
BX, *Biopsy only or unresectable;* Ch, *chemotherapy;* CR, *complete response;* DSS, *disease-specific survival;* MS, *median survival;* OS, *overall survival;* RT, *radiation therapy;* SR, *subtotal resection or debulking;* TR, *total or complete resection;* ±, *with or without.*

of resection in completely resected tumors or outlining regions of residual disease are useful in guiding postoperative irradiation. The planning target volume (PTV) should include the gross tumor volume (GTV) and the thymus, if any, and the tumor bed with a 1.5-cm to 2-cm margin. A four-dimensional breathing scan, if available, should be used to determine tumor motion and can be used to create an internal target volume (ITV) or to plan for radiation-coordinated breathing control, which can provide superior sparing of normal lung.[278] Areas of suspicious subclinical disease and regional lymphatics are commonly included in the field. However, treatment of the entire mediastinal and supraclavicular nodal basin prophylactically is not advised because of the low incidence of lymph node involvement and a higher normal tissue complication rate.[279,280] A SEER database analysis of 1334 patients from 1973 to 2005 by Fernandes et al found no increase in long-term cardiac mortality rates or rates of secondary malignant tumors for patients treated with RT compared with patients treated with surgery alone.[281]

Conventional port arrangements may include two opposed anteroposterior ports (weighted 2:1 or 3:2), wedged-pair techniques, and other multiple-field arrangements. Given the advanced technical capabilities available, three-dimensional conformal RT (3DCRT) or IMRT should be considered to provide dose homogeneity and allow better sparing of normal critical structures. Figure 46-5 shows a postoperative radiation therapy field with multileaf collimators shaping the surgical tumor bed. Figure 46-6 shows a plan with IMRT. The isodose lines more closely conform to the PTV. The risks of side effects depend on normal tissue tolerance, surrounding critical organs, prior treatments, irradiation dose, other concurrent therapies, and the general health of the patient.

Various dose and fractionation schemes for thymoma have been reported.[205,282] Although one retrospective study did not find any relationship between radiation dose and local control rates,[209,264] others have found that radiation dose was a significant prognostic factor for local control, with good results reported when doses higher than 40 Gy were used for subclinical disease.[213,283] Retrospective data from Zhu found a 5-year survival rate of 82% in patients given greater than 50 Gy,[215] compared with 70% for doses less than or equal to 50 Gy. The most important prognostic factors were Masaoka stage and extent of resection.

Postoperative doses of 45 Gy to 55 Gy given by conventional fractionation have been used effectively in most cases.[121,136,202,214,235] The dose to the spinal cord should be limited to 45 Gy and can be accomplished using oblique mediastinal fields or IMRT. For patients with gross residual disease, doses of 60 Gy or more are probably required,[213,234] but higher doses correlate with higher risks of complications.[284] IMRT may facilitate delivery of high doses to gross tumor while respecting dose limits to organs at risk.[285]

Treatment Algorithm and Controversies

The initial treatment for thymic tumors is surgery if the disease is resectable. Adjuvant irradiation or chemotherapy should be considered for patients with features indicating a high risk for recurrent disease and those with an unresectable or inoperable tumor. Optimal treatment must be customized, and the following guidelines should be considered:

1. Pathologic stages I to II thymoma (WHO types A, AB, B1, B2, B3) should not receive adjuvant therapy after a complete thymectomy (R0 resection, negative margins). Adjuvant RT may be considered in patients with B2 and B3 disease. If observation without RT is decided on, patients with B2 and B3 disease should be closely observed with biannual or annual CT scans.
2. Patients with pathologic stage II thymoma (WHO types A, AB, B1, B2, B3) with less than a complete thymectomy (as outlined in guideline 1) may benefit from postresection thoracic irradiation. A dose of 50 Gy to 66 Gy (depending on the amount of residual disease) can usually be safely administered.
3. Pathologic stage II thymic carcinoma (WHO type C) can be treated with multimodality adjuvant therapy, which includes concomitant chemoradiation with or without

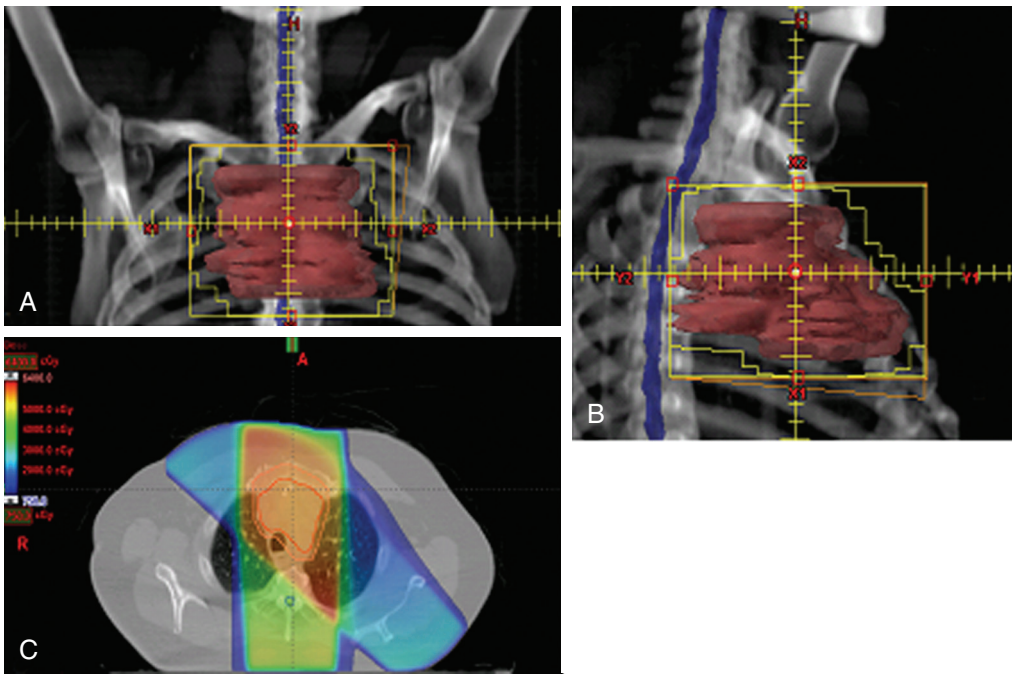


Figure 46-5 Anteroposterior view **(A)**, oblique view off the spinal cord **(B)**, and multifield view **(C)** by computed tomography (CT). Postoperative radiation therapy field *(outer white square)* with custom blocks *(black lines)* covering the surgical tumor bed *(inner white line)* and upper mediastinum. The isodose lines cover the planning target volume *(orange)* very well.

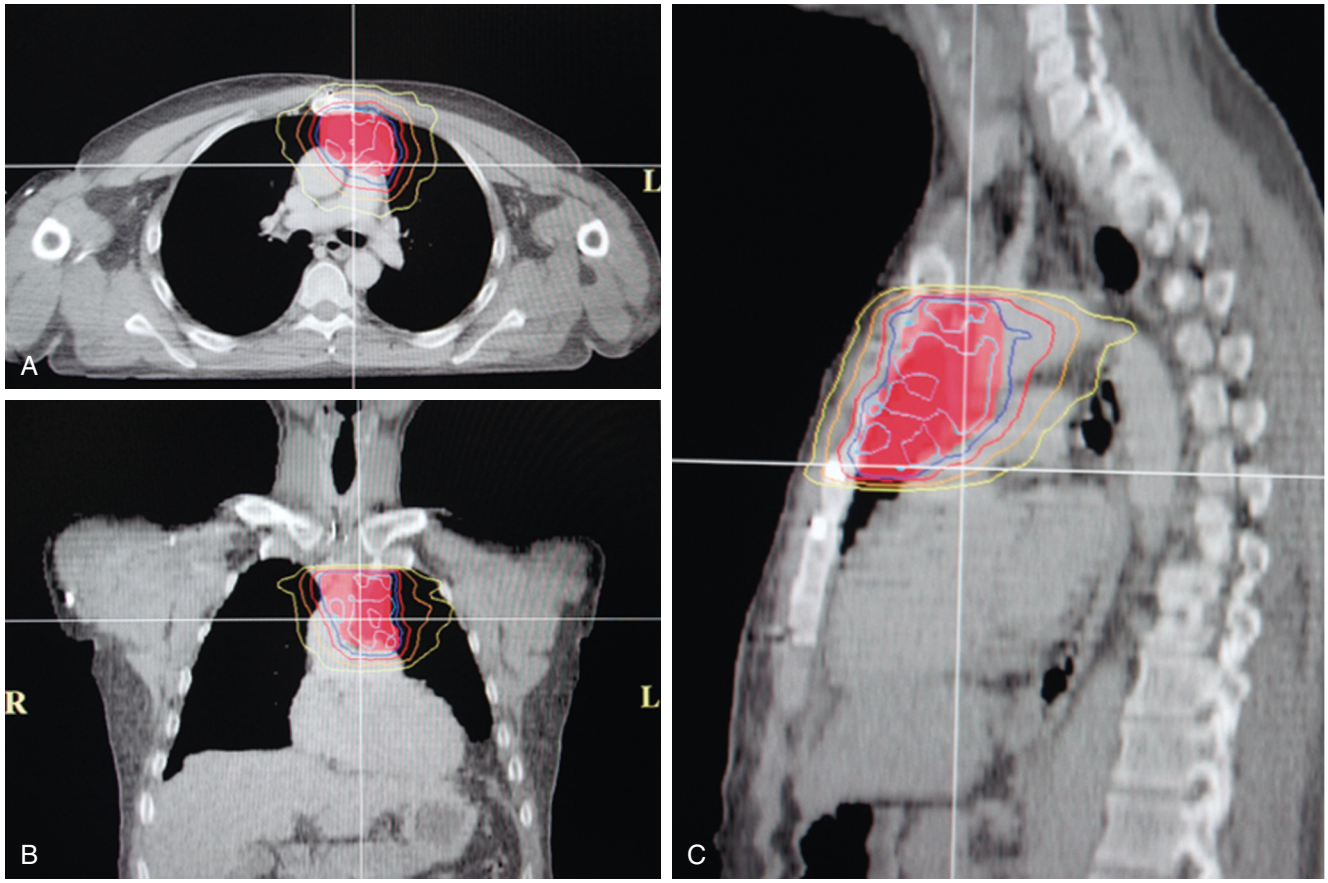


Figure 46-6 Axial **(A)**, coronal **(B)**, and sagittal **(C)** views for intensity-modulated radiation therapy (IMRT). Isodose lines are closely conformal to the shape of planned target volume *(red)*.

consolidation chemotherapy after a complete thymectomy (R0 resection, negative margins).

4. Pathologic stages III to IVA thymic neoplasms (WHO types A, AB, B1, B2, B3, C) are treated with multimodality adjuvant therapy (as outlined in guideline 3) even after a complete thymectomy (R0 resection, negative margins).
5. Clinically unresectable stages III to IVA thymic neoplasms are treated with neoadjuvant chemoradiation, followed by sequential thymectomy, postoperative thoracic irradiation, and consolidation chemotherapy.

PULMONARY CARCINOID TUMORS

Neuroendocrine lung tumors have a spectrum of clinical behaviors and include typical carcinoids (the most indolent type), atypical carcinoids, large cell neuroendocrine tumors, and small cell lung carcinomas (the most aggressive type).[286] The term *carcinoid* was originally defined as a carcinoma-like lesion without malignant characteristics by Oberndorfer in 1907.[287] Pulmonary carcinoids used to be known as bronchial adenomas because they were believed to be benign, but they are now recognized as malignant because of their potential to metastasize. Pulmonary or bronchial carcinoid tumors are typically low-grade malignant neoplasms that arise from neuroendocrine cells of the amine precursor uptake and decarboxylation (APUD) system that have migrated from the embryonic neural crest. These cells are the Kulchitsky (enterochromaffin) cells, which are located in the basal layer of bronchial epithelium.[288,289] Approximately 25% of carcinoids are located in the respiratory tract, which is the second-most common site after the gastrointestinal tract. Pulmonary carcinoids are frequently centrally located and confined to the main or lobar bronchi.[290] These tumors are rare, and their biologic behavior mostly depends on their histologic characteristics.

Etiology and Epidemiology

The cause of pulmonary carcinoid is unknown, and no environmental risk factors have been identified. Carcinogens that are associated with lung cancer have not been consistently associated with pulmonary carcinoids,[291] although a few studies revealed a higher frequency of smokers with atypical carcinoids.[292-294] Some of the neoplastic cells express mutant retinoblastoma *(RB1)* or mutant *TP53* gene products, and they show occasional loss of heterozygosity, especially in atypical carcinoids.[295] In atypical carcinoids, there is also a high frequency of molecular alterations and inactivation of tumor suppressor genes, such as the *TP53, RB1, CDKN2A* (previously designated *p16*), and *CDKN2D* (previously designated *p19*) genes. Most familial pulmonary carcinoids have been reported in patients with multiple endocrine neoplasia type 1 (MEN 1). In cases of atypical and typical lung carcinoids, there is a characteristic allelic loss within the region of 11q-13, which harbors the *MEN1* gene, a tumor suppressor gene.[296-300] Other frequently detected genetic alterations in lung carcinoids, especially atypical carcinoids, include losses of 3p, 5p, 9p, 10q, and 13q.[297,300] Ki-67 expression in more than 5% of nucleoli is a poor prognostic factor for survival.[301]

The annual incidence of carcinoid tumors is one or two cases per 100,000 people in the United States.[2,291] For

bronchopulmonary carcinoids, improved diagnostic tools have led to an increase in incidence from 0.6 to 1.35 per 100,000 people/year.[3,302] Carcinoid tumor of the lung represents about 3% of all lung malignant tumors, with an equal frequency in men and women,[3,291] approximately 3500 new cases were reported in 2004.[303,304] Bronchial carcinoids are the most common primary lung tumor in children, typically presenting in late adolescence. Typical carcinoids are about four times more common than atypical carcinoids. Data from the SEER program of the National Cancer Institute have shown a trend of relative increase of pulmonary carcinoids.[291,302]

Prevention and Early Detection

There is no known preventive measure for pulmonary carcinoids. Carcinoids are detected like other space-occupying tumors. The most common findings on a chest radiograph include a hilar mass with occasional atelectasis. Functioning carcinoids are suspected on the basis of the symptoms and signs, and the diagnosis is confirmed by demonstrating increased urinary excretion of the serotonin metabolite 5-hydroxyindoleacetic acid (5-HIAA). Thyroid transcription factor-1 is expressed in 80% of metastatic pulmonary carcinoids but not in intestinal carcinoids, and it may be of value in the workup and diagnosis of pulmonary carcinoids.[305,306]

Biologic Characteristics and Molecular Biology

Carcinoid tumors occur sporadically and are thought to arise from neuroendocrine cells. The WHO classification of lung neuroendocrine tumors describes two different subtypes of carcinoids, typical and atypical, with distinctive clinical behaviors and different prognoses.[304,307] Based on the criteria proposed by Travis,[286,307] the spectrum of neuroendocrine tumors also includes large cell neuroendocrine carcinoma and small cell lung carcinoma.

Although most pulmonary carcinoids are nonfunctional, some secrete a variety of physiologically active substances, leading to paraneoplastic syndromes, including carcinoid syndrome, Cushing's syndrome, and acromegaly.[288] Serotonin (5-hydroxytryptamine [5-HT]) is a frequently encountered vasoactive substance released by carcinoid tumors. Other substances, including corticotropin, histamine, dopamine, substance P, neurotensin, prostaglandins, and kallikrein, have been reported.[308-313]

The biologic behavior of these tumors varies depending on the histologic characteristics. Typical carcinoid tumors of the lung have a better prognosis than other primary lung cancers, with a 5-year survival rate greater than 90%. For atypical carcinoids, 5-year survival rates range from 25% to 75%.[314-319]

A population-based study of more than 1400 patients from Europe showed a 5-year OS rate of 78% for pulmonary carcinoids as a whole.[320] Although typical carcinoids have an indolent clinical course, atypical carcinoids behave more aggressively, with nodal involvement in 20% to 60% of cases and a higher rate of distant metastases. Figure 46-7 shows a right-sided hilar atypical carcinoid tumor with associated mediastinal adenopathy. The recurrence rates and stage at presentation are higher than for typical carcinoids. The proliferation rates, as assessed by MIB-1 and Ki-67, are also higher than for typical carcinoids.[304,321,322]

Pathology and Pathways of Spread

Carcinoids are thought to be derived from different embryonic divisions of the gut and are classified accordingly. Foregut carcinoids are often found in the lungs, bronchi, and stomach,

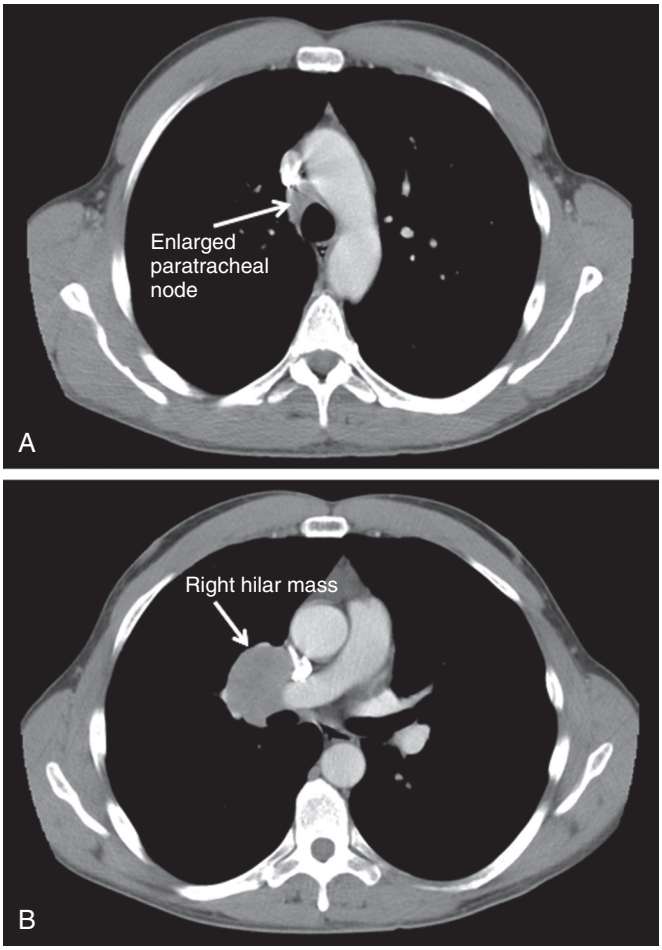


Figure 46-7 Atypical carcinoid. **A,** The preoperative CT scan shows a right hilar mass. **B,** There was also right paratracheal adenopathy. Lymph node involvement is seen more commonly in atypical carcinoid than typical carcinoid.

and midgut and hindgut tumors are seen in the small and large intestines. Histologically, they may stain positive with silver or Grimelius stains, cytokeratin 7 and 11, neuron-specific enolase, synaptophysin, carcinoembryonic antigen, and chromogranin; there is no marker exclusive to carcinoids, however.[305,321,323] Microscopically, they are characterized by small uniform cells and the presence of numerous membrane-bound, neurosecretory eosinophilic granules containing a variety of hormones and biogenic amines in the cytoplasm. Most pulmonary carcinoids (70% to 90%) are typical carcinoids or well-differentiated neuroendocrine tumors, which are characterized by small cells with well-rounded nuclei; atypical carcinoids (10% to 30%), or poorly differentiated neuroendocrine tumors, have malignant histologic features of increased nuclear atypia with high mitotic activity (more than two mitoses per 10 high-power fields), lymphovascular invasion, nuclear pleomorphism, and areas of necrosis.[307,323-326]

It is sometimes difficult to establish the specific diagnosis of carcinoid because of small biopsy samples or to differentiate atypical carcinoid from small cell lung carcinoma without immunohistochemical tests.[307,327-329] Well-differentiated carcinoids are often indolent, with a relatively low risk of nodal or distant metastasis of 3% to 15%.[303,326,330-332] Atypical carcinoid may have an aggressive clinical course, with frequent organ metastases.[295,333,334] The risk of nodal metastasis, frequently to mediastinal lymph nodes, is 30% to 57%.[303,335,336] Distant

metastases occur in more than 20% of patients.[303] The most common sites of distant metastasis include liver, bone, adrenal glands, brain, skin, and soft tissue.[304,317,337-339]

Clinical Manifestations, Patient Evaluation, and Staging

Median age at diagnosis for pulmonary carcinoid tumors is around 64 years.[3] Carcinoids in children are rare.[340] Between 70% and 80% of these tumors are located centrally near the hilum within the tracheobronchial tree and may produce a variety of clinical symptoms and neuroendocrine manifestations.[341,342] About 25% of patients present with symptoms such as recurrent pneumonia, cough, hemoptysis, or chest pain. Carcinoids are vascular tumors and can bleed secondary to bronchial irritation. Hyperparathyroidism may be seen. At least 50% of pulmonary atypical carcinoid tumors present in the periphery of the lung.[343] Patients with peripheral lesions may be asymptomatic, and their lesions are usually discovered incidentally.[319,344]

Carcinoids may produce various amines and polypeptides with corresponding signs and symptoms, often precipitated by emotional upset, food ingestion, or alcohol. The serotonin metabolite 5-HIAA, which is excreted in urine, acts on smooth muscle to produce bronchoconstriction or diarrhea, colic, and malabsorption. Histamine and bradykinin, through their vasodilator effects, cause flushing. The release of such vasoactive substances into the systemic circulation can cause the *carcinoid syndrome*, characterized by episodic flushing, typically of the head and neck; asthmatic wheezing; abdominal cramps with recurrent diarrhea resulting in malabsorption syndrome; and valvular heart disease, including right-sided endocardial fibrosis, leading to pulmonary stenosis and tricuspid regurgitation.[345] Bronchial carcinoids generally have low serotonin content because the tumor cells lack the aromatic amino acid decarboxylase enzyme and cannot make serotonin and its metabolites. Hence, the secretion of 5-hydroxytryptamine (5-HTP) is increased and 5-HIAA urinary excretion is normal. Lesions of the left side of the heart, which have been reported with bronchial carcinoids, are rare because serotonin is destroyed during passage through the lung. Some patients complain of decreased libido and impotence. However, the incidence of carcinoid syndrome or other paraneoplastic syndromes, including Cushing's syndrome and acromegaly, is no more than 3% to 5% of cases, and these syndromes mainly occur in patients with larger tumors (>5 cm) or metastatic disease.[346] Paraneoplastic syndromes in the absence of lymph node or distant metastases do not affect the prognosis.[344,347] Levels of human chorionic gonadotropin and pancreatic polypeptide are occasionally elevated.

Patients with a suspected lung mass require a thorough history and physical examination. Routine blood tests and chemistry tests may give clues to the presence of associated syndromes (Table 46-5). The differential diagnosis, in addition to bronchopulmonary carcinoid, includes lung carcinoma and metastasis from an extra-pulmonary primary tumor. CT and bronchoscopy are two of the most valuable diagnostic procedures. Up to 80% of carcinoids manifest with type 2 somatostatin receptors, and the receptors can be targeted by radioactive octreotide or pentetreotide. Somatostatin receptor scintigraphy with indium-111–radiolabeled octreotide (^{111}In-octreotide) has demonstrated reliable uptake in primary tumors and been used to detect early recurrence.[348-350] FDG-PET scans are often normal.[9,10,292,351]

Transbronchial biopsy or CT- or ultrasound-guided fine-needle aspiration biopsy may establish the diagnosis. Bronchoscopy, video-assisted thoracoscopic surgery, or mediastinoscopy may help yield a diagnosis before resection, especially if enlarged lymph nodes are present. Three-quarters of bronchopulmonary carcinoids are centrally located and are amenable to a bronchoscopic biopsy.

The prognostic factors are atypical histologic findings, staging, and the presence of symptoms at the time of presentation.[340-342,348,351] A high mitotic rate, tumor size larger than 3.5 cm, and female gender have also been implicated as prognostic factors for patients with atypical pulmonary carcinoids.[293] There is no specific staging system for pulmonary carcinoids, but the AJCC lung cancer staging system (TNM) is commonly used. In an analysis of 513 carcinoid tumors from the International Association for the Study of Lung Cancer (IASLC) and 1619 cases from the SEER database, TNM staging was found to correlate with survival.[353]

Treatment

Primary Therapy

Curative resection is the treatment of choice.[304,338,339,354,355] After complete resection, the long-term results are generally excellent.[303,338,341,354] Conservative surgical resection, consisting of wedge or segmental resection, is the preferred therapy for localized pulmonary carcinoids.[356,357] Patients with central lesions may require bronchial sleeve resection or sleeve lobectomy.[355] Endoscopic laser ablation is not considered curative but may be used to alleviate tumor obstruction, improve atelectasis, and reduce inflammation before resection.[331] Intraoperative nodal evaluation should be performed, and if the

TABLE 46-5 Presenting Symptoms in Patients with Pulmonary Carcinoids

Symptoms	Schrevens et al[341] (*n* = 67)	Kaplan et al[333] (*n* = 144/62)*	Fink et al[303] (*n* = 142)	Machuca et al[352] (*n* = 126)
Cough	—	39%/45%	35%	24%
Dyspnea, wheezes	—	17%/25%	41%†	—
Chest pain	7%	9%/18%	—	12%
Infection, fever	42%	—	—	30%
Weight loss	—	11%/20%	15%‡	—
Hemoptysis	21%	16%/12%	23%	—
Paraneoplastic syndromes	0%	1%/3%	<1%	—
Asymptomatic	24%	—	30%	20%

**Typical/atypical groups.*
†Bronchial obstruction, including dyspnea, pain, and pneumonitis.
‡Others include weight loss, weakness, nausea, and neuralgia.

results are positive, complete nodal dissection is indicated. Because of higher rates of local recurrence in patients with atypical carcinoids, a more extensive surgical procedure, such as lobectomy or pneumonectomy with nodal dissection, should be considered.[304,338,339,356] Patients may present with metastatic or unresectable disease, however, and curative resection may not be obtainable. Debulking and other cytoreduction procedures may be of benefit in gastrointestinal carcinoids,[358,359] but these procedures are of uncertain benefit for patients with pulmonary carcinoids.

Medical Treatment

Certain symptoms, including flushing, can be relieved by pharmacologic agents. Ondansetron, one of the specific 5-hydroxytryptamine-3 (5-HT3) antagonists, provides sustained symptomatic relief in patients with carcinoid syndrome.[360] Somatostatin analogs are potent inhibitors of neuropeptide release and gut exocrine or endocrine function. These analogs are effective in relieving symptoms by binding to somatostatin receptors (mainly, receptor 2),[361] which are present in approximately 80% of carcinoids, leading to inhibition of hormone secretion.[362,363] Octreotide and lanreotide, long-acting analogs of somatostatin, are the drugs of choice. The response rate is about 70% for symptomatic improvement, and there is a more than 50% reduction in urinary 5-HIAA secretion, with a median duration of response of 12 months. Data suggest that these somatostatin analogs may have a direct antitumoral effect, with stabilization of tumor growth and reduction of tumor size in patients with carcinoids of various sites.[361,362]

More recently, peptide receptor radionuclide therapy with radiolabelled somatostatin analogues have shown promise in clinical trials. 90Y-DOTATOC (90Y-edotreotide) has an yttrium-90 (90Y) atom with high binding affinity for somatostatin receptors.[364] Two trials with 39 and 90 patients with progressive/metastatic neuroendocrine tumors have shown symptom improvement in 63% to 74% of patients, although it is unclear what the response rate would be in pure bronchial carcinoid.[365,366] 177Lu-DOTATATE (177Luoctreotate) can be given therapeutically but also can be used for imaging and dosimetry after therapy.

Radiation Therapy

There are no prospective trials that address the use of adjuvant therapy for patients with bronchopulmonary carcinoids. In general, typical carcinoids do not require adjuvant radiation therapy or chemotherapy after curative resection.[303,338,341,354,367] A series of 25 patients (12 typical and 13 atypical tumors) with node-positive bronchial carcinoids treated at the Memorial Sloan Kettering Cancer Center (MSKCC) found no survival benefit from postoperative radiation therapy.[290] Recurrence and survival rates appeared to depend on cell type rather than nodal status. In another study of 163 patients (including three fourths of patients with typical carcinoids, most of which were stage N0), however, the prognosis depended on the presence and extent of nodal involvement rather than histologic subtype.[318] The role of adjuvant radiation therapy is unsettled because of the retrospective nature of studies and the small number of patients.[293,333,368] However, adjuvant radiation therapy has been used in patients at high risk for locoregional recurrence, including those with large tumor size (>3 cm), positive nodes, positive margins, atypical histologic findings, residual disease, and inoperable disease.[326,333,368,369]

Palliative radiation therapy can be considered in patients with metastatic typical or atypical pulmonary carcinoids. Tumor-targeted irradiation with radioactive somatostatin analogs (^{111}In-octreotide or ^{131}I-metaiodobenzylguanidine [^{131}I-MIBG]) has been used, often as second- or third-line therapy.[369-371] The results are inconclusive, with occasional long-term survivors reported.

Chemotherapy

Unlike chemotherapy for small cell lung cancer, systemic chemotherapy has produced only limited success in patients with metastatic carcinoid tumors.[369] Although no effective chemotherapeutic regimen has been established, aggressive treatment with adjuvant systemic chemotherapy is recommended in high-risk patients with stage III atypical or metastatic carcinoid.[335] Several trials have shown response rates of 21% to 33% with various combinations of doxorubicin, streptozocin, cyclophosphamide, etoposide, and fluorouracil in patients with metastatic carcinoids.[335,372-375] Patients with atypical carcinoids treated with cisplatin and etoposide appear to have a higher response rate than patients treated with other regimens.

Targeted Agents

mTOR mutations occur in about 15% of pancreatic neuroendocrine tumors.[376] Everolimus, an oral mTOR inhibitor, is approved for use in advanced pancreas neuroendocrine tumors.[377] Everolimus plus octreotide was tested for advanced carcinoid tumors, and appeared to improve progression-free survival (PFS). Neuroendocrine tumors exhibit angiogenesis and increased vascularity.[378] Bevacizumab and sunitinib have been tested in advanced neuroendocrine tumors, with bevacizumab exhibiting a more favorable toxicity profile.[379-382] Although Phase II data has been encouraging, Phase III data are pending.[379,383]

Locally Advanced Disease and Palliation

For patients with locally advanced or metastatic disease, surgery is generally limited to those whose metastases are confined to one site amenable to local resection.[359,384] Radiation therapy has been used successfully to palliate symptoms in patients with locally advanced or metastatic disease.[385] Local control and symptomatic relief can be achieved in most patients with 4000 cGy to 5000 cGy. Endoscopic resection and laser photoablation have been used for palliation of symptoms.[331] Somatostatin analogs alone or in combination with chemotherapy or interferon-alpha may be considered for symptomatic treatment or tumor stabilization.[386]

Results of Therapy

Patients with typical carcinoid tumors treated with surgery alone have a good outcome. However, patients with atypical pulmonary carcinoid tumors and regional lymph node metastases are at high risk for recurrent disease and have worse survival rates when they are treated with surgical resection alone.[334] The 5-year OS rate ranges from 78% to 100% for all resected pulmonary carcinoids, 90% to 100% for typical carcinoids, 25% to 69% for atypical carcinoids, and 18% to 38% for metastatic carcinoids.[330-332,334,336,339] Ten-year rates are 10% to 20% lower than 5-year rates. Some of the published results are summarized in Table 46-6. Although the role of adjuvant radiation therapy as part of multimodality treatment is undefined, adjuvant irradiation may improve the outcome of high-risk patients with atypical carcinoid tumors, positive nodes, or positive margins.[337] The National Comprehensive Cancer Network (NCCN) recommends adjuvant therapy for stages II and III atypical carcinoids.[387]

Irradiation Techniques

The same general principles of thoracic irradiation apply to irradiation of pulmonary carcinoids. High-energy (>10-MV) x-rays are preferred with a CT scan for treatment planning. As in treating other tumors, surgical clips denoting the extent of

TABLE 46-6 Treatment Results for Pulmonary Carcinoids

Study	Year	No. Patients	Treatment	Radiation Dose	Local Control Rate (%)	Survival Time/Rate	Comments
Wirth et al[388]	2004	8 typical 10 atypical (advanced or metastatic)	4 Ch + RT 14 Ch (no surgery)	46 Gy-54 Gy	22% (OS)	20 mo MS	4 of 18 responded to Ch ± RT without surgery (inoperable patients).
Beasley et al[293]	2000	106 atypical	Surgery ± RT/Ch	Various (not stated)	—	61% OS at 5 years 35% OS at 10 years 28% OS at 15 years	Higher mitotic rate, size ≥3.5 cm, female gender, presence of rosettes are independent variables (multivariate analysis) for worse survival rates.
Choi et al[337]	2004	19 atypical	15 surgery 3 surgery + RT/Ch 1 Ch + RT	54 Gy	89%	79% OS at 3 years 41 mo MS 74% DSS at 3 years	Adjuvant RT may improve rates in those with positive margins or positive nodes.
Kaplan et al[333]	2003	144 typical 62 atypical	129 surgery 12 surgery + RT/Ch 2 Ch + RT 35 surgery 19 surgery + RT/Ch 9 Ch + RT	Various (not stated)	92% at 5 years (surgery, stage I) 77% at 5 years (surgery, stage I)	79% DSS at 5 years 63% DSS at 10 years 39% DSS at 20 years 60% DSS at 5 years 37% DSS at 10 years 28% DSS at 20 years	Poor prognostic factors: male gender, high stage, symptoms at presentation, and age ≥60 years; 56 of 206 had second malignant tumors; atypical carcinoids had worse outcome.
Han et al[389]	2013	12 atypical	6 surgery 2 surgery + RT 3 surgery + Ch 1 surgery + RT/Ch	Various (not stated)	92%	37 mo MS	Although only 1 patient developed a local recurrence, 5 of 12 patients developed distant metastasis.
Carretta et al[368]	2000	36 typical 3 atypical 5 LCNEC	Surgery ± RT/Ch	45 Gy-58 Gy	—	93% AS at 5 years 70% AS at 5 years	Patients with nodal metastases had worse outcome.
Schrevens et al[341]	2004	59 typical 8 atypical	All surgery	—	—	92% at 5 years 67% at 5 years (92% OS at 5 years, 84% OS at 10 years)	Independent prognostic factors were nodal status and pathologic type; size of primary tumor did not correlate with nodal metastasis.
Fink et al[303]	2001	128 typical 14 atypical	All surgery (four inoperable or refusal)	—	—	89% at 5 years 82% at 10 years 75% at 5 years 56% at 10 years	Long-term results are excellent with typical carcinoids.
Ferguson et al[390]	2000	109 typical 26 atypical	All surgery	—	—	90% at 5 years 70% at 5 years	Early-stage tumors did well regardless of histologic type.
Zhong et al[391]	2012	106 typical 25 atypical	All surgery	—	—	96% at 3 years 87% at 5 years 71% at 10 years	Nodal status and histology were independent prognostic factors on multivariate analysis.
Machuca et al[352]	2010	— 88 typical	All surgery All surgery	— —	— —	91% at 5 years for typical, 56% at 5 years for atypical 92% OS at 5 years 90% OS at 10 years	 Early-stage (I) disease did well.
Mezzetti et al[392]	2003	10 atypical	—	—	—	71% OS at 5 years 60% OS at 10 years	

AS, *Actuarial survival rate;* Ch, *chemotherapy;* DSS, *disease-specific survival rate;* LCNEC, *large cell neuroendocrine carcinoma;* MS, *median survival rate;* OS, *overall survival rate;* RT, *radiation therapy.*

resection or outlining regions of residual disease are useful in guiding postoperative irradiation. The PTV should include the gross or residual tumor volume and tumor bed with a 1.5-cm to 2-cm margin. Depending on the histologic and surgical findings, areas of suspicious subclinical disease and regional lymphatics are included. Treatment field arrangements may resemble the typical lung tumor fields. There are no consistent guidelines regarding dose and fractionation regimens. Postoperative doses of 45 to 58 Gy delivered in 1.8 Gy to 2 Gy per day have been reported (see Table 46-6). For patients with gross residual or unresectable disease, a higher total dose may be justified as long as the dose to other critical structures does not exceed the tolerance of normal tissues.

Treatment Algorithm and Controversies

Surgery is the primary treatment for typical and atypical pulmonary carcinoids. Although conservative resection has resulted in low recurrence rates and excellent long-term survival rates for patients with well-differentiated pulmonary carcinoids, the adequacy of such resection in patients with atypical carcinoids has not been settled. More extensive surgical procedures, with higher treatment-related morbidity rates, have been advocated by some investigators.[335,393] Adjuvant radiation therapy or systemic chemotherapy may be considered even for patients with early-stage disease because of the high incidence of regional and distant failure.[333] Palliative irradiation should be considered for those with symptomatic disease.

MESOTHELIOMA

MPM is an aggressive malignant disease, and local disease progression is the main cause of symptoms and death. Disseminated disease is usually reported only very late in the course of MPM.[394-398] MPM spreads by direct extension and seeding throughout the pleural space, including fissures, diaphragmatic and pericardial surfaces, through the chest wall, and into the mediastinum, peritoneum, and lymph nodes. The major problem for patients with MPM is poor local disease control in the thorax. Aggressive surgery alone, even in carefully selected patients with early-stage disease, has not improved the 2-year survival rate of 10% to 33%.[396,397,399] Combined-modality treatment suggests improved local control and survival rates,[399-401] but local recurrence is still the most common site of first relapse.[402]

Even after EPP, the diffuse nature of most malignant mesotheliomas and the manipulation of the exposed tumor during surgery put the entire ipsilateral chest cavity, diaphragm insertion, pericardium, mediastinum, and bronchial stump at high risk for local recurrence. The hemithorax and mediastinum have an irregular shape and are adjacent to critical structures, such as the spinal cord, liver, kidneys, esophagus, heart, and contralateral lung. Conventional irradiation of the hemithorax and mediastinum is limited by the ability of these organs to tolerate radiation[397,402,403] and by the total volume of tissue being irradiated.

Etiology and Epidemiology

MPM has an incidence of approximately 10 cases per million people per year in the United States.[404] The incidence has been increasing and represents a significant clinical problem in populations exposed to asbestos. The Center for Lung Cancer and Related Disorders estimates approximately 3000 new cases of MPM per year, with a peak incidence of approximately 4000 per year expected to occur in about 2025. The incidence is rising as a result of the long latency between asbestos exposure and clinically apparent disease; most cases occur more than 20 years after exposure. The median age at diagnosis is approximately 60 years.

Approximately 90% of mesothelioma cases can be attributed to prior asbestos exposure. This is typically an occupational exposure (e.g., construction work, automotive brake repair, boiler work, shipbuilding), and it explains the approximately 90% male predominance. However, other sources of exposure may include a spouse or parent asbestos worker. Even a history of living near asbestos-using businesses, such as automotive shops (from brake linings) or cement manufacturers (which may have added asbestos), can increase the risk of mesothelioma. Patients from certain regions of the world (e.g., central Turkey, Western Australia) also have endogenous environmental asbestos exposure. There is no direct association between mesothelioma and smoking, but smoking greatly increases the risk when there is also asbestos exposure.[405] Radiation exposure has been shown to be causatively linked to mesothelioma, with an increased incidence identified in adults with previous thoracic radiation treatment.

Clinical Evaluation and Staging

Dyspnea, chest pain, cough, and weight loss are common presenting symptoms of MPM. All patients should be asked about their history of asbestos exposure. Pulmonary function tests demonstrate a restrictive pattern resulting from "trapping" of the lung or chest wall involvement. MPM has a tendency to grow along tracks of previous chest tubes. All sites of previous instrumentation should be identified and examined for evidence of tumor seeding. Such chest wall progression may manifest as pain, a nodule, or an ulcer. Particularly when transthoracic extension is identified, the axillary and supraclavicular lymph nodes should be palpated for involvement. Sometimes, scoliosis can occur because of ipsilateral lung volume loss.

Imaging

A chest radiograph should be used for initial evaluation. Careful attention should be paid to the presence of pleural effusions or calcified pleural plaques. Nodular irregularities often can be identified. Sites of rib tenderness should be evaluated for direct tumor extension, although chest pain is more often attributable to involvement of the endothoracic fascia.

Contrast-enhanced CT of the chest is the mainstay of radiographic staging. Circumferential pleural thickening, an irregular pleural contour, or contraction of the ipsilateral hemithorax are common findings. Invasions of the diaphragm or chest wall are difficult to detect in early cases, so CT may underestimate the extent of disease. Miliary disease can be present on the undersurface of the diaphragm or peritoneum and remain undetected by imaging. MPM tends to manifest late in the disease course, often with large masses and pleural effusions. Pleura-based irregular masses are common, particularly in dependent regions. The interlobar fissures are often involved. MPM can invade adjacent structures, such as the chest wall, mediastinum, great vessels, vertebral body, or heart. Mediastinal and hilar lymph nodes can be involved with tumor, but the pattern of spread is often different from that of non–small cell lung cancers. MPM spreads to the lower paraesophageal nodes (level 8), pulmonary ligament nodes (level 9), and diaphragmatic nodes much more commonly than lung cancers. Pericardial effusions and ascites can also be seen on CT, and they should be evaluated pathologically before any attempt at curative resection. The anteromedial extent of tumor, particularly extension across the midline, should be determined before surgery. Because surgery obliterates the costomediastinal space, the anterior pleural reflection cannot be accurately delineated on postoperative studies.

The utility of MRI in the staging of mesothelioma is controversial. MRI may slightly more accurately predict the extent of invasion into the chest wall, diaphragm, and great vessels. The finding of chest wall invasion should not preclude surgery, however, as long as the region of invasion can be removed with a limited chest wall resection. Invasion to the peritoneal surface of the diaphragm cannot always be appreciated without invasive staging. FDG PET/CT scanning has been applied to mesotheliomas because they tend to avidly take up FDG. Sensitivity and specificity of 90% or more has been reported and is helpful in distinguishing between benign pleural thickening and MPM.[406-408] Furthermore, PET/CT, when compared with CT, in a series of 35 patients, upstaged tumors and therefore prevented unnecessary surgery in 40% of patients.[409]

Invasive Staging

The diagnosis of mesothelioma can be difficult because of the relative rarity of the disease and the cytologic similarity to more common metastatic neoplasms, such as adenocarcinoma. Thoracentesis is often the first procedure performed to obtain diagnosis, but it has a diagnostic sensitivity of only 32%.[410] Percutaneous fine-needle aspiration biopsy similarly has low diagnostic sensitivity, although ultrasound-guided core-needle biopsy has been reported to improve accuracy.[411] Before beginning multimodality treatment, accurate preoperative staging is necessary. Historically, an open pleural biopsy has been the gold standard.[412] More recent data has shown that thoracoscopic biopsy should be the preferred method for obtaining tissue for diagnosis.[413-415] Diagnostic thoracentesis is an alternative, though it has a lower yield than video-assisted thoracoscopic surgery.[416]

Mesothelioma has a tendency to track along sites of chest wall violation, and tumor may recur at previously placed thoracoscopy port sites if they are not excised at the time of definitive surgery. Limiting the number of port sites at the time of video-assisted thoracoscopic surgery and placing the port sites where they are easily excised help to reduce local chest wall recurrence. When it is difficult to establish entrance into the pleural space, it is preferable to perform a limited open biopsy of the parietal pleura by extending the port site incision slightly, rather than to perform a formal thoracotomy. A thoracotomy performed for diagnosis significantly compromises potentially curative surgery.

Unfortunately, preoperative assessment of mesothelioma tumor stage is less than ideal. Although CT, PET, and MRI are reasonably accurate in defining tumor volume within the thorax and chest wall and in identifying sites of distant disease, they are less successful in determining tumor involvement at two critical sites: contralateral mediastinal nodal involvement and tumor invasion through the diaphragm. Tumor involvement at either site negates resection, and therefore an accurate assessment of these areas is necessary before performing EPP. Some experienced clinicians obtain pretreatment laparoscopy with peritoneal lavage and cervical mediastinoscopy in all patients considered for resection. At the M. D. Anderson Cancer Center, of 118 patients with MPM who were clinically and radiographically determined to have resectable disease, laparoscopy and peritoneal lavage revealed transdiaphragmatic or peritoneal involvement in 12 (11%) of 109 patients and mediastinoscopy identified positive contralateral nodes in 4 (4%) of 111 patients. Overall, 15 (13%) patients were identified with occult advanced disease and spared unnecessary EPP.

Staging

The AJCC seventh edition staging system for mesothelioma is shown in Table 46-7 and is based on the International Mesothelioma Interest Group (IMIG) staging system. The staging systems are useful only after surgical staging, and no clinical staging system has been developed.

Several important prognostic markers have been identified for MPM. Metastases to any nodal station predict a worse outcome. However, unlike non–small cell lung cancer, it is not clear that mediastinal metastases reflect a worse prognosis than hilar or intrapulmonary nodal metastases. The completeness of resection is also prognostic. Patients with R1 or R2 resections have been reported to have a worse outcome in some series.[417]

Another poor prognostic marker is nonepithelioid histologic findings. Epithelioid histologic characteristics are found in 50% of cases. Pure epithelioid mesothelioma may be difficult to distinguish from metastatic adenocarcinoma of the lung, so immunohistochemistry or electron microscopy is essential.[418] Patients with sarcomatoid (10% of patients), mixed (30% of patients), and desmoplastic tumors fare much worse than patients with epithelioid histologic types.[226,419,420] Thrombocytosis and high levels of platelet-derived growth factor may also predict a worse outcome. Several reports suggest that serum levels of mesothelin are elevated in most patients at diagnosis and that they fall after surgery. Serum mesothelin may be a marker for tumor recurrence.[421] Good prognostic factors include young age, early-stage disease, performance status of 0 to 1, lack of chest pain, and presence of symptoms for longer than 6 months.[420]

Treatment

Surgery

Pleurectomy

Pleurectomy for treatment of MPM has been advocated by many surgeons even though cytoreduction is not as complete as that achieved with EPP. Pleurectomy is effective in allowing expansion of the trapped lung and reduces the likelihood of recurrent pleural effusion. A large retrospective study of 663 patients actually showed improved OS rates with pleurectomy as compared with EPP. Patients treated with pleurectomy and decortication had a higher rate of local recurrence of disease, whereas patients undergoing EPP had greater surgical morbidity and mortality rates.[422] The ability to administer postoperative external beam radiation therapy may be compromised after pleurectomy, leading some centers to explore the addition of photodynamic therapy (PDT).

Extrapleural Pneumonectomy

Many centers of expertise consider EPP to be the operation of choice for mesothelioma because it achieves the greatest[423] degree of cytoreduction and may allow for safer delivery of adjuvant therapy compared with pleurectomy. A review of 34 studies of EPP for patients with MPM found a perioperative mortality rate of nil to 11.8% and a median OS time of 9.4 months to 27.5 months. Without adjunctive therapy, EPP has been associated with recurrence rates as high as 80%. Studies including EPP as part of multimodality therapy have reported local recurrence rates of between 40% and 50%, with local recurrence as low as 13% (7 of 55 patients) in one study using 54-Gy hemithoracic irradiation after EPP.[424]

EPP is an extensive surgical procedure, removing the ipsilateral lung along with the parietal pleura, pericardium, and most of the hemidiaphragm, so patients require careful assessment preoperatively to exclude the presence of locally advanced or distant disease (which would preclude resection) and meticulous cardiopulmonary screening to ensure that the operation can be tolerated physiologically. Surgical staging of the mediastinum and abdomen (with washings) should be

TABLE 46-7 TNM Staging of Mesothelioma

PRIMARY TUMOR (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor limited to the ipsilateral parietal pleura, with or without mediastinal pleura and with or without diaphragmatic pleural involvement
T1a	No involvement of the visceral pleura
T1b	Tumor also involving the visceral pleura
T2	Tumor involves each of the ipsilateral pleural surfaces (parietal, mediastinal, diaphragmatic, and visceral pleura) with at least one of the following: 1. involvement of diaphragmatic muscle 2. extension of tumor from visceral pleura into underlying pulmonary parenchyma
T3	Locally advanced but potentially resectable tumor. Tumor involving all of the ipsilateral pleural surfaces (parietal, mediastinal, diaphragmatic, and visceral pleura) with at least one of the following: 1. Invasion of the endothoracic fascia 2. Invasion into mediastinal fat 3. Solitary completely resectable focus of tumor invading the soft tissues of the chest wall 4. Nontransmural involvement of the pericardium
T4	Locally advanced, technically unresectable tumor. Tumor involving all of the ipsilateral pleural surfaces (parietal, mediastinal, diaphragmatic, and visceral pleura) with at least one of the following: 1. Diffuse extension or multifocal masses of tumor in the chest wall, with or without associated rib destruction 2. Direct transdiaphragmatic extension to the peritoneum 3. Direct extension to mediastinal organs 4. Direct extension to the contralateral pleura 5. Direct extension into the spine 6. Extension to the internal surface of the pericardium with or without a pericardial effusion or tumor involving the myocardium
REGIONAL LYMPH NODES (N)	
NX	Regional nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastases in the ipsilateral bronchopulmonary or hilar lymph node(s)
N2	Metastases in the subcarinal or ipsilateral mediastinal lymph nodes (including ipsilateral internal mammary and peridiaphragmatic nodes)
N3	Metastases in the contralateral mediastinal, internal mammary, or hilar lymph node(s) or the ipsilateral or contralateral supraclavicular or scalene lymph node(s)
DISTANT METASTASIS (M)	
MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis
STAGE GROUPINGS	
I	T1N0M0
IA	T1aN0M0
IB	T1bN0M0
II	T2N0M0
III	T1-2N1M0 T1-2N2M0 T3N0-2M0
IV	T4 Any NM0 Any TN3M0 Any T Any NM1
RESIDUAL TUMOR (R)	
RX	Presence of residual tumor cannot be assessed
R0	No residual tumor
R1	Microscopic residual tumor
R2	Macroscopic residual tumor

From Edge SB, Byrd D, Compton CC, et al, editors, for the American Joint Committee on Cancer: AJCC cancer staging manual, ed 7, New York, 2010, Springer.

performed when assessing patients for EPP. In general, patients should have adequate cardiac function (i.e., ejection fraction >40% and no reversible ischemia on radionuclide imaging) and have an estimated postoperative forced expiratory volume in 1 second (FEV_1) value of greater than 0.8 L/min, or 30% of predicted. The ideal patient is young, with epithelial histologic typing and a good performance status and without lymph node involvement. Even in centers with extensive experience with carefully selected patients, EPP has a high rate of complications.[425] Because of the extremely poor prognosis of the sarcomatoid subtype, EPP may be less of a consideration for this histologic group.[426]

A recent multicenter randomized trial in the United Kingdom compared EPP plus adjuvant radiation to radiotherapy without EPP, in patients with mesothelioma that had no evidence of disease progression following three cycles of platinum-based chemotherapy.[11] Out of 50 patients randomized, 24 were assigned to EPP, and 16 of 24 patients satisfactorily completed EPP. The hazard ratio for OS between EPP and no EPP was 1.9 (p = 0.082). Median survival was 14.4 months in the EPP group and 19.5 months in the no EPP group. Quality of life appeared similar between the two groups. Authors concluded that EPP appears to offer no benefit and may possibly harm patients. On the other hand, a large retrospective experience including 540 patients from Australia showed EPP to be associated with improved survival on multivariate analysis.[427]

Chemotherapy

Reviews describe modest success with several chemotherapeutic agents in MPM.[428,429] Reported response rates of more than 25% have been obtained with methotrexate (37%),[430] gemcitabine plus cisplatin (48%),[431] pemetrexed plus carboplatin (25%),[432] pemetrexed plus cisplatin (38%),[433] mitomycin plus cisplatin (26%),[434] raltitrexed plus oxaliplatin (26%),[435] and doxorubicin plus cisplatin (28%).[436] The British Thoracic Society performed a randomized trial to assess the role of chemotherapy in palliation.[437] Patients were randomized to active symptom control or one of two chemotherapy regimens (i.e., mitomycin C, vinblastine, and cisplatin or vinorelbine alone). They found that active symptom control with chemotherapy provided better palliation of chest pain and shortness of breath than active symptom control alone.

The combination of cisplatin plus the antifolate pemetrexed has a well defined role in patients with advanced mesothelioma[438]; 456 patients were randomized to cisplatin alone versus

cisplatin and pemetrexed. The median survival time was 12.1 months for the pemetrexed plus cisplatin arm and 9.3 months for the cisplatin alone arm ($p = 0.020$). Toxicity was dramatically reduced by the addition of vitamin supplementation, but this did not influence the effectiveness of therapy. Time to progression was improved from 3.9 months to 5.7 months by the addition of pemetrexed ($p = 0.001$). The response rate was 17% for cisplatin alone compared with 41% for combined treatment.

Combination cisplatin and pemetrexed has also been studied as part of multimodality therapy in localized disease. Krug et al reported the results of a multicenter Phase II trial of neoadjuvant pemetrexed plus cisplatin followed by EPP and irradiation for MPM, with a promising median survival time of 29.1 months and a 2-year survival rate of 61.2%.[439] For patients who cannot tolerate cisplatin, carboplatin plus pemetrexed is moderately active and has an acceptable toxicity profile.[432,440,441] Pemetrexed-based chemotherapy is currently incorporated as part of the treatment regimen, either before or after surgery, for patients treated with EPP.[427] An alternative approach of hyperthermic intraoperative cisplatin has been used following EPP, with an MPM recurrence rate of 51% and an ipsilateral recurrence rate of 17%.[442]

Rationale for Irradiation

Although technical challenges remain, several lines of evidence suggest that radiation therapy can be effective in treating mesothelioma. First, mesothelioma cell lines are not particularly radioresistant in vitro, and they have radiosensitivities similar to those of non–small cell lung cancer.[443,444] Second, some evidence suggests a dose-response relationship for symptom palliation, such that doses greater than 40 Gy seem more effective than lower doses.[395,445] This dose-response relationship suggests that clinically significant cell killing results from modest radiation doses. Third, modest radiation doses can dramatically reduce the local failure rate at thoracotomy or other instrumentation sites. Thus, postoperative irradiation may be effective in reducing locoregional recurrence and potentially improve survival rates.

Curative Radiation Therapy

Radiation Therapy Alone

Irradiation alone is not considered curative given the extent and distribution of disease and the proximity of the pleural surface to many dose limiting structures. Radiation therapy without surgery is best considered a palliative treatment.

Radiation Therapy Combined with Surgery

Several groups have reported promising outcomes for MPM patients treated with surgery and irradiation, with or without chemotherapy.

Radiation Therapy after Pleurectomy or Decortication

A study performed between 1982 and 1988 at Helsinki reported high rates of pulmonary toxicity and pulmonary function deterioration in 34 patients (29 after partial pleurectomy) treated with high doses of adjuvant hemithorax radiotherapy (55 Gy to 70 Gy).[446,447] A larger experience from MSKCC[448] included 123 patients treated with pleurectomy or decortication from 1974 to 2003 with adjuvant external beam RT[449]; 54 patients also received an intraoperatively placed ^{125}I or ^{192}Ir boost to gross disease, and a subset of patients received ^{32}P. Photon and electron fields were combined to treat the superficial chest wall and spare the underlying lung. Radiation doses were 45 Gy to the pleural surface, but the dose to "most of the lung" was kept below 20 Gy by combining electron and photon fields. As in the Helsinki report, substantial toxicity was noted including 25% grade-3 to grade-4 toxicity, 10% severe pulmonary symptoms and two treatment-related mortalities within 1 month of treatment. Median survival time was 13.5 months, with 1-year actuarial local control of 42%.

More recently IMRT has been explored in treating mesothelioma. A series from MSKCC reported 36 patients treated from 2005 to 2010,[450] with both lungs intact and a median dose 46.8 Gy (range, 41.1 Gy to 50.4 Gy) to the hemithorax. Twenty (56%) patients underwent a pleurectomy or decortication before radiation, and 32 (89%) patients received chemotherapy before RT. Acutely, 7 (20%) patients developed grade-3 or worse pneumonitis (1 death) and 2 patients had grade-3 fatigue. Long term, 5 of 30 patients had continuing grade-3 pneumonitis. Despite substantial toxicity median survival and 1-year local failure were 26 months and 48%, respectively, in the cohort treated with pleurectomy.

Intraoperative radiation therapy (IORT) has been explored as an adjunct to external radiotherapy though results have not been encouraging. A report from the University of California–San Francisco included 24 patients treated with IORT. Major complications included radiation pneumonitis in 4 patients, pericarditis in 1 patient, and esophageal stricture in 1 patient. Tumor recurrence was "mostly locoregional" at sites of previous gross tumor. Despite the relatively early stage of disease, the outcome was relatively poor, with a median OS time of 18 months and a PFS rate of 12 months. The MSKCC group also reported their experience with high-dose-rate IORT after pleurectomy or EPP. There were serious complications in 3 of 6 patients (50%) of the EPP/IORT group and in 1 of 5 patients (20%) of the PD/IORT group, and they have abandoned IORT after EPP.[451]

Though outcomes of studies using radiotherapy adjuvant to pleurectomy or decortication suggest reduced locoregional failure rates compared with historical controls of surgery alone, local failure remains common and toxicity is substantial. Expected median survival approximates 2 years in most studies, whereas median survival exceeding 4 years in select reports may relate to selection of patients with early-stage disease.[401] Current NCCN guidelines caution against use of radiotherapy after pleurectomy outside of a clinical trial without following strict normal tissue constraints.[452]

Intrapleural Photodynamic Therapy

PDT uses light activation of sensitized tumor cells to achieve sterilization. It can be delivered intraoperatively immediately following pleurectomy or EPP with the goal of sterilizing microscopic disease throughout the thorax.[422,453] One advantage of PDT is direct visualization of regions at risk for recurrence. The depth of penetration of the light is a few millimeters, which may limit potential pulmonary toxicity. A Phase I trial of Foscan-mediated PDT found that the maximum tolerated dose of photosensitizer was 0.1 mg/kg 6 days before surgery.[454] Dose-limiting toxicity at the next dose level consisted of systemic capillary leak syndrome and led to death in two of three patients treated. Other PDT-related toxicities included wound burns and skin photosensitivity. Fourteen patients were treated at the maximum tolerated dose (MTD) without significant complications.

Photodynamic therapy can be used with other adjuvant therapies.[455] One encouraging series out of the University of Pennsylvania treated 38 patients with radical pleurectomy and PDT.[456] Most patients (97%) had stages III/IV disease. Median survival was 31.7 months for all patients, but only 6.8 months for the 7 of 38 patients with nonepithelial histology. Median PFS was only 9.6 months. Further studies are ongoing.

Radiation Therapy after Extrapleural Pneumonectomy

Reports have been conflicting regarding the impact of aggressive adjuvant therapy on patterns of failure after EPP. A study from the Dana Farber Cancer Institute included 49 patients treated with EPP, and 35 patients received radiotherapy, 30.6 Gy to the "hemithorax" followed by a boost to about 50 Gy, following four to six cycles of chemotherapy.[402] The most-common site of first recurrence was local (35% of patients), whereas abdominal and contralateral thorax relapse was also common. It is likely that abdominal recurrences were related to extension of local disease (Figure 46-8). Isolated distant relapses were uncommon. On the other hand, a Phase II study from MSKCC evaluating hemithorax radiotherapy adjuvant to surgical resection reported only 13% locoregional relapse (in the pleura or regions lymph nodes) in the subset of 55 patients treated with EPP.[457] Distant relapse was a frequent site of first recurrence, particularly in stage III disease. The treatment technique involved photon irradiation to a dose of 54 Gy in 30 fractions.[458] The spinal cord was shielded after 41.4 Gy, and the liver, heart, and stomach were appropriately shielded. The chest wall in the shielded regions was irradiated with matched electron fields so that the goal dose of 54 Gy could be more safely achieved. A report of 86 patients treated with EPP followed by IMRT M. D. Anderson Cancer Center also supports the contention that high-dose radiotherapy may limit local tumor relapse.[459] The goal dose was 45 Gy to 50 Gy to the hemithorax, with 13 patients receiving a boost to 55 Gy to 60 Gy. All irradiation was completed in 25 fractions.

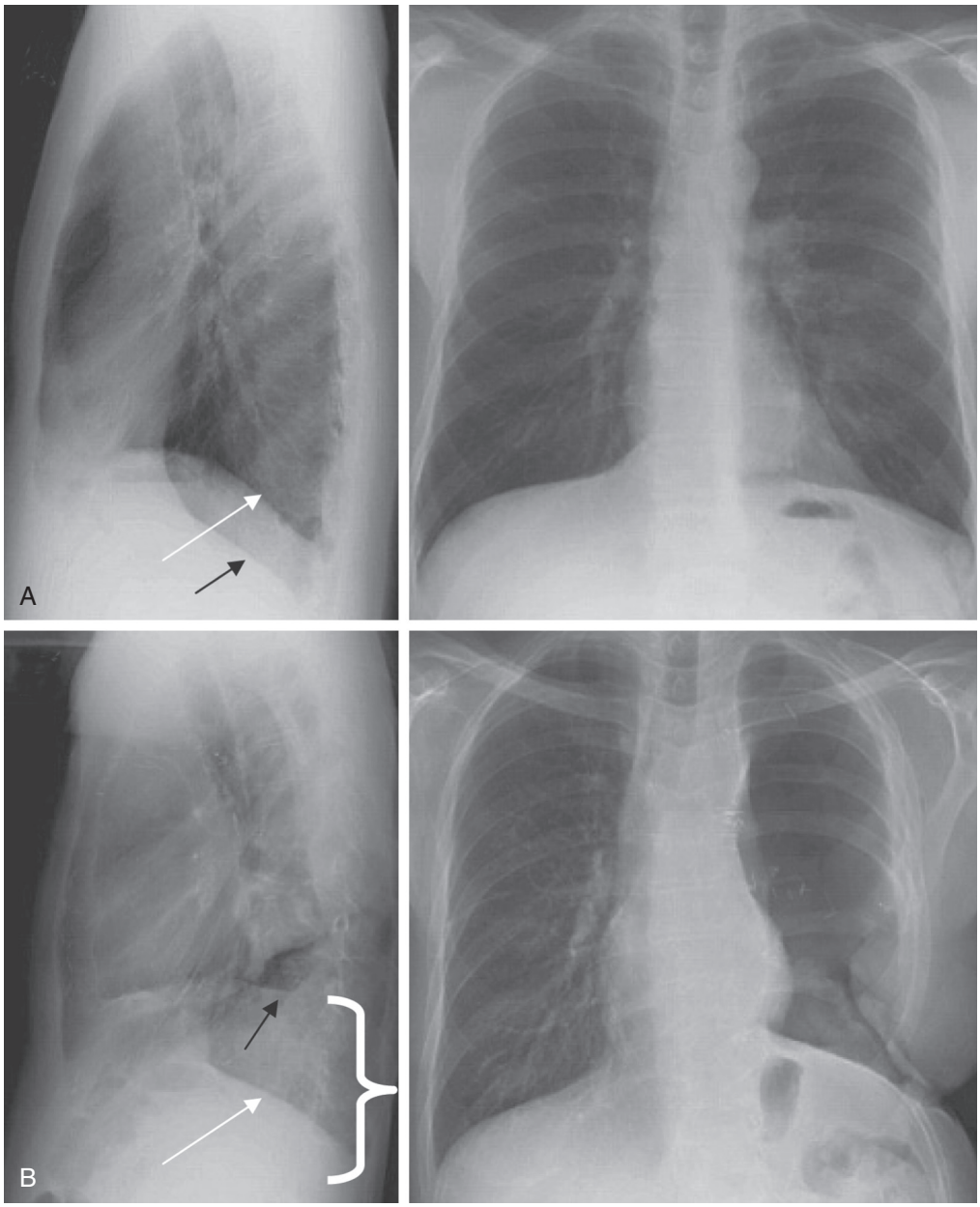


Figure 46-8 Extrapleural pneumonectomy (EPP) can abdominalize portions of the posterior costophrenic recess. **A,** A preoperative radiograph shows that the diaphragm on the contralateral side *(black arrow)* is higher than the ipsilateral hemidiaphragm *(white arrow).* **B,** After EPP, the posterior insertion of the reconstructed hemidiaphragm *(white arrow)* is well above the now flattened, remaining hemidiaphragm *(black arrow).* In this example, the posterior insertion of the diaphragm is about 15 cm higher than before surgery.

Although most patients (77 of 86) had T3 or T4 disease, only 14 (16%) patients experienced a local recurrence while 51 (59%) patients developed distant metastasis.

The results of multimodality EPP studies are difficult to interpret due to patient selection as well as variable interpretation of whether a relapse should be categorized as local or distant. It is critical to distinguish marginal failures, which require better definition of the clinical target volume from in-field failures that may require higher dose. OS appears to correlate well with stage, with much worse outcomes reported for lymph node–positive disease. For example, median survival was 33.8 months for stages I/II disease compared with 10 months for stages III/IV disease in the MSKCC experience. In a recent Canadian series of 60 patients treated with induction chemotherapy, EPP, and hemithoracic RT (≥50 Gy),[460] median survival was a provocative 59 months for N0 disease but dropped to <14 months in the remaining patients.

Multimodality therapy including EPP is reasonably well tolerated in select reports from experienced centers, but treatment is rigorous with potential for substantial toxicity and many patients do not complete planned therapy. The use of IMRT after EPP is controversial given initial reports of fatal radiation pneumonitis.[457] More recent accumulating data suggests that severe pneumonitis may be avoided if stringent dose constraints for the remaining lung are used in IMRT planning.[461]

A summary of large trials for MPM is shown in Table 46-8. Though definitive conclusions can not be reached, it appears that high-dose postoperative irradiation can dramatically reduce ipsilateral thoracic failures in patients undergoing EPP. Local relapse is more common with pleural decortication than after EPP, and the role of radiotherapy after pleural decortications remains unclear. To get a true sense of the benefit of radiotherapy, accurate in-field failure needs to be well documented. Although postoperative irradiation may be well tolerated in experienced hands, the potential for severe toxicity must be considered. The impact of including chemotherapy is difficult to discern and further assessment of systemic therapy is of importance given the benefit in advanced disease.

Palliative Radiation Therapy

Pain Control

Irradiation can provide effective palliation for patients with MPM. A radiation dose-response relationship has been reported after the review of outcomes of 29 courses of palliative external beam radiation therapy delivered to 17 patients with MPM.[398] Four of six patients treated with more than 40 Gy achieved significant relief of symptoms. Only one patient treated with lower doses achieved significant palliation of any symptom, and this was for a painful chest wall mass.

In another study,[464] 26 radiation therapy courses were reviewed for symptomatic improvement. Pain was improved in 13 of 18 cases, and the response was similar regardless of dose or fractionation (i.e., 20 Gy in 5 fractions or 30 Gy in 10 fractions). Although the sample size is small, palliation was achieved in about half of the cases in this mixed patient group. The duration of response was not assessed in either study. These data demonstrate that symptoms from mesothelioma can usually be palliated effectively with brief courses of irradiation.

Therapy for Drain Sites

Unlike most malignant tumors, MPM has a tendency to recur along tracks of previous chest wall instrumentation.[465,466] There is randomized evidence both in support of and against use of local irradiation to drain and biopsy sites.[467] One group took 40 consecutive patients with pathologically proven MPM and randomized them to immediate irradiation to each site of instrumentation or to observation. Elective treatment was 21 Gy in three fractions delivered using en face electron fields. There were no local failures in the irradiated patients

TABLE 46-8 Large Studies Combining Surgery with Postoperative Radiotherapy

Study	Year	Surgery	No. Patients	RT Dose	Local Failure	Survival Time
Maasilta[446]	1991	Pleurectomy	34	55 Gy-70 Gy	33% progression, but remainder with "stable" disease	12 mo median
Lee et al[462]	2002	Pleurectomy	24	41.4 Gy (median) 5-15 Gy IORT	"Most"	18 mo median
Gupta et al[449]	2005	Pleurectomy	123	42.5 Gy (median) 54 of 123 patients IORT	69 of 123	13.5 mo median
Rosenzweig et al[450]	2012	Pleurectomy	20	46.8 Gy (median)	48% local failure at 1-year	26 mo median
Friedberg et al[456]	2012	Pleurectomy + PDT	38		25 of 38	31.7 mo median
Baldini et al[402]	1997	EPP	49	30.6 Gy ≈ 20 Gy boost	21 of 49	22 mo median
Ahamad et al[463]	2003	EPP	28	45-50 Gy	0 2 marginal misses	Not yet reached (2-year OS 62%)
Yajnik et al[458]	2003	EPP	35	54 Gy	13/35	Not reported
Gomez et al[459]	2013	EPP	86	45 Gy-50 Gy, 13 of 86 boosted to 55 Gy-60 Gy	14/86	14.7 mo median
Weder et al[459a]	2004	Chemotherapy + EPP	19	Selected volumes	8 of 13 (13 patients completed all therapy)	16.5 mo median

EPP, *Extrapleural pneumonectomy;* Gy, *gray;* IORT, *intraoperative radiation therapy;* mo, *months;* OS, *overall survival rate;* PDT, *photodynamic therapy.*

compared with eight failures (40%) in the untreated patients.[465] A slightly larger randomized trial found no reduction in the incidence of tumor seeding in the irradiated patients.[453] Because such recurrences typically are painful, elective irradiation is a reasonable means of maintaining the patients' quality of life.

Irradiation Techniques

Patient Immobilization and Setup

Two basic techniques have been described for thoracic irradiation following EPP.[458,468] A description of the IMRT techniques for the postoperative treatment of MPM has been described.[459,468] This level of detail is required to ensure that the complex target volumes can be identified and reproducibly treated for 5 weeks.

Computed Tomography Simulation

MPM tends to recur at sites of previous instrumentation, and all incision and drain sites should be included in the CTV. Laparoscopy or mediastinoscopy sites have not been included within the CTV as long as the mediastinoscopy was pathologically negative. Radiopaque wires mark the surgical incisions, and the tissue equivalent bolus extends to 4 cm around the wires. Patients are immobilized supine on the CT simulator using a combination of a vacuum bag and an "extended wing board with T-bar handgrip" immobilization device used in conjunction with a headrest. The patient should be scanned from the middle neck to the anterior superior iliac spine. This low inferior border allows complete definition of both kidneys so that accurate dose-volume histograms can be constructed. Four-dimensional simulation with assessment of respiratory motion should ideally be performed.

Target Volume Delineation

The ipsilateral mediastinum should be included in the target volume,[463,467] even for patients who are node-negative. The superior border should be placed at the thoracic inlet. The medial border includes the ipsilateral nodal regions, the trachea and subcarinal regions, or the vertebral body.[458,468] The posterior mediastinal structures behind the heart need not be included, because no failures in this region have been recorded (unpublished data) despite their omission from the CTV.[463]

The anteromedial pleural reflection is a potential problem for target volume delineation. As shown in Figure 46-9, *A*, the medial pleural space sometimes can cross the midline. This anatomic relationship can be lost after surgery (see Figure 46-9, *B*). When possible, this region should be marked intraoperatively with radiopaque clips. Alternatively, the medial extent of the pleura could be identified on preoperative CT scans and then estimated on the treatment-planning CT scan. This has been the site of a marginal miss in our series (see Figure 46-9, *C*, *arrow*).

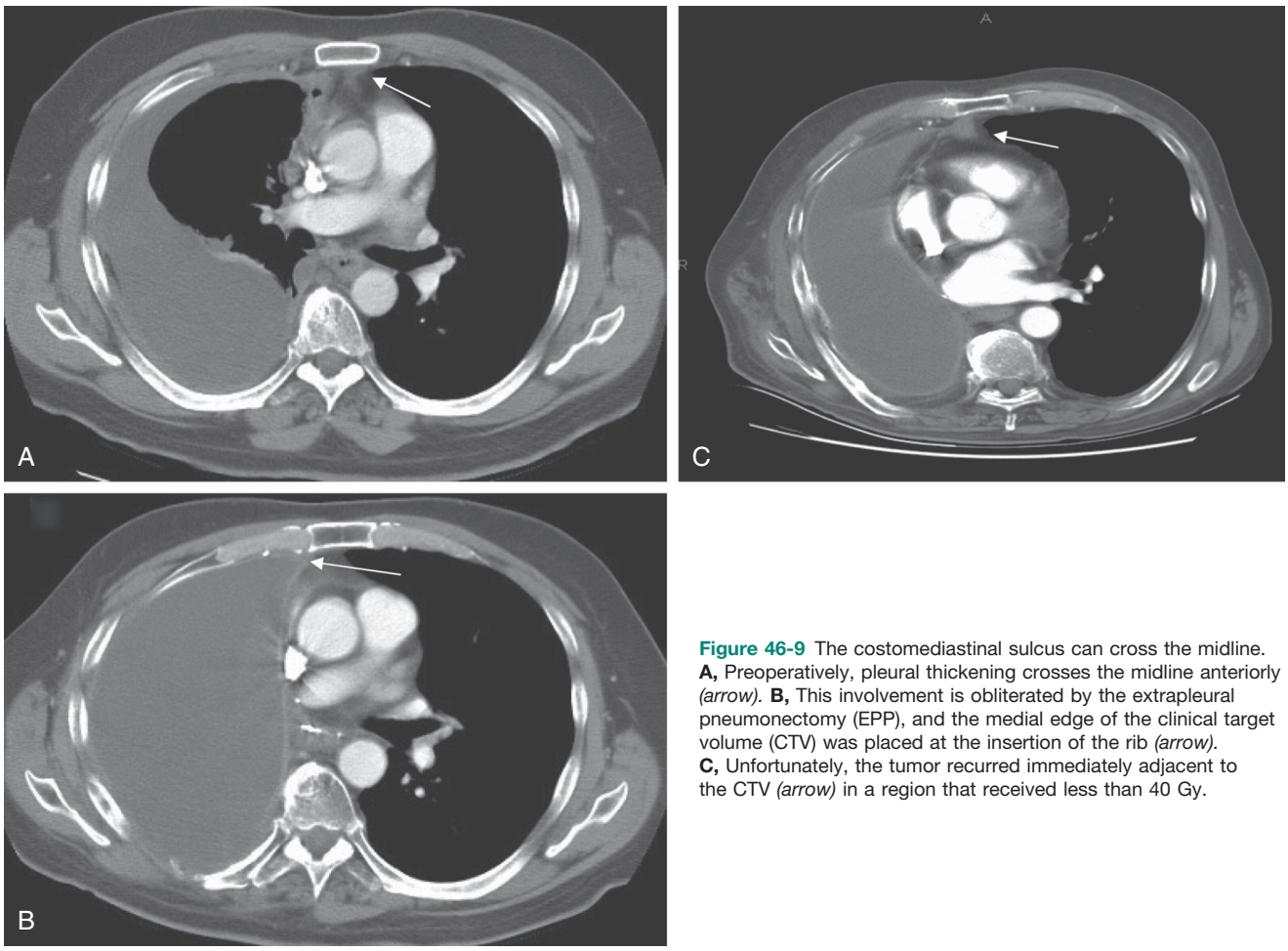


Figure 46-9 The costomediastinal sulcus can cross the midline. **A,** Preoperatively, pleural thickening crosses the midline anteriorly *(arrow).* **B,** This involvement is obliterated by the extrapleural pneumonectomy (EPP), and the medial edge of the clinical target volume (CTV) was placed at the insertion of the rib *(arrow).* **C,** Unfortunately, the tumor recurred immediately adjacent to the CTV *(arrow)* in a region that received less than 40 Gy.

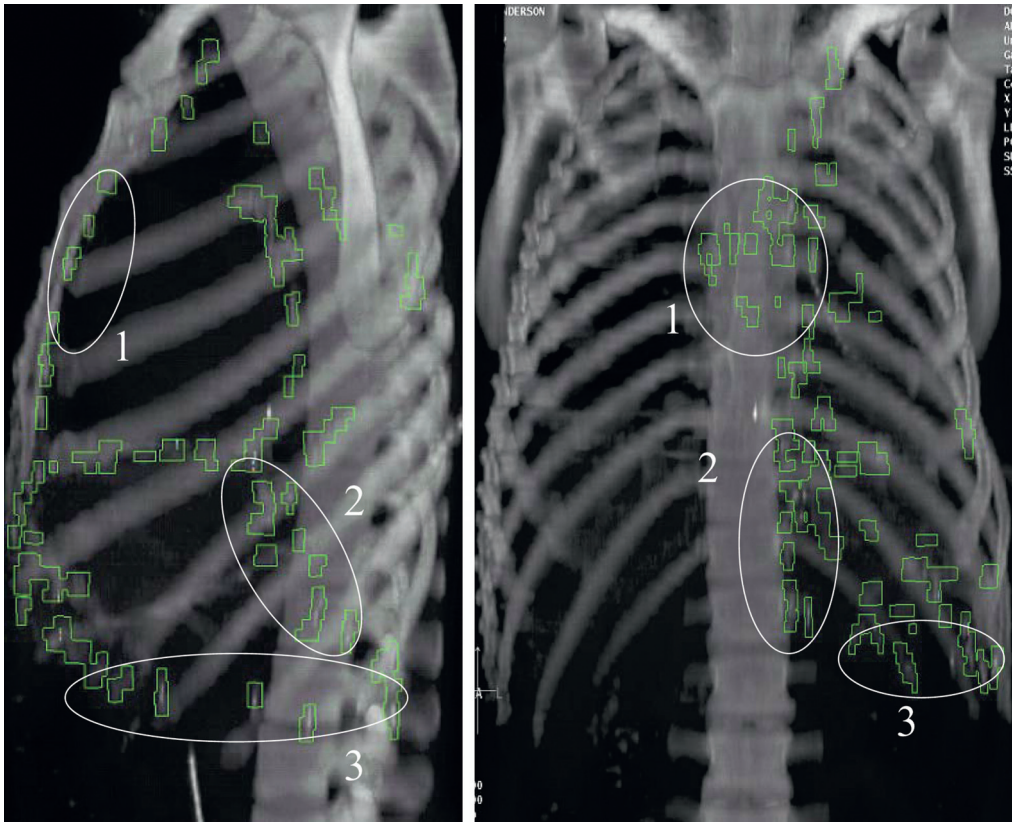


Figure 46-10 Potential problem areas for clinical target volume (CTV) determination. Three parts of the CTV are potentially difficult to discern without great care: the anteromedial pleural reflection of the sternopericardial recess (1), the inferior and medial extents of the crus of the diaphragm (2), and the inferior insertion of the diaphragm (3).

The inferior border should be the insertion of the diaphragm. The location of this is quite variable, ranging from vertebrae L1 to L4. Because of this variability, the diaphragm insertion should be marked by intraoperative placement of radiopaque clips[469] or by suturing the neodiaphragm in this location.[458] When the border of the intrathoracic contents and the abdominal contents is well marked, the radiation therapy margins can be maximally reduced. Because there can be great difficulty in differentiating liver from thoracic fluid, the use of radiopaque Gore-Tex patches for diaphragm reconstructions is helpful.

Another potential source of contouring error is the medial extent of the crus of the diaphragm, especially at its most inferior extent. The ipsilateral crus is usually difficult to identify after surgery without clips. The best way to individualize the inferior edge of the target volume is with intraoperative placement of radiopaque clips, with particular attention to the crus.

When the entire region is extensively clipped, a pattern such as that seen in Figure 46-10 emerges, with regions of potential pitfall highlighted. These potential problem areas include the anterior medial pleural reflection, the crus of the diaphragm, and the inferior aspect of the diaphragmatic insertion.

Treatment Planning

Three-Dimensional Conformal Radiation Therapy

The 3DCRT therapy approach has been described best in two reports from the MSKCC.[457,458] The technique applies anteroposterior-posteroanterior beam geometry to the hemithorax using the volumes described previously as the CTV. For right-sided cases, an abdominal block is present throughout treatment, and the region is boosted with electrons at 1.53 Gy per day, which accounts for scatter under the block. For left-sided cases, the kidney and heart are blocked. The kidney block is present throughout treatment, and the heart block is added after 19.8 Gy. The spinal cord is shielded after 41.4 Gy in all cases. The goal dose to the target volume is 54 Gy in 30 fractions, with the dose calculated at the midplane with equally weighted beams. Patients were treated with arms akimbo.

Treatment by this approach results in good coverage of most volumes at risk to the target dose of 54 Gy. Doses are homogeneous within the regions at risk, although regions such as the crus, the pericardium, and the neodiaphragm may be difficult to treat. Radiosensitive structures such as the liver and heart can be spared well. Protection of the ipsilateral kidney is better than with IMRT.

Intensity-Modulated Radiation Therapy

The target doses and the dose-volume limits for the critical structures are listed in Table 46-9. Treatment is delivered with 13 to 27 intensity-modulated fields using 8 to 11 gantry angles, typically with 100 segments per intensity-modulated field. Because patients have only one lung after EPP, the Duke group recommends contralateral lung irradiation limited to a mean lung dose of less than 9.5 Gy.[470] This is consistent with the results of whole-lung irradiation.[471] The University of Pennsylvania dose constraints are slightly more conservative, with a

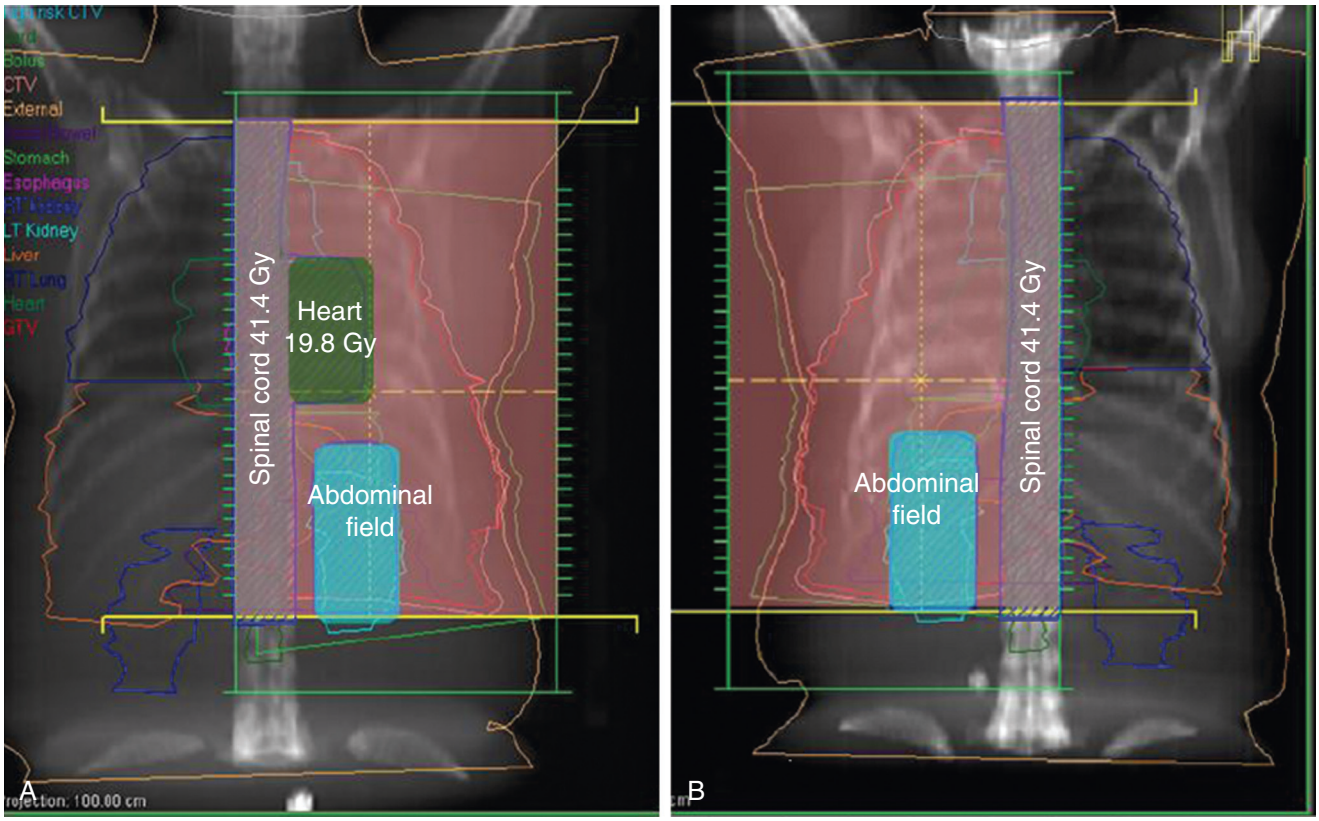


Figure 46-11 The total prescribed dose from the anteroposterior **(A)** and posteroanterior **(B)** photon fields and supplemental electron fields was 54 Gy in 1.8-Gy fractions. At the start of treatment, blocks were placed in the region of the abdomen. During treatment of the left hemithorax, an anterior heart block was placed at 19.8 Gy. Blocked areas were subsequently delivered 1.53 Gy daily through an en face electron field. At 41.4 Gy, anterior and posterior blocks were placed over the spinal cord.
(Used with permission from Hill-Kayser CE, Avery S, Mesina CF, et al: Hemithoracic radiotherapy after extrapleural pneumonectomy (EPP) for malignant pleural mesothelioma. A dosimetric comparison of two well-described techniques. J Thorac Oncol 4:1431–1437, 2009.)

TABLE 46-9 Goal Dose or Constraint Dose of the Target or Organ

Target or Organ	Goal Dose or Constraint Dose
CTV	50 Gy in 25 fractions
bCTV	60 Gy in 25 fractions
Lung	<20% to receive >20 Gy and mean <9.5 Gy
Liver	<30% to receive >30 Gy
Contralateral kidney	<20% to receive >15 Gy
Heart	<50% to receive >45 Gy
Spinal cord	<10% to receive >45 Gy No portion to receive >50 Gy
Esophagus	<30% to receive >55 Gy

bCTV, *Boost clinical target volume;* CTV, *clinical target volume;* Gy, *gray.*

mean lung dose of less than 9 Gy, a V5 of less than 60%, and a V20 of less than 20%.[461] With experience, the mean lung dose can be kept to well under 8 Gy.[461,471]

IMRT is more complicated and takes longer to deliver than 3DCRT, but good coverage of the target can be achieved. IMRT has dosimetric advantages over 3DCRT because of to improved coverage and homogeneity, but there is more dose spillage into the contralateral lung and an increase in the mean lung dose.[472,473] A combined electron and 3DCRT to a dose of 54 Gy had significant reduction to the contralateral lung, contralateral kidney, and heart when compared with IMRT to a dose of 45 Gy.[473] Figure 46-11 shows field and block arrangements employed with the use of a combined electron-photon technique. The IMRT plan of 50 Gy to the isodose line in Figure 46-12 encompasses most of the CTV. Review of the dose-volume histogram for this case (Figure 46-13) demonstrates that the target volume is well covered and the normal tissue constraints are met. The liver and contralateral lung are spared with this technique. In this patient, it was possible to spare the ipsilateral kidney because the organ was particularly low. The ipsilateral kidney usually receives a high dose because the CTV typically abuts its posterior edge. Adequate contralateral renal function is confirmed by pretreatment renal scans. For left-sided lesions, the spleen is likely to receive a high radiation dose and pneumococcal prophylaxis is recommended.

There has been increasing interest in the use of IMRT to treat mesothelioma in patients who have not had pneumonectomy. Rosenzweig et al describe the technique used at MSKCC for treating patients with mesothelioma who have not undergone pneumonectomy.[450] Essentially, a rind of tissue around 15 mm in diameter is treated, including the pleura and chest wall of the entire hemithorax, from thoracic inlet down to the insertion of the diaphragm. Dose constraints are similar to treatment of patients with locally advanced non–small cell lung cancer, with mean lung dose less than 20 Gy. Figure 46-14

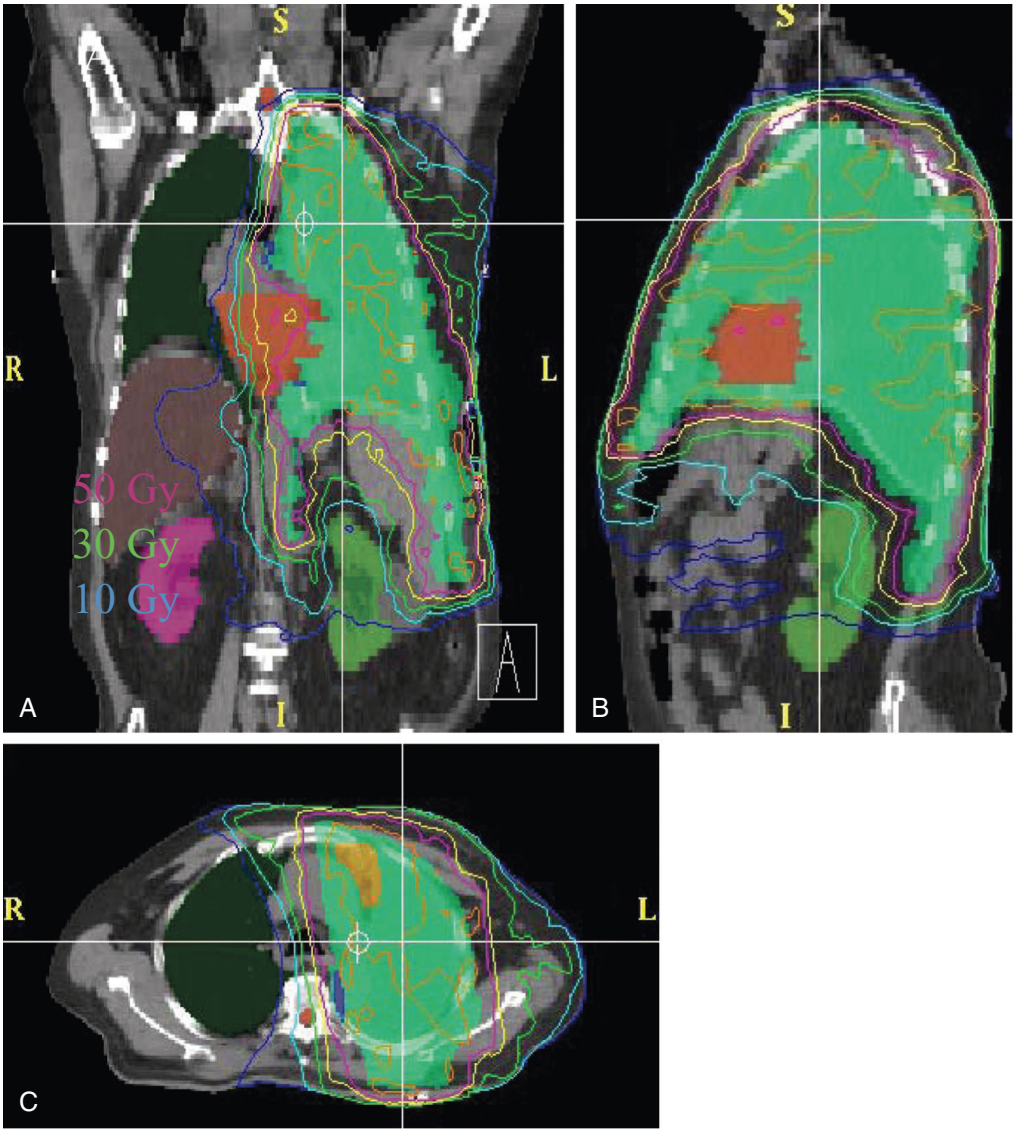


Figure 46-12 **A** to **C,** The dose distributions for intensity-modulated radiation therapy (IMRT) demonstrate good coverage of the clinical target volume (CTV) and the high-dose gradients achievable with this technique. The goal was 50 Gy to the CTV. The 50-Gy, 40-Gy, 30-Gy, and 10-Gy isodose lines are shown in *magenta, orange, green,* and *blue,* respectively.

shows isodose lines and dose-volume histogram (DVH) for a patient postpartial pleurectomy with mesothelioma treated with IMRT to 45 Gy.

SUMMARY

A review of the limited patient studies (see Table 46-8) in MPM suggests that EPP followed by irradiation gives better local control than pleurectomy followed by irradiation in selected patients. The addition of PDT to pleurectomy may improve local control rates, but randomized data are lacking. Postoperative irradiation should include the entire volume immediately adjacent to the pleural space that is at highest risk for microscopic residual disease. This volume should include all sites of pleural reflection, the ipsilateral mediastinum, and the insertion of the diaphragm. The technique by which irradiation is delivered (traditional technique or IMRT) is probably not as important as the target volume delineation and coverage. Integrating systemic therapy with EPP and postoperative irradiation has become standard practice and additional prospective trimodality studies are being conducted.

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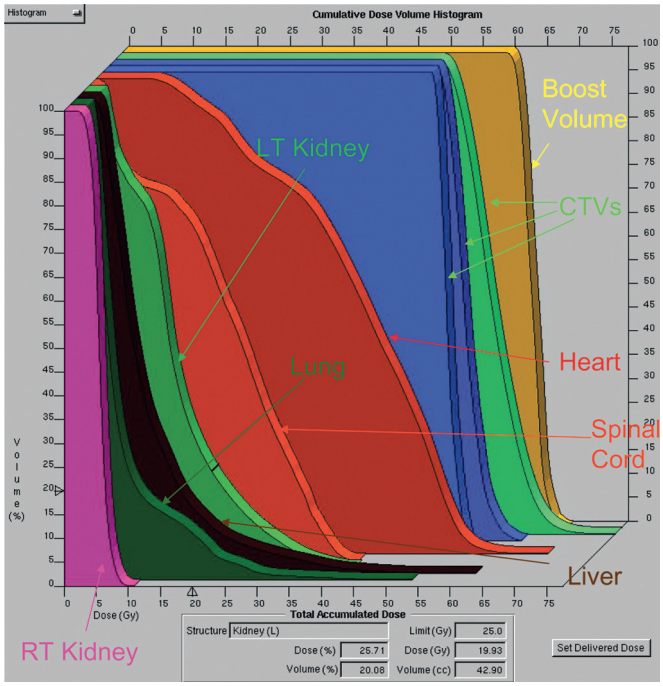


Figure 46-13 The dose-volume histogram demonstrates that coverage of the target volumes is adequate. The contralateral kidney was well below the goal dose, as was about 25% of the ipsilateral kidney. The mean lung dose was about 9.5 Gy. In this left-sided case, the heart dose was slightly higher than the goal dose (60% to 45 Gy, rather than 50%).

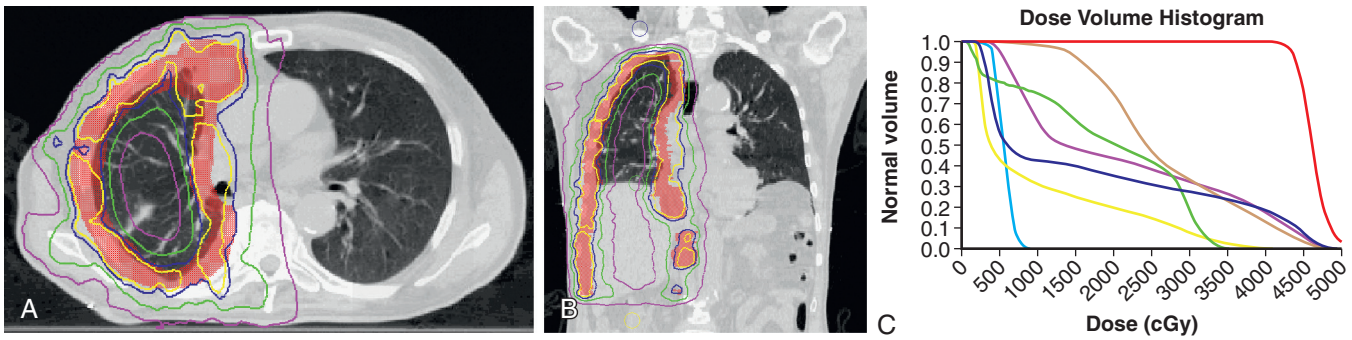


Figure 46-14 Axial **(A)** and coronal **(B)** views for intensity-modulated radiation therapy (IMRT) in mesothelioma with two intact lungs. Isodose lines are closely conformal to the shape of planned target volume *(red)*. Goal was 45 Gy to the PTV. The 45-Gy, 42.75-Gy, 36-Gy, and 22.5-Gy isodose lines are shown in *yellow*, *blue*, *green*, and *purple*, respectively. **(C)** The dose-volume histogram demonstrates that coverage of the target volumes and sparing of normal tissue (PTV = red). The mean lung dose was 17 Gy with V20Gy of 36% *(dark blue)*. Contralateral kidney received little dose *(light blue)* and ipsilateral kidney dose was also acceptable *(yellow)*. Cord max was 37 Gy *(green)*. Mean heart dose was 21 Gy *(pink)*, and mean liver dose was 27 Gy *(brown)*.

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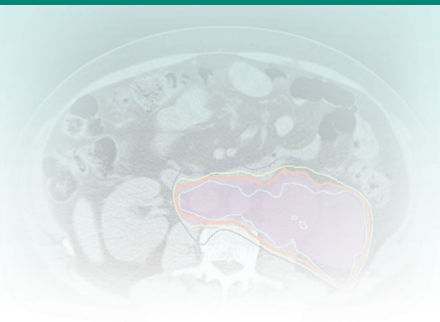
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Overview



Joel E. Tepper and Leonard L. Gunderson

Gastrointestinal (GI) cancer continues to be a common health problem. Approximately 290,200 new cases of GI malignant disease were estimated to occur in the United States in 2013.[1] Although colorectal tumors account for almost 50% of the cases in the United States (142,720), cancers of the esophagus, stomach, liver, and pancreas continue to occur with regularity and have high mortality rates, and the incidence of hepatoma is increasing rapidly. Although the death rate from colon and rectal cancer is gradually decreasing, and that from gastric cancer has been decreasing for a century, there has been a marked increase in the incidence of tumors arising at the gastroesophageal junction and of primary liver cancers. Pancreatic cancer also continues to gradually increase in incidence and there has been little improvement in overall survival rates. Gastric and hepatic cancers are two of the most common causes of cancer incidence and death worldwide. Hereditary factors play a role in the etiology of GI cancer, and environmental toxins are causative agents in certain diseases. Because these are a diverse group of tumors, the etiology, epidemiology, diagnosis, and treatment vary enormously between diseases and are discussed in the respective chapters.

A significant problem with many GI cancers relates to a delay in clinical presentation. Signs that give early warning of other types of cancer (e.g., pain or palpation of a mass) do not occur early in most patients with GI cancers. For example, the severe back pain that can occur with pancreatic cancer is usually a manifestation of unresectability because of posterior tumor extension. Patients with alimentary tract GI cancers often present with symptoms of bleeding and occasionally bowel obstruction that may be associated with a large primary tumor, a high risk of metastasis, and a low chance of cure.

Physicians should be aware of the early signs and symptoms of GI cancer and educate their patients to be aware of certain symptoms to make earlier diagnoses, and to perform screening procedures (especially for colorectal cancer), as indicated. In general, the early warning signs include vague abdominal discomfort, evidence of GI bleeding, unexplained weight loss, change in bowel habits, or new onset of anemia. Routine colonoscopy or sigmoidoscopy and stool testing for occult blood are recommended screening procedures for colorectal cancer, and virtual colonoscopy may be a viable alternative. With these procedures, survival rates are affected because cancers are found at an early stage and benign polyps are removed before they have had a chance to progress to invasive cancers. Colorectal cancer is one of the few cancer types that can often be prevented, in this case by removing benign polyps before progression to malignancy. Other tests such as routine contrast radiography, upper endoscopy, or cytologic analysis have yet to demonstrate cost effectiveness in the United States as general screening procedures for upper GI malignant diseases, but they may be appropriate for select high-risk populations. There is a major controversy regarding aggressive screening procedures for patients with Barrett's esophagus because although these patients have a significant risk of neoplastic progression, the annual progression rate is quite low. There is substantial interest in innovative approaches of screening, such as molecular analyses of stool or bile for changes such as *RAS* mutations, that could be important in the future. There is also hope that advances in proteomics may lead to development of a blood assay for identifying patients with early cancers; but at the present time this is more a hope than reality.

This overview discusses conceptual issues pertinent to a variety of GI cancers, with site-specific details covered in the disease site chapters. Topics covered here include epidemiology and prevention, biology, anatomy and pathway of tumor spread, staging, prognostic factors and patterns of relapse, treatment issues of surgery alone versus primary chemoradiation or trimodality treatment (surgery, radiation therapy, and chemotherapy), and tolerance of organs and structures that limit the radiation dose in the treatment of abdominopelvic GI cancers.

EPIDEMIOLOGY AND PREVENTION

It has long been known that colon and rectal cancers are related to dietary factors, and these tumors have therefore been used as a model for cancer epidemiology. There is a strong association of colorectal tumors with high-fat and low-fiber diets.[2] It has been argued as to whether high fat or low fiber is most important in the process of cancer development, or whether there are other nutrients associated with these diets that are most important. However, data now suggest that neither high fat nor low fiber is critical but rather that high-fat/low-fiber diets tend to be low in nutrients such as folate.[3,4] Confirmation of this is critical in designing prevention strategies because dietary supplementation is far easier to implement than is a major change in the eating habits of the population. Other environmental factors, specifically exercise, are important in colorectal carcinogenesis, perhaps related to alterations in insulin-like growth factors. It is fortunate that a lifestyle that is healthy for the heart is also beneficial in decreasing colorectal cancer incidence. The same strong dietary correlate with cancer formation is unfortunately not present for most other GI tract tumors. Smoking is a major risk factor primarily for esophageal cancer and, to a lesser extent, for pancreatic cancer.

Along with the dietary factors just described, there have been major epidemiologic changes in geographic location and histopathologic findings for tumors of the esophagus, stomach, colon, and rectum over the last half-century, although the

reason for these changes is largely unknown. The primary histopathologic type of esophageal cancer has changed rapidly from squamous cell carcinoma of the proximal and midesophagus to adenocarcinomas of the distal esophagus, gastroesophageal junction, and proximal stomach. At many U.S. institutions, three fourths of all patients with esophageal cancer have distal esophageal/gastroesophageal junction adenocarcinomas, although this was a relatively rare entity only 20 to 30 years ago. The reasons for these changes are uncertain but are likely related to the increased incidence of Barrett's esophagus and esophageal reflux.[5] One theory is that the increased use of H_2-receptor blockers has relieved the symptoms of reflux but has not decreased the inflammatory response in the distal esophageal mucosa, so that Barrett's lesions continue to form and undergo metaplastic changes to become esophageal cancers. The concomitant substantial increase in the incidence of proximal (cardia) gastric cancers suggests that a similar etiology is present for both cardia and gastroesophageal junction carcinomas and that the increased incidence of esophageal cancers is not simply a misclassification of proximal gastric cancers as esophageal adenocarcinomas.[6]

At the same time that there has been an increased incidence of proximal gastric adenocarcinomas, the overall incidence of gastric cancers is decreasing. At the beginning of the 20th century, gastric cancer was the most common malignant disease in the United States. Although gastric cancer is still a common cause of death, it has decreased in incidence so much that it is now only the 11th-most common cause of death from cancer in the United States.[1] The change has been attributed to dietary modifications, although the exact cause is unknown. The incidence of gastric cancer worldwide is much higher than in the United States.

In the large bowel, there has been a more gradual epidemiologic change. Previously, the majority of colorectal cancers were located in the rectum, but now most are located in the right colon. Although screening for, and removal of, precancerous polyps in the rectum and sigmoid colon with sigmoidoscopy could be producing some of these changes, it is unlikely to be a major factor. Dietary changes are suspected, but unproved, as a cause.

There has also been a major increase in the incidence of hepatocellular carcinoma (HCC) in the United States, although it is not nearly as high as the incidence worldwide. Some of the reasons for this are known, such as the strong association of HCC with hepatitis B and C virus infection. Improved prevention and treatment of hepatitis B and C infections should decrease the incidence of these diseases over the long term.

A major emphasis in the future will be to determine ways to prevent tumor formation or to find tumors early enough so that the risk of tumor mortality is minimized. Data strongly suggest that prevention strategies can be used to decrease the incidence of colorectal cancers. Screening for and removal of polyps before they become malignant interferes with the polyp-to-cancer sequence that occurs in the majority of colon and rectal cancers. Studies of patients screened with flexible sigmoidoscopy have demonstrated a markedly decreased incidence of cancers in areas within reach of the sigmoidoscope but no decrease in areas that could not be effectively screened.[7,8] Convincing data demonstrate the value of regular screening and stool guaiac studies in decreasing colorectal cancer mortality rates.[9,10] However, neither of these interventions is used widely enough to decrease markedly the overall incidence of these diseases. Virtual colonoscopy, a computed tomography (CT)-based radiographic examination, has generated a great deal of interest as a screening tool. However, the data do not yet support its widespread use and patients currently still need to do what many consider to be the worst part of an endoscopic procedure, the bowel preparation. Controlled studies are being performed to determine whether the bowel preparation is necessary or whether electronic deletion techniques can be used to exclude stool from the images.

Screening approaches have also been considered for tumors of other sites in the GI tract, but cost-effective strategies have not been defined. The incidence of gastric cancer in the United States and many Western countries is not high enough to justify the cost and morbidity of screening endoscopy for gastric or esophageal cancer, and radiographic studies such as CT scans are not sensitive. If it were possible to define a high-risk group of patients, then perhaps screening could be used successfully. Although controversial, the one other situation in the upper GI tract in which screening may be useful at the present time is in patients with Barrett's esophagus, where the incidence of esophageal cancer is high and regular endoscopy or elective surgery may be justified, at least for high-grade dysplastic lesions.

Prevention strategies have been studied extensively, especially for colon and rectal cancers. There are a variety of agents that have substantial potential as preventive agents for people at high risk. These include aspirin[11,12] and other nonsteroidal anti-inflammatory drugs (NSAIDs) and calcium.[13,14] The data are now quite convincing that the incidence of polyps can be decreased with the use of NSAIDs, presumably reflecting their activity as inhibitors of cyclo-oxygenase-2 (COX-2).[15] The finding of increased cardiovascular events in patients taking selective COX-2 inhibitors will have a major impact on the use of these agents for cancer prevention, but aspirin use is advocated by some.

BIOLOGY OF GASTROINTESTINAL CANCERS

Over the past decade, an enormous amount of information has been gathered regarding the molecular correlates of GI carcinomas. As is true for other anatomic sites, there are a large number of molecular changes in most of these tumors, but most of the changes occur in only a relatively small subset of tumors. A wide spectrum of molecular abnormalities has been found that likely define the genetic characteristics of the tumor. The specific molecular abnormalities probably have a major effect on both the pace of disease progression and the response of the tumor to therapy, but the relationship is clearly complex. Colorectal cancer is one of the best-studied adult solid tumors in this regard and illustrates the type of information that we are likely to obtain about other solid tumors. The detailed molecular changes associated with GI tumors and the general issues related to carcinogenesis are beyond the scope of this introduction but are covered elsewhere in this book, as well as in multiple reviews.[16]

Although there are a large number of molecular changes observed in colorectal cancer, a few are most common. These include altered promoter methylation, mutations of the *RAS* oncogene, mutations in the *TP53* tumor suppressor gene, mutations of a gene on the short arm of chromosome 18 (in an area referred to as the *DCC* gene [deleted in colon cancer]), and mutations in chromosome 5 in a region associated with the familial polyposis syndrome (FAP). Although there is clearly no orderly progression from one molecular change to another, there is a tendency for certain of these changes to occur early in the oncogenesis pathway. For example, changes in the *FAP* gene and altered methylation tend to occur early, whereas *TP53* mutations tend to occur late.[17]

As one probes deeply into the genome, a large number of abnormalities are being found, but many of these may be secondary to a generalized chromosomal instability. The significance of some types of molecular abnormalities is now

better understood. For example, microsatellite instability in colon cancer is associated with right-sided colon tumors but with an improved prognosis compared with those with no microsatellite instability. These tumors may also have altered (i.e., less) chemosensitivity, especially to 5-FU, compared with tumors without microsatellite instability. There is also awareness that changes in miRNA (and other nonprotein-coding RNAs) can have major importance in defining outcomes and perhaps response to therapy. Some investigators now classify colorectal cancer into three categories: those that have microsatellite instability (MIS), characterized clinically as right colon lesions with a relatively good prognosis (10% to 20% of tumors); those of the CpG island methylator phenotype (CIMP), which have a poor prognosis and relatively poor responsiveness to standard chemotherapy (10% to 30% of tumors); and those with chromosomal instability (CIN; 50% to 70% of tumors). This classification may help in the understanding, subclassification, and management of these diseases. More recently work of the The Cancer Genome Atlas (TCGA), sponsored by the National Cancer Institute (NCI), has compiled a comprehensive analysis of molecular changes in these tumors,[18] including not only mutational analysis, but also methylation, copy number variation, and miRNA changes.

An area of interest is the correlation of the known epidemiologic factors for cancer formation and the molecular abnormalities. For example, it is unknown how dietary changes are related to observed molecular alterations. Determining which dietary factors are of true importance and which dietary factors produce which molecular changes, and the mechanisms by which they do so, may be critical in designing effective prevention strategies.

For other tumors of the GI tract, the molecular correlates are not nearly as well established. Pancreatic cancer is unusual because approximately 90% of these tumors have a mutation in the *K-RAS* oncogene,[18] and mutations in the *P16, TP53*, and *MADH4* genes are common. This has been emphasized by the results of sequencing of pancreatic cancers, where a relatively small number of common mutational events were found, and most of the findings were unexpected from previous data. The finding of abnormalities that are present in most cancers of a certain type produces exciting possibilities for detection, prevention, and therapy because it suggests that these mutational events may be required for cancer formation. In addition, even when a specific mutation is not present, an abnormality in the same pathway may be present and produce the cancer of interest. However, the abnormality may be produced by one of many mutational events or even by gene silencing through altered methylation.

There is a major effort to develop pharmaceuticals that will block the function of critical pathways and thereby either inhibit tumor growth or kill the tumor. Many of the drugs that have been developed as pure molecular inhibitors for primary therapy do not seem to be effective when used alone. However, most of these agents (e.g., endothelial growth factor receptor [EGFR] or vascular endothelial growth factor [VEGF] inhibitors) have substantial radiation sensitization properties and may be useful adjuncts to standard radiation therapy (see Chapter 5).

A great deal of interest exists in using molecular analysis techniques to improve prognostication and to better define which tumors would be best treated with which modalities. These include whole genome sequencing, sequencing of the transcriptome, expression array analyses, epigenetic analyses (such as methylation), and so on. These studies are still in their early phases and require much additional work before routine clinical application. The further work of TCGA may provide additional information on the molecular characteristics of these tumors.

ANATOMY AND PATHWAYS OF TUMOR SPREAD

Upper GI (i.e., stomach, pancreas, and biliary tract) and colorectal cancers have anatomic similarities that lead to common patterns or pathways of tumor spread. The four common mechanisms of tumor spread for these sites include direct extension, lymphatic spread, blood-borne hematogenous metastases, and peritoneal seeding. Esophageal and anal cancers have no risk for peritoneal seeding because of their anatomic location, unless they extend to involve organs with access to the peritoneal cavity (e.g., stomach or upper rectum).

Direct extension of tumor that may lead to surgical unresectability because of fixation to or involvement of surrounding organs or structures is more common with upper GI cancers than with lower GI cancers. Within the triad of upper GI cancers, gastric cancers are most likely to be resectable at the time of diagnosis.

Lymphatic spread and nodal involvement are common at all GI sites. For the alimentary sites (i.e., esophagus, stomach, colorectum, and anus), the risk is minimal for lesions limited to the mucosa. The risk increases with direct extension into the submucosa in view of the presence of submucosal lymphatics, which are especially prominent in the stomach and esophagus. The mechanism of tumor spread within submucosal and subserosal lymphatics can also lead to subclinical tumor spread 5 cm to 10 cm or more from the margin of the gross tumor for both esophageal and gastric cancers. For colorectal cancers, it is unusual to have subclinical tumor extension in the bowel wall for more than 1 cm to 1.5 cm beyond the gross tumor, but nodal spread can occur at more distant locations.

Hematogenous dissemination from GI cancers is usually to the liver or lungs. With esophageal, anal, and rectal cancers, both sites are at risk. Gastric, colon, or pancreas cancers that do not extend beyond the wall or organ to involve other organs or structures have venous drainage via the portal circulation, placing the liver at primary risk for blood-borne metastases.

Peritoneal seeding can theoretically occur when a tumor extends to a free peritoneal surface. The finding of peritoneal seeding at initial surgical exploration is highest for gallbladder and pancreatic cancers, is rare with low rectal cancers, and can sometimes be found with gastric, colon, bile duct, and upper (with or without mid) rectal cancers.

STAGING

The current TNM (tumor, lymph nodes, metastasis) staging system of the American Joint Committee on Cancer (AJCC) is the accepted staging system for GI cancers.[19] However, because of either lesser nodal dissections or incomplete pathology, the pathologic examination of 10 to 15 nodes in gastric cancer does not always occur, and this can decrease the value of the N classification (N1, metastases in 1 to 2 regional lymph nodes; N2, metastases in 3 to 6 regional nodes; and N3, metastases in 7 or more regional nodes [N3a, 7 to 15 regional nodes; N3b, 16 or more regional nodes]). However, for both gastric and colorectal tumors, the aggressiveness of lymph node staging is of enormous prognostic importance. The prognosis is much inferior for "N0" tumors when few lymph nodes have been evaluated compared with these tumors when large numbers of nodes have been studied.[20] The ratio of positive lymph nodes to the total number of lymph nodes in a specimen is also becoming a more widely used measure because it partially compensates for inadequate nodal sampling. These variations in nodal count result in both understaging and stage migration, which make it difficult to compare results by

series. Some individuals have used the lymph node ratio (percentage of nodes that are involved with tumor) as an alternative to lessen the problem of poor nodal sampling.

Colorectal Cancers

The TNM system applies to both clinical and pathologic staging, defines the degree of primary tumor extension for lesions confined to and extending beyond the bowel wall, and defines node involvement by the number of nodes involved (N1, three or fewer nodes; N2, four or more nodes). The updated 2010 AJCC/UICC (Union for International Cancer Control) TNM classification should be used as the standard staging system (see Table D-1).

Considerable improvements in TNM staging for colon and rectal cancer have been achieved as a result of both the sixth and seventh editions of the AJCC staging manual.[21,22] Through the fifth edition of the manual, substaging was not used despite marked differences in outcomes by TN category of disease for patients with stages II and III disease. In both the sixth and seventh editions of the manual, substaging, based on available outcomes data, has been used to account for those differences in survival.[20-28]

Before making substantive changes in the AJCC seventh edition for colon and rectal cancer, the AJCC hindgut task force sought population-based validation that depth of invasion and nodal status interact to affect survival rates. Surveillance Epidemiology and End Results (SEER) survival data were obtained for patients with invasive colon and rectal cancer and evaluable TN category of disease (35,829 patients with rectal cancer and 109,953 patients with colon cancer).[27,28] T4N0 category cancers were stratified by "tumors that perforate visceral peritoneum" (T4a) versus "tumors that invade or are adherent to adjacent organs or structures" (T4b). N1 and N2 categories were stratified according to the number of involved nodes (N+): N1a and N1b (one node versus two to three nodes), and N2a and N2b (four to six nodes versus seven or more nodes). The 5-year observed and relative survival data were obtained for each TN category. The analyses indicated the following information: Survival times are better for patients with T1-2N0 cancers than for those with T3N0 cancers; survival times are better for patients with T3N0 tumors than for those with T4N0 tumors; and survival times are better for patients with T1-2N2 tumors than for those with T3-4N2 tumors. Survival times for patients with T4bN1 tumors are similar to those for T4N2 tumors.

In addition, patients with T4a lesions have better survival times than patients with T4b tumors by N category, and the number of positive nodes affects survival times for each T category. The SEER population-based colon and rectal cancer analyses supported subdividing T4 into T4a and T4b, N1 into N1a and N1b, and N2 into N2a and N2b, and supported revised substaging of II and III (shift of T1-2N2 lesions from IIIC to IIIA or IIIB and T4bN1 lesions from IIIB to IIIC).

Other Gastrointestinal Cancers

Staging of pancreatic, biliary, and esophageal cancers is less useful. The major factors defining therapy are whether the tumor is resectable, borderline resectable, or locally unresectable and whether distant metastatic disease is present. As therapy becomes more sophisticated and treatment outcomes improve, we will likely be better able to use more precise staging information. The ability to evaluate stage more effectively preoperatively through positron emission tomography (PET) scans (especially in esophageal and anal cancer but also in colorectal cancers) and endoscopic ultrasound (in esophageal and gastric cancers) should be of benefit over the long term with regard to choice of treatment (single-modality versus bimodality or trimodality treatment) and sequencing of various modalities (preoperative or postoperative, or both). HCC is generally not staged in the usual manner, but both patient and tumor factors are important in determining therapy and outcome.

TABLE D-1 Comparison of Staging Systems for Colorectal Adenocarcinoma

AJCC TNM Stage*	T	N	M	Dukes Stage	Modified Astler-Coller Stage
0	Tis	N0	M0	—	—
I	T1	N0	M0	A	A
	T2	N0	M0	A	B1
IIA	T3	N0	M0	B	B2
IIB	T4a	N0	M0	B	B2
IIC	T4b	N0	M0	B	B3
IIIA	T1-2	N1/N1c	M0	C	C1
	T1	N2a	M0	C	C1
IIIB	T3-4a	N1/N1c	M0	C	C2
	T2-3	N2a	M0	C	C1/C2
	T1-2	N2b	M0	C	C1
IIIC	T4a	N2a	M0	C	C2
	T3-4a	N2b	M0	C	C2
	T4b	N1-2	M0	C	C3

From Edge SB, Byrd DR, Compton CC, et al, editors: AJCC cancer staging handbook, ed 7, New York, 2010, Springer.

*Tis, *Carcinoma in situ;* T1, *tumor invades submucosa;* T2, *tumor invades muscularis propria;* T3, *tumor invades through the muscularis propria into pericolorectal tissues;* T4a, *tumor penetrates to the surface of the visceral peritoneum; T4b, tumor directly invades or is adherent to other organs or structures (surgical/pathologic definition).*

N0, *no regional lymph node metastases;* N1, *metastasis in one to three regional lymph nodes; (*N1a, *one regional node; N1b, two to three regional nodes);* N2, *metastasis in more than four regional lymph nodes; (*N2a, *four to six regional nodes;* N2b, *seven or more regional nodes);* M0, *no distant metastasis;* M1, *distant metastasis;*

Lymph nodes beyond those encompassed by standard resection of the primary tumor and regional lymphatics (e.g., retroperitoneal nodes) are considered distant metastases.

PROGNOSTIC FACTORS AND PATTERNS OF RELAPSE

Adjuvant Colorectal Cancer

Survival and disease relapse after surgery with or without adjuvant treatment for colon and rectal cancer are a function of both degree of bowel wall penetration of the primary lesion and nodal status. Nodal involvement is not the only important pathologic factor determining survival and relapse.

Impact of TN Category on Relapse and Survival

In the sixth edition of the AJCC staging manual, stage II was subdivided into IIA (T3N0) and IIB (T4N0) and stage III was subdivided into IIIA (T1-2N1M0), IIIB (T3-4N1M0), and IIIC (any TN2M0), based on improved outcomes for patients with stage IIA versus IIB disease and for those with stage IIIA versus IIIB cancers.[21] The placement of all patients in the TN2 category into stage IIIC, however, was not based on in-depth outcomes analyses because the prognostic impact of the depth of bowel wall invasion (T category) in N2 patients had not been evaluated in detail.

TABLE D-2 Pooled Rectal Analyses: Impact of NT Category on Survival

NT Category	Overall Survival (5-year)* No. Patients	%	*p* Value	Disease-Free Survival (5-year)* No. Patients	%	*p* Value
N0T3	668	74	0.046	664	66	0.05
T4	95	65		95	54	
N1T1-2	225	81	<0.001	225	74	<0.001
T3	544	61		536	50	
T4	59	33		59	30	
N2T1-2	180	69	<0.001	180	62	<0.001
T3	663	48		659	39	
T4	84	38		84	30	

From Gunderson LL, Sargent DJ, Tepper JE, et al: Impact of T and N substage on survival and disease relapse in adjuvant rectal cancer. A pooled analysis. Int J Radiat Oncol Biol Phys 54:390, 2002.
**Unadjusted Kaplan-Meier estimates.*

TABLE D-3 Pooled Rectal Analyses: Impact of NT Category on Disease Relapse

NT Category	Local Recurrence (5-year)* No. Pts	%	*p* Value	Distant Metastasis (5-year)* %	*p* Value
N0T3	664	8	0.04	19	0.04
T4	95	15		28	
N1T1-2	225	6	0.002	15	<0.001
T3	536	11		34	
T4	59	22		39	
N2T1-2	180	8	0.14	26	<0.001
T3	659	15		45	
T4	84	19		50	

From Gunderson LL, Sargent DJ, Tepper JE, et al: Impact of T and N substage on survival and disease relapse in adjuvant rectal cancer. A pooled analysis. Int J Radiat Oncol Biol Phys 54:390, 2002.
**Cumulative incidence rates.*

Rectal Cancer Pooled Analyses

Rectal cancer pooled analyses subsequently demonstrated the independent prognostic significance of each TN and NT category of resected rectal cancer with regard to both disease relapse and survival rates[23,24] (Tables D-2 to D-4). Patients with T1-2N1-2 disease had a more favorable prognosis than previously thought, and those with T4N1 lesions (stage IIIB in the AJCC sixth edition, along with T3N1 lesions) had a prognosis more akin to that of patients with T3-4N2 lesions (stage IIIC in the sixth edition). For patients with N2 disease, data from the rectal cancer pooled analyses showed that N2 disease does not by itself confer a poor prognosis (see Tables D-2 and D-3). Substaging by T category influenced both the 5-year overall survival (N2T1-2, 67%; N2T3, 44%; and N2T4, 37%; $p < 0.001$) and the 5-year disease-free survival (58% versus 36% and 30%; $p < 0.001$). Placement of all N2 patients within AJCC substage IIIC in the sixth edition did not reflect the markedly different prognosis of patients who were N2 found in the two rectal cancer pooled analyses.[23,24] Outcomes data from the pooled analyses supported revised substaging of stage III because of improved survival rates for patients with T1-2N2 cancers versus T3-4N2 cancers, and survival rates for those with T4N1 lesions were more similar to those of T3-4N2 tumors than T3N1 tumors.

SEER Colon and Rectal Analyses

As shown in Table D-5, data in the large SEER population-based colon and rectal cancer analyses were highly consistent with those of the rectal cancer pooled analyses with regard to the more favorable prognosis of patients with T1-2N1-2 category lesions (stage IIIC, AJCC sixth edition) and the less favorable prognosis of patients with T4N1 category cancers (IIIB, sixth edition).[27,28] Data from the SEER colon and rectal analyses and the rectal pooled analyses supported shifting T1-2N2 lesions from IIIC to an earlier stage of disease (stage IIIA or IIIB) and shifting T4N1 lesions from stage IIIB to IIIC (see Table D-5).

SEER colon and rectal cancer outcomes data (see Table D-5) supported the substaging of T4, N1, and N2 tumors.[27,28] Patients with T4a cancers (penetration to the surface of the visceral peritoneum [revised definition in the AJCC seventh edition]) have a better prognosis than those with T4b cancers (direct invasion of or adherent to other organs or structures) for each N category of disease (N0, N1, N2). For patients with N0T4a versus T4b lesions, there is a 15% to 20% improvement in absolute 5-year relative and overall survival rates, and for N1T4a versus T4b and N2T4a versus T4b disease, there is a 15% to 25% improvement in 5-year survival rates. Earlier analyses with much smaller data sets had suggested that patients with perforated T4 lesions may have a worse prognosis than those with invasion of or adherence to other organs or structures. However, as has been shown in the large SEER colon and rectal cancer datasets, patients with T4 lesions that penetrate to the surface of the visceral peritoneum have a more favorable prognosis than those with lesions that invade or adhere to other organs or structures.[27,28]

As shown in the SEER colon and rectal cancer analyses and prior series, both the number of positive nodes and the number of nodes examined had prognostic significance.[20,27,28] In the large SEER colon and rectal cancer analyses, patients with one positive node (N1a) have a 5% to 13% better 5-year survival rate than those with two to three positive nodes (N1b) by T category, with improved survival rates for all TN categories. Patients with four to five positive nodes (N2a) have a 5-year survival that is 5% to 19% better than those with more than seven positive nodes (N2b) by T category, with improved survival rates for all TN categories except T1N1a versus T1N1b.

These data in total suggest that both the extent of the primary tumor and the extent of the nodal disease are independent prognostic factors for patients with colorectal cancer. Both must be taken into consideration in designing appropriate therapy.

TABLE D-4 Rectal Cancer Pooled Analyses: Survival and Relapse Rates by Stage or TN Category of Disease

Risk for Relapse*	Stage: TN Category	Stage: Modified Astler-Coller	Survival Rate (5 year)†: Overall (%)	Survival Rate (5 year)†: Disease-Free (%)	Relapse Rate: Local (%)	Relapse Rate: Distant (%)	Stage: Dukes	Stage: TNM (6th ed)
Low‡	T1-2N0	A, B1	~90	~90	≤5	~10	A	I
Intermediate	T1-2N1	C1	81	74	7	15	C	IIIA
	T3N0	B2	74	66	9	20	B	IIA
Moderately high	T1-2N2	C1	69	62	8	31	C	IIIC
	T4N0	B3	65	54	13	28	B	IIB
	T3N1	C2	61	50	12	37	C	IIIB
High	T3N2	C2	48	39	14	47	C	IIIC
	T4N1	C3	33	30	23	39	C	IIIB
	T4N2	C3	38	30	17	53	C	IIIC

From Gunderson LL, Sargent DJ, Tepper JE, et al: Impact of T and N substage on survival and disease relapse in adjuvant rectal cancer. A pooled analysis. Int J Radiat Oncol Biol Phys 54:393, 2002.

**Data from rectal cancer pooled analyses in AJCC Hindgut Taskforce: Colon and rectum. In Greene FL, Page DL, Fleming ID, et al, editors: AJCC cancer staging manual, ed 6, New York, 2002, Springer, pp 113–124.*

†Survival rates based on unadjusted Kaplan-Meier estimates.

‡Data are derived from prior publications because patients who were low-risk were not eligible for the five Phase III trials in the rectal cancer pooled analyses.

TABLE D-5 Changes in Substaging of AJCC Stages II and III Colorectal Cancer Based on Rectal Cancer Pooled Analyses and SEER Rectal and Colon Cancer Analyses

TN Category	Rectal Pooled Analyses* (5-yr OS): No. Patients	Rectal Pooled Analyses* (5-yr OS): %	AJCC TNM Stage (6th ed)	AJCC TNM Stage (7th ed)	SEER Rectal Analyses† (5-year Observed Survival): No. Patients	SEER Rectal Analyses† (5-year Observed Survival): %	SEER Rectal Analyses† (5-year Observed Survival): SE	SEER, Colon Analyses‡ (5-year Observed Survival): No. Patients	SEER, Colon Analyses‡ (5-year Observed Survival): %	SEER, Colon Analyses‡ (5-year Observed Survival): SE
T1-2N0	—	—	I	I	9,961	77.6	0.5	23,861	76.3	0.3
T1N0	—	—	I	I	3,348	81.4	0.8	10,930	78.7	0.5
T2N0	—	—	I	I	6,613	75.7	0.6	12,931	74.3	0.3
T3N0	1060	77	IIA	IIA	10,615	64.0	0.5	40,338	66.7	0.3
T4N0	111	65	IIB	T4a, IIB	818	55.7	1.9	5,020	60.6	0.8
				T4b, IIC	769	44.7	2.1	3,088	45.7	1.0
T1-2N1	355	79	IIIA	IIIA	2,008	72.1	1.2	3,134	71.1	1.0
T1-2N2	226	67	IIIC	IIIA/IIIB§	508	56.1	2.6	499	61.5	2.6
T3N1	887	60	IIIB	IIIB	5,787	52.4	0.8	17,866	54.9	0.4
T4N1	62	35	IIIB	T4a, IIIB	480	48.2	2.5	2,771	47.0	1.1
				T4b, IIIC	423	24.3	2.5	1,774	27.9	1.2
T3N2	935	44	IIIC	T3N2a, IIIB	1,964	42.5	1.3	5,331	42.8	0.8
				T3N2b, IIIC	1,791	32.0	1.3	3,235	30.4	0.9
T4N2	108	37	IIIC	T4a, IIIC	397	34.3	2.7	1,653	26.6	1.2
				T4b, IIIC	308	15.6	2.5	1,383	15.8	1.1

OS, Overall survival; SE, standard error.

**Modified from Gunderson LL, Sargent DJ, Tepper JE, et al: Impact of T and N stage and treatment on survival and relapse in adjuvant rectal cancer. A pooled analysis. J Clin Oncol 22:1785–1796, 2004.*

†Modified from Gunderson LL, Jessup JM, Sargent DJ, et al: Revised TN categorization for rectal cancer based on SEER and rectal pooled analysis outcomes. J Clin Oncol 28:256–263, 2010.

‡Modified from Gunderson LL, Jessup JM, Sargent DJ, et al: Revised TN categorization for colon cancer based on national survival outcomes data. J Clin Oncol 28:264–271, 2010.

§IIIA–T1N2a; IIIB–T2N2a, T1-2N2b, T3N2a.

Adjuvant Gastric Cancer

As with other alimentary tract cancers, the two most important prognostic features are depth of invasion and extent of lymph node involvement. Nodal involvement reduces survival times, and the number of positive nodes is of prognostic importance. However, if the primary lesion is confined to the gastric wall (T1 or T2) when nodes are involved, the prognosis at 5 years (40% survival rate) is similar to that of patients with T2N0 or T3N0 lesions (~50% 5-year survival rate; see Chapter 45).

SINGLE-MODALITY VERSUS COMBINED-MODALITY TREATMENT

Radiation therapy has a role as a component of primary therapy in most cancers of the GI tract. It is used as part of the

initial management for patients with locally advanced cancers of the esophagus, stomach, pancreas, colon, rectum, and anus in most U.S. institutions and for hepatobiliary cancer in some institutions.

Chemoradiation: 5-Fluorouracil–Based

Although combined-modality therapy with chemotherapy and external beam radiation therapy (EBRT) is of great importance in many adult solid tumors, its use in the treatment of GI tumors is substantial and of long duration. 5-fluorouracil (5-FU) has been used as an anticancer therapy since the 1950s, and since the late 1960s, it has been used in combination with radiation therapy for GI tumors (concomitant with or without maintenance) (Figure D-1). Early studies of the combination were reported from the Mayo Clinic in the treatment of locally advanced pancreatic, gastric, and large bowel cancers.[29] Although modifications of this therapy have been developed, the use of concomitant 5-FU–based chemotherapy plus radiotherapy has remained a standard therapy for treatment of selected patients with tumors at almost all sites in the GI tract.

Although drugs such as cisplatin or mitomycin C are used in combination with 5-FU in a number of these anatomic sites (especially, the esophagus and anus), they have not replaced 5-FU but are used in conjunction with 5-FU and irradiation. There is now routine use of oral 5-FU analogs (e.g., capecitabine), with the hope that the oral formulation will make this treatment more acceptable to patients while maintaining similar efficacy; however, it has not markedly changed the toxicity profile although tumor efficacy appears as good as 5-FU infusional approaches.

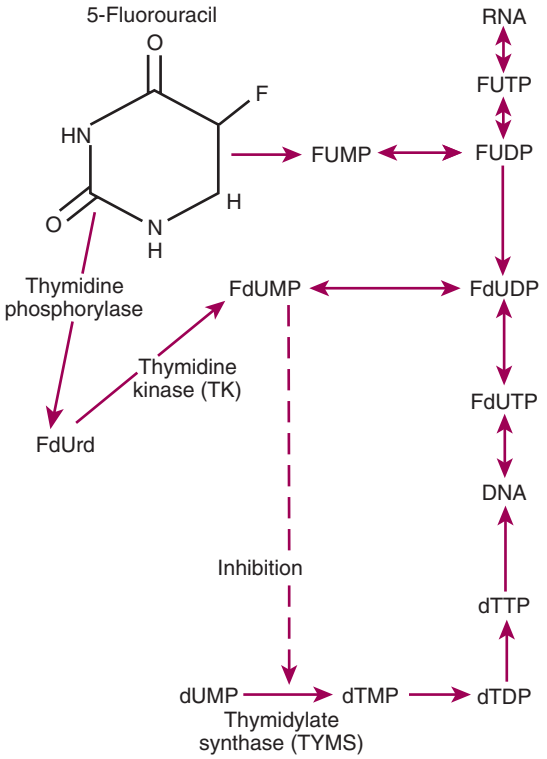


Figure D-1 The agent 5-fluorouracil (5-FU) has, as its primary mode of action, conversion into fluorodeoxyuridine monophosphate (F-dUMP), which acts to inhibit the enzyme thymidylate synthase, which is necessary for production of DNA. 5-FU can also be converted into fluorouracil triphosphate (FUTP) and incorporated into RNA or into fluorodeoxyuridine triphosphate (FdUTP) and incorporated into DNA. *FUMP*, Fluorouridine monophosphate.

For decades, 5-FU was essentially the only drug useful in colorectal and pancreatic cancer. Gemcitabine has now displaced 5-FU as the primary adjuvant drug treatment for pancreatic cancer, but other more aggressive combinations are being used for fit patients with metastatic disease. The combination of 5-FU or capecitabine and oxaliplatin or irinotecan is routinely used in the chemotherapeutic management of colorectal cancer. All of these agents have substantial radiation-sensitizing properties, and their use in rectal cancer has been extensively explored. The Phase III studies of oxaliplatin plus EBRT and 5-FU in rectal cancer have caused increased toxicity with no improvements in disease outcomes,[30] and irinotecan has not been as well studied because of additive toxicity (diarrhea) with radiation plus fluoropyrimidine. As mentioned, the use of EGFR or VEGF inhibitors as radiation sensitizers in a variety of sites in the GI tract, especially rectum, has generated substantial interest, but have not yet produced encouraging results beyond demonstration of tolerability.

Although surgery remains the primary mode of curative treatment for gastric, pancreatic, and large bowel cancers, combined chemotherapy plus irradiation has become the primary treatment for anal cancer and may offer an equivalent option to surgery alone for some patients with esophageal cancer. Although surgical techniques have continued to evolve, most prominently with the use of total mesorectal excision for rectal cancer, therapy with surgery alone is unlikely to significantly improve the survival rates for gastric, pancreatic, esophageal, and large bowel cancers. Adjuvant and neoadjuvant radiation therapy or chemotherapy, or both, offer the best prospect for improving cure rates.

A large number of studies have been performed using the aforementioned strategies. With unresected esophageal cancers, combined chemotherapy plus irradiation has clearly improved rates of disease control and 5-year survival over irradiation alone in Phase III randomized trials.[31] In an important Phase III trial from the Netherlands preoperative chemoradiation, using carboplatin and paclitaxel as the chemotherapy, improved survival rates compared with surgery alone in patients with resectable esophageal/gastroesophageal junction cancer.[32] For resected high-risk rectal cancers, postoperative chemoradiation has improved rates of local and distant disease control, disease-free survival, and overall survival compared with surgery alone or adjuvant irradiation.[33,34] Preoperative irradiation has demonstrated improved local control and survival when compared with surgery alone for resectable rectal cancer in a large randomized trial in Sweden,[35] and a large German trial[36] has shown the superiority of preoperative chemoradiation over the same therapy delivered postoperatively. Adjuvant postoperative chemoradiation has resulted in improved local control and survival in some Phase II and Phase III trials for resected pancreatic cancer.[37-40] Postoperative chemoradiation has also improved local control and survival rates when compared with surgery alone in patients with resected high-risk gastric cancers in a Phase III U.S. GI intergroup trial.[41]

For resected node-positive colon cancers, adjuvant chemotherapy has produced improved disease-free survival and overall survival compared with surgery alone. Postoperative chemoradiation has been evaluated in patients with resected high-risk colon cancers,[42] and although it has not been shown to be of value for the typical patient, it may be of value in selected clinical situations, as when microscopic residual disease remains (although this is not truly an adjuvant setting). A preferred approach would be to use imaging to identify patients who would likely have marginal resection if surgery were the initial component of treatment (e.g., a T4 lesion with adherence to a surgically unresectable structure). In such patients, preoperative chemoradiation would preferably

precede surgical resection. Finally, chemoradiation has replaced surgical resection as the primary treatment for anal carcinomas, with surgical resection being reserved for salvage therapy. Although these positive trials are exciting and encouraging, refinements in multimodality therapy will necessitate continued enrollment of patients in clinical trials to help develop the most effective combined-modality treatment strategies for the future.

Chemoradiation: New Chemotherapy Drugs

For the first time in many years, there are a variety of new drugs that may supplement or supplant 5-FU when used in combination with radiation therapy in the treatment of GI cancers. These new cytotoxic drugs include gemcitabine, irinotecan, oxaliplatin, and oral 5-FU compounds.

Gemcitabine is the first drug developed in many years with single-drug activity against pancreatic cancer.[43] Reliable data demonstrate that gemcitabine has substantial radiation-sensitizing properties,[44] and clinical studies are continuing with this drug used in combination with radiation therapy for patients with both locally advanced and resected pancreatic cancer.[45] Because gemcitabine is a potent radiation sensitizer, it needs to be used cautiously. In view of positive survival outcomes for gemcitabine plus nab-paxitaxal (Abraxane) versus gemcitabine alone for patients with metastatic pancreas cancer[46] it may be of interest to determine if both drugs can be given during concurrent EBRT. Although the combination of gemcitabine and irradiation may be effective in other sites in the GI tract, the fact that gemcitabine lacks substantial activity when it is used alone in colon and rectal cancer makes its use for these diseases unlikely.

A number of other drugs have substantial activity in colon and rectal cancer, including the topoisomerase inhibitor irinotecan (CPT-11) and the platinum compound oxaliplatin. Data exist to demonstrate radiation sensitization with irinotecan[45] and oxaliplatin.[47] Both of these drugs have been tested in combination with radiation therapy for patients with rectal cancer. Although preliminary Phase II data suggested that they appeared to increase the rates of pathologic complete response when used with 5-FU and irradiation in the preoperative setting, subsequent larger studies have suggested that this may not be true.[48-50]

Another group of important drugs are oral analogs of 5-FU, although they may behave slightly differently than the infusional approaches. Some of these agents are 5-FU prodrugs, and some act to inhibit the degradation of 5-FU, either by direct or indirect inhibition of the degradation pathway. Others attempt to increase tumor selectivity, and yet others act as specific inhibitors of thymidylate synthase (in contrast to the nonspecific action of 5-FU).[51] The major potential advantages of these compounds are the convenience for patients and the elimination of the continuous infusion pumps needed for 5-FU. The toxicity spectrum of these agents does not differ substantially from that of 5-FU given by conventional infusion.

Capecitabine is an agent that has entered routine clinical use both as a single-modality chemotherapeutic agent and used in combination with irradiation.[52] Capecitabine is delivered twice daily, and although serum levels are much flatter than after a 5-FU bolus, major variations in serum levels do exist. Therefore, the timing of irradiation and capecitabine may still be important. The recommendation is to take capecitabine approximately 1 hour before the delivery of radiation therapy to maximize radiation sensitization. Capecitabine doses used with concurrent radiation are less than doses of the drug used alone (typically, 1650 mg/m^2/day delivered in two doses) and investigators vary on whether the drug should be delivered 7 days per week or Monday to Friday with EBRT.

IRRADIATION TECHNIQUE AND TOLERANCE

Irradiation Field Definition

Because treatment tolerance to irradiation is usually a function of both dose and volume, proper definition of tumor and target volumes is of utmost importance. If patients are referred for primary or preoperative EBRT, the radiation oncologist can obtain the necessary imaging studies to define both the primary tumor and the nodal areas at risk. If the patient is referred after complete resection, however, the radiation oncologist is dependent on the availability of pertinent preoperative imaging studies or placement of surgical clips at sites of tumor adherence or microscopic residual disease.

For unresected alimentary tract cancers (e.g., esophageal, stomach, colorectal, anal cancers), the primary lesions and nodal areas at risk are best defined with CT scanning. The chest plus the abdomen are imaged for esophageal cancers, the abdomen and generally the chest for gastric cancers, and the chest, abdomen, and pelvis for colorectal and anal cancers. PET/CT scans are preferable for esophageal and anal cancers because these tumors are usually PET avid and the primary tumors are often not well seen on conventional CT scan. Endoscopic ultrasound (EUS) can also be used in esophageal, gastric, and rectal tumors to determine both the depth of invasion in the wall and the presence of nodal involvement. The ability to biopsy suspicious areas is an advantage for endoscopic evaluation. None of these tests adequately define longitudinal disease extension in esophageal cancer, however. EUS is the best widely used imaging technique for determining the T category of disease for esophageal, gastric, and rectal cancers before resection, but it is most useful in rectal cancer for defining the patients who need preoperative therapy. MRI is considered by many to be superior to EUS in rectal cancer because of its ability to assess the adequacy of the surgical mesorectal excision. The use of endoscopy to both define lesions and obtain biopsies has essentially eliminated the use of preoperative contrast radiographs, so the preoperative CT, PET, or MRI imaging is essential to construct proper irradiation fields if patients are referred after resection. However, some important structures (such as the anal verge) are not well defined with cross-sectional imaging unless markers are placed at the site of interest.

For unresected biliary tract cancers, endoscopic retrograde cholangiopancreatography (ERCP), percutaneous transhepatic cholangiography (PTHC), and MRI or magnetic resonance cholangiopancreatography (MRCP) demonstrate the distal and proximal extent of disease most precisely. If transhepatic catheters have been placed at the time of PTHC imaging, the radiation oncologist can reinject the catheter with contrast medium to reconstruct the ductal system and define target volumes. If stents have been placed at ERCP, the relationship of the stent to ductal involvement as demonstrated on ERCP imaging can be used to define tumor and target volumes. MRI can also effectively reveal these tumors and is commonly used. The medial and lateral disease extent is best distinguished with MRI/MRCP or PET/CT imaging.

With unresected pancreatic cancers, abdominal CT or MRI best demonstrates tumor and nodal target volumes, and PET/CT is used by some to better define the primary lesion and rule out early metastatic disease. If the tumor has been resected, postoperative CT or MRI scans of the abdomen can help rule out liver metastases and define postoperative nodal volumes, and the preoperative CT scan and surgical clips can be used to define the tumor bed.

Conformal three-dimensional radiation therapy with CT-based treatment planning is recommended for the

treatment of most, if not all, patients with GI cancer, and intensity-modulated radiation therapy (IMRT) is appropriate for some GI cancer sites, especially anal canal cancers. For patients with esophageal and gastroesophageal junction cancers, CT-based planning is useful in defining the medial-lateral and anteroposterior extent of tumor, but it should be combined with contrast radiographs, endoscopic information, and PET/CT imaging to determine the proximal and distal extent of the primary lesion. In patients with gastric cancer, the proximal stomach or gastric remnant is best defined by oral contrast images plus CT scanning because CT imaging alone may underestimate the anatomic location. With CT scanning for rectal cancer treatment planning, the precise location of the anal sphincter should be defined by placing BB markers or another type of metal marker at the anal verge. The anorectal margin is not visualized on a CT scan without contrast medium in the rectum. Fusion of PET/CT images may be helpful in defining the gross tumor extent for both rectal and anal lesions.

Definition of irradiation fields can be difficult in hepatic irradiation. It is critical to use high-quality CT or MR imaging and to have control over the liver position during the breathing cycle. Diagnostic images often need to be fused with treatment planning scans, and placement of fiducial markers can be useful for some radiation techniques, including stereotactic body irradiation (SBRT). Typically, these tumors do not have a large degree of extension into the hepatic parenchyma, but margins for uncertainty and breathing are critical.

Normal Tissue Tolerance

When irradiating the abdomen and pelvis, there are numerous normal structures that can be dose limiting and must be considered in treatment planning. These include the stomach, small intestine, spinal cord, large intestine, liver, and kidneys, in addition to the soft tissue in the abdomen. A full discussion of the tolerance of these structures is beyond the scope of this overview, but a brief review is given here.

Upper Gastrointestinal and Extrapelvic Colon Cancers

The tolerance of the liver is dose limiting when a substantial portion of the liver is included in the radiation field. The hepatic parenchyma is relatively sensitive to radiation, with total organ tolerance doses in the range of 30 Gy, using conventional fractionation (1.5 Gy to 2.0 Gy), being near tolerance. The ability to tolerate higher doses to portions of the liver is primarily dependent on the volume of liver receiving high doses because recovery of the hepatic parenchyma is dependent on hypertrophy of the unirradiated liver. In an individual with normal baseline hepatic function, it is possible to irradiate approximately 50% to 60% of the liver to high doses without undue problems if the remainder of the liver remains untreated (see Chapter 49). If hepatic function is compromised, less parenchyma can be safely treated, although an exact determination of the safe amount is not defined. Because it is possible to totally irradiate and destroy a portion of the liver without danger to the patient, there is essentially no limit to the dose that can be given to small portions of the liver, although biliary obstruction may be produced after high doses to the major biliary radicals. Dawson et al[53] have conducted a series of elegant clinical trials that define hepatic tolerance better than has been done for most other organs.

Hepatic tolerance is becoming a major issue with the increased interest in irradiating hepatocellular carcinomas and liver metastases. Although radiation oncologists have historically not had a major role in treatment of hepatocellular cancers, improvements in technology has allowed for better radiation dose delivery and a greater use of radiation in selected clinical situations, especially for localized but unresectable hepatocellular carcinomas. Preliminary data suggest that radiosurgical or fractionated SBRT approaches will be effective complements to surgical resection and radiofrequency ablative approaches.

The tolerance of the kidney is conceptually similar to that of the liver in that irradiation of a portion of the kidney to a high dose is well tolerated if the baseline renal function is good and if a significant portion of the remaining kidney is unirradiated to allow for hypertrophy (e.g., only 20% to 30% of the kidney receives more than 20 Gy). It is important to be certain that the baseline renal function is adequate (by measuring creatinine clearance or by estimating the clearance based on the creatinine level, age, gender, and weight of the patient, using the Cockcroft formula) and that the contralateral kidney is functioning properly so that it can take over the renal function. The latter is best done with a functional renal scan (such as a dimercaptosuccinic acid [DMSA] scan) that can provide the percentage of function from each kidney. Although the data on renal tolerance are fairly old, even moderate doses (in the range of 25 Gy) can produce substantial renal injury. Doses higher than 30 Gy are likely to produce major renal parenchymal injury. Studies suggest that clinically significant sequelae are unlikely after conventional abdominal irradiation if the preceding factors are taken into consideration.[54] Although it is possible to produce severe kidney injury with secondary renovascular hypertension, this is an uncommon event.

The stomach has generally been considered to be a radiation-sensitive structure, with ulcer formation occurring after doses greater than 45 Gy to 50 Gy (1.8-Gy to 2-Gy fractions), but precise gastric tolerance has not been well established. Although a large number of patients have received moderate to high doses of radiation therapy to the upper abdomen, this has usually been done for tumors that have a poor cure rate and for patients where survival of longer than 2 years is relatively unusual. The experience in the treatment of Hodgkin's disease clearly demonstrates gastric tolerance to doses of 45 Gy. When irradiating a portion of the stomach in the treatment of upper GI cancers, one must minimize both the volume and the dose to the stomach. It is of interest, however, that there are few recent data describing gastric ulceration, suggesting that some of the old tolerance data may not be reliable. Mayo Clinic data on the treatment of bile duct cancers suggest that gastroduodenal tolerance is best if doses of 54 Gy or less (in 1.8-Gy fractions) are used. With EBRT plus 5-FU, the rate of grade-3 or higher GI intolerance is 10% with doses of 54 Gy or less and 30% to 40% with doses of more than 54 Gy.[55]

Tolerance of the pancreas to radiation therapy is not often discussed, but there is anecdotal evidence that both exocrine and endocrine dysfunction can result, although analyses are complicated by the effects of the tumor and of surgery. It is appropriate for the radiation oncologist to consider the possibility of pancreatic dysfunction during patient follow-up. Pancreatic enzymes are commonly needed during and after therapy, and insulin is required at times.

Pelvic Gastrointestinal Cancers

The small bowel is the organ that has produced the most clinical problems after conventional radiation therapy in the pelvis. Moderate doses to the small bowel (50 Gy in 1.8-Gy to 2-Gy fractions) will begin to cause clinically significant problems. It has been suggested that risk factors for injury include diabetes and hypertension as well as prior surgery, but this finding has not been well substantiated. It is clear that the volume of irradiated small bowel is also important, but it has not been well quantified as to how much bowel can be treated safely. When

larger volumes are treated, small bowel obstruction is the most likely complication.[56] The obstructive episodes can be recurrent, and 50% or more of patients may require laparotomy for resolution. At surgery, it is often not possible to resect the damaged small bowel, which is usually enveloped in a fibrotic mass, and a surgical bypass may be the treatment of choice. However, if the damaged bowel can be resected with low morbidity, that approach is optimal. Dissection of irradiated bowel in an attempt to free up all adhesions may result in enterotomy and subsequent fistula. Small bowel complications are most common with irradiation of the pelvis, an area that has commonly been exposed to extensive surgery with associated adhesions and small bowel fixation. Although complications are less likely in the upper abdomen, they can still occur, and efforts should be made to minimize the volume of irradiated small bowel.

There are a number of manipulations that the radiation oncologist can use to minimize the amount of small bowel in a pelvic irradiation field, including the use of IMRT or three-dimensional conformal irradiation techniques. The first action is to determine the location of the small bowel. This can be done by giving oral small bowel contrast medium at least 45 minutes before a radiographic imaging study, either by conventional simulation or CT scanning. With this information, the radiation oncologist can design fields that will minimize the volume of small bowel irradiated. It is also helpful to work with a surgeon who can perform surgical manipulations to move the small bowel out of the pelvis. A number of techniques have been tried, including reperitonealization of the pelvic floor after abdominoperineal resection, using a vascularized omental sling or pedicle to displace small bowel out of the pelvis, retroverting the uterus to act as a space-occupying device, and putting mesentery or a foreign body into the pelvis for the same purpose. In addition, during simulation, one can use bladder distention or displacement devices to shift small bowel out of the pelvis. Having the patient lay in the prone position on a false tabletop located at or superior to the radiation field (9-cm × 12-cm opening) is one technique that has been effective for many patients. These techniques work to a varying extent on individual patients.[57] Small bowel being fixed in the pelvis is much less of a problem when patients are receiving preoperative radiation therapy for rectal cancer, the standard of care at this time. Whichever approach is taken, the treating physician must pay attention to the location of the small bowel and dose to the organ or risk significant complications.

There is less information on the tolerance of the large bowel (colon and rectum) to high radiation doses, and much of the information available comes from irradiation of non-GI tumors, especially those of the prostate and cervix. There is little information on the tolerance of the colon, partially because there has been little high-dose irradiation of the intraperitoneal or retroperitoneal colon. Rarely is the colon a dose-limiting structure. The rectum or portions of it have been treated to doses of 65 Gy to 70 Gy or higher for cervical, prostate, and anal cancers and for localized treatment of rectal cancers. It is clear that portions of the rectum can be treated to high doses with minimal late effects. The most obvious example of this is in the use of endocavitary radiation therapy of small rectal cancers. In this technique, doses of approximately 90 Gy to 120 Gy have been delivered in four fractions. Although the rectal muscular wall receives a low dose from the first two fractions because of rapid dose fall-off, it receives a full dose for the last one to two fractions. Late complications such as bleeding and ulceration occur in 10% to 15% of patients, and only an occasional temporary diverting colostomy is needed, likely because the rectal mucosa can be repopulated from surrounding normal tissue and because the area of scarring is not large enough to cause stricture formation.

However, when high doses of radiation are given to a substantial portion of the rectal circumference (i.e., more than half), the tolerance is much less. With circumferential irradiation, the dose to a 10-cm length of rectum is preferably limited to 60 Gy or less in 2-Gy fractions to prevent problems with bleeding, ulceration, and narrowing of the rectum. Even with partial organ radiation therapy, there have been significant problems with bleeding (10% to 15% incidence) reported at doses of approximately 72 Gy. Although conservative treatment with bulk agents and steroid preparations can alleviate most situations, laser therapy at the time of endoscopy may be necessary to control bleeding. Difficult management problems are rare but at the extreme can require surgical correction, usually a temporary diverting colostomy.

There is even less information available on anal tolerance. However, it is generally thought that doses higher than 55 Gy to 60 Gy to the whole anal canal in conjunction with chemotherapy, as used in the treatment of anal cancer, have a risk of stricture formation or poor anal sphincter function. In the treatment of rectal cancer, one should try to minimize the amount of anus in the radiation field because anal irradiation produces a large amount of acute morbidity, occasional stricture formation, or poor late functioning of the anus. There is clearly a significant risk of late morbidity in anorectal function that can cause clustering and frequency of bowel movements with suboptimal control and intolerance to certain foods.[58] These effects are likely the result, at least partially, of anal dysfunction as well as poor rectal capacity from surgery or irradiation. Minimizing the radiation dose and volume and careful surgical techniques need to be used to minimize the risk of late complications.

Irradiation Boost Techniques

For completely resected, margin-negative GI cancers, adjuvant doses of irradiation (50 Gy to 54 Gy) plus concomitant 5-FU–based chemotherapy are adequate to achieve local control in 85% to 90% of patients. For margin-positive or unresected GI cancers, the dose of irradiation required to achieve adequate local control would usually exceed the normal tissue tolerance (e.g., >70 Gy in 1.8-Gy to 2-Gy fractions). Therefore, the use of brachytherapy or intraoperative electron irradiation (IOERT) as a supplement to EBRT and chemotherapy after resection may improve local control rates in the treatment of locally advanced GI cancers.

The use of IOERT as a component of treatment for a variety of disease sites is discussed in Chapter 17 and for GI malignant diseases in Chapters 47, 48, 50, and 51. IOERT plus EBRT (with or without 5-FU) and maximal resection appear to improve rates of both local control and survival for locally unresectable and locally recurrent colorectal cancers.[59-61] With unresectable pancreatic cancers, the addition of IOERT to EBRT with or without 5-FU improves local control rates but has no apparent impact on survival rates in view of the high rates of relapse in the liver and peritoneal cavity.[62-64]

Brachytherapy has been used as a supplement to EBRT with biliary tract cancers.[65,66] There is a suggestion of improved survival rates in patients treated with both EBRT and brachytherapy compared with either alone (see Chapter 49), but Phase III trials are unlikely in view of small patient numbers.

SUMMARY

Radiation therapy is now a part of the therapeutic approach for many patients with cancers of the GI tract, although mostly for patients with moderately advanced locoregional disease. In most of these sites, the combination of radiation therapy

and 5-FU–based chemotherapy is standard therapy, although cisplatin or mitomycin is used with 5-FU in tumors of the esophagus and anus. In many GI cancer sites, chemoradiation is used as an adjuvant to surgical resection because of the propensity of GI rumors to recur locally and the difficulty in obtaining a wide resection margin, usually relating to the anatomic site. Careful attention to radiation therapy technique and respect for normal tissue tolerance are essential if local control is to be obtained without producing unacceptable normal tissue morbidity.

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CHAPTER

47 Gastric/GE Junction Cancer

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INCIDENCE

For 2015, the predicted incidence of stomach cancer in the United States was 24,590 cases, and the predicted number of deaths was 10,270.

The site of origin within the stomach is shifting in the United States as more proximal lesions are diagnosed.

BIOLOGIC CHARACTERISTICS

The main prognostic factors relate to locoregional tumor extent and include both nodal involvement and direct tumor extension beyond the gastric wall.

STAGING EVALUATION

Initial evaluation should include history and physical examination, complete blood count, liver chemistries, endoscopy with biopsy and ultrasonography (determine degree of direct tumor extension), and computed tomography (CT) of the abdomen (define extragastric disease) and chest (especially for gastroesophageal junction [GEJ] lesions).

Additional studies that may help define extent of disease include laparoscopy (rule out peritoneal seeding or early liver metastasis) and positron emission tomography (PET), especially for for GE junction tumors.

PRIMARY THERAPY

Surgical resection is the primary therapy for resectable gastric cancers. Cure rates of 80% or higher are achieved with early lesions (nodes negative, confined to mucosa or submucosa), which are uncommon in the United States.

Extended D2 node dissection has not improved survival in randomized trials.

ADJUVANT THERAPY (RADIATION, CHEMOTHERAPY)

Adjuvant therapy is indicated on the basis of patterns of relapse and survival results with surgery alone (high incidence of locoregional relapse and distant metastases).

A U.S. Intergroup Phase III trial of 556 patients (pts) demonstrated a survival benefit for combined modality postoperative chemoradiation (postop CRT) versus a surgery alone control arm (3-year relapse-free survival [RFS] 48 versus 31%, $p = 0.001$; 3-year overall survival [OS] 50 versus 41%, $p = 0.005$).

The Phase III ARTIST trial (458 pts) compared postop chemo to postop CRT after D2 resection. In a subset analysis of pts with positive nodes (396 pts), 3-year disease-free survival (DFS) was improved with CRT (77.5% versus 72%, $p = 0.0365$).

Preoperative irradiation improved locoregional control and OS in a Beijing Phase III trial of 370 patients (5-year OS 30% versus 20%, $p = 0.009$).

Preoperative chemoradiation improved survival in a CROSS Phase III trial comparing surgery alone with preop CRT for 366 analyzable patients with adenocarcinoma (ACA) of the esophagus or GE junction. Median OS was 49.4 versus 24 months, 3-year OS 58 versus 44%, and 5-year OS 47% versus 34% ($p = 0.003$).

The POET trial of 120 pts with GEJ lesions tested preoperative (preop) chemotherapy versus CRT; outcomes trends favored preop CRT over chemo alone for both OS ($p = 0.07$) and local control ($p = 0.06$).

Although most Western trials of postoperative chemotherapy alone are negative for both single and multiple drugs, a British Phase III trial of 503 patients demonstrated a survival advantage for perioperative epirubicin, cisplatin, 5-fluourouracil ([5-FU]; ECF) chemotherapy (when compared with surgery alone (5-year OS 36% versus 23%, $p = 0.009$). In addition, a French Phase III trial of 224 patients found a survival advantage for perioperative cisplatin and 5-FU (CF) compared with surgery alone (5-year OS 38% versus 24%, $p = 0.02$).

Postoperative and preop CRT and perioperative ECF or CF are all appropriate appropriate standards of care.

LOCALLY ADVANCED DISEASE

Both external beam radiation plus chemotherapy and intraoperative radiation result in long-term survival in 10% to 20% of patients in randomized and nonrandomized trials.

Neoadjuvant chemotherapy may increase resection rates, but the incidence of locoregional relapse is still high. Pathologic complete response specimens are uncommon (0% to 9%).

PALLIATION

Multidrug chemotherapy regimens have response rates of 30% to 50%, but survival improvements are modest.

The ECF regimen produced improved response rates and survival when compared with the combination of 5-fluorouracil, doxorubicin (Adriamycin), and high-dose methotrexate (FAMTx) in a British Phase III trial.

A recent study of vascular endothelial growth factor (VEGF) inhibition with the monoclonal antibody refucirumab has shown a survival advantage, and HER2 blockade in tumors with HER2 overexpression produces a survival benefit.

European Phase III trials demonstrate improvement in quality and duration of life with palliative chemotherapy versus supportive care.

The primary therapy for resectable gastric cancer for patients who can tolerate the procedure is surgical resection. At the time of diagnosis, gastric cancers are localized and surgically resectable in approximately 50% of patients; however, regional nodal metastases or direct invasion of surrounding organs or structures is frequently encountered and precludes cure by surgery alone in many patients. For patients with lower risk lesions (confined to gastric wall, nodes negative; T1-2N0M0) adjuvant treatment is usually not recommended. Because both local and systemic relapses are common after resection of

high-risk gastric cancers (beyond wall, nodes positive, or both; T3-4N0, Tany N1-3), adjuvant treatment is indicated for these patients. The results of Phase III trials that demonstrate a survival benefit for postoperative chemoradiation, preoperative external beam irradiation (EBRT), preoperative chemoradiation, and perioperative ECF or CF versus surgery alone will be summarized and future trial designs will be discussed. Results of Surveillance, Epidemiology and End Results (SEER) analyses and meta-analyses that support the role of adjuvant irradiation or chemoradiation will be summarized.

For patients with locally advanced disease that appears unresectable for cure, several treatment options appear to favorably impact disease control and survival. These include EBRT plus concurrent chemotherapy, maximal resection plus intraoperative irradiation (IORT), and preoperative chemotherapy or chemoradiation.

In the setting of metastatic disease, there are many active chemotherapy agents that can produce meaningful response alone or in combination with other agents, but the duration of response is usually limited. Phase III trials demonstrate both a survival and quality of life benefit for multidrug chemotherapy versus best supportive care for patients with metastatic cancers.

EPIDEMIOLOGY AND ETIOLOGY

Epidemiology

In the United States, gastric cancer now ranks 14th in incidence among the major types of malignancy. Over the past 60 years, there has been a significant decline in the incidence of gastric cancer among both sexes in Western countries[1] (eFigure 47-1). In the United States, from 1930 to 1980, the incidence decreased from 38 to 10 (per 100,000) for men and from 30 to 5 (per 100,000) for women. In 2015, it was estimated that 24,590 new cases and approximately 10,270 deaths would occur.[2] The disease rarely occurs before the age of 40 years, but its incidence increases steadily thereafter and peaks in the seventh decade. African Americans, Hispanic Americans, and American Indians are twice as likely to develop gastric cancer as are whites.[3] There has been a slight improvement in overall 5-year survival among U.S. patients: 11% (1900 to 1963), 15% (1974 to 1976), 18% (1980 to 1982), and 21% (1989 to 1994).[3]

Although gastric cancer incidence has decreased significantly in the United States, on a worldwide scale, gastric cancer has a high incidence rate and is still a leading cause of cancer death.[2,4] Of the 45 countries in which age-adjusted death rates for gastric cancer were compared for 2000 (eFigure 47-2), the United States ranked 45th for both males and females.[2] Kyrgyzstan ranked first for both males (47.0 in 100,000) and females (18.9 in 100,000).

The site of origin within the stomach has changed in frequency in the United States over recent decades, with proximal lesions now being diagnosed and treated much more commonly than previously. The largest percentage of gastric cancers still arise within the antrum or distal stomach (≈ 40%), are least common in the body of the stomach (≈ 25%), and are of intermediate frequency in the fundus, cardia, and gastroesophageal (GE) junction (≈ 35%). In 1930, most cases of gastric carcinoma originated in the distal stomach (body and antrum). The reduction in incidence of gastric cancer from 1930 to 1980 primarily is attributable to a decline in distal lesions.[5]

Since the 1970s, there has been a steady rise in the incidence of adenocarcinoma of the GE junction and proximal stomach. For both sites, the rate of increase during the 1970s and 1980s surpasses that of any other cancer, including melanoma, lung cancer, and non-Hodgkin's lymphoma.[6] Similar trends in the increased incidence of gastric cardia cancer have also been reported in Denmark, where rates were much higher in men, and in the United Kingdom, where rates were highest among those in higher socioeconomic classes.[7]

Etiology

Although the precise etiology is unknown, environmental factors are likely to be important. The incidence of gastric cancer in first- and second-generation Japanese who have moved to the United States is much lower than in native Japanese citizens.[8] Studies of immigrant populations from Japan and Eastern Europe show that the risk of the disease declines markedly in the second and third generations.[9] The excess risk of first-generation immigrants is largely restricted to the intestinal type.[10] The risk of gastric cancer is inversely associated with socioeconomic status throughout the world,[11] and the marked decline in the incidence of gastric cancer in industrialized countries, including the United States, suggests that environmental factors play an important role. These may be related to poor nutrition, inadequate sanitation facilities, and substandard quality of food preservation.

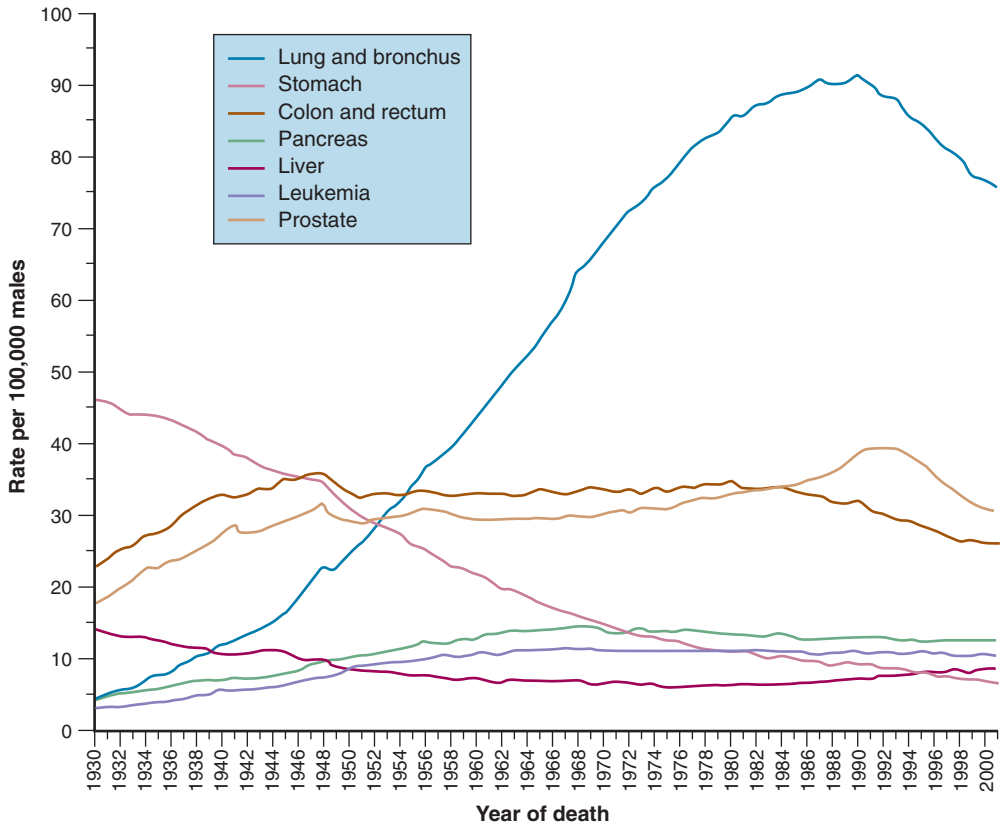
Diets rich in fruits or vegetables are associated with a reduced risk of gastric cancer,[12] whereas diets containing abundant quantities of smoked, heavily salted, or poorly preserved foods are associated with an increased risk of this disease.[12,13] Excessive dietary salt has been associated with atrophic changes in the gastric mucosa.[14] Chronic atrophic gastritis and the associated abnormality, intestinal metaplasia, are most closely linked to the intestinal type of gastric adenocarcinoma. These lesions can progress to dysplasia and carcinoma.[15] The prevalence of atrophic gastritis and intestinal metaplasia is highest in regions of the world that have the highest rates of gastric cancer.[16]

It has been postulated that endogenous formation of *N*-nitroso compounds (amine or amides) can occur in the stomach when both an amino compound and a nitrating agent such as nitrate are present.[13] Anaerobic bacteria that colonize stomachs in which achlorhydria occurs can convert nitrates and nitrites to potentially carcinogenic nitroso compounds.[12]

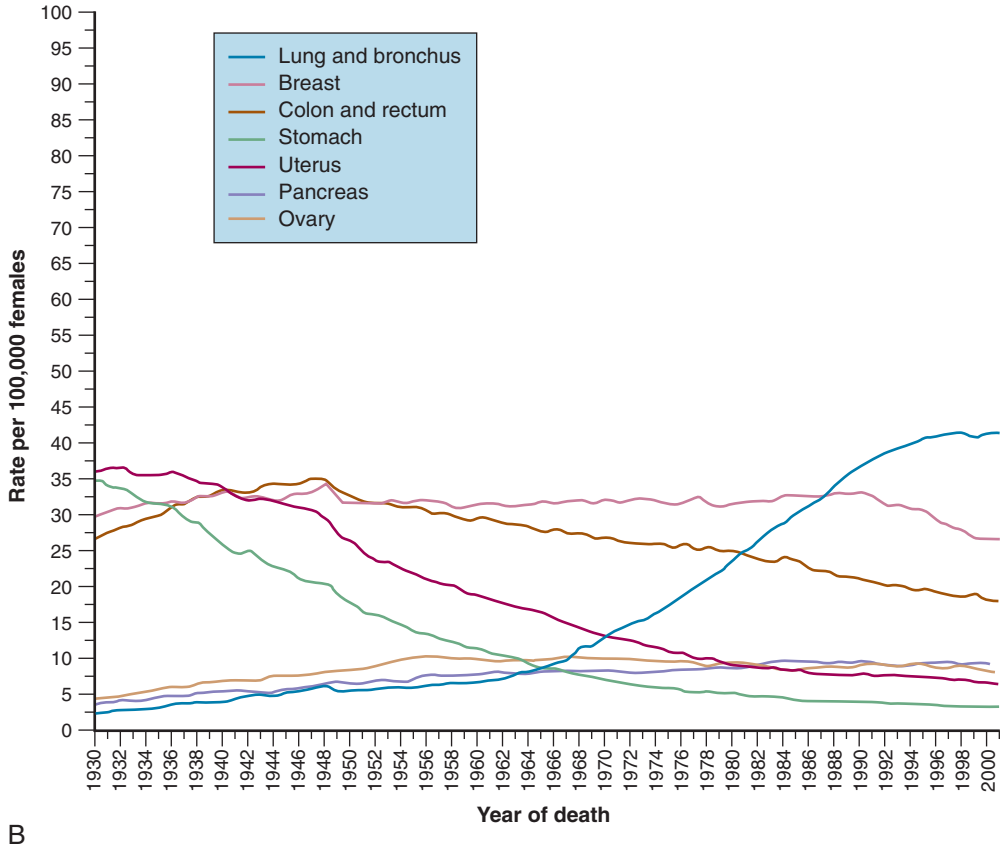
Epidemiologic studies have demonstrated an association between *Helicobacter pylori* infection and risk of gastric cancer.[17] Serologic studies have reported that persons with *H. pylori* infection have a threefold to sixfold higher risk of distal gastric cancer than those without infection.[18,19] The exact role of *H. pylori* in gastric carcinogenesis is still to be determined, although infection is associated with the development of chronic atrophic gastritis and decreased acid production.[12] However, only a minority of infected patients develops gastric cancer, and data do not yet exist on the effect of treatment of the *H. pylori* infection on subsequent malignancy. Proximal gastric cancers (GE junction, cardia) do not appear to be related to either *H. pylori* infection, atrophic gastritis, or decreased acid production; it is possible that an inverse relationship exists.

There has been a dramatic increase in the incidence of GEJ and gastric cardia carcinoma over the past few decades, similar to the increase in distal esophagus adenocarcinomas, suggesting that they may have similar etiologies.[20,21] Although the reasons for these changes are unknown, they may be related to the increased incidence of gastric reflux and Barrett's esophagus.

In summary, the worldwide decline in distal, predominantly intestinal-type gastric adenocarcinoma may be the result of improved food handling (refrigeration and storage). In contrast, proximal (mostly diffuse-type) gastric cancer, which is equally prevalent in both high-risk and low-risk regions, is probably attributable to other, as yet unrecognized, factors.[20] The exact role of *H. pylori* in gastric carcinogenesis remains to be defined.[14]

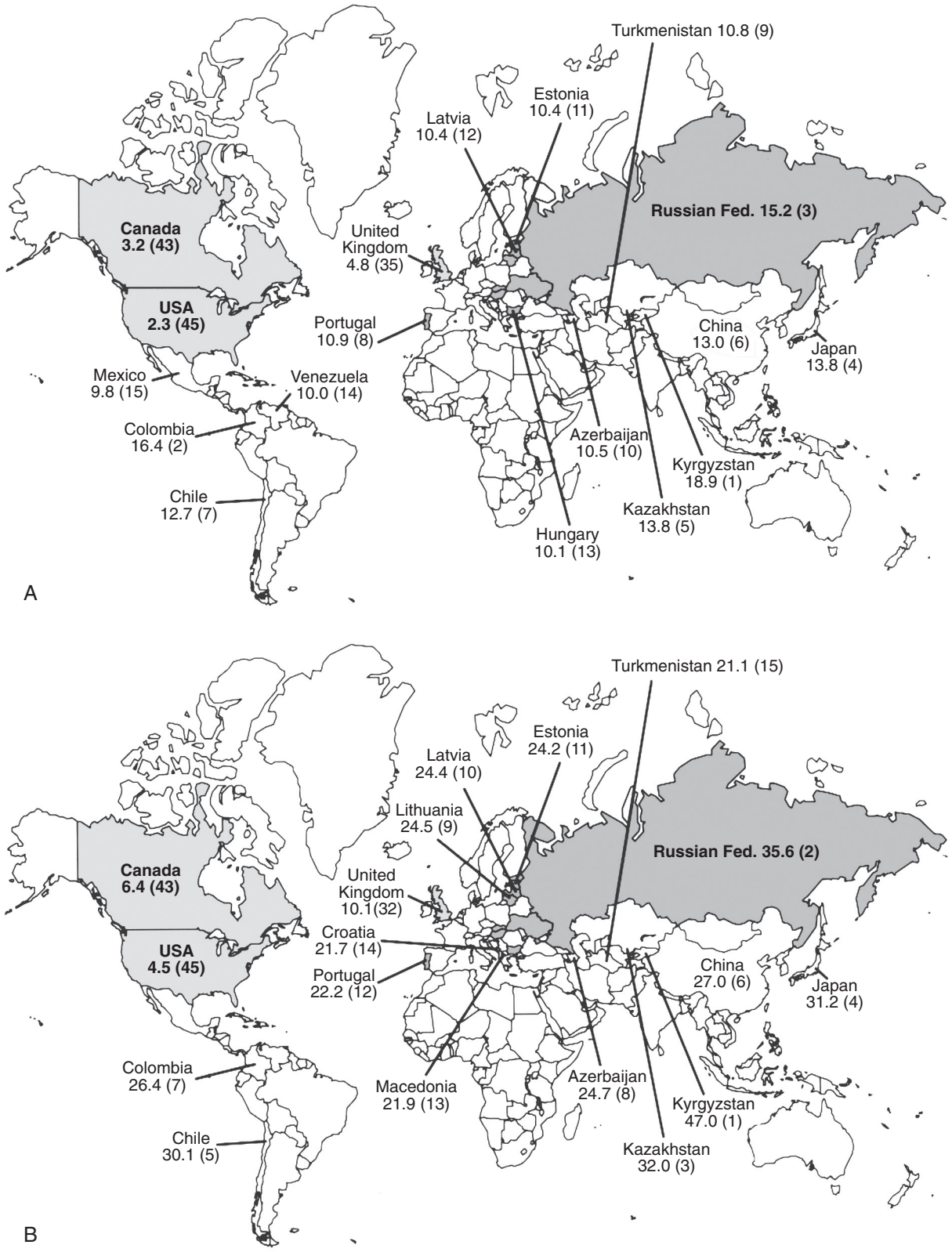


A



B

eFigure 47-1 Age-adjusted (to U.S. 1970 standard population) cancer death rates in the United States from 1930 to 2001 in selected sites for males **(A)** and females **(B)**. In females there is a steady decrease in death rates for stomach, breast, and colorectal cancers. From 1960 to 1998, a marked increase in death rates has occurred for lung cancer in females. For males, a similar decrease in death rates has occurred with gastric cancer. An increase in death rates for lung cancer existed in males from 1930 to 1990 with a continual decrease during the 1990's.
(Redrawn from Jemal A, Murray T, Ward E, et al: Cancer statistics, 2005. CA Cancer J Clin 55:10–30, 2005.)



eFigure 47-2 Age-adjusted (to World Health Organization world standard population) death rates for gastric cancer from 2000 in 45 countries for males **(A)** and females **(B)**. Rates in the United States, Canada, and United Kingdom are compared with selected countries, including the 15 countries with the highest death rates.
(Data from Jemal A, Thomas A, Murray T, Thun M: Cancer statistics, 2002. CA Cancer J Clin 52:23–47, 2002.)

PREVENTION AND EARLY DETECTION

Early detection would markedly improve prognosis of gastric cancer because surgical resection has a high cure rate with lesions limited to the mucosa or submucosa. In the United States, however, the incidence of early gastric cancer is less than 5% in most series. In Japan, whereas the incidence of carcinoma confined to the mucosa or submucosa was only 3.8% in the 1955 to 1956 period, by 1966 the incidence of early lesions had increased to 34.5% because of vigorous screening procedures (5-year survival rates of 90.9% in this cohort of patients). The value of screening is evidenced by the 5-year survival rate of 53% for all gastric cancers in Japan versus 21% for the world.[4]

Although mass screening has been useful in Japan to detect early cancers, defined high-risk populations do not exist in the United States to justify the expense of widespread screening. Individual practitioners could use endoscopy to screen patients who have occupational or precursor risk factors or patients with persistent dyspepsia or GE symptoms, but it is not clear that this strategy is appropriate for populations as the conversion rate to cancer per year is low. It is not yet known whether screening of patients with *H. pylori* infection will be of value in achieving diagnosis of early gastric cancer, although treating *H. pylori* infection could reduce incidence.

Germline mutations in the *CDH-1* gene, which encodes the E-cadherin protein, have been recognized in families with hereditary diffuse gastric adenocarcinoma. Carriers of these mutations have a 70% lifetime risk of developing gastric cancer. Several reports of prophylactic gastrectomy have demonstrated the routine presence of microscopic intraepithelial carcinomas for patients having regular endoscopic surveillance with multiple random biopsies.[22-24] Early total gastrectomy has been recommended for this small patient population because of the lack of effective early tumor detection. Microscopic evaluation of the proximal and distal resection margins for complete removal of the gastric mucosa is necessary because residual gastric mucosa can degenerate and result in a gastric cancer.[24]

BIOLOGIC CHARACTERISTICS AND MOLECULAR BIOLOGY

Prognostic Factors

The most valuable prognostic indicators relate to tumor extent. With either blood-borne metastasis or peritoneal seeding, cure is rare to nonexistent. Survival decreases with progressive direct tumor extension both within and beyond the wall of the stomach.[25-29] Lymph node involvement, per se, is not as important as the number and location of nodes.[26,30] Minimal lymph node involvement adjacent to the primary lesion is the most favorable.[31] The solitary finding of either involved lymph nodes or extension beyond the gastric wall is not as ominous as the presence of both.[26-30]

Tumor grade and gross and microscopic pathologic appearance of the primary malignancy appear to provide some prognostic information, but none of these factors is an independent prognostic variable relative to tumor stage. Prognosis is generally worse with higher-grade and diffuse-type carcinomas, which usually present with a higher stage of disease. Borrmann's types I and II carcinomas have a relatively favorable 5-year survival rate, whereas patients with type IV tumors (linitis plastica) have a poor prognosis.[31,32]

Prognostic factors evaluated in a British Study Group Trial included tumor size, macroscopic aspect, number of sites involved, wall invasion (pT), involvement of surgical resection limits, nodal stage, and histologic grade. Multivariate analyses established as prognostic features the depth of pT, nodal involvement, and surgical resection margins involvement.[33]

Some investigators have suggested that tumors of the gastric cardia may have different epidemiologic factors than cancers of the distal stomach[34,35] and may exhibit different tumor biology.[36] Prognosis appears worse for cardia lesions.[37,38]

Molecular Biology

The molecular biology of gastric cancer reflects the heterogeneity of its causes and its histologic subtypes. Identification of the genetic and phenotypic variables existing among gastric cancers may lead to more directed therapeutic approaches and a more accurate prediction of clinical outcome. There are rare genetic mutations that produce a hereditary predisposition to diffuse gastric cancer, and these are dominated by mutations in E-cadherin (CDH1).[39] CDH1 mutations (nongerm line) are also one of the most common mutational events in gastric cancer. Investigators have found a number of pathways critical to cell function that have aberrant regulation in gastric cancer and these often relate to genetic abnormalities seen in multiple types of tumors. Most gastric cancers have a large degree of genomic instability, as is also true for colon cancer. These are then associated with aberrations in a number of specific genes and pathways, often caused by copy number variations with both gains and loss of function.

Loss of tumor-suppressor gene function, especially inactivation of the *p53* gene, plays a critical role and is one of the most common alterations found in gastric cancer. The *p53* gene is located on the short arm of chromosome 17 and plays a key role in tumor suppression and cell-cycle regulation.[40] The *p53* gene puts a brake on DNA replication and triggers programmed cell death in response to DNA damage.[41] Loss of *p53* function is associated with the development of malignancy, impacts the effectiveness of chemotherapy and irradiation,[42,43] and predisposes cells to genetic instability. The latter is particularly important because *p53* mutations typically occur early in carcinogenesis.

Another dominant mutation occurs in SMAD4 that affects cell signaling and modulates the TGFβ protein that is involved in many areas of cellular function. Alterations in Wnt pathway result in a loss of pathway regulation.[44,45] ARID1A, PIK3CA, and CDKN2A have also been found to be significantly mutated in GE junction adenocarcinomas.[46] MET gene overexpression or signaling are common in gastric cancer, and aberrations can occur in multiple sites along the Wnt pathway.[47] However Dulak[46] found only 9% of esophageal adenocarcinomas with mutations. Loss of TTF1 (a trefoil peptide) occurs in perhaps 50% of gastric cancers and likely reflects amplification occurs in more than 50% of gastric cancers, is a poor prognostic factor, and is being explored as a therapeutic target.[48]

Another major aberration affecting gastric epithelial cells is the impact of alterations in mismatch repair genes. Similar to colorectal tumors, there is a substantial subset of patients who demonstrate microsatellite instability, with many of these tumors exhibiting loss of function of the mismatch repair genes MLH1 or MSH2. In gastric cancer these changes appear to be almost entirely as a result of epigenetic, rather than germ line alterations. Hypermethylation of CpG island promoter regions of the mismatch repair gene appear to produce the abnormality. The MSI high phenotype appears to be related to primary tumors located distally in the stomach and to the intestinal variety and with a relatively improved prognosis.[49] Mutations in these genes are implicated in cancer family syndromes and hereditary nonpolyposis colorectal cancer (HNPCC), a syndrome associated with an increased tendency

for the development of colorectal and gastric tumors.[50] Mutations in these genes generate genetic instability and have the potential to lead to further alterations in oncogenes.

Several peptides including estrogen receptor[51] and epidermal growth factor receptor[52] appear to affect prognosis adversely. The expression of epidermal growth factor receptor and high levels of epidermal growth factor correlate with a higher incidence of primary tumor infiltration, poor histologic differentiation, and linitis plastica. The pathophysiologic relationship between these peptide receptors and poor patient prognosis is not clear.

HER2 (ERBB2) overexpression has been shown to occur in approximately 20% of patients with gastric cancer and is associated with a poorer prognosis.[53] Perhaps more importantly, the use of the anti-HER2 antibody trastuzumab has been demonstrated to improve survival by approximately 2.5 months in patients with metastatic disease.[54]

Modern molecular biology observations confirm the heterogeneity of human gastric cancer. Genetic alterations potentially associated with worse prognosis, included CD44 expression; telomerase reactivation; *p53* gene inactivation; dysfunction of repair genes; overexpression of proto-oncogenes like *erb-B2, bcl-2, c-met*; estrogenic receptor expression; and presence of viral genome.[55] Gastric cancers with class II major histocompatibility complex antigen expression (HLA-DR) have a better prognosis, but the loss of expression is not an independent prognostic factor.[56]

Dulak et al[57] have done an extensive survey of genome instability and oncogenesis in esophageal, gastric and colon cancer adenocarcinomas and have found substantial similarities and differences. Focal amplifications were more prevalent in gastric and esophageal cancers than in colon with amplification in 37% of tumors including those that are potential drug targets (ERBB2, FGFR1 and 2, EGFR, and MET).

PATHOLOGY AND PATHWAYS OF SPREAD

Pathology

ACA histology accounts for 90% to 95% of all gastric malignancies, and the terms *gastric* and *stomach cancer* usually refer to such. Other histologies include lymphoma, leiomyosarcoma, carcinoid, adenoacanthoma, and squamous cell carcinomas.[58]

Gastrointestinal stromal tumors (GISTs) were previously classified as leiomyosarcomas but commonly arise in the stomach. GISTs need to be recognized because their management (surgery alone or plus imatinib) is distinctly different from ACA (surgery plus postoperative chemoradiation).

Gastric carcinomas have been categorized with regard to both microscopic and gross pathologic features. The Lauren classification system includes an intestinal type with improved prognosis (predominates in regions with high prevalence of gastric cancer) and a diffuse histologic type with poor prognosis (occurs more commonly in countries with low prevalence).[59] Diffuse carcinomas occur more often in young patients and develop throughout the stomach but especially in the cardia. Intestinal-type lesions are frequently ulcerative and occur in the distal stomach more commonly than the diffuse type. Grossly, gastric cancers can be categorized according to Borrmann's five types: I, polypoid or fungating; II, ulcerating lesions surrounded by elevated borders; III, ulceration with invasion of the gastric wall; IV, diffusely infiltrating (linitis plastica); and V, not classifiable.[60] The Japanese Research Society for Gastric Cancer has a classification system that divides lesions into protruded (I), superficial (II) (with elevated [IIa], flat [IIb], and depressed [IIc] subtypes), and excavated (III) types.[58]

Pathways of Spread

Direct Extension

The stomach is surrounded by organs and structures that can be involved by direct tumor extension when a lesion has spread beyond the gastric wall. These include the omenta, pancreas, diaphragm, transverse colon or mesocolon, duodenum, jejunum, spleen, liver, superior mesenteric and celiac vessels, abdominal wall, left adrenal gland, and kidney. Although adherence from inflammatory conditions can mimic direct extension of tumor, all adhesions between a gastric carcinoma and adjacent structures should be regarded as malignant, and en bloc resection of involved structures is preferred, if feasible.

Lymphatics

Abundant lymphatic channels are present within the submucosal and subserosal layers of the gastric wall. Microscopic or subclinical spread beyond the visible gross lesions (intramural spread) occurs commonly via the lymphatic channels. Frozen sections of the gastric resection margins should therefore be obtained intraoperatively to ensure that margins of resection are uninvolved microscopically. The submucosal lymphatic plexus is also prominent in the esophagus and the subserosal plexus in the duodenum, allowing both proximal and distal intramural tumor spread.

Because of the numerous pathways of lymphatic drainage in the stomach, it is difficult to perform a complete nodal dissection (eFigure 47-3). Although initial drainage is usually to lymph nodes along the lesser and greater curvatures (perigastric or N1 nodes using the Japanese Research Society for Gastric Cancer designation), primary nodal drainage includes nodes along all three branches of the celiac (left gastric, common hepatic, splenic) and the celiac itself (Japanese N2 nodes).[58] Node groups that are more distal include hepatoduodenal, peripancreatic, root of mesentery (Japan N3), periaortic, and middle colic (N4). When proximal gastric lesions extend into the distal esophagus, that nodal system is at risk.

Hematogenous Spread

For cancers that are limited to the gastric wall, venous drainage is primarily to the liver via the portal system, although spread can occur to virtually any organ. At initial exploration, liver involvement is found in up to 30% of patients, predominantly resulting from hematogenous metastases but sometimes because of direct tumor extension. When cancers extend proximally to involve the esophagus or extend posteriorly, the lung may be at increased risk for metastasis.

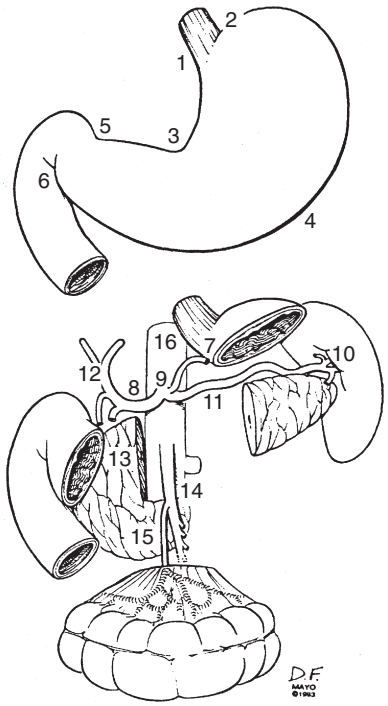
Peritoneal Involvement

Because the stomach is an intraperitoneal organ, peritoneal spread is possible when a lesion extends beyond the gastric wall to a free peritoneal (serosal) surface. Peritoneal involvement may initially be a localized process limited by surrounding organs and ligaments (gastrohepatic, gastrosplenic, and gastrocolic), but is most often a diffuse process.

CLINICAL MANIFESTATIONS, PATIENT EVALUATION, AND STAGING

Clinical Manifestations

Neither patient symptoms nor routine physical examination leads to an early diagnosis of gastric cancer. The most common presenting symptoms and signs are loss of appetite, abdominal discomfort, weight loss, weakness (as a result of anemia), nausea and vomiting, and melena. The duration of symptoms



eFigure 47-3 Classification and anatomic location of lymph node groups. 1, right paracardial; 2, left paracardial; 3, lesser curvature; 4, greater curvature; 5, suprapyloric; 6, infrapyloric; 7, left gastric artery; 8, common hepatic artery; 9, celiac artery; 10, splenic hilus; 11, splenic artery; 12, hepatic pedicle; 13, retropancreatic; 14, mesenteric root; 15, middle colic artery; 16, paraaortic.
(By permission of Mayo Foundation for Medical Education and Research.)

is less than 3 months in nearly 40% of the patients and longer than 1 year in only 20%.

Patient Evaluation

Positive physical examination findings are those of advanced disease. These may include an abdominal mass (representing the primary tumor, hepatic metastasis, or ovarian metastasis [Krukenberg tumor]); remote nodal metastasis (left supraclavicular [Virchow's node]; periumbilical [Sister Mary Joseph node]; or left axillary [Irish's node]), ascites, or a rectal shelf (peritoneal seeding).

The diagnosis of gastric cancer is usually confirmed by upper gastrointestinal (UGI) endoscopy or radiographs (Table 47-1). Endoscopy is the preferred diagnostic study because it allows direct tumor visualization, cytology, and histologic biopsy that yield the diagnosis in 90% or more of patients with exophytic lesions. Ulcerated cancers and linitis plastica lesions may be harder to diagnose endoscopically, but multiple deep biopsies and washings enhance the probability of accurate diagnosis. Endoscopic ultrasonography (EUS) has a high degree of accuracy in determining depth of tumor invasion before resection (i.e., whether the lesion extends beyond the muscularis propria) but is less accurate in detecting regional nodal metastasis.[61,62] Needle biopsies of suspicious nodes can be performed at the time of endoscopy with EUS. Although EUS may not affect therapy decisions with most current management approaches, the use of EUS may lead to selective management strategies based on tumor stage.

TABLE 47-1 Diagnostic Algorithm: Gastric/Gastroesophageal Junction Cancer

Diagnostic Procedure	Diagnosis and Staging Capability	Recommend Routine Use
PRIMARY TUMOR/REGIONAL NODES*		
Gastroscopy	Accurate modality to detect and define primary lesion, ≈ 90% confirmation rate	Yes; use to screen patients who are symptomatic or are high risk
Ultrasound-endoscopy	Most accurate method of determining extension within and beyond gastric wall	Yes; biopsy node(s), if feasible
CT: abdomen + chest	Most valuable modality to determine degree of extragastric extension and distant metastases	Yes
METASTATIC TUMORS		
Chest films	Good for detecting metastases	Yes
Laparoscopy	May allow visualization of small serosal implants or liver metastases	Optional; recommended if plan preoperative chemotherapy or chemoradiation
Positron emission tomography	Excellent for detecting unsuspected metastases	Optional; recommended if plan preop chemo/chemoradiation

**Laboratory studies: CBC, creatinine, liver function studies (alkaline phosphate, bilirubin, SGOT, LDH), albumin.*

The abdominal extent of disease at laparoscopy or exploration is usually more extensive than is suggested on radiographs or endoscopy. Abdominal computed tomography (CT) is valuable in determining the abdominal extent of disease with regard to liver metastasis, involvement of celiac or periaortic nodes, or extragastric extension (may help determine which lesions extend to surgically unresectable structures) but is of little value in ruling out peritoneal seeding. Diagnostic laparoscopy, often done immediately before resection, allows visualization and biopsy of small peritoneal implants or surface liver metastases.

The value of laparoscopy in the staging of gastric cancer is still being defined. In 71 patients with CT criteria of resectable disease, 69 completed a laparoscopic evaluation.[63] Laparoscopy confirmed disease in 16 of the 17 patients with peritoneal metastasis (avoiding 12 laparotomies) and 1 of 3 patients with small liver metastases and negative CT scan. The combination of CT scan and laparoscopy staging information yielded a resectability rate of 93% for patients defined as potential candidates for curative gastric cancer surgery.

Distant (hematogenous) metastases should be ruled out with a chest and abdominal CT. CT scans also provide valuable tumor localization information should irradiation be indicated. If a proximal gastric cancer extends to involve the esophagus, CT of the chest helps to rule out involvement of mediastinal nodes. Positron emission tomography fused with CT (PET/CT) is an imaging tool that can help to both rule out occult metastatic disease and determine response to treatment although it is less sensitive in gastric than in esophageal cancer.

Treatment planning in patients with gastric cancer could be improved by accurate preoperative classifications of depth of invasion (T category) and lymph node involvement (N category). A prospective study in 108 consecutive patients evaluated EUS, CT scan, and intraoperative surgical assessment for T and N classification.[64] Staging of the T category was correct with CT scan in 43% of the cases, 86% with EUS, and in 56% with intraoperative assessment. Staging of N1 and N2 lymph nodes was correct with CT in 51% of the cases, with EUS in 74%, and with intraoperative assessment in 54%. Advanced gastric tumors tended to be more accurately staged with CT; CT in general overstaged the T category and understaged the N category. Endoscopic ultrasound showed high and similar accuracy for all the T categories, although it also tended to under-stage N categories. Finally, intraoperative assessment was equally accurate for all N categories, but tended to overstage early T stages and to understage N categories.

Staging

The current TNM (tumor, lymph nodes, metastasis) staging system (American Joint Committee of Cancer, seventh edition) is depicted in Table 47-2.[65] The TNM system is the standard system for reporting outcomes in this disease.

Follow-up

Patients who are treated for gastric cancer should be followed for nutritional problems as well as disease relapse. Generally, patients are seen at 3- to 6-month intervals for the first 2 to 3 years and then less frequently. There are no agreed on follow-up strategies, as curative salvage therapy for recurrent gastric cancer after trimodality therapy is unusual. However, it is reasonable to have endoscopy performed one or two times and to use periodic CT scans to detect intraabdominal relapse. There are little data to suggest that early treatment of systemic metastases improves outcomes.

TABLE 47-2 TNM Staging for Carcinoma of the Stomach, AJCC, 7th Edition

Stage	T	N	M
O	Tis	0	0
IA	1	0	0
IB	2	0	0
	1	1	0
IIA	3	0	0
	2	1	0
	1	2	0
IIB	4	0	0
	3	1	0
	2	2	0
	1	3	0
IIIA	4a	1	0
	3	2	0
	2	3	0
IIIB	4b	0-1	0
	4a	2	0
	3	3	0
IIIC	4b	2	0
	4a-b	3	0
IV	Any	Any	0

TNM definitions are as follows:

Tis: carcinoma in situ; intraepithelial tumor without invasion of the lamina propria.

T1: Tumor invades lamina propria, muscularis mucosa or submucosa.
- T1a: tumor invades lamina propria or muscularis mucosa
- T1b: tumor invades submucosa

T2: Tumor invades the muscularis propria

T3: Tumor penetrates subserosal connective tissue without invasion of visceral peritoneum or adjacent structures.

T4: Tumor invades serosa (visceral peritoneum) or adjacent structures.
- T4a: tumor invades serosa (visceral peritoneum)
- T4b: tumor invades adjacent structures†

N0: No regional lymph node metastasis.
N1: Metastasis in 1-6 regional nodes.
N2: Metastasis in 7-15 regional nodes.
N3: Metastasis in more than 15 regional nodes.
M0: no distant metastasis.
M1: distant metastasis.

†*Adjacent structures include the spleen, transverse colon, liver, diaphragm, pancreas, abdominal wall, adrenal gland, kidney, small intestine, and retroperitoneum.*

PRIMARY THERAPY

Surgical Method

Surgical excision of the gastric and nodal components of disease remains the primary therapy for all potentially curable gastric carcinomas. Most cancers can be removed with adequate margins by subtotal gastrectomy, and total gastrectomy is used only when mandated by proximal cancer location or disease extent. Routine total gastrectomy does not improve survival by providing wider margins and eliminating multicentric disease but does increase morbidity and mortality. Surgical resection alone is an excellent treatment for carcinomas limited to the mucosa or submucosa without nodal involvement (Tis or T1N0M0). Although these early gastric cancers occur with an incidence of more than 30% in Japan, the incidence is less than 5% in the United States and other Western countries. For the more invasive gastric carcinomas, surgical resection is indicated for 50% to 60% of patients at the time of disease presentation, but only 25% to 40% of patients will have potentially curative procedures.

Although only one small prospective randomized trial has been performed with regard to extent of the gastric resection,[66] extensive experience exists with various surgical procedures, and appropriate generalizations can be made. The preferred treatment for lesions arising in the body or antrum of the stomach is a radical distal subtotal resection. This removes approximately 80% of the stomach along with the first portion of the duodenum, the gastrohepatic and gastrocolic omenta, and the nodal tissue adjacent to the three branches of the celiac axis. Extensive or proximal cancers will require a total gastrectomy to achieve an adequate proximal gastric margin. However, total gastrectomy is not necessary when subtotal gastrectomy will provide a 5-cm clearance of the gross tumor.[67,68] The propensity for gastric carcinoma to spread via submucosal and subserosal lymphatics dictates the need for a 5-cm surgical resection margin of normal stomach beyond the visible lesion. It may be necessary to extend the resection to include some (or additional) esophagus or duodenum if frozen section pathologic evaluation of the surgical margins fails to confirm the adequacy of proximal and distal resection margins. If total gastrectomy is necessary, a splenectomy is sometimes performed particularly in gastric cancers of the proximal third of the stomach, and tumors of the body near the greater curvature. Cancers in these locations are more apt to metastasize to lymph nodes in the splenic hilum that cannot be completely excised without a splenectomy. Although the value of routine splenectomy has not been addressed in prospective randomized trials, retrospective Japanese and American data do not provide evidence of a survival benefit with the routine use of this procedure and this may increase morbidity.[69,70]

Direct extension beyond the gastric wall should be treated with en bloc extended resection to achieve negative margins if a curative resection is contemplated. Common examples of local tumor extension include involvement of the body or tail of the pancreas (treated by distal pancreatectomy and splenectomy), invasion of the transverse mesocolon (often requires transverse colectomy), and involvement of the spleen (splenectomy) or left lobe of the liver (usually requires wedge resection with a 1-cm or wider clearance).

The optimal extent of lymph node dissection for gastric cancer remains controversial. Several studies have shown that the presence and extent of lymph node metastasis correlate with the depth of primary tumor invasion.[71-73] Although several nonrandomized clinical trials have suggested that extended lymphadenectomies may improve survival,[70,74-78] other nonrandomized[79,80] and randomized trials[81-87] have not demonstrated an advantage. A large multicenter Phase III study in the Netherlands accrued 996 evaluable patients and provides additional objective data on the lack of value of extended lymphadenectomy in gastric carcinoma.[82] Among the 711 patients having curative resections, both morbidity and mortality were significantly higher with the more extensive nodal dissection.[83-85] A randomized study of 400 patients conducted by the Medical Research Council (MRC) in the United Kingdom has also demonstrated higher morbidity and mortality in the extended lymphadenectomy cohort.[86,87] No benefit in DFS or OS was found in either the Dutch or British trials (Table 47-3). Any apparent survival benefit seen with the extended node dissection performed in Japan may be a result of the phenomenon of a shift in stage rather than superior surgery. Although most patients with five or more lymph node metastases or node metastasis not adjacent to the primary tumor have a poor outcome, extended node dissection seems

reasonable when it can be performed by experienced surgeons without significant additional surgical morbidity or mortality. Recent systematic review and meta-analysis demonstrate the safety and feasibility of D2 resection with or without paraaortic nodal dissection but fail to show a benefit in OS.[88,89]

Endoscopic laser surgery has been used in selected patients with early gastric cancer.[90] Small lesions (≤3 cm) that are pedunculated, do not invade the submucosa, and are well differentiated infrequently have lymph node metastasis (<5%). Nearly 75% of these select tumors can be completely removed endoscopically. Advanced techniques such as endoscopic submucosal dissection may further expand the indications for endoscopic therapy as more widespread technical expertise is obtained and long-term data is reported. Although early gastric cancer may have a long natural history before progression, standard surgical resection rather than endoscopic removal is still preferable.[91] Irradiation plus chemotherapy should be considered as adjuvant therapy when the tumor is endoscopically treated.

Quality of life (QOL) after gastrectomy is being analyzed.[92,93] In a University of Heidelberg report of 104 patients, 12 months after gastrectomy, postoperative symptoms of heartburn or dumping in the group undergoing total gastrectomy with pouch reconstruction did not differ significantly from the group having only distal gastric resection.[94] In a recent prospective trial of 120 patients requiring total gastrectomy plus pouch who were randomized to two different types of reconstruction (jejunal interposition versus Roux-en-Y), there were no differences in food passage, body weight, or QOL parameters.[95] However, for all patients there are significant QOL issues related to decreased absorption of fats, iron, and calcium, as well as the loss of intrinsic factor, and thus B12 deficiency. These losses need to be addressed with dietary supplements (iron, calcium), monitoring for osteoporosis, and possible monthly B12 injections.

Surgery Alone Survival Results

OS with surgery alone remains poor, despite improved perioperative care that has resulted in a substantial decline in postoperative mortality.[96] A large review from Europe reported excellent 5-year survival for early gastric cancer patients (83%) but a marked diminution in survival for more invasive cancers (31% for tumors of the antrum, 24% for the midstomach, and 16% for the cardia).[97] Survival in excess of 90% has been achieved throughout the world with resection of lesions confined to the mucosa or submucosa.[98-102] In reports with lower 5-year survivals for the early lesions, most of the mortality is from noncancer causes.[99,103] For gastric cancers with deeper invasion or nodal involvement, survival decreases proportional to the degree of invasion or nodal involvement. When N1 or N2 nodes are involved, Western reports continue to show 5-year OS of 10 to 30%,[104,105] whereas Japanese authors report 5-year OS of 25% to 60% (versus less than 10% with N3 or N4 involvement) (eTable 47-1).[70,105a–d] Although pathologic staging differences, different tumor biology, and more radical surgical extirpation have been proposed as explanations, the cause of the difference in U.S. and Japanese results with N1 or N2 disease remains uncertain. Even in the Orient, half of all patients with more invasive gastric cancer do not survive their disease, a fact that underlies the need for new nonsurgical therapies. Results of Phase III trials, to be discussed subsequently, demonstrate improvements in survival with the addition of adjuvant chemoradiation or neoadjuvant chemotherapy to surgical resection.

TABLE 47-3 Extent of Surgery: Randomized Trials of D1 Versus D2 Dissection

Series	No. of Patients	5-year Survival		Operative Mortality		*p* Value
		D1	D2	D1	D2	
Dutch[84,85]	711	45%	47%	4%	10%	<0.05
MRC[86,87*]	400	35%	33%	6.5%	13%	<0.05

**Defined D1 dissection as resection of AJCC nodes (those within 3 cm of primary tumor).*
Both trials showed significantly increased morbidity and mortality with more extensive dissections.

Relapse Patterns after "Curative Resection"

Local relapse or failure (LF) in the tumor bed and regional lymph nodes (RF) or distant failures (DF) via hematogenous (DM) or peritoneal (PS) routes are all common mechanisms of relapse after "curative resection" in clinical, reoperative, and autopsy series.[28,29,106-114] For lesions of the GE junction, both the liver and lungs are common sites of DM. With gastric lesions that do not extend to the esophagus, the initial site of DM is usually the liver, and many relapses could be prevented if an effective "abdominal" or liver therapy could be combined with treatment of the primary tumor and regional lymph nodes.

Locoregional failures occur commonly within the region of the gastric bed and nearby lymph nodes (Table 47-4 and Figure 47-1). Tumor relapse in anastomoses, the gastric remnant, or the duodenal stump is also frequent. In a University of Minnesota reoperative analysis,[28,29] locoregional failure occurred as the only evidence of relapse in 29% of the 86 patients with relapse (23% of the 105 evaluable patients at risk) and as any component of failure in 88%. More extensive operative procedures including routine splenectomy, omentectomy, and radical lymph node dissection neither improved survival[112] nor decreased the incidence of LF-RF[28,29] in the reoperative analysis. Subsequent relapse within the scope of the initial node dissection occurred in a high percentage of the patients even when radical node dissections were performed (removal of N1 and N2 with or without N3 nodes)[29] (eTable 47-2). These data indicate the difficulty of performing a complete lymph node and lymphatic resection in this anatomic location and

TABLE 47-4 Gastric Cancer: Patterns of Locoregional Relapse in Clinical, Reoperation, and Autopsy Series

Failure Area	Incidence: Any Component of Local or Regional Relapse (No. [%])			
	MGH[108] (Clinical) (*n* = 130)	U. Minn.[28,29] (Reoperation) (*n* = 105)	McNeer et al[109] (Autopsy) (*n* = 92)	Thomson and Robins[110] (Autopsy) (*n* = 28)
Gastric bed	27 (21)	58 (55)	48 (52)	19 (68)
Anastomosis or stumps	33 (25)	28 (27)	55 (60)	15 (54)
Abdominal or stab wound	—	5 (5)	—	—
Lymph node(s)	11 (8)	45 (43)	48 (52)	—

eTABLE 47-1 Comparison of 5-Year Survivals in Japan Versus United States Following Surgery for Gastric Carcinoma

Tumor Classification	Nodal Status	5-Year Survival (%)	
		Japan	United States
T1	N0	90	90
T2	N0	60	52
T3	N0	30	47
T4	N0	5	15
—	N1	53	20
—	N2	26	10
—	N3	10	—
—	N4	3	—

Modified from Noguchi Y, Imada T, Matsumoto A, et al: Radical surgery for gastric cancer: A review of the Japanese experience. Cancer 64:2053, 1989. Copyright © 1989 American Cancer Society. Reprinted by permission of Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc.

eTABLE 47-2 Extent of Gastrectomy and Node Dissection versus Type of Locoregional Relapse: Reoperation Series

Operative Procedure‡	No. of Failures/ Total at Risk	Any Component of Locoregional Relapse*							
		Gastric Bed		Anastomosis or Stumps		Abdomen or Stab Wound		Nodes (LN)	
		N	(%)	*N*	(%)	*N*	(%)	*N*	(%)
Subtotal gastrectomy	53/72	36	(50)	18	(25)	3	(4)	29	(40)
Method 1†	25/36	18	(50)	13	(36)	0	—	11	(31)
Method 2†	15/17	9	(53)	4	(24)	1	(6)	9	(53)
Method 3†	13/19	9	(47)	1	(5)	2	(11)	9	(47)
Total gastrectomy	27/33	20	(61)	8	(24)	2	(6)	15	(45)
Method 1†	0	—	—	—	—	—	—	—	—
Method 2†	14/15	10	(67)	5	(33)	1	(7)	11	(73)
Method 3†	13/18	10	(56)	3	(17)	5	(6)	4	(22)
Total	80/105‡	56	(53)	26	(25)	5	(5)	44	(42)

Modified from MacDonald JS, Cohn I, Gunderson LL: Carcinoma of the stomach. In Devita V, Hellman S, Rosenberg S, editors: Principles and practice of oncology, ed 2. Philadelphia, 1985, Lippincott, pp 659–690.

**Figures in parentheses represent percentage of patients at risk with complete follow-up.*

†Method 1 (pre-1950): subtotal or total gastrectomy, greater omentectomy, regional node dissection; Method 2 (1950-1954): method 1 plus splenectomy, total omentectomy, additional node dissection regarding splenic, suprapancreatic, and central celiac axis; Method 3 (1954 on): methods 1 and 2 plus extension of node dissection to porta hepatis and pancreaticoduodenal (intent: total lymph node dissection of all primary node areas equivalent to current D2 or D3 dissection).

‡An additional 6 patients had a relapse; 80 of 86 patients were evaluable regarding both operative method and pattern of relapse.

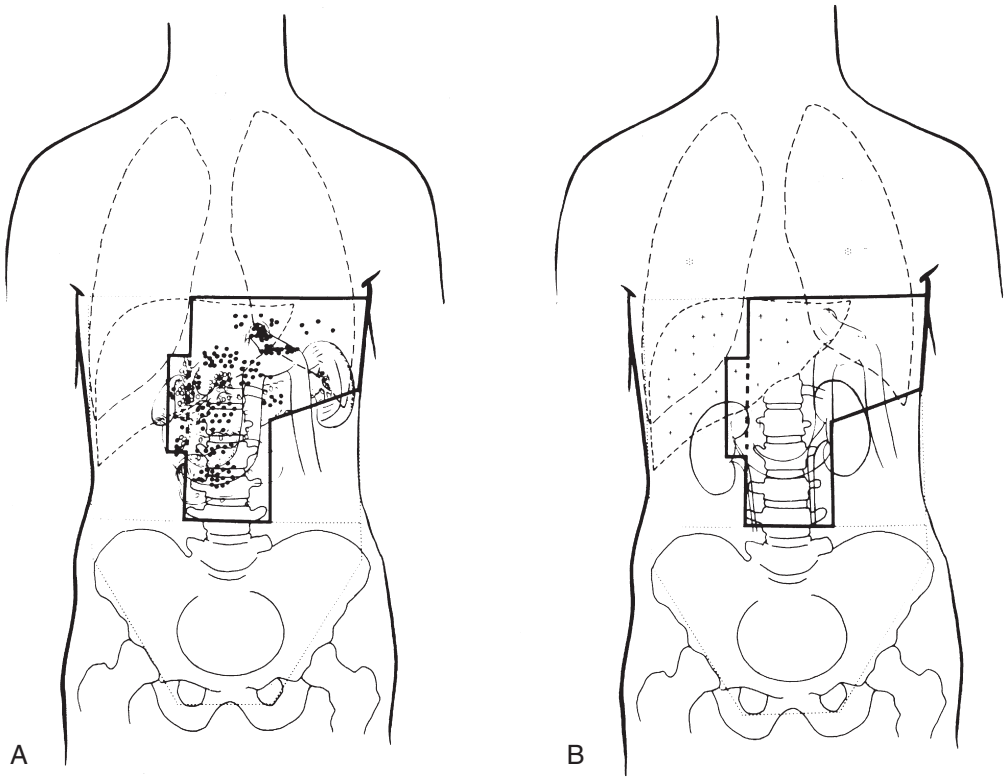


Figure 47-1 Patterns of failure in the University of Minnesota gastric cancer reoperative series with superimposed idealized irradiation fields **(A** and **B)** and relationship to dose-limiting organs or structures. ●, Local failures in surrounding organs or tissues; *O*, lymph node failures; *, lung metastases; +, liver metastases.
(Modified from Gunderson LL, Sosin H: Adenocarcinoma of the stomach areas of failure in a reoperation series [second or symptomatic looks]: Clinicopathologic correlation and implications for adjuvant therapy. Int J Radiat Oncol Biol Phys 8:1, 1982. Copyright 1982.)

provide a partial explanation for the lack of survival benefit with a D2 compared to D1 node dissection in Phase III surgical trials discussed previously. In a more recent clinical analysis of patterns of relapse from Memorial Sloan Kettering Cancer Center, 50% of patients with relapse had a locoregional component.[114]

Patterns of relapse by stage were analyzed in detail in a series of 130 patients who underwent resection with curative intent at the Massachusetts General Hospital (MGH).[108] Locoregional relapse occurred as any component of failure in 49 patients (38%) and as the sole failure in 21 (16% of 130 patients at risk and 24% of the 88 with disease progression). The incidence of locoregional relapse by stage was in excess of 35% for modified Astler-Coller stages B2 (T3 N0), B3 (T4 N0), C2 (T3 N1-3), and C3 (T4N1-3). The sites at higher risk for locoregional relapse included the gastric bed (27 of 130 patients, 21%) and the anastomosis or gastric remnant (33 of 130 patients, 25%). The true incidence of gastric bed, regional lymph node, and peritoneal failures may be higher because this was neither a reoperative nor an autopsy series (see comparative findings in Table 44-4). Additional information on patterns of relapse by stage exists in both the University of Minnesota reoperation analysis[28,29] and the University of Washington autopsy analysis.[111] Although patterns of relapse data are more accurate in such analyses, patient selection is biased.

All of these data suggest that the development of an effective therapy for locoregional disease as an adjuvant to surgery could potentially benefit at least 20% of patients. Effective systemic therapy is also essential to improve the outcome for patients who have resected high-risk gastric cancer s in view of the risks of both intraabdominal (liver and peritoneal) and extraabdominal metastasis (lung, other).

Adjuvant Chemotherapy

The role of adjuvant chemotherapy in gastric cancer has been extensively studied over the past decades, being the first attempt to improve the prognosis of resected gastric cancer.[115-137] Results of randomized clinical trials of adjuvant single-agent chemotherapy, following curative resection in gastric cancer have generally not shown any survival benefit when compared with surgical resection alone.

A Spanish trial compared high-dose mitomycin C following surgical resection (33 patients) versus surgery alone (37 patients).[117] This small trial showed a significant 5-year OS advantage (p = 0.001) in the group receiving chemotherapy (76% versus 30%), and a low rate of relapse in the treated arm (7 of 33 or 21% of the patients) versus the control arm (23 of 37 patients or 62%). This trial was extended to 134 patients with median follow-up of 8.75 years and still showed a survival advantage for postoperative mitomycin (p = 0.025). A subsequent randomized Spanish trial observed a significantly better 5-year survival for mitomycin plus Ftorafur (67%) versus mitomycin alone (44%) in resected high-risk gastric cancer, suggesting a strong benefit in patients with node-negative and early stage disease.[118]

Neri et al treated patients who were surgically resected, node-positive with the addition of adjuvant epirubicin, 5-FU, and leucovorin (68 patients) and compared them to 69 patients who were surgery-alone control.[119] The authors noted an

Two Phase III clinical trials evaluated the impact of 5FU, Adriamycin, Mitomycin-C (FAM) combination chemotherapy after curative surgery in resected high-risk gastric cancer.[115,116] Coombs et al[115] included 315 patients, and no difference was observed in either OS (FAM 45% versus control 35%) or relapse rates (FAM 56% versus control 56%). In a Southwest Oncology Group (SWOG) study, no advantage to adjuvant treatment with FAM was reported, either.[116]

improvement in 5-year OS from 13% to 30% for those receiving adjuvant chemotherapy.

In view of the success of the oral fluoropyrimidine S-1 in metastatic gastric cancer, a Phase III trial was done in Japan of surgery alone compared with surgery plus adjuvant S-1 for 1049 patients with resected Stages II/III disease.[120] Five-year OS was improved with adjuvant S-1 (5-year hazard ratio, 0.669; 95% confidence interval [CI], 0.540 to 0.793).

Perioperative Chemotherapy

In the British MAGIC trial, 503 patients with resectable ACA of the stomach (372 patients), GE junction (58 patients) or lower esophagus (73 patients) were randomized to receive either surgery alone or surgery plus three cycles of preoperative ECF and three cycles of postoperative ECF.[124] The use of perioperative chemotherapy was associated with significant improvement in survival compared with surgery alone (median survival 24 versus 20 months, 5-year OS 36% versus 23%, $p = 0.009$). Overall 103 patients completed all six cycles of chemotherapy.

A separate Phase III French trial of 224 patients with potentially resectable ACA of the lower esophagus, GE junction, or stomach evaluated perioperative CF ($n = 113$ patients; cisplatin plus infusion 5-FU for two to three cycles before and three to four cycles after surgery) compared to surgery alone ($n = 111$).[125] A survival advantage was found for perioperative CF (5-year OS, 38% versus 24%, $p = 0.02$; 5-year DFS 34% versus 19%, $p = 0.03$). Grade-3 or grade-4 toxicity was found in 38% of patients receiving chemotherapy, primarily neutropenia.

Meta-Analysis of Adjuvant Trials

Because many of the trials conducted to date have been underpowered to adequately assess potential differences between the control and treatment arms in regard to OS, seven meta-analyses have been performed since 1990 to better assess the use of adjuvant chemotherapy.[126-132] Three meta-analyses showed a significant survival advantage to the use of chemotherapy following surgical resection of gastric cancer. Seventeen randomized clinical trials, involving 3118 patients, were included in the meta-analysis by Panzini et al.[126] The pooled odds ratio was 0.72 (95% CI, 0.62 to 0.84). The meta-analysis by Janunger et al included 21 randomized clinical trials, involving 3962 patients, a slightly larger and somewhat different group of studies.[127] The pooled odds ratio from this study was 0.84 (95% CI, 0.74 to 0.96). In a subanalysis, Western and Asian studies were assessed separately. The meta-analysis of the Western studies did not show a benefit to adjuvant therapy (pooled odds ratio of 0.96; 95% CI, 0.83 to 1.12), whereas the Asian studies did show evidence of benefit (pooled odds ratio of 0.58; 95% CI, 0.44 to 0.76). In 2010, a meta-analysis by Paoletti et al identified 17 trials with individual patient data availability (3838 patients) and a median follow-up exceeding 7 years. There were 1000 deaths in the 1924 patients assigned to chemotherapy and 1067 deaths in 1857 patients assigned to surgery only. Adjuvant chemotherapy achieved a significant benefit in 5-year OS (55.3% versus 49.6%, $p = 0.001$).[132]

Adjuvant Irradiation

Irradiation has only been minimally evaluated as the sole adjuvant treatment following complete surgical resection in randomized Phase III trials. Adjuvant EBRT reduced locoregional failures when compared with the surgery-alone control arm in the British adjuvant trial noted later, but no survival benefits were found.[135,138] Although Phase III trials from Japan[139,140] and China[141] suggest some survival benefit for IORT versus a surgery-alone control arm, the advantage was found only in subset analyses.

Postoperative EBRT

The British Stomach Cancer Group (BSCG) completed a prospectively randomized trial of surgery alone versus postoperative FAM or EBRT (45 Gy in 25 fractions with or without 5-Gy boost).[135,138] A total of 436 patients were randomized and followed for a minimum of 12 months; arms were well balanced with regard to prognostic factors. No survival differences by treatment arm were seen (median, 15 months). However, locoregional failure was documented in only 15 of 153 patients (10%) in the adjuvant irradiation arm versus 39 of 145 (27%) in the surgery-alone arm, and 26 of 138 (19%) in the FAM group. Interpretation of the results is complicated by the inclusion of 93 patients with resection but gross residual disease and 78 patients (18%) with gross total resection but microscopically positive resection margins. Neither group of patients would be candidates for current gastric surgical adjuvant trials in the United States. In addition, nearly one third of the patients randomized to receive adjuvant treatment did not receive the assigned therapy. Of 153 patients randomized to the irradiation arm, only 104 (68%) received a dose of 40.5 Gy or more. Only 62% of the patients received six or more cycles of chemotherapy. The results of this study are similar to results seen in the adjuvant treatment of rectal cancer, in which adjuvant pre- and postoperative irradiation improve local control but did not increase patient survival unless combined with chemotherapy.

Preoperative EBRT

Randomized trials testing preoperative irradiation have been performed in both Russia and China. All have reported a positive survival benefit when compared with surgery-alone control arms.

Three prospective randomized Russian trials have evaluated preoperative irradiation in potentially resectable gastric cancer.[142-144] The first trial randomly assigned 293 patients to receive either surgery alone, surgery after preoperative EBRT (20 Gy in four fractions), or surgery after the same EBRT plus daily hyperthermia. The survival rates at 3 and 5 years were improved in both irradiation arms compared with surgery alone, and the improvement with combined EBRT and hyperthermia was statistically significant at both 3 and 5 years.[142] The second trial compared preoperative EBRT (20 Gy) versus surgery alone in 279 patients. Three- and 5-year survival rates were increased, and no increase in operative morbidity was observed.[143] The third trial compared surgery alone versus preoperative EBRT (32 Gy with concomitant inhalation of oxygen) plus surgery. A survival advantage was observed with preoperative treatment, and the resection rate was increased by 17%.[144] There are methodologic uncertainties with all three of these trials, and their applicability to Western gastric carcinoma is not clear.

A randomized trial from Beijing, conducted from 1978 to 1989, compared a surgery-alone control arm ($n = 199$) with preoperative EBRT plus surgery ($n = 171$) for patients with ACA of the gastric cardia.[145] Irradiation was given with 8-MV photons or cobalt with anteroposterior and posterior-anterior fields to a dose of 40 Gy in 20 fractions of 2 Gy over 4 weeks. Surgery was performed 2 to 4 weeks after completion of irradiation. The addition of preoperative EBRT produced downstaging of disease and improvements in radical resection rates (radical resection rates of 80% versus 62% with preoperative EBRT versus surgery alone).

Survival and locoregional disease control were improved in the patients assigned to preoperative EBRT versus surgery alone.[145] The 5- and 10-year OS were 30 versus 20% and 20% versus 13%, respectively (Figure 47-2; $p = 0.009$ Kaplan-Meier log rank). The divergence in survival curves began in the first

Adjuvant chemotherapy with FAM2, seven cycles, was compared with surgery alone in a European Organization for Research and Treatment of Cancer (EORTC) randomized Phase II trial that included 314 patients with stages II and III gastric ACA.[121] Five-year OS was 70% for patients who were stage II, and 32% for patients who were stage III with no significant differences between groups. Toxicity was high with FAM2 but time to disease progression was significantly longer in this group. DFS increased to a borderline significant value. Similarly, an adjuvant FAM randomized trial done by the SWOG, failed to show improved survival results.[122]

EORTC and the International Collaborative Cancer Group (ICCG) conducted independent randomized Phase III studies of either adjuvant 5FU, Adriamycin, Methotrexate (FAMTX) or 5FU, Epirubicin, Methotrexate (FEMTX) compared to surgery alone.[123] Both studies were closed when they failed to reach accrual after being open for 7 years. A pooled analysis of the two studies demonstrated that they both caused substantial toxicity but had no significant effect on OS, the primary endpoint of each study.

The use of ECF was generally well tolerated in the preoperative setting. The incidence of overall postoperative complications was similar (45.7% versus 45.3%) as well as 30-day mortality rates (5.6% versus 5.9%). Of the 237 patients who started chemotherapy, 215 completed the planned three cycles of preoperative therapy. Of the 209 patients who went to surgery, 137 started postoperative chemotherapy. The most common reasons for not starting included disease progression, early death, postoperative complications, and patient choice.

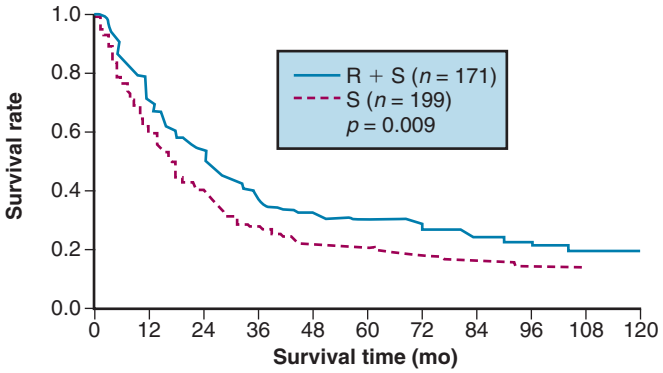


Figure 47-2 Overall survival rates in Beijing Phase III randomized trial of surgery alone or plus preoperative external beam irradiation for adenocarcinoma of the gastric cardia.
(From Zhang ZX, Gu XZ, Yin WB, et al: Randomized clinical trial combination on the preoperative irradiation and surgery in the treatment of adenocarcinoma of the gastric cardia [AGC]: Report on 370 patients. Int J Radiat Oncol Biol Phys 42:931, 1998. Copyright 1998.)

year of follow-up and persisted through 9 years. Local and regional disease control were also improved with combined modality treatment with local relapse rates of 39% versus 52% ($p < 0.025$) and regional node relapse rates of 39% versus 54% ($p < 0.005$). The rates of distant metastases were the same at 24% versus 25%. The improvements in survival and disease control (locoregional) were accomplished with no increase in treatment-related morbidity or mortality (operative mortality 0.6% versus 2.5% with or without preoperative EBRT; intrathoracic leak rates were 1.8% and 4.2%, respectively).

Adjuvant Irradiation Plus Chemotherapy

Postoperative EBRT Plus Chemotherapy

Phase II Trials

Phase II single-institution gastric cancer trials that showed promise for postoperative adjuvant chemoradiation included series from MGH,[146] Israel (Hadassah),[147] Thomas Jefferson University Hospital (TJUH),[148,149] the University of Pennsylvania,[150] and Mayo Clinic.[151] Information on the Phase II trials is provided on the Expert Consult website (eTable 47-3).

Phase III Trials: Mayo Clinic, U.S. GI Intergroup 0116

A prospective randomized trial was conducted at the Mayo Clinic and included 62 patients with poor prognosis completely resected gastric cancers (Table 47-5).[164] Patients were randomized to either surgery alone or surgery followed by EBRT plus concomitant 5-FU (37.5 Gy in 24 fractions over 4 to 5 weeks; 5-FU, 15 mg/kg/day 1-3 by IV bolus). A nonstratified, prerandomization scheme was used with a 2:3 ratio favoring treatment. Informed consent was requested only of the 39 patients randomized to treatment. Ten of the 39 refused further therapy and were observed. When analyzed by intent to treat, the adjuvant arm had statistically significant improvement in both relapse-free and OS (5-year OS 23% versus 4%; $p < 0.05$).

Because of conflicting results in prior small Phase III studies, a U.S. GI Intergroup trial (INT 0116) was initiated to evaluate postoperative combined 5-FU–based chemotherapy and irradiation to the gastric bed and regional nodes versus surgery only in patients who were resected but were high risk.[169] Patients eligible had completely resected ACA of the stomach or GE junction with complete penetration of the muscularis propria (T2-4N0) or involved nodes (T1-4N1-3). After an en-bloc resection, 556 patients were randomized to either surgery alone or postoperative combined modality therapy. This consisted of one 5-day cycle of 5-FU and leucovorin followed by concurrent chemoradiation (45 Gy in 25 fractions plus concurrent 5-FU and leucovorin, 4 days/week 1, 3 days/week 5) followed by two additional 5-day cycles of 5-FU and leucovorin given at 1-month intervals. Nodal metastases were present in 85% of patients. With median follow-up of 5 years, RFS at 3 years is 48% for adjuvant treatment and 31% for observation ($p = 0.001$); 3-year OS is 50% for treatment and 41% for observation ($p = 0.005$) (see Table 47-5). The median OS in the surgery-only group was 27 months, as compared with 36 months in the chemoradiation group. The median duration of RFS was 30 months in the chemoradiation group and 19 months in the surgery-only group (Figure 47-3).

Patterns of relapse were based on the site of first relapse only and were categorized as local, regional, or distant.[169] Local recurrence occurred in 29% of the patients who relapsed in the surgery-only group and 19% of those who relapsed in patients who had chemoradiation. Regional relapse—typically abdominal carcinomatosis—was reported in 72% of those who relapsed in the surgery-only group and 65% of patients who relapsed in the chemoradiation group. Extraabdominal distant metastases were diagnosed in 18% of patients who relapsed in the surgery-only arm and 33% of patients who relapsed in the chemoradiation arm. Treatment was tolerable, with three toxic deaths (1%). Grade-3 and grade-4 toxicity occurred in 41% and 32% of cases, respectively.

The results of this large randomized Phase III U.S. GI Intergroup trial demonstrate a clear survival advantage to the use of postoperative chemoradiation in patients who are resected and are high risk.[169] Furthermore, the results strongly support the integration of postoperative chemoradiation into the routine care of patients with curatively resected high-risk carcinoma of the stomach and GE junction. This approach is viewed as an appropriate standard of care in the United States.

Quality control (QC) of irradiation field design in INT 0116 was conducted during the cycle of chemotherapy given before the start of concurrent chemoirradiation.[170] The upfront QC provided the mechanism to correct most of the major or minor deviations (35% incidence) in field design before the start of treatment and resulted in only a 6.5% final major deviation rate. Utilization of up-front QC may have been a key factor in achieving a positive survival advantage for adjuvant chemoradiation.

An updated long-term analysis of INT 0116 was done with over 10-year median follow-up. Continued strong benefit from adjuvant postoperative chemoradiation was found with regard to both OS and RFS (OS: HR 1.32, $p = 0.0046$; RFS: HR 1.51, $p < 0.0001$).[171]

The successor US GI Intergroup phase III trial (CALGB 80101) was designed to build on the positive results of INT 0116 by testing infusion 5-FU compared to bolus 5-FU+leucovorin as concurrent chemotherapy during EBRT, and ECF compared to 5FU+leucovorin as maintenance chemotherapy.[156] Preliminary analyses have not found a survival benefit for the nonstandard treatment arm. Irradiation fields were based on idealized field design by site of the primary lesion and TN category of disease.[165]

Postoperative Chemoradiation Plus D2 Resection

The final results of the Phase III British and Dutch multicenter trials evaluating the value of extended lymphadenectomy (D1 versus D2 resection) demonstrated that D2 resection produced greater morbidity with no impact on survival.[84-87] Despite these negative results because D2 resections were not

eTABLE 47-3 Surgery with or without Adjuvant Therapy for Resected Gastric Cancer (or Gastroesophageal Junction), Phase II Trials

Institution/Disease Site/Treatment/Ref	Patient No.	Survival: Median (mo)	Survival: Long Term*(%)	*p* Value	Locoregional Relapse: No.	Locoregional Relapse: (%)	*p* Value
1. MGH (gastric)[108,146]							
a. Surgery alone[108]	110	—	38 (B2, B3) 15 (C1-3)		46	42	—
b. Postop EBRT + CT[146]	14	24	43 (4 year)	—	2	14	—
2. TJUH (gastric)[148]							
a. Total group T3, T4, or N+	120						
• Surgery alone	70	12	13		17 of 38	45	—
• Postop CT, EBRT, both	50	19	17	<0.05	13 of 36	36	—
• Postop EBRT + CT	20 of 50	19	21		3 of 16	19	—
b. T3/T4, N1/N2 (surg ± adjuv)	44,30	9 vs 13	4 vs 22	0.04	—	—	—
3. Univ. Penn (gastric or EG)*[150]							
a. Surgery alone	40	16	31 (2 year)	—	31	75	—
b. Postop EBRT	17	15	50 (2 year)		4	24	—
c. Postop EBRT + CT	27	21	55 (2 year)	—	4	15	—
4. Mayo Clinic (gastric, GEJ)[151]							
Postop EBRT ± CT T3, T4 or N+	25	19	31 (4 year)	—	5	20	—
5. TJUH (GEJ)†,[149]	S EBRT		S EBRT				
Surgery + EBRT + CT	37 18	12 vs 20	— —	—		74 vs 36	.0014
• T3, T4	— —	—	11 14	—	—	87 vs 47	.0016
• LN (–)	— —	—	42 100	—	—	—	—
• LN (+)	— —	—	0 15	0.001	—	97 vs 14	.0001
6. Samsung Medical Center[152]							
a. Surgery, D2 resection	446	62.6	51		97	21.7	
b. D2 resection + postop chemoRT	544	95.3	57	0.02	81	14.9	0.005
6. U Navarre[153-155]							
a. Surgery + EBRT	35	—	38	—	7	20	
b. Surgery + IORT + EBRT	27	—	41 (8 year)	—	3	11	
7. H U Lyon (pT3 or N+)[160,161]							
a. Surgery	NA	—	28			42	
b. Surgery + IORT + EBRT	49	—	50				

adjuv, *Adjuvant therapy;* chemoRT, *chemoradiation;* CT, *chemotherapy;* EBRT, *external beam radiation*; GEJ, *gastro-esophageal junction; IORT*, *intraoperative radiation;* MGH, *Massachusetts General Hospital;* LN, *lymph node;* N+, *Node positive;* postop, *postoperative;* S, *surgery;* TJUH, *Thomas Jefferson University Hospital*
**Long-term survival, 5 year data unless specified; †Mehta and Mohuidden, ASTRO abstract, IJROBP 30(1):272, 1994.*

Gunderson et al reported a median survival of 24 months and 4-year survival of 43% in 14 patients from MGH who had complete resection of tumors with extension beyond the wall, nodal involvement, or both.[146] Patients received postoperative EBRT (45 Gy to 52 Gy, 1.8 Gy/day) plus concurrent 5-FU–based chemotherapy. Subsequent locoregional relapse was documented in 2 of 14 patients (14%) in contrast to a 42% incidence in patients who were similarly high risk treated with surgery alone at MGH.[108]

In a gastric series from TJUH, 120 patients had surgical resection but were at high risk for relapse because of extension beyond the gastric wall, nodal metastases, or positive margins of resection.[148] Seventy patients had surgery alone and 50 received adjuvant therapy. Apparent improvements in local control as well as median and 5-year survival were noted with additional therapy. For patients with negative resection margins, 2-year local control with surgery alone was 55% versus 93% with adjuvant irradiation with or without chemotherapy ($p = 0.03$). For patients with T3 and T4 tumors and lymph node involvement, median survival was 9 months versus 13 months (surgery alone or plus adjuvant treatment), and 5-year survival was 4% versus 22% ($p = 0.03$). In a separate TJUH analysis of 55 patients with cancers of the GE junction, local relapse with surgery alone was 74% versus 36% in patients with adjuvant EBRT with or without chemotherapy ($p = 0.0014$).[149] Survival trends for patients who were node positive appeared better in patients who received adjuvant treatment (5-year survival 15% versus 0%, $p > 0.01$).

In a University of Pennsylvania analysis, treatment intensification appeared to improve both disease control and survival. The incidence of local relapse with surgery alone was 75% (31 of 40) versus 24% with adjuvant irradiation (4 of 17) and 15% with adjuvant irradiation plus chemotherapy (4 of 27).[150] Five-year survival trends favored adjuvant chemoradiation over surgery alone at 55% versus 31%.

In a retrospective Mayo analysis, 63 patients received postoperative EBRT with or without 5-FU after resection of carcinoma of the stomach or GE junction.[151] Twenty-five of the 63 patients had complete resection with no residual disease but had high-risk factors for disease relapse (extension beyond gastric wall, 92% of the patients; involved nodes, 92%; both high-risk factors, 84%). Concurrent 5-FU with or without leucovorin was given with EBRT in 84% of the 25 patients who were treated adjuvantly, but maintenance chemotherapy was given in only 20%. Locoregional control was achieved in 20 of the 25 (80%) with median survival of 19 months. Four-year survival was 31% despite the poor prognostic factors in these 25 patients.

When patient outcome was compared by actual treatment received (29 adjuvant treatment, 33 surgery alone), 5-year survival still favored the adjuvant group (20% versus 12%), but the differences were not statistically significant. The 10 patients who refused assignment to adjuvant treatment had more favorable prognostic findings than the other two groups of patients. When the two groups with equally poor prognostic factors were compared, 5-year OS was 20% versus 4%, with an advantage to those receiving adjuvant treatment. When analyzed by treatment delivered, locoregional relapse was decreased with adjuvant treatment (54% incidence with surgery alone versus 39% with irradiation plus 5-FU).

TABLE 47-5 Surgery with or without Adjuvant Therapy for Resected Gastric Cancer (or Gastroesophageal Junction), Phase III Trials

Series/Treatment Method	Survival						Locoregional Relapse			
	Patient No.		Median (mo)	Long-term,%*		*p* Value	No.	(%)	*p* Value	Ref. No.
1. Japan: Surgery ± IOERT†	S	IOERT		S	IOERT					139,140
	110	101								
a. Stage I	43	24	—	93	87					
b. Stage II	11	20	—	62	84					
c. Stage III	38	30	—	37	62					
d. Stage IV	18	27	—	0	15	—	—	—	—	
2. China: Surgery ± IOERT†	100	100								141
a. Stage III (5 year)	—	—		30	65	<0.01				
b. Stage III (8 year)	—	—	—	22	52		—	—	—	
3. Mayo Clinic‡										164
a. Surgery alone	23		15	4		—	—	54	—	
b. Postop EBRT + 5-FU	39		24	23		0.05	—	39	—	
4. China: Beijing										145
a. Surgery alone	199		—	20			—	52	<0.025	
b. Preop EBRT	171		—	30		0.009	—	39		
5. U.S.GI Intergroup (0116)				(3 yr)				RFS (3-year)		169
a. Surgery alone	275		27	41				31		
b. Postop EBRT + 5-FU/Leuc	281		36	50		0.005		48	0.001	
6. S. Korea: ARTIST Trial				(3-yr DFS)						172
a. Postop chemo	228		—	74.2				8.3		
b. Postop chemoradiation	230		—	78.2§		0.0862§		4.8	0.353	
7. CROSS Trial				3 yr (OS)	5 yr					167,168
a. Surgery alone	178		24.0	44	34			34		
b. Preop chemoradiation	188		49.4	58	47	0.003		14	<0.001	
8. British Magic Trial				3 yr (OS)	5 yr			RFS (3 y)		124
a. Surgery alone	253		20	31	23			26		
b. Perioperative ECF	250		24	45	36	0.009		39	<0.001	
9. POET Trial (GE junction)				3 yr (OS)	5 yr‖			Loc RFS (3 yr)		175
a. Preop chemo	60		21.1	27.7	23			59		
b. Preop chemoradiation	60		33.1	47.4	37	0.07		76.5	0.06	

CT, *Chemotherapy;* DFS, *disease-free survival;* EBRT, *external beam radiation;* ECF, *epirubicin, cisplatin, 5-fluourouracil;* GE, *gastro-esophageal;* IORT, *intraoperative radiation;* Leuc, *leucovorin;* Loc RFS, *local relapse-free survival;* N+, *node positive;* postop, *postoperative;* preop chemo, *preoperative chemotherapy;* RFS, *relapse-free survival;* S, *surgery.*

**Long-term survival = 5-year data unless otherwise specified.*

†*Advantage to IOERT in subset analyses: Japan Stage II-IV, China Stage III (37% of patients).*

‡*Survival data based on intent to treat, relapse data on actual treatment.*

§*In subgroup of 396 patients with positive lymph nodes, 3-year DFS 72.3 versus 77.5%, advantage to chemoRT,* p = *0.0365.*

‖*Survival estimated from published OS curves (Magic Trial, 5-year OS published, 3-year estimated; POET trial, 3-year published, 5-year estimated).*

commonly performed as a component of surgery in the U.S. GI Intergroup Phase III gastric adjuvant trial, some have questioned whether chemoradiation would give added benefit following a D2 resection.

The potential role of postoperative chemoradiation in patients who were D2 resected was evaluated in a series of 990 patients treated in Seoul, South Korea (eTable 47-3, Table 47-6).[152] Surgery alone was used in 446 patients, and postoperative chemoradiation was given to 544 patients (disease and patient characteristics and method of chemoradiation paralleled the US GI INT 0116 trial). Both disease control and survival were improved in patients who received trimodality treatment (median OS 95.3 versus 62.6 months, 5-year OS 57% versus 51%, $p = 0.02$; 5-year RFS 54.5% versus 47.9%, $p = 0.016$; locoregional relapse 14.9% versus 21.7%, $p = 0.005$). Five-year RFS and OS were consistently better with trimodality treatment for each stage grouping.

A Phase III study (ARTIST trial) was subsequently performed in South Korea to compare postoperative chemotherapy with capecitabine plus cisplatin (XP; $n = 228$ pts) compared with XP plus concurrent chemoradiation ($n = 230$) following D2 resection.[172] Patients on the chemoradiation arm received two cycles of XP followed by 45 Gy in 25 fractions plus concurrent capecitabine 825 mg/m^2 twice daily during EBRT. On univariate analysis, in the subgroup of 396 patients with positive nodes, 3-year DFS was improved in those who received chemoradiation (77.5% versus 72.3%, $p = 0.0365$; see Table 47-5), and the statistical significance was retained on multivariate analysis ($p = 0.0471$).

Preoperative EBRT Plus Chemotherapy

Although no randomized trials testing preoperative EBRT plus chemotherapy for gastric cancer have yet been published, four Phase III trials for patients with esophagus cancer (alone

or combined with GE junction or cardia lesions) included patients with ACA. This includes studies by Walsh et al,[173] Urba et al,[174] the U.S. GI Intergroup trial published by Tepper et al,[166] and the CROSS trial.[167]

In the Dublin trial by Walsh et al[173] patients with ACA of the esophagus and gastric cardia were randomized to either immediate surgery (control arm) or preoperative EBRT plus 5-FU and cisplatin (40 Gy in 15 fractions; 5-FU, 15 mg/kg/day for 5 days weeks 1 and 6 as a continuous infusion or approximately 600 mg/m^2/day for 5 days; XP 75 mg/m^2 on the first day of each 5-FU infusion), followed by surgical resection 8 weeks after completion of EBRT plus chemotherapy. A highly significant difference in survival was observed with combined modality therapy (intent to treat: median survival 16 versus 11 months; 3-year OS, 32% versus 6%; $p = 0.01$; actual treatment: median survival 32 versus 11 months; $p = 0.001$; 3-year OS, 37% versus 7%; $p = 0.006$). Survival rates for the control group of patients were inferior to other historical data.

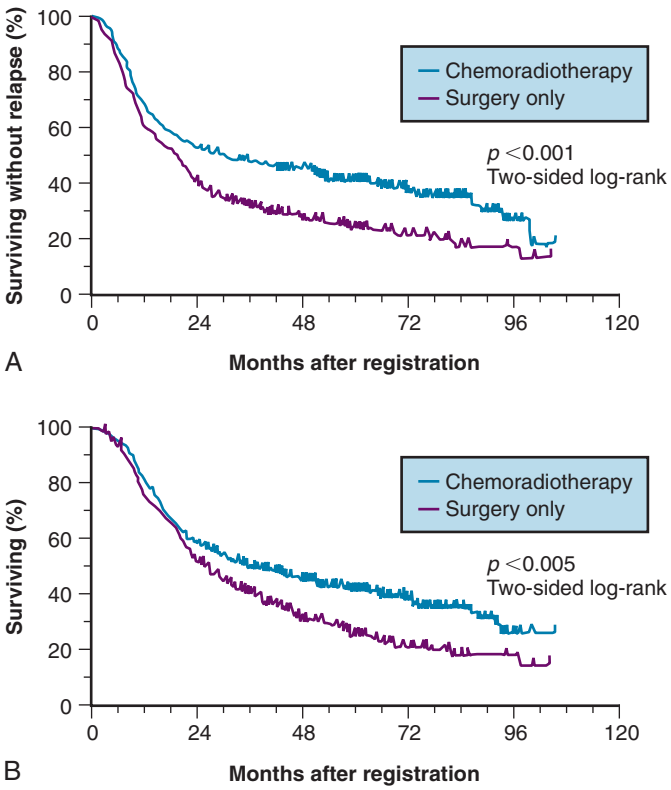


Figure 47-3 Relapse-free survival (RFS) **(A)** and overall survival (OS) **(B)** curves from the U.S. Gastrointestinal (GI) Intergroup Phase III randomized trial (INT 0116) demonstrate a survival benefit for combined modality postoperative chemoradiation versus a surgery alone control arm. Patients had resected high-risk adenocarcinoma of the stomach or GE junction. (3-year RFS 48% versus 31%, $p = 0.001$; 3-year OS 50% versus 41%, $p = 0.005$).
(From MacDonald JS, Smalley SR, Benedetti J, et al: Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. N Engl J Med 345:725–730, 2001.)

Urba et al at the University of Michigan found a borderline survival advantage for patients treated with preoperative chemoradiation compared to surgery alone.[174] Preoperative treatment involved 5-FU, XP, and vinblastine given concurrent with EBRT (45 Gy/1.5 Gy twice daily/3 weeks). Patients with either squamous cell (SCC) or ACAs were eligible, but 75 of the 100 randomized patients had ACA. Survival differences favoring trimodality treatment compared with surgery alone did not appear until several years of follow-up (3-year OS, 30% versus 16%; $p = 0.15$ Cox regression; 0.09 log rank multivariate analysis).

A confirmatory US GI Intergroup trial (CALGB 9781) included patients with either esophagus or GE junction cancers (SCC or ACA); this was stopped prematurely because of poor accrual. Despite the low accrual, patients randomized to trimodality treatment had a survival benefit when compared with patients randomized to surgery alone (median survival 54 months versus 21.6 months; 5-year OS 39% versus 16%, $p = 0.008$).[166]

Perhaps most impressive are the results of the Phase III CROSS trial of 366 analyzable patients with ACA ($n = 275$) or SCC ($n = 84$) of the esophagus and GE junction treated with either surgery alone ($n = 188$) or preoperative chemoradiation ($n = 178$; concurrent chemotherapy with carboplatin and taxol).[167] This study found a major increase in OS with the trimodality therapy (Table 47-8; median OS 49.4 months versus 20 months, 3-year OS 58% versus 44%, 5-year OS 47% versus 34%; HR, 0.657, $p = 0.003$). In a subsequent analysis of CROSS I and II trials, preoperative chemoradiation reduced locoregional recurrence from 34% with surgery alone to 14% ($p < 0.001$) and also had a small but significant effect on hematogenous spread (35% versus 29%, $p = 0.025$).[168] These data strongly suggest that radiation therapy was a critical component of the improvement in outcome and may have been the dominant component. Because this is the single-most convincing positive study of neoadjuvant therapy in this disease, many institutions have now adopted this as their standard of care for patients with esophageal and GE junction tumors.

Summary: Adjuvant EBRT Alone or Plus Chemotherapy

In summary, postoperative chemoradiation[169,171] has been demonstrated to be superior to surgery alone for resectable gastric and GE junction cancers in randomized Phase III trials.

TABLE 47-6 Survival by Stage with D2 Resection Alone or Plus Postoperative Chemoradiation, Samsung Medical Center

	5-year Relapse-Free Survival			5-year Overall Survival		
Stage	**Surgery (%)**	**Adj CRT (%)**	***p* Value**	**Surgery (%)**	**Adj CRT (%)**	***p* Value**
II	66.6	76.2	0.0347	70.9	78.8	0.0433
IIIA	42.3	57.6	0.0015	43.9	61.6	0.0013
IIIB	17.5	39.6	0.0056	20.5	40.8	0.0045
IV(M0)	11.3	26.3	0.0246	12.1	26.4	0.0147
Total	47.9	54.5	0.0161	51.0	57.1	0.0198

Modified from Kim S, Lim KH, Lee J, et al: An observational study suggesting clinical benefit for adjuvant postoperative chemoradiation in a population of over 500 cases after gastric resection with D2 nodal dissection for adenocarcinoma of the stomach. Int J Rad Onc Biol Phys 63:1279–1285, 2005.
Adj CRT, *Adjuvant chemoradiation.*

For GE junction tumors, neoadjuvant chemoradiation has convincing evidence for its local control and survival benefit compared with surgery alone.[166-168,173,174]

GE Junction: Preoperative Chemoradiation versus Chemotherapy (POET Trial)

The POET Phase III trial by Stahl et al included 120 eligible patients with T3-4 ACA of the GE junction treated with either preoperative chemoradiation (CRT; $N = 60$) or chemotherapy alone (N = 60).[175] All patients received two cycles of cisplatin, leucovorin, 5FU, (PLF) chemotherapy weeks 1 to 6 and 7 to 13 (cisplatin 50 mg/m^2 for 1 hour on day 1, 15, 29; leucovorin 500 mg/m^2 for 2 hours, and 5-FU 2 gm/m^2 per 24 hours via infusion on days 1, 8, 15, 22, 29, 36) followed by either PLF alone (weeks 14 to 17) or CRT with 30 Gy EBRT/15 × 2 Gy/3 wk (weeks 14 to 17) plus concurrent PE week 1 of EBRT (cisplatin 50 mg/m^2 for 1 hour on days 2 and 8; etoposide 80 mg/m^2 four 1 hour on days 3 to 5). Outcomes analyses trends favored preoperative CRT over chemo alone with regard to both OS ($p = 0.07$, see Table 47-5) and freedom from local relapse ($p = 0.06$).

SEER Analysis, Gastric Cancer: Adjuvant Irradiation or Chemoradiation

Coburn et al[176] evaluated the impact of postoperative adjuvant EBRT or CRT in 4041 patients who had resection of nonmetastatic gastric ACA from May 2000 to December 2003 (SEER database). Patients treated with postoperative EBRT (alone or plus concurrent chemotherapy) compared with surgery alone had improved median OS for stages III (31 months versus 24 months; $p = 0.005$) and IVM0 (20 months versus 15 months; $p < 0.001$) and the difference approached significance for stage II ($p = 0.0535$). Adjusted analysis using a propensity score suggested that the benefit of adjuvant irradiation was similar for patients in stages II and III (HR of death 0.733 and 0.773, respectively). One must interpret these retrospective analyses with care because biases can inadvertently be introduced.

Meta-Analyses, Gastric/Esophageal Cancer: EBRT, Chemoradiation, and Chemotherapy

A meta-analysis by Fiorica et al[177] evaluated the impact of adjuvant EBRT or CRT in the reduction of all-cause mortality in patients with resectable gastric ACA (nine published Phase III trials: four preoperative EBRT, five postoperative CRT). For patients treated with preoperative EBRT, the HR for all-cause mortality was 0.62 ($p = 0.002$). In patients treated with postoperative CRT, the HR for all cause mortality was 0.45 ($p < 0.00001$).

An Australian meta-analysis published by Gebski et al[178] evaluated the impact of either preoperative CRT or preoperative chemotherapy in patients with resectable esophagus ACA or SCC. For patients treated with preoperative CRT, the HR for all-cause mortality was 0.81 ($p = 0.002$) with similar results for patients with ACA (HR 0.75, $p = 0.02$) and SCC (HR 0.84; $p = 0.04$). In patients treated with preoperative chemotherapy, the HR for all-cause mortality was 0.90 ($p = 0.05$) with significant benefit found for patients with ACA (HR 0.78; $p = 0.014$) but no benefit for those with SCC (HR 0.88; $p = 0.12$).

IORT Alone or Plus EBRT

The pioneering work of Abe at Kyoto University, Japan, in the 1970s, fostered a renewed interest in the old idea of irradiating tumor-bearing areas under direct vision during laparotomy.[139,140] Although Abe's work triggered gastric IORT trials around the world, only a few investigators have favored the use of IORT as the only adjuvant treatment after surgical resection.[157,179-183] Most Western IORT protocols included the delivery of EBRT pre- or postoperatively (45 Gy to 50 Gy in 1.8-Gy to 2.0-Gy fractions) and used IORT doses in the range of 10 Gy to 20 Gy as a boost.[153-155,158-161,184,185] (Figure 47-4).

Survival and Locoregional Relapse Outcomes

Survival results of IORT (with or without EBRT) are reviewed in Table 47-5 and eTable 47-4.

IORT Alone

Takahashi and Abe[140] reported results from a large Japanese trial in which 211 patients were selected, on the basis of day of hospital admission, to receive surgery only or surgery plus IORT (28 Gy to 35 Gy). Five-year OS for Japanese stages II to IV were improved approximately 15% to 25% in the IORT group versus those treated with surgery alone (see Table 47-5; stage II, 84% versus 62%; stage III, 62% versus 37%; stage IV, 15% versus 0%). This magnitude of survival improvement correlates nicely with the approximately 20% of patients who fail only locoregionally after complete surgical resection. However, this method of treatment selection is susceptible to bias, and the trial failed to stratify for important prognostic factors.

In an analysis from Beijing, patients with stage III (serosal involvement or node-positive tumors) or stage IV (unresectable metastasis or adjacent organ involvement) disease were randomized to surgery alone or plus IORT (25 Gy to 40 Gy).[141] In a report of 200 patients, a survival advantage with IORT was demonstrated for patients in stage III (see Table 47-5; 65% versus 30% 5-year OS; 52% versus 22% 8-year OS; $p < 0.01$).

IORT Versus EBRT

At the National Cancer Institute (NCI), Sindelar et al[179] performed a small randomized trial of IORT compared to EBRT following complete surgical resection that demonstrated improved local control with IORT but no survival benefit. The incidence of locoregional recurrence was lower in the IORT versus control group, at 31% versus 80% ($p < 0.01$). The 5-year OS was 10% for 15 patients with resected gastric cancer stages III and IV treated with radical surgery plus IORT.[179] Median survival time for this subset of patients was 25 months. The median survival of the surgery with EBRT arm of 25 patients was 21 months, and the 5-year OS was 20%. No patients in stage III or IV in the control group survived after a median follow-up of 7 years, whereas 3 out of 15 (20%) in the IORT group were alive with no evidence of disease (NED) at the time of the analysis ($p = 0.06$).

IORT Plus EBRT or Chemoradiation

Phase II single or multiinstitution gastric cancer trials that showed promise for IORT plus EBRT or chemoradiation included series from Pamplona, Spain (Calvo et al)[153-155,158]; RTOG/USA (Avizonis et al)[159]; Lyon, France (Gilly et al)[160,161,184]; and China (Zhang et al).[185] Information on the Phase II trials is provided on the Expert Consult website (eTable 47-4).

LOCALLY ADVANCED DISEASE AND PALLIATION

Locally Advanced Disease

The term *locally advanced disease* has different interpretations depending on the author and institution. For the purposes of this chapter, the term refers to cancers that the surgeon would not expect to resect with negative pathologic margins (i.e., unresectable for cure as determined at surgical exploration or as defined preoperatively). Other authors use the term to

eTABLE 47-4 Treatment Strategy and Results in IORT Clinical Series

Series	No. Patients	IORT Dose (Gy)	EBRT Dose (Gy)	Locoregional Relapse (%)	Survival
Ogata[181]	58	28-30	None	—	Stage II, 100% Stage III, 55% Stage IV, 12%
Sindelar[179]	15	20	None	31	10%, 5 year
Kramling[182,183]	54	28	None	12	55 mo, mean
Drognitz[157]	61	23	None	10	58%, 5 year
Calvo[153-155]	59	10-15	40-46*	10	45%, 5 year
Avizonis[159]	27	12.5-16.5	45*	37	47%, 2 year
Coquard[184]	30	12-15	46	25	44%, 5 year
Calvo[158]	37	10-15	45-50.4	15	48%, 5 year
Zhang[185]	46	12-15	39.5-45	4	28%, 5 year

EBRT, *External beam radiation;* IORT, *Intraoperative radiation.*
**EBRT field derived from University of Minnesota reoperation data.*

Ogata et al reported a study from the Kochi Medical School, Japan, with 178 patients with gastric cancer, Japanese Research Society (JRS) stages II through IV treated with surgery alone (120 patients) or surgery plus IORT (58 patients) from August 1983 to July 1992.[181] The patients were not randomized, but a surgery-alone group served as controls. In general, the patients who had IORT had more unfavorable features. The IORT results by stage (see eTable 47-4) demonstrated a survival advantage in stages III and IV that was not statistically significant; the survival in patients in stage II was surprisingly high but did not reach statistical significance.

Calvo et al described a 5-year OS of 39% and a locoregional failure rate of 10.4% in 48 patients with gastric cancer treated with IORT plus EBRT in Pamplona.[153-155,158] This report included 16 patients with AJCC stages I and II and 8 patients with anastomotic or nodal recurrences. The proportion of patients with serosal involvement was 70% and of nodal involvement 56%. An update by Martinez-Monge et al[154] of the 28 patients with serosal (89%) or lymph node involvement (63%) revealed a 10-year OS of 38% and a locoregional failure rate of 11%.

Avizonis et al reported the RTOG series of 27 patients with gastric cancer treated with surgery plus IORT 12.5 Gy to 16.5 Gy with or without EBRT 45 Gy.[159] Seventy percent of the patients had AJCC stages III and IV tumors. The 2-year OS was 47%, 2-year DFS 27%, and median survival 19.3 months.

Gilly et al reported on 45 patients with gastric cancer treated in Lyon with surgical resection, IORT 15 Gy, and EBRT 44 Gy.[160] The 5-year OS for patients who were node positive (N1/N2) was 51%. In the last update of the Lyon experience with 82 patients,[161] 8-year OS among the 49 patients with pT3 or pN+ treated with surgery plus IORT plus EBRT was 50% compared to 28% in similar stage patients treated with surgery alone during the same time period.

The addition of intraoperative electron irradiation (IOERT) to adjuvant chemoradiation and resection has been evaluated in series from Spain[158] and China.[185] In a series of 53 patients with esophagus or GE junction cancer, Calvo et al found on multivariate analysis that locoregional control was improved with the addition of an IOERT boost (n = 37 patients) after preoperative chemoradiation and resection ($p = 0.01$).[158] Zhang et al found on multivariate analysis that the addition of IOERT to resection and postoperative chemoradiation (n = 46) improved both locoregional control (p = 0.02) and DFS (p = 0.05) when compared to results found in 51 patients treated only with adjuvant postoperative chemoradiation for T3/4 or N+ gastric ACA.[185]

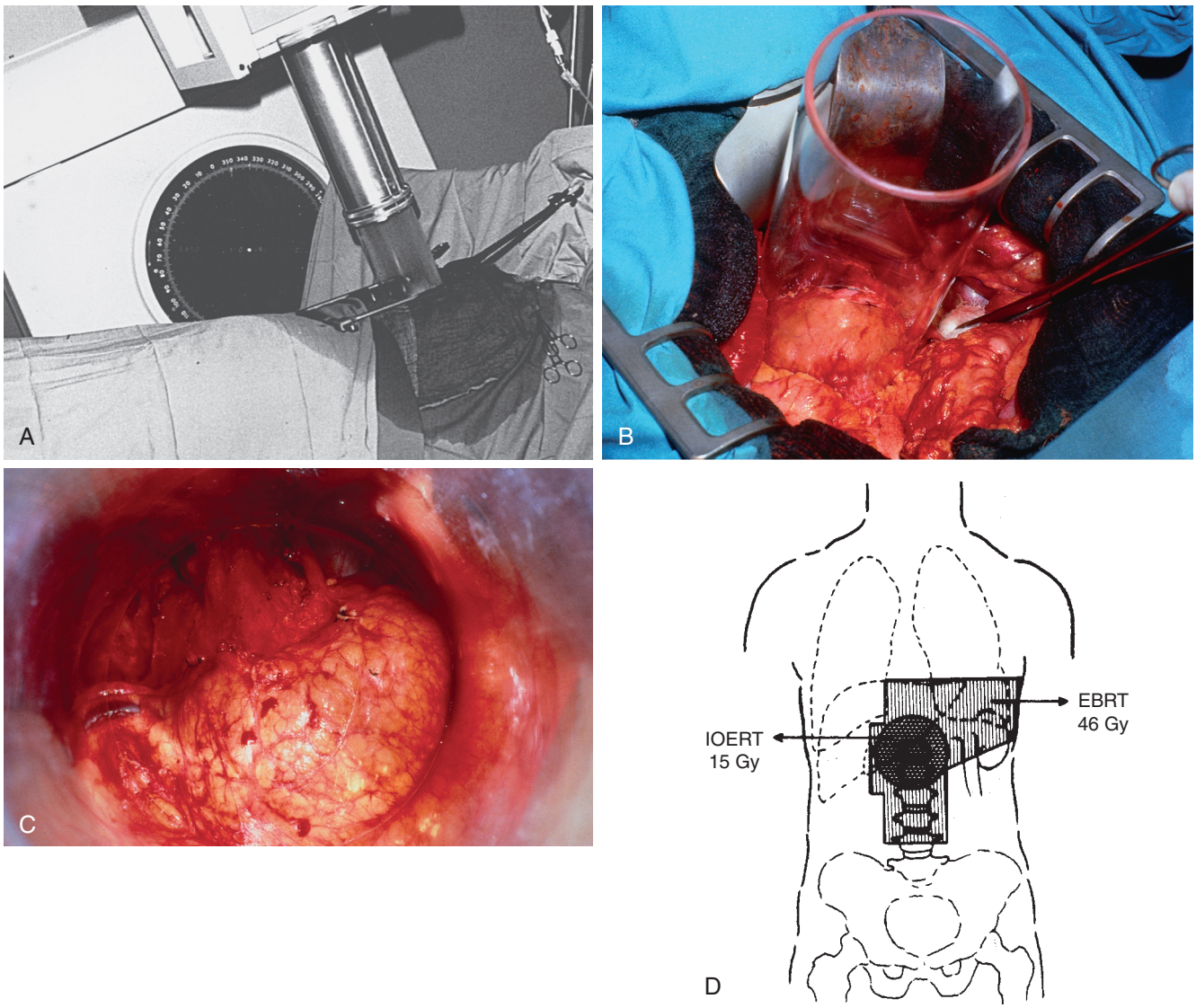


Figure 47-4 Intraoperative electron radiation (IOERT) procedure in a patient with gastric cancer. **A,** View of the linear accelerator and electron beam Lucite applicator. **B,** Applicator (9-cm diameter) positioned for treatment; visceral structures are mobilized from field. **C,** IOERT applicator beam's-eye view of the IOERT target volume: body of pancreas, celiac trunk, and peripancreatic nodal regions. **D,** Idealized artist's depiction of integration of the IOERT and external beam radiation (EBRT) treatment components.

include lesions that are completely resected but have high-risk factors for local recurrence or distant metastasis (nodal involvement, extension beyond the gastric wall, or both).

Surgery

The extent of a surgical procedure must be tempered by the knowledge that cure is at best improbable. Patients with symptomatic obstruction, hemorrhage, and ulceration, and some with perforation, can be successfully relieved of symptoms by even limited gastric resection. Radical subtotal or total gastrectomy may be indicated in some patients whose lesions cannot be completely resected with negative pathologic margins to achieve symptomatic palliation. Results with total gastrectomy in advanced gastric cancer showed good quality of life when this procedure was indicated for bulky or proximal tumors, but symptom relief was less likely for patients with linitis plastica.[162] Although adjacent organ resection can be undertaken if all gross tumors can be removed, it is rarely justified if gross residual tumor (visible or palpable) would remain. Because total (or near-total) gastrectomy has the risk of both acute and long-term morbidity (severe early satiety), it should be used sparingly. If sites of adherence or residual disease are marked with surgical clips, postoperative irradiation plus chemotherapy can be delivered with greater accuracy.

Irradiation with or without Chemotherapy

Although some patients with no resection have long-term survival using irradiation alone or plus chemotherapy, this is not a viable alternative to surgical resection plus adjuvant therapy if that therapy is appropriate. The initial bulk of disease and the limited tolerance of the stomach and surrounding organs prevent a suitable therapeutic ratio between cure and complications. When locally unresectable disease is diagnosed preoperatively, preoperative chemoirradiation would preferably be delivered before an attempt at resection of all gross primary and lymph node disease.

Irradiation

The available literature suggests that ACA of the stomach is radioresponsive. Wieland and Hymmen used 60 Gy when

feasible (1.5 Gy to 2.0 Gy daily) with 11% (9 of 82) 3-year and 7% (5 of 72) 5-year survival.[163] Takahashi compared historical controls with patients whose tumors were unresectable or who had palliative procedures and received postoperative radiation (unknown if chemotherapy was also used).[186] The average survival for irradiated patients was 9 to 10 months longer, with 74% 1-year (32 of 43) and 27% 2.5-year survival (12 of 43).

Abe and Takahashi reported 5-year survival rate of 15% with a single dose of IORT after resection (28 Gy to 33 Gy) in a group of 27 patients with stage IV disease.[140,141] Three of the four long-term survivors had proven residual disease after maximal resection. In the same study, 18 patients in stage IV were randomized to a surgery-alone control arm; the 5-year survival was 0%.

Irradiation Plus Chemotherapy

Most reports of combined irradiation and chemotherapy for gastric cancer involve patients with residual and unresectable disease, and most Phase III trials in this setting show an advantage for combined modality treatment over single-modality treatment. In a randomized series from the Mayo Clinic, 5-FU was used during the first 3 days of EBRT in half of the patients (EBRT, 35 Gy to 37.5 Gy in 4 to 5 weeks; 5-FU 15 mg/kg for 3 days, week 1 of EBRT).[187,188] For the combined treatment group, mean and OS was improved (13 versus 5.9 months and 3 of 25 or 12% versus 0 of 23 for 5-year survival) (Table 47-7). In a randomized study by the GITSG,[189,190] the combination of EBRT and 5-FU followed by maintenance 5-FU plus MeCCNU resulted in statistically superior long-term survival when compared with 5-FU MeCCNU alone (3- and 4-year survivals of 18% versus 6% to 7%; $p < 0.05$). GITSG performed a second trial in which combined irradiation plus chemotherapy did not produce a survival advantage when compared with chemotherapy alone.[191] Because 46% of the patients on the combined arm either did not receive full-course EBRT or had a major deviation in the delivery of the EBRT, the results are difficult to interpret. In a randomized EORTC trial of EBRT with or without 5-FU, residual disease after resection was identified in 22 patients.[192] The three long-term survivors (14%) received EBRT plus 5-FU.

Data from nonrandomized single-institution or group analyses also suggest that the combination of EBRT and chemotherapy may have an impact on disease control and survival. In published series from the Mayo Clinic[194] and MGH,[164] long-term survival of 10% or more was demonstrated in patients who received EBRT plus chemotherapy following subtotal surgical resection with residual disease (MGH) or with unresectable lesions. In a University of Pennsylvania analysis of patients with unresected ACA of the GE junction or esophagus, local control was better with combined- versus single-modality treatment (irradiation, 1 of 23, or 4%; chemotherapy, 0 of 8; irradiation plus chemotherapy, 11 of 21, or 52%). Median survival with the combined modality treatment was 10 months compared with 5 months for irradiation alone. In a Mayo Clinic- North Central Cancer Treatment Group (NCCTG) dose escalation pilot study, EBRT was combined with 5-FU plus low-dose leucovorin (400 mg/m^2 and 20 mg/m^2, respectively, for 3 to 4 days, week 1, or 1 plus 5 of irradiation).[195] Two of six patients with locally advanced gastric cancer were alive and disease free beyond 3 years.

Published analyses from both GITSG and MGH suggest an improvement in survival if partial resection with gross residual disease or gross total resection with microscopic residual can be accomplished. In the GITSG series 3-year survival was about 25% versus 10% in patients who were partially resected compared with unresected.[189,190] In the MGH analysis, median survival for patients with irradiation plus chemotherapy was 24 months for microscopic residual, 15 months with gross residual, and 14 months in unresected.[164] Four-year OS was 0% for patients who were unresected compared to 10% in those patients with residual disease after maximal resection.

TABLE 47-7 Unresectable or Residual Gastric Cancer: Treatment Results

Group or Institution	Treatment Arms	EBRT Dose/ Schedule (Gy)	Chemotherapy	No. of Patients	Results (Failure Patterns) and Survival
RANDOMIZED					
Mayo Clinic[187,188]	EBRT ± 5-FU	35-40/9-12 Gy/wk	5-FU 15 mg/kg, d 1-3 k wk 1 EBRT	48	Increased SR for EBRT + 5-FU with mean SR 13 vs. 5.9 mo and 3/25 (12%) vs. 0/23 5-year SR
GITSG[189,190]	CT ± EBRT	50/8 wk-2 wk split after 25/3 wk	5FU 500 mg/m^2 d 1-3 wk 1/ 6 EBRT; 5-FU + MeCCNU maint. vs. 5 FU/MeCCNU	90	Advantage in long-term SR with EBRT + CT at 18% vs. 7% ($p < 0.05$)
Japan[139,140]	Operation ± IORT*	IORT, 28-40	None	110 101 IORT	Increased 5-year SR for 27 patients with IORT + operation for stage IV disease vs. 18 patients with operation alone (15% vs. 0%)
NONRANDOMIZED					
MGH[146]	EBRT ± CT	45-55/5-6½ wk	5-FU 500 mg/m^2, 3 d wk 1 EBRT ± maint. FAM, 5 FU/MeCCNU	32†	Median SR res(m) 24 mo, res(g) 15 mo, unresected 14 mo; survival ≥30 mo, unresected 0%, residual after resection ≈ 10%
Mayo Clinic[193]	EBRT ± CT ± IOERT	45-54/5-6½ wk; IOERT boost 13 patients	5-FU 500 mg/m^2, 3 d wk 1, 5 or 5-FU 400 mg/m^2, + leucovorin 20 mg/m^2	87	Median SR res(m) 17 mo, unresectable 12 mo; locally recurrent 10 mo; 4-year SR ≤9% res(m) and res(g), 18% unresectable or locally recurrent

5-FU, *5-fluorouracil;* d, *day;* FAM, *5-FU, Adriamycin, mitomycin-C;* CT, *chemotherapy;* EBRT, *external beam irradiation;* GITSG, *Gastrointestinal Tumor Study Group;* IORT, *intraoperative irradiation;* maint., *maintenance;* MGH, *Massachusetts General Hospital;* SR, *survival;* res(m), *microscopic residual;* res(g), *gross residual;* wk, *week.*

**Treatment method based on date of hospitalization.*

†An additional 14 had "curative resection" with high-risk LF: 40% 4-year actuarial SR with EBRT + CT.

In a Mayo Clinic analysis of irradiation with or without chemotherapy for gastric or GE junction cancers, an improvement in median survival was also suggested for patients with gross total resection but microscopic residual when compared with higher-risk subsets of patients.[193] In these analyses, the results of irradiation or chemoradiation were evaluated in 87 patients with either locally advanced primary or locally recurrent ACA of the stomach or GE junction treated from 1980 through 1996 at the Mayo Clinic. Of those with primary lesions, 28 had unresectable disease and 39 had resection but residual disease (R1 resection, 28 pts; R2, 11). An additional 21 presented with a local or regional relapse with no evidence of abdominal (liver, peritoneal) or extraabdominal metastasis (lung, other). Chemotherapy with 5-FU (with or without leucovorin) was given during or following EBRT in 75% of the patients with R1 resection and 92% of the other subgroups (concomitant with EBRT in 84%). IOERT supplement to EBRT was given in 13 patients. Median survival in patients with primary cancer was 16.7 months for patients with R1 resection, 9.6 months with R2 resection, or 12 months with unresectable disease. Patients who presented with local or regional relapse had a median survival of 10 months.

Prognostic factor analyses showed that long-term survival appeared slightly poorer in patients who had resection before irradiation or chemoradiation in the Mayo Clinic analysis.[193] Actual 4-year survival was 0% versus 9% in patients with R2 resection (1 of 11 patients alive NED 2 years after treatment), 9% in those with R1 resection, and 18% in patients with unresectable primary or locally recurrent cancers. The survival trends may be a reflection of both treatment sequence and higher irradiation dose, since 12 of 13 patients with EBRT plus IOERT had unresectable primary or locally recurrent cancers. In the 21 patients with local or regionally recurrent cancers, irradiation dose greater than 54 Gy had a trend for improved survival (median survival 25.6 versus 5.5 months, $p = 0.06$). If patients with R1 resection are excluded, an increase in the number of cycles of chemotherapy appeared to correlate with an improvement in median survival (less than two cycles, median 5.2 months versus 11.5 months with two or three cycles and 14.5 months with four or more cycles, $p = 0.014$).

Although problems with excess toxicity were encountered in the GITSG study,[189,190] such problems were minimal or nonexistent in the MGH series of 46 patients.[146] In the MGH series, shaped radiation portals and single fraction size of 1.8 Gy were used; 43 of 46 patients received both irradiation and chemotherapy.

Neoadjuvant Chemotherapy

The use of adjuvant preoperative (neoadjuvant) chemotherapy has been less well studied in patients with locally advanced disease compared to adjuvant postoperative therapy. Because of the inability of adjuvant (postoperative) systemic therapy to prolong survival in surgically managed gastric cancer, several investigators have pursued the approach of neoadjuvant chemotherapy in an attempt to increase resectability and improve survival. These studies involve a mix of patients including those with clinically operable, "locally advanced" or unresectable lesions. All but one of these studies are Phase II protocols.[196-210] eTable 47-5 summarizes the results of these reports.

One of the few randomized trials to assess the potential benefit of preoperative chemotherapy to surgery alone in potentially resectable patients failed to show any benefit.[209] In this Dutch study, patients were randomized to either FAMTX followed by surgery or surgery alone. The study was closed early because of poor accrual, but analysis of the enrolled patients showed no benefit to rate of curative resectability, rate of relapse, or median survival.

Unresectable

Wilke et al examined the role of etoposide, Adriamycin, and cisplatin (EAP) in a group of 34 patients with laparotomy-determined unresectable stomach cancer.[196] This study was prompted by the promising results with this regimen in advanced disease (21% complete remission and 73% overall response rate).[211] Following exploratory laparotomy, patients were begun on EAP. Twenty patients (59%) who achieved clinical response went on to a second-look operation followed by two additional courses of chemotherapy. Fifteen patients (44%) out of the original cohort were able to have a resection and 5 patients were pathologic complete responders (15% of the original 34). Median survival in this Phase II trial was 18 months for the entire study group. In an update of these data, results were reported in 21 patients who had total resection after EAP chemotherapy for locally unresectable disease.[212] Fourteen of 21 patients had relapsed, and 11 of 14 had a locoregional component of disease (79% of relapses, 52% of group at risk).

Verschueren et al evaluated 17 patients with unresectable gastric cancer.[197] Fifteen of them were defined as unresectable at laparotomy whereas two were deemed unresectable on the basis of CT imaging. After receiving up to four courses of sequential 5-FU and high-dose methotrexate, 13 patients (76%) underwent attempted resection. Although 7 patients had resectable tumors (41%), locoregional relapse occurred in 5 of 7.

Summary

The high response rates achieved with neoadjuvant chemotherapy are of interest in these patients with locally advanced or unresectable tumors, and this form of treatment will undoubtedly be the subject of further investigation. The roles of neoadjuvant systemic treatment in increasing resectability rates and improving survival in localized gastric cancer are unknown. Although resectability rates seem higher than the median rate of 40% from several studies, the patients in the neoadjuvant studies were highly selected. Except for the two trials in which tumors were unresectable on the basis of exploratory laparotomy, the successful resection in these reports may not have been influenced by neoadjuvant chemotherapy. In general, pathologic CR rates are low (≤15%), and no proof exists that primary lesions are made more resectable by such treatment. The impact of preoperative systemic treatment on survival is even less clear. The one randomized trial that has been reported shows a nonsignificant improvement in survival for neoadjuvant chemotherapy in borderline resectable locally advanced disease.[199,200] Newer technologies such as EUS may identify patients who will do poorly with standard therapy alone and would be reasonable candidates for adjuvant studies.[213]

In view of the high incidence of locoregional relapse in several series of patients whose tumors were resected after neoadjuvant chemotherapy for initially unresectable lesions, irradiation should be incorporated into the study design of future trials for patients with high-risk factors. Patients with unresectable lesions who do not respond to neoadjuvant chemotherapy may still respond to preoperative EBRT plus chemotherapy. The favorable outcomes with preoperative chemoradiation compared with surgery alone for patients with potentially resectable cancers have previously been discussed.[152,165-168,172-174]

Palliation for Metastatic Disease

This section is limited to discussion of patients with hematogenous or peritoneal metastasis at time of disease presentation.

eTABLE 47-5 Neoadjuvant Therapy for Gastric Cancer

Author	Patients	Regimen	Response Rate (%)	Explored (%)	Resected (%)	Pathologic CR (%)	Median Survival (mo)
UNRESECTABLE							
Wilke[196]	34	EAP	68	59	44	15	18
Verschueren[197]	17	5-FU/MTX	NS	76	41	NS	14
BORDERLINE RESECTABLE, LOCALLY ADVANCED							
Ducreux[198]	30	5-FU/CDDP	50	93	77	0	16
Kang[199,200]	53	EAP	NS	89	70	7	43
	54	Control	—	100	61	0	30
RESECTABLE							
Ajani[202]	25	EFP pre/postop	24	100	72	0	15
Ajani[203]	48	EAP pre/postop	31	85	77	0	15.5
Kelsen[204,205]	56	FAMTX preop, ip5-FU/ CDDP, IV 5-FU postop	51	89	61	0	15.3
Crookes, Leichman[206,207]	59	5-FU, LV, CDDP preop; IP FUDR, CDDP postop	54	95	68	9	52
Songun[209]	27	FAMTX	30	100	56	7	13.1
	29	Control	—	100	62	—	12.8

5-FU, *5-Fluorouracil;* CDDP, *cisplatin;* CF, *citrovorum factor (leucovorin);* ci, *continuous infusion;* EAP, *etoposide, Adriamycin, cisplatin;* EFP, *etoposide;* EFP, *etopaside;* 5-FU, *cisplatin;* FAMTX, *5-FU, Adriamycin, high-dose methotrexate;* IP, *intraperitoneal;* Med, *Median;* mo, *months;* MTX, *methotrexate;* NS, *Not stated;* postop, *postoperative;* preop, *preoperative.*

Locally Advanced

Two studies have tested the use of preoperative systemic treatment for patients with locally advanced stomach cancer. Ducreux et al treated 30 patients with two or three cycles of cisplatin and 5-FU before surgery.[198] Twenty-eight (93%) patients subsequently underwent laparotomy, and 23 (77%) had their tumor resected; the pathologic response rate was not reported. Median survival was 16 months. Kang et al randomized 107 patients with locally advanced gastric cancer to receive two or three cycles of EFP (etoposide, fluorouracil, Platinol) followed by surgery versus surgery alone.[199,200] Of the 53 patients randomized to preoperative treatment, 47 (89%) were explored, and 37 (70%) had a complete resection. A complete pathologic response rate of 7% was noted. More patients were able to undergo a curative resection in the treated group when compared with surgery alone (70% versus 61%). Median survival was 43 versus 30 months in favor of neoadjuvant treatment, but this did not achieve statistical significance ($p = 0.114$).

Potentially Resectable

Ajani et al reported two Phase II studies of preoperative chemotherapy (EFP, EAP) in patients thought clinically to have potentially resectable disease.[202,203] Patients were treated with two or three cycles of EFP/EAP preoperatively plus an additional two or three cycles postoperatively if a positive response to neoadjuvant treatment could be detected. No pathologic complete responses were seen with either EFP ($n = 25$ patients) or EAP ($n = 48$ patients), and median survival was 15 and 15.5 months, respectively. The impressive results obtained with neoadjuvant EAP in Wilke et al's study could not be reproduced in this group of patients who had potentially smaller tumor burdens.

Other investigators have examined the utility of combining preoperative chemotherapy and postoperative treatment with intraperitoneal chemotherapy in view of the high peritoneal failure rate following resection of gastric cancer.[204-207] Schwartz et al[204,205] delivered three cycles of neoadjuvant FAMTX plus postoperative intraperitoneal (IP) 5-FU and cisplatin along with infusional 5-FU. No complete pathologic responses were observed. Leichman et al[206,207] delivered two cycles of 5-FU, leucovorin, and cisplatin preoperatively, and two cycles of IP 5-fluoro-2′-deoxyuridine (5-FUDR) and cisplatin postoperatively. In the updated report of 59 potentially resectable patients, 96% underwent exploration and 68% had complete resection.[207] The pathologic CR was only 9%, but median survival was about 52 months.

Surgery

Surgical intervention in the patient with metastatic gastric cancer requires sound judgment. The underlying health and function (performance status) of the patient, the estimated duration of patient survival, and the nature of the symptoms must all be taken into account before deciding to proceed with an operation. Resection for palliation is generally better than bypass or intubation in appropriately selected patients, leading to better symptomatic relief and often longer survival.[162] Obstructing lesions may be resected with excellent palliation, but endoluminal stents, endoscopic laser treatments, or gastrostomy tube placement should be considered for poor operative candidates.[214] Although significant hemorrhage from an ulcerating or necrotic polypoid tumor may be temporarily controlled by endoscopic techniques, stabilization and urgent surgical intervention should be undertaken when appropriate. A perforated gastric cancer usually presents as an emergency and may be unrecognized preoperatively. Aggressive treatment with gastric resection should be carried out in the fit patient; pain control and hydration alone are preferable for the moribund or unfit patient.

Laser or Irradiation

If palliative resection is not indicated in symptomatic patients with metastases, laser treatment, stent placement, or a shortened course of EBRT alone or plus 5-FU could be used (37.5 Gy in 15 fractions over 3 weeks, for example), or stereotactic body irradiation (SBRT, see Ch 24), to be followed by systemic treatment. Patients who have proximal lesions with esophageal obstruction may be candidates for laser or esophageal stents instead of irradiation, although stents in the distal esophagus often cause problems with migration. If either method is successful in overcoming obstruction, patients could proceed directly to treatment with chemotherapy.

Chemotherapy

Traditional chemotherapy agents with 20% or more response rates include doxorubicin,[215,216] cisplatin,[217] 5-FU,[218] etoposide,[219] and mitomycin C.[220] More recently a variety of chemotherapy drugs have shown promising response rates in advanced gastric cancer including taxotere (23%), irinotecan (23%), and paclitaxel (17% to 21%).[221-223] Complete remissions with single-agent chemotherapy are exceedingly rare, and remission duration is usually 3 to 5 months. For patients with measurable disease, survival is usually only 3 to 6 months. Single-agent chemotherapy therefore offers little practical benefit to the patient.

Combination chemotherapy regimens, which almost universally incorporate a fluorinated pyrimidine, obtain reliable responses in 25% to 50% of patients.[220-232] Combination chemotherapy regimens that have produced response rates of 30% to 45% include the following: the FAM regimen[220]; 5-FU + BCNU[224]; 5-FU + MeCCNU[225]; 5-FU + mitomycin C[216]; 5-FU + doxorubicin + MeCCNU (FAMe)[215,225]; 5-FU + doxorubicin + BCNU (FAB)[226]; 5-FU + doxorubicin + cisplatin (FAP)[227-229]; EAP[230]; FAMTX[229,231]; and etoposide, leucovorin, and 5-FU (ELF).[232] Most of the combination chemotherapy regimens report median survival of 5 to 7 months, which is similar to the survival of patients receiving single-agent chemotherapy. Many of the combinations that had promising activity in single institution evaluations were less active and more toxic in subsequent Phase II and III trials.

Platinum Regimens

See expert consult website for additional information on platinum regimens.

A regimen combining epirubicin, cisplatin, and infusional 5-FU (ECF) was introduced by investigators at the Royal Marsden Hospital for patients with advanced esophagogastric adenocarcinoma. An overall response rate of 71% was obtained with a CR rate of 12%.[247] A subsequent randomized Phase III trial, which compared FAMTX with ECF, showed that ECF was associated with a superior response rate (45% versus 21%) and OS (median 9 versus 6 months).[248] In view of the promising results of this trial, ECF has become the standard regimen to which other regimens are compared.

A Phase III trial for gastroesophageal cancer was conducted to assess the potential benefit of replacing cisplatin with oxaliplatin and infusional 5-FU with capecitabine using a 2×2 design.[249] This trial enrolled 1002 patients from 61 centers. Using a noninferiority statistical design for the trial, the combination of epirubicin, oxaliplatin, and capecitabine (EOX) was shown to be the most active of the four regimens evaluated. Compared to ECF, patients receiving EOX had both an improved 1-year survival (46.8% versus 37.7%) and a statistically improved median survival (11.2 months versus 9.9 months; HR, 0.80; 95% CI, 0.65 to 0.97).

Taxane Regimens

Several Phase II studies have evaluated non–5-FU-containing combinations. The response to combinations, such as docetaxel and cisplatin, paclitaxel and cisplatin, have been comparable to 5-FU-containing regimens.[250,251]

The combination of docetaxel and cisplatin has been evaluated in a number of clinical trials as either the two-drug combination or in combination with other chemotherapy agents. As a two-drug combination in Phase II trials the reported response rate is 28% to 46% and median survival of 10.4 to 11.5 months.[252-255] Other trials explored the added benefit of 5-FU and reported response rates of 40% to 43% and median survivals of 9.0 to 9.7 months.[256,257] A multicenter randomized Phase II trial, involving 158 patients, assessed docetaxel and cisplatin with or without 5-FU as potential support for a Phase III trial.[257a] In this trial the combination of docetaxel and cisplatin gave a response rate of 26% and a median survival of 10.5 months. The addition of 5-FU increased the response rate to 43%; however, the median survival was only 9.6 months.

The combination of docetaxel, cisplatin, and 5-FU was compared to cisplatin and 5-FU in a Phase III trial.[258] Overall survival was significantly longer with docetaxel, cisplatin, and 5-FU ($p = 0.02$). The response rate was also higher with this combination (69% versus 59%, $p = 0.01$). However, the combination of docetaxel, cisplatin, and 5-FU was also more toxic with 69% of patients developing treatment-related grade-3 or grade-4 adverse events compared to 59% of patients receiving cisplatin and 5-fluorouracil. Neutropenia and neutropenic fever were both significantly higher with the three-drug combination.

As is true in most malignancies, there is an enormous interest in using biologics for the treatment of metastatic gastric cancer. For patients who are HER2-positive, the Trastuzumab for GAstric cancer trial (ToGA) trial demonstrated a survival advantage to the use of trastuzumab, a HER2 inhibitor, when combined with chemotherapy (extension of median survival by 2.7 months compared to chemotherapy alone).[259] An international Phase III trial recently reported a benefit to single agent ramicirumab, a VEGFR2 inhibitor, in therapy of previously treated patients with metastatic gastric cancer (extension of median survival by approximately 1.5 months).[260] How well this, or other VEGF inhibitors, will impact survival when combined with chemotherapy is uncertain. Other biological manipulations have not as yet shown much efficacy.

Supportive Care versus Chemotherapy

Chemotherapy has been shown to be advantageous to best supportive care in both retrospective analyses and Phase III trials. These analyses are reviewed on the Expert Consult Website.

Several trials have compared single-agent 5-FU with combination chemotherapy in advanced gastric cancer. Most of the trials have been unable to demonstrate improved survival for multiagent regimens. The NCCTG reported a prospective randomized Phase III trial comparing 5-FU with 5-FU + doxorubicin to FAM. Overall responses were quite similar, and no differences were seen in survival.[233] A large Korean study randomized 324 patients to 5-FU, 5-FU plus cisplatin, or FAM. Responses were observed more often in the patients treated with 5-FU plus cisplatin, but OS was similar in all three treatment arms.[234] Others have reported similar problems in demonstrating improved survival for multiagent regimens in Phase III trials.[235,236] Several trials have also used pharmacologic manipulation of 5-FU with leucovorin in gastric carcinoma in attempts to follow up on the apparent benefit that this combination achieved with patients who had colorectal carcinoma.[237] Responses varied between 11% and 50%, but median survival rates were almost identical to those of 5-FU alone at 5.5 months.

Many of the combination chemotherapy regimens, which achieved response rates of 30% to 50% in single-institution trials, have often failed to reproduce the initially high response rates when subjected to confirmatory trials. A case in point is the EAP regimen. The initial Phase II trial reported overall response rates of 64% (complete and partial) and 21% (complete) and median survival of 9 months.[211] The studies that followed did not confirm such high response rates, and toxicity was sometimes substantial.[238]

FAMTX Regimens

The combination of 5-FU, doxorubicin, and methotrexate (FAMTX) was a widely used regimen in the 1990s. Klein first reported a 58% response rate for the combination in a Phase II study.[239] The EORTC group performed a randomized Phase II trial of FAM versus FAMTX in 213 patients with advanced measurable or nonmeasurable gastric cancer.[230] FAMTX was found to have a significantly superior response rate (41% versus 9%; $p < 0.0001$) and survival (median 42 versus 29 weeks; $p = 0.004$). The authors considered FAMTX the reference chemotherapy for future advanced gastric trials.

Kelsen et al[231] randomly compared FAMTX and EAP for advanced disease in 60 patients. Response rates were similar, at 33% compared to 20% (advantage to FAMTX; $p = 0.24$), and tolerance was better for FAMTX with a significantly higher toxic death rate for EAP. Accordingly, the trial was stopped.

In 1991, the combination of etoposide, leucovorin, and 5-FU (ELF) was introduced as an alternative to more aggressive regimens for patients with cardiac or poor medical conditions or advanced age.[240] It achieved a response rate of 53%, and a median survival time of 11 months. Multiple clinical trials have now evaluated the activity and tolerability of ELF, and have generally shown OS in the range of 8 to 10 months and response rates of about 30%.[241-243]

FAMTX has been compared to ELF and infusional 5-FU/cisplatin (FUP) in a Phase III EORTC study. No apparent differences in response rates or survival have been demonstrated to date.[244]

The Italian Group for the Study of Digestive Tract Cancer reported an intensive, multiagent regimen including the most active agents in gastric cancer, cisplatin, epirubicin, leucovorin and 5-FU (PELF).[245] Administered weekly with growth factor support, this regimen produced an overall response rate of 62%, CR rate of 17%, and a median survival time of 11 months.

PELF was subsequently compared to FAMTX in a randomized Phase III trial. Although both the overall and CR rates with PELF were significantly higher (overall, 39% versus 22%; complete, 13% versus 2%), only a nonsignificant improvement in OS was seen with PELF.[246]

In 1993 Murad et al published results of a randomized trial where a modified FAMTX regimen was compared to best supportive care.[261] The trial was interrupted after entry of 22 patients because the treated patients were enjoying a significantly better outcome. The next 18 patients were assigned directly to treatment. Median survival for all the treated patients was 10 months versus 3 months for the untreated controls ($p = 0.001$).

Pyrhonen et al reported the results of 41 patients randomized to 5-FU, epirubicin, and methotrexate (FEMTx) plus vitamins A and E versus the same vitamins and best supportive care.[262] In patients treated with FEMTX, 29% had an objective response and 33% had stable disease for greater than 2 months. In control patients, 20% had stable disease. Median time to progression (5.4 versus 1.7 months, $p = 0.0013$) and median survival (12.3 versus 3.1 months, $p = 0.0006$) both favored treatment with FEMTx.

Glimelius et al studied, in a group of 61 patients with inoperable gastric cancer, the cost-effectiveness of palliative therapy by randomly assigning patients to primary chemotherapy with ELF or 5-FU leucovorin versus best supportive care.[263] Improved or prolonged high QOL was documented in patients receiving chemotherapy versus supportive care alone. Patients in the chemotherapy arm had a significantly longer median survival at 8 months versus 5 months ($p = 0.003$, adjusted) and QOL ($p < 0.05$) also favored the treated patients.

Park et al performed a retrospective analysis of 409 patients with incurable gastric cancer in which 202 patients were treated with a modified FAM regimen and 207 were not treated.[264] The 1-year survival was 34.1% for patients treated with FAM versus 22.5% for the control group. Details on how treatment decisions were made were not in the report.

A 2010 meta-analysis reviewed the efficacy of chemotherapy versus best supportive care, combination versus single-agent and different combinations regimens in advanced gastric cancer.[265] A total of 5726 patients from 35 trials were analyzed. Survival benefit was observed in favor of chemotherapy versus supportive care, combination chemotherapy versus single agent (but with an increased toxicity) and cisplatin-containing regimens.

Summary

The response rate of gastric cancers to combination chemotherapy is somewhat higher than some other gastrointestinal malignancies. Patients who respond to therapy with acceptable tolerance have the potential of achieving symptomatic benefit from this palliative treatment. Nevertheless, aggressive combination regimens are costly, toxicity is sometimes formidable, and remissions are of short duration. If possible, all patients with disseminated gastric cancers should be considered for entrance into well-designed clinical trials.

IRRADIATION TECHNIQUE AND TOLERANCE

Irradiation Field Design

For patients who receive postoperative EBRT following surgical resection or exploratory laparotomy, the irradiation field should include unresected or residual tumor or the tumor bed plus major nodal regions (lesser and greater curvature; celiac axis including pancreatico-duodenal; suprapancreatic, splenic, and porta hepatis; paraesophageal with proximal lesions). The pattern of tumor bed and nodal failures in the reoperative series from the University of Minnesota is demonstrated in Figure 47-1, *A*. This represents an idealized, shaped irradiation field that incorporates the areas of locoregional relapse.[28] The tumor bed and nodal volumes are reconstructed with the aid of preoperative and postoperative imaging studies and surgical clip placement. In Figure 47-1, *B*, the idealized field is superimposed on the organs and structures that define irradiation tolerance. For individual patients, the idealized field needs to be modified depending on the surgical or pathologic extent of disease (primary site, TN extent of disease) and the adjacency of tolerance organs or structures[165,170,266] (Figures 47-5 and 47-6; eFigures 47-4 to 47-6).

The relative risk of nodal metastases at a specific nodal location is dependent on both the site of origin of the primary tumor and other factors including width and depth of invasion of the gastric wall. Tumors that originate in the proximal portion of the stomach and the GE junction have a higher propensity to spread to nodes in the mediastinum and pericardial region but a lower likelihood of involvement of nodes in the region of the gastric antrum, periduodenal area, and porta hepatis. Tumors that originate in the body of the stomach can spread to all nodal sites, but have the highest likelihood of spreading to nodes along the greater and lesser curvature, near the location of the primary tumor mass. Tumors that originate in the distal stomach have a high likelihood of spread to the periduodenal, peripancreatic, and porta hepatis nodes but a lower likelihood of spread to nodes near the cardia of the stomach, the periesophageal and mediastinal nodes, or splenic hilar nodes.[165] Any tumor originating in the stomach has a high propensity to spread to nodes along the greater and lesser curvature, although they are most likely to spread to those sites in close anatomic proximity to the primary tumor mass.

With preoperative or primary chemoradiation for GE junction or proximal gastric cancers because of the risk of submucosal or subserosal lymphatic spread, a margin of 5 cm or more of uninvolved esophagus/proximal stomach should be included proximally, and the distal/lateral field extent should include a margin of 5 cm or more of uninvolved stomach (Figures 47-7 to 47-9 and eFigure 47-7). If the lesion extends beyond the gastric/GE junction wall, a major portion of the left hemidiaphragm should be included. Cerrobend blocks or multileaf collimators (MLC) should be used to decrease the volume of irradiated heart and lung, when technically feasible (see Figure 47-7 and eFigure 47-7). Preoperative EBRT fields can usually be much more conservative than postoperative fields with regard to both heart and lung volumes, especially for GE junction tumors, and are preferred, if preoperative imaging and EUS demonstrate indications for preoperative adjuvant treatment (compare Figures 47-7 and 47-8 to eFigures 47-5 and 47-6). Intensity-modulated irradiation (IMRT) may reduce dose to normal structures, especially to the heart, when dose-volume histogram (DVH) are compared with three-dimensional (3D) conformal techniques for patients with GE junction cancers and reduce kidney doses for more distal lesions (see Figure 47-9), but there is uncertainty whether this will improve short- or long-term treatment tolerance.

With postoperative irradiation of GE junction cancers (see eFigures 47-5 and 47-6), the irradiation field may include the anastomotic site and some or all of the remaining stomach. Postoperative fields are larger than preoperative fields unless an involved field approach is chosen for select T3N0 patients (eFigure 47-6).

Dose-Limiting Organs and Structures

Dose-limiting organs and structures in the upper abdomen are numerous (stomach, small intestine, liver, kidneys, and spinal cord). With properly shaped fields, doses of 45 Gy to 50.4 Gy in 1.8-Gy to 2.0-Gy fractions can be delivered to the stomach and small intestine with a 5% or less risk of severe toxicity.[165,171,266] In most patients a portion of both kidneys will be within the treatment fields, but at least two thirds or three fourths of one kidney should be excluded (can include entirety of both kidneys to a dose of 20 Gy if necessary).

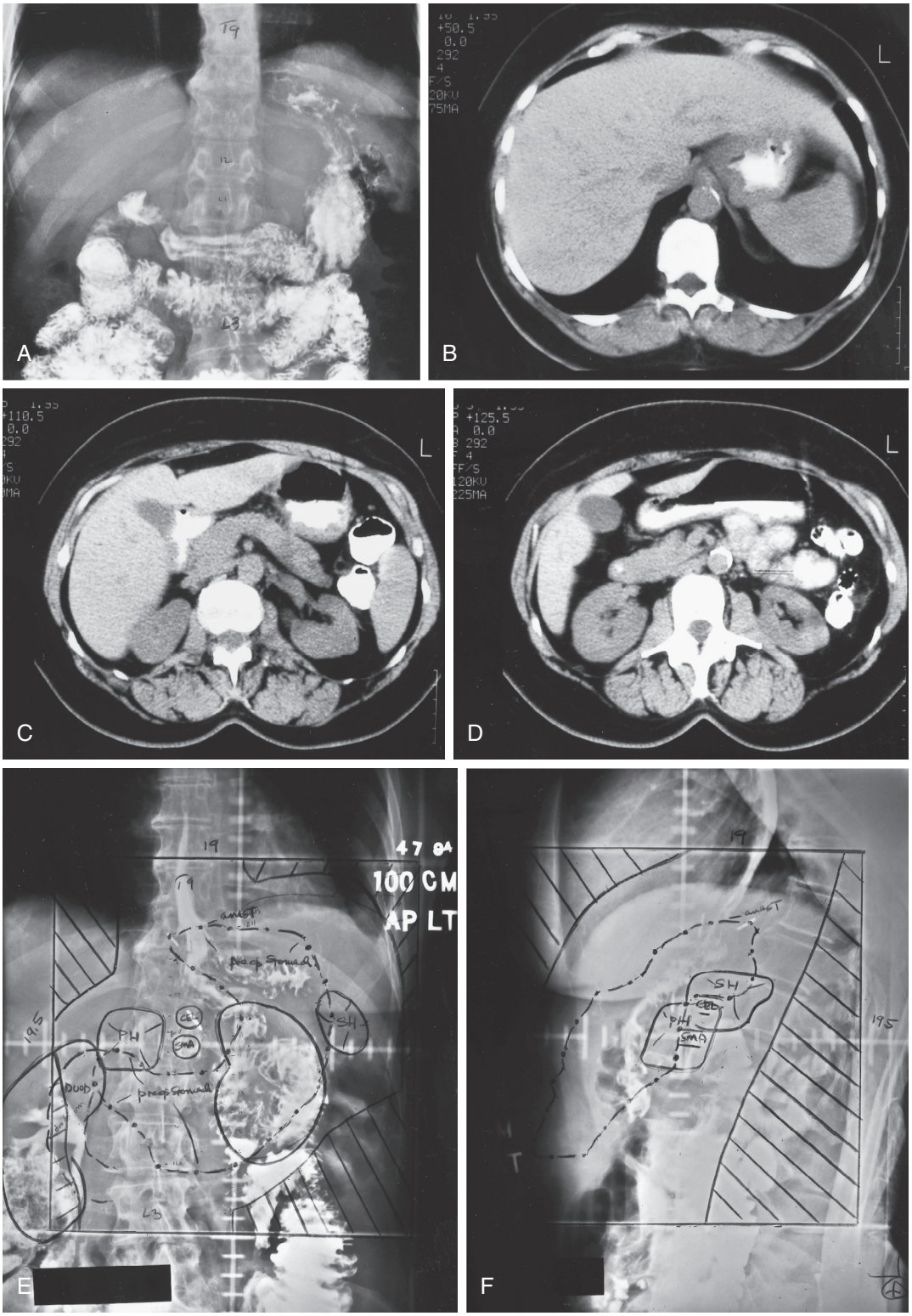
For patients with GE junction, or proximal to midgastric cancers one half to two thirds of the left kidney can often be spared as a result of accurate field definition, which is aided by pre- and postoperative imaging studies and surgical clip placement (see Figures 47-5, 47-7, 47-8 and eFigures 47-4 to 47-7). The pancreatic-duodenal nodes can be included, if indicated, while sparing 75% to 90% of the right kidney.

In patients with distal gastric lesions and narrow or positive duodenal resection margins, the duodenal circumference should be included as target volume (see Figure 47-6). In such instances 50% or more of the right kidney is within the field, and two thirds to three fourths of the left kidney should be spared. Chronic renal problems are infrequent when these techniques are used.[267]

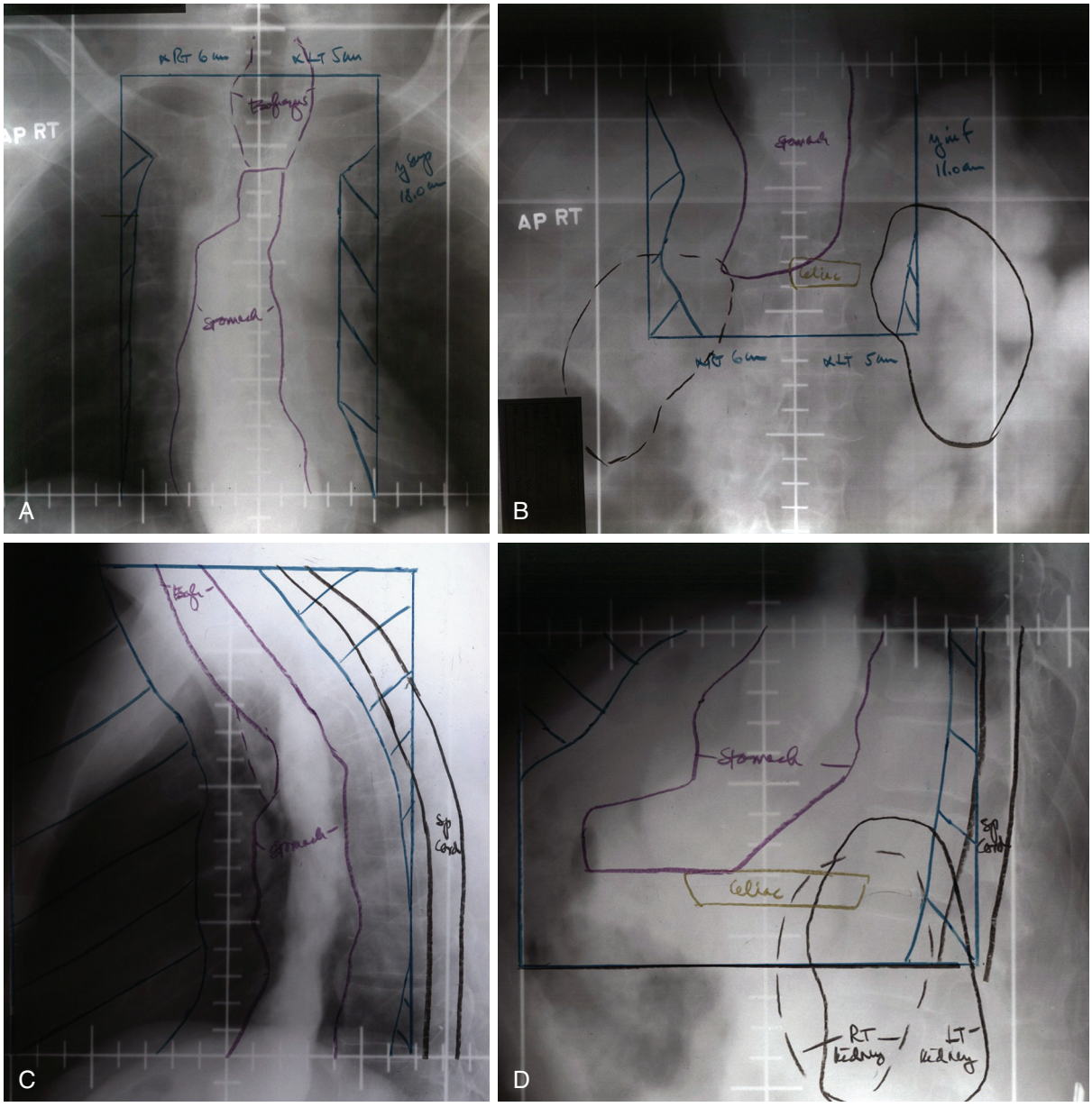
As noted in the GI Tumors Overview, 3D conformal irradiation with CT-based planning is recommended in most patients because of the ability to spare more normal organs/structures (heart, lung, liver, kidneys, and spinal cord). IMRT may optimize sparing of normal organs and structures (see Figures 47-8 and 47-9).[268-274] As noted by Wysoka et al, planning target volume margins need to account for respiratory motion during conformal EBRT for gastric cancer.[275]

Multiple-Field Techniques

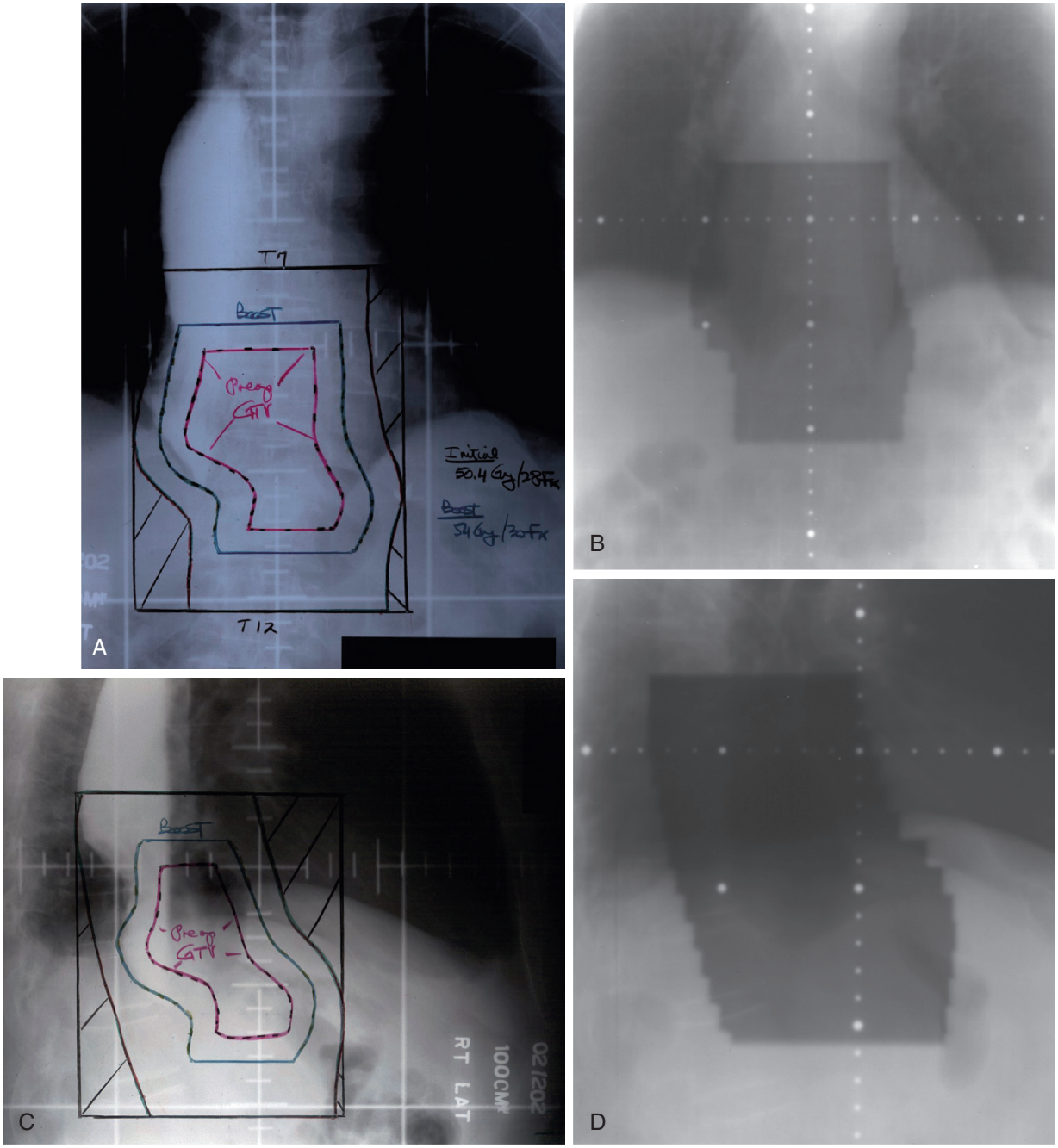
Routine use of multiple field techniques should be considered even for postoperative irradiation, when preoperative imaging exists to allow accurate reconstruction of target volumes (see Figures 47-5 to 47-9) Single-institution data suggest that multiple-field arrangements may produce less toxicity.[151] When patients are treated preoperatively, paired lateral fields can be combined with anteroposterior and posterior-anterior fields to achieve improved dose distributions on normal



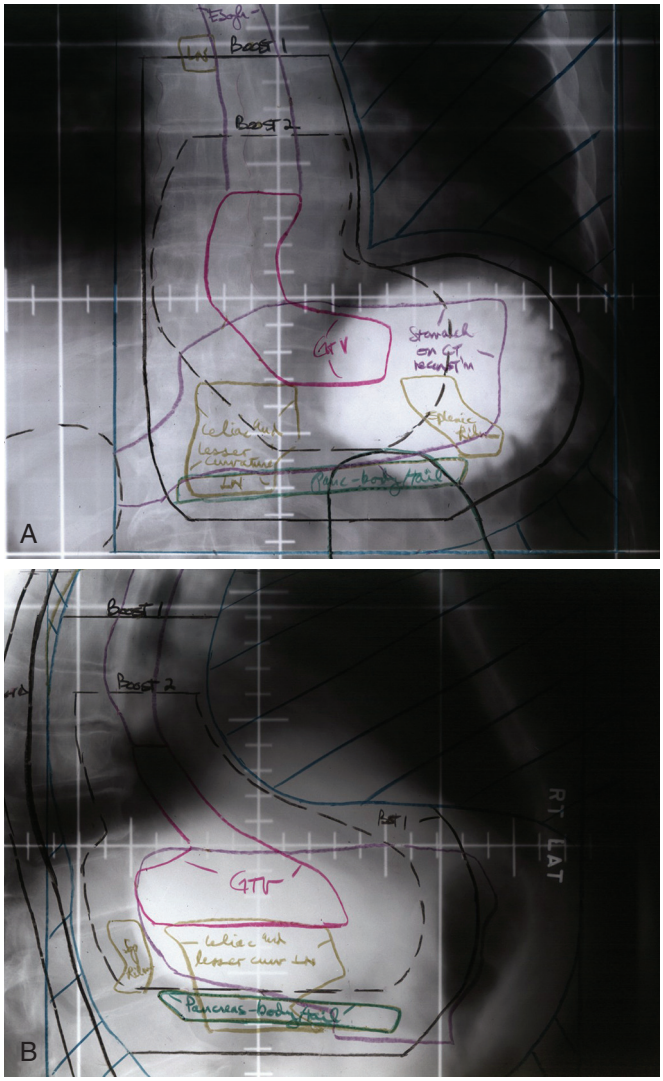
eFigure 47-4 Postoperative radiation fields based on preoperative radiographs following complete resection of a proximal gastric cancer (T3N2M0); the patient was randomized to the irradiation plus chemotherapy arm on the U.S. GI Intergroup 0116 gastric adjuvant study. Tumor bed and target volumes were reconstructed using the preoperative upper GI **(A)** and CT **(B-D)**. Computed tomography cuts demonstrated thickened gastric wall proximally **(B** and **C)** and normal thickness distally **(D)** as well as relationship of the stomach to surrounding organs including liver and spleen **(B)**, liver, body and tail of pancreas, and splenic flexure **(C)**, and head of pancreas **(D)**. Anteroposterior-posteroanterior (AP-PA) irradiation field **(E)** with crosshatched blocks encompasses all of the left kidney but less than 20% of the right. Nodal groups at risk and preoperative gastric duodenal locations (-●-●) are demonstrated on the AP-PA and lateral **(F)** simulation fields. *CEL,* Celiac; *PH,* porta hepatis; *SH,* splenic hilum; *SMA,* superior mesenteric artery.
(From Gunderson LL, Donohue JH, Burch FA: Stomach. In Abeloff MD, Lichter AS, editors: Clinical oncology, ed 2, Philadelphia, 1999, Churchill Livingstone.)



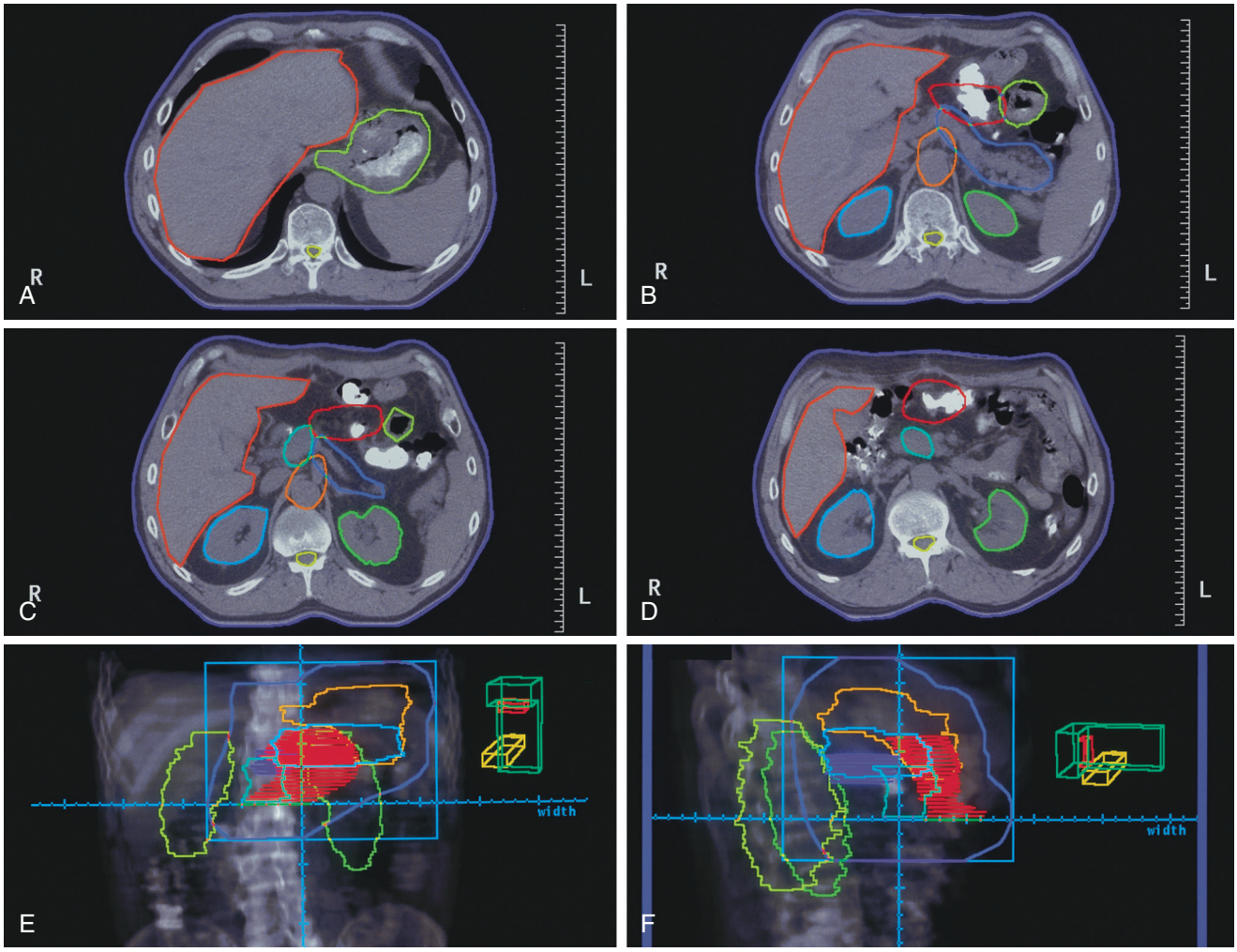
eFigure 47-5 Radiation fields in a patient with a T2N1 adenocarcinoma (ACA) of the gastroesophageal (GE) junction who had a transhiatal esophagectomy with cervical esophagogastrostomy (see Table 47-9). Postoperative chemoradiation was recommended, and the patient was placed on the current Phase III U.S. GI Intergroup trial. At the time of simulation, oral contrast medium was used to define the esophageal (EG) anastomosis at the thoracic inlet **(A** and **C)**, the residual stomach within the mediastinum, and the duodenal sweep inferiorly **(B** and **D)**. A combined treatment planning and diagnostic CT was obtained to define the celiac artery and dose-limiting structures including heart, lungs, spinal cord, kidneys, and liver. Irradiation fields were defined to include the distal cervical esophagus and supraclavicular nodes superiorly, the remaining stomach and perigastric nodes and nodal groups in the mediastinum and celiac axis **(A-D)**. Lateral simulation films **(C** and **D)** demonstrate the ability to spare heart and spinal cord with appropriate use of blocks *(crosshatched blocks)*. The patient received 45 Gy in 25 fractions plus concurrent protracted venous infusion (PVI) 5-FU (200 mg/m^2/24 hours) in addition to systemic multidrug chemotherapy before and after concurrent chemoradiation.



eFigure 47-6 Radiation and port films on a 65-year-old patient with Ivor Lewis esophagogastrectomy (transthoracic plus abdominal approach) for a T3N0 ACA of the gastroesophageal (GE) junction (see Table 47-9). Postoperative chemoradiation, as per INT 0116 was recommended. Simulation films **(A, C)** were obtained with contrast in the remaining stomach, and a treatment planning CT was obtained for purpose of reconstructing tumor bed volumes. The patient was concerned about treatment-related morbidity, so the decision was made to treat with a more involved treatment field approach in view of pathologic findings of 12 negative nodes and adequate proximal and distal resection margins (~5 cm). The involved fields included the tumor bed (preoperative gross tumor volume), as generated from preoperative CT imaging, but excluded the remaining stomach and nodal sites to decrease normal tissue morbidity. The initial anteroposterior and posteroanterior fields **(A, B)** included tumor bed with 3-cm superoinferior and 2-cm lateral margin to block edge (clinical target volume [CTV]/planning target volume PTV]). Lateral fields **(C, D)** were generated with an anterior margin of 2 cm to block edge and demonstrate sparing of heart and spinal cord. Initial fields were treated to 45 Gy in 25 fractions; boost fields **(A, C)** received an additional 9 Gy in 5 fractions to gross tumor volume plus 1-cm margin to block edge (total 54 Gy in 30 fractions). The patient received 5-fluorouracil (5-FU) plus leucovorin before, during, and after external beam radiation therapy (EBRT) as per INT 0116.



eFigure 47-7 Patient is a 73-year-old male with T3N0 ACA of the gastroesophageal (GE) junction (see Table 47-9) who preferred primary chemoradiation treatment with surgery reserved for salvage, as indicated. Baseline positron emission tomography with computed tomography (PET/CT) scan and CT chest were negative for nodal or blood-borne metastases. Radiation fields were generated using treatment planning CT and beam's-eye reconstruction. The patient was treated with a four-field technique of anteroposterior and posterior-anterior **(A)** and paired lateral fields **(B)**. The initial fields included a margin of more than 5 cm of uninvolved esophagus superiorly, a margin of about 5 cm of stomach in all directions and nodal groups including celiac artery and lesser curvature nodes, suprapancreatic (body/tail of pancreas) and splenic hilum. The patient received external beam irradiation (EBRT) plus one cycle of concurrent carboplatin/taxol and infusion 5-fluorouracil (5-FU) during the first week of EBRT but did not receive further concurrent chemotherapy in view of intolerance. The extended fields received 39.6 Gy in 22 fractions of 1.8 Gy; boost 1 received an additional 4.5 Gy in 3 fractions (total 45 Gy in 25 fractions) and boost two received an additional 9 Gy in 5 fractions for a total dose of 54 Gy in 30 fractions over 6 weeks.



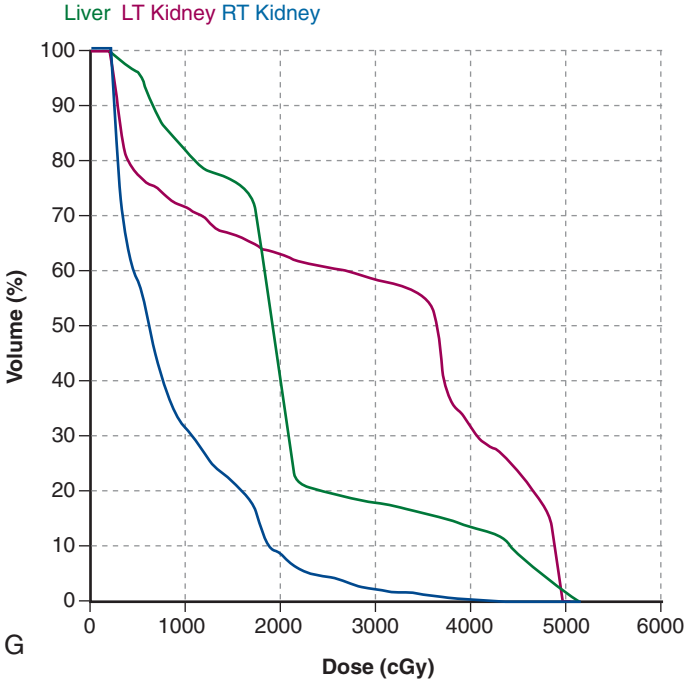
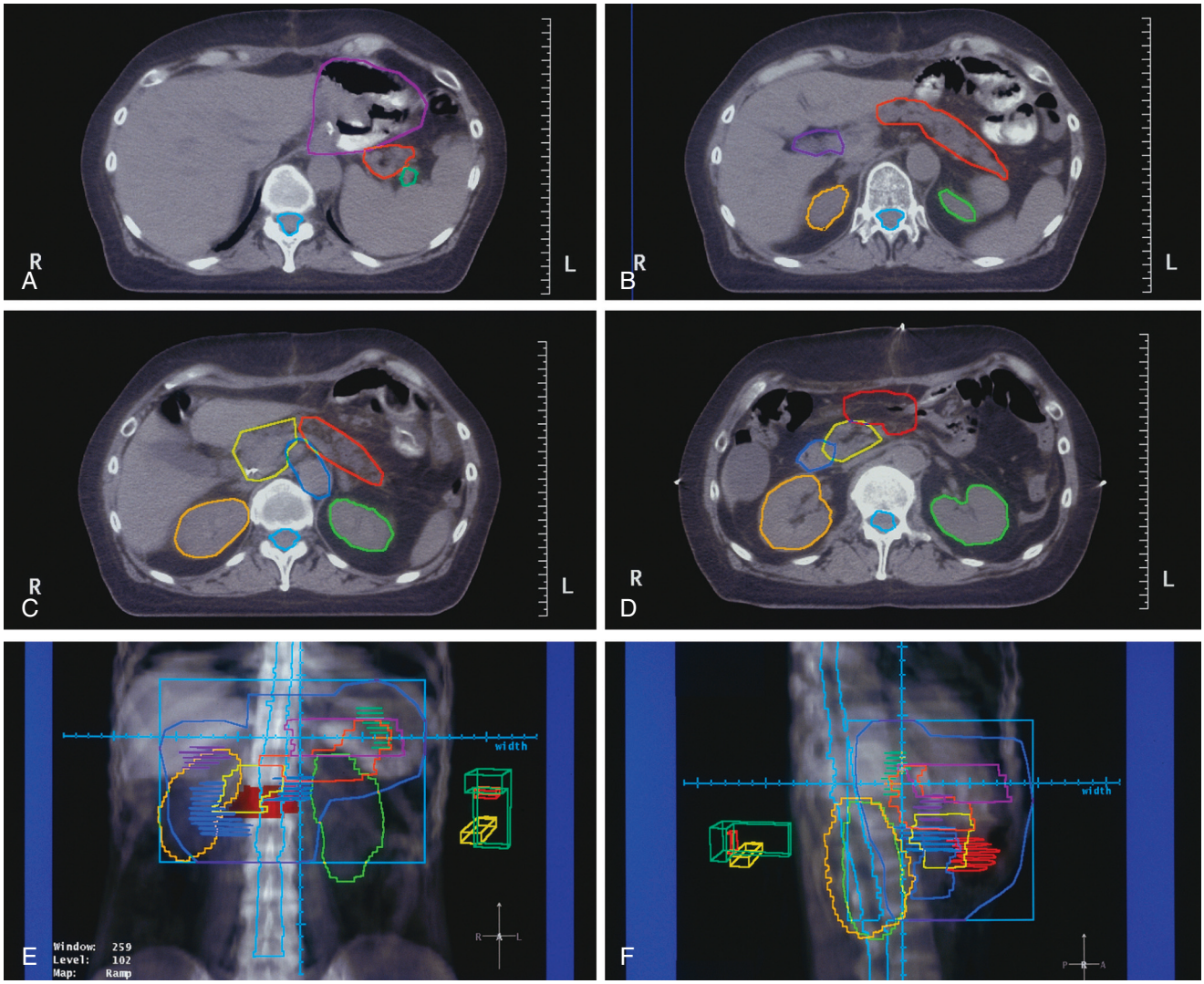


Figure 47-5 Optimized postoperative radiation fields for patient with T4N0 ACA of the posterior wall of the body of the stomach (middle third, see Table 47-10). CT simulation was performed and structures of interest were delineated based on pre- and postoperative CT imaging and operative/pathologic findings (**A-D;** tumor bed; gastric remnant; tolerance organs/structures: kidneys, liver, spinal cord). **A,** Gastric remnant and distal esophagus *(yellow-green)* are adjacent to liver *(red-orange)* and spleen. **B,** CT image demonstrates tumor bed *(red)*, body/tail of pancreas *(blue)*, celiac artery *(orange)*, and kidneys (right—*light blue*; left—*green*). **C,** Head of pancreas *(blue-green)* and splenic artery/body of pancreas are shown at level of mid-kidney. **D,** Tumor bed and head of pancreas on more distal CT image. Radiation fields were designed with the aid of digitally reconstructed radiographs (DRR; **E-F**) and a dose-volume histogram (DVH) was performed with regard to tolerance organs/structures **(G)**. A four-field technique of anteroposterior and posteroanterior and paired lateral fields was selected (field margins in *medium blue*). The fields included the gastric remnant *(yellow-orange)*, tumor bed *(red)*, and nodal regions at risk based on sites of adherence of the primary lesion (celiac [*blue-purple cross-hatched*]), suprapancreatic [body of pancreas, *light blue*], superior mesenteric, pancreatico-duodenal [head of pancreas, *blue-green*]). **E,** The anteroposterior and posteroanterior field includes ~two thirds of the left kidney and a portion of the left lobe of the liver but excludes most of the right kidney and the right lobe of the liver. **F,** The lateral field demonstrates exclusion of the spinal cord and posterior kidneys. **G,** DVH demonstrates a dose of 20 Gy to >60% of the left kidney versus less than 10% of the right kidney.



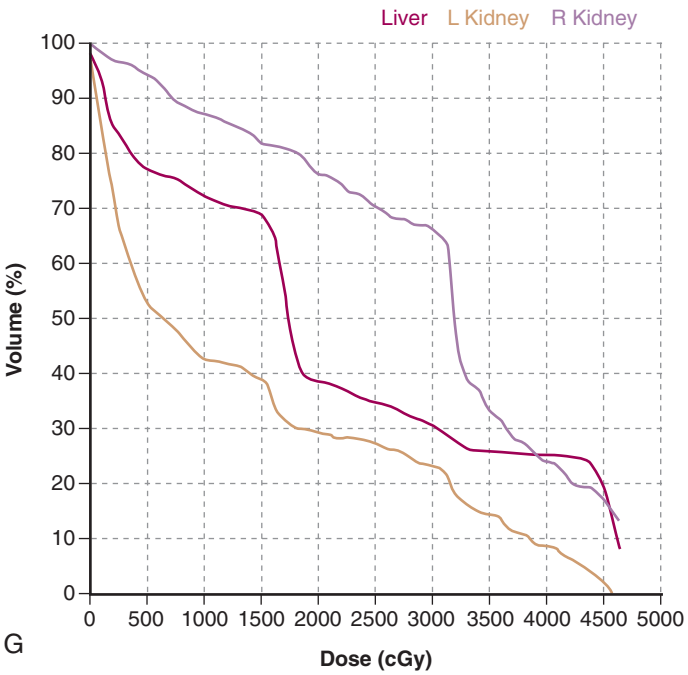


Figure 47-6 Optimized postoperative radiation fields for patient with T3N2 antral primary (distal third, see Table 47-11). Structures of interest were delineated at time of CT simulation **(A-D)**. **A,** Gastric remnant *(lavender)* is demonstrated along with the body/tail of pancreas *(red-orange)*, and splenic hilum *(light green)*. **B,** Porta hepatis *(blue-purple)* and kidneys (left, *yellow green*, right, *yellow orange*) are delineated. **C**, Head of pancreas *(yellow)* and celiac versus superior mesenteric artery *(light blue)* are shown. **D,** Antral tumor bed *(red)* and duodenum *(medium blue)* are delineated. Irradiation fields were designed with the aid of DRR **(E, F)** and a dose-volume histogram (DVH, **G**) was performed with regard to dose-limiting structures (liver, kidneys, spinal cord). A four-field technique of anteroposterior and posteroanterior and paired lateral fields was chosen (field margins shown in *medium blue*). Treatment fields include the gastric remnant, tumor bed, head of pancreas, first and second part of the duodenum (*medium blue cross hatched*), pertinent nodal volumes (perigastric, pancreaticoduodenal [head of pancreas], porta [*blue blue-purple cross hatched*], celiac, suprapancreatic [body/tail pancreas]) and the optional nodal volume of splenic hilum (light green cross hatched). **E,** Anteroposterior and posteroanterior field (field margins exclude ~two thirds of the left kidney and include ~90% of the right kidney). Exclusion of optional splenic hilar nodes would not have allowed additional sparing of the left kidney in view of the adjacency of the gastric remnant and splenic hilum. **F,** Lateral field demonstrates exclusion of the spinal cord *(turquoise)* and substantial portions of both kidneys. **G,** The DVH, combining doses from all four fields, demonstrated that the dose volume of 20 Gy included ~30% of the left kidney versus ~75% of the right kidney. With regard to the liver, ~30% receives a dose of 30 Gy and ~25% receives a dose of 35 Gy to 40 Gy.

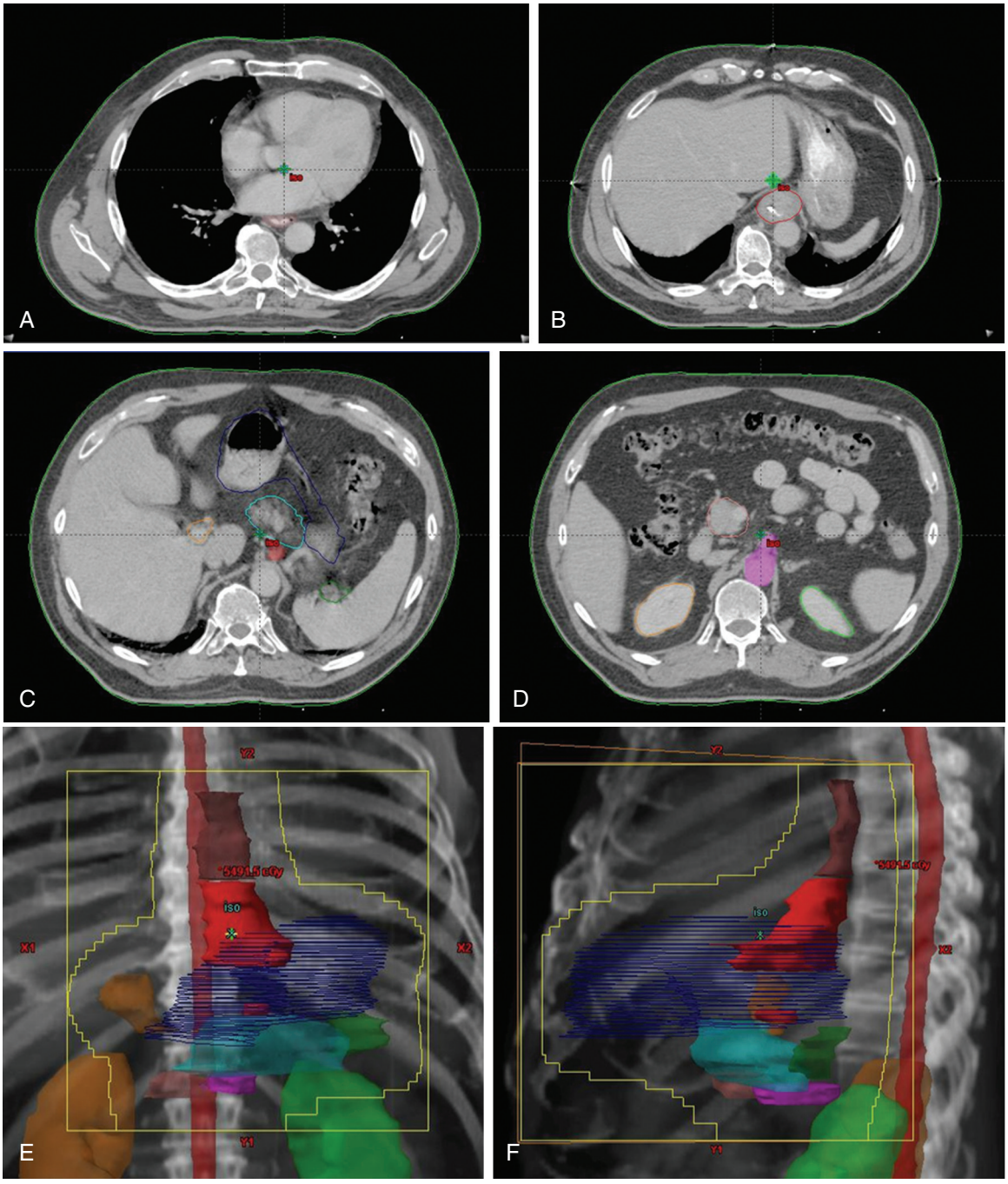


Figure 47-7 Patient is a 54-year old male with a T3N1 adenocarcinoma of the GE junction treated with preoperative chemoradiation at Mayo Clinic in Arizona (45 Gy in 25 fractions over 5 weeks to an extended field and 50.4 Gy/28 fractions within boost field). CT simulation was done with intravenous and oral contrast and organs/structures of interest were delineated **(A-D)**. The normal thickness of the more proximal esophagus wall **(A)** contrasts with the markedly thick distal esophagus wall at the level of the GE junction **(B)**. An enlarged gastrohepatic node **(C)** was biopsy positive for cancer. Other outlined organs/structures include celiac artery, body/head of pancreas, porta hepatis and splenic hilum **(B-D)**. Three-dimensional conformal irradiation fields **(E, F)** were designed to include primary tumor (red) with greater than 5 cm margins of esophagus proximally and stomach distally, plus nodal volumes (periesophageal and celiac, as per Table 47-9; porta hepatis, suprapancreatic, and splenic hilar nodes were also included in view of the documented gastrohepatic nodal disease [also shown in *red*]). Lateral fields **(F)** were used as a component of treatment to spare heart and spinal cord. The patient subsequently had a laparoscopic esophagogastrectomy, mediastinal and celiac node dissection, pyloroplasty and neck anastomosis (esophagogastrostomy) at Mayo Hospital in Arizona. Pathologic examination revealed a 3.5- × 2.5- × 1.5-cm ulcerated mass at the GE junction that consisted microscopically of pauci-cellular and acellular mucin and rare tumor cells floating in muscle with 0 of 20 positive nodes.
(From Gunderson et al in Abeloff Ed 4, with permission.)

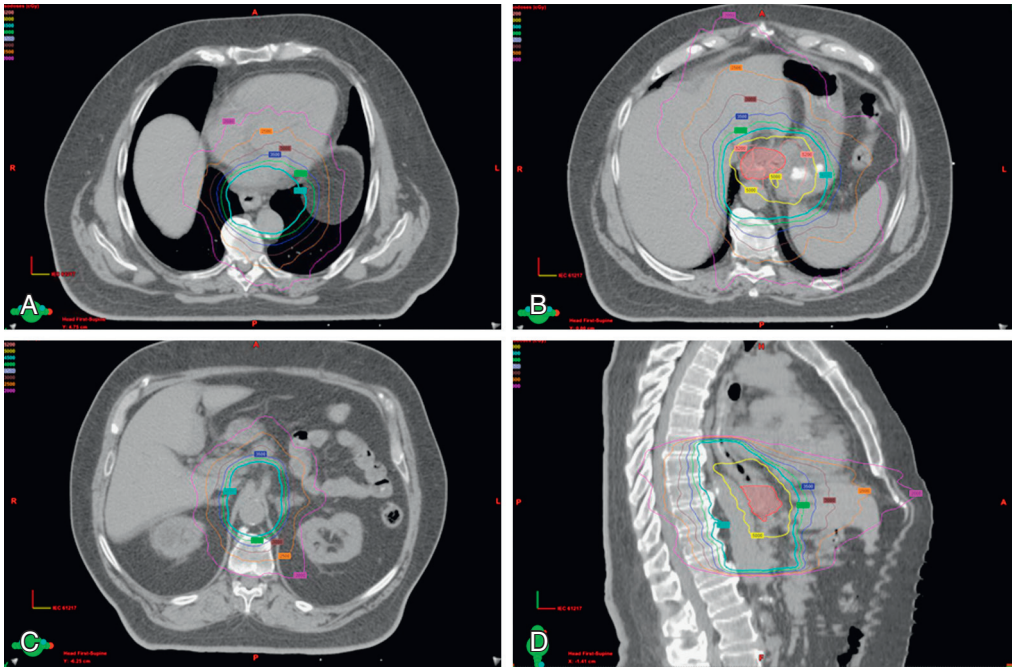


Figure 47-8 Intensity modulated radiation (IMRT) fields for patient with T3N1M0 adenocarcinoma of the gastroesophageal junction on endoscopic ultrasonography (EUS) was treated with preoperative concurrent chemoradiation at Mayo Clinic in Arizona. A volumetric modulated arc therapy (VMAT) technique was used to deliver 45 Gy in 25 fractions (Fx) of 1.8 Gy in 5 weeks to an extended volume (*yellow* isodose curves), which extends superiorly to include ~5-cm margin on the gross tumor volume (GTV, *red*) and inferiorly to include the celiac axis. A simultaneous integrated boost field received 50 Gy in 25 fractions of 2 Gy in 5 weeks (GTV plus ~2-cm margin plus margin for organ motion; *light blue* isodose curves). Isodose curves are shown in the axial plane at the superior portion of the field **(A),** limiting dose to the heart, at the isocenter **(B)** including the proximal stomach, and at the inferior portion of the field **(C)** including the celiac axis and limiting dose to the kidneys. Isodose curves are shown in the sagittal plane **(D)** demonstrating the borders of high- and low-dose volumes and limiting dose to the spinal cord posteriorly and the heart anteriorly.

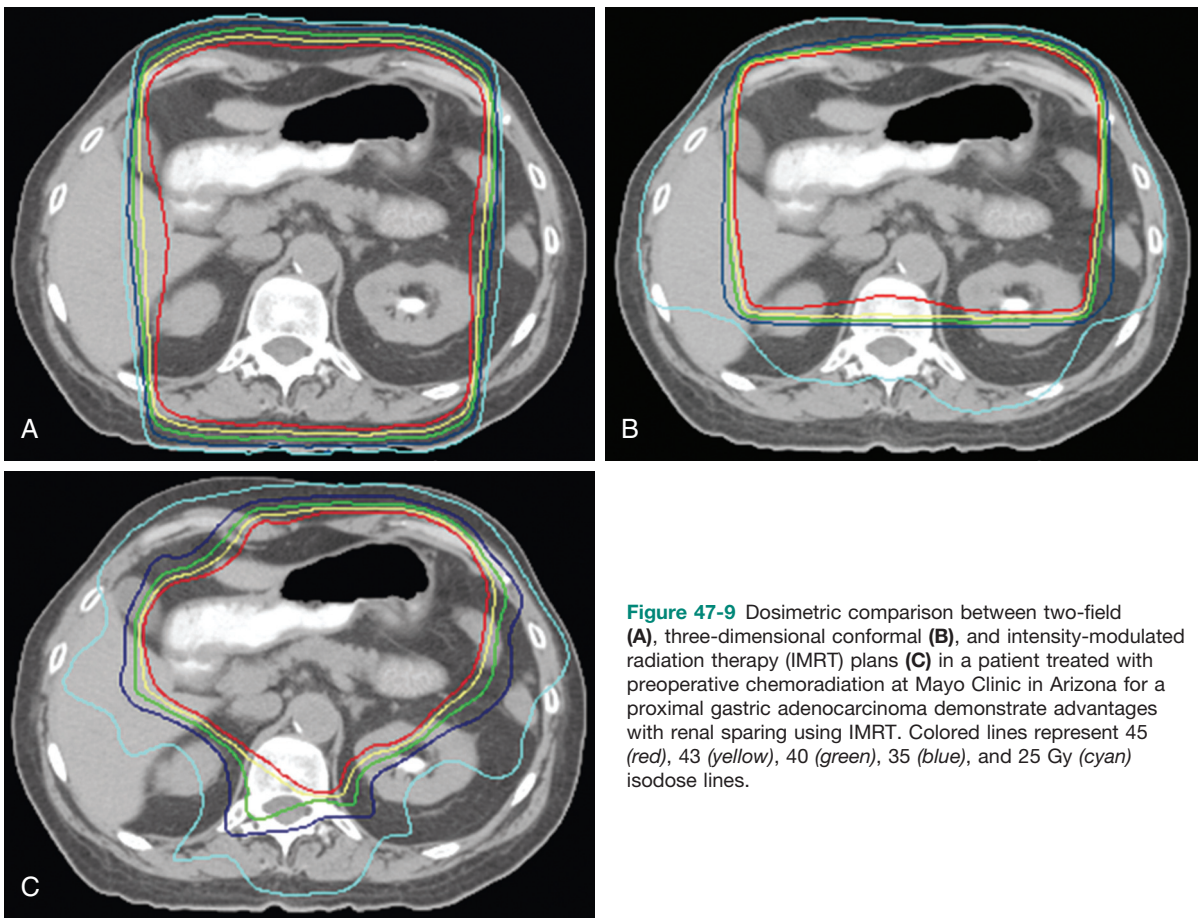


Figure 47-9 Dosimetric comparison between two-field **(A)**, three-dimensional conformal **(B)**, and intensity-modulated radiation therapy (IMRT) plans **(C)** in a patient treated with preoperative chemoradiation at Mayo Clinic in Arizona for a proximal gastric adenocarcinoma demonstrate advantages with renal sparing using IMRT. Colored lines represent 45 *(red)*, 43 *(yellow)*, 40 *(green)*, 35 *(blue)*, and 25 Gy *(cyan)* isodose lines.

tissue. Depending on the posterior extent of the gastric fundus, either obliqued or lateral fields can be used to deliver a 10-Gy to 20-Gy component of radiation to spare spinal cord and kidney. Liver and kidney tolerance limits the use of lateral fields to 20 Gy or less for patients with gastric cancer; for patients with GE junction cancers, the contribution from lateral fields is generally limited to 10 Gy to 15 Gy because of lung tolerance issues.

With the wide availability of 3D conformal treatment-planning systems, it may be possible to target more accurately the high-risk volume and to use unconventional 3D conformal field arrangements or IMRT to produce superior dose distributions (Figures 47-8 and 47-9). To accomplish this without marginal misses it is necessary to both carefully define and encompass the various target volumes because target volumes that would be included in anteroposterior and posterior-anterior fields may be missed with other field arrangements (oblique, lateral, non-coplanar). Extent of disease on EUS and PET/CT should be incorporated into target definition and field design.

When treating patients with GE junction cancers, irradiation dose to the heart and lung is of particular concern in the neoadjuvant setting, because of potential perioperative morbidity.[276-279] The volume of lung spared from doses of 5 Gy or more (V5) was the only independent predictor of perioperative pulmonary complications in an analysis by Wang et al.[276] Because IMRT may result in increased lung volumes exposed to low doses, it has not gained widespread acceptance over 3D conformal approaches. However, a Mayo Clinic Arizona analysis found a decrease in lung and heart doses in patients treated with IMRT compared with 3D conformal techniques with no compromise in early clinical outcomes (disease control, treatment tolerance including perioperative complication).[277,278] At a median follow up of 24 months, 2-year OS was 58%.[279] With regard to the heart, longer follow-up will be required to see if dosimetric improvements of IMRT will reduce long-term cardiac toxicity. Hybrid IMRT and conformal plans may also be used to improve target conformality while minimizing dose to the lungs and heart.[280] Acceptable treatment plans can be achieved with either 3D conformal or IMRT planning techniques.

Idealized Treatment Field Guidelines

Guidelines for defining the clinical target volume for postoperative radiation fields have been developed by Tepper and Gunderson based on location and extent of the primary tumor (T-category) and location and extent of known nodal involvement (N category).[165] Table 47-8 presents general guidelines on the impact of T and N category on inclusion of the remaining stomach (gastric remnant), tumor bed, and nodal sites, whereas Tables 47-9 to 47-11 and eTable 47-6 present treatment guidelines based on TN category for each of the four primary sites (GE junction, proximal, mid, and distal stomach). In general, for patients with node-positive disease, there should be wide coverage of tumor bed, remaining stomach, resection margins, and nodal drainage regions. For node-negative disease, if

TABLE 47-8 General Guidelines of Impact of T and N Category on Inclusion of Remaining Stomach, Tumor Bed, and Nodal Sites within Radiation Fields

TN Category	Remaining Stomach†	Tumor Bed	Nodes
T1-2 N0 (not into subserosa)	No	No	No
T2 N0 (into subserosa)*	Variable	Yes	No
T3 N0	Variable	Yes	No
T4 N0	Variable	Yes	Variable
T1-2 N+	Yes	No	Yes
T3-4 N+	Yes	No	Yes

Modified from Tepper JE, Gunderson LL: Radiation treatment parameters in the adjuvant postoperative therapy of gastric cancer. Semin Rad Oncol 12:187–195, 2002.

**Posterior wall T2N0 lesions that extend beyond muscularis propria in the proximal or distal stomach are at risk for local relapse. Patients with T1-2 N0 disease with close or positive surgical margins should be considered for treatment to the tumor bed.*

†Inclusion of the remaining stomach is preferable in most patients if two thirds of one kidney can be excluded. This is dependent on the extent of surgical resection and uninvolved margins (in cm).

TABLE 47-9 Impact of Site of Primary Lesion and TN Category on Irradiation Treatment Volumes: GE Junction (General Guidelines)

Site of Primary and TN Category	Remaining Stomach‡	Tumor Bed Volumes‡	Nodal Volumes
GE junction*	If allows exclusion of two thirds right kidney	T category dependent	N category dependent
T2 N0, invasion of subserosa	Variable, dependent on surgical pathologic findings†	Medial left hemidiaphragm; adjacent body of pancreas	None or perigastric, periesophageal§
T3N0	Variable, dependent on surgical pathologic findings†	Medial left hemidiaphragm; adjacent body of pancreas	None or perigastric, periesophageal, mediast, celiac§
T4N0	Preferable, dependent on surgical pathologic findings†	As for T3 N0 plus site(s) of adherence with 3cm-5 cm margin	Nodes related to site of adherence, ± celiac, perigastric, periesophageal, mediastinal
T1-2 N+	Preferable	Not indicated for T1, as above for T2 into subserosa	Periesophageal, mediast, prox perigastric, celiac
T3-4 N+	Preferable	As for T3 N0, T4 N0	As for T1-2 N+ and T4 N0

Modified from Tepper JE, Gunderson LL: Radiation treatment parameters in the adjuvant postoperative therapy of gastric cancer. Semin Rad Oncol 12:187–195, 2002.

**Tolerance organs or structures: heart, lung, spinal cord, kidneys, and liver.*

†For tumors with wide (>5 cm) surgical margins confirmed pathologically, treatment of residual stomach is optional, especially if this would result in substantial increase in normal tissue morbidity.

‡Use preoperative imaging (CT, barium swallow), surgical clips, and postoperative imaging (CT, barium swallow).

§Optional node inclusion for T2-3 N0 lesions if adequate surgical node dissection (D2 dissection) and at least 10-15 nodes examined pathologically.

GE, *Gastroesophageal.*

eTABLE 47-6 Impact of Site of Primary Lesion and TN Category on Irradiation Treatment Volumes: Cardia/Proximal Third of Stomach (General Guidelines)

Site of Primary and TN Category	Remaining Stomach†	Tumor Bed Volumes‡	Nodal Volumes
Cardia/prox third of stomach*	Preferred, but spare ⅔ of one kidney (usually right)	T category dependent	N category dependent
T2 N0, invasion of subserosa	Variable dependent on surgical pathologic findings†	Medial left hemidiaphragm, adjacent body of pancreas (± tail)	None or perigastric§
T3 N0	Variable dependent on surgical pathologic findings†	Medial left hemidiaphragm, adjacent body of pancreas (± tail)	None or perigastric; optional: periesophageal, mediastinal, celiac§
T4N0	Variable dependent on surgical pathologic findings†	As for T3 N0 plus site(s) of adherence with 3 cm-5 cm margin	Nodes related to site of adherence, ± perigastric, periesophageal, mediastinal, celiac
T1-2 N+	Preferable	Not indicated for T1, as above for T2 into subserosa	Perigastric, celiac, splenic, suprapancreatic, ± periesophageal, mediastinal, pancreaticoduodenal, porta hepatis¶
T3-4N+	Preferable	As for T3 N0, T4 N0	As for T1-2 N+ and T4 N0

**Tolerance organs or structures: kidneys, spinal cord, liver, heart, lung.*
†For tumors with wide (>5 cm) surgical margins confirmed pathologically, treatment of residual stomach is not necessary, especially if this would result in substantial increase in normal tissue morbidity.
‡Use preop imaging (CT, barium swallow), surgical clips, and postop imaging (CT, barium swallow).
§Optional node inclusion for T2-3N0 lesions if adequate surgical node dissection (D2 dissection) and at least 10-15 nodes are examined pathologically.
¶Pancreaticoduodenal and porta hepatis nodes are at low risk if nodal positivity is minimal (i.e., 1-2 positive nodes with 10-15 nodes examined), and this region does not need to be irradiated. Periesophageal and mediastinal nodes are at risk if there is esophageal extension.
Modified from Tepper JE, Gunderson LL: Radiation treatment parameters in the adjuvant postoperative therapy of gastric cancer. Semin Rad Oncol 12:187–195, 2002.

TABLE 47-10 Impact of Site of Primary Lesion and TN Category on Irradiation Treatment Volumes: Body/Middle Third of Stomach (General Guidelines)

Site of Primary and TN Category	Remaining Stomach	Tumor Bed Volumes†	Nodal Volumes
Body/mid third of stomach*	Yes, but spare two thirds of one kidney	T category dependent	N category dependent, spare two thirds of one kidney
T2 N0, invasion of subserosa	Yes	Body of pancreas (± tail)	None or perigastric. Optional: celiac, splenic, suprapancreatic, pancreatic duodenal, porta hepatis‡
T3N0	Yes	Body of pancreas (± tail)	None or perigastric. Optional: celiac, splenic, suprapancreatic, pancreatic duodenal, porta hepatis‡
T4N0	Yes	As for T3 N0 plus site(s) of adherence with 3 cm-5 cm margin	Nodes related to site of adherence ± perigastric, celiac, splenic, suprapancreatic, pancreatic duodenal, porta hepatis
T1-2 N+	Yes	Not indicated for T1	Perigastric, celiac, splenic, suprapancreatic, pancreatic duodenal, porta hepatis
T3-4N+	Yes	As for T3 N0, T4 N0	As for T1-2 N+ and T4 N0

Modified from Tepper JE, Gunderson LL: Radiation treatment parameters in the adjuvant postoperative therapy of gastric cancer. Semin Rad Oncol 12:187–195, 2002.

**Tolerance organs or structures: kidneys, spinal cord, liver.*

†Use preoperative imaging (CT, barium swallow), surgical clips, and postoperative imaging (CT, barium swallow).

‡Optional node inclusion for T2-3N0 lesions if adequate surgical node dissection (D2 dissection) and at least 10-15 nodes examined pathologically.

TABLE 47-11 Impact of Site of Primary Gastric Lesion and TN Category on Irradiation Treatment Volumes: Antrum/Pylorus/Distal Third of Stomach (General Guidelines)

Site of Primary and TN Category	Remaining Stomach†	Tumor Bed Volumes‡	Nodal Volumes
Pylorus/distal third of stomach*	Yes, but spare two thirds of one kidney, usually left	T category dependent	N category dependent
T2 N0, invasion of subserosa	Variable, dependent on surgical pathologic findings†	Head of pancreas (± body), first and second portion of duodenum	None or perigastric. Optional: pancreatic duodenal, porta hepatis, celiac, suprapancreatic§
T3N0	Variable, dependent on surgical pathologic findings†	Head of pancreas (± body), first and second portion of duodenum	None or perigastric. Optional: pancreatic duodenal, porta hepatis, celiac, suprapancreatic§
T4N0	Preferable, dependent on surgical pathologic findings†	As for T3 N0 plus site(s) of adherence with 3 cm-5 cm margin	Nodes related to site(s) of adherence ± perigastric, pancreatic duodenal, porta hepatis, celiac, suprapancreatic
T1-2 N+	Preferable	Not indicated for T1	Perigastric, pancreatic duodenal, porta hepatis, celiac, suprapancreatic. Optional: splenic hilum
T3-4N+	Preferable	As for T3 N0, T4 N0	As for T1-2 N+ and T4 N0

From Tepper JE, Gunderson LL: Radiation treatment parameters in the adjuvant postoperative therapy of gastric cancer. Semin Rad Oncol 12:187–195, 2002.

**Tolerance organs or structures: kidneys, liver, and spinal cord.*

†For tumors with wide (>5 cm) surgical margins confirmed pathologically, treatment of residual stomach is optional if this would result in substantial increase in normal tissue morbidity.

‡Use preoperative imaging (CT, barium swallow), surgical clips, and postoperative imaging (CT, barium swallow).

§Optional node inclusion for T2-3N0 lesions if adequate surgical node dissection (D2 dissection) and at least 10-15 nodes examined pathologically.

there is a good surgical resection with pathologic evaluation of at least 10 to 15 nodes, and there are wide surgical margins on the primary tumor (at least 5 cm), treatment of the nodal beds is optional. Treatment of the remaining stomach should depend on a balance of the likely normal tissue morbidity and the perceived risk of local relapse in the residual stomach. Calvo et al have discussed guidelines for idealized IORT field design for institutions with IORT availability.[281]

Nutritional Support (before, during, and after Chemoradiation)

Patients who have surgical resection for gastric cancer can have significant management problems. Postoperatively, especially after removal of more than three fourths of the stomach, maintaining adequate nutrition can be a major clinical problem. Placement of a feeding jejunostomy tube during surgery can be critical in getting the patient past the first 2 months postoperatively. Problems of early satiety are extremely common, and it is usually not feasible to start postoperative adjuvant therapy until the patient has stabilized their weight.

During the course of postoperative chemoradiation, strict attention must also be paid to nutritional support. It is rare that a patient will manage with three meals per day; most need to eat five or six planned meals, often with nutritional supplements. Postoperative problems of dumping syndrome are fairly common but are often not recognized by the

treating physician. Dumping is expressed by the enhanced gastrocolic reflex with clustered bowel movements in association with meals. What is not as well recognized is the reactive hypoglycemia that can occur in these patients, related to the rapid transit of the gastric contents into the small bowel, rapid absorption of glucose into the circulation, and the associated insulin secretion. As there is no residual food in the stomach (as would normally occur), a reactive hypoglycemia occurs, typically 1.5 to 2 hours after meals. Proper patient awareness of this problem can alleviate many of the associated difficulties.

Many patients who receive preoperative chemoradiation (with plans to proceed to surgical resection) or primary chemoradiation may also require parenteral or enteral hyperalimentation during treatment. Improvement in nutritional status may require stent placement during endoscopy or feeding jejunostomy. Feeding jejunostomy is strongly preferred to percutaneous endoscopic gastrostomy (PEG) tube placement to preserve use of the stomach for reconstruction.

Nutritional problems can exist long-term in these patients. The lack of acid production results in poor absorption of a number of minerals but most importantly iron and calcium. The iron loss is usually noted because of the associated anemia, but the calcium malabsorption is not usually appreciated until many years later. Calcium supplementation (with calcium citrate, not calcium carbonate) will usually need to be lifelong, but iron requirements can be assessed during follow-up. Periodic bone densitometry is appropriate. Malabsorption of fat and other nutrients should also be observed. Loss of vitamin B12 absorptive capacity is well known after a total gastrectomy secondary to loss of intrinsic factor. However, the body typically has vitamin B12 stores to last for up to 3 years, so it is possible to observe the patient carefully to assess whether the patient will require lifelong monthly vitamin B12 injections.

TREATMENT ALGORITHM, CHALLENGES, AND FUTURE POSSIBILITIES

Primary and Adjuvant Therapy

Although the Dutch and British Phase III multicenter trials evaluating extended lymphadenectomy found increased morbidity but no benefit in survival because experienced surgeons can perform extended node dissection without significant additional surgical morbidity or mortality, use of D2 nodal dissection is reasonable in patients felt to be node-positive. Patients with extended resection are still at high risk for locoregional and systemic relapse,[113] however, and should receive postoperative chemoradiation (see treatment algorithm by TNM extent, Figure 47-10 and Table 47-12). The nonrandomized Samsung Medical Center analysis by Kim et al appeared to demonstrate an advantage in disease control and survival in the 544 patients who received postoperative chemoradiation following D2 resection compared to the 446 surgery-alone patients (5-year OS 57 versus 51%, $p = 0.02$; 5-year RFS 54.4 versus 47.9%, $p = 0.016$).[152] In the subsequent Phase III trial by Lee et al, the subset analysis of 396 patients with D2 resection and positive nodes found improved 3-year DFS with postoperative chemoradiation compared to chemotherapy only (3-year DFS 77.5% versus 72%, $p = 0.0365$).[172]

The most recent U.S. GI Intergroup Phase III randomized postoperative chemoradiation trial (CALGB 80101) tested ECF versus 5-FU leucovorin as both initial and maintenance chemotherapy (control arm was from the Phase III GI Intergroup Trial 0116). Preliminary analyses did not demonstrate a survival benefit for ECF chemotherapy.[156] Accordingly, the postoperative chemoradiation arm of US GI INT 0116 (with concurrent and maintenance bolus 5 FU-leucovorin) remains an appropriate standard of care for patients who are resected and are high risk with gastric or GE junction cancers.

Preoperative chemoradiation (preop chemoRT)[166-168,173] and perioperative chemotherapy (periop chemo)[124,125] have also become appropriate standards of care in view of positive Phase III trials testing those approaches versus surgery-alone control arms. A survival advantage was found for periop ECF or CF compared to surgery alone for resectable gastric/distal esophageal cancers in the MAGIC and French trials (MAGIC trial: 5-year OS 36% versus 23%, $p = 0.009$; French trial: 5-year OS 38% versus 24%, $p = 0.02$).[124,125] Preop chemoRT improved survival in a large CROSS Phase III trial comparing surgery alone with preop chemoRT for 366 analyzable patients with ACA of the esophagus or GE junction (median OS 49.4 versus 24 months, 5-year OS 47% versus 34%, $p = 0.003$).[167,168] In addition, the POET Phase III trial of 120 pts with GEJ lesions tested preop chemo compared to chemoRT; outcomes trends favored preop chemoRT over chemo alone for both OS ($p = 0.07$) and local control ($p = 0.06$).

Current and Future Trials

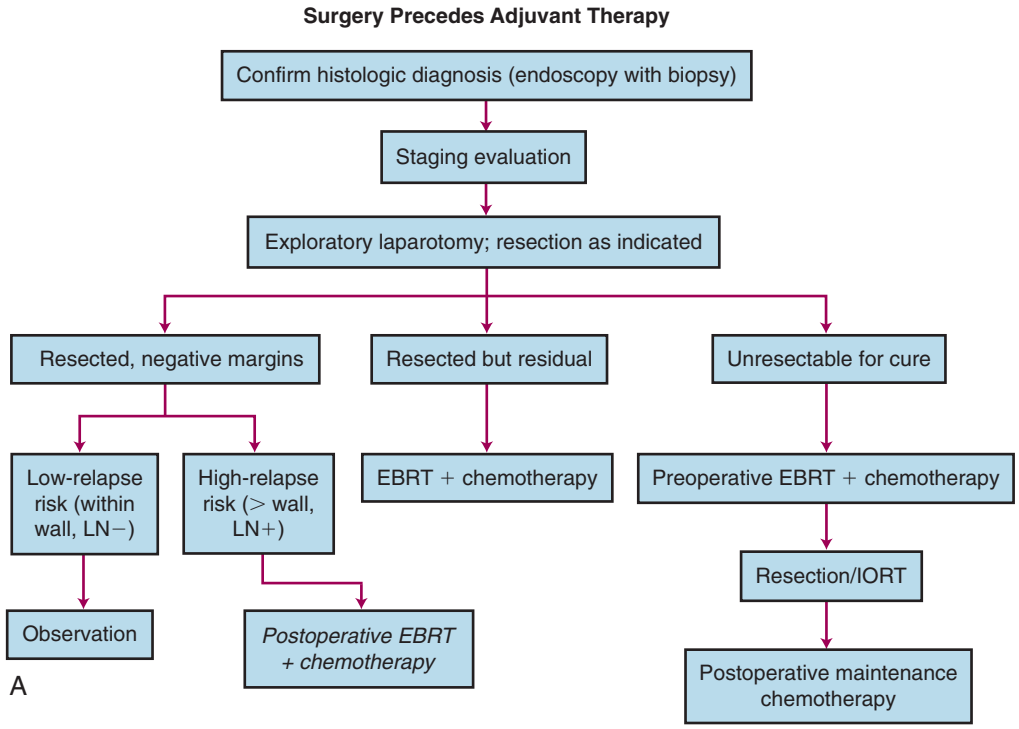
In summary, for patients with potentially resectable high-risk gastric cancer, appropriate treatment approaches include postop chemoRT and periop chemo (ECF or CF). Although

TABLE 47-12 Treatment Algorithm: Gastric or GE Junction Cancer

TNM Extent	Surgery	Irradiation (Alone or with Chemotherapy)	Chemotherapy
T1-2N0M0	Radical subtotal gastrectomy and regional nodes	Not routinely recommended; exception: posterior wall T2N0M0	Evaluate in view of distant metastasis rates of ~30% with T1-2N0 lesions
T1-2N1-3M0; T3N0-3M0	Radical subtotal and regional nodes	Postop chemo EBRT, 45 Gy-50 Gy; evaluate preop EBRT-CT, gastric; prefer preop EBRT-CT, GE junction*	5-FU/leucovorin bolus wk 1, 5: CCRT and maintenance
T4N0-3M0	Radical subtotal and regional nodes; attempt en bloc resection, involved organ(s)	Preop EBRT-CT, 45 Gy-50 Gy; attempt resection and IOERT	5-FU-leucovorin, bolus wk 1, 5; eval alternate CCRT (i.e., infusion 5-FU); eval other maint CT (ECF, EOX, other)
T any N any M1	Palliative if feasible	Palliative CCRT if indicated	MACT; ICT Phase I, II, or III

CCRT, *Concurrent chemoradiation;* EBRT, *external beam irradiation;* EBRT-CT, *external beam irradiation + chemotherapy;* eval, *evaluate;* GE, *gastroesophageal;* ICT, *investigational chemotherapy clinical trials;* IOERT, *intraoperative electron irradiation;* MACT, *multiagent chemotherapy;* maint, *maintenance;* NR, *not recommended;* postop, *postoperative;* preop, *preoperative.*

**Prefer preoperative CRT for gastroesophageal junction cancers found to be T1-2 N1-3 M0 or T3 N0-3 M0 on EUS, as can usually design safer EBRT fields with preoperative CRT rather than postoperative CRT. If transhiatal resection is performed, keeping the reconstructed stomach in the mediastinal midline, postoperative CRT can be given more safely than if Ivor-Lewis resection is performed.*



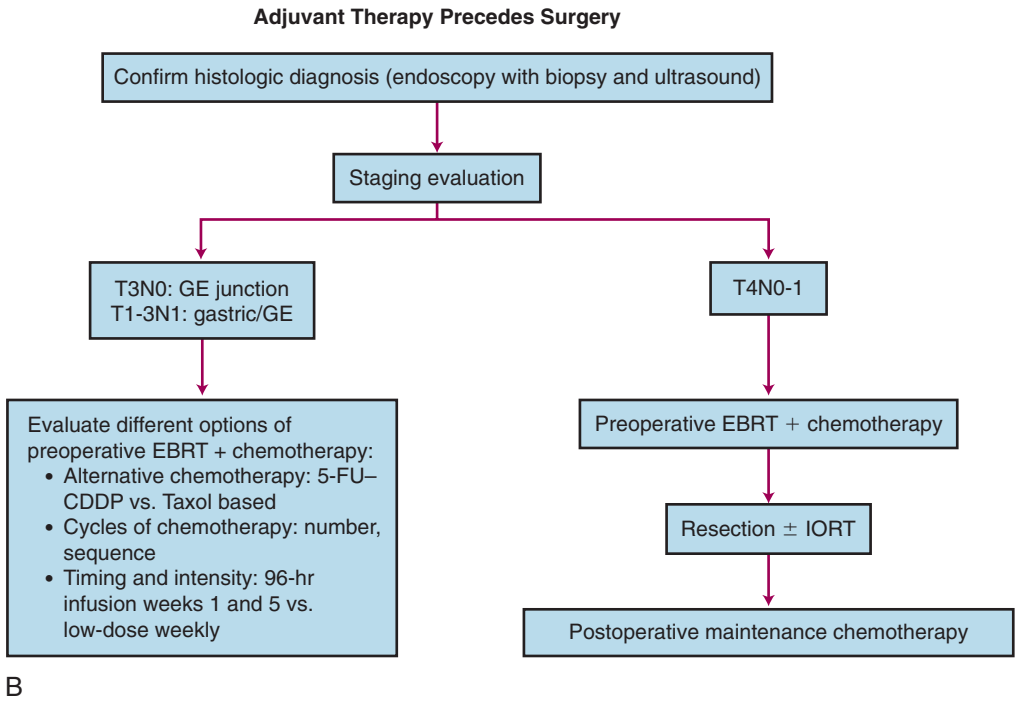


Figure 47-10 Treatment algorithms for patients with newly diagnosed gastric or gastroesophageal junction cancer. *5-FU,* 5-fluorouracil; *EBRT,* external beam radiation; *GE,* gastroesophageal; *IORT,* intraoperative irradiation; *LN–,* lymph nodes negative; *LN+,* lymph nodes positive.

some investigators and institutions may prefer to simply replace postop chemoRT with periop ECF or CF in these patients, it would seem advantageous to attempt to combine the advances in disease control and survival found with both approaches because neither approach by itself resulted in optimal relapse or survival outcomes.[282] In patients with potentially resectable high-risk GE junction cancer, however, the preferred treatment option is preop chemoRT in view of positive Phase III trials and the advantage of treating more conservative EBRT fields with less associated morbidity.

Current and future trial designs are attempting to build on or further define preop chemoRT and periop chemo (alone or followed by postop chemoRT). A Phase III AGITG/ESTRO study is testing periop multidrug chemotherapy (three cycles ECF or ECX [xeloda/capecitabine] before and after surgery) compared to preop chemoRT and postop chemo (preop: two

cycles ECF/ECX plus 45 Gy in 25 fractions for 5 weeks with concurrent PVI 5 FU; postop: three cycles ECF/ECX) for patients with gastric or GEJ cancers. The European CRITICS Phase III trial is testing periop chemo (three cycles ECC [etoposide/capecitabine/cisplatin] before and after surgery) compared with three cycles preop ECC plus postop chemoRT (45 Gy for 5 weeks plus concurrent capecitabine/cisplatin). A U.S. GI Intergroup Phase IIR trial is randomizing patients with esophagus or GEJ cancers to one of two preop chemo regimens (FOLFOX6 versus carboplatin plus paclitaxel) and using PET response to determine the type of chemo to be given concurrent with preop RT (PET responders continue same chemo with RT, nonresponders crossover to alternative chemo with RT; 50.4 Gy in 28 fractions for 5.5 weeks).

Locally Unresectable and Borderline Resectable Disease

For patients with locally unresectable or borderline resectable disease, it seems reasonable to build on existing positive treatment data (primary chemoRT, IORT, preop chemoRT, postop chemoRT, preop chemo) plus patterns of relapse information (see Figure 47-10; Table 47-12).

For patients with gastric cancer whose treatment is initiated with preop chemo, those with marginal gross total or subtotal resection with residual disease or complete resection but high-risk factors for relapse (beyond the gastric wall, nodes positive, or both) should be placed on studies that evaluate IORT, postop chemoRT, or both in conjunction with concurrent and maintenance chemotherapy. For patients whose tumors are unresectable after preop chemo but who still have localized tumor on the basis of preoperative staging (including laparoscopy) or exploratory laparotomy, preop chemoRT should be given. Decisions regarding attempts at later resection with or without IORT could be individualized.

With locally unresectable GE junction cancers, our preferred approach is to initiate treatment with preop chemoRT followed by restaging, resection (with or without IORT), and postoperative maintenance chemotherapy. Questions to be addressed with this approach include whether to give several cycles of multiagent chemotherapy before initiating concurrent chemoRT, how many cycles of chemo to deliver, and which agents to give both with EBRT and in the systemic component of treatment.

Combinations of EBRT and new drugs should continue to be evaluated. This is best accomplished in the setting of locally advanced primary or locally recurrent cancers.

Metastatic Disease

Although newer combination chemotherapy regimens have produced better response rates than single agents, survival has not been dramatically enhanced. Clearly new drug regimens need to be tested in advanced gastric cancer. The topoisomerase I inhibitors and taxanes are presently being evaluated. Alternative approaches such as biologicals, gene therapy, angiogenesis inhibitors, and metastasis inhibitors will also be evaluated in clinical trials. Given the limitations of available chemotherapy, continued evaluation of novel agents, either alone or in combination with chemotherapy, is indicated.

Treatment Algorithm by TNM Disease Extent

T1-2N0M0

Total surgical resection of the adenocarcinoma with a radical subtotal gastrectomy and reconstruction with gastrojejunostomy is recommended as standard treatment (see Table 47-12 and Figure 47-10). Patients with posterior wall T2N0M0 lesions should be evaluated for postoperative chemoradiation (chemoRT; see T1-2 N1-3 M0; T3 N0-3 M0).

T1-2N1-3M0; T3 N0-3 M0

Postoperative chemoradiation or perioperative chemotherapy is the preferred adjuvant treatment for patients with gastric cancer. If transhiatal resection is performed, keeping the reconstructed stomach in the mediastinal midline, postop chemoRT is facilitated. For GE junction cancers found to be T1-2 N1-3 M0 or T3 N0-3 M0 on EUS, preop chemoRT is preferable because safer EBRT fields can be designed for preop chemoRT rather than postop chemoRT.[21,277]

T4 N0-3 M0

Preoperative chemoradiation followed by restaging, gross total resection (may include en bloc resection of adjacent organs), and IOERT is recommended for potentially resectable T4N0-3 lesions in institutions with that capability. Postop chemoRT has also been used for completely resected lesions. For locally unresectable cancers, preop or primary chemoRT or multidrug chemotherapy can be used, preferably in the setting of controlled prospective clinical trials.

T any N any M1

Multidrug chemotherapy combinations are the preferred treatment for patients with metastatic cancers. Patients should be placed on controlled trials if available.

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CHAPTER

48 Pancreatic Cancer

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INCIDENCE AND EPIDEMIOLOGY

In the United States in 2015, an estimated 48,960 patients will be diagnosed with pancreatic cancer (PCA) and 40,560 will die of the disease. PCA is the 12th-most commonly diagnosed cancer and the 4th-leading cause of cancer-related death in men and women in the United States. Incidence rates are highest in Western and developed countries. Cigarette smoking, high dietary fat intake, obesity, diabetes mellitus, and chronic pancreatitis are associated with a higher risk of PCA.

BIOLOGIC CHARACTERISTICS AND MOLECULAR MECHANISMS

The most frequently activated oncogene in pancreatic adenocarcinoma is *KRAS* (>95%). The *CDKN2A, TP53,* and *SMAD4* tumor suppressor genes are inactivated in about 90%, 80%, and 55% of PCA, respectively. Molecular abnormalities may be used to define precursor lesions that may lead to invasive malignancies, facilitate characterization of histologically ambiguous lesions, develop novel screening modalities, and advance personalized, targeted therapies.

STAGING EVALUATION

The baseline evaluation for a patient who presents with a pancreatic mass includes a history and physical examination, complete blood count, serum chemistries, and a carbohydrate antigen 19-9 (CA 19-9). Either pancreatic sequence computed tomography (CT) or magnetic resonance imaging (MRI) of the abdomen may be used for diagnostic and staging evaluation. The role of fludeoxyglucose positron emission tomography (FDG-PET)/CT imaging remains unclear, although it may be useful for assessing response and detecting metastases that could be missed with CT alone. Management decisions would preferably be based on multidisciplinary consultation at a high-volume center with high-quality imaging to evaluate the extent of disease.

Although preoperative biopsy is not required for resectable tumors, biopsy to confirm histologic diagnosis is necessary before neoadjuvant or definitive therapy for patients with borderline resectable, unresectable, or metastatic PCA. A variety of biopsy techniques are acceptable, but endoscopic ultrasound-guided fine needle or core biopsy is preferred.

PRIMARY THERAPY

For patients with resectable PCA (15% to 20%), immediate surgery with a pancreaticoduodenectomy (Whipple procedure) or distal pancreatectomy remains the standard of care. Laparoscopic or robotic-assisted surgeries may decrease surgical morbidity. Resections should preferably be done at institutions that perform at least 15 to 20 pancreatic resections annually. Following resection, median overall survival (OS) ranges from 15 to 23 months and the 5-year OS is ~20%. Tumor grade, differentiation, size, margin status (R0), and extent of lymph node involvement are the strongest prognostic factors for long-term survival following curative-intent resection. The most common sites of postoperative relapse are the abdomen (liver, peritoneum, or regional nodes) and lung.

ADJUVANT THERAPY

The standard adjuvant regimen for patients with resected PCA continues to evolve. In both prospective and retrospective studies, adjuvant chemotherapy (CTX) or chemoradiation (CRT) with gemcitabine (GEM) or 5-fluorouracil (5-FU) has demonstrated a survival advantage over observation after surgical resection in both prospective and retrospective studies. However, it is unclear whether CRT improves survival compared with CTX alone. The results of the Radiation Therapy Oncology Group (RTOG) 0848 trial should provide needed insight into the role of modern adjuvant RT.

Neoadjuvant therapy offers some theoretical advantages, but in patients with truly resectable disease only a few cancer centers use this approach routinely. In patients with borderline resectable disease, neoadjuvant CTX followed by CRT is being prospectively evaluated.

UNRESECTABLE AND LOCALLY ADVANCED DISEASE

In patients with locally unresectable and borderline resectable pancreas cancer (LUPC, BRPC), treatment decisions are based on performance status (PS), patient preferences, and tumor relationship with arterial structures. Patients with excellent PS typically receive aggressive combination CTX and dose-escalated RT. Patients with poor PS may receive single-agent CTX single-agent CTS; RT is reserved for patients with pain or other symptoms of local progression.

Since about 20% of patient with LUPC and BRPC develop early metastatic disease, an appropriate standard of care is 2 to 3 months of CTX followed by restaging. Concurrent CRT should be considered if patients have achieved maximal response from or can no longer tolerate CTX and in patients who have local progression on CTX or have pancreas-related pain. Standard treatment includes 5-FU- or GEM-based RT for 50 Gy to 63 Gy in 1.8-Gy to 2-Gy fractions. Stereotactic body radiation therapy (SBRT) and proton therapy are being evaluated.

METASTATIC DISEASE, PALLIATION, AND SYSTEMIC THERAPY

Nearly 60% of patients present with metastatic disease, with a median survival of 6 months from diagnosis. Specific palliative interventions to relieve biliary or bowel obstruction (e.g., stent placement) and cancer-related pain (e.g., celiac block) can provide excellent symptomatic relief. Systemic and local therapies can palliate symptoms and, in select cases, improve survival.

PCA is almost invariably fatal and is projected to become the second-leading cause of cancer death by 2020.[1] Despite tremendous clinical and laboratory research efforts, mortality rates have remained nearly unchanged over the past 30 years. PCA is rarely detected at an early stage and the patient population is predominantly elderly. The biologic aggressiveness, decreased vascular density, and immune suppression associated with PCA further enhance its therapeutic resistance.[2] Nevertheless, advances in systemic therapy (e.g., combination CTX, targeted therapy), interventional procedures, radiation therapy, and supportive care (e.g., antinausea medication, pain control, pancreatic enzyme supplementation) can improve the quality and quantity of life in patients with PCA.

Managing PCA is a challenging endeavor for physicians, patients, and their families. Multidisciplinary care (MDC) involving radiation oncology, surgical oncology, medical oncology, interventional radiology, pathology, and palliative care are imperative for optimal management of patients with PCA. MDC ensures consensus regarding treatment plans and improved communication among the care team. At specialized, high-volume PCA treatment centers, MDC changes the initial management plan (from referring providers) in nearly 25% of patients and results in more accurate staging and diagnosis.[3,4]

Surgical resection remains the only potentially curative option for patients with PCA. However, few (~15% to 20%) patients present with resectable disease, and 5-year postoperative survival rarely exceeds 20%, even for patients with histologically negative (R0) margins.[5,6] The remaining 80% to 85% of patients with PCA present as follows: ~10% borderline resectable (BRPC), ~30% locally unresectable (LUPC), and ~50% metastatic.[7] Unfortunately, 5-year survival for locally unresectable and metastatic PCA is less than 5%, even with aggressive treatment.[8]

EPIDEMIOLOGY AND ETIOLOGY

Epidemiology

Between 1973 and 2002, the incidence rate for pancreatic adenocarcinoma of the head of the pancreas remained stable (5.6 per 100,000), whereas the rate for body/tail tumors increased by 46% (to 1.6 per 100,000).[9] Higher survival rates are observed among patients with pancreatic head tumors in comparison with body/tail tumors.[10,11]

In 2015, it is estimated that there will be 48,960 cases of PCA and 40,560 PCA-attributable deaths in the United States.[12] Although it is the 12th-most common malignancy in terms of incidence, PCA is the 4th-leading cause of cancer death. Incidence rates of PCA are highest in Western and industrialized countries. Most patients with PCA present with advanced disease. The median age of diagnosis in the United States is 72, and more than 66% of patients are older than 65.[13]

Etiology

PCA has historically been associated with cigarette smoking, high dietary fat intake, obesity, diabetes mellitus, and chronic pancreatitis. Cigarette smoking is the most consistent risk factor associated with PCA, with smokers having a twofold increased risk.[14] Obesity and chronic diabetes mellitus increase PCA risk by 20% and 50%, respectively.[15] Additional risk factors for PCA include advanced age, non-O blood group, African American origin, high alcohol consumption, occupational exposure to chlorinated hydrocarbon solvents or nickel, hepatitis B or C, history of cholecystectomy, and cystic fibrosis.[7,16-19] Although dietary factors such as increased consumption of red or processed meat, dairy products, and vitamin D have been suggested to be associated with an elevated PCA risk, the published data on these risk factors are inconclusive.[15]

A family history of PCA has become increasingly recognized as a risk factor for PCA. Approximately 10% of PCA is caused by hereditary factors that are associated with an increased risk of both pancreatic and nonpancreatic cancers including breast, ovarian, and bile duct cancers.[20] First-degree relatives of patients with PCA have an 18-fold increased risk of PCA, whereas individuals with three or more affected family members have a 57-fold increased risk of PCA.[21]

Known associations exist between PCA and hereditary breast and ovarian cancer (HBOC) syndrome, which involves *BRCA1* and *BRCA2* gene mutations. Inherited *BRCA2* mutations increase the risk of PCA 3- to 10-fold.[20,22] Furthermore, germline mutations in *CDKN2A/p16* (familial atypical melanoma mole syndrome), *STK11* (Peutz-Jeghers syndrome),[23] *MLH1* or *MSH2* (hereditary nonpolyposis colorectal cancer),[24] *APC* (familial adenomatous polyposis),[23] and *PRSS1* (hereditary pancreatitis)[25] have been associated with familial PCA. Establishing factors that are associated with a genetic predisposition for PCA improves our understanding of PCA signaling pathways and advances the development of personalized therapies. The current understanding of familial PCA is regularly updated on the Johns Hopkins National Familial Pancreatic Tumor Registry (NFPTR) webpage (pathology.jhu.edu/pancreas/PartNFPTR.php).

PREVENTION AND EARLY DETECTION

Given the poor outcomes in PCA, risk reduction and early detection are crucial. Smoking cessation, avoiding excessive alcohol consumption, dietary improvements, and increased exercise may help to reduce the risk of PCA.[26] Unfortunately, many serious risk factors for PCA are related to hereditary factors and acquired genetic changes that currently cannot be prevented or modified.

Anatomical and functional imaging has improved the ability to detect, diagnose, and stage PCA although detection at early stages remains uncommon. Multidetector computed tomography (MDCT) scans with thin slices (≤3 mm) and three-dimensional (3D) reconstruction are now considered the gold standard for PCA and have an overall sensitivity for PCA of 95% to 100%.[27-30] MDCT can capture an image of the entire body in one breath-hold and create multiplanar reconstructions and isotropic volume rendering, making it the preferred option for preoperative staging and treatment planning.[31] A recent study demonstrated a good correlation between tumor size on 3D MDCT and at pathologic analysis after resection.[32] Detection of small tumors (<2 cm) or peritoneal metastases with MDCT remains a challenge.

BIOLOGIC CHARACTERISTICS AND MOLECULAR BIOLOGY

The molecular characteristics of PCA can influence the natural history of disease, patterns of failure, and sensitivity to targeted therapies that may consequently guide therapeutic management. Pancreatic carcinogenesis is a complex process that includes somatic alterations affecting a combination of oncogenes, tumor suppressor genes, and proteins that alter cell behavior or the tumor microenvironment. In some instances, these proteins limit the immune system's ability to control the tumor while simultaneously enhancing resistance to standard therapies such as CTX and RT.

Mutated oncogenes cause uncontrolled cell proliferation by inhibiting apoptosis and promoting cell growth (eTable 48-1). *KRAS* is the most frequent oncogene mutation in PCA and is mutated in more than 95% of PCA tumors. Activating mutations in *KRAS* causes chronic activation of downstream proliferative and survival signaling pathways (e.g., *PI3K, MAPK,* and *RAF*), which leads to inhibition of apoptosis, migration angiogenesis, cytoskeleton alteration, and proliferation despite the presence of inhibitory growth signals.[23,26,33-35] Activation of the *AKT* oncogene through phosphorylation in the *PTEN/PI3K/AKT* pathway allows cancer cells to overcome cell cycle arrest, block apoptosis, and promote angiogenesis.[26] Additional oncogenes that are activated by mutation or gene amplification in PCAs include *BRAF* (in *KRAS* wild-type tumors specifically), *C-MYC, MYB,* and *AKT2*.[23,34,36,37]

Tumor suppressor genes act in the opposite manner than that of oncogenes; when tumor suppressor genes are inactivated by mutations, deletions, or methylation, uncontrolled cellular proliferation can occur. *CDKN2A/TP16* is the most commonly inactivated tumor suppressor gene in PCA (95% of cases); loss of *CDKN2A* promotes cell cycle progression through the G2/M checkpoint.[23,26,33] *TP53* is also frequently inactivated in PCAs, with inactivated mutations observed in 80% of cancers.[38] In normal cells that suffer DNA damage, *TP53* stops the cell cycle to allow for DNA repair or the initiation of apoptosis. *TP53* inactivation results in the loss of this important checkpoint, thereby permitting accumulation of DNA damage and additional genetic alterations.[33,35]

A third significant tumor suppressor gene in PCA is *SMAD4 (DPC4)*. *SMAD4* encodes a protein, Smad4, which is a central mediator of the canonical transforming growth factor-beta (TGF-β) signaling pathway, which, in turn, regulates diverse cellular processes including proliferation, differentiation, apoptosis, and migration.[38] TGF-β also leads to a decrease in activity of helper T cells, and subsequently suppresses the body's immune system reaction against abnormal cancer cells.[33] *SMAD4* is inactivated in approximately 55% of pancreatic tumors (Figure 48-1). Several studies have suggested that immunolabeling to detect Smad4 protein expression or determining the genetic mutation or deletion status of *SMAD4* can aid in predicting OS following PCA resection.[39,40] In an autopsy series of patients with advanced PCA, Smad4 status was highly correlated with the pattern of relapse.[41] Patients whose cancers expressed Smad4 tended to have a limited metastatic burden and more often died of localized disease, whereas patients whose PCA did not express Smad4 (indicating a deleted or mutated *SMAD4* gene) more often died of widely disseminated metastatic disease.[36]

In addition to the aforementioned genetic alterations, several other proteins are abnormally expressed in PCA, including insulin-like growth factor (IGF), p21 and p27, and epidermal growth factor receptor (EGFR). Overexpression of IGF leads to the abnormal activation of many downstream pathways, whereas p21 and p27 mutations cause loss of regulation at the G1 checkpoint. EGFR overexpression induces activation of the mitogen-activated protein kinase (MAPK) pathway, which influences cell proliferation, differentiation, and survival.[35,42]

Epigenetic modification is the alteration of gene expression by mechanisms other than changes in the actual DNA sequence and plays a role in PCA tumor development and progression. The primary epigenetic mechanisms associated with PCA include DNA methylation, histone modification, and changes in microRNA expression.[7,23] A variety of proteins that play critical roles in embryonic development pathways are also aberrantly expressed; these include members of the Hedgehog (Hh), Notch, and Wnt signaling pathways. The Hh signaling pathway plays an important role in embryogenesis, and

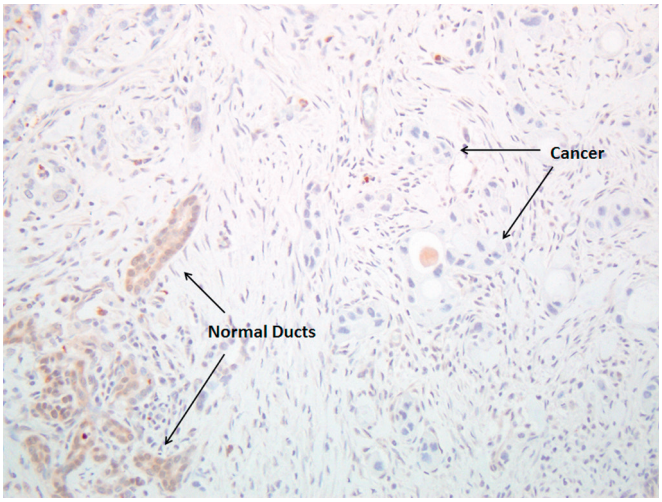


Figure 48-1 Example of Smad4 immunolabeling in resected pancreatic cancer. Normal ducts show intact labeling for Smad4 protein, whereas the infiltrating carcinoma cells are negative indicating a mutation or deletion of the SMAD4 gene in this patient's tumor.

overexpression of Hh ligands has been shown to promote tumor progression in mouse models of PCA. Whereas Hh expression is largely confined to the cancer cells during carcinogenesis, it is predominantly produced by the tumor-associated stroma in infiltrating PCAs and has paracrine activity on the tumor cells.[34,42] Similarly, the Notch pathway is primarily active during normal embryogenesis, where it is an important factor in cell differentiation.[34,42,43] Aberrant activation of the Notch pathway in PCA allows cells to remain in an undifferentiated state, thereby contributing to tumor growth and the oncogenic phenotype. The Wnt signaling pathway also plays a role in stem cell maintenance in normal cells and is hyperactivated in some PCAs as a result of reduced expression of Wnt inhibitors (e.g., *Dkk1*).[26,44]

The PCA microenvironment is comprised of stromal cells (fibroblasts), inflammatory cells, and endothelial cells. Cancer cell secretion of the growth factors IGF-1, TGF-β, fibroblast (FGF), vascular endothelial (VEGF), and platelet-derived (PDGF) have been shown to stimulate the pancreatic stellate cells within the stroma (also called myofibroblasts) to secrete excess amounts of extracellular matrix. The matrix and its stromal cells, in turn, secrete cytokines and growth factors that promote cancer cell growth, invasion, and dissemination. This tumor stromal environment is associated with the development of abnormal vasculature that inhibits the delivery of chemotherapeutic drugs to the pancreatic cells; therefore, targeting the stroma may enhance the efficacy of CTX and RT in PCA.

Secreted protein acidic and rich in cysteine (SPARC), or osteonectin, comprises a family of proteins that is typically overexpressed in the pancreatic stroma. The role of SPARC is complex, cell type-specific, and displays both anti- and pro-oncogenic functions. Overexpression of SPARC has been shown to promote tumor invasion through deregulation of inflammatory response and immune surveillance, and induction of epithelial-to-mesenchymal transition (EMT), cell-adhesion, invasion and metastasis.[45] Nab-paclitaxel (NP) may target SPARC overexpression in PCA, enhancing intratumoral drug penetration and stromal collapse.[46] Identification of tumor-specific biomarkers predictive for local and distant recurrence based on these molecular mechanisms could guide future targeted therapy in patients with PCA.

eTABLE 48-1 Genetic Mutations in Pancreatic Cancer

Gene	Chromosome	Prevalence (%)	Function	Significance
ONCOGENES				
KRAS	12p	95	Growth-factor initiated signaling	*KRAS* mutations occur early, may be a target for early detection
TUMOR SUPPRESSOR GENES				
p16/CDKN2A	9p	95	Regulation	
TP53	17p	80	Cell cycle apoptosis	
SMAD4 (DPC4)	18q	55	TGF-β signaling	*SMAD4* loss associated with poor prognosis and widespread disease

PATHOLOGY AND PATHWAYS OF SPREAD

Pathology

Recent work has shed some light on the mechanisms underlying the malignant transformation of pancreatic lesions. Potentially curable, noninvasive precursor lesions that give rise to PCA called *pancreatic intraepithelial neoplasia* (PanIN) have become a subject of increasing interest. However, the small size of most PanIN tumors makes direct observation difficult, and the best estimates of the timeline for progression of PanIN lesions to invasive carcinoma come from genetic sequencing studies.[47] Iacobuzio-Donahue et al sequenced a series of primary invasive PCAs and multiple matched metastases from the same patients. Evolutionary modeling was applied to the patterns of genetic alterations present in multiple lesions from the same patient. It was estimated that it takes at least a decade for a cell with an initiating mutation in the pancreas to progress to what was designated as the "parental, nonmetastatic founder cell" (a cell likely to present in an advanced PanIN lesion, before the onset of the invasion required to define the lesion as an adenocarcinoma). This study estimated that it takes at least another 5 years for the neoplastic clone to develop the ability to metastasize.

Classification

Pancreatic neoplasms may be broadly classified as either solid or cystic tumors. This classification facilitates diagnosis, influences prognosis, and affects decisions about patient management.

Solid Neoplasms

The most common solid pancreatic tumors are the infiltrating ductal adenocarcinomas and are the tumors most often referred to as *pancreatic cancer*. These malignant epithelial neoplasms arise from cells that give rise to the ductal epithelium and consequently often have glandular or ductal differentiation. Infiltrating ductal adenocarcinoma is typically poorly defined, infiltrating, firm, and solid; vascular and perineural invasion, as well as invasion of peripancreatic tissues, is common.[48] These tumors elicit an intense desmoplastic reaction, which causes significantly elevated interstitial fluid pressure that may act as a barrier to imaging and therapy.[49] Treatments incorporating NP (targeting SPARC) or Hh inhibitors show promise for targeting the desmoplastic stroma.[50]

A number of other variants of ductal adenocarcinoma of the pancreas have been described. Pancreatic neuroendocrine tumors (PanNETs) are the second most common type of pancreatic solid tumors, and arise from endocrine cells of the pancreas located within the islets of Langerhans. PanNETs are less aggressive than invasive ductal adenocarcinomas, with a 10-year survival rate of 45%.[52] Prognosis is indicated by tumor grade, size, and stage.[53] Adenosquamous carcinoma is a rare histological variant with squamous differentiation in addition to ductal differentiation.[151] These cancers disseminate aggressively and are associated with a particularly poor prognosis. Anaplastic carcinoma is another rare variant of ductal adenocarcinoma that tends to present as a large tumor involving the pancreatic body and tail.[51] This is an aggressive cancer with poor OS and no reported 5-year survivors. Anaplastic carcinomas with associated giant cells resembling bony osteoclasts, known as undifferentiated carcinoma with osteoclast-like giant cells, have a slower rate of metastasis and a somewhat better prognosis.[52] Acinar cell carcinomas are a rare type of carcinoma that arises from acinar cells of the pancreas. Survival and patterns of spread are parallel to that of standard adenocarcinoma of the pancreas.

Cystic Neoplasms

With advanced cross-sectional imaging, cystic pancreatic lesions are increasingly identified. Only 5% to 15% of pancreatic cystic lesions are actually neoplastic; most are nonneoplastic lesions such as pseudocysts, congenital cysts, and retention cysts.

The cystic neoplasms of the pancreas are either serous or mucinous neoplasms. Most serous cystic neoplasms are serous cystadenomas, also known as microcystic adenomas and glycogen-rich cystadenomas. Serous cystic neoplasms of the pancreas are typically benign, whereas mucinous cystic neoplasms are more frequently malignant. Mucinous cystic neoplasms are usually in the body/tail, without communication with the main pancreatic ductal system.[54] Interestingly, mucinous cystadenocarcinomas are associated with a better prognosis than typical adenocarcinoma of the pancreas, with approximately 50% of patients surviving 5 years.

Intraductal papillary mucinous neoplasms (IPMNs) are cystic tumors that arise in the larger pancreatic ducts. They are detectable and curable noninvasive precursors to invasive PCA and are associated with a better prognosis than invasive pancreatic malignancies.[48] A more aggressive variant is papillary mucinous carcinoma, which has significant cytologic and architectural atypia or overt invasion. IPMNs with a colloid component tend to have a better prognosis than those with a tubular component.[156]

Solid-pseudopapillary neoplasms, or Hamoudi tumors, are low-grade malignant neoplasms that primarily occur in women in the third decade of life. Patients present with abdominal distention, discomfort, or pain. These tumors are often large, typically ranging from 5 cm to 15 cm in diameter. Other rare pancreatic neoplasms include pancreatoblastoma, acinar cyst adenocarcinoma, and primary mesenteric mesenchymal tumors.

Pathways of Spread

The anatomy of the pancreas also plays an important role in tumor spread and associated symptomatology. The pancreas is a retroperitoneal organ with rich lymphatic drainage that lies in close relationship to the stomach, duodenum, jejunum, kidneys, spleen, celiac trunk, superior mesenteric artery (SMA), superior mesenteric vein (SMV), common bile duct, liver, and portal vein (PV) (Figure 48-2). At the time of diagnosis, more than 85% of PCAs extend into adjacent organs, lymph nodes, fat, or soft tissue, allowing for early metastasis to regional and distant lymph nodes.

Lymphatic invasion, and specifically nodal involvement, is the strongest predictor for survival in nonmetastatic tumors. Tumor cells enter the lymphatic system by migration through the interendothelial valves or by destroying the vessel walls. Entrance into the smaller intralobular lymphatic vessels located within the pancreas are followed by drainage into the four main lymphatic branches of the pancreas: the anterior, posterior, inferior, and superior pancreaticoduodenal lymphatic vessels. These branches then drain into regional lymph nodes, which are typically located around larger blood vessels (most commonly around the celiac artery, common hepatic artery, SMA, and aorta for head/neck tumors and around the splenic artery for body/tail tumors). Frequently involved nodal sites include the posterior pancreaticoduodenal, superior pancreatic head, inferior pancreatic head, superior pancreatic body, and porta hepatis nodes.[55] There is also a relationship between paraaortic lymph node involvement and involvement of posterior pancreaticoduodenal nodes by direct interlymphatic communication (Figure 48-3). Finally, there is direct lymphatic drainage from the pancreas to the liver via

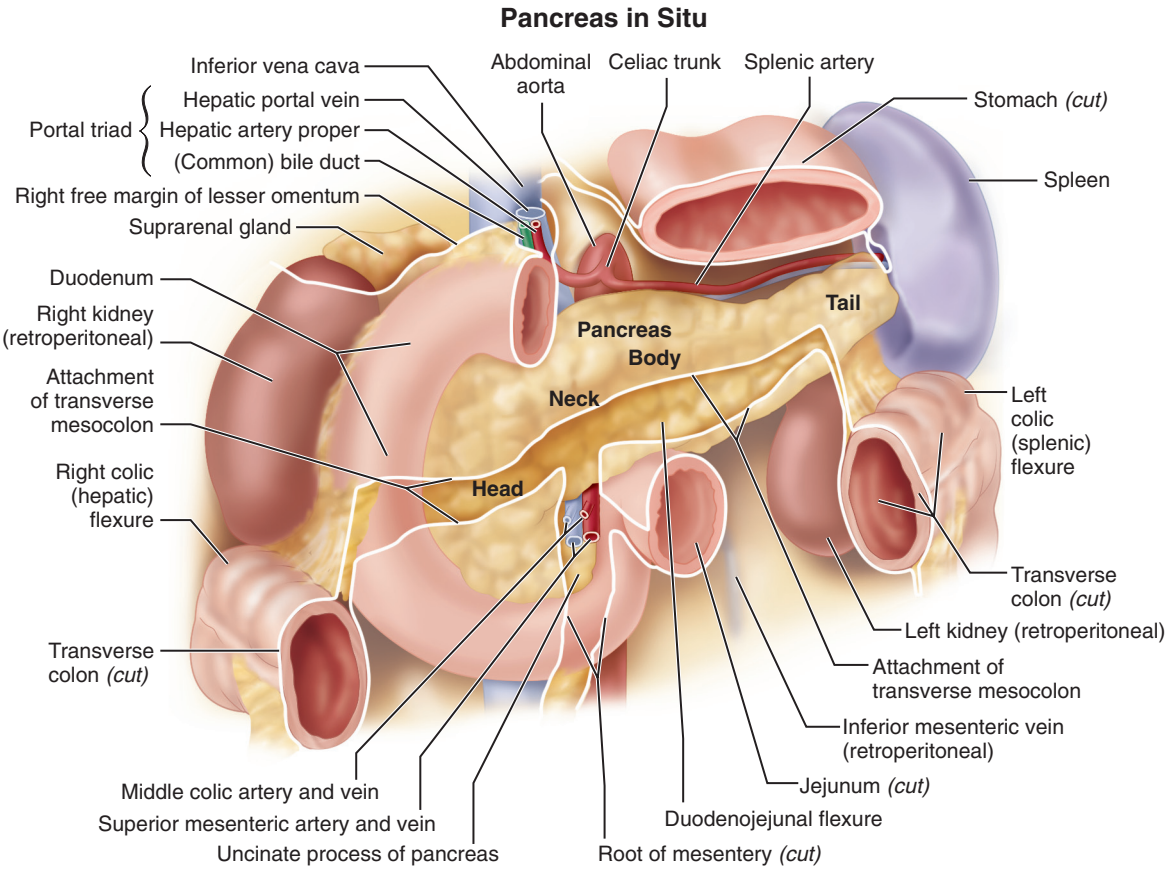


Figure 48-2 Anatomy of the pancreas.

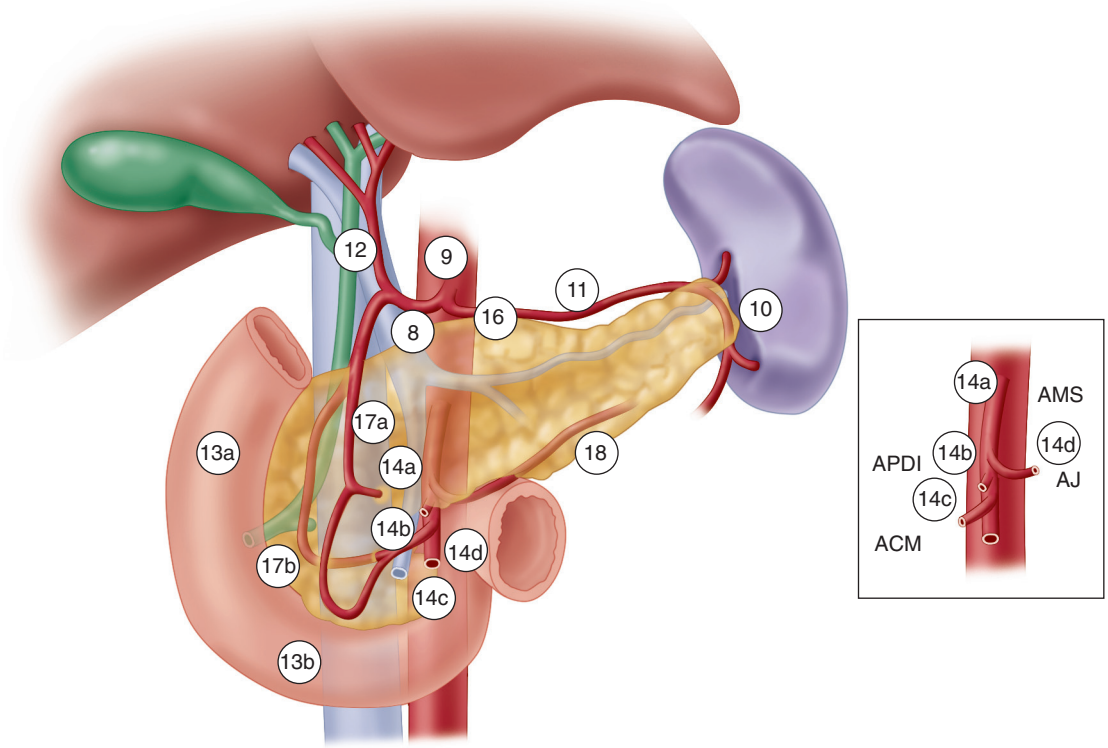


Figure 48-3 Classification of regional lymph nodes of the pancreas. *Inset,* Subdivision of area 14 described: *8,* Hepatic arterial; *9,* celiac axis; *10,* splenic hilum; *11,* distal splenic artery; *12,* portacaval; *13a,* superior pancreaticoduodenal; *13b,* interior pancreaticoduodenal; *14a,* superior mesenteric artery (AMS); *14b,* inferior pancreaticoduodenal artery (APDI); *14c,* medial colic artery (ACM); *14d,* jejunal artery (AJ); *16,* proximal splenic artery; *17a,* proximal gastroduodenal artery; *17b,* lymph node along the posterior surface of pancreatic head; *18,* inferior margin. *From Cubilla AL, Forter J, Fitzgerald PJ: Lymph node involvement in carcinoma of the head of the pancreas area. Cancer 41:880, 1978.*

the hepatoduodenal ligament,[56] whereas venous drainage of the pancreas to the liver proceeds through the PV. At least 75% of all resected tumors also have positive lymph nodes.[57]

The head of the pancreas is innervated by the superior mesenteric ganglion and the pancreaticus capitalis I and II plexi (branches of the celiac plexus); these are the main routes for malignant perineural invasion in pancreatic head tumors. Cancers of the body and tail primarily spread through the celiac plexus and the splenic plexus. Intrapancreatic or extrapancreatic neural invasion is seen in virtually all advanced stage tumors and in greater than 70% to 75% of stage I tumors, implying that this is an early event in the tumor's progression. The head and neck of the pancreas are supplied by the superior pancreaticoduodenal arteries, which arise from the celiac trunk, and the inferior pancreaticoduodenal arteries, which arise from the SMA. These areas drain into the SMV, inferior vena cava (IVC), PV, and inferior mesenteric vein. The pancreatic body and tail, which are supplied by the splenic artery (arising from the celiac trunk) and pancreatic branches off the SMA, mostly drain into the splenic vein. Given their proximity to the pancreas, the SMV and SMA are the most commonly involved arteries and veins in PCA, especially in pancreatic head tumors. The celiac artery, splenic artery, hepatic artery, PV, and, more rarely, the IVC and aorta may also be involved.[58]

Haeno et al investigated progression of pancreatic tumors in more than 300 patients with PCA by using a mathematical framework of metastasis formation.[59] Initially, PCA growth was determined to be exponential. After estimating the rates of PCA growth and dissemination, the authors determined that patients likely harbor metastases at diagnosis and predicted the number and size distribution of metastases as well as patient survival. It was concluded that therapies that efficiently reduce the growth rate of cells earlier in the course of treatment (neoadjuvant therapy) appear to be superior to immediate tumor resection. These findings are being evaluated in additional datasets.

Tumor cells travel along nerves, lymphatics, or vessels to form distant metastases. The liver is the most common site of metastasis, and the peritoneal cavity is the next most common site of distant spread. Recent reports emphasize the influence of the retroperitoneal margin, poor differentiation, and lymph node involvement in determining relapse risk, especially locally.[60,61] In addition, rapid autopsy results from Johns Hopkins Hospital (JHH) indicate that local recurrence may be associated with alterations in *SMAD4* and that local recurrence may be the cause of death in up to 30% of patients with overt metastatic disease.[41] Determination of *SMAD4* status (among other biomarkers) at diagnosis (fine-needle aspiration or core biopsy) may be helpful to design personalized treatment regimens that target individual risks for local versus systemic disease progression.[62]

CLINICAL MANIFESTATIONS, PATIENT EVALUATION, AND STAGING

Patients with PCA typically present with locally unresectable or metastatic disease. The presenting symptoms depend on the location of the pancreatic tumor. Most tumors occur in the periampullary region of the pancreas (head, neck, uncinate process), and tumors in this area often cause obstructive jaundice with pruritus, choluria, hypocholia, and steatorrhea. They may also cause pain or gastric outlet obstruction through celiac plexus involvement and duodenal compression or invasion, respectively. Nearly 25% of patients present with new-onset diabetes. In fact, a recent study revealed that baseline hemoglobin-A1c values at presentation can correlate with clinical stage and be associated with OS.[63] Recent-onset depression and anxiety, as well as pancreatitis and cholangitis, may antedate the diagnosis of PCA.[64]

In contrast to cancers of the pancreatic head, tumors in the body or tail are usually more advanced at presentation. For these tumors, jaundice is a late manifestation; however, severe back pain is quite common (often indicating posterior extension into the celiac plexus). Patients with tumors in the tail of the pancreas may have evidence of "left-sided" portal hypertension, gastrointestinal bleeding, or splenomegaly from splenic vein obstruction or thrombosis.

Initial laboratory results may show elevated levels of serum bilirubin, alkaline phosphatase, gamma glutamyl transpeptidase, and hepatic aminotransferase. Historically, serum carbohydrate antigen 19-9 (CA 19-9) has been useful for the detection of PCA. A preoperative CA 19-9 level of more than 100 U/mL to 200 U/mL may predict unresectability and poor survival for patients with PCA[65]; however, it is not an entirely reliable diagnostic marker. CA 19-9 levels may be elevated as a result of cholangitis, pancreatitis, poorly controlled diabetes, and obstruction of the pancreaticobiliary tree. Additionally, CA 19-9 may be undetectable in patients lacking Lewis antigens.[66] Nonetheless, when it is elevated as a result of PCA, CA 19-9 is widely used to monitor the course of disease and response to therapy. In the Radiation Therapy Oncology Group (RTOG) 9704 trial, a postoperative CA 19-9 level (>90 U/mL) was a highly significant predictor of OS in pancreatic head tumors.[67]

Patient Evaluation

Patients are initially evaluated based on presenting symptoms, physical examination, PS, imaging, and laboratory tests (Figure 48-4). Following detection of disease, resectability should be determined, ideally in a multidisciplinary setting at a high-volume center with high-quality imaging available to stage the patient and evaluate the extent of disease.

The accuracy of radiologic diagnosis and staging of PCA has increased substantially with improvements in CT and MRI. Patients with body or tail lesions are often diagnosed incidentally (e.g., on imaging) or when symptomatic local or systemic progression occurs. If a pancreatic mass appears suspicious for malignancy and subsequent imaging deems it resectable, then immediate surgery is standard. However, a biopsy is required if the mass is not clearly malignant or if the plan is to proceed with neoadjuvant CTX or CRT. Endoscopic ultrasound (EUS) can be used to guide fine-needle or core biopsies of the pancreatic tumor to confirm the diagnosis. EUS guidance can also be used to place biliary or duodenal stents in cases where the tumor obstructs the bile duct or duodenum.[68] Endoscopic retrograde cholangiopancreatography (ERCP) is another endoscopic approach for biopsy, decompression of the biliary tree, and identification of the source of obstruction. Biliary obstruction can also be relieved by percutaneous and transhepatic cholangiography; however, EUS is the preferred modality because of the higher complication rate (particularly pancreatitis) associated with ERCP and percutaneous approaches.

Multi-detector CT (MDCT) remains the standard imaging modality for PCA detection and staging although MRI provides improved tumor resolution and better visualization of tissue planes for surgical assessment and radiation planning. The accuracy of MRI is comparable to that of CT and should be considered if intravenous (IV) contrast MDCT cannot be performed (e.g., in patients who are allergic to iodine-containing contrast) or if findings require clarification. In addition to biopsy, EUS can be used to evaluate whether the tumor invades the duodenum or stomach and to determine the extent of venous/arterial involvement (PV, SMV, SMA, celiac artery) and nodal status. In fact, one study suggested that MRI and

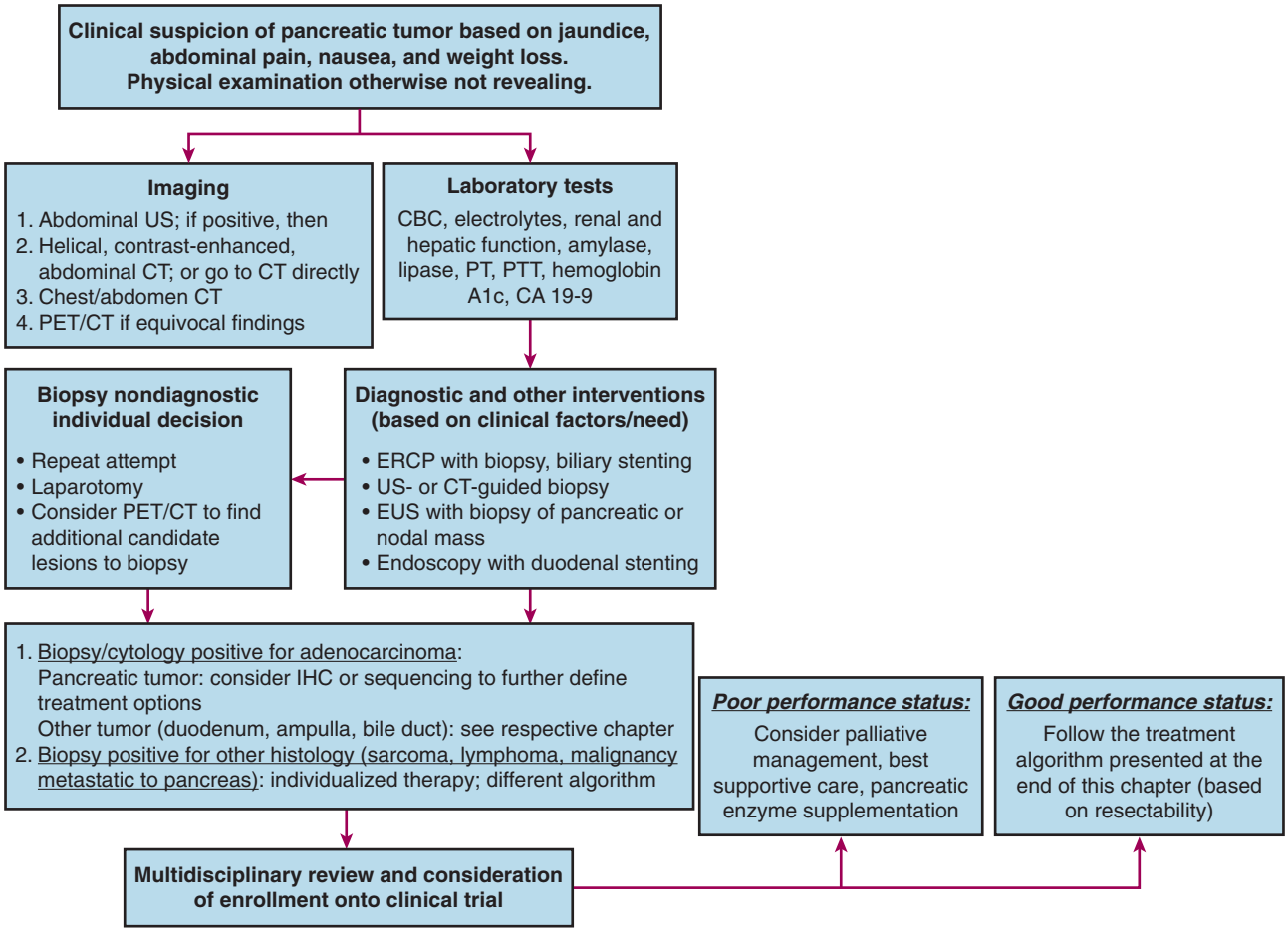


Figure 48-4 Diagnostic algorithm for pancreatic tumors. *CBC*, Complete blood count; *CT*, computed tomography; *ERCP*, endoscopic retrograde cholangiopancreatography; *EUS*, endoscopic ultrasound; *IHC*, immunohistochemistry; *PET*, positron emission tomography; *PT*, prothrombin time; *PTT*, partial thromboplastin time; *US*, ultrasound.

EUS are actually superior to CT in detecting pancreas lesions.[69] However, EUS is operator-dependent and is often not as accurate as MDCT in determining PV or arterial involvement.[70]

The role of FDG-PET in pancreatic imaging is evolving.[71,72] FDG-PET imaging is particularly useful when combined with the detailed anatomic technique of MDCT to depict the tumor and adjacent normal structures. FDG-PET/CT can also be used to analyze tumor response to therapy and detect occult distant metastases that could be missed with CT alone. A retrospective study demonstrated that the use of FDG-PET/CT after a standard CT protocol increased sensitivity for the detection of metastatic disease when compared with the standard CT protocol or PET/CT alone.[73] The sensitivity for metastatic disease for standard CT alone, FDG-PET/CT alone, and the combination of FDG-PET/CT and standard CT were 57%, 61%, and 87%, respectively. The clinical management of 11% of patients with invasive PCA was changed as a result of the PET/CT findings. Recently, baseline PET/CT parameters, including metabolic tumor volume and total lesion glycolysis, have been demonstrated to be associated with survival outcomes in patients with LUPC receiving SBRT.[74]

Diagnostic laparoscopy may also be useful for detecting metastatic PCA before surgery or CRT. Laparoscopy may identify occult disease in up to 30% of patients that may otherwise have been missed with other modalities.[75,76] The use of laparoscopy has become less common, although it may be beneficial in patients with a high CA 19-9 level, cancer in the body or tail of the pancreas, a large tumor, before the delivery of RT, or if imaging is suggestive of metastatic disease.[77,78]

The quality and interpretation of imaging studies are operator-dependent. Therefore, predictive and prognostic biomarkers may be useful predictors of tumor differentiation, treatment sensitivity, and progression risk and could ultimately aid in making individualized treatment decisions. Advances in endoscopic techniques now permit multiple fine-needle aspiration passes or core biopsies that can be made into cell blocks. Such cell blocks and core biopsies may help improve staging evaluations through immunohistochemistry and next generation sequencing. Moreover, plasma may be used as a "liquid biomarker" to assess changes prior to and following treatment. For example, proximal ligation assay technology has been used to create multiplexed, PCA-specific serological biomarker panels.[79,80]

Staging

The American Joint Committee on Cancer (AJCC) is the standard staging system for PCA (Box 48-1). Although the AJCC system is useful in stratifying patients by outcome, differentiation by the categories of resectable, borderline resectable, locally unresectable, and metastatic disease more accurately depicts features likely to influence management decisions. Therefore, a number of institutional panels including the National Comprehensive Cancer Network (NCCN)

BOX 48-1 American Joint Committee on Cancer (AJCC) TNM Staging and Definitions for Pancreatic Cancer

PRIMARY TUMOR (T)

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Tumor limited to the pancreas ≤2 cm in greatest dimension
T2	Tumor limited to the pancreas >2 cm in greatest dimension
T3	Tumor extends beyond the pancreas but without involvement of the celiac axis or the superior mesenteric artery
T4	Tumor involves the celiac axis or the superior mesenteric artery (unresectable primary tumor)

REGIONAL LYMPH NODES (N)

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis

DISTANT METASTASIS (M)

MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

have proposed a staging system to stratify patients based on resectability.[81] More recently, a PCA consensus guideline was recommended by the Americas Hepato-Pancreato-Biliary Association (AHPBA).[82] Borderline resectable disease is a relatively new category and Katz et al recently published a summary of the definition of BRPC that has been adopted by the NCCN (eTable 48-4).[83]

The resectability of PCA depends on the presence or absence of metastatic disease and on the degree of involvement of major vessels. The assessment of vascular involvement is made separately for the arterial axes and the portovenous system. With regard to the latter, any degree of involvement of the PV or SMV is still considered resectable as long as the vessel can be reconstructed following en bloc resection. Pancreatic tumors staged as T1, T2, or T3 using the AJCC TNM system are generally considered to be resectable. The extent of resection also carries prognostic significance; a patient who underwent a complete (R0) resection has a better prognosis than a patient who underwent a resection with microscopically (R1) or grossly (R2) positive margins. Margin clearance greater than 1.5 mm is needed to optimize locoregional control, and the extent of clear margins in R0 resections may be used to estimate the risk of locoregional failure.[84]

In contrast, involvement of the major arteries is frequently based on the degree of encasement identified on the axial plane of cross-sectional imaging. The arteries of interest include the superior mesenteric, celiac, and hepatic arteries. Greater than 180 degrees encasement of any of these vessels is considered locally unresectable.[81] Rare exceptions are made in which a short segment of an encased hepatic artery is resected en bloc and can be reconstructed. Less than 180 degrees of involvement is considered borderline resectable (eTable 48-4).

PRIMARY THERAPY

Surgery

A margin-negative (R0) resection is the primary goal of surgical resection and is achieved in 60% to 80% of cases. However, the poor long-term survival rates suggest that microscopic disease may frequently be left behind.[57] Even after an R0 resection, the 5-year OS is 25%, whereas 10-year survival is less than 10%.[85] Resections should be done at high-volume institutions that perform a large number (at least 15 to 20) of pancreatic resections annually as this has been shown to correlate with short- and long-term outcomes.[3]

The classic operation for carcinoma of the head of the pancreas is a pancreaticoduodenectomy (PD), or Whipple procedure. This operation includes resection of the head of the pancreas, distal common bile duct, gallbladder, part of the duodenum, and regional lymph nodes. In a classic PD, the stomach is divided proximal to the antrum, whereas the first portion of the duodenum is transected distal to the pylorus in a pylorus-preserving PD (Figure 48-5). Studies comparing the efficacy of these procedures reported no significant differences in outcomes.[86,87]

It is important that radiation oncologists understand the changes in upper abdominal anatomy that occur as a result of PD. As illustrated (Figure 48-5), gastrointestinal reconstruction after PD requires enteric (stomach to jejunum), biliary-enteric, and pancreatic-enteric anastomoses. Although postoperative mortality is less than 2%,[57] the morbidity rate of PD remains high at 30% to 45%.[88] Pancreatic leaks and infections, delayed gastric emptying, and pancreatic fistula are among the most common postoperative complications.[57]

For body and tail tumors, surgery includes a distal pancreatectomy with an en bloc splenectomy. Carcinoma of the body of the pancreas tends to extend superiorly beyond the pancreas and often involves the celiac trunk, common hepatic artery, and base of the splenic artery at its take-off from the celiac trunk; therefore, the determination of resectability is based on the extent of involvement of the celiac axis.[48] A select subset of patients can undergo an Appleby procedure, which involves an en bloc resection of the body and tail of the pancreas along with the celiac artery, proximal common hepatic artery, and splenic artery as well as a total gastrectomy.

Minimally invasive surgery is an alternative to traditional pancreatectomy and includes laparoscopic or robotic surgery. These techniques are believed to have similar oncological outcomes—including margin status and lymph node counts—to the standard approach.[89,90] Furthermore, minimally invasive surgery may lower the risk of postoperative complications in comparison with an open approach, although additional investigation is warranted.

Selection of Surgical Candidates

A number of factors should be considered when evaluating resectability in a patient with PCA; therefore, a multidisciplinary approach to patient evaluation is highly recommended.[3] Preexisting comorbidities (e.g., cardiac disease, chronic obstructive pulmonary disease, dementia) and certain biological characteristics of the tumor (e.g., size, differentiation) may preclude surgical resection of PCA.

An Early Mortality Risk Score (EMRS) was created to identify patients most likely to benefit from surgery.[91] Records of 740 patients who underwent upfront curative resection were analyzed to identify predictors of early mortality, defined as death at 9 and 12 months. EMRS factors were age >75 years, tumor size greater than 3 cm, poor differentiation, and comorbid diseases. Patients with these factors may be less likely to benefit from upfront surgery because of the high risk of postoperative complications, although prospective validation is needed.

Prognostic Factors Associated with Results of Surgical Resection

The most significant independent prognostic factor for survival in PCA has historically been extent of lymph node

eTABLE 48-4 EBRT with or without IOERT for Locally Unresectable and Borderline Resectable Pancreatic Cancer

Series	*n*	Overall Survival (%)				Relapse (%)		
		Med (mos)	2-Year (%)	3-Year (%)	*p* Value	Local	*p* value	Liver/PS
THOMAS JEFFERSON								
EBRT ± CTX[200]	46	7.3	—	—		78		—
IOERT/5-FU-LV/EBRT*[204]	49	16	22	7		29		55
MASSACHUSETTS GENERAL								
EBRT + 5-FU/IOERT[207]	22	16.5	33	20	>0.05	69 (2-year)		—
EBRT± 5-FU/IOERT + Miso[207]	63	12	20	—		55 (2-year)	>0.05	—
EBRT± 5-FU/IOERT[206]	150	13	15	7		—		—
MAYO CLINIC ROCHESTER								
EBRT + CTX[202]	122	12.6	16.5	—		80 (2-year)		56
IOERT/Postop EBRT + 5-FU[202]	37	13.4	12	—	0.25	34 (2-year)	0.0005	54
IOERT/Postop EBRT + 5-FU[203]	56	10.5	6	0		35 (2-year)		—
NAdj EBRT + 5-FU/IOERT[203]	27	14.9	27	20	0.001	32 (2-year)†		52
MAYO CLINIC ARIZONA								
EBRT + 5-FU or Gem/ IOERT[208]	31	19	31	16		16		71
R0/R1 Resection	16	23/17	48	36	0.002	6	—	69
R2 Resection/Unresectable	15	10	13	0		26.7		73

5-FU, *5-Fluourouracil;* CRT, *chemoradiation therapy;* CTX, *chemotherapy;* EBRT, *external beam radiation therapy;* Gem, *gemcitabine;* IOERT, *intraoperative electron radiation;* LV, *Leucovorin;* Miso, *misonidazole;* NAdj, *neoadjuvant;* Postop, *postoperative;* PS, *performance status.*

**Perioperative 5-FU/LV was given before, during, and after EBRT.*

†*2-year local relapse of 19% in the 23 patients with tumor diameter <7 cm compared with 75% in the 4 patients with >7 cm tumors.*

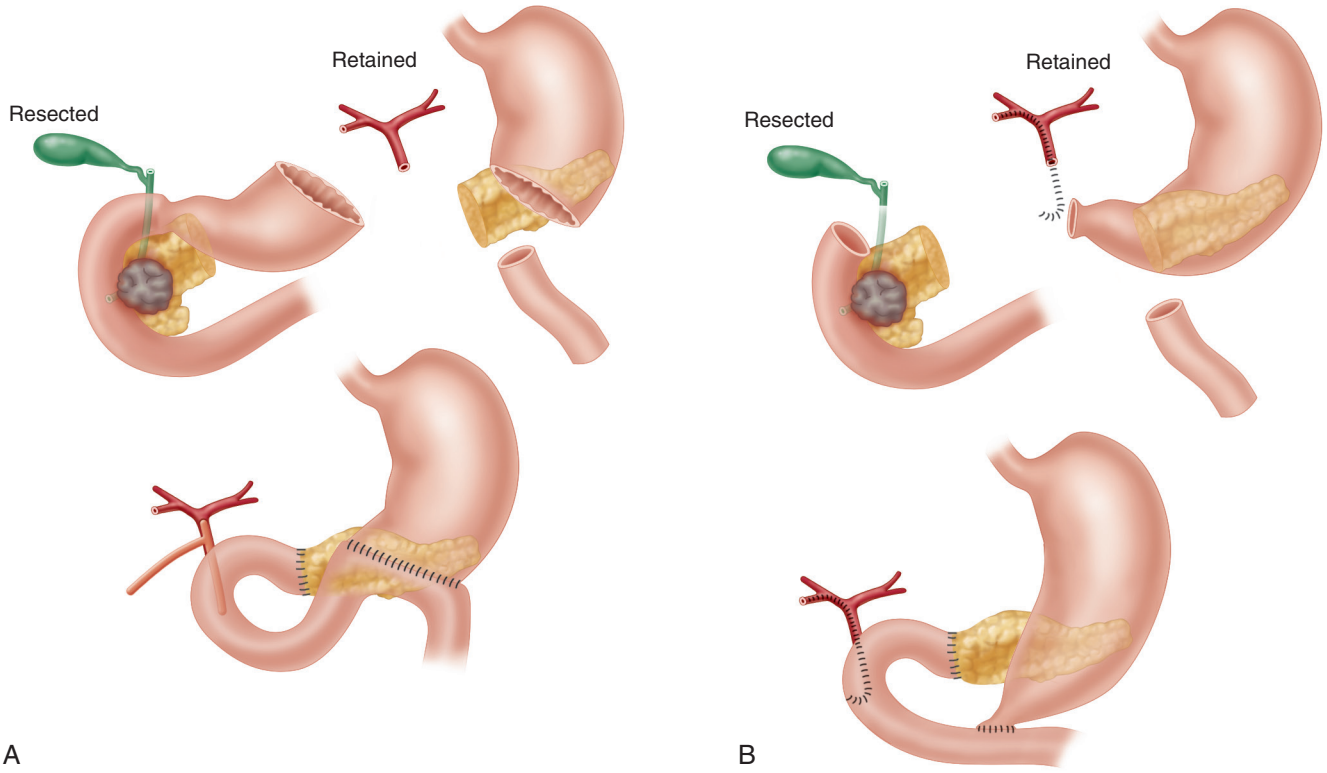


Figure 48-5 **(A)** Classic Whipple procedure and **(B)** pylorus-preserving pancreaticoduodenectomy.
From Yeo CJ, Cameron JL: The pancreas. In Hardy JD, editors: Hardy's textbook of surgery, ed 2, Philadelphia, 1988, JB Lippincott, pp 717, 718.

involvement.[92,93] After extensive review of periampullary malignancies, Yeo et al reported that lymph node involvement, tumor differentiation, and resection margin status are significant prognostic factors following resection.[93-95] Patients with lymph node metastases had a shorter median OS (16.5 months) compared with patients who were node-negative (25.3 months; $p = 0.001$). Rather than the total number of lymph node metastases or the number of nodes examined, lymph node ratio (LNR) was the most significant predictor of survival. As the LNR increased, median OS decreased. After adjusting for other factors associated with survival, LNR remained an independent predictor of OS ($p < 0.001$). A high number of metastatic lymph nodes (>5) and LNR >0.4 have also been associated with a high risk of local failure.[61]

Tumor size is also an important prognostic factor for PCA. Large surgical series report that 5-year and median OS were significantly improved in tumors smaller than 2 cm (23 to 30 months) in comparison with tumors larger than 2 cm (10 to 15 months).[96,97] The 5-year and median OS in patients with tumors 1.5 cm or less were 75% and 62 months, respectively, significantly better than that of tumors between 2.1 cm and 4.0 cm ($p = 0.02$). Of note, although size has prognostic importance in PCA, small size does not always confer a good prognosis.[98]

Tumor differentiation has also been associated with survival and progression of PCA. In a Japanese study, tumors less than or equal to 2 cm were more likely to be well-differentiated than tumors larger than 2 cm (44% versus 15%, $p = 0.001$).[99] This suggests that small tumors may represent a more indolent subset of disease rather than a precursor to large tumors. Furthermore, patients with poorly differentiated large tumors had 5-year OS of 0% and a median OS of 13 months. Poor tumor differentiation was also correlated with local recurrence ($p = 0.01$).

Resection margin status is an additional predictor of survival following surgery for PCA. A close (2 mm to 3 mm) margin appears to be equivalent to having an R1 resection, whereas a R2 resection is essentially equivalent to having LUPC. Therefore, resection should only be attempted when it is likely that a R0 resection can be achieved. Winter et al reported on the prognostic value of resection margin status in addition to tumor size, lymph node status, and histologic grade as pathological factors that significantly impact survival of pancreatic patients.[57]

Patterns of Failure Following Surgical Resection

Despite curative-intent resection in PCA, more than 60% of patients develop relapse within 2 years of PD. The most commonly reported sites of relapse are within the abdominal cavity and include the SMA margin, liver, lung, and peritoneum. A retrospective analysis of 145 consecutive resections for PCA between 1998 and 2005 sought to define patterns of failure of patients with PCA.[60] The most common distant sites were liver ($n = 57$), peritoneum ($n = 35$), and lung ($n = 15$). Isolated locoregional or extrapancreatic relapse was observed in 9 and 60 patients, respectively, whereas 41 patients developed combined locoregional and extrapancreatic recurrence. More than 50% of all liver metastases developed in the first 6 months following surgery, even in patients with early-stage tumors. The majority of peritoneal relapses developed between the 4th and 15th postoperative month, and lung metastases developed less frequently and more gradually over the postoperative course.

Patterns of local recurrence in patients with resected PCA were recently mapped to inform adjuvant RT planning (Figure 48-6).[100] Of 202 patients that underwent a PD, 40 (20%), 34 (17%), and 128 (63%) received no adjuvant therapy, adjuvant CTX, and adjuvant CRT, respectively. Local recurrence

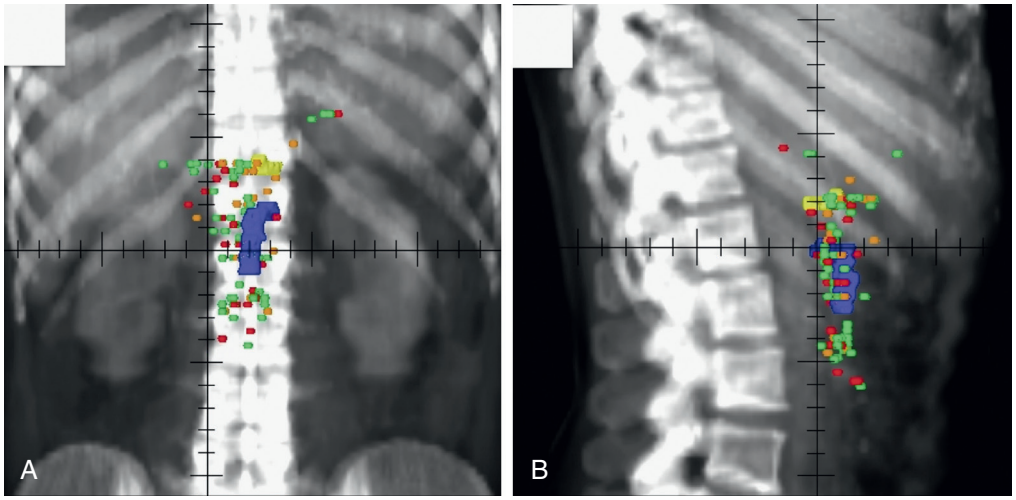


Figure 48-6 Local recurrence map. **(A)** Anterior-posterior and **(B)** lateral views of local recurrence plots in relation to the celiac artery *(yellow)* and superior mesenteric artery *(blue)* after pancreaticoduodenectomy for patients receiving no adjuvant therapy *(red)*, chemotherapy alone *(orange)*, and chemoradiation *(green)*.
From: Dholakia AS, Kumar R, Raman SP, et al: Mapping patterns of local recurrence after pancreaticoduodenectomy for pancreatic adenocarcinoma: A new approach to adjuvant radiation field design. Int J Radiat Oncol Biol Phys 87(5):1007-1015, 2013.

occurred in 90 of 202 patients overall (45%), with 48% ($n = 19$), 65% ($n = 22$), and 38% ($n = 49$) in the no adjuvant therapy, adjuvant CTX, and adjuvant CRT groups, respectively. Ninety percent of the recurrences were within a few centimeters of the celiac axis and SMA. Mapping guidelines outlined 80% to 90% of locoregional recurrences.

Adjuvant Therapy

The observed patterns of failure in the preceding analyses indicate the need for adjuvant interventions to address both local and systemic relapses. Although a clear benefit of adjuvant CTX has been demonstrated, the optimal adjuvant regimen remains unclear. Theoretically, adjuvant CRT would be a preferred option for patients with PCA who are at risk of local recurrence (margin-positive resection) or concurrent risk of locoregional and distant failure. A summary of adjuvant CTX and CRT studies in PCA can be found in Table 48-1.

Adjuvant Chemoradiation

Extensive evaluation of concurrent 5-FU–based CTX with external beam radiation therapy (EBRT) pioneered the acceptance of adjuvant CRT in resected PCA. A well-designed prospective, randomized trial ($n = 42$) conducted by the Gastrointestinal Tumor Study Group (GITSG) was the first to demonstrate the benefit of this regimen.[101] EBRT was delivered as two courses of 20 Gy in 10 fractions, each with a planned 2-week rest, and 5-FU CTX was given on the first 3 days of each half of RT at a dose of 500 mg/m^2 (intravenous bolus). Superior survival was observed in the patients treated with combined CRT (20 months) as opposed to the patients treated with surgery alone (11 months; $p = 0.03$). Two-year OS was 42% versus 15% in the CRT versus observation group, whereas 5-year OS was 19% versus 5%, respectively.

Investigators at JHH retrospectively reviewed 616 patients treated between 1993 and 2005.[107] Adjuvant CRT and maintenance CTX improved median, 2-year, and 5-year OS (21.2 months, 44%, 32%, respectively) when compared to surgery alone (14.4 months, 20%, 15%, respectively; $p < 0.001$). This survival advantage persisted even after controlling for age, medical comorbidities, and surgical complications.

Mayo Clinic investigators also demonstrated a survival advantage with adjuvant CRT over surgery alone in a retrospective analysis of 472 patients with R0 resections.[108] Despite the significantly increased number of adverse prognostic factors ($p = 0.001$) in the CRT group ($n = 274$), median, 2-year, and 5-year OS were superior in patients with adjuvant CRT (25.2 months, 50% and 28%) in comparison with surgery alone ($n = 180$; 19.2 months, 39% and 17%; $p = 0.001$).

Furthermore, collaboration between JHH and Mayo Clinic Rochester resulted in an analysis of 1092 patients (JHH, $n = 618$; Mayo, $n = 474$) who underwent PD with curative intent.[109] Five hundred and eighty-three patients received adjuvant 5-FU–based CRT (median RT dose of 50.4 Gy). Propensity scores and matched-pair analyses were performed to account for biases associated with nonrandom allocation of patients to adjuvant CRT or surgery alone. OS was significantly longer among patients who received adjuvant CRT compared with PD alone (median 21.1 versus 15.5 months, 2-year OS 44.7% versus 34.6%, 5-year OS 22.3% versus 16.1%, $p < 0.001$). In propensity score analysis, adjuvant CRT improved survival compared with surgery alone for all patients (relative risk [RR] = 0.67, $p < 0.001$) after adjusting for covariates. Matched-pair analysis demonstrated that OS was longer with adjuvant CRT versus PD alone ($p < 0.001$).

A subsequent multiinstitutional, randomized trial performed by the European Organization for Research and Treatment of Cancer (EORTC) demonstrated similar results to those of the GITSG randomized trial and the Johns Hopkins-Mayo Clinic nonrandomized cohorts although small patient numbers hindered the ability to produce a statistical advantage. The trial evaluated surgery alone versus adjuvant 5-FU–based CRT in 218 patients with periampullary cancers including PCA.[102] The radiation dose and fractionation were the same as in the GITSG trial (40 Gy in split-course fashion over 6 weeks) although continuous infusion (CI) 5-FU was administered rather than bolus 5-FU and no maintenance 5-FU was given. In a subset of 114 patients with PCA, patients in the CRT arm ($n = 60$) had a median OS of 17.1 months versus 12.6 months in the surgery alone arm ($n = 54$). The 2-year OS for the two trial arms were 37% versus 23%, whereas 5-year OS was 20% versus 10%, respectively ($p = 0.099$). There were no differences

TABLE 48-1 Adjuvant Chemoradiation or Chemotherapy Outcomes in Pancreatic Cancer

Study	*n*	Treatment	Median OS (months)	2-year OS (%)	5-year OS (%)
RANDOMIZED STUDIES					
GITSG (1985)[101]	22	A) Observation	11.0	15.0	5.0
	21	B) 40.0 Gy RT + bolus 5-FU	20.0	42.0	19.0
EORTC 40891 (1999)[102]	54	A) Observation	12.6	23.0	10.0
	60	B) 40.0 Gy split-course RT + CI 5-FU	17.1	37.0	20.0
ESPAC-1 (2004)[103]	69	A) Observation	16.9	—	11.0
(2 × 2 randomization)	73	B) 40.0 Gy split-course RT + bolus 5-FU/LV	13.9	—	7.0
	72	C) 40.0 Gy split-course RT + bolus 5-FU → 5-FU/LV	19.9	—	13.0
	75	D) Bolus 5-FU/LV	21.6	—	29.0
CONKO-001 (2007)[6]	175	A) Observation	20.2	42.0	11.5
	179	B) GEM	22.1	47.5	22.5
RTOG 9704 (2008)[104]	155	A) GEM → CI 5-FU + 50.4 Gy RT → GEM	20.6	—	31 (3-year)
	173	B) 5-FU → CI 5-FU + 50.4 Gy RT → 5-FU	16.9	—	22 (3-year)
ESPAC-3 (2009)[105]	537	A) GEM	23.6	49.1	—
	551	B) Bolus 5-FU	23.0	48.1	—
EORTC 40013/FFCD 9203/GERCOR (2010)[106]	45	A) GEM	24.4	53.8	—
	45	B) GEM → GEM + 50.4 Gy RT	24.3	53.8	—
NONRANDOMIZED STUDIES					
Herman et al, Johns Hopkins (2008)[107]	271	A) Observation	14.4	31.9	15.4
	345	B) Median 50.0 Gy RT + 5-FU	21.2	43.9	20.1
Corsini et al, Mayo Clinic (2008)[108]	180	A) Observation	19.2	39.0	17.0
	274	B) Median 50.4 Gy RT + 5-FU	25.2	50.0	28.0
Hsu et al, Johns Hopkins-Mayo Clinic (2010)[109]	509	A) Observation	15.5	34.6	16.1
	583	B) Median 50.0 Gy + 5-FU	21.1	44.7	22.3

5-FU, *5-Fluorouracil;* LV, *leucovorin;* GEM, *gemcitabine;* OS, *overall survival;* RT, *radiation therapy.*

in locoregional recurrence rates, which were high among the CRT (34 of 104, 33% of patients at risk) and surgery alone (37 of 103, 36% of patients at risk) arms.

The randomized Phase III European Study Group for Pancreatic Cancer (ESPAC)-1 study evaluated the independent effects of adjuvant CTX and CRT in 541 patients with grossly resected PCA.[103] A subset of 285 patients underwent randomization (2 × 2 factorial design) to essentially three separate but concurrent trials with the following regimens: (A) observation; (B) concurrent CRT alone (20 Gy in 10 fractions over 2 weeks with 500 mg/m^2 5-FU intravenous bolus during the first 3 days of RT and then repeated after a planned 2-week break) followed by no additional CTX; (C) CTX alone (leucovorin 20 mg/m^2 bolus followed by 5-FU 425 mg/m^2 administered for 5 consecutive days repeated every 28 days for six cycles); and (D) CRT followed by six cycles of adjuvant 5-FU/leucovorin. Patients were randomized to two separate but concurrent trials testing one of the main treatment comparisons (adjuvant CTX versus none, n = 188; adjuvant concurrent CRT versus none, n = 68). Background therapy was allowed before enrollment into the latter two trials, and RT was performed according to the standard of the individual institutions in all three trials. Interestingly, adjuvant CTX was associated with superior survival, whereas adjuvant CRT resulted in inferior survival. Initial analysis demonstrated a survival advantage for adjuvant CTX only by merging data from the three separate randomized trials; median OS was 19.7 months in the 238 patients randomized to receive adjuvant CTX and 14 months in the 235 patients randomized to no adjuvant CTX (p = 0.005).[112] However, the latest analysis of the ESPAC-1 trial analyzed only the patients randomized to the 2 × 2 factorial design (no background therapy allowed). Patients randomized to receive adjuvant CTX (two of the four arms, n = 147) had a survival advantage (2-year 40% versus 30% and 5-year 21% versus 8%; p = 0.009).[103] Local recurrence was a component of relapse in 99 patients (34%). Major concerns regarding the design and execution of this trial, however, warrant attention.[113] More than one randomization scheme, optional background therapy in two of the three trials, no restaging before adjuvant therapy, heterogeneity among patient populations, and lack of quality assurance guidelines for the delivery of radiation (i.e., no section in the protocol on appropriate field design, no central audit of radiation fields) are study limitations. These results must therefore be interpreted with caution.

Newer Chemoradiation Regimens

Although 5-FU–based CRT is traditionally administered in the adjuvant setting, new systemic agents have been coupled with RT over the past decade. Many feasibility studies have shown that these regimens can be safely administered although further randomized trials are necessary to assess treatment efficacy.

Interferon-Based Chemoradiation

In 2000, the Virginia Mason Medical Center published their experience of 33 patients with resected PCA who received concurrent CRT.[114] EBRT was given to a dose of 45 Gy to 54 Gy with CI 5-FU 200 mg/m^2/day, weekly cisplatin 30 mg/m^2 IV bolus, and interferon-alpha 3 million units subcutaneously every other day. After CRT, CTX alone was administered (CI 5-FU 200 mg/m^2/day) in two 6-week courses during weeks 9 to 14 and 17 to 22. The median and 2-year OS were statistically

The conclusion of the EORTC trial was that there was no discernible benefit from adjuvant CRT, although survival trends favored adjuvant CRT for the 114 patients with PCA. Matters of concern include exclusion of patients with T3 lesions, lack of clear pathologic criteria to distinguish between pancreatic and nonpancreatic periampullary lesions, and inadequate assessment of the retroperitoneal margin. Moreover, 20% of patients assigned to the CRT arm never received treatment but were analyzed by intent-to-treat principles. Many have criticized the use of a two-sided log-rank test, and it has been suggested that if a one-sided test had been used, the survival benefit of CRT would have reached significance.[110] The lack of statistical survival advantage persisted in an update of the trial in 2007 after a median follow-up of 11.7 years.[111] Although this trial is used as evidence against CRT, it undoubtedly has several methodological flaws.

superior in the patients treated with interferon-based CRT than those treated with the GITSG regimen (24 versus 18.5 months and 84% versus 54%, $p = 0.04$). Significant grade-3 to grade-4 gastrointestinal toxicity occurred in the interferon-based group, requiring hospitalization in 35% of patients; however, the majority of patients were still able to receive more than 80% of the planned therapy. A follow-up study included 53 patients with resected PCA treated with similar interferon-based CRT.[115] The clinical efficacy of this regimen was encouraging, with median OS of 46 months and 2-year OS of 53%.

The American College of Surgeons Oncology Group (ACOSOG) conducted a multiinstitutional Phase II study further evaluating the interferon-based CRT regimen in patients with resected PCA. Patients received adjuvant RT to 50.4 Gy with 1.8-Gy fractions given concomitantly with 5-FU (175 mg/m^2 CI, days 1 to 38), cisplatin (30 mg/m^2 intravenously weekly), and interferon-alpha (3 million units subcutaneously every other day). This was followed by CI 5-FU for two cycles. The radiation fields in this study were designed to include the regions at highest risk for local recurrence (surgical margins, celiac axis, and SMA/uncinate regions). Initial results demonstrated promising 2-year and median OS (55% and 27.1 months) although the study was closed early due unexpected high acute toxicity rates (only slightly higher than that observed in the GEM arm of RTOG 9704).[116] Similar results were confirmed at Barnes Hospital and Washington University in St. Louis (2-year OS, 56%; median OS, 25 months).[117]

Gemcitabine-Based Chemoradiation

With the success of GEM alone in the adjuvant setting, researchers have explored GEM-based CRT. The optimal method of combining RT with GEM is still being studied, with investigators publishing the use of full-dose, twice-weekly low-dose, and reduced-dose weekly GEM. Researchers from the University of Michigan performed a Phase I dose escalation study with full-dose GEM (1000 mg/m^2) after curative intent surgery.[118] To give full doses of GEM with RT, treatment volumes were constrained by avoiding elective nodal areas. They found a maximal tolerated dose of 39 Gy given with 2.6-Gy fractions. Blackstock et al used twice-weekly low-dose GEM concurrent with upper abdominal RT including elective nodes to 50.4 Gy after resection.[119] This regimen was well tolerated and shows promising results in comparison with historic controls. Other series have demonstrated the feasibility of reduced-dose weekly GEM (around 300 mg/m^2) concurrent with RT in the adjuvant setting.[120]

A Phase II prospective European Intergroup study evaluated concurrent CRT versus GEM alone (EORTC-40013-22012/FFCD-9203/GERCOR).[106] Patients with PCA of the pancreatic head ($n = 90$) were randomized to either four cycles of GEM alone (1000 mg/m^2 by 30-minute infusion during 3 consecutive weeks followed by 1 week of rest) or two cycles of GEM followed by weekly GEM (300 mg/m^2) with concurrent RT (50.4 Gy in 28 fractions). Median disease-free survival (DFS) was similar (12 versus 11 months) among patients receiving CRT versus CTX alone, whereas median and 2-year OS were equivalent at 24 months and 50%, respectively. Rates of distant progression were similar between the two arms although significantly fewer first local recurrences occurred in the CRT arm (11 versus 24%, $p = 0.16$). Therefore, the investigators concluded that adjuvant GEM-based CRT is a feasible, well-tolerated regimen that should be evaluated in larger Phase III trials.

The goal of RTOG 9704 ($n = 451$) was to explore the outcomes of CTX in addition to the standard CRT arm following gross total resection (R0 resection, 66% of patients; R1, 34%).[104] There were no exclusion criterion relative to postoperative CA 19-9 levels. Patients were randomized to receive either one cycle of GEM (1000 mg/m^2 weekly for 3 weeks on/1 week off) or 5-FU (250 mg/m^2 per day for 3 weeks) before CRT. RT was delivered in a continuous fashion to a total dose of 50.4 Gy along with CI 5-FU (250 mg/m^2). Three to five weeks following CRT, additional CTX was delivered, either as 3 months of CI 5-FU (4 weeks at 250 mg/m^2 followed by 2 weeks off for 2 cycles) or 3 months of GEM (3 cycles of 1000 mg/m^2 weekly given for 3 weeks before a 1-week break). The initial report showed a nonstatistically significant trend for patients with pancreatic head tumors with adjuvant GEM as opposed to 5-FU. The updated 5-year report failed to show a survival difference between the two arms; median OS was 20.5 months versus 17.1 months and 5-year OS was 22% versus 18% in the GEM and 5-FU arms, respectively.[121] RTOG 9704 was the first trial to evaluate whether radiation field design influenced outcomes.[122] Failure to adhere to specified RT guidelines was associated with reduced survival and, for patients receiving GEM, a trend toward increased nonhematologic toxicity. In fact, nearly 50% of the RT plans deviated from protocol guidelines. There are now consensus panel guidelines to delineate the clinical target volume.[123]

RTOG, in cooperation with the Southwest Oncology Group (SWOG) and EORTC, opened the RTOG 0848 trial (NCT01013649) in 2009. This two-step randomized Phase III trial aims to 1) determine whether GEM plus erlotinib produces superior survival results to GEM alone and 2) evaluate the role of RT (50.4 Gy) added to 5-FU– or capecitabine-based CTX. The trial stratifies for known prognostic variables, includes a surgical quality assurance component as well as real-time online quality assurance to ensure RT guideline adherence and requires the enrollment of more than 900 patients over 4 years. This study is the only Phase III trial currently open that will address the role of adjuvant fractionated CRT.

Chemoradiation Using IMRT or SBRT

Acute toxicity with conformal CRT can be substantial as shown in RTOG 9704. In this study, 70.5% patients had any grade-3 or greater toxicity and 59% had grade-3 or greater nonhematologic toxicity. Yovino et al reported significantly reduced toxicity when comparing a cohort of 46 patients treated with adjuvant capecitabine-based CRT (per the RTOG 9704 schema) to a dose of 50.4 Gy with intensity-modulated radiation therapy (IMRT) compared to a cohort treated per RTOG 9704 with conventional CRT.[124] The investigators found an 8% rate of acute nonhematologic grade-3 or greater toxicity with a 21% local regional failure rate, consistent with the rates seen in the larger randomized trials discussed previously. Given the high local recurrence rate even with adjuvant CRT, IMRT allows for dose escalation which may lead to improved local control, especially in patients with R1 resections. Furthermore, Abelson et al reported an 8% rate of acute nonhematologic grade-3 or greater than toxicity in 47 patients treated with up to 56 Gy with IMRT, and, similarly, Ben-Josef et al reported a 7% rate of acute nonhematologic grade-3 or greater toxicity in 15 patients treated with up to 55 Gy with IMRT.[125,126]

IMRT also allows for the addition of more aggressive concurrent CTX (e.g., full-dose GEM) or targeted therapies such as erlotinib. A Phase I adjuvant trial of the EGFR inhibitor gefitinib with capecitabine and three-dimensional conformal radiation therapy (3D-CRT) resectable and locally unresectable PCA produced significant dose-limiting diarrhea that precluded determination of a recommended Phase II gefitinib dose.[127] Another adjuvant study included a similar targeted therapy (erlotinib) with capecitabine-based IMRT. The fact that 83% these patients were able to complete CRT with erlotinib suggests that IMRT may have reduced toxicity; however,

no definitive conclusions can be drawn in this single-arm study. Rates of severe (grade-3 to grade-4) toxicity observed in this study were similar to those reported for other adjuvant therapies (see Table 48-1) and suggest that erlotinib can be safely combined with CRT and CTX in the adjuvant setting. The large magnitude of improvement in toxicity strongly argues for further prospective investigation of IMRT.

SBRT has typically been used in the treatment of unresectable PCA and high rates of tumor control have been reported.[128-130] In the adjuvant setting, SBRT theoretically would have the greatest advantage in the treatment of patients with close or positive margins, where increased dose to the tumor bed may improve outcomes. A limited series examining SBRT to 24 Gy to 30 Gy (over one to three fractions) in 24 patients that had undergone resection with close or positive surgical margins reported a 1-year local control rate of 66%.[131] Ongoing studies are evaluating the potential efficacy of adjuvant SBRT with more aggressive CTX and immunotherapy.

Adjuvant Chemotherapy

Following the ESPAC-1 trial,[103] European studies have focused on CTX regimens in the adjuvant setting. The Charité Onkologie (CONKO)-001 trial enrolled patients with PCA who had undergone curative-intent resection, excluding patients with a postoperative CA 19-9 value ≥2.5 times the upper limit of normal. Patients were randomized to six cycles of GEM (1000 mg/m^2 weekly, 3 of every 4 weeks) versus observation. At first publication, the use of GEM significantly improved DFS from 6.9 to 13.9 months ($p < 0.001$), and there was a trend toward an improvement in OS.[6] An update with longer follow-up showed that patients in the GEM arm had a significant improvement in median OS (22.8 versus 20.2 months, $p = 0.005$), as well as improvements in 5-year OS (21.0% versus 9.0%).[132] The significance of these results has established GEM as an important component of adjuvant therapy for PCA.

Subsequently, the ESPAC-3 trial evaluated the survival benefit of bolus 5-FU versus GEM in the adjuvant setting.[105] This trial randomized patients with R0 or R1 resections (n = 1088) to either 5-FU/leucovorin or GEM for 6 months. There was no difference in median survival between the 5-FU/leucovorin (23.0 months) and GEM groups (23.6 months; p = 0.39). Furthermore, there was no significant difference in the effect of treatment across subgroups according to extent of resection (R0 or R1), progression-free survival (PFS), or global quality of life (QOL) scores. Of note, increased high-grade treatment-related toxicity was associated with the bolus 5-FU arm (14% versus 7.5%, p = 0.001). Therefore, GEM was concluded to be the preferred chemotherapeutic agent over bolus 5-FU.

Because of the conflicting results of GEM CTX in the adjuvant setting, further investigation is necessary. The ESPAC-4 trial (ISRCTN96397434) is currently open to enrollment and aims to compare the survival of patients receiving adjuvant GEM versus capecitabine.

Novel Combination Chemotherapy

Treatment regimens with demonstrated survival benefit in advanced and metastatic PCA are now also being tested as adjuvant therapy. These regimens include 5-FU, leucovorin, irinotecan, and oxaliplatin (FOLFIRINOX) as well as gemcitabine/nab-paxitaxel (GEM/NP).[132a]

Vaccination and Immunotherapy Strategies in the Adjuvant Setting

An improved understanding of the complex signaling pathways associated with PCA has contributed to the design of a novel approach to adjuvant therapy with vaccine immunotherapy. Immune-based strategies use tumor-specific antigens and regulators of the antitumor immune response in an effort to destroy malignant cells and prevent progression of disease. To date, peptide, recombinant microorganism, and whole cell vaccines along with anticytotoxic T-lymphocyte antigen 4 blockade and anti-CD40 strategies have been explored.[133]

Multiple studies have investigated the use of vaccines targeting tumor-specific *ras* mutation.[134-136] Other studies are attempting to target the catalytic subunit of telomerase (hTERT), which is expressed in 85% to 90% of PCAs and is an attractive target. A GV1001 peptide vaccine is in use to induce telomerase-specific CD4+ and CD8+ T-cell responses.[137,138] The genetically modified allogeneic whole cell vaccine (GVAX) has also been developed as a promising granulocyte-macrophage colony-stimulating factor (GM-CSF)–based immunotherapy.[139,140] Moreover, a unique technique has been introduced involving a "hyperacute" rejection as used in transplant immunotherapy. This irradiated whole cell vaccine induces complement-mediated cell lysis and activation or recruitment of antigen-presenting cells following acute rejection and immune response.[141] Integration of standard CRT or SBRT in the adjuvant or neoadjuvant setting may enhance immunotherapy.[142] A study at JHH is currently evaluating a combination of adjuvant GVAX vaccine, SBRT, and FOLFIRINOX.[132a]

Present Status of Adjuvant Therapy

Although surgery alone is no longer an appropriate option for patients with PCA, even after R0 resection, the role of adjuvant therapy needs to be more clearly defined. The most convincing level I data currently available are from the CONKO-001 trial, which has clearly established a role for GEM as an effective adjuvant treatment. However, every Phase III trial exploring adjuvant RT to date is subject to serious criticism (e.g., GITSG, EORTC, ESPAC-1) or has not directly addressed the efficacy of adjuvant RT (e.g., RTOG 9704). Current practice and guidelines reflect this unresolved controversy. A consensus has not been reached on the role, timing, dose, or technique of RT, nor has the optimal CTX regimen been established. The NCCN guidelines for adjuvant management of PCA include CTX (GEM, capecitabine, 5-FU) or CTX followed by CRT, although participation in a clinical trial is highly recommended. Future studies will continue to evaluate novel CTX regimens (S-1), targeted agents, and immunotherapy as well as advances in surgery (laparoscopic) and radiotherapy (IMRT/SBRT). There is a clear need for blood and tumor biomarkers to guide personalized management in this patient population.

Neoadjuvant Therapy

There are many unique advantages to the use of neoadjuvant (NAdj) treatment of patients with localized PCA. Most compelling is the ability to treat virtually all patients that present with localized, resectable PCA with therapy that immediately addresses the limitations of curability—micrometastatic disease that is often already present in regional lymph nodes, liver, lung, or peritoneum. A second important advantage is improved patient selection for pancreatic surgery, which is often associated with significant patient morbidity even when performed by an experienced surgical team. Allowing tumors with aggressive biology to declare themselves can spare patients from nontherapeutic surgery. Third, up to half of patients may not be good candidates for adjuvant therapy because of delayed recovery from surgery. The use of NAdj therapy allows nearly all patients to receive some adjuvant therapy. Finally, pancreatectomy appears to be safer following NAdj CRT (with a reduced risk of pancreatic anastomotic leak resulting from the pancreatic fibrosis induced by preoperative therapy) and, based on BRPC data, the R0 and node-negative resection rate is likely to be improved with NAdj therapy.[143]

Numerous small and mostly nonrandomized studies have considered both NAdj CTX and CRT options; however, because of the lack of large randomized trials, NAdj therapy remains controversial.

Neoadjuvant Therapy in Resectable Disease

One of the earliest studies on NAdj therapy in PCA reported on 54 consecutive patients with seemingly resectable disease.[144] Some patients ($n = 31$) went directly to surgery whereas others ($n = 23$) received 50 Gy EBRT to the region of the pancreatic head. No difference in resectability, 3-year OS, or 5-year OS was observed. However, a slight advantage was seen in 1-year OS of the patients treated with NAdj EBRT. Furthermore, there was a decreased incidence of regional relapse among patients who received NAdj therapy. A NAdj GEM-based CRT regimen was also tested in 20 patients with potentially resectable PCA.[145] These patients received three cycles of full-dose (1000 mg/m^2) GEM with concurrent RT (36 Gy in 2.4-Gy fractions) given during the second cycle. Overall, 80% of patients had stable disease, 15% had partial response, and 5% had progressive disease. Seventeen (85%) patients underwent curative resection with a 94% rate of R0 resection and 65% had a node-negative resection. At median follow-up of 18 months, preliminary survival data were promising in resected patients (median OS 26 months, 2-year OS 61%), with 41% of the patients alive with no evidence of disease.

M. D. Anderson Cancer Center (MDACC) enrolled a total of 176 patients on two GEM-based CRT trials for potentially resectable PCA.[146,147] In these trials, the most common reason precluding resection following CRT was metastatic disease. Only 1 out of 176 patients had isolated local progression following surgical resection. Median OS in all (22.7 and 17.4 months) and resected patients (34 and 31 months), were promising and better than historical controls.

A multicenter Phase II trial provided additional data on the use of full-dose GEM (three cycles of 1000 mg/m^2) and 36 Gy RT (2.4 Gy × 15 fractions) in resectable PCA ($n = 13$).[148] The results were promising, with a 94% 1-year survival rate following resection.

More recently, a retrospective review revealed that resectable patients receiving NAdj GEM and S-1 combination therapy had significantly longer median OS (39.4 versus 20.8 months, $p = 0.0009$) and higher R0, "true" R0 (R0 with tumor marker normalization after resection), and N0 rates (85%, 69%, 44% versus 72%, 48%, 24%, respectively) than patients who underwent surgery without prior therapy.[149]

Further evaluation of NAdj GEM-based CRT in resectable PCA was performed in a multiinstitutional Phase II trial.[150] Patients received two cycles of GEM (1000 mg/m^2) and oxaliplatin (85 mg/m^2) concurrently with 30 Gy (2 Gy × 15 fractions) of RT delivered during the first cycle of CTX. Following treatment, patients were evaluated for surgery. Patients who underwent surgery received two additional cycles of adjuvant CTX. For patients who presented with resectable disease ($n = 13$), median survival was 44.7 months in comparison with 26.5 months for patients who did not undergo resection.

Rare Tumors

Optimal treatment of rare tumors of the pancreas (e.g., adenosquamous carcinoma, PanNET, acinar cell carcinoma, pancreatoblastoma, IPMN, solid-pseudopapillary neoplasm) is unclear because of the infrequent presentation of these tumors and limited clinical research available. Little is known about the underlying genetic mechanisms of these rare tumors and further insight into therapeutic strategies is necessary. Current treatment options demonstrated to be effective based mainly on retrospective reports can be found in eTable 48-2.

LOCALLY ADVANCED DISEASE AND PALLIATION

For the purpose of this chapter, the term *locally advanced disease* is intended to include both BRPC and LUPC. The nuances of differentiating BRPC from LUPC and sequencing of treatment will be discussed.

Borderline Resectable Disease

Patients with BRPC have tumors that can technically be resected; however, there is an increased risk of margin-positive resection due to extensive vessel involvement. Because a margin-positive resection is associated with poor survival, NAdj therapy is typically recommended. The most widely recognized definition of BRPC can be found in the NCCN guidelines: having tumor abutment of the SMA involving 180 degrees or less of the arterial circumference, but without distant metastases or tumor extension to the celiac axis. However, other groups such as the MDACC Group[159] and the Americas Hepato-Pancreato-Biliary Association (AHPBA)/Society of Surgical Oncology (SSO)/Society for Surgery of the Alimentary Tract (SSAT)[82] have introduced other anatomic criteria. In an attempt to standardize the definition and treatment for BRPC, Katz et al proposed the first prospective clinical trial with the Alliance for Clinical Trials in Oncology (ACTO) group (Alliance Trial A021101). See eTable 48-3 for a comparison of BRPC definitions.[83]

Nearly 10% of all patients with PCA present with borderline resectable tumors.[83] Because BRPC is one of the most challenging stages of PCA, multidisciplinary review at baseline and subsequent imaging is highly recommended. Collaboration among multiple specialties will allow for more accurate staging to ensure optimal initiation of therapy and coordination of care. Patients with BRPC who undergo upfront surgery have a higher risk for an R1/R2 resection, local recurrence, and distant metastases because they often require a larger, more complex, and high-risk operation to remove their primary tumor.[159] Therefore, upfront CTX followed by CRT is considered a standard approach. In fact, some series suggest that patients with BRPC receiving multimodality therapy (CRT and CTX) before surgical resection can expect equally favorable survival as patients who present with resectable tumors in some series.[160] Numerous studies using NAdj CRT have demonstrated the benefit of NAdj therapy in BRPC (Table 48-2). Despite the common perception that tumors can be downstaged from borderline to resectable disease, there is little evidence that the radiographic stage of BRPC changes after NAdj CTX or RT. However, NAdj CRT is an effective way to sterilize the interface of the tumor and vascular structure. Furthermore, prospective evaluation from 1999 to 2006 demonstrated that patients with BRPC who received NAdj therapy before pancreatic resection had significantly better survival than those who did not undergo pancreatectomy.[159] Patients with BRPC who require vein resections have been suggested to benefit from adjuvant treatment.[161]

Takahashi et al reported their experience with NAdj GEM-based CRT for resectable and BRPC.[168] Of a total of 268 patients, 188 had resectable primary tumors and 80 had borderline resectable tumors. Unsurprisingly, the resection rate of patients with resectable disease was higher than that of patients with BRPC (87% versus 54%, $p < 0.001$) but a high rate of R0 resections was achieved in both groups. The 5-year OS rates of resectable and BRPC cases were 57% and 34%, respectively ($p = 0.029$). Although the 5-year cumulative incidence of local recurrence was comparable in both groups (15% and 13%, respectively; $p = 0.508$), the 5-year cumulative incidence of

eTABLE 48-2 Treatment Recommendations for Rare Tumors of the Pancreas

Rare Tumor	Recommended Course of Therapy*
SOLID TUMORS	
Adenosquamous carcinoma	*Adjuvant*: CRT recommended, the addition of platinum agents (cisplatin or oxaliplatin) to GEM appears to improve outcomes[151,152]
Neuroendocrine tumor (PanNET)	*Adjuvant:* CRT in patients with residual disease or adverse pathologic features (large tumor, node-positive disease) *Definitive:* CTX and targeted agents (e.g., sutinib and everolimus appear to improve PFS) *Metastatic*: liver-directed therapies (e.g., surgical resection, SBRT, transarterial chemoembolization, radioembolization)[153]
Acinar cell carcinoma	*Adjuvant/Definitive*: the role of RT is unclear[154,155]
Pancreatoblastoma	*Adjuvant*: the role of adjuvant therapy is unknown *Definitive/Metastatic*: there are case reports describing palliative benefit of RT[155]
CYSTIC NEOPLASMS	
IPMN with invasive component	*Adjuvant*: CRT appears to be beneficial in patients with high-risk features (tubular versus colloid, node-positive disease)[156-158]
Solid-pseudopapillary (Hamoudi) tumor	*Adjuvant/Definitive*: the role of RT is unclear

IPMN, *Intraductal papillary mucinous neoplasm;* CRT, *chemoradiation;* CTX, *chemotherapy;* GEM, *gemcitabine;* PFS, *progression-free survival;* SBRT, *stereotactic body radiation therapy.*
**Recommendations are limited primarily to retrospective studies and case series.*

eTABLE 48-3 Comparison of Radiographic Definitions of Borderline Resectable Pancreatic Cancer

	AHPBA/SSAT/SSO[212]	M. D. Anderson[159]	NCCN Version 1.2014*	Intergroup Trial (Alliance A021101)[83]
Superior mesenteric vein-portal vein (SMV-PV)	Abutment,† encasement,‡ or occlusion	Occlusion	Abutment† with distortion or narrowing, or reconstructable§ occlusion	Encasement‡ or reconstructable§ occlusion
Superior mesenteric artery (SMA)	Abutment†	Abutment†	Abutment†	Abutment†
Common hepatic artery (CHA)	Abutment† or short-segment encasement‡	Abutment† or short-segment encasement‡	Abutment† or short-segment encasement‡	Reconstructable§ encasement‡
Celiac trunk	No abutment† or encasement‡	Abutment†	No abutment† or encasement‡	Abutment†

AHPBA, *Americas Hepatopancreaticobiliary Association;* CHA, *common hepatic artery;* NCCN, *National Comprehensive Cancer Network;* PV, *portal vein;* SMA, *superior mesenteric artery;* SMV, *superior mesenteric vein;* SSAT, *Society for Surgery of the Alimentary Tract;* SSO, *Society of Surgical Oncology.*
**The most recently published NCCN clinical practice guidelines endorse the use of stricter criteria (Intergroup Trial) of borderline resectable tumors in clinical trials.*
†*Defined as tumor-vessel interface less than 180 degrees of vascular circumference.*
‡*Defined as tumor-vessel interface greater than or equal to 180 degrees of vascular circumference.*
§*Defined as suitable for safe resection and reconstruction of the normal vein or artery proximal and distal to the site of suggested tumor-vessel involvement.*

TABLE 48-2 Neoadjuvant Therapy in Borderline Resectable Pancreatic Cancer

Study	*n*	Treatment	Resection	R0 Resection	Median OS (mo.) Unresected BRPC	Median OS (mo.) Resected BRPC
RETROSPECTIVE DATA						
Katz (2012)[162]	129	(1) GEM, 5-FU, or CAP + EBRT; (2) GEM → GEM, 5-FU, or CAP + EBRT	85 (66%)	81 (95%)	12.0 mo	33.0 mo
Chuong (2013)[163]	57	GTX → SBRT	32 (56%)	31 (97%)	16.4 mo	19.3 mo
Dholakia (2013)[164]	50	(1) GEM, FOLFIRINOX, or FOLFOX → GEM, CAP, or GEMOX + RT; (2) GEM, CAP, or GEMOX + RT§	29 (58%)	27 (93%)	13.0 mo	22.9 mo
PROSPECTIVE DATA						
Katz (2008)[159]	84	GEM, CAP, 5-FU, or paclitaxel + EBRT*	32 (38%)	31 (97%)	15 mo	40 mo
Stokes (2011)[165]	34	CAP + EBRT; adjuvant GEM (88%)	16 (46%)	12 (75%)	12.0 mo	23.0 mo
Lee (2012)[166]	18	GEM + CAP	11 (61%)	9 (82%)	—	17.0 mo
Kim (2013)[150]	39	GEMOX + EBRT; adjuvant GEMOX (63%)	24 (62%)	84%‡	18.4 mo	25.4 mo
Motoi (2013)[167]	16	GEM + S-1; adjuvant GEM	86%‡	87%‡	10.0 mo‡	35.0 mo‡
Takahashi (2013)[168]	80	GEM + EBRT	43 (54%)	42 (98%)	14.0 mo	25.0 mo†

5-FU, *5-Fluorouracil;* BRPC, *borderline resectable pancreatic cancer;* CAP, *capecitabine;* EBRT, *external beam radiation therapy;* FOLFIRINOX, *5-fluorouracil, leucovorin, irinotecan, and oxaliplatin;* FOLFOX, *5-fluorouracil, leucovorin, and oxaliplatin;* GEM, *gemcitabine;* GEMOX, *gemcitabine and oxaliplatin;* GTX, *gemcitabine, docetaxel, and capecitabine;* OS, *overall survival;* SBRT, *stereotactic body radiation.*

**The most common sequence was 2 to 4 months of chemotherapy followed by chemoradiation.*

†*Estimated from graphs.*

‡*Includes resectable and borderline resectable patients.*

§*Radiation consisted of three-dimensional conformal radiation, intensity-modulated radiation, or volumetric arc therapy.*

peritoneal and distant relapse was significantly higher in the patients with BRPC (43% and 76%) than in the patients with resectable disease (17% and 43%).

Recent data suggests that dose-escalation using SBRT or IMRT with CTX may be an effective NAdj regimen for patients with BRPC. A single-institution retrospective study ($n = 32$) of induction CTX followed by SBRT in BRPC revealed excellent rates of R0 resection (97%) and local control at 1 year (81%) among a group of a patients without arterial involvement.[163] IMRT has been used to safely deliver higher doses of RT to the tumor while limiting the dose to adjacent normal tissue.[169,170] Although the studies of this approach were small ($n = 14$ and 34, respectively), IMRT for NAdj CRT delivery has shown promise in decreasing tumor volume[171] and increasing pathologic complete response rates.[165]

Gemcitabine-based CRT has historically been the first-line of treatment for BRPC. However, the use of more aggressive CTX regimens such as FOLFIRINOX[172] or GEM/NP with CRT may result in better systemic and local control among patients with BRPC. A recent study demonstrated that 55% ($n = 12$) of patients initially presenting with BRPC underwent successful R0 resection following FOLFIRINOX, with or without SBRT.[173] A multiinstitutional, single-arm, pilot Alliance Trial A021101 has been initiated to evaluate the efficacy and toxicity of NAdj FOLFIRNOX followed by capecitabine and EBRT for patients with BRPC.[83] Rigorous standards of clinical trial design are incorporated into this trial, such as centralized review of the radiation plan and mandatory imaging review before enrollment. Because a radiographic response is rarely seen after NAdj therapy, attempted resection is required for all patients with a good PS (ECOG 0-1, KPS 70-100) in the absence of radiographic evidence of cancer progression.

Serum CA 19-9 levels following NAdj therapy for patients with BRPC may be a prognostic factor for survival. In 84 patients with BRPC who underwent resection following NAdj CRT (GEM or 5-FU–based with or without GEM-based induction CTX), a decrease in CA 19-9 levels during NAdj therapy had a positive predictive value of 70% for successful resection, while an 88% negative predictive value for unresectability was achieved when CA 19-9 failed to decrease.[174] Posttreatment CA 19-9 levels were a better predictor of metastases than pretreatment levels. Moreover, normalization of CA 19-9 during NAdj therapy was associated with longer OS both in patients who were resected and unresected.

Locally Unresectable Disease

LUPC involves a tumor that has grown beyond the pancreas to involve >180 degrees of the SMA or celiac axis or where tumor involvement precludes reconstruction of the SMV or PV. For patients who receive treatment, median OS is between 8 and 12 months. Survival benefits are typically limited to patients with adequate PS (ECOG 0-2) who receive CTX or CRT. Palliative care and comfort-directed measures are recommended for patients with poor PS (ECOG 3-4). The timing and optimal regimen of therapy in patients with LUPC remain unclear. Options include CRT followed by CTX, CTX followed by CRT, or single- or multi-agent CTX alone.

Chemoradiation or Chemotherapy

The role of CRT in patients with LUPC has been established for decades. However, the benefit of CRT versus CTX has recently become controversial. The NCCN guidelines currently recommend the use of an initial course of CTX (two to six cycles) followed by CRT for patients with LUPC with stable disease or with an objective response to initial CTX.[81,175] This approach aims to control systemic disease while allowing identification of patients with occult metastatic disease who are not likely to benefit from CRT. However, immediate CRT is sometimes recommended for patients with pain or locally obstructive symptoms.

Results of some Phase III trials have favored the use of CRT for the treatment of this patient population[176-178] while others have yielded conflicting results (Table 48-3).[179,180] A GITSG trial found improved median OS ($p < 0.01$) with 5-FU–based split-course CRT (40 Gy over 6 weeks, median OS 8.3 months;

TABLE 48-3 Chemotherapy versus Chemoradiation in Locally Unresectable Pancreatic Cancer

Trial	Treatment	*n*	Median survival	Overall survival	Median TTP
GITSG (1981)[176]	40.0 Gy RT* + bolus 5-FU (500 mg/m² on d 1-3 of each 20 Gy course of RT)	83	8.3 mo	40% (1 year)	6 mo
	60.0 Gy RT* + bolus 5-FU (500 mg/m² on d 1-3 of each 20 Gy course of RT)†	86	11.3 mo	40% (1 year)	8 mo
	60.0 Gy RT*	25	6.0 mo	10% (1 year)	3 mo
ECOG (1985)[179]	40.0 Gy RT* + 5-FU (600 mg/m² IV bolus on d 1-3 of each course of RT and weekly after RT)	34	8.3 mo	28% (1 year)	4.4 mo
	5-FU (600 mg/m²/wk)	37	8.0 mo	28% (1 year)	4.2 mo
GITSG (1988)[177]	54 Gy RT* + bolus 5-FU (350 mg/m² on d 1-3 of each course of RT) → SMF for 2 years (starting on d 64) until progression	24	10.5 mo	41% (1 year)	Not stated
	SMF for 2 years or until progression	24	8.0 mo	19% (1 year)	
GERCOR (2007)[175]	(A) 55.0 Gy RT with 10 Gy boost in last 2 wks, plus either FOLFUGEM or GEMOX‡	72	15.0 mo	65.3 % (1 year)	10.8 mo
	(B) FOLFUGEM or GEMOX‡	56	11.7 mo	47.5% (1 year)	7.4 mo
FFCD/SFRO (2008)[181]	60.0 Gy RT + 5-FU (300 mg/m²/d, d 1-5 × 6) + CIS (20 mg/m²/d, d 1-5, wk 1 & 5)	59	8.6 mo	32% (1 year)	6 mo
	GEM (1000 mg/m²/wk × 7)	60	13.0 mo	53% (1 year)	7 mo
ECOG 4201 (2011)[178]	50.4 Gy RT + GEM (600 mg/m²/wk × 6 → 4 wks rest → 1,000 mg/m²/wk × 3 of 4 wks for 5 cycles)	34	11.1 mo	50% (1 year)	6.0 mo§
	GEM (1,000 mg/m²/wk × 6 of 7 wks) → GEM (1,000 mg/m²/wk × 3 of 4 wks for 5 cycles)	37	9.2 mo	32% (1 year)	6.7 mo§
SCALOP (2013)[182]	(A) 50.4 Gy RT + GEM (300 mg/m²/wk)	35	13.4 mo	64.2% (1 year)	10.4 mo
	(B) 50.4 Gy RT + CAP (830 mg/m² ×2 daily with RT)	35	15.2 mo	79.2% (1 year)	12.0 mo
LAP-07 (2013)[183]	54.0 Gy RT + CAP (1,600 mg/m²)	133	15.3 mo	Not stated	12.5 mo
	GEM (1000 mg/m²/wk × 3 or GEM 1000 mg/m²/wk ×3) + CAP (1600 mg/m² for 2 cycles)	136	16.5 mo		11.8 mo

5-FU, *5-Fluorouracil;* CAP, *capecitabine;* CIS, *cisplatin;* d, *day;* GEM, *gemcitabine;* mo, *months;* SMF, *steptozocin + mitomycin + 5-fluorouracil;* RT, *radiation therapy;* wk, *week.*

**2-week break between each 20-Gy course.*

†*Maintenance 5-FU every 4 wks for 2 yrs after completion of RT + CT.*

‡FOLFUGEM, *Leucovorin 400 mg/m² in a 2-hour fusion, 5-FU 400 mg/m² bolus and 3 g/m² continuous infusion over 46 hours, and gemcitabine 1 g/m² on day 3 as a 30-minute infusion after 5-FU; repeated every 2 weeks for 4 cycles;* GEMOX, *gemcitabine 1,000 mg/m² as a 10-mg/m²/min infusion on day 1 and oxaliplatin 100 mg/m² as a 2-hour infusion on day 2 every 2 weeks.*

§*Note: 21% and 46% of patients in arms A and B, respectively, did not have scans performed at adequate intervals to appropriately assess response duration.*

60 Gy over 10 weeks, 11.3 months) versus EBRT alone (60 Gy over 10 weeks; 5.5 months). A subsequent GITSG trial found that combination chemotherapy with streptozocin, mitomycin E, 5-FU (SMF) was inferior to 5-FU–based CRT (54 Gy, nonsplit-course) followed by SMF (median OS 8 months versus 10.5 months, $p < 0.02$). ECOG 4201 randomized patients with LUPC ($n = 74$) to either GEM alone or GEM-based CRT followed by GEM.[178] Although the study was closed early because of poor accrual, the OS was 11.1 months in the CRT arm as opposed to 9.2 months for those who received GEM alone ($p = 0.017$).

The Francophone de Cancérologie Digestive-Société Francophone de Radiothérapie Oncologique (FFCD-SFRO) trial evaluated patients with LUPC who were randomized to GEM alone or an intensive induction regimen of CRT with 5-FU plus cisplatin followed by GEM.[181] The safety of the CRT regimen had not been evaluated in Phase I or II trials before this study, and large fields treating a large volume of the duodenum to a dose of 60 Gy were used. Therefore, patients receiving CRT experienced high rates of toxicity. GEM alone was associated with increased 1-year OS in comparison with CRT (53% versus 32%, $p = 0.006$). The observed differences in survival were possibly attributable to the toxicity of the CRT regimen.

Preliminary results of the international Phase III Groupe Coopérateur Multidisciplinaire en Oncologie (GERCOR) LAP 07 trial revealed no clear survival benefit with the addition of conventional CRT following four cycles of NAdj CTX.[183] Using a 2 × 2 randomization, patients initially received GEM with or without erlotinib for four months and were subsequently randomized to two additional months of CTX or capecitabine with 54 Gy RT. Nearly 40% of patients progressed before the second random assignment. There was no difference in OS between the CTX and CRT groups (16.5 versus 15.3 months, $p = 0.083$) after a median follow-up of 36 months. Of note, there were several deviations in the delivery of RT, at least 20% of patients in the CTX alone arm received CRT off-study, and a subset of patients randomly assigned to receive CRT did not receive treatment.

In the GERCOR Phase II and III trials, patients with LUPC were given upfront CTX with the option of receiving CI 5-FU–based CRT if no progression occurred. Retrospective analysis demonstrated that the OS of patients receiving CRT was superior (15.0 months versus 11.7 months) to that in patients receiving CTX only.[175]

Multiple studies have also assessed the efficacy of the upfront CRT approach in LUPC. In an Italian study, 28 patients with nonmetastatic PCA received RT (39.6 Gy) plus 5-FU (CI, days 1-4 at 1000 mg/m²/day).[185] After 4 weeks, patients were evaluated for surgical resection. In patients who were resected ($n = 9$), a dose of 10-Gy IOERT was selectively given before reconstruction. Three of 19 patients with unresectable tumors had tumor downstaging (15.8%). Two patients showed partial

response (7.1%) and 4 (14.3%) had minimal tumor response. Median OS was 20.5 months in resected patients. Only one local failure was recorded in 8 patients with an R0 resection. This study suggests that select patients with LUPC may benefit from attempted resection/IOERT after upfront CRT.[185] A Phase II trial ($n = 69$) explored the role of GEM and oxaliplatin followed by CRT (50.4 Gy with capecitabine) in LUPC.[62] Survival rates were encouraging, with a median OS of 19.2 months and 1-year, 2-year, and 4-year OS rates of 66%, 25%, and 11%, respectively. Moreover, *SMAD4* expression in cytology specimens correlated with a local pattern of disease progression ($p = 0.016$).

GEM has been combined with cisplatin and RT in published Phase I trials, following up on promising preclinical data suggesting synergy among these agents. A study based at the Mayo Clinic administered twice-weekly GEM and cisplatin for 3 weeks during EBRT (50.4 Gy in 28 fractions). Dose-limiting toxicities consisted of grade-4 nausea and vomiting. The recommended Phase II dose was GEM 30 mg/m^2 and cisplatin 10 mg/m^2.[186] In this trial, 10 of 30 patients with LUPC underwent curative surgery with promising R0 resection and complete response rates.[184]

Because the ESPAC-3 and RTOG 9704 studies showed no difference in OS or DFS in patients treated with GEM or 5-FU in the adjuvant setting, it is unclear which drug to use concurrently with RT in the definitive setting for patients with LUPC. The MDACC retrospectively examined its database of 114 patients with LUPC treated with combination EBRT (rapid-fractionation 30 Gy in 10 fractions) with either concurrent CI 5-FU 200 mg/m^2 to 300 mg/m^2 (61 patients) or GEM 250 to 500 mg/m^2 weekly for 7 weeks (53 patients).[187] Patients receiving GEM had significantly higher incidences of severe acute toxicity, defined as toxicity requiring a hospital stay of more than 5 days, mucosal ulceration with bleeding, more than three dose deletions of GEM, or toxicity resulting in surgical intervention or death compared with those patients receiving 5-FU (23% versus 2%, $p < 0.0001$). Five of 53 patients treated with GEM-based CRT subsequently underwent surgical resection compared with 1 of 61 patients treated with 5-FU–based CRT. However, with short median follow-up, median OS was similar (11 versus 9 months, $p = 0.19$). The recent randomized Phase II SCALOP trial ($n = 70$) evaluated GEM-based compared with capecitabine-based CRT in LUPC. When compared to GEM, the addition of capecitabine was associated with improved 1-year OS, PFS, and less toxicity.[182] However, the results of this trial should be interpreted with caution because of inconsistent treatment planning and dosing techniques.[188] Additional investigation of these agents and their optimal dosages and treatment sequences is necessary.

Alternate Chemotherapy Regimens

As mentioned in the prior adjuvant section, there has been considerable interest in identifying more effective CTX regimens. Agents that have been tested in the metastatic or locally unresectable setting include 5-FU, cisplatin, oxaliplatin, irinotecan, exatecan, and capecitabine. Unfortunately, these trials have not shown survival advantages, with the exception of the combination of GEM/erlotinib or GEM/NP.

GEM and erlotinib was tested in advanced PCA by Moore et al in a large randomized Phase III trial of 569 patients, of whom about one fourth (24%) had LUPC.[189] Subgroup analysis did not suggest a greater effect in patients with LUPC. With the use of an intent-to-treat analysis, survival was improved with the addition of erlotinib, with a hazard ratio of 0.82 (6.24 versus 5.91 months; $p = 0.038$). PFS and 1-year OS were also significantly improved with the addition of erlotinib. However, the recently reported results of the Phase III LAP 07 trial revealed that erlotinib demonstrated no clear benefit in LUPC.[183] Median OS was 13.6 and 11.9 months for GEM and GEM + erlotinib, respectively (HR 1.19, 95% CI [0.97, 1.45], $p = 0.0930$), with increased grade-3 to -4 toxicity associated with the addition of erlotinib.

Since the Metastatic Pancreatic Adenocarcinoma Clinical Trial (MPACT) trial demonstrated that combination CTX with GEM and NP in PCA is superior to GEM alone for metastatic PCA,[190] its potential role in LUPC should be evaluated. In that regard, a single-center retrospective experience reported a promising 1-year OS of 77% and a 38% conversion of patients from locally unresectable to resectable disease with GEM/NP.[191] Additional studies are under way to evaluate the effect of adding NP to the standard GEM regimen in LUPC.

FOLFIRINOX is another promising regimen for LUPC. A retrospective experience at the Massachusetts General Hospital Cancer Center (MGHCC) demonstrated successful conversion of >20% of initially unresectable patients to surgical candidates using FOLFIRINOX and concurrent CRT, with a median PFS of 11.7 months.[192] Overall, 5 of 22 (23%) resections achieved R0 status although 3 of 5 (60%) patients experienced distant relapse within 5 months.

Alternate Radiation and Chemoradiation Approaches

The chemoradiation studies previously discussed involved standard EBRT. Typical EBRT doses are 45 Gy to 54 Gy in 1.8-Gy to 2.0-Gy fractions for 5-FU–based or low dose GEM-based therapy and 36 Gy in 2.4-Gy fractions for full-dose GEM-based therapy. With recent developments establishing local progression as a contributor to mortality in LUPC, modern studies are focusing efforts toward identifying ways to intensify radiation dose. Alternative RT techniques used to escalate radiation dose such as IMRT, SBRT, and intraoperative radiation therapy (IORT) have been explored in the context of LUPC.

Intensity-Modulated Radiation Therapy and Stereotactic Body Radiation Therapy

In comparison with 3D-CRT, IMRT has demonstrated an ability to significantly increase target volume dose while substantially decreasing the dose to local organs at risk (OARs).[193] Ben-Josef et al demonstrated the use of 55 Gy of IMRT in 1.8-Gy fractions in 50 patients with LUPC.[169] Median and 2-year OS were 14.8 months and 30%, respectively. Furthermore, 12 patients (24%) underwent resection (10 R0, 2 R1) and survived a median of 32 months. Unfortunately, the 2-year freedom from local progression remained at 59%. In an attempt to determine the maximum tolerated dose using IMRT and concurrent full-dose GEM, this study suggests that IMRT can be used to effectively escalate the dose of RT above 55 Gy as long as normal tissue dose constraints are met. However, optimal results will not be observed with IMRT until improved systemic control can be achieved.

SBRT is similar to IMRT in that it uses multiple fields of RT to conformally treat the planning target volume (PTV). However, SBRT is typically delivered in 1 to 5 fractions (versus 25 to 28 fractions) and smaller margins are used around the tumor (2 mm to 5 mm) to limit dose to normal tissues. CTX is generally given before and after SBRT instead of concurrently. Early data on 45 Gy SBRT in 15-Gy fractions reported poor outcomes and unacceptable toxicity.[194] Single-fraction SBRT (25 Gy × 1 dose) demonstrated disease stability but with high rates of duodenal toxicity.[195,196] Compared to conventional CRT, delivery of fractionated SBRT (3 to 5 fractions) demonstrates favorable tumor response rates (~30%) and less acute toxicity.[129,197,198] Most recently, a prospective multicenter Phase II trial evaluating 33 Gy SBRT in 6.6-Gy fractions in patients with LUPC reported more acceptable acute and late toxicity rates than single-fraction SBRT.[199] Median OS was 13.9 months,

A trial conducted by Brunner et al used strictly time-scheduled GEM (dosing on days 2, 5, 26, and 33 after a weekly regimen was too toxic) and cisplatin (days 1 to 5 and 29 to 33) combined with RT, with a recommended Phase II dose of 20 mg/m^2 for cisplatin and 300 mg/m^2 for GEM.[184]

with low rates of grade 2 or greater acute (2%) and late (11%) GI toxicity and stable QOL scores. Additional studies are necessary to evaluate the optimal dose of fractionated SBRT and determine how to best integrate SBRT into NAdj treatment paradigms for BRPC and LUPC.

Intraoperative Irradiation

IORT is another method of RT dose escalation to the operative bed when combined with EBRT/CRT. Initial trials on electron-based IORT (IOERT) combined with EBRT/CRT for patients with LUPC demonstrated improved local control rates in series from Mayo Clinic Rochester and Thomas Jefferson University Hospital (TJUH) (eTable 48-4).[200-206] This did not, however, translate into improvement in median or 2-year survival in view of problems with abdominal relapse. In a Mayo Clinic Rochester analysis of 159 patients by Roldan et al,[202] the local control rate at 1 year was 82% for EBRT plus IOERT (n = 37) versus 48% for EBRT alone (n = 122) and 2-year local control was 66% versus 20% (p = 0.0005). Median and 2-year OS were similar, however, with median survival of 13.4 versus 12.6 months (IOERT versus none) and 2-year OS of 12% versus 16.5%. The lack of survival improvement was related to a high incidence of abdominal relapse in both groups of patients (IOERT: 54% with liver or peritoneal metastases versus 56% in patients undergoing non-IORT).

IOERT Plus EBRT or CRT. Generally, IOERT has been given in combination with EBRT in the range of 45 Gy to 50.4 Gy in 25 to 28 fractions with 5-FU alone or 5-FU–based combination CTX. The dose of IOERT is typically in the range of 10 Gy to 20 Gy (usually 20 Gy for patients with locally unresectable cancers; for those with resection before or after CRT, the IOERT dose varies from 10 Gy to 12.5 Gy).

In experienced hands, IOERT can be given with acceptable morbidity. However, there are occasional reports of high complication rates. RTOG reported on 51 patients with IOERT for locally unresectable PCA.[201] In this multiinstitution Phase II trial, there was a major postoperative complication rate of 12% and 2 patients with major morbidity leading to death. There was no obvious improvement in median survival.

In a 2005 update of the MGH experience, 150 patients with LUPC received IOERT as a component of treatment from 1978 to 2001 in conjunction with EBRT and 5-FU–based CTX.[206] Long-term survival was seen in 8 patients, and 5 were alive at or beyond the 5-year interval. Actuarial 1-, 2-, 3-, and 5-year OS rates for the 150 patients was 54%, 15%, 7%, and 4%, respectively, and median OS was 13 months. Survival was significantly related to the diameter of the IOERT treatment applicator (which is a surrogate for tumor size). In the 26 patients treated with a 5-cm or 6-cm applicator, 2- and 3-year OS were 27% and 17%; none of the 11 patients treated with a 9-cm diameter applicator survived beyond 18 months, and those treated with a 7-cm or 8-cm applicator had intermediate survival ($p < 0.05$). In an updated MGH analysis of 194 IORT patients with LUPC, median OS was 12 months.[209] On multivariate analysis, an IORT applicator diameter ≤8 cm (p = 0.009), a Charlson age-comorbidity index ≤3 (p = 0.001), and receipt of CTX ($p < 0.001$) predicted improved OS. The median OS for patients with all three of these prognostic factors was 21.2 months.

Neoadjuvant CRT Plus IOERT. In an *attempt* to improve patient selection and survival, a number of institutions have altered the sequencing of IORT and EBRT/CRT. Garton et al from the Mayo Clinic Rochester evaluated neoadjuvant EBRT with or without concurrent 5-FU followed by IORT in 27 patients with LUPC.[203] Median survival from diagnosis was 14.9 months with a 2-year OS rate of 27% and 5-year OS of 7% (eTable 48-4). Local control was achieved in 78% of patients, but 52% developed liver or peritoneal relapse.

Investigators from Mayo Clinic Arizona have used only the sequence of preoperative CRT followed by restaging and surgical exploration with resection/IORT for select patients with BRPC or LUPC.[208] NAdj CRT was delivered with concurrent 5-FU– or GEM-based regimens and 45 Gy to 50.4 Gy (25 fractions to 28 fractions) in 27 of 31 patients who were explored after restaging. Twenty-eight patients received IOERT (10 Gy to 20 Gy) and 16 patients had gross total resection (R0, 11 patients; R1, 5 patients). Sixteen patients also received adjuvant CTX. Median survival for the total group was 19 months, with a 2-year OS of 31% and a 3-year OS of 16%. Survival outcomes were improved in patients who underwent R0 or R1 resection after NAdj CRT (n = 16) versus those who had R2 or no resection (n = 15) (median OS 23 versus 10 months; 2-year OS 40% versus 17%; 3-year OS, 40% versus 0%; p = 0.002). Liver or peritoneal relapse was documented in 22 of 31 patients (71%). Local failure in the EBRT field or central failure in the IORT field occurred in 5 of 31 patients (16%).

Neoadjuvant Therapy in Locally Unresectable Disease

In patients with LUPC, NAdj treatment serves to provide local control and prevent disease progression. Infrequently, conversion to resectability can occur.

NAdj combination CTX regimens have been suggested to be more beneficial than single-agent CTX.[214,215] A meta-analysis of NAdj therapy in PCA reported on 4394 patients enrolled on 111 trials.[216] Patients who were nonresectable (BRPC and LUPC) had a disease control rate of 76.6%, including a 4.8% complete response rate, 30.2% partial response, and 41.6% stable disease. Forty-seven percent of the initial patients who were unresectable underwent surgical exploration, with an overall resection rate of 33% and an R0 resection rate of 79%. Median OS among patients who were resected and unresected were 20.5 and 10.2 months, respectively.

Initial CTX is an effective way to select patients who are most likely to benefit from CRT. Two retrospective analyses identified induction CTX as an appropriate tool to identify patients with LUPC who may benefit from subsequent treatment with CRT. After at least 3 months of initial CTX, Huguet et al evaluated whether outcomes could be used to select patients who would benefit from CRT.[175] The patients who received CRT after CTX had a markedly better OS than those patients who continued with CTX alone (15.0 versus 11.7 months, p = 0.0009). Another retrospective analysis analyzed 323 patients with LUPC who were treated with initial CRT (n = 247) or who received induction CTX with GEM for 2.5 months before CRT (n = 76).[217] Induction CTX was associated with significantly improved PFS (6.4 versus 4.2 months, $p < 0.001$) and OS (11.9 versus 8.5 months, $p < 0.001$).

Metastatic Disease and Palliation

Median survival for the vast majority of patients with metastatic PCA is extremely poor (3 to 6 months).[218] Both the NCCN and National Cancer Institute (NCI) treatment guidelines recommend that all patients be referred for CTX or enrollment in clinical trials. Therapy for patients with five or fewer metastases is directed toward improving clinical outcome whereas those with more than five metastases should seek best supportive care.

Chemotherapy

First-line treatment for patients with metastatic PCA with good PS includes FOLFIRINOX or GEM/NP. GEM has been established as an approved regimen for advanced disease since 1997.[219] GEM combinations such as GEM/NP, GEM plus capecitabine, GEM/docetaxel/capecitabine (GTX), and GEM/

In 2009, TJUH published an update of their IOERT experience.[210] Thirty-six patients treated with PD and IOERT were compared with 46 patients who underwent surgery without IOERT using a propensity score analysis. Approximately 75% of the IOERT patients also received EBRT, and almost 90% received CTX. Although IOERT was determined to be safe in resectable PCA without increasing perioperative morbidity, it did not seem to significantly increase OS or locoregional control.

The MDACC experience also showed a nonsignificant increase in locoregional control in patients treated with IOERT (9% versus 4%).[211] It is likely that these rates of recurrence are lower than the TJUH experience because fewer patients had positive margins. The investigators suggest that a local control advantage large enough to cause a survival benefit would only be possible in a group with high risk of locoregional recurrence (e.g., R1 or R2 resections). Improvements in CTX will likely be necessary for the possible local control benefits of IOERT to have survival implications.

A pooled analysis of 270 patients undergoing IOERT from five European institutions was performed.[205] Radical surgery was performed in 247 cases (91.5%; R0 resection, 53.4%; R1, 27.4%; R2, 19.2%) and exploratory laparotomy in 8.5%. Surgery was preceded by EBRT in 63 patients (concurrent CRT in 38%) and 106 received postoperative EBRT (concurrent CRT was given in only 7.5%). Median OS was 19 months for the entire cohort, and 5-year OS was 17.7%. Survival and local control appeared to be superior in patients treated with preoperative EBRT/CRT before IOERT compared with adjuvant EBRT (or CRT) or IOERT alone (median OS: 30 months versus 22 months versus 13 months; local control: median not reached versus median 28 months versus median 8 months, respectively). This may be because the patients destined to fail early systemically would do so during preoperative EBRT, sparing them from the attempt at surgery and IORT. On multivariate analysis, nodal status and timing of EBRT significantly affected survival. In the subset of patients who remained free from local relapse for more than 2 years, the 3- and 5-year OS were 32% and 28% versus 12% and 0% in patients with local relapse within 2 years.[209]

Irreversible Electroporation

Irreversible electroporation (IRE) is a novel, minimally invasive technique that has recently been evaluated in the management of LUPC. IRE uses electrical impulses to alter the cell membrane and disturb homeostasis.[213] This triggers apoptotic cell death without damage to protein-based structures (vascular elastin, collagenous structures). IRE is an alternative to thermal ablation techniques (e.g., radiofrequency ablation, microwave ablation, cryoablation), which often cause damage to adjacent structures and blood vessels. Patients should be selected for IRE following evaluation by a multidisciplinary team. A Phase I trial (NCT01939665) is currently under way to evaluate the efficacy of IRE in palliating symptoms and improving local tumor control in LUPC. At JHH, IRE is typically offered to patients with LUPC who have received optimal systemic and radiation therapy (CRT or SBRT) for greater than 6 months from the date of diagnosis.[216a] Because investigation of IRE is in its early stages, additional study is required to determine its optimal use.

erlotinib plus bevacizumab offer clinical advantages, although only a subset of patients may benefit.[189,220-222] A combination of GEM and cisplatin is recommended for patients with metastatic disease and known hereditary factors (e.g., *BRCA* or *PALB2* mutations).[223] Recently, the MPACT study established the GEM/NP regimen as a new option for the first-line treatment of metastatic PCA.[190,224] A significant improvement in OS, PFS, and response rates was associated with combined GEM/NP over GEM alone in patients with metastatic PCA. GEM/NP also demonstrated promising results in LUPC.[191] NP added to GEM has particular efficacy because of its ability to increase the activity of GEM by depleting the stroma and increasing the concentration of GEM in the tumor. FOLFIRINOX has shown increased treatment response rates (>30%) and improvements in survival and QOL in patients with metastatic PCA.[225-227]

A select number of PCA patients with oligometastatic disease who have been stable on CTX for greater than 6 months may receive concurrent CRT. For patients with oligometastatic or unstable disease or poor PS, palliation is of the utmost importance although the potential for improvement in clinical outcome is unclear. The NCCN currently recommends administration of GEM alone in patients with poor PS although the addition of NP is being evaluated. Patients presenting with poor PS may benefit from GEM; however, comfort-directed measures are given priority.

Symptom Palliation

Setting medically appropriate goals while maintaining open and honest communication with the patient is the best approach to palliative care. Patients with PCA have many physical and emotional challenges; therefore, the goal of palliative medicine is to relieve suffering and to improve QOL by addressing a patient's specific needs. Control of pain and nonpain symptoms, clear and effective communication, and addressing psychosocial needs are essentials of palliative care.[228] Given the poor survival rate and distressing symptom profile of PCA, palliative care should be offered upon diagnosis. Pain management is a particular concern among patients with PCA. Although opioid medications are the backbone of therapy, interventional therapies such as percutaneously or endoscopically placed celiac plexus block are often effective for patients with refractory pain or intolerable side effects of opioid therapy. Palliative CTX or RT may also help to improve symptoms, as will be detailed below. Nausea, gastric outlet obstruction, and obstructive jaundice are other common and distressing symptoms in this patient population; careful attention should be paid to optimizing both medical and interventional therapies for such symptoms.

Palliative Chemotherapy

Single-agent GEM is the standard therapy for poor PS or patients who are elderly with PCA regardless of stage (localized or systemic disease); however, median survival remains a mere 6 months in this group. Hsu et al reported that elderly patients (>75 years) with multiple comorbidities have a high mortality rate 9 months after surgery[229] and are less likely to benefit from adjuvant therapy than younger patients.[230] Therefore, patients who are elderly or have poor PS may benefit from more aggressive NAdj therapy and be spared the morbidities of surgery. In metastatic patients with poor PS (KPS > 70), GEM/NP was superior to GEM alone.[190] In fact, most patients with poor PS receiving GEM/NP did not require a dose reduction, and the addition of NP increased the cumulative GEM dose with no increase in significant toxicity. GEM/NP may also improve outcomes with limited toxicity in patients with nonmetastatic PCA who are not well-suited for aggressive CTX or surgery; however, further study of the regimen is required in this group of patients.

Palliative Radiation Therapy

Radiation therapy may be able to improve symptoms such as pain, biliary obstruction, gastric outlet obstruction, or duodenal obstruction. To date, only one clinical trial in LUPC has specified pain control as a study endpoint.[231] This small randomized study from Taiwan demonstrated higher rates of pain control (39% versus 6%) in patients who received GEM-based CRT (50.4 Gy to 61.2 Gy) compared with 5-FU–based CRT. Interpretation of these results is difficult given the small sample size (n = 34) and the fact that outcomes in the 5-FU group were significantly worse than what would be expected based on historical data. CRT has also been compared to best supportive care (with no antineoplastic therapy) in a small randomized trial from Japan.[232] The study enrolled 31 patients, 16 of whom were randomized to 5-FU–based CRT and 15 of whom received supportive care. Ten patients had pain before the start of treatment; of these, 8 had improvement in pain after treatment. The median duration of pain control was 5.2 months. Although this study is unlikely to be replicated, it does support the use of RT to control tumor-related pain.

In selected patients, salvage reirradiation with SBRT may be an option for palliative care, as suggested by a recent retrospective series.[233] Median RT dose was 25 Gy (in 5-Gy fractions) prescribed to the gross tumor alone (plus a 2-mm to 3-mm margin). Although the number of patients treated was fairly small (n = 18), the rate of pain control among patients with pain at baseline was 57%. Therapy was well-tolerated with no acute grade-3 toxicity and a single episode of late grade-3 late toxicity (small bowel obstruction). Furthermore, a multicenter Phase II trial explored the benefit of 33-Gy SBRT (6.6 Gy × 5 fractions) in combination with GEM in patients with LUPC (median age, 67.9). Patients reported a significant improvement in pain 4 to 6 weeks after SBRT (p = 0.001).[199]

The available, although limited, evidence suggests that RT is an effective option for symptom palliation in patients with PCA. The expected response rate is approximately 40% to 80%. As rates of acute treatment-related toxicity are fairly low with the use of modern radiation techniques including IMRT and SBRT,[124,196] RT should be considered as a palliative option in patients whose pain is not adequately controlled by optimal medical management or interventional procedures such as celiac plexus block. Further studies are needed to better quantify the expected clinical benefit of RT in this setting, particularly in terms of pain control.

Palliative Surgery and Stenting

Surgery has historically been used to alleviate symptoms such as duodenal or biliary obstruction. Surgical palliative procedures may include a surgical bypass such as hepaticojejunostomy or gastrojejunostomy. At the time of a surgical bypass, intraoperative celiac plexus block could be considered if the surgeon is comfortable with the technique.[234] Routine palliative bypass has been advocated for patients with PCA who are explored with curative intent but are found to have inoperable disease at the time of surgery. However, with enhanced imaging techniques and improved patient selection and categorization of disease, fewer surgeries of this type are performed.

With the advent of improved endoscopic techniques, rates of duodenal and biliary duct stent placement have increased while the need for palliative surgical bypasses has declined. There is limited data regarding the performance of a prophylactic gastrojejunostomy versus duodenal stent placement at the time of a later duodenal obstruction. However, a meta-analysis of duodenal stents versus gastrojejunostomy found that the latter were preferable for those with a longer (>3 months) projected survival.[237] If survival is likely to be short, endoscopic stent placement is preferred to surgery.[238] Patients

Patients with poor PS—whether due to comorbidities, cancer-related symptoms, or advanced age—are a PCA population that is often overlooked. Equally important is support of the caregivers and family members who are also affected by a PCA diagnosis. A multidisciplinary clinic or tumor board involving established palliative care programs can help provide the necessary resources for patients and families to gain access to the information needed to better understand their diagnosis, decide on treatment options, control pain, understand nutrition, and cope with the associated social stressors.

A recent JHH experience reported on 1913 patients who were surgically explored for cancers of the head of the pancreas between 1996 and 2010.[235] Interestingly, the rate of palliative bypass procedures decreased over time because of improved patient selection. Of the 1913 patients, 583 (30.5%) underwent a palliative procedure. Most patients who underwent surgical palliation (64.5%) had a double bypass, and a minority had either gastrojejunostomy (28.2%) or hepaticojejunostomy (7.2%) alone. Although the number of PDs remained relatively stable over time, there was a temporal decrease in palliative bypass rates ($p < 0.001$). When considering palliative bypass, one should consider several factors that are predictive of poor outcome: the presence of distant metastatic disease (HR 2.59, $p < 0.0001$), poor tumor differentiation (HR 1.71, $p = 0.009$), severe preoperative nausea and vomiting (HR 1.48, $p = 0.013$), and lack of previous placement of a biliary stent (HR 1.36, $p = 0.048$).[236] Patients with a prognostic score of 0 were significantly more likely to survive past 6 months than those with a prognostic score of 1 (HR 2.71, $p < 0.0001$), 2 (HR 3.70, $p < 0.0001$), or ≥3 (HR 5.63, $p < 0.0001$).

can initiate or resume CTX within a few days of endoscopic stenting, whereas recovery from a palliative bypass may take 3 to 6 weeks, therefore delaying CTX.

IRRADIATION TECHNIQUES AND TOLERANCE

Overview

The standard treatment approach is to use 3D-CRT with concurrent GEM or 5-FU (CI or oral capecitabine). The goal of NAdj RT in potentially resectable PCA patients is to (1) select patients who are likely to benefit from aggressive curative surgical resection and (2) increase the likelihood of a margin- and node-negative resection to prevent subsequent local recurrence. In patients with truly unresectable PCA, the goal is to improve median survival, prevent local progression, palliate pain, and perhaps decrease the risk of subsequent systemic spread.[239] The goal of adjuvant RT is to prevent locoregional progression. Before delivering adjuvant treatment, it is important to 1) thoroughly review the tumor location on preoperative and postoperative imaging, the operative note, and pathology report and 2) assess PS and nutritional status (e.g., the need for pancreatic enzymes). Integration of newer techniques such as IMRT and SBRT/stereotactic ablative radiotherapy (SABR) will be briefly discussed.

Simulation and Treatment Planning

Patients should undergo a CT simulation (thin slices through the pancreas or tumor bed and locoregional nodal basins) with intravenous and oral contrast for improved delineation of the tumor or tumor bed and adjacent normal structures.[81] Patients are simulated supine in an Alpha Cradle (Smithers Medical Products Inc, North Canton, OH) or equivalent immobilization device with arms up. Patients should be scanned from the carina through the top of the pelvis using 2-mm to 3-mm slices. For resected cases, preoperative CT scans and strategically placed clips are used to determine the tumor bed. In the neoadjuvant, borderline resectable and locally unresectable settings, the pancreatic gross tumor volume (GTV) and pathologic nodes (minimum >1 cm) are contoured with assistance from anatomical (CT/MRI) and functional imaging (PET). The planning target volume (PTV), defined per ICRU-62 guidelines, should be constructed using image guidance.[240] A GTV should be defined for intact pancreatic tumors.

Elective nodal irradiation (ENI) is commonly used for adjuvant cases but is controversial for neoadjuvant, borderline resectable, and locally unresectable PCA cases. Standard margin expansions for intact tumors include the gross tumor and any pathologic lymph nodes (gross tumor volume, GTV) plus a 0.5-cm to 1.5-cm margin to target microscopic extension (clinical target volume, CTV) and an additional 0.5-cm to 2.0-cm volume to account for tumor or breathing motion and patient set-up errors (planning target volume, PTV). Breath-hold and gating techniques in conjunction with 3D-CRT or IMRT can result in improved PTV coverage with decreased dose to OARs. With regards to SBRT, smaller margins are used (0.2 cm to 0.5 cm) and the PTV does not cover locoregional nodes (Figure 48-7).

Motion Management

Both interfractional and intrafractional variations are important when considering margin expansions. Interfractional motion is mainly due to setup error, whereas intrafractional variations are typically the result of breathing motion or bowel or stomach distension. Portal imaging does not take into account breathing motion or bowel distension. On average, portal imaging for radiation (PORT) films are associated with a 5-mm to 6-mm difference in each translation whereas cone-beam computed tomography (CBCT) has systematic errors of 2.4 mm left-right (LR), 2 mm anterior-posterior (AP), and 3.2 mm cranio-caudal (CC), as well as random errors of 3.2 mm LR, 1.8 mm AP, and 3.6 mm CC.[241] Based on these data, at least a 1-cm CTV to PTV is recommended when using PORT imaging.

Respiratory motion is a major source of intrafractional motion. Reese et al summarized several studies that described a large range of potential respiratory motion from 5 mm to 43 mm, indicating the need for individualized margins.[242] Four-dimensional (4D) CT may underestimate motion compared to fluoroscopy, ultrasound, and MRI. In fact, studies have shown that both under- and overestimation with 4D CT can occur as a result of technique, patient comfort level, and parameters. In general, regular or real-time verification of patient positioning during treatment is ideal, especially if tight margins are used. When possible, a combination of tumor fiducial placement in or around the tumor, 4D CT simulation, gating or breath-hold, and image-guided radiation therapy (IGRT) can effectively result in "personalization" of nonuniform PTVs (as opposed to uniform PTV expansion).[243] Motion of the pancreatic head, body, and tail appears to be different.[244-246] The SMA, celiac, and other vessels have been found to move less than 5 mm, which is substantially less than the pancreas.[247,248] Given these variations, individual patient assessment of motion is paramount.

If patients have a greater than 3 mm breathing motion on fluoroscopy or 4DCT scan, tumor immobilization techniques should be employed. There are two approaches to motion management: immobilization of the target motion (abdominal compression or breath-hold techniques) or physiologically monitoring tumor motion (tracking or gating). Abdominal compression limits diaphragmatic excursion while breath-hold techniques (active or passive) stabilize the tumor for a short period of time to ensure delivery of RT while the breath is held within a previously established tidal volume. Abdominal compression should be used with caution because it may compress the duodenum or bowel into the pancreas, thus increasing the volume of normal tissue that may be exposed to RT. In general, if breathing motion is less than 3 mm, patients can be treated free-breathing with an internal target volume (ITV) based on the 0% and 50% phases of the breathing cycle or in a gated manner. FDG-PET or MRI simulation may enhance the ability to better delineate the pancreas tumor and adjacent structures and can provide a baseline to assess treatment response.

Tracking often requires fiducial markers to be placed within the tumor such that the radiation beam follows the tumor motion. A recent study showed rates of migration of gold fiducials to be minimal in patients with LUPC receiving SBRT.[249] Before simulation for IG-IMRT or SBRT/SABR, three or more gold fiducials should be implanted into or adjacent to the pancreatic tumor using endoscopic ultrasound (preferred) or percutaneous guidance. Pancreatic stents appear to have potential as a surrogate for pancreatic motion given their proximity.[250] However, the stent motion may be greater than GTV motion creating a larger expansion than necessary.[251] Although the use of the stent for image guidance during daily treatment is attractive as it is easily seen with on-board imaging; however, studies have shown that the mean migration of the stent has been found to be approximately 1 mm over the course of RT, and spontaneous loss of the stent has been reported to occur in 5.8% of patients.[249] As the motion and loss rate may be greater for standard fractionated therapy, stents are not completely reliable markers for daily image guidance.

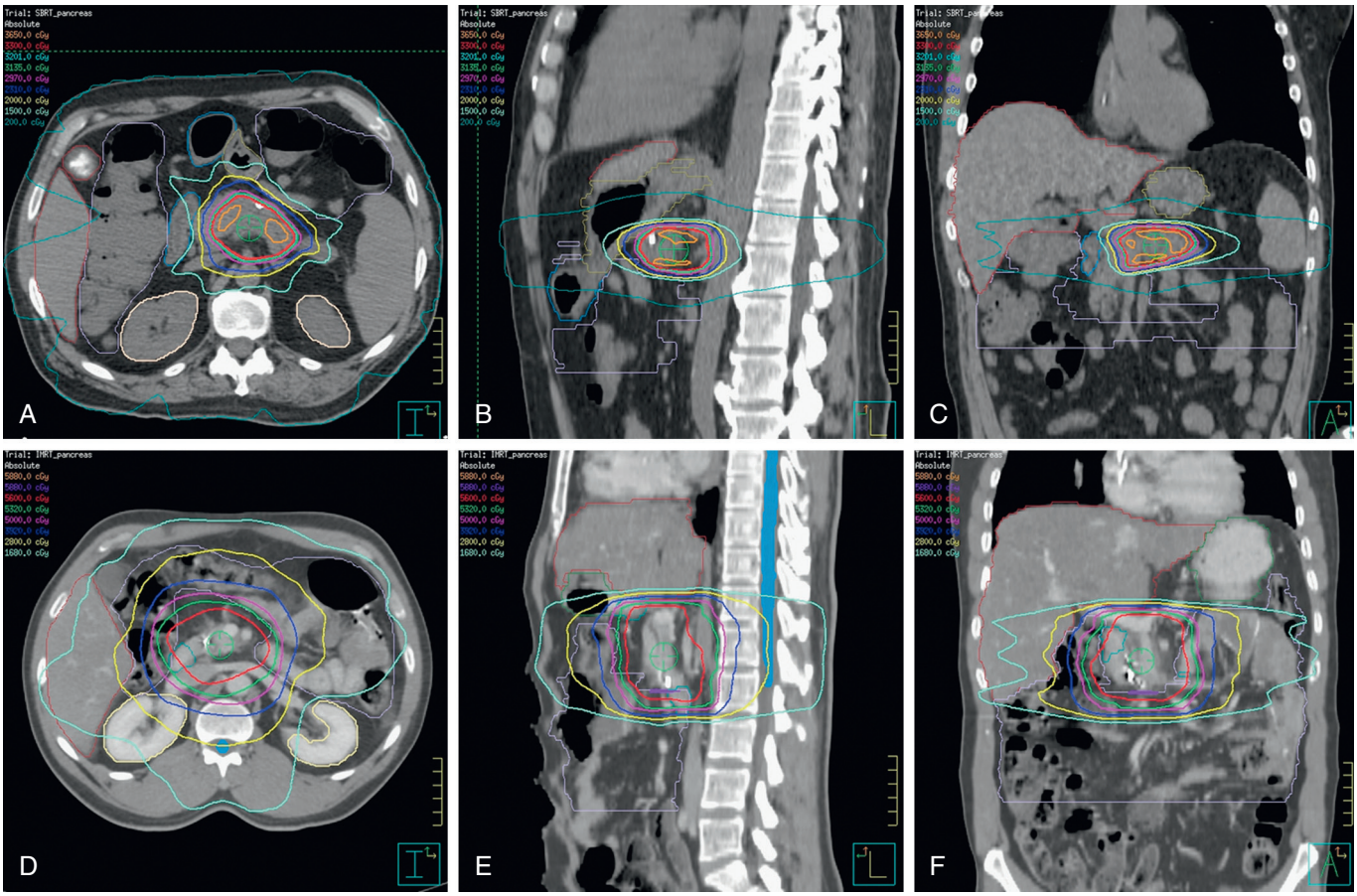


Figure 48-7 Stereotactic body radiation therapy (SBRT) and intensity-modulated radiation therapy (IMRT) treatment plans. Modern conformal radiation techniques allow precise dose delivery to the pancreas and nodal stations at risk. SBRT (panels **A-C**) and IMRT plans (panels **D-F**) are shown in orthogonal cross-section projections. Note the steeper dose fall off and smaller obligate low-dose region with SBRT compared to IMRT.

The pancreas is also affected by motion of the gastrointestinal tract. The stomach is a remarkably distensible adjacent organ and can quadruple in size with oral intake.[252] The pancreas has been shown to move when the stomach is injected with 500 mL to 900 mL of fluid, with the pancreatic tail and SMA having the greatest motion (median motion of 5.3 mm and 5.7 mm, respectively).[253] Gastric distension must therefore be accounted for during simulation and treatment. To ensure a consistent gastric volume, it is recommended that patients take no food or drink for 2 hours before simulation and treatment of any pancreatic target (whether postoperative or intact anatomy is present). Two hundred and forty mL of oral contrast (simulation) or water (treatment) is given to ensure consistent stomach and bowel filling, maximizing the reliability of dose calculations to the stomach and duodenum.

Treatment Planning and Radiation Delivery

Conventional RT or 3D-CRT is generally given using three or four fields whereas IMRT and SBRT/SABR use multiple coplanar isocentric (linac-based) or noncoplanar nonisocentric (CyberKnife) beams. High-energy photons (>10 MeV) are preferred; lower energy megavoltage beams can be used but may result in more gastrointestinal toxicity.

In RTOG 0848 (NCT01013649), the principles utilized in two-dimensional (2D) RT planning from RTOG 9704 have been extended to 3D and IMRT planning. In addition, an atlas of images illustrating these principles has been posted on the RTOG website (RTOG.org). The resulting CTV and PTV are significantly smaller than historical standards that used 2D imaging and planning. This protocol targets the areas of greatest subclinical tumor concentration based on anatomic landmarks not readily apparent in 2D imaging (celiac and SMA, PV, pancreaticojejunostomy, GTV location of the resected tumor) and more precisely specifies suggested tolerance parameters for critical normal organs.

Intensity-Modulated Radiation Therapy

IMRT and intensity-modulated proton beam therapy (IMPT) using IG have become increasingly popular in the management of PCA. Implementation of IMRT requires a high level of precision in treatment planning and dose delivery because multiple beams are used to irradiate the target volume. Compared with 3D-CRT, IMRT improves dose conformality and decreases toxicity, even allowing for the safe delivery of boost doses up to 64.8 Gy while meeting normal tissue constraints.[126,169,254] Furthermore, IMRT effectively reduces the mean dose to the liver, kidneys, stomach, and small bowel, resulting in improved toxicity.[255] A recent dosimetric study conducted by van der Geld et al revealed that 4D IMRT planning significantly reduced the mean volume of right kidney exposed to 20 Gy by more than 11%, while also lowering the mean dose to the stomach, liver, and small bowel.[256] These dosimetric improvements may allow for larger systemic doses of concurrent CTX to be given safely. Small reductions in margin size can result in a substantial reduction in the volume to be irradiated.

Abrams et al emphasize the significance of adherence to standard guidelines and quality assurance with RT delivery.[122] By using prospectively defined guidelines, patients' treatment plans were scored as per protocol, variation acceptable, and variation unacceptable. Of the 416 evaluable patients, 52% were per protocol, whereas 48% were less than per protocol. Survival was increased for all per protocol patients compared with less than per protocol (1.74 years versus 1.47 years, $p = 0.019$). This result persisted on multivariate analysis. The Kaplan-Meier curves comparing per protocol and less than per protocol patients appeared to diverge at approximately 14 months, which the authors thought implied an effect on tumor control.

Proton Beam Radiation Therapy

IMPT has a unique advantage in its ability to deposit energy directly into the tumor while minimizing radiation to normal tissue. A feasibility study reported that NAdj capecitabine and a short course of proton beam therapy is a feasible regimen.[257] IMPT involved 240-MeV protons generated from a cyclotron and delivered using 3D passively scattered protons. The first dose level consisted of 3 GyE delivered daily 5 days per week for 2 weeks for a total of 30 Gy. In levels 2 to 4, patients were treated with 5 GyE per fraction for a total fraction of 25 GyE in progressively shorter schedules. Further research is necessary because high-dose proton plans do not appear to be as conformal as high-dose photon plans.[258] In a dosimetric study conducted at MDACC, investigators virtually translated a 3-cm pancreatic tumor every 5 mm over a 5-cm length extending from the head to tail of the pancreas.[259] For eleven tumor locations, 3D-CRT, IMRT, and IMPT plans were generated. IMRT was the most conformal in higher gradient dose regions, whereas IMPT reduced low doses to gastrointestinal OARs. Thus, IMRT seems to be the more appropriate tool for dose escalation whereas proton therapy would be expected to have a modest impact on low-grade acute toxicities such as nausea and fatigue and is not currently an optimal choice for dose escalation. Multiple clinical trials are currently under way to investigate the role of proton radiation in PCA (clinicaltrials.gov).

Stereotactic Body Radiotherapy

Advances in IGRT and radiation technology have resulted in SBRT, or stereotactic ablative radiotherapy. SBRT delivers high doses of RT to the pancreas tumor or tumor bed plus a small margin (~2 mm to 3 mm) while sparing adjacent normal tissues. To date, Phases I and II trials for lung, liver, spine, pancreas, kidney, and prostate tumors have suggested that SBRT may provide equivalent tumor control to surgical resection, without the typical morbidities associated with an invasive approach.[260,261]

Initially analyzed in LUPC, SBRT also shows promise in the borderline resectable and metastatic setting. Current literature has suggested that fractionated SBRT appears to be an effective and well-tolerated treatment for LUPC because of its ability to improve QOL and increase survival and local control (Table 48-4).[129,130,195-197,262,263] SBRT is a complement to standard RT because local control rates appear comparable, toxicity is favorable, and delay of CTX is limited. However, more data is needed. As the role of pancreatic SBRT has evolved, dosimetric margins, patient positioning, and motion management have proven to be essential for accurate targeting.[263a] Severe gastrointestinal toxicities have been reported as a result of SBRT in past studies[194,195]; however, continuing efforts to establish specific dose constraints have been able to minimize normal tissue toxicity. In cases in which the PTV is in close proximity to critical OARs, the maximum point doses and dose-volume histograms of those structures should be evaluated.[264] The following dose constraints have shown efficacy in minimizing treatment-related toxicity with the delivery of 33 Gy (in 6.6-Gy fractions) SBRT to patients with LUPC based on results of a multicenter study: proximal duodenum and stomach (9 mL <15 Gy; 3 mL <20 Gy; 1 mL <33 Gy), liver (50% <12 Gy), combined kidneys (75% <12 Gy), and spinal cord (1 mL >8 Gy).[199]

Intraoperative Radiation Therapy

Intraoperative RT is used to escalate RT dose to the unresected pancreas cancer or operative tumor bed. High single-fraction doses of 15 Gy to 20 Gy are typically delivered as nearby dose-limiting structures can be physically removed from the radiation field during the procedure. Two techniques may be used: IOERT and high-dose-rate brachytherapy (HDR-IORT). HDR-IORT allows for the delivery of a more concentrated dose at the surface of the target area, whereas IOERT delivers RT more homogenously throughout the unresected tumor or tumor bed.[267,268] The flexible applicators associated with HDR-IORT can be shaped to precisely conform to individual tumor beds.[269] Ideally, IORT is performed in cases in which surgical resection may result in close or positive margins. However, the role of IORT in PCA is still being evaluated, and this procedure should only be performed at specialized centers and in well-selected cases.[81]

Toxicity and Dose Constraints to Normal Tissues

Critical OARs (e.g., kidney, stomach, small bowel, liver, spinal cord) should be contoured and evaluated in the dose-volume histogram to maximize treatment response while minimizing toxicity. Dose-volume recommendations based on the NCCN guidelines can be found in Table 48-5.

The small intestine is an important RT dose-limiting structure in the abdomen; a relatively small volume of the small bowel receiving a high dose of RT may lead to severe, irreversible side effects. In 1991, Emami et al demonstrated the maximal dose limit to the small intestine was 45 Gy to 50 Gy.[270] More recent data from the Quantitative Analyses of Normal Tissue Effects (QUANTEC) investigators at the RTOG compiled data from multiple studies to update the initially identified dose constraints. In general, the RT dose limit to the small intestine should be limited to no more than 195 mL of small bowel receiving greater than 45 Gy (V45, or volume receiving 45 Gy or more, should be <195 mL). MDACC recently reported that duodenal V55 Gy >1 mL is an important dosimetric predictor of grade-2 or greater duodenal toxicity in the management of LUPC with concurrent CRT.[271] With SBRT, definitive dose constraints have not been established; however, a proposed limit is 12.5 Gy in a single fraction (V12.5 <30 mL), or limited to 30 Gy in a 3- to 5-fraction regimen.

Acute side effects of RT to the small intestine include malabsorption, altered gut mobility, diarrhea, nausea, and vomiting, whereas chronic/late side effects may include mucosal ulceration, eventually developing into perforations, fistulae, bleeding, and abscesses. The development of fibrosis may cause a stricture or small bowel obstruction, and chronic malabsorption may lead to severe anemia and hypoalbuminemia. Although many of the acute side effects resolve quickly after RT, late side effects may be severe, progressive, and irreversible. Acute RT enteritis can be managed conservatively by using antidiarrheal, antispasmodic, and antiemetic medications as necessary. In patients with ongoing diarrhea despite medical management, a low-residue diet should be considered. In cases of mild nausea, compazine or ondansetron can be beneficial, whereas total parenteral nutrition may be needed in extreme cases. Given the rapid repair capacity of the small bowel, a short break from RT often leads to functional improvements. Small bowel obstruction after RT may be a consequence of stricture or adhesions leading to bowel loop entrapment, which should be managed as any acute abdomen case would proceed. Initially, patients should have nothing by mouth to allow the bowel to rest and to allow for decompression. In certain cases, strictureplasty or dilation of the affected segment may be an option; however, this is not the preferred technique for treatment. Anastomosis with a proximal, nonirradiated segment of bowel has been performed with good results. With IORT plus EBRT approaches, efforts to decrease overlap of RT treatment fields and confirm removal of normal structures out of the IORT field results in less toxicity.

TABLE 48-4 Stereotactic Body Radiation Therapy in Locally Unresectable Pancreatic Cancer*

Study	Regimen	*n*	FFLP, 1 year (%)	OS (mo.)	Toxicity, Acute/Gr ≥ 3	Toxicity, Late/Gr ≥ 2	Dose Constraints for Organs at Risk
Koong et al. 2004[128]	25 Gy SBRT, 1 fraction	6	100%	8.0	33%	—	Duodenal wall (50% isodose line)
Hoyer et al. 2005[194]	45 Gy SBRT, 3 fractions	22	57% (6 mo)	5.4	79%	94%	—
Schellenberg et al. 2008[195]	GEM, 25 Gy SBRT, 1 fraction, GEM	16	100%	11.4	19%	44%	Stomach, duodenum, bowel, liver, kidney, spinal cord
Chang et al. 2009[130]	25 Gy SBRT, 1 fraction	77†	95%	11.9	5%	13%	Liver (50% <5 Gy), kidney (75% <5 Gy), spinal cord (<5 Gy max), stomach (<4% <22.5 Gy), duodenum (<5% <22.5 Gy, <50% <12.5 Gy), bowel (<21 Gy max, <5% <20 Gy)
Mahadevan et al. 2010[129]	24 Gy-36 Gy SBRT, 3 fractions → GEM	36	78%	14.3	41%	6%	Liver (<30% ≥21 Gy; <50% ≥15 Gy), kidney (<25% ≥12 Gy), spinal cord (12 Gy max), bowel (<10 Gy/fx max)
Polistina et al. 2010[197]	GEM → 30 Gy SBRT, 3 fractions	23	50%	10.6	0	0	Mean dose to 50%: duodenum (14.5 Gy), bowel (1.1 Gy), liver (0.7 Gy), left kidney (1.5 Gy), right kidney (2.0 Gy)
Schellenberg et al. 2011[196]	GEM, 25 Gy SBRT, 1 fraction, GEM	20	94%	11.8	15%	20%	Duodenum (≤5% ≥22.5 Gy, ≤50% ≥12.5 Gy), spinal cord (<6 Gy max), liver (50% <5 Gy), kidney (75% <5 Gy)
Lominska et al. 2012[265]	20 Gy-30 Gy SBRT/3-5 fractions	28‡	86%	5.9	4%	7%	Stomach (10 Gy-30 Gy max), small bowel (13 Gy-30 Gy max)
Tozzi et al. 2013[266]	GEM → 45 Gy SBRT, 6 fractions	30	86%	11.0	20%	0	Duodenum (1 mL <36 Gy), stomach and small bowels (3 mL <36 Gy), kidney (<35% 15 Gy), liver (total spread volume > 700 mL), spinal cord (1 mL <18 Gy)
Gurka et al. 2013[198]	GEM, 25 Gy SBRT, 5 fractions → GEM	10	40%	12.2	0%	0	Duodenum and bowel (<1 mL 25 Gy)
Chuong et al. 2013[263]	GTX, 25 Gy-50 Gy SBRT, 5 fractions	16	81%§	15.0	0%	5.3%	Kidney (<10 Gy), duodenum/small bowel/stomach (35 Gy max, 5 mL <30 Gy, 1 mL <35 Gy), liver (10% 30 Gy), spinal cord (20 Gy max)
Herman et al.	(GEM), 33 Gy SBRT, 5 fractions → GEM	49	83%	13.9	12.2%‖	10.6%	Proximal duodenum and stomach (9 mL <15 Gy; 3 mL <20 Gy; 1 mL <33 Gy), liver (50% <12 Gy), combined kidneys (75% <12 Gy), spinal cord (1 mL >8 Gy)

Fx, *fractions;* GEM, *Gemcitabine;* Gr, *grade;* GTX, *gemcitabine, docetaxel, and capecitabine;* mo., *months;* SBRT, *stereotactic radiation therapy.*
**Unless otherwise indicated, event times for median survival were measured from the date of diagnosis.*
†*Sample contains all unresectable patients (locally unresectable and metastatic).*
‡*Sample includes patients with previous chemotherapy with various agents (5-FU or GEM, other) and some received concurrent chemotherapy.*
§*Freedom from local progression at 1 year of all 73 patients in the study (locally unresectable and borderline resectable).*
‖*One (2%) case of an ulcer and five (10.2%) cases of ALT/AST elevation.*

TREATMENT ALGORITHM, CHALLENGES, AND FUTURE DIRECTIONS

A treatment algorithm for PCA is provided in Figure 48-8.

Given the high risk of systemic progression, upfront CTX is recommended in all stages of nonmetastatic PCA. In general, RT should be considered in patients who have: (1) localized disease with favorable response or stable disease after initial CTX treatment, (2) local progression on CTX, (3) high-risk features following surgery and adjuvant CTX (narrow margin R0, R1-2, N+), and (4) local pain or obstructive symptoms not controlled with other measures (pain medication, stents).

The most optimal results for patients with potentially curable PCA (R0 resection) will likely be achieved with trimodality treatment (surgery, CTX, and RT), including NAdj therapy; however, the safest, most effective, or optimal combination of all three components is yet to be determined. Future trials should address sequencing of systemic treatment and concurrent CRT or SBRT, particularly with regard to optimizing pre-RT CTX regimens.[217,272] The RTOG 0848 study results may help to establish the role of adjuvant CRT in PCA.

TABLE 48-5 Normal Tissue Dose-Volume Recommendations Based on the National Comprehensive Cancer Network Guidelines[81]

Structure	Unresectable/Preoperative Recommendations	Adjuvant/Resected Recommendations
Kidney (right and left)	No more than 30% of the total volume can receive ≥18 Gy. If one kidney is functional, not more than 10% of the total volume can receive †18 Gy.	If two functioning kidneys present, not more than 50% of the right and 65% of the left kidney should receive >18 Gy. For IMRT planning, mean dose to bilateral kidneys should be ≤18 Gy. If only one kidney is present not more than 15% should receive †18 Gy and no more than 30% should receive †14 Gy.
Stomach, duodenum, jejunum	Max dose ≤55 Gy. No more than 30% of the volume can be between 45 Gy and 55 Gy.	Max dose ≤55 Gy; <10% of each organ volume can receive between 50 Gy and 53.99 Gy. <15% of each organ volume can receive 45 Gy-49.99 Gy.
Liver	Mean dose cannot exceed 30 Gy.	Mean dose cannot exceed 25 Gy.
Spinal cord	Max dose to a volume of at least 0.03 mL must be ≤45 Gy.	Max dose cannot exceed 45 Gy.

Max, *maximum.*

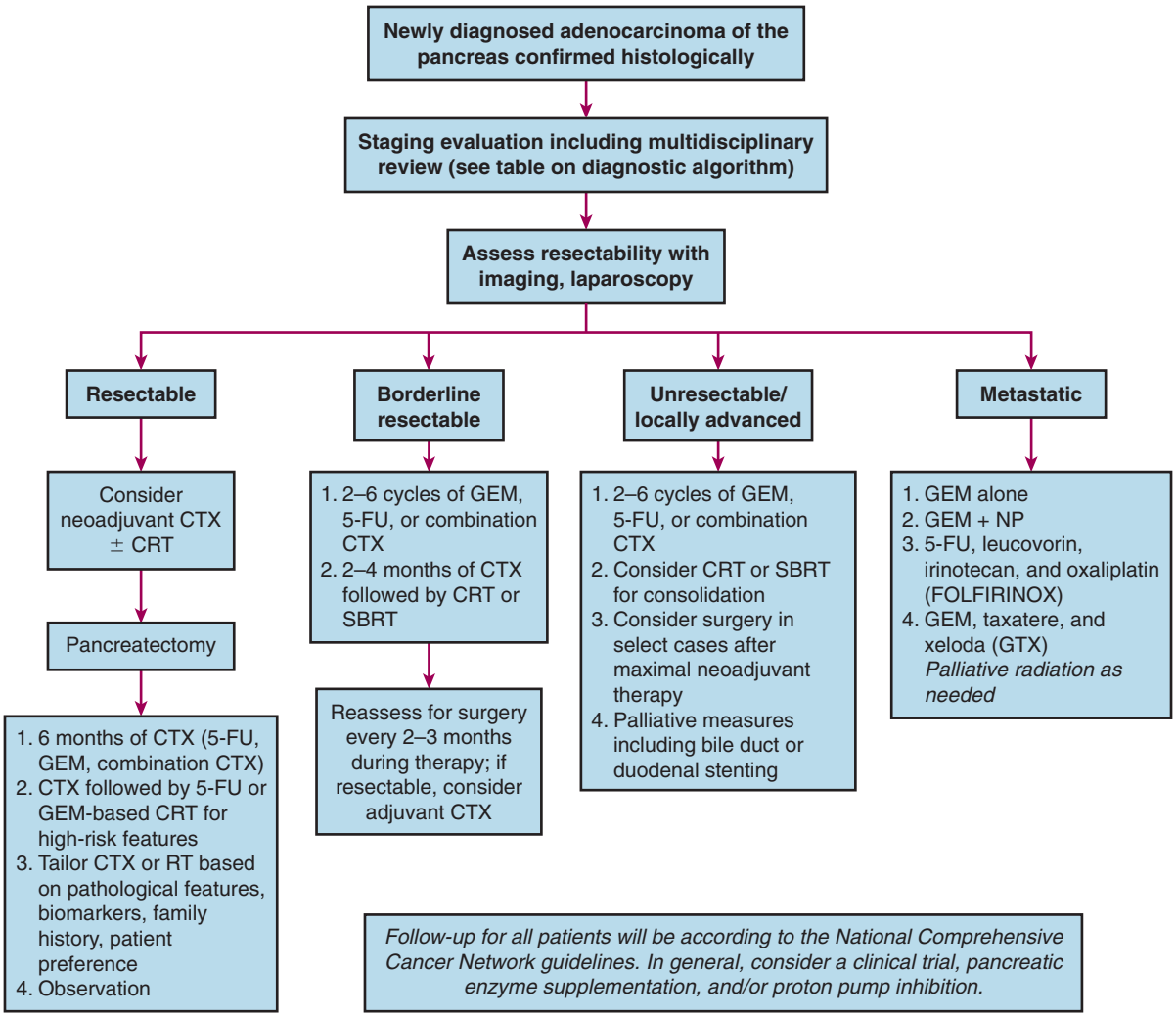


Figure 48-8 Treatment algorithm for pancreatic cancer. *5-FU,* 5-fluorouracil; *CRT,* chemoradiation therapy; *CTX,* chemotherapy; *GEM,* gemcitabine; *NP,* nab-paclitaxel; *RT,* radiation therapy; *SBRT,* stereotactic body radiation therapy.

However, it is unknown whether the 0848 regimen will be effective enough to prevent local and subsequent systemic relapse in patients with resected PCA. Therefore, future treatment regimens should use IMRT or SBRT to safely escalate the dose of RT or allow for more aggressive molecular, immunotherapy, or CTX treatments to improve outcomes.

The definition of borderline resectable PCA has been evolving, which can complicate the interpretation of BRPC studies. The Alliance A021101 trial will evaluate the efficacy of NAdj FOLFIRNOX followed by capecitabine and EBRT and provide insight into implementation of future multiinstitutional BRPC trials.[83] This trial provides a standardized definition and incorporates centralized review of images, treatment plans, and pathology. Future trials should address the efficacy of novel systemic regimens and targeted therapies in combination with new radiation technologies (IMRT/SBRT/IOERT). Novel tumor or blood prognostic biomarkers are desperately needed.

The future of LUPC treatment requires the development of more effective systemic therapies and RT technologies. In the absence of metastases, high-dose NAdj EBRT with simultaneous maintenance CTX appears to be a valid option for patients with poor PS. Furthermore, EBRT boosts with SBRT should be explored. Preliminary studies with fractionated SBRT suggest similar survival with less acute toxicity and improved QOL; however, additional prospective data is needed. The results of the LAP-07 trial question the benefit of CRT following CTX in LUPC, but problems with the trial along with prior positive studies for CRT over CTX (GITSG, ECOG) cannot be dismissed. The high rates of progression following induction CTX (40%) in LAP-07 may highlight the need for more aggressive NAdj CTX to select a subset of patients who may benefit from RT. An additional challenge is how to select patients who may benefit from resection/IOERT after NAdj CTX plus CRT or SBRT.

Studies investigating more aggressive systemic therapies such as GEM/NP and FOLFIRINOX are under way (CTX alone or in conjunction with CRT). Because the MPACT trial suggested that GEM/NP may improve survival and have limited toxicity in patients with resected PCA, this regimen is currently being explored in the adjuvant setting. A Phase II multicenter randomized trial (NCT01964430) aims to evaluate whether adjuvant GEM/NP is associated with a delay or prevention of relapse or death in comparison with GEM alone. Patients will be randomized to 6 months of GEM (1000 mg/m^2) and NP (125 mg/m^2), or GEM alone (1000 mg/m^2). An additional Phase II study (NCT02047513) aims to evaluate NAdj plus adjuvant versus adjuvant GEM/NP. Patients with resectable PCA will be randomized to either two cycles of NAdj GEM plus NP followed by surgery and adjuvant GEM plus NP, or surgery followed by six cycles of GEM plus NP CTX. A recently initiated Phase III trial (NCT01526135) serves to evaluate mFOLFIRINOX (omission of bolus 5-FU) versus GEM in resected PCA (I = 490). Trial enrollment began in 2012 and endpoints will include DFS, OS, and toxicity. A current Phase I/II trial (NCT01693276) is accruing patients to evaluate survival and local control in patients with LUPC receiving GEM/NP CTX both before and after CRT with 60 Gy IMRT (2-Gy fractions). The Phase II/III SCALOP-2 trial (NCT02024009) has recently been developed in the United Kingdom to analyze survival, toxicity, and QOL associated with CRT including GEM/NP (with or without capecitabine or nelfinavir) as well as GEM/NP alone in the LUPC setting.

The challenge with oligometastatic PCA is when to treat the primary tumor and systemic disease as opposed to primarily providing palliative care. These decisions rely heavily on patient selection; of all patients diagnosed with PCA, there is a subgroup of patients who have a low burden of metastatic disease. If these select patients can be identified, physicians will know when to proceed with aggressive treatment strategies such as SBRT, radioembolization, ablation, or resection.

Novel agents are emerging for the treatment of metastatic PCA such as nonbiologic, nanoparticle paclitaxel (NBN-Pac),[273] sunitinib,[274] and a Hh pathways inhibitor called GDC-0449 (NCT01088815).

The treatment of patients with poor PS remains controversial as approximately 50% of the PCA population (23,000) has a poor PS, advanced age, or other comorbidities preventing them from eligibility for clinical trials. Additional studies are needed to define treatment regimens and develop techniques to improve survival for this patient population.

Research on predictive and prognostic biomarkers is crucial for the future of PCA management. Understanding the genetic mutations and underlying biological processes that are associated with a patient's tumor and proliferation of cancerous cells will confer an advantage in more accurate diagnosis and staging such that individualized treatment decisions may ultimately be possible. SPARC expression is increasingly studied as high expression is suggestive of improved survival. Investigation of tumor radiosensitivity in PCA holds promise as a modern method to predict tumor response and clinical outcome.[275] Furthermore, circulating tumor DNA may be able to differentiate between localized and metastatic disease, detect tumor burden, and evaluate resistance or response to therapy.[276,277] To establish a relationship between genetic features, tumor dynamics (e.g., patterns of failure, sensitivity), and clinical outcome (e.g., tumor response, survival, quality of life), next-generation sequencing and mathematical modeling will be employed as we advance toward personalized medicine.

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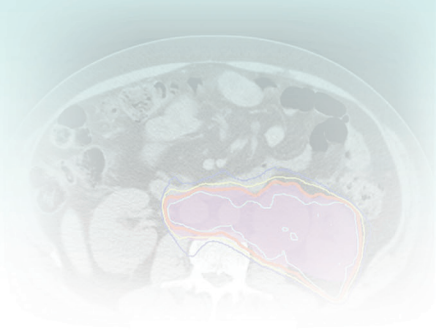
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CHAPTER

49 Hepatobiliary Cancer



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INCIDENCE

Globally, hepatobiliary cancer is the fifth-most common cause of cancer and the second cause of cancer death. In 2015, the expected incidence of hepatobiliary cancer in the United States was 46,570 cases, with 28,250 deaths.

BIOLOGIC CHARACTERISTICS

The primary risk factors for hepatocellular carcinoma (HCC) are chronic hepatitis B infection and hepatitis C infection, although liver cirrhosis from any cause increases the risk. The occurrence of cholangiocarcinoma is especially high in patients with primary sclerosing cholangitis. Gallbladder cancer may be related to cholelithiasis.

STAGING EVALUATION

In addition to a history and physical for cancer signs and symptoms, underlying liver disease and liver function need to be considered. The workup includes a complete blood count, liver function tests, liver enzymes, and multiphasic liver computed tomography (CT) or magnetic resonance (MR) imaging, chest and pelvis CT. The evaluation of biliary tumors usually also includes endoscopic retrograde cholangiography or MR cholangiopancreatography.

PRIMARY THERAPY

For hepatobiliary tumors, the best outcomes are seen in patients who are treated with surgery. Patients with resected early stage HCC have a 5-year overall survival (OS) of 30% to 50%; 5-year OS for cholangiocarcinoma ranges from 10% to 40% following surgery, with worse outcomes in hilar cancers. Liver transplantation for selected patients with HCC and hilar cholangiocarcinoma is associated with 5-year OS ranging from 70% to 85% (extrahepatic cholangiocarcinoma [EHCC], transplant alone, 5-year OS 20% to 35%). Preoperative concurrent chemoradiation (chemoRT) plus transplant can result in excellent long-term outcomes (5-year OS of 65% to 74%) in carefully selected patients with EHCC that are unresectable with standard surgery. Five-year OS for gallbladder cancer generally ranges from less than 10% to 30%.

Radiofrequency ablation (RFA) and other ablative techniques can also lead to cure in selected HCC. There is a growing literature on radiation therapy (RT) for early stage HCC, with excellent long-term outcomes in selected patients.

ADJUVANT THERAPY

For HCC, there is no role for adjuvant therapy following surgery or transplant. For biliary carcinoma, it has been suggested that adjuvant chemoRT reduces the risk of relapse, especially in the setting of positive nodes or margins.

LOCALLY ADVANCED DISEASE

For locally advanced HCC, transarterial chemo-embolization (TACE) is associated with a survival benefit compared to best supportive care. Sorafenib is used in patients unsuitable for TACE and also improves survival. RT for locally advanced HCC has been associated with long-term local control, but there is a lack of level-1 evidence.

For locally advanced biliary carcinomas, RT plus concurrent chemotherapy (chemoRT) alone or plus brachytherapy may lead to sustained local control and higher than expected OS. As noted previously, preoperative chemoRT plus liver transplant yields excellent results in carefully selected patients.

PALLIATION

Gemcitabine plus cisplatin had better OS and progression-free survival than gemcitabine alone in a Phase III trial of patients with metastatic or locally advanced biliary cancer (EHCC, gallbladder, or ampullary; 75% had metastases).

Low-dose whole-liver RT may reduce pain or discomfort from HCC unsuitable for standard therapies. RT may also be used for biliary obstruction from cholangiocarcinoma, although biliary stents are the preferred palliative intervention.

Hepatobiliary carcinoma includes HCC, gallbladder cancer, EHCC, and intrahepatic cholangiocarcinoma (IHCC). Globally, hepatobiliary carcinoma is the fifth-most common cause of cancer, and the second-most frequent cause of cancer death.[1] In 2015, the estimated number of new cases in the United States was 46,570, with 28,250 deaths.[2] Relative 5-year survival in the United States has increased from less than 5% in the 1970s to 18% from 2003 to 2009.[1]

Liver cancer is one of the fastest-rising causes of cancer and cancer death in North America, largely as a result of the hepatitis C epidemic.[3] Obesity and nonalcoholic steatohepatitis (NASH) are also an increasing cause of cirrhosis and subsequent HCC. A similar increase in the incidence of IHCC has been reported but for less clear reasons. This may be partially because of the misclassification of hilar cholangiocarcinoma (Klatskin tumors) as IHCC instead of EHCC.[4,5]

The best therapy for hepatobiliary tumors is resection, but only a minority of patients is suitable for surgery because of locally advanced cancer or impaired liver function. Nonsurgical options for HCC include RFA, TACE, sorafenib, and RT. RFA can control HCCs less than 3 cm, which are not adjacent to large vessels. There is a growing literature on the use of RT for the treatment of early stage HCC, with excellent long-term outcomes; however there are no comparative studies. For locally advanced HCC, TACE improves survival compared to best supportive care (2-year OS 63% versus 27% in patients with hepatitis C, and 31% versus 11% in patients with hepatitis B).[6,7] Sorafenib improves survival in HCC unsuitable for TACE. For patients with metastatic or locally advanced biliary carcinoma, gemcitabine plus cisplatin improves median survival from 8.1 to 11.7 months, compared to gemcitabine alone (75% of patients had metastases).[8]

RT did not historically played a role in the treatment of HCC, largely as a result of the low tolerance of the whole liver to RT.[9,10] It was not until conformal RT planning and intensity-modulated radiation therapy (IMRT), that delivery of high doses to focal liver cancers became possible. Protons and more recently stereotactic body radiation therapy (SBRT) have been used to treat selected, hepatobiliary cancers. RT (external beam or brachytherapy) has been associated with improved local control and higher than expected survival rates in locally advanced cholangiocarcinoma, and preoperative chemoRT plus liver transplant can result in excellent 5-year OS in carefully selected patients.

EPIDEMIOLOGY AND ETIOLOGY

Epidemiology

The most common hepatobiliary cancer is HCC, followed by gallbladder cancer, EHCC, and IHCC. About half of cholangiocarcinomas arise in the perihilar region (Klatskin tumor).[11] Other cancers of the liver, such as carcinoid tumors, hepatoblastoma, angiosarcoma, and leiomyosarcoma, are rare. HCC and IHCC are twice as common in men as in women, gallbladder cancer is about three times more common in women, and EHCC occurs with approximately equal frequency.[5]

Worldwide, liver cancer is the fifth and seventh most common cancer and the second and sixth most common cause of cancer death in men and women, respectively.[12] HCC accounts for 70% to 85% of liver malignancies, and there is considerable variation in the incidence globally, which largely mirrors the variation in the incidence of hepatitis B infection.[12] In Asia, southeast Asia, and middle/western and sub-Saharan Africa, HCC is 15 to 100 times more common than in North America,[13] although the incidence is increasing in the United States and Europe.[14]

Gallbladder cancer also has substantial geographic variation. The incidence in northeastern Europe is more than 20 times higher than in the United States, and it is common in Chile.[15] Although EHCC has a fairly uniform incidence, IHCC is more common in southeast Asia than in other parts of the world, likely because of the higher incidence of liver fluke in this region.

Hepatobiliary carcinoma accounts for about 2% of new cancer cases in the United States[16]; however, there has been a significant increase in HCC incidence and death from HCC and IHCC, in North America, over the past 30 years. From 1992 to 2010, the incidence of HCC and IHCC increased 3.7% and 2.9% per year in males and females, respectively, while deaths increased 2.3% and 1.4% per year in males and females.[1] This change is as a result in part of increasing hepatitis C infection, increase in immigrants from hepatitis B–endemic countries, and increasing NASH.

In the United States, HCC is about four times more common in Asians than whites, and two times more common in African Americans than in whites.[17] Gallbladder cancer is 15 times more common among Native American women than white women in New Mexico.[18] Other hepatobiliary tumors are of approximately equal distribution or show a slight preponderance among whites.

Etiology

Hepatocellular Carcinoma

The primary risk factor for HCC is chronic viral hepatitis B. In developing countries, approximately 60% of HCC is caused by hepatitis B, and 33% is caused by hepatitis C virus. In Korea and Taiwan, approximately 90% of patients with HCC are positive for hepatitis B surface antigen (HBsAg). Prospective studies found that hepatitis B carriers have a 200-fold increase in relative risk for HCC.[19] The risk of HCC is increased in patients with hepatitis C, with a 17-to 20-fold increase compared to people who are negative for hepatitis C. Cirrhosis resulting from nonviral etiologies, including alcohol, NASH, autoimmune chronic active hepatitis, hemochromatosis, and alpha1-antitrypsin deficiency, is responsible for a substantial proportion of HCC in the United States.[14,20] NASH results from metabolic syndrome, obesity, insulin resistance, hypertriglycerimia, and low low-density lipoprotein. Increased free fatty acids in the liver lead to NFKB activation and inflammation and cirrhosis.

Aflatoxin B, a metabolite of *Aspergillus flavus* found in stored grain and peanuts in humid parts of Africa and Asia, has been linked with HCC development.[20] A reactive intermediate metabolite of aflatoxin B binds to guanine, which is excised and replaced with thymidine. This mutation is commonly found in the *TP53* tumor suppressor gene in HCC occurring in areas of high aflatoxin ingestion.

Gallbladder Cancer

Traditional risk factors for gallbladder cancer are female gender and chronic cholelithiasis.[15] Gallbladder cancer is two to six times more common in women than in men, with significant geographic variability correlating with cholelithiasis prevalence.[21] Although more than two thirds of patients with gallbladder cancer have cholelithiasis, only 1% to 3% of patients with cholelithiasis will develop gallbladder cancer.[22] Among patients with cholelithiasis, typhoid carrier state, smoking, high intake of fried food and green leafy vegetables, and diabetes have been associated with gallbladder cancer.[23,24] Additional reported risk factors include smoking, obesity, chemical exposures, family history of gallbladder disease, and reproductive factors including increasing parity, number of pregnancies, and younger age at menarche.[15,18,24,25]

Cholangiocarcinoma

Risk factors for development of cholangiocarcinoma include liver fluke infection, hepatolithiasis, choledochal cysts, and thorium dioxide exposure.[26] Primary sclerosing cholangitis (PSC) is the most common risk factor in the West, with a lifetime risk of 5% to 10%.[27] IHCC development is associated with both hepatitis B and hepatitis C infection, as well as cirrhosis.[28] Other risk factors for cholangiocarcinoma include inflammatory bowel disease independent of PSC, smoking, alcohol consumption, fatty liver disease, diabetes, cholelithiasis, and choledocholithiasis.[26]

PREVENTION AND EARLY DETECTION

Hepatocellular Carcinoma

The prevention of HCC by hepatitis B vaccination has been supported by the reduced childhood HCC rates in Taiwan after introduction of a nationwide vaccination program in 1986.[19] The incidence of HCC among 6- to 14-year olds significantly declined from 0.7 to 0.36 per 100,000, with corresponding reductions in mortality, and larger differences expected in the future as the immunized population ages.

Serum alpha-fetoprotein (AFP) has limited utility on its own for screening HCC, even in high-risk populations.[29] In contrast, early detection of HCC in endemic areas of hepatitis B was demonstrated with use of liver ultrasonography (US) and AFP for screening high-risk populations. In a Chinese trial, approximately 19,000 people were randomized between screening AFP and US every 6 months compared to observation. Mortality from HCC was significantly lower (83/100,000 versus 132/100,000) and survival was significantly better (5-year OS 46% versus 0%) in screened patients.[30] The National

Comprehensive Cancer Network practice guidelines recommend screening patients at high risk for HCC (hepatitis B carriers and cirrhotics), potentially suitable for treatment, with AFP and US every 6 months.[31]

Cholangiocarcinoma

There is no established screening or early detection method for cholangiocarcinoma. In patients with increased risk as a result of PSC, a screening strategy of serum CA 19-9 along with cross-sectional liver imaging has been employed.[32] Patients with CA 19-9 levels above 20 U/mL or abnormal liver imaging may undergo brushings for cytology, digital imaging analysis (DIA), and florescence in situ hybridization (FISH) analysis for early detection. Preliminary data suggests that the combination aneusomy on FISH and aneuploidy on FISH is associated with 50% to 64% sensitivity, and 100% specificity and positive predictive value.[32]

Potential preventive strategies for cholangiocarcinoma in high-risk regions include preventative and therapeutic programs for liver fluke infection,[33] vaccination against hepatitis B infection,[34] and modification of dietary factors including decreased consumption or alcohol, fermented meats and raw fish, and increased consumption of fruits and vegetables.[35] Even though cholelithiasis is a risk factor for gallbladder cancer[33] and cholangiocarcinoma, there is no evidence to justify cholecystectomy as a preventive measure.[18]

BIOLOGIC CHARACTERISTICS AND MOLECULAR BIOLOGY

Hepatocellular Carcinoma

The hepatitis C virus has been implicated in the pathogenesis of HCC but without evidence of host genome integration of the viral DNA.[13] Fragments of hepatitis B viral DNA are frequently found within the genome of the HCC,[13,20] leading to the hypothesis that viral integration activates oncogenes or interferes with tumor suppressor genes. The normal liver of patients with chronic hepatitis B infection shows viral DNA integration early in the course of the disease, suggesting that the HCC originated from clonal expansion of the affected hepatocytes.[36] Against this argument is the finding that the sites of viral DNA integration are not consistent and do not occur near known oncogenes or tumor suppressor genes. The most frequent amplifications of genomic material involve 1q, 8q, 6p, and 17q. Common losses involve 8p, 16q, 4q, and 17p. The viral DNA itself does not contain any known oncogenes. Therefore, if the integration of viral DNA is necessary for carcinogenesis, the mechanism may be caused by genomic instability from deletions and chromosomal rearrangement rather than specific oncogene activation or disruption of tumor suppressor genes.[36]

Hepatocarcinogenesis involves many pathways, such as those involving vascular endothelial growth factor (VEGF), epidermal growth factor (EGF), hepatocyte growth factor (HGF), and insulin like growth factor (IGF). VEGF binds to VEGFR, promoting HCC angiogenesis. EGF binds to the epidermal growth factor receptor (EGFR), triggering signal transduction via the RAS/MAPK pathway. HGF binds to the c-MET receptor, upstream of the RAS/MAPK pathway. Activation of the RAS/MAPK pathway leads to HCC growth and proliferation. Hepatocarcinogenesis may be related to the ability of the liver to respond to damage by regeneration. The continuous liver damage seen with chronic hepatitis or cirrhosis leads to increased turnover of hepatocytes. During normal hepatocyte regeneration, proto-oncogene activation and inactivation of suppressor genes occur. Chronic liver damage leads to a cellular reproduction, which may allow carcinogenic molecular changes to accumulate without repair.[36] The observation of apparent stepwise progression of small HCCs from regenerating nodules of liver cirrhosis supports this hypothesis.[37]

Cholangiocarcinoma

Inflammation appears to be a contributory factor to cholangiocarcinoma pathogenesis. Inflammatory signaling pathways are associated with DNA damage, blocking of apoptosis, and promotion of cell proliferation.[26] Development of malignant phenotype is associated with overexpression of proinflammatory cytokines in tumor stroma and upregulation of HER-2 signaling in epithelium.[37] Epigenetic factors including promoter region hypermethylation and microRNA dysregulation have been associated with development of cholangiocarcinoma.[8a] Dysregulation of developmental pathways including Notch signaling, Hedgehog signaling, and Wnt signaling may play a role in cholangiocarcinogenesis.[26]

Molecular analysis of IHCC specimens has suggested the presence of two distinct classes of IHCC with different outcomes. The more favorable inflammatory class is characterized by the activation of inflammatory signaling pathways, overexpression of cytokines, and STAT3 activation. The poorer prognosis proliferation class is characterized by activation of oncogenic signaling pathways including RAS, MAPK, and MET.[38] *KRAS* mutations have been associated with poor prognosis and are more commonly found in hilar EHCC than in IHCC or distal EHCC.[26,38a] Genomic profiling of EHCC specimens has suggested a poor prognosis group characterized by HER2 upregulation with frequent coactivation of ERBB3, EGFR, MET, and mTOR.[38]

PATHOLOGY AND PATHWAYS OF SPREAD

Primary liver tumors can be classified as benign or malignant and by their tissue of origin (hepatocyte or biliary). Benign tumors constitute 6% to 12% of all liver tumors and include hepatocellular hyperplasia, adenomas, hepatic cysts, mesenchymal hamartomas or hemangiomas, lipomas and fibromas. Of all malignant primary tumors, 85% to 95% are of epithelial origin (including HCC, fibrolamellar HCC, cholangiocarcinoma, and hepatoblastoma), whereas 1% to 3% are malignant mesenchymal tumors.

Hepatocellular Carcinoma

On gross examination, HCC appears as expanding (well-defined margin), infiltrative (poorly defined margin), or multifocal (with multiple tumors throughout the liver).[39] The microscopic appearance of HCC is similar to normal liver, both in cytologic features and in its platelike growth.[40] HCC commonly invades the portal vein, the inferior vena cava (IVC) and sometimes the hepatic vein. It may also invade the diaphragm. Portal nodes are the most likely nodes to be involved, but spread to celiac, gastric, and peritoneal nodes may also occur.[17] Metastases are uncommon at presentation, most often involving the abdominal cavity, the lungs, or bone.

Fibrolamellar HCC is a unique subtype that makes up about 5% of the cases in North America.[40] It is associated with the longest survival of HCC subtypes and is typically found in young women. Grossly, fibrolamellar carcinoma is an expanding, sclerosing tumor, characterized by septa of retracted collagenous structures radiating from a central region.[39] On cytologic examination, the tumor cells are large and polygonal, with a granular cytoplasm resulting from numerous

mitochondria and abundant fibrous stroma arranged in parallel lamellae around nests, cords, and sheets of tumor cells.[41]

Gallbladder Cancer

More than 98% of gallbladder cancers are adenocarcinomas and two thirds are moderately or poorly differentiated. Rare histologic types include squamous cell carcinoma, adenosquamous carcinoma, carcinoid, gastrointestinal stromal tumor, and small cell carcinoma.[42] Most gallbladder cancers arise in the setting of inflammation and associated gastric type or intestinal type metaplasia that progresses to dysplasia and then cancer.[43] Transformation from adenoma to adenocarcinoma also occurs in the gallbladder but is seen in less than 1% of cases.[42]

The gross appearance of gallbladder adenocarcinoma can vary from localized nodular growths to involvement of the entire organ.[44] Histologically, both grade and vascular invasion are of prognostic value. Papillary adenocarcinoma is a variant histologic type that makes up about 5% of the total number of cases and a significantly better prognosis than the more common type.[45] Mucinous carcinoma is another variant of adenocarcinoma, occurring in about 5% of cases and associated with perforation of the gallbladder.[44] Liver invasion is common and may occur by direct spread through the thin wall and singular muscular layer of the gallbladder or by lymphatic spread along portal tracts.[46] Spread to regional lymph nodes including cystic, pericholedochal, hilar, common hepatic, pancreaticoduodenal, and celiac nodes in found in 45% to 55% of patients treated surgically who undergo pathologic nodal evaluation.[47-49] Up to 80% of T3-4 patients will have involvement of regional nodes.[49] About 40% of patients with gallbladder cancer present with distant metastatic disease, most commonly involving liver or peritoneum.[50] Despite increased use of cholecystectomy for gallstone disease, there has been no decrease in the proportion of patients presenting with advanced disease.[51]

Cholangiocarcinoma

Cholangiocarcinomas are typically classified by location as intrahepatic, perihilar, and distal.[11] Most cholangiocarcinomas are mucin-producing adenocarcinomas arising from cholangiocytes that line the biliary tree.[27,52] IHCC may be classified based on macroscopic growth pattern as mass forming, which is the most common type, periductal infiltrating extending along the bile duct, and intraductal, which may have a papillary or tumor thrombus appearance.[53] EHCC can have an intraductal or exophytic (mass-forming) growth pattern. Exophytic tumors may exhibit a nodular or a periductal infiltrating growth pattern.[54] An abundant fibrous stroma with tumor cells in the center is characteristic.[50] As with gallbladder cancer, the papillary variant histologic type has a better prognosis.[55]

Cholangiocarcinoma typically spreads by direct extension along the biliary tree.[56] Tumor involvement of the cystic, hilar, or celiac lymph nodes is found in 30% to 50% of patients.[11,17,55] The incidence of distant metastases, most commonly involving liver, lung, or distant nodal sites, is about 30%, with a lower incidence of peritoneal disease than for gallbladder cancer.[11,56,57]

CLINICAL MANIFESTATIONS, PATIENT EVALUATION, AND STAGING

Symptoms and Signs

Site of origin can alter the typical presentation of patients with hepatobiliary cancer. Patients with HCC or IHCC frequently present with right upper abdominal or epigastric pain or discomfort.[13,58-60] The pain is usually dull but may be sharp because of tumors causing capsular stretch. Occasionally, patients with HCC present with sudden, severe pain related to an acute HCC rupture and bleed. Patients may also present with awareness of an abdominal mass or increased girth related to ascites. Occasionally, HCC in patients with known cirrhosis may cause deterioration of liver function, leading to ascites, variceal bleed, jaundice, or encephalopathy. In contrast to primary liver tumors, 90% of patients with EHCC present with painless jaundice.[28] Cholangitis is present in 10% of patients, but more than half have nonspecific symptoms including malaise, abdominal discomfort, nausea, anorexia, and weight loss.[28] Patients with gallbladder cancer commonly present with abdominal pain and jaundice and may also have weight loss, anorexia, and fatigue.[61-63]

The most common physical finding in patients with primary hepatic tumors is hepatomegaly.[59,60] The liver is often smooth but may be nodular from tumor or cirrhosis. Patients with HCC may have a hepatic bruit because of a highly vascular tumor. Splenomegaly is also common in patients with cirrhosis or from portal hypertension secondary to tumor invasion of the portal vein. Ascites is a particularly ominous finding because it represents either peritoneal tumor involvement or hepatic dysfunction resulting from advanced cirrhosis, extensive replacement of the liver with tumor, or vascular tumor invasion. HCC invasion to the hepatic vein may lead to rapid decline in liver function, tense ascites, and tender hepatomegaly.

Patients with EHCC or gallbladder cancer are usually jaundiced and may have hepatomegaly or right upper quadrant tenderness on examination. Although a mass may be palpable, patients with gallbladder cancer are often thought to have benign disease until laparotomy and cholecystectomy.

Laboratory Studies

The goals of the workup of patients with malignant hepatobiliary tumors are to define the extent of the tumor and to assess liver function. The workup includes a complete blood count, liver function tests (albumin, bilirubin and coagulation studies), liver enzymes, and routine biochemistry (Table 49-1).

TABLE 49-1 Diagnostic Algorithm for Hepatobiliary Cancers

GENERAL
• History
• Physical examination
LABORATORY STUDIES
• Complete blood count
• Biochemistry panel, including liver function studies (albumin, bilirubin) and liver enzymes
• Coagulation studies (INR)
• Serum CA19-9 (if suspicious for cholangiocarcinoma)
• Alpha-fetoprotein (if suspicious for hepatocellular carcinoma)
• Hepatitis studies (HBsAg, HBsAb, HBcAb, anti-HCV)
RADIOGRAPHIC STUDIES
• Multiphasic liver CT or MR
• Transhepatic or endoscopic cholangiography (if bile duct blockage is present)

Anti-HCV, *Antibody to hepatitis C virus;* CT, *computed tomography;* HBcAb, *hepatitis B core antibody;* HBsAb, *hepatitis B surface antibody;* HBsAg, *hepatitis B surface antigen;* MR, *magnetic resonance;* INR, *international normalized ratio.*

Serum AFP is a widely used tumor marker for HCC, with normal values of 20 µg/L or less, and levels greater than 400 µg/L (4000 µg/L in patients with hepatitis) strongly suggestive of HCC.[64] Elevations in AFP between 20 µg/L and 400 µg/L may represent either an exacerbation of hepatitis or HCC.[29] Approximately 10% to 15% of HCCs do not secret AFP.[65] Serum CA19-9 has value as a tumor marker for cholangiocarcinoma but is less specific for EHCC than for IHCC as levels are affected by cholestasis and cholangitis.[26]

HCC outcomes in patients with hepatitis B or hepatitis C differ, as does toxicity and tolerability of treatment. High viral load before therapy has been associated with worse survival,[66] and reactivation of hepatitis B has been reported following treatment for HCC. Screening for viral hepatitis should be considered in all at-risk individuals.[67]

Approximately 5% of patients with HCC have a paraneoplastic syndrome,[68] such as hypoglycemia, erythrocytosis, hypercalcemia, or hypercholesterolemia.[59]

Radiographic Studies

Patients with suspected hepatic malignancy are often evaluated initially with US, which is operator dependent and less helpful in obese patients. The use of Doppler contrast US and harmonic imaging have improved its usefulness.[68,69] In planning for treatment, CT and MR imaging are the primary imaging modalities because of their ability to display hepatic segmental anatomy, the extent of tumor invasion to vasculature, and extrahepatic spread. Multislice spiral CT is required for liver imaging to be done in a single breath-hold to improve spatial resolution. Multiphasic imaging (arterial hepatic, portal venous, and delayed phase) is vital for assessing lesion vascularity, extent of tumor, and for diagnosis.[69] HCC is hypervascular and typically displays enhancement during the hepatic arterial phase with washout in venous and delayed phases (Figure 49-1), whereas cholangiocarcinoma demonstrates delayed enhancement. Modern MR protocols usually include parenchymal imaging with one or more types of contrast agents, MR angiography, or MR cholangiopancreatography (MRCP). Some have suggested that MR should be the imaging examination of choice for the liver in patients with cirrhosis because of the superior contrast resolution and inherent capability of multiplanar evaluation.[69,70] CT of the thorax, abdomen, and pelvis is recommended to rule out extrahepatic spread. Positron emission tomography (PET)-CT has been used to evaluate extrahepatic metastases; it is not as sensitive as multiphasic liver CT or MR for evaluating the hepatic extent of tumor, but it may be complementary to CT, MR, and MRCP, especially for Klatskin tumors.

In patients with hilar cholangiocarcinoma, MRCP has limited the role of endoscopic cholangiopancreatography to instances when drainage and decompression of the biliary system are required.[68] In addition to being noninvasive, MRCP has an accuracy of 95% in defining the location and extent of bile duct involvement.[71,72] The accuracy of prediction of vascular involvement and hepatic parenchyma invasion is around 70% to 80%[73,74] PET-CT has not been shown to be better than contrast enhanced CT scan for the detection of cholangiocarcinoma. Both modalities are poor for detection of regional lymph node metastases.[75] Endoscopy US with fine-needle aspiration of regional nodes has the highest sensitivity for the detection of nodal metastases.[54]

The usual appearance of EHCC on cholangiography is a stricture at the site of involvement with dilatation of the biliary

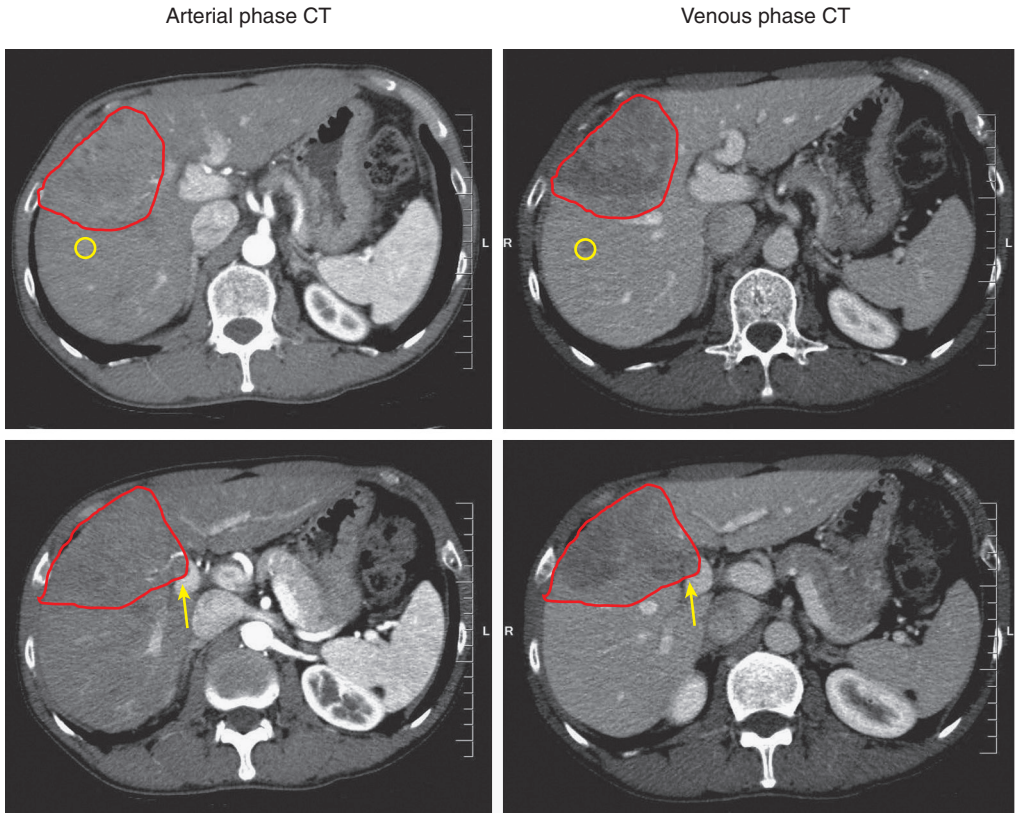


Figure 49-1 Arterial and delayed venous phase exhale breath-hold CT simulation images. The primary HCC *(red)* and satellite HCC *(yellow)* demonstrate arterial enhancement and washout on venous phase images. The *yellow arrow* highlights HCC invasion to the portal vein.

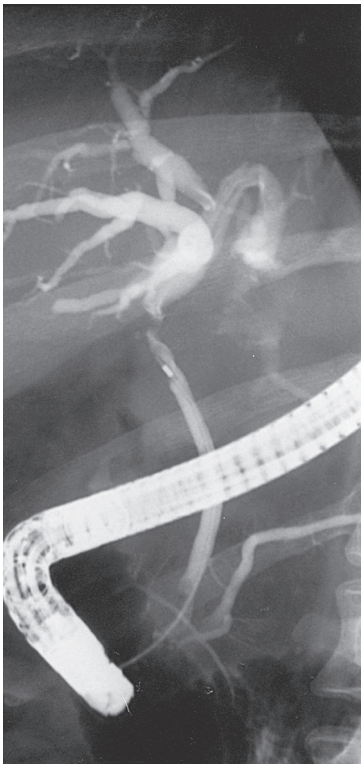


Figure 49-2 Endoscopic retrograde cholangiogram of a patient with a cholangiocarcinoma of the common hepatic duct. A stricture of the common hepatic duct can be seen proximal to the catheter, with dilatation of the intrahepatic biliary tree.

tract proximal to the stricture (Figure 49-2). The tumor itself may extend for some distance along the biliary tract. US, CT, and MR imaging of the abdomen frequently show only intrahepatic biliary dilatation (with or without hepatic atrophy) but no identifiable mass.[76] One area of particular difficulty is distinguishing bile duct cancer from PSC, with the latter typically showing diffuse rather than focal biliary narrowing.[77]

Although US is frequently obtained in patients suspected of having gallbladder disease, it is rarely helpful in diagnosing gallbladder cancer.[63] CT scan is the imaging modality of choice for postoperative evaluation of residual and metastatic disease.

Diagnosis

Hepatocellular Carcinoma

Multiphasic CT or MR imaging is most often used to obtain a HCC diagnosis with high predictive value, so that a biopsy can be avoided in most patients. Guidelines recommend no need for a biopsy of lesions greater than 1 cm in diameter in at-risk patients if there is classic arterial enhancement and delayed washout.[78] If there are nonclassic changes, a second imaging modality should be used. If that imaging study does not demonstrate classic HCC characteristics, then a biopsy is required. Repeat imaging is recommended for lesions less than 1 cm. There is a small risk of bleeding or tumor spillage following percutaneous biopsy.

Cholangiocarcinoma

Establishing a diagnosis of hilar cholangiocarcinoma can be difficult given the desmoplastic nature of the malignancy and the scant number of cells obtained by endoscopic brushing.[52] Conventional exfoliative or brush cytology has a sensitivity of around 50% for detection of cholangiocarcinoma.[79] The finding of polysomy using FISH is specific for malignancy with a positive predictive value approaching 100%.[225,226] The finding of polysomy on FISH combined with a dominant malignant stricture may be considered sufficient for diagnosis of cholangiocarcinoma.[52] Endoscopic US may be useful for evaluation of patients with suspected hilar cholangiocarcinoma, but transperitoneal fine-needle aspiration of the primary tumor is not recommended because of the potential for tumor seeding.[80]

Staging

The American Joint Committee on Cancer staging manual, seventh edition, has defined separate TNM staging systems for HCC, IHCCs, gallbladder tumors, and EHCCs and is divided into perihilar and distal bile duct lesions[81] (Table 49-2). The staging for both gallbladder cancers and EHCC tumors is primarily surgical.

For HCC, the Barcelona Clinic Liver Cancer (BCLC) staging system is widely used for treatment decision making (Figure 49-3). It is dependent on tumor factors, liver function (Child-Pugh score), and performance status. Very early (O) and early (A) BCLC stage HCC are potentially curable, whereas regional and systemic therapies are generally used for intermediate stage (B) and advanced stage (C) BCLC stage HCC.

Follow-up

After transplant or locoregional therapy with surgery, RT or RFA, imaging is recommended every 3 to 6 months for 2 years, and then every 6 to 12 months for 3 more years.

PRIMARY THERAPY

Hepatocellular Carcinoma

Very early and early (BCLC stage O and A) HCC are potentially curable with a variety of treatment. The most established treatments are hepatectomy, liver transplant, and RFA. Resection and transplantation result in the best outcomes, with 5-year OS of 50% to 85%. RFA has excellent outcomes in selected small HCC, with 5-year OS of 50% to 70%.[83-86] There is an emerging literature on the use of definitive RT for early stage HCC.

Surgical Resection

HCC resection is challenging because most patients have underlying liver dysfunction. The potential for tumor control needs to be balanced against the risk of complications. Tumor location, baseline liver function, and tumor biology should all be considered when making the decision for resection. In patients with cirrhosis considered for resection, portal hypertension is one of the strongest predictors of poor outcome, and surgery should not be offered in patients with manifestations of portal hypertension including hepatic encephalopathy, gastrointestinal bleeding, ascites, esophageal varices, splenomegaly, platelet count less than 100,000/mm^3, or a hepatic venous pressure gradient greater than or equal 10 mm Hg. Portal vein embolization (PVE) is sometimes used before hepatectomy to assess the ability of the future liver remnant to hypertrophy following surgery. The ability to hypertrophy after PVE is correlated with lower risk of liver failure postoperatively, and lack of hypertrophy has been suggested to be a contraindication to hepatectomy.

Anatomic resections are recommended for HCC, provided that adequate remnant liver volume can be preserved; however, nonanatomic resections are an option, and there is a growing literature on laparoscopic resections. Complications and

TABLE 49-2 TNM Classification for Hepatobiliary Cancers

PRIMARY TUMOR: LIVER	
T0	No evidence of primary tumor
T1	Solitary tumor without vascular invasion
T2	Solitary tumor with vascular invasion, or multiple tumors, none more than 5 cm
T3a	Multiple tumors, any more than 5 cm
T3b	Tumors involving a major branch of the portal or hepatic vein(s)
T4	Tumor(s) with direct invasion of adjacent organs other than the gallbladder or with perforation of the visceral peritoneum
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis
M0	No distant metastases
M1	Distant metastases
PRIMARY TUMOR: INTRAHEPATIC BILE DUCT	
T0	No evidence of primary tumor
Tis	Carcinoma in situ (intraductal tumor)
T1	Solitary tumor without vascular invasion
T2a	Solitary tumor with vascular invasion
T2b	Multiple tumors, with or without vascular invasion
T3	Tumor perforating the visceral peritoneum or involving the local extrahepatic structures by direct invasion
T4	Tumor with periductal invasion
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis present
PRIMARY TUMOR: GALLBLADDER	
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Tumor invades lamina propria or muscle layer
T1a	Tumor invades lamina propria
T1b	Tumor invades muscle layer
T2	Tumor invades perimuscular connective tissue; no extension beyond serosa or into liver
T3	Tumor perforates the serosa (visceral peritoneum) or directly invades the liver or one other adjacent organ or structure, such as the stomach, duodenum, colon, pancreas, omentum, or extrahepatic bile ducts
T4	Tumor invades main portal vein or hepatic artery or invades multiple extrahepatic organs or structures
N0	No regional lymph node metastasis
N1	Metastases to nodes along the cystic duct, common bile duct, hepatic artery, or portal vein
N2	Metastases to periaortic, pericaval, superior mesentery artery, or celiac artery lymph nodes
PRIMARY TUMOR: PROXIMAL EXTRAHEPATIC CHOLANGIOCARCINOMA/PERIHILAR (RIGHT, LEFT, AND COMMON HEPATIC DUCT)	
Tis	Carcinoma in situ
T1	Tumor confined to the bile duct, with extension up to the muscle layer or fibrous tissue
T2a	Tumor invades beyond the wall of the bile duct to surrounding adipose tissue
T2b	Tumor invades adjacent hepatic parenchyma
T3	Tumor invades unilateral branches of the portal vein or hepatic artery
T4	Tumor invades main portal vein or its branches bilaterally, common hepatic artery, or the second-order biliary radicals bilaterally, or unilateral second-order biliary radicals with contralateral portal vein or hepatic artery involvement
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis (including nodes along the cystic duct, common bile duct, hepatic artery, and portal vein)
N2	Metastasis to periaortic, pericaval, superior mesenteric artery, or celiac artery lymph nodes
PRIMARY TUMOR: DISTAL EXTRAHEPATIC CHOLANGIOCARCINOMA (FROM CYSTIC DUCT INSERTION INTO COMMON HEPATIC DUCT)	
Tis	Carcinoma in situ
T1	Tumor confined to the bile duct wall
T2	Tumor invades beyond the wall of the bile duct
T3	Tumor invades the gallbladder, pancreas, duodenum, or other adjacent organs without involvement of the celiac axis or the superior mesenteric artery
T4	Tumor involves the celiac axis or the superior mesenteric artery
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis
DISTANT METASTASIS	
M0	No distant metastasis
M1	Distant metastasis

From Edge SB, Byrd DR, Compton C, et al, editors: AJCC cancer staging manual, ed 7, New York, 2009, Springer.

postoperative liver insufficiency are closely associated with increased mortality following hepatectomy. State-of-the-art surgery is associated with operative mortality rates of 1% to 3% and 5-year OS of 40% to 50%.[87] Approximately 40% to 80% of patients relapse. Positive resection margins, microvascular invasion, poorly differentiated HCC, and satellite lesions predict for relapse.[87]

Adjuvant Therapy

Adjuvant or neoadjuvant systemic, regional chemotherapy, or TACE has not been shown to be beneficial following surgery in high-risk HCC.[88] There is limited evidence that adjuvant Lipiodol therapy or immunotherapy may improve disease free survival after HCC resection.[89]

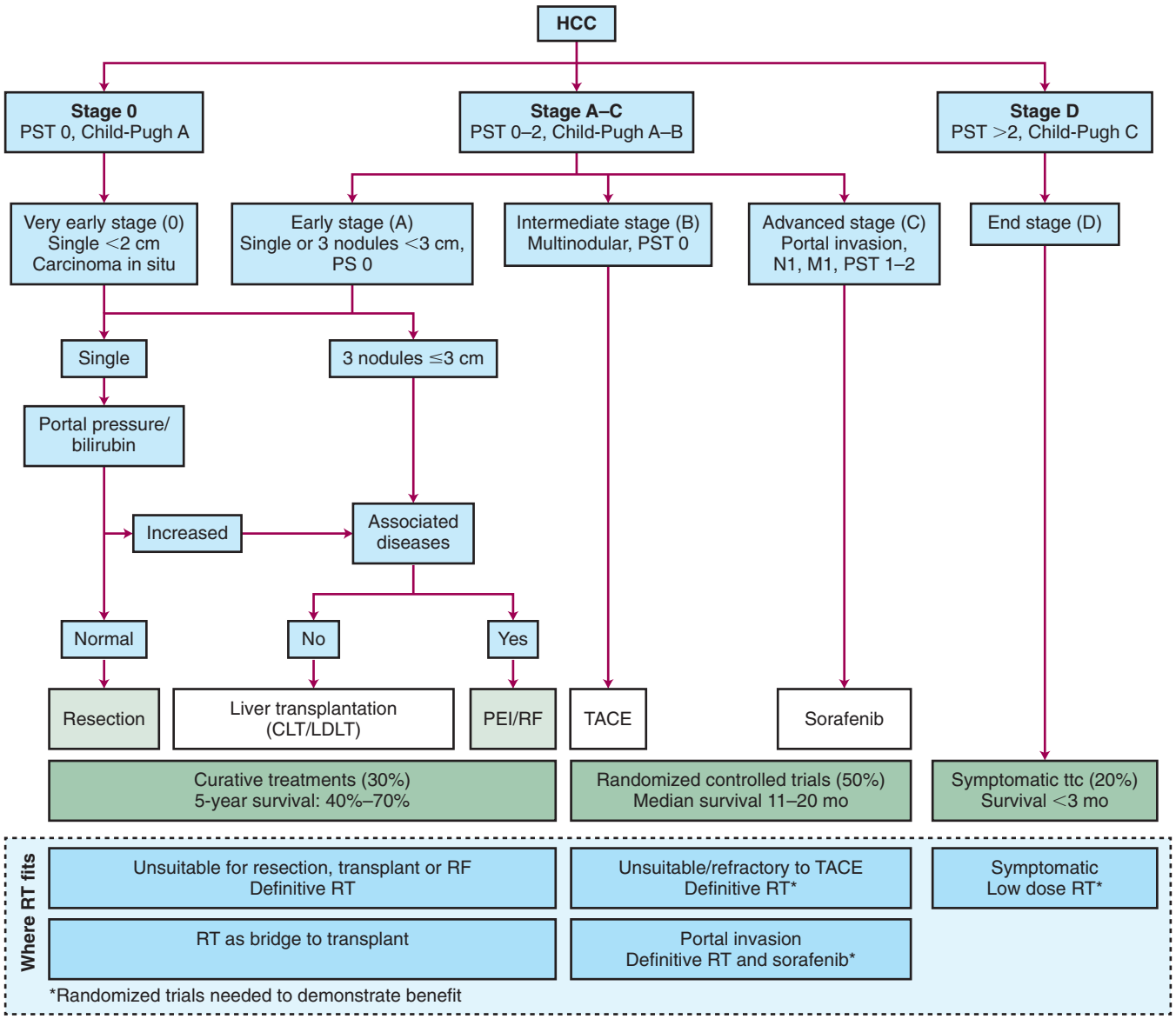


Figure 49-3 BCLC classification for HCC with potential role for RT highlighted in bottom two rows. CLT, cadaver liver transplant; LDLT, living donor live transplant; M, metastases; N, nodal stage; *PEI,* Percutaneous ethanol injection; *ttc,* treatment.
From Dawson LA: Overview: where does radiation therapy fit in the spectrum of liver cancer local-regional therapies? Seminars in radiation oncology, vol 21, no 4, Philadelphia, 2011, WB Saunders.

Liver Transplantation

An advantage of liver transplantation for patients with HCC and underlying cirrhosis is that the entire liver is removed, eradicating all microscopic and gross hepatic HCC and treating the underlying cirrhosis. Limitations of liver transplantation are the shortage of donor organs and the high cost. Only selected early HCC are eligible for transplantation (e.g., one lesion less than 5 cm),[90] and many patients drop off the wait list for a transplant because of HCC progression. Five-year OS of at least 70% and relapse rates lower than 15% are expected after transplant for HCC.[90,91] TACE, RFA, or RT are often used as bridging therapies for patients with HCC at risk of growing while on the wait list.

Percutaneous Ablation

RFA is an alternative treatment for small HCC with long-term survival in selected patients.[85,92] RFA involves placing a needle electrode in the tumor and applying a high-frequency alternating current to heat the surrounding tissue to produce necrosis. The best results are seen in tumors less than 3 cm that are not adjacent to large vessels.[92] In one review of 3670 patients treated by RFA, the mortality rate was 0.5% and the complication rate was 9%.[93] Subcapsular location and poorly differentiated HCC have been implicated in needle-track seeding. Comparative studies of RFA with surgery have been inconclusive. Ablation may also be accomplished with microwave, laser coagulation, or cryoablation or with the alcohol injection. A randomized trial demonstrated reduced rates of local progression (2% versus 11%) and improved survival (74% versus 57%) with RFA compared with percutaneous ethanol injection.[94] Cryoablation is associated with higher complications and inferior outcomes. Microwave and laser coagulation clinical data are emerging.[95]

Radiation Therapy As Definitive Therapy

Proton therapy has been used to treat early stage HCC with excellent outcomes, as recently reviewed by Dionisi et al.[96] Most studies, predominantly retrospective from Asia, have used standard or hypofractionation (e.g., 77 GyE in 35 fractions for tumors less than 2 cm from luminal tissues, 72.6 GyE in 22 fractions for tumors less than 2 cm from the porta hepatis, and 66 GyE in 10 fractions for peripheral tumors). Excellent 5-year OS ranging from 34% to 45% and 5-year local control (LC) of 83% to 90% have been observed, as summarized in Table 49-3.[97-101] Smaller prospective studies reported similar outcomes for 51 patients with peripheral HCC[101] and complete responses in selected patients who went on to liver transplantation following 63 GyE in 15 fractions.[102] Carbon ions (49.5 GyE to 79.5 GyE in 15 fractions) have also been used to treat early stage HCCs, with 5-year LC and OS of 80% and 25%, respectively.[100,103] Hypofractionated carbons (e.g., 40 GyE in 4 fractions) has also been used with excellent local control.[104]

A French multiinstutional prospective Phase II study of conformal RT (66 Gy in 2 Gy per fraction) in 25 Child-Pugh A and B patients with cirrhosis with early stage HCC (less than or equal to 5 cm for single nodules and less than or equal to 3 cm for two nodules) reported 78% local control at a median follow up of 29 months. Grade-4 toxicities occurred only in patients with Child-Pugh B (22%).[105]

SBRT (33 Gy to 60 Gy in three to eight fractions) results have also been reported in small prospective and larger retrospective studies for definitive treatment,[106-119] or as a bridge to transplant,[120] in patients with early stage HCC (Table 49-3). A Korean registry study of 93 patients with HCC (26% with Child-Pugh B, 1 cm to 6 cm) treated with 30 Gy to 40 Gy in three to four fractions reported 3-year LC and OS of 92% and 54%, respectively.[109] LC was 100%, 93%, and 76% for tumors less than 2 cm, 2 cm to 3 cm, and 3 cm to 6 cm, respectively. A Japanese retrospective study of 185 patients (84% T1, 27 Child-Pugh B) reported 3-year LC and OS of 91% and 70%, respectively, following 35 Gy to 40 Gy in four fractions.[107] A decline in Child-Pugh score was seen in 10% at 3 months. Other studies have had similar outcomes, as shown in Table 49-3.

Intrahepatic Cholangiocarcinoma

Surgery is the treatment of choice for resectable patients, but less than 20% are candidates for resection, usually as a result of the extent of hepatic involvement.[121] Of those who are resected, more than 60% relapse, most commonly in the remnant liver.[121,122] R0 resection is predictive of survival, but positive margins are common.[11] Five-year OS following resection ranges from 17% to 40% for all patients and 44% to 63% for R0 patients[11] and median survival is about 3 years.[121,122] In addition to margin status, other factors predictive of survival include regional node metastases, multiple tumors in the liver, tumor diameter greater than 5 cm, and cirrhosis.[11,121-123] Liver transplantation for IHCC is not standard because of high relapse rates and 5-year OS of only 20% to 30%.[124] The strategy of neoadjuvant therapy with chemotherapy and locoregional therapy with TACE or SBRT before transplant is being investigated.[124]

Gallbladder Carcinoma

Complete surgical resection is the only curative therapy for gallbladder cancer, but most nonincidentally discovered gallbladder cancers are not resectable for cure.[125,126] Even when surgery is performed with curative intent, complete resection (R0) is only achieved in about half of cases.[127] Most T1 cancers are discovered incidentally after cholecystectomy for cholelithiasis.[128] T1a cancers are adequately treated with simple cholecystectomy with 5-year OS of about 60%.[129] Extended cholecystectomy including resection of 2 cm of liver margin and dissection of N1 lymph nodes may be beneficial for patients with T1b cancers.[128,129] Five-year OS may be increased from 40% with simple cholecystectomy to 60% with extended cholecystectomy.[129] Diagnosis of incidental gallbladder cancer laparoscopically may require excision of the port sites given the 10% to 20% rate of port site recurrence.[128]

For patients with T2 cancers, extended cholecystectomy is associated with improved survival.[51,127,128] The most important prognostic factor for relapse is lymph node metastases. Positive nodes are found in about half of T2, most commonly in the pericholedochal and pericystic nodal regions followed by portal vein, hepatic artery, and peripancreatic nodes.[129a,130,131] Five-year OS may exceed 50% in pT2N0 patients, but falls to around 20% in patients who are node-positive.[48]

A minority of patients with T3-4 or node-positive disease may be cured with radical surgery alone.[132-138] Five-year OS is 20% to 25% for T3N0 or T1-2N1 disease but falls to less than 10% for T3N1 or T4 disease.[48] Lymph node metastases are found in 70% to 80% of T3 patients.[48,49] The role of more extensive surgery, including pancreaticoduodenectomy, right colectomy, and nephrectomy, has not been established. Paraaortic lymph node metastasis is present in 19% to 25% of patients with locally advanced disease,[139] but paraaortic lymphadenectomy is not warranted.[140]

Adjuvant Therapy

The majority of patients with gallbladder cancer experience disease relapse following curative intent surgery.[57] Following simple cholecystectomy, one literature review reported an 86% rate of local relapse in patients dying within 5 years of surgery.[141] Although isolated locoregional relapse is less common following extended cholecystectomy, locoregional relapse may approach 30%.[57] Despite the high risk of disease relapse, there are no prospective trials demonstrating a survival benefit to adjuvant therapy.

Retrospective studies suggest the possibility of benefit of adjuvant chemoRT. A Mayo Clinic series evaluated adjuvant chemoRT in 73 patients who underwent curative-intent surgery, 25 of whom received postoperative chemoRT (median dose of 50.4 Gy in 28 fractions with 5-fluorouracil [5-FU]–based concurrent chemotherapy).[142] Patients receiving adjuvant therapy had disease of a significantly higher stage, with 80% of the patients in the adjuvant group having stage II disease compared with only 21% in the surgery alone group ($p < 0.0001$). In the multivariate Cox model, increasing T and N classification as well as histologic type other than adenocarcinoma were significant predictors for worse OS rates. Additionally, adjuvant chemoRT was statistically significant for improved OS after adjusting for these multivariate prognostic factors (hazard ratio [HR] for death, 0.3; 95% CI, 0.13 to 0.69; $p = 0.004$). A Korean retrospective series of 100 patients and a Surveillance, Epidemiology and End Results (SEER) analysis both suggest a survival benefit to adjuvant chemoRT following resection in patients who are node positive.[143,144] In patients with pathologically evaluated lymph nodes, another SEER analysis found adjuvant RT to be associated with a 35% risk of death reduction.[48] A propensity score–matched analysis using SEER data also suggested a survival benefit to adjuvant RT (chemoradiation not evaluated) at 1 year, but not at 5 years.[145]

Extrahepatic Cholangiocarcinoma

Curative options for hilar EHCC include surgical resection and neoadjuvant chemoradiation followed by liver

TABLE 49-3 Selected Series of Radiation Therapy for Predominantly Early-Stage Hepatocellular Carcinoma

Study	No. Pts	CP Class	Tumor Size cm med (range)	PVT	Dose (Gy) GyE	No. Fx	Local Control				Survival				Grade ≥3 Toxicity
							1 year	2 year	3 year	5 year	1 year	2 year	3 year	5 year	
PROTONS															
Fukmitsu	51	A 80%, B	NA	0%	66	10	100%	92%	92%	88%	94%	70%	48%	39%	
Bush	76	A, B, C	5.7 (1.5-10) cm	5%	63	15	90%	75%	—	—	75%	55%	—	—	—
Nakayama	318	A 73%, B 24%, C 3%	NA	17%	72.6-77	22-35	—	—	—	83%	—	—	—	45%	1 gr 3 GI
Komatsu	242	A, B, C	<15	26%	56-84	10-38	—	—	—	90%	—	—	—	38%	8 pt
Chiba	162	A 51% B 38% C 11%	3.8 (1.5-14.5)	6%	50-84	10-26	—	—	—	87%	—	—	—	24%	3 biliary
SBRT					**Gy**										
Sanuki	185	A 96%, B	2.7 (0.8-5)	NR	30-40	5	99%	—	91%	—	95%	—	70%	—	13%, 10% decline in CP class
Jang	108	A, B	1 cm-7 cm	NR	51 (33-60)	3	—	87%	—	—	—	63%	—	—	10%
Yoon	93	A 76%, B	1 cm-6 cm	0%	45 (30-60)	3-4	95%	—	92%	—	86%	—	54%	—	10% decline in CP class
Bibault	75	A, B	3 cm-4.4 cm	NR	45 (24-45)	3	90%	—	—	—	79%	—	—	—	16%
Honda	30	A, B	1 cm-3 cm	0%	48-60	4-8	100%	—	—	—	100%	—	100%	—	14%
Huang	36	A, B, C	1.1-12.3 cm	NR	37 (25-48)	4-5	98%	—	—	—	—	64%	—	—	3%
Andolino	60	A 60%, B	3.1 (1-6.5)	NR	44 (24-48)	3-5	—	90%	—	—	—	67%	—	—	37%, 20% decline in CP class
Kwon	42	A 90%, B	3.0 mL-82 mL	0%	30-39	3	72%	—	68%	—	93%	—	59%	—	2%

CP Class, *Child-Pugh class;* Fx, *fractions;* NR, *not reported;* Pts, *Patients;* PVT, *portal vein thrombosis.*

transplantation.[26] Standard surgical resection consists of lobar hepatic and bile duct resection, regional lymph node dissection, and Roux-en-Y hepaticojejunostomy.[26] Contraindications to standard resection include contralateral or bilateral vascular encasement or extension to secondary biliary branches.[26] Major prognostic factors include margin and nodal status. A minimum of seven lymph nodes should be evaluated.[146] R0 resection is possible in 20% to 40% of patients explored with curative intent.[11,147,148] R0 resection is more likely to be achieved with hepatic resection than with bile duct resection alone.[148] Five-year OS is in the range of 30% to 40% after R0 resection and 10% to 25% after R1 resection.[11] In a series of 44 patients with hilar EHCC from the University of Louisville treated since 2002, R1 resection followed by EBRT with or without chemotherapy was associated with better survival than nonoperative management (median survival 21 months versus 8 months).[149]

Distal cholangiocarcinoma is best treated by pancreaticoduodenectomy.[26] R0 resection is more frequently achieved with rates approaching 80%.[11] Lymph node metastases are more commonly reported compared with hilar EHCC with rates as high as 60%.[11] Five-year OS is usually in the range of 20% to 30%[11,153a-156a] but may exceed 50% in patients who are node-negative who undergo R0 resection.[154] A minimum of 11 lymph nodes should be evaluated in resected patients.[155] For patients who undergo R0 resection, survival rates are similar for hilar and distal EHCC.[156]

Adjuvant Therapy

Potential indications for postoperative chemoradiation include positive margins (R1 resection) and regional lymph node metastases. Locoregional relapse is the predominant failure pattern for hilar EHCC and locoregional relapse has been reported in 50% or more of patients who were resected.[150,151] Locoregional relapses have been reported to comprise 65% of all relapses of hilar EHCC and nearly 60% of patients with relapse have isolated locoregional disease.[57] Despite this, there is a paucity of prospective data evaluating adjuvant therapy following resection.

Retrospective series have suggested the possibility of a survival benefit associated with adjuvant RT. In an EORTC multiinstitutional survey of 55 resected hilar EHCC patients (51 of 55 R1), adjuvant radiation in 38 patients was associated with a 19-month median and 31% 3-year survival compared to 8-month median and 10% 3-year survival in 17 patients treated with surgery alone ($p = 0.0005$).[152] A University of Amsterdam report of 91 patients with resected hilar EHCC found an 8-month median survival in 20 patients with surgery alone compared to 24 months in 71 patients treated with adjuvant EBRT with or without brachytherapy ($p < 0.01$).[153] A systematic review of 20 adjuvant studies evaluated chemotherapy alone, RT alone, and chemoradiation (chemoRT) in EHCC and gallbladder cancer. A trend toward improved survival was observed with any adjuvant therapy (OR, 0.74, $p = 0.06$) with better results in patients treated with chemotherapy or chemoRT. Significant benefit for adjuvant therapy was noted in node positive patients and following R1 resection.[157]

A prospective single arm SWOG (S0809) study evaluating postoperative chemoRT in 80 patients with EHCC or gallbladder cancer has been completed. Eligibility included T2-T4 primary or positive nodes or positive margins and treatment consisted of four cycles of gemcitabine and capecitabine followed by RT with capecitabine (three-dimensional: 54 Gy in 30 for RO, 59.4 Gy in 33 for R1 resection, and 52.5 Gy to 55 Gy in 25 for R0 and R1 resections). Two-year overall survival was 65% in 79 eligible patients (54 R0 67%, 25 R1 60%).

Neoadjuvant Chemoradiation Plus Transplant

Given the predominant local relapse pattern of hilar EHCC, liver transplant has been investigated as a curative option for patients who are unresectable. Early results with transplant alone were disappointing with relapse rates of 53% to 84% and 5-year OS in the 25% to 30% range. Interestingly, about half of the relapses were in the liver allograft.[158,159] A small group of patients at Mayo Clinic were treated with EBRT with 5-FU and brachytherapy with a 22% 5-year OS (Table 49-4).[160] Based on this observation, a protocol of neoadjuvant chemoRT including brachytherapy followed by liver transplantation was developed.[161] Patients with unresectable hilar cholangiocarcinoma above the cystic duct, less than 3 cm maximum diameter without intrahepatic or extrahepatic metastases, are potential candidates for liver transplantation. In addition, any patient with PSC with hilar cholangiocarcinoma is a potential candidate. The diagnosis may be established by transcatheter biopsy or brush cytology or by the combination of a malignant appearing stricture on imaging and a CA 19-9 >100 U/mL or polysomy on FISH. Concurrent chemoradiation, EBRT of 45 Gy in 1.5 Gy fractions twice daily over 3 weeks with concomitant PVI 5-FU or capecitabine, is followed by transcatheter iridium (20 Gy to 30 Gy to a 1-cm radius with low dose rate [LDR] or 16 Gy in four twice daily fractions over 2 days with high dose rate [HDR] brachytherapy). Exploratory laparotomy or laparoscopy with sampling of regional nodes is performed before liver transplant to confirm lymph nodes are not involved.[26,159-164]

From 1992 to 2011, 215 patients initiated neoadjuvant therapy at Mayo Clinic and 136 have undergone liver transplant. Overall survival at 5 years is 56% in patients who initiated neoadjuvant therapy and 74% in transplanted patients (Table 49-4). Five-year OS is higher in transplanted patients with PSC (79% versus 64%). Only 18% of transplanted patients have experienced disease relapse. Vascular complications including portal vein stenosis with or without thrombosis have been observed in 20% of patients.[158,164] Five-year OS in a contemporary group of patients who are resectable treated with standard resection at Mayo Clinic was 21% (Table 49-4).[163]

A multiinstitutional report from 12 transplant centers found neoadjuvant chemoradiation followed by transplant to be associated with 53% 5-year survival in all patients and 65% in patients who underwent transplant.[158] Patients with tumors greater than 3 cm maximum diameter and those who underwent transperitoneal biopsy had shorter survival times[158] In addition, CA 19-9 ≥ 500 U/mL and tumors greater than 3 cm at presentation predicted for dropout before transplant and elevated CA 19-9, portal vein encasement, and residual tumor in explant predicted for disease relapse after transplant.[151]

LOCALLY ADVANCED DISEASE AND PALLIATION

Hepatocellular Carcinoma

Intermediate Stage

BCLC intermediate (B) and advanced (C) stage HCC are most often unresectable and thought to be incurable. If resection may be conducted safely, it is associated with the best outcomes. In patients who are unresectable Child-Pugh A, regional and systemic therapies improve survival. Experience with RT is increasing, although there are no published comparative studies. Prognostic factors for patients with unresectable HCC include Child-Pugh score, AFP levels, portal vein tumor thrombosis, the presence of serologic markers for hepatitis B or C virus, and overall HCC burden.[164,165] More patients

TABLE 49-4 Results of High-Dose Radiotherapy or Chemoradiation in Extrahepatic Bile Duct Cancers

Series/Treatment Method	No. Patients	Survival Time				*p* Value
		Median (mo)	12 Mo (%)	24 Mo (%)	60 Mo (%)	
IWASAKI ET AL (JAPAN)[210]						
Noncurative Resection						
Alone	13	—	44	8	—	
Plus IORT	13	—	46	15	—	
Unresected						
Biliary drainage only	21	—	<5	—	—	
Plus IORT	6	—	33	17	—	
MAYO CLINIC						
Unresected						
EBRT ± 5-FU[151]	11	12	55	—	—	
EBRT ± 5-FU + ^{192}Ir[160]	24	12.8	67	19	14	
EBRT + 5-FU + ^{192}Ir	9	13	67	22	22	
EBRT + ^{192}Ir	15	12	67	16	8	
EBRT ± 5-FU + IOERT[211,212]	14	18.5	71	29	7	
EBRT/5-FU/^{192}Ir ± transplant[159,161-164]	215	60+	81	62†	56	
EBRT/5-FU/^{192}Ir + transplant	136	60+	92	81†	74	
Standard resection ± EBRT/5-FU[163,164]	26	35	82	70	21	
THOMAS JEFFERSON UNIVERSITY HOSPITAL[207]						
No irradiation	24	5.5	—	17	—	
Irradiation ± 5-FU ± ^{192}Ir			—		—	
<55 Gy	14	7	36		—	
>55 Gy	18	17	67		—	
EORTC[152]						
Noncurative resection alone	17	8.3	36	18	—	
Noncurative resection plus EBRT	38	19	85	42	—	<0.05
UNIVERSITY OF HEIDELBERG[150]	30	10	34	18	8	
EBRT + HDRB	21	7.9	38	5	0	
EBRT + HDRB + noncurative resection	9	12.1	64	32	32	<0.05
UNIVERSITY OF PITTSBURGH						
EBRT ± 5-FU ± resection[227]	55	9	32	10	—	
EBRT ± 5-FU + transplant	9/55	12	50	22	—	
EBRT + chemotherapy; Bx or partial resection[228]	38*	14	60	20	0	
EBRT + chemotherapy; transplant or total resection	23*	60+	82	68	53.5	<0.05

5-FU, *5-Fluorouracil;* Bx, *biopsy;* chemotherapy, *5-FU/leucovorin/interferon alpha or paclitaxel;* EBRT, *external beam irradiation;* HDRB, *high-dose-rate brachytherapy;* IOERT, *intraoperative electron irradiation.*

**Biopsy, 34; subtotal resection, 4; orthotopic liver transplantation, 17; other total resection, 6.*

†*3-year survival.*

ultimately develop liver failure because of HCC progression, underlying liver dysfunction, or treatment inducted liver toxicity.

Regional Treatment

Because HCC derives 80% of its blood supply from the hepatic artery compared to the liver parenchyma that derives most its blood supply from the portal vein, hepatic arterial–directed therapies are attractive options for HCC. Hepatic arterial chemotherapy, transarterial embolization (TAE), TACE, and transarterial radiation embolization (TARE) have been used on their own or combined with other therapies. Although hepatic arterial chemotherapy has had good response rates,[166] there was no significant improvement in survival in one randomized trial.[167]

TACE refers to delivery of embolization material (typically gelatin sponge, polyvinyl alcohol, or starch microspheres) with or without chemotherapy via injection into the right or left hepatic artery or a first-, second-, or third-order branch, depending on the disease extent. Meta-analyses and Phase III studies have shown a survival advantage to TACE versus supportive care in locally advanced HCC (2-year OS, 33 versus 11% in predominantly patients with hepatitis B[7] and 63% versus 27% in predominantly patients with hepatitis C.[6] The best results have been confined to patients with Child-Pugh A without main branch portal vein thrombosis. TACE is often delivered multiple times until the HCC no longer enhances, if toxicity is acceptable. Common transient complications from TACE include abdominal pain, nausea, fever, fatigue, and elevation of liver enzyme levels. Rare complications include exacerbation of liver failure, liver abscess, gastrointestinal bleeding, and bile duct injury. TAE has not been as extensively studied, but it is sometimes used to treat a ruptured HCC.

There is an emerging experience with TARE, or selective internal RT, which involves delivery of radioactive particles

(e.g., iodine-131 [^{131}I]–labeled Lipiodol or yttrium-90 [^{90}Y]–tagged microspheres) via the hepatic artery, with minimal embolization. Studies of ^{131}I Lipiodol have suggested efficacy, but it is not available in the Unites States.[168] There are many single institutions series of ^{90}Y-tagged microspheres (delivered via glass [TheraSphere MDS Nordion, Ottawa, Canada]) or resin spheres (SIR-Spheres SIRTeX Medical, Lake Forest, IL) showing response rates of 40% to 60% and median time to progression of 7.9 months in one prospective series of 291 patients, with worse outcomes in patients with Child-Pugh B and patients with tumor thrombosis.[169] Side effects include fatigue, pain, nausea/vomiting, and liver toxicity.

Systemic Treatment

Sorafinib, an oral multikinase inhibitor that has activity against Raf-1, B-Raf, VEGFR2, DGFR, c-Kit, and other tyrosine kinases, improves survival in patients with advanced HCC unsuitable for TACE. In the SHARP trial of 602 patients, patients randomized to sorafenib had improved median survival (10.7 months versus 7.9 months, $p < 0.001$), and time to progression (5.5 months versus 2.8 months).[170] Side effects including diarrhea, hand-foot skin reaction, and weight loss were tolerable. A second randomized trial in Asia reported an improvement in median survival from 4.2 months to 6.5 months with sorafenib, ($p < 0.05$).[171] Chemotherapy is generally toxic for patients with HCC and has not been associated with high response rates.[172,173] Doxorubicin has activity against HCC and is being investigated in a Phase III study comparing sorafenib to sorafenib plus doxorubicin (NCT01840592).

Radiation Therapy

Although RT has not been accepted as a standard therapy for locally advanced HCC, HCC is a radiosensitive tumor and should be considered in selected patients, especially if other local therapies are not feasible. The challenge is to delivery enough RT for tumor control, without causing liver toxicity. HCC tends to remain liver confined and frequently invades the portal vein, providing rationale for a local therapy such as RT.

The University of Michigan group first showed that tumoricidal doses could be delivered to focal unresectable HCC, with dose based on volume of spared liver or estimate of normal tissue complication probability (NTCP).[174-177] The prescribed dose ranged from 40 Gy to 90 Gy (median 60.75 Gy) in 1.5 Gy twice daily with hepatic arterial FudR. One-year LC and survival were 81% and 57%, respectively, in 35 patients with unresectable HCC without portal vein invasion.[177]

Conformal RT has been used to treat unresectable HCC, sometimes in combination with TACE, mostly in Asia (Table 49-5).[178-186] A recent review[178] suggested that patients treated with TACE plus RT had improved survival rates compared with patients treated with TACE alone (OR, 2.23); however, there is a need for confirmatory studies. Definitive RT has been used to treat HCC with tumor vascular invasion, with high local control and median survival generally better than that expected following other therapies.[186a,186b,187-192] One notable Phase II study from Korea, reported a median survival of 13.1 months in 40 patients with HCC with portal vein tumor thrombosis after 45 Gy in 25 fractions delivered with concurrent 5-FU.[190]

SBRT has also been used, with or without TACE, for locally advanced HCC, including patient with portal vein tumor thrombosis, with doses ranging from 30 Gy to 50 Gy in doses per fraction of 6 Gy to 15 Gy[186b,193-195] (Table 49-5). In sequential Phase I (Trial 1) and Phase II (Trial 2) trials at Princess Margaret Cancer Centre, SBRT was used to treat 102 patients with unresectable HCC unsuitable for TACE or RFA (55% with vascular invasion). LC at 1 year was 87% following a median dose of 36 Gy in six fractions (24 Gy to 54 Gy in six fractions). Median survival was 17 months and on multivariate analysis, absence of tumor vascular thrombosis and being treated on Trial 2 were associated with improved survival.[195] Five-fraction SBRT is being investigated in a Phase III study comparing sorafenib with SBRT followed by sorafenib (NCT01910909). Protons have also been used to treat locally advanced HCC with excellent outcomes.[196]

Advanced Stage

BCLC terminal stage (D) HCC has a poor prognosis and best supportive care is generally recommended. Many patients develop hepatic pain or discomfort, and low-dose palliative RT may be used with the sole goal of reducing patient pain. In one study, 8 Gy in one fraction to the whole liver resulted in a patient reported improvement of pain in 50% of patients.[197] Other palliative fractionations include 10 Gy in five fractions and 21 Gy in seven fractions.

TABLE 49-5 Selected Series of Radiation Therapy for Predominantly Advanced Stage Hepatocellular Carcinoma

Author	Year	No. Pts	Tumor Size (range)	PVT %	Dose (Gy)	No. Fx	Median Survival (months)	Grade ≥3 Toxicity
SBRT								
Bujold et al	2013	102	9.9 (1.8-43.1) cm	55%	36 (24-54)	6	17 (PVT-11.0; No PVT-20.5)	36%
Xi et al	2013	41	NA	100%	36 (30-48)	6	13	2%
Choi et al	2008	31	3.9 mL-47.7 mL	30%	36 (30-39)	3	8	16%
CONFORMAL RT								
Han et al	2008	40	NA	100%	45	25	13.1	
Huang et al	2009	326	≥10 cm in 39%	100%	60	20-30	3.8	0%
Kim	2005	59	11 cm	100%	30-54	10-24	10.7	
Rim et al	2012	45	1.5 cm-17.3 cm	100%	61.2 (38-65)	20-30	13.9	2%
Toya	2007	38	4 (0.9-9.3) cm*	100%	17.5-50.4	15-25	9.6	
Yoon et al	2012	412	2 cm-21 cm	100%	40 (21-60)	8-30	10.6	10%

CP Class, *Child-Pugh class;* Fx, *fractions;* NA, *not available;* Pts, *Patients;* PVT, *portal vein tumor thrombosis.*
**Diameter of PVT.*

Intrahepatic Cholangiocarcinoma

For the majority of patients with unresectable disease, a number of locoregional therapies have been investigated. TACE is associated with a 12-month to 15-month median survival in several series.[198] TARE with ^{90}Y has been shown to be tolerable with partial response or stable disease in 85% of patients and median survival of 22 months.[199] Preliminary reports on the use of SBRT for IHCC using doses of 24 Gy to 60 Gy in three to six fractions suggest the treatment is well tolerated with local control rates in excess of 50% and median survival of 11 months to 15 months.[188,200] RFA for IHCC <5 cm in diameter was associated with a 39-month median survival and 15% 5-year survival in a small series of 13 patients.[201]

Gallbladder Cancer and Extrahepatic Cholangiocarcinoma

The combination of gemcitabine and cisplatin was compared to gemcitabine alone in the 410 patient ABC-02 Trial, which included patients with locally advanced or metastatic cholangiocarcinoma, gallbladder cancer, or ampullary cancer. Seventy-five percent of patients on the trial had metastatic disease. A significant survival benefit was demonstrated for the two-drug combination with median survival of 12 months versus 8 months ($p < 0.001$). Progression-free survival was 8 months versus 5 months ($p < 0.001$). Most patients died within 3 years.[8]

Patients with unresectable hilar cholangiocarcinoma experience progressive bile duct obstruction resulting in hepatic dysfunction and potentially fatal sepsis.[202] Palliative of obstruction may be accomplished with operative bilioenteric bypass or preferably with endoscopic or percutaneous stent placement.[203,204] For patients who are not surgical candidates, metal stents are preferred over plastic because of longer patency and fewer re-interventions.[203] The median survival for patients treated with palliative stent placement alone is generally 3 months to 6 months.[202] Small prospective studies evaluating photodynamic therapy (PDT) in addition to stenting have suggested improvement in median survival to 14 months to 16 months compared to 3 months to 6 months with stent alone.[202,205] Three-year survival is less than 10%.[204]

External Beam Irradiation with or without Chemotherapy or Brachytherapy

A summary of published series of high dose RT (alone or plus brachytherapy or concurrent chemotherapy) for EHCC is shown in Table 49-4.[150-152,159-164,207,210-214] The combination of EBRT and brachytherapy has been used in selected patients with unresectable hilar EHCC and is associated with a median survival of approximately 12 months.[206] Some investigators have reported better survival in patients receiving >55 Gy,[207] and brachytherapy allows for significant dose escalation. A SEER analysis found a median survival of 11 months in patients whose treatment included a brachytherapy component compared to 4 months without brachytherapy.[206] In contrast to the predominantly locoregional pattern of relapse observed after surgical resection, some investigators have reported distant relapse, primarily in liver and peritoneal cavity, to be the predominant relapse pattern following chemoRT with or without brachytherapy.[208]

The combination of concomitant 5-FU–based chemotherapy with EBRT and brachytherapy appears promising. In a Mayo Clinic analysis of 24 patients with proximal EHCC treated with EBRT and brachytherapy, 9 patients received concurrent 5-FU and 5-year OS was observed in 22%.[160] In the Mayo Clinic transplant experience with this regimen of concurrent chemoRT plus brachytherapy given before transplant, there was pathologic complete response in 53% of patients.[159,161-164]

Early experience with charged particle therapy also supports the concept of dose response in cholangiocarcinoma. In a series of 28 patients with primary and recurrent cholangiocarcinoma including IHCC, EHCC, and gallbladder cancer treated with protons, biologic effective doses (BEDs) >70 Gy[10] was associated with 83% local control at 1 year compared to 22% for lower effective doses.[209]

Intraoperative RT is another technique that has been used to achieve dose escalation.[210-212]

IRRADIATION TECHNIQUES AND TOLERANCE

Dose-Limiting Organs

The potential for serious treatment related intolerance (RT or concurrent chemoRT) necessitates individualization of prescription dose for patients with hepatobiliary carcinoma, based on the volume of liver that may be spared from RT, baseline liver function (Child-Pugh A, B7 versus higher), and proximity of tumor to luminal gastrointestinal tissues. The major dose-limiting organ for RT to the hepatobiliary system is the liver. RT or chemoRT-induced liver disease (RILD) is separated into "classic" and "nonclassic" RILD. Classic RILD presents with anicteric hepatomegaly and ascites, typically occurring between 2 weeks to 3 months after RT or chemoRT, with an elevated alkaline phosphatase.[214] Nonclassic RILD is more challenging to prevent and includes any liver toxicity occurring within 3 months of radiation (e.g., decline in Child-Pugh score or elevated liver enzymes). It is more likely in patients with baseline cirrhosis or Child-Pugh B or C liver disease. Reactivation of hepatitis B has been reported after RT, and antiviral therapy before RT can reduce this risk.[213,214] For any patients with RILD, restaging, possible paracentesis of the ascitic fluid to rule out disease relapse, and referral to hepatology is recommended. RILD has been treated with diuretics, steroids, and occasionally anticoagulation.[214]

The risk for RILD is dependent on the volume of liver irradiated (or volume of liver spared from RT).[214] For patients with Child-Pugh A, whole-liver RT to a total dose less than 28 Gy in 2 Gy fractions has a low risk of toxicity, whereas 36 Gy in 2 Gy fractions is associated with a 50% risk of toxicity. With conformal RT planning, far higher doses can be delivered to partial liver volumes safely. Using standard fractionation, it is recommended that the mean liver dose be kept less than 28 Gy for patients with Child-Pugh A HCC. For SBRT, it has been recommended to maximize the volume of liver spared from RT (e.g., >800 cc to receive <10 Gy to 18 Gy in three to five fractions). Effective liver volume irradiated (Veff) or mean dose to the liver (minus the GTV) has also been used to allocate dose for SBRT. Patients with Child-Pugh B or C are at far higher risk for liver toxicity than those with Child-Pugh A liver cancer. For patients with Child-Pugh B treated with four to six fractions, the mean liver dose should be kept as low as possible (<6 Gy). Patients with Child-Pugh B7 fare better than those with Child-Pugh scores of B8 or higher,[215] who are not recommended to be treated outside the bridge to transplant setting.[214]

The luminal gastrointestinal (GI) tissues often limit the safe dose that may be delivered to HCCs in close proximity to GI luminal tissues. Of 128 University of Michigan patients with primary hepatobiliary malignant tumors treated with 40 Gy to 90 Gy (in 1.5 Gy per fraction, twice daily), 7% developed upper GI bleeding. The maximum dose to the stomach or duodenum was <68 Gy. A dose of 60 Gy to one third of the stomach has been associated with a 5% risk of ulceration or

perforation.[216] The Mayo Clinic data for biliary tract cancer suggest that a dose of approximately 55 Gy to the stomach or duodenum is associated with a 5% to 10% risk of severe GI complications[217]; and the risk increases to 30% to 40% with doses of more than 55 Gy. For SBRT, the maximal doses to luminal GI tissues should be kept to a minimum (<30 Gy to 36 Gy in five to six fractions), and there is a suggestion that delivering SBRT every other day may reduce the risk of toxicity.[218] The proximity of HCC to luminal GI tissues was an independent risk factor for local failure in one proton series.[100]

Biliary toxicity may lead to biloma and cholangitis 1 to 3 years post RT,[102] and the risk is higher hypofractionation or brachytherapy. It has been suggested that doses less than 40 Gy in five fractions to the common bile duct are associated with a low risk of toxicity, but the number of long-term survivors investigated is low.

Kidney toxicity is a theoretical consideration, although few patients develop clinical toxicity. Mean dose to both kidneys should be less than 18 Gy, and traditional three-dimensional treatment planning goals are to spare at least two thirds of a functioning kidney from 18 Gy or more. Other toxicities such as skin toxicity, rib pain, or fracture are uncommon toxicities seen after SBRT.

Irradiation Technique

Hepatocellular Carcinoma and Intrahepatic Cholangiocarcinoma

Radical RT of hepatobiliary tumors is only possible with three-dimensional CT–based, conformal techniques. Ideally arterial, venous, and delayed phase CT or MR images should be obtained in breath-hold at the time of simulation and fused for optimal contouring (Figure 49-4). If that is not possible, image registration of diagnostic quality images with the planning CT is needed. MR is often complementary to CT. The gross target volume (GTV) should include all enhancing parenchymal tumor and vascular HCC. The clinical target volume should include the GTV as well as any adjacent regions at risk such as a RFA cavity or prior TACE zone. Care is needed to ensure delineation of the entire extent of tumor thrombus, often best seen on delayed phase imaging.

Breathing motion management is important to allow the planning target volumes (PTV) to be reduced, sparing more nontumor liver and reducing the risk of toxicity. Voluntary breath-hold, active breathing control (ABC), gating the beam to a specified phase of the respiration cycle and abdominal compression are common strategies used to reduce the impact of breathing motion. Measuring reproducibility of breath-hold or patient-specific tumor motion is important for individualization of PTV margins. Four-dimensional CT, kV fluoroscopy, and cine MR can be used to measure liver (or tumor) motion. Typical PTV margins for breath-hold or gated patients treated with image guided radiation therapy (IGRT) are 5 mm. PTV margins need to be larger in the cranial-caudal direction and sometimes the anterior-posterior directions for patients who are nonbreath-hold.

Three-dimensional conformal RT, arc therapy, IMRT, volumetric arc therapy (VMAT), and ions have all been used to treat HCC. HDR RT has the advantage of allowing the treatment beam-on time to be reduced, with less chance for patient movement during a single fraction. Planning goals are to cover the PTV with the prescription isodose (e.g., to 95% PTV), maintain dose limits to the luminal GI tissues and other critical organs, and to conform dose to the PTV, with most rapid dose fall off in adjacent critical normal tissues. Sometimes, less conformality is acceptable, to reduce the dose to a fragile cirrhotic liver. Although IMRT and VMAT allow high doses to be more conformal around complex PTVs (Figure 49-5; see Figure 49-4), there is the potential for interplay of residual

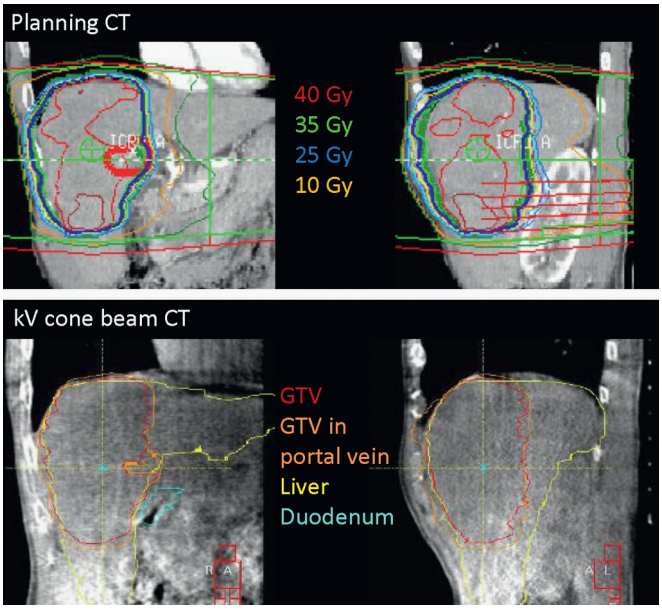


Figure 49-4 Breath-hold SBRT VMAT plan and breath-hold kV cone beam CT (CBCT) for a patient with HCC with invasion to the right portal vein, treated with 35 Gy in five fractions. The PTV around primary HCC I shown in thick blue and the HCC portal vein thrombus is shown in thick red. Contours from planning (GTV, red and orange; liver, yellow; duodenum, light blue) are overlaid on the CBCT to aid in IGRT (based on liver-matching). *CBCT,* Cone beam CT; *HCC,* hepatocellular carcinoma; *IGRT,* image guided radiation therapy; *kV,* kilovoltage; *PTV,* planning target volume; *SBRT,* stereotactic body radiation therapy; *VMAT,* volumetric modulated arc therapy.

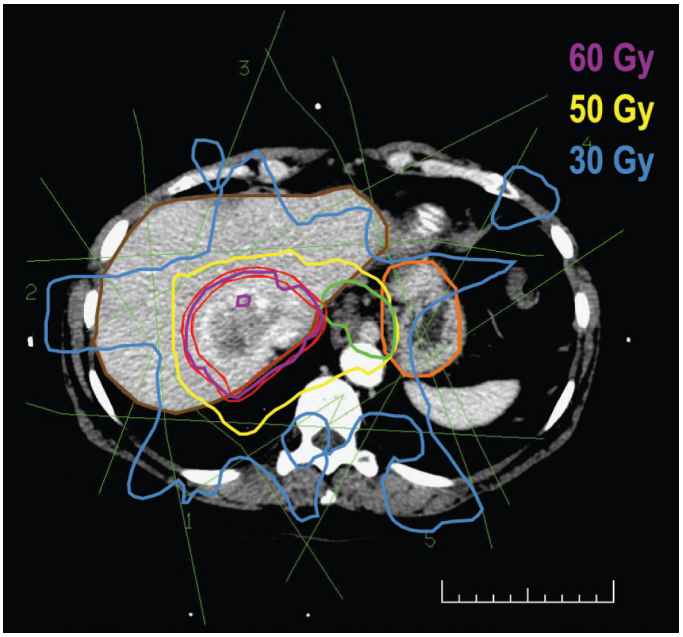


Figure 49-5 IMRT treatment plan for a patient with T3N1 intrahepatic cholangiocarcinoma, treated with definitive chemoradiation. Doses were 61.6 Gy to the primary site *(red)* and 50.4 Gy to regional nodes *(green)*, in 2.2-Gy and 1.8-Gy daily fractions, respectively.

tumor motion with moving multileaf collimators. Thus, a prudent goal should be to reduce the RT plan complexity when possible.[219] The doses required to control small HCCs are lower than those needed to control secondary liver tumors (e.g., high local control following 50 Gy in 20 fractions or 35 to 40 Gy in 5 fractions). The prescription dose may need to be modified based on volume or spared liver or proximity to organs at risk.[220]

IGRT is crucial to account for shifts in the liver position that may occur day-to-day, despite the use of breathing motion management. Such shifts occur even when breathing motion is of a small magnitude, providing rationale for the use of daily, soft-tissue guided IGRT. Inserted radioopaque fiducial markers or Lipiodol from prior TACE treatment may be used with two-dimensional planar kV imaging, fluoroscopy, or cone beam CT for targeting. The liver itself can be used for guidance using kV cone beam CT; accuracy is improved with breath-hold and four-dimensional respiratory sorted CBCT[220-222] (see Figure 49-4).

Gallbladder and Extrahepatic Cholangiocarcinoma

For gallbladder cancer, the treatment fields should be designed to include the gallbladder fossa and the hilar and celiac lymph node-bearing areas (eFigure 49-1). Doses in the range of 45 Gy to 54 Gy (1.8-Gy to 2-Gy fractions) for subclinical disease and 60 Gy to 65 Gy for microscopically positive margins are appropriate. Fields may be reduced to exclude the regional nodes and boost the tumor bed after 45 Gy. IMRT may be used to spare liver or kidney and may be especially useful when high doses are required for treatment of microscopic residual disease. A 25-fraction dose painting regimen with 45 Gy to the regional nodes, 52.5 Gy to the tumor bed following R0 resection and 55 Gy to the tumor bed following R1 resection is appropriate.

The target volume for EHCC can require inclusion of large portions of normal liver if the tumor is located in the hilum. In this case, the target volume may be extended to between 3 cm and 5 cm within the liver to include subclinical spread along the biliary tree. Although more distal EHCC requires considerably less irradiation of the hepatic parenchyma, higher duodenal or distal gastric doses may be necessary. On the basis of Mayo Clinic tolerance data, if doses greater than 55 Gy are indicated for tumor control (i.e., unresectable or residual disease), IMRT should be used to decrease normal tissue high-dose volumes. IMRT may also be indicated for lower doses to spare liver and both kidneys. Caution with regard to liver dose in the adjuvant setting should be exercised because RT may impact liver regeneration following major resection and liver tolerance may be significantly lower.

Brachytherapy[150,160,223] has frequently been used for EHCC and is an excellent technique for dose escalation for unresectable disease. Brachytherapy is typically given as a supplement to 45 Gy to 50 Gy EBRT (1.8-Gy to 2-Gy fractions) of EBRT. For patients who are not having transplants, brachytherapy may be delivered using transhepatic catheters or via endoscopically placed 10-FR nasobiliary catheters.[223] Potential transplant candidates should not have placement of transhepatic catheters. For LDR, a dose of 20 Gy to 30 Gy may be delivered with iridium-190 to a 1-cm radius.[160] With HDR, a dose of 16 Gy in 4 fractions to a 1-cm radius delivered twice daily over 2 days is calculated to have similar biologic effect to 20 Gy with LDR. Endoscopically placed two-catheter brachytherapy is depicted in Figure 49-6. With HDR placement, CT-based treatment planning may be used to limit dose to adjacent duodenum and stomach (Figure 49-7).

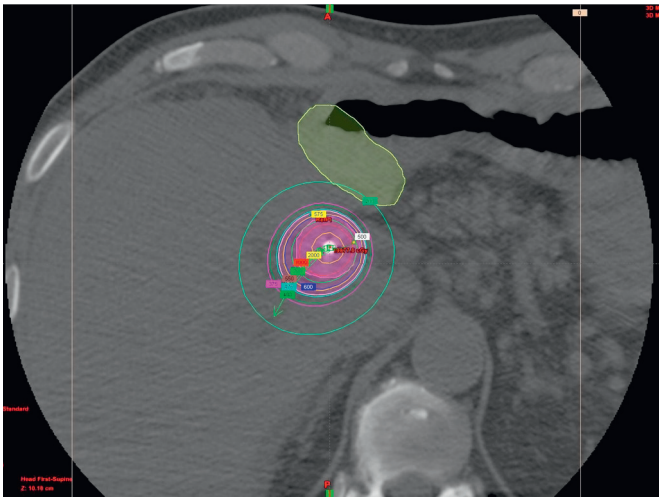


Figure 49-6 Endoscopically placed two-catheter brachytherapy. Low-dose rate iridium-190 lines loaded hot through endoscope inside nasobiliary catheter.

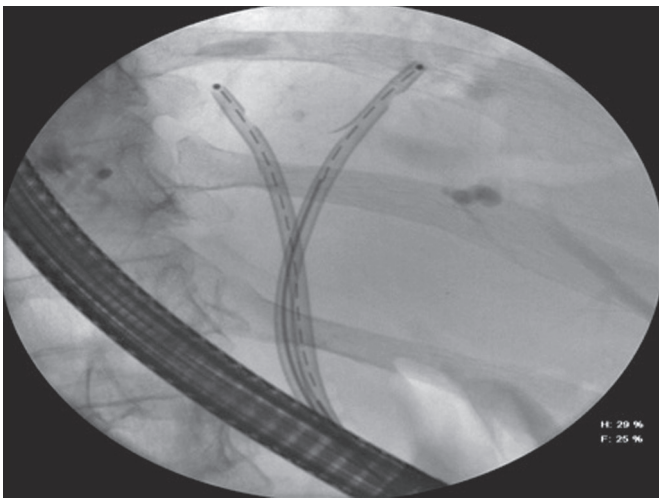
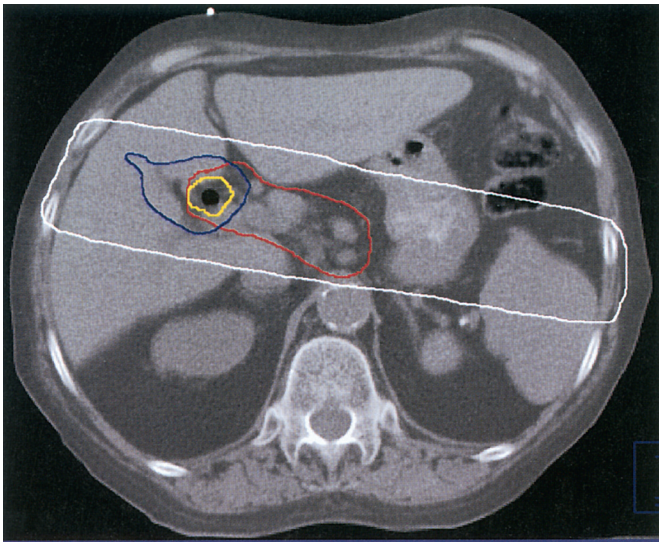


Figure 49-7 Isodose curves for high-dose rate biliary brachytherapy plan for single 5-Gy fraction. Fifteen-Gy in three fractions or 16 Gy in four fractions delivered over 2 days is typically delivered.

TREATMENT ALGORITHM AND FUTURE DIRECTIONS

Treatment algorithms for hepatobiliary cancer are shown in Figures 49-3 and 49-8. Figure 49-3 displays a treatment algorithm for hepatocellular carcinoma, based on the BCLC classification system, with the last rows indicating where RT has the potential to be used.[224] Figure 49-8 reflects a treatment algorithm for EHCC.

The use of state of the art imaging for target delineation, breathing motion management, conformal and IMRT planning, and soft-tissue IGRT have permitted the delivery of much higher doses of RT for hepatobiliary cancers than would have been possible using standard techniques. The addition of brachytherapy to EBRT has done the same for EHCC. However there are many unanswered questions and research opportunities. The potential for liver toxicity in patients with underlying cirrhosis is high; functional liver imaging, novel treatments for liver toxicity, and regenerative medicine are



eFigure 49-1 Treatment plan for a patient with resected carcinoma of the gallbladder. The cystic duct margin was positive and a cystic lymph node contained metastatic disease. The clinical target volumes included the draining regional lymph nodes in the celiac axis *(red)* and the common hepatic and common bile ducts *(yellow)*. Opposed oblique fields were used to deliver an initial dose of 50.4 Gy *(white)*, and an anterior wedge pair was used to deliver a boost to the positive margin to a total dose of 63 Gy *(blue)*.

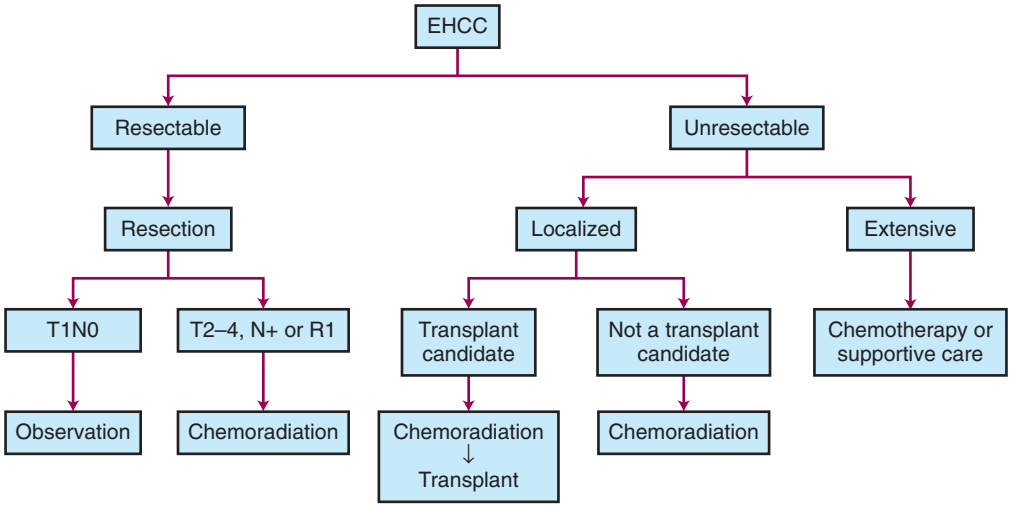


Figure 49-8 Treatment algorithm for extrahepatic cholangiocarcinoma (EHCC).

exciting areas of research that will benefit from collaborations of radiation oncologists with basic and imaging scientists and hepatologists.

Striving for the minimum RT doses required for a local control with a low chance of toxicity is a goal. Although it is becoming apparent that HCC is a relatively RT-sensitive tumor, the most appropriate doses and dose fractionations are not well defined. Collaborative efforts will be required to obtain evidence demonstrating the ideal patients, risk factors for relapse and toxicity, optimal doses and fractionation schedules and how to most appropriately combine RT with other regional and systemic therapies. Despite the growing literature on the use of RT for hepatobiliary cancer, there is a lack of level-1 evidence. At least two Phase III studies are planned for locally advanced HCC (NCT01910909, RTOG1112, PI Dawson) and intrahepatic cholangiocarcinoma (NRGGI001, PI Hong).

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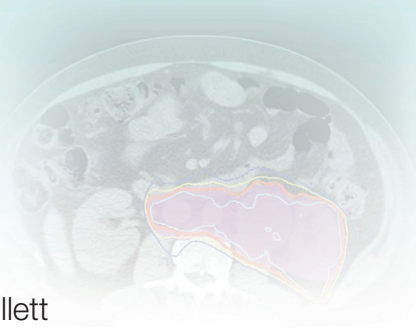
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CHAPTER

50 Colon Cancer



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EPIDEMIOLOGY/ETIOLOGY

In 2014, it is estimated that nearly 140,000 patients were diagnosed with colon or rectal cancer and 50,000 deaths occurred in the United States.

Linkage between diet and environmental factors with colon cancer is supported by epidemiologic studies. Risk factors include advanced age, race, male sex, family history of colorectal cancer, increasing body mass index, low physical activity level, and red meat and processed meat consumption.

The site of origin is shifting in the United States, with a higher frequency of proximal tumors.

Adenomas are precursor lesions, and polypectomy decreases the subsequent risk of malignancy.

BIOLOGIC CHARACTERISTICS AND PATHOLOGY

Most colon tumors are adenocarcinomas.

The most important prognostic factor is tumor extent, including extension through the bowel wall, nodal spread, and the presence of metastatic disease.

Approximately 10% of colorectal cancers arise in the setting of a hereditary syndrome. These syndromes are characterized by multiple adenomatous polyps (familial adenomatous polyposis) or hereditary nonpolyposis colorectal cancer (Lynch syndrome) with fewer polyps.

Inflammatory bowel disease increases the risk of developing colon cancer.

STAGING EVALUATION

Staging should include history and physical examination, complete blood count, general chemistry panel (liver functions, creatinine), carcinoembryonic antigen (CEA), and computed tomography (CT) of the chest, abdomen, and pelvis with colonoscopy.

In advanced cases, magnetic resonance imaging (MRI) or positron emission tomography (PET) may be helpful in assessing the extent of tumor spread outside the colon.

PRIMARY THERAPY

Resection is the principal therapy of primary and nonmetastatic colon cancers. This treatment modality results in mean 5-year survival rates of approximately 97% (T1N0), 90% (T2N0), 78% (T3N0), 74% (T2N+), 63% (T4N0), 48% (T3N+), and 38% (T4N+).

ADJUVANT THERAPY

For patients undergoing resection with curative intent, recurrence may arise from micrometastatic disease that is present at time of surgery. Therefore, the goal of adjuvant therapy is the eradication of micrometastases. Adjuvant chemotherapy (5-fluorouracil [5-FU] with leucovorin- and oxaliplatin-based therapy) is efficacious for patients with node-positive disease.

Retrospective studies from the Massachusetts General Hospital (MGH) and other centers have evaluated the role of adjuvant external beam radiation therapy (EBRT) in resected colon cancer. These studies found postoperative EBRT with or without 5-FU improved local control and disease-free survival for patients with resected stage T4N0 or T4N+ tumors compared to historical rates with surgery alone.

An Intergroup randomized trial compared 12 months of adjuvant 5-FU/levamisole with or without tumor bed and nodal irradiation in patients who were T4N0-2 and select T3N1-2. Results showed no overall survival or local control difference with the addition of radiation therapy. Interpretation of study results is limited by low accrual, high ineligibility rates, and low rates of preoperative imaging and surgical clip placement to assist radiation field design.

LOCALLY ADVANCED DISEASE

In a Mayo Clinic analysis of locally advanced disease, postoperative EBRT resulted in a 5-year actuarial local failure rate of 54% for patients with microscopic residual disease and 79% for patients with gross residual tumors. In patients receiving intraoperative electron irradiation (IOERT) and EBRT, local failure was observed in 11% of patients compared with 82% of patients receiving EBRT only. The 5-year survival was 76% for patients receiving IOERT and EBRT compared with 26% for patients receiving EBRT alone.

Preoperative radiation therapy and chemotherapy followed by resection with IOERT and maintenance chemotherapy should be considered for patients with locally advanced cancers (T4N0-2).

PALLIATION

For patients with metastatic disease, 5-FU and leucovorin have been given with partial response rates of 20% to 30%. The addition of newer agents (irinotecan, oxaliplatin, bevacizumab, cetuximab, panitumumab) has improved response rates and survival.

Palliative irradiation, often with 5-FU–based chemotherapy, should be considered for patients with symptomatic metastatic disease.

INTRODUCTION

The rationale for adjuvant treatment of colon cancer stems from patterns of failure analyses of patients undergoing resection. Given high rates of distant failure for patients with stages II and III colon tumors, investigators implemented treatment strategies employing systemic (chemotherapeutic) approaches. Early data prompted multicenter randomized prospective trials where survival was improved in patients with resected, "high-risk" colon cancer receiving adjuvant chemotherapy with 5-FU and leucovorin. More recently, the addition of

oxaliplatin to fluorouracil and leucovorin has been shown to significantly improve long-term disease-free and overall survival in patients with stage III disease. Similarly, patterns of failure analyses have suggested that high locoregional failure rates occur in subsets of patients with resected colon cancer. This has stimulated investigation of adjuvant radiation therapy with concurrent and maintenance chemotherapy. Although there is a compelling rationale for adjuvant radiation therapy combined with 5-FU chemotherapy for selected patients with resected high-risk colonic cancer, its efficacy has not been validated by a randomized prospective study. The benefit of adjuvant radiation therapy thus remains unclear. This chapter reviews the rationale for radiation therapy combined with chemotherapy as well as results in patients with resected colon cancer.

ETIOLOGY AND EPIDEMIOLOGY

In 2014, the American Cancer Society estimated that 136,830 patients were diagnosed with colorectal cancer and 50,310 deaths occurred.[1] Although this malignancy may be linked to chemical carcinogens within the bowel lumen, it is not established whether these are ingested, the result of chemical activation of substances in the fecal stream, or a bacterial byproduct.[2] Emerging evidence suggests that infection with *Helicobacter pylori*, *Fusobacterium*, and other potential infectious agents might be associated with an increased risk of colorectal cancer. Environmental and dietary factors have been established as contributing to colorectal cancer. Factors shown to increase the risk of developing this disease include increasing age, race, male sex, family history of colorectal cancer, inflammatory bowel disease, increasing height, increasing body mass index, processed meat intake, diabetes, excessive alcohol intake, smoking, and low folate consumption. Of these risk factors, only increasing age, male sex, and excessive alcohol use have been found to be associated with rectal cancer.[3,4] The value of consumption of fruits and vegetables in the prevention of colon and rectal cancer remains controversial, and some studies have suggested that these associations have been overstated.[5] Contemporary prospective and randomized data do not support a high-fiber diet in the prevention of colorectal cancer.[6] Other studies have strongly suggested that nonsteroidal antiinflammatory drugs may reduce the risk of colorectal cancer. The role of chemopreventive agents (carotenoids, polyamine inhibitors, aspirin, and other nonsteroidal antiinflammatory drugs) in colorectal cancer remains under active investigation. Other preventive factors include physical activity and use of hormone replacement therapy with risk reduction on the order of 20% to 30%. Although less consistent, some data suggest a protective effect of diets rich in dairy products or fish, as well as statin therapy. Epidemiological studies have also demonstrated an inverse association between serum vitamin D concentrations and risk of colorectal cancer, but whether and to what extent this association is valid remains uncertain.[4]

PREVENTION AND EARLY DETECTION

Neoplastic polyps, including tubular adenomas, villous adenomas, and tubulovillous adenomas, are precursors of colon cancers. Most colorectal cancers arise from preexisting polyps.[7] APC gene mutations are an early event in colorectal cancer development and occur in more than 70% of colorectal adenomas. This is promoted by activating mutations of the KRAS oncogene and inactivating mutations of the *TP53* tumor suppressor gene. These mutations are often associated with chromosomal instability. Patients with neoplastic polyps should be considered at high risk for large bowel cancer, and polypectomy may reduce this risk. With the availability of the flexible colonoscope and endoscopic polypectomy, polyps can be removed at a premalignant stage and patients followed closely with an associated decrease in cancer incidence.[4]

Screening

Because the cumulative lifetime risk of developing colorectal cancer in the United States is about 6%,[8] screening programs for the general population have been undertaken. The goal of screening is to detect and remove preinvasive polyps or early invasive cancer. The presence of polyps increases the risk for cancer to approximately 15%. Data from programs in which proctoscopy is performed annually suggests that routinely scheduled polypectomy reduces the development of subsequent bowel cancer by 80% or more.[2] The American Cancer Society has recommended that screening should begin at age 50 in the average-risk patient by (1) flexible sigmoidoscopy every 5 years, (2) double-contrast barium enema every 5 years, (3) colonoscopy every 10 years, or (4) CT colonography every 5 years. The use of barium enema as a screening procedure is uncommon at the present time because of lower sensitivity and inability to resect polyps, and sigmoidoscopy screens only a portion of the bowel. Additional screening tests including yearly fecal occult blood test and fecal immunohistochemical tests using multiple take-home samples and follow up with colonoscopy if positive. More intensive surveillance is recommended for patients at high risk (patients with adenomatous polyps, history of colorectal cancer, first-degree relative diagnosed with colorectal cancer or adenomas, inflammatory bowel disease, or high risk because of family history or genetic testing). Genetic fecal testing continues to be studied as a potential screening tool. Although screening methods can detect colorectal cancer at an early stage, less than 40% of patients are diagnosed with early disease, likely reflecting low rates of disease awareness as well as the infrequency of screening in eligible candidates.[8,9]

BIOLOGIC CHARACTERISTICS AND MOLECULAR BIOLOGY

A detailed discussion of the biologic and genetic pathways of development of colorectal cancer is beyond the scope of this chapter. In brief, it has been established that the development of colon cancer is a multifactorial process, involving changes in many genes including both proto-oncogenes and tumor suppressor genes. Colorectal cancers appear to arise through a complicated process that often includes inactivation of the tumor suppressor genes adenomatous polyposis coli (APC) and P53 as well as mutations in the KRAS proto-oncogene. Wnt pathway signaling alterations occur in almost all patients, with the majority of these related to APC mutations. A large number of other genetic abnormalities occur in these tumors, including copy number alterations, altered methylation with associated gene silencing, and alterations in miRNA. In an effort to characterize somatic alterations in colorectal carcinoma, a genome-scale analysis of 276 samples was performed by investigators from the Cancer Genome Atlas Network. In total, 16% of colorectal carcinomas were found to be hypermutated; three fourths of these had the expected high microsatellite instability, usually with hypermethylation and MLH1 silencing, and one fourth had somatic mismatch-repair gene and polymerase ε (POLE) mutations. Excluding the hypermutated cancers, colon and rectum cancers were found to have considerably similar patterns of genomic alteration. Twenty-four genes were significantly mutated. Recurrent copy-number alterations include potentially drug-targetable amplifications of ERBB2 and newly

discovered amplification of IGF2. Recurrent chromosomal translocations include the fusion of NAV2 and WNT pathway member TCF7L1. Integrative analyses suggested new markers for aggressive colorectal carcinoma and an important role for MYC-directed transcriptional activation and repression. These tumors appear to be categorized broadly as those with chromosomal instability, those with microsatellite instability, and the remainder.[10]

Microsatellites are mutated short-repeat DNA sequences, usually consisting of one to five nucleotides. Microsatellite "instability" is found in a majority of patients with hereditary nonpolyposis colorectal cancer (HNPCC or Lynch syndrome) as well as a minority of patients with sporadic colorectal cancers, and this can be used to identify patients and families affected by Lynch syndrome. Additionally, BRAF mutational analysis can be used to distinguish sporadic versus Lynch-associated colorectal cancers because BRAF mutations are almost exclusively seen in sporadic microsatellite-high type tumors. It has been shown that this instability occurs in patients with mutations in genes encoding enzymes that repair DNA replication errors. These defects in mismatch repair lead to high-frequency microsatellite instability. Studies have suggested that patients with tumors possessing a high-frequency of microsatellite instability have a more favorable outcome and develop fewer metastases.[11] Furthermore, systematic reviews have suggested that microsatellite instability phenotypes may not benefit from adjuvant therapy with 5-FU, although this remains controversial.[12] Further elucidation of the genetic pathways in the development of colorectal cancer remains an active area of investigation and may ultimately impact therapy of this disease.

From a clinical standpoint, analysis of KRAS mutational status has important implications for treatment selection. Such mutations render these tumors unresponsive to treatment with anti-EGFR antibodies,[13] and the same likely holds true for patients with BRAF-activating mutations.

PATHOLOGY AND PATHWAYS OF SPREAD

Tumors of the colon arise in the mucosa and are virtually all (>90%) adenocarcinomas. Other histologic types include squamous cell carcinoma, carcinoid, leiomyosarcoma, and lymphoma. Most grading systems classify adenocarcinoma as well, moderately, or poorly differentiated.

Large bowel tumors invade from mucosa through the bowel wall and beyond, with involvement of lymphatic channels and lymph nodes. Lymphatic drainage from the colon follows the superior and inferior mesenteric nodes, in accordance with the arterial supply of the colon. Specifically, the lymphatics of the ascending colon drain to the ileocolic nodes, whereas those of the transverse colon drain to right and middle colic nodes. These both drain to the superior mesenteric system and subsequently paraaortic nodal basins. The lymphatics of the descending colon enter the left colic nodes, and those of sigmoid colon drain to the sigmoid nodes. These both drain to the inferior mesenteric system and subsequently paraaortic nodal basins. Hematogenous spread can occur, primarily to the lung and liver. There is little propensity for colon cancer to spread longitudinally within the bowel wall, in contrast to esophageal or gastric cancers.

CLINICAL MANIFESTATION, PATIENT EVALUATION, AND STAGING

Colon cancer often produces minimal or no symptoms, emphasizing the need for screening programs in the general population. Many colon cancer symptoms are nonspecific, including changes in bowel habits, weakness, intermittent abdominal pain, nausea, and vomiting. The persistence of such symptoms as well as any evidence of iron deficiency anemia should be investigated.

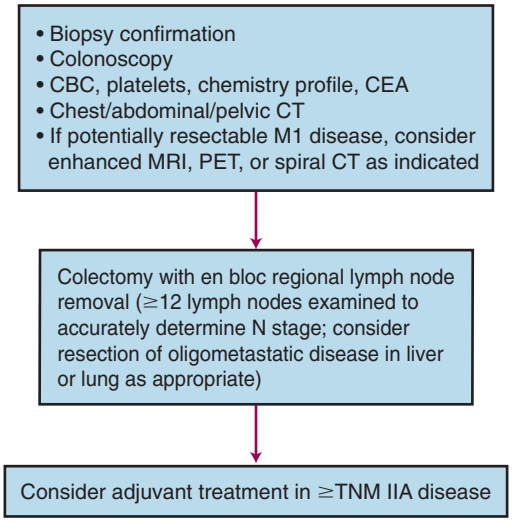


Figure 50-1 Diagnostic algorithm of the management of patients with potentially resectable colon cancer. *CBC*, Complete blood count; *CEA*, carcinoembryonic antigen; *CT*, computed tomography; *MRI*, magnetic resonance imaging; *PET*, positron emission tomography.

The clinical presentation of colon cancer is determined largely by site of the tumor. Cancers of the right colon are often exophytic and commonly associated with iron deficiency anemia as a result of occult blood loss. During the past 20 years, the relative incidence of right colon cancers has increased and accounts for one third of large-bowel cancers. Many of these are diagnosed late.[2] Cancers of the left colon and sigmoid colon are often deeply invasive, annular, and accompanied by partial obstruction and rectal bleeding.

For patients undergoing resection, preoperative evaluation should include pathological confirmation of adenocarcinoma, colonoscopy to evaluate extent of tumor and rule out synchronous primaries (occurring in 3% to 5% of patients), baseline blood counts with liver function tests, and CEA levels. Patients should undergo chest, abdominal, and pelvic CT scan to evaluate extent of locoregional disease as well as the presence or absence of distant metastases. PET scan, MRI, and ultrasound may be useful in evaluating patients with oligometastatic disease who may be appropriate candidates for resection of metastatic disease with curative intent. Figure 50-1 shows a diagnostic algorithm of the management of patients with potentially resectable colon cancer.

Prognostic factors influencing survival in patients with colon cancer include depth of tumor invasion into and beyond the bowel wall, the number of involved regional lymph nodes as well as the presence or absence of distant metastases. The TNM system of the American Joint Committee on Cancer (AJCC) can be used as a clinical (preoperative) or postoperative staging system (Tables 50-1 and 50-2). Additionally, site-specific prognostic factors have been identified and are included in the AJCC staging form (Box 50-1).

PRIMARY THERAPY

Surgery

Surgery remains the primary treatment for patients with colonic tumors. Resection with curative intent is possible in approximately 75% of patients.[14] Surgical resection of primary colon cancer is based on the anatomy and mechanisms by

TABLE 50-1 American Joint Committee on Cancer TNM Staging for Colorectal Cancer (2010)

Stage	Description
PRIMARY TUMOR (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ: intraepithelial or invasion of lamina propria
T1	Tumor invades submucosa
T2	Tumor invades muscularis propria
T3	Tumor invades through the muscularis propria into pericolic tissues
T4a	Tumor penetrates to the surface of the visceral peritoneum*
T4b	Tumor is adherent to or directly invades other organs or structures*†
REGIONAL LYMPH NODES (N)	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in one to three regional lymph nodes
N1a	Metastasis in one regional lymph node
N1b	Metastasis in two to three regional lymph nodes
N1c	Tumor deposit(s) in the subserosa, mesentery, or nonperitonealized pericolic or perirectal tissues without regional nodal metastasis
N2	Metastasis in four or more regional lymph nodes
N2a	Metastasis in four to six regional lymph nodes
N2b	Metastasis in seven or more regional lymph nodes
DISTANT METASTASIS (M)	
MX	Distant metastasis cannot be assessed.
M0	No distant metastasis
M1	Distant metastasis
M1a	Metastasis confined to one organ or site (e.g., liver, lung, ovary, nonregional node)
M1b	Metastases in more than one organ/site or the peritoneum

From Edge SB, Byrd DR, Compton CC, et al, editors: Colon and rectum. In American Joint Committee on Cancer staging manual, ed 7, New York, 2010, Springer.

Note: *A satellite peritumoral nodule in the pericolorectal adipose tissue of a primary carcinoma without histologic evidence of residual lymph node in the nodule may represent discontinuous spread, venous invasion with extravascular spread (V1/2), or a totally replaced lymph node (N1/2). Replaced nodes should be counted separately as positive nodes in the N category, whereas discontinuous spread or venous invasion should be classified or counted in the site-specific factor category of tumor deposit (TD).*

**Direct invasion in stage T4 includes invasion of other organs or segments of the colorectum by way of the serosa, as confirmed by microscopic examination (e.g., invasion of the sigmoid by a carcinoma of the cecum). For cancers in a retroperitoneal or subperitoneal location, direct invasion involves other organs or structures by virtue of extension beyond the muscularis propria (e.g., a tumor on the posterior wall of the descending colon invading the left kidney or lateral abdominal wall or a mid or distal rectal cancer with invasion of the prostate with invasion of the prostate, seminal vesicles, cervix or vagina).*

†Tumor grossly adherent to other organs or structures is classified as cT4b. However, if no tumor is present in the adhesion microscopically, the classification should be pT1 to pT4a depending on the anatomic depth of wall invasion. The V and L classifications should be used to identify the presence or absence of vascular or lymphatic invasion where the pN site-specific factor should be used for perineural invasion.

TABLE 50-2 Stage Groupings for Colorectal Cancer

AJCC Stage	TNM Staging T	N	M	Dukes*	Modified Astler-Coller*
0	Tis	N0	M0		
I	T1	N0	M0	A	A
	T2	N0	M0	A	B1
IIA	T3	N0	M0	B	B2
IIB	T4a	N0	M0	B	B2
IIC	T4b	N0	M0	B	B3
IIIA	T1/T2	N1/N1c	M0	C	C1
	T1	N2a	M0	C	C1
IIIB	T3/T4a	N1/N1c	M0	C	C2
	T2/T3	N2a	M0	C	C1/C2
	T1/T2	N2b	M0	C	C1
IIIC	T4a	N2a	M0	C	C2
	T3/T4a	N2b	M0	C	C2
	T4b	N1/N2	M0	C	C3
IVA	Any T	Any N	M1a		
IVB	Any T	Any N	M1b		

Note: *cTNM is the clinical classification, pTNM is the pathologic classification. The y prefix is used for those cancers that are classified after neoadjuvant pretreatment (e.g., ypTNM). Patients who have a complete pathologic response are ypT0N0cM0, which may be similar to stage group 0 or I. The r prefix is to be used for those cancers that have recurred after a disease-free interval (rTNM).*

**Dukes B is a composite of better (T3N0M0) and worse (T4N0M0) prognostic groups, as is Dukes C (Any TN1M0 and Any TN2M0).*

BOX 50-1 Site-Specific Prognostic Factors for Colorectal Cancer

Preoperative or pretreatment carcinoembryonic antigen (CEA)
Tumor deposits (TD)
Circumferential resection margin (CRM)
Perineural invasion (PN)
Microsatellite instability (MSI)
Tumor regression grade (with neoadjuvant therapy)
KRAS gene analysis
18q loss of heterozygosity (LOH) assay

From Edge SB, Byrd DR, Compton CC, et al, editors: Colon and rectum. In American Joint Committee on Cancer staging manual, ed 7, New York, 2010, Springer.

which this disease spreads. Adenocarcinomas of the colon may grow by direct extension into the lymphatics of the submucosa and bowel wall. To avoid cutting across tumor in intramural lymphatics, sufficient lengths of bowel must be resected proximal and distal to the primary cancer. Colon cancer often extends through the serosa into mesenteric lymphatics that run along the blood vessels draining into the portal watershed at the root of the mesentery. Resection includes removal of the major lymphatic drainage system in the mesentery. Because anatomic resections designed to include named blood vessels also include the draining lymphatics, the boundaries for resecting large bowel cancer are relatively uniform (Figure 50-2). Right hemicolectomy, transverse colectomy, left hemicolectomy, and sigmoid resection are performed by adherence to surgical oncologic principles without major sacrifice of large bowel function. More recently, laparoscopic colonic resection has been implemented in the treatment of colon cancer. Several meta-analyses have demonstrated that a laparoscopic approach results in similar

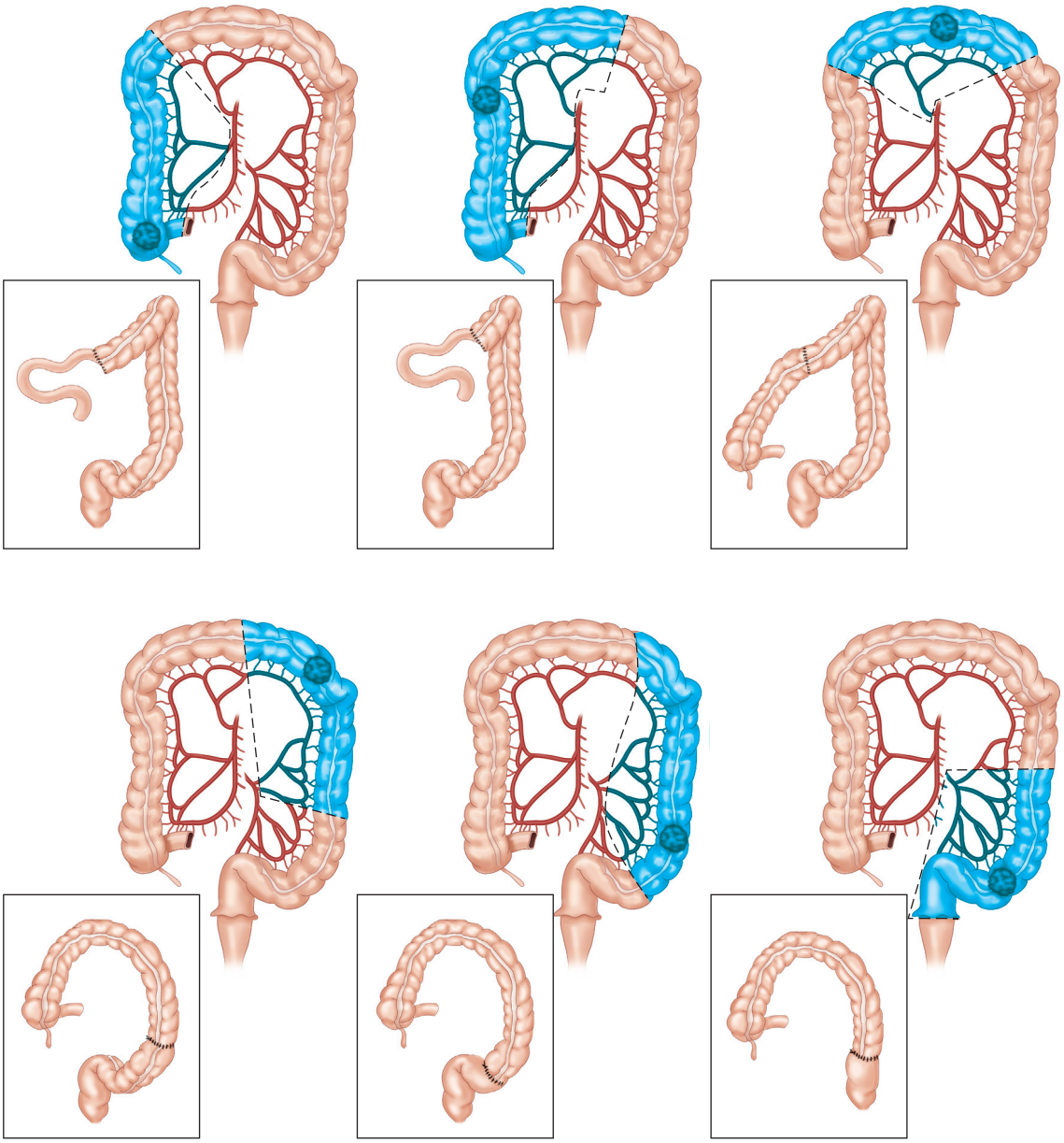


Figure 50-2 Extent of surgical resection at various colonic sites. The *darkened circle* represents primary disease site (anastomoses are shown in the *insets*).

long-term disease-related outcomes and is associated with fewer blood transfusions, faster return of bowel function, and shorter hospital stays postoperatively, albeit at the expense of increased operative time and costs compared to open resection.[15-17]

Resection results in excellent cure rates for lesions limited to the bowel wall with negative nodes (estimated 5-year survival, 97% for T1N0; 85% to 90% for T2N0). With a single high-risk feature of extension beyond the colonic wall (T3-T4N0) or involved nodes (T0-2N+), 5-year survival with surgery falls to 65% to 75%, and adjuvant treatment is often indicated. When both high-risk features are present (T3-4N+), 5-year survival with surgery alone drops to approximately 50% (T3N+) and 35% (T4N+), and adjuvant treatment is usually advised. Recent Surveillance, Epidemiology and End Results (SEER) analyses have allowed further refinement of survival outcomes based on TNM stage (Table 50-3).[18]

Adjuvant Chemotherapy

Patients with stage III colorectal cancer and no treatment other than surgery have a >50% chance of developing recurrent disease, and early trials in the 1980s showed that the risk of death could be reduced by 30% with the use of adjuvant therapy.[14,19] Based on these data, the NIH Consensus Conference panel recommended fluorouracil (FU)-based adjuvant chemotherapy for medically fit patients with completely resected stage III colon cancer.[20] However, it remained unclear whether or not patients with stage II disease, who are generally at a lower risk of recurrence than patients

TABLE 50-3 Surveillance, Epidemiology and End Results (SEER) Survival Outcomes Based on 2010 AJCC TNM Staging

TN Stage	SEER Relative Survival (5-year)*	AJCC Stage	SEER Observed Survival (5-year)
T1N0	97.4%	I	78.7%
T2N0	96.8%	I	74.3%
T3N0	87.5%	IIA	66.7%
T4aN0	79.6%	IIB	60.6%
T4bN0	58.4%	IIC	45.7%
T1-T2N1a	90.7%	IIIA	73.7%
T1-T2N1b	83.0%	IIIA	67.2%
T1-T2N2a†	79.0%	IIIA, IIIB†	64.7%
T3N1a	74.2%	IIIB	58.2%
T4aN1a	67.6%	IIIB	52.2%
T3N1b	65.3%	IIIB	51.7%
T1-T2N2b	62.4%	IIIB	51.8%
T4aN1b	54.0%	IIIB	42.1%
T3N2a	53.4%	IIIB	42.8%
T4aN2a‡	40.9%	IIIC	32.5%
T3N2b	37.3%	IIIC	30.4%
T4bN1a	38.5%	IIIC	30.6%
T4bN1b	31.2%	IIIC	25.4%
T4bN2a	23.3%	IIIC	18.3%
T4aN2b	21.8%	IIIC	17.5%
T4bN2b	15.7%	IIIC	12.9%

From Edge SB, Byrd DR, Compton CC, et al, editors: Colon and rectum. In American Joint Committee on Cancer staging manual, ed 7, New York, 2010, Springer.
**Net survival measure representing cancer survival in the absence of other causes of death.*
†T2N2 colon lesions did better than rectal T2N2a (both categories placed in stage IIIB).
‡T4aN2a colon lesions did worse than rectal T4aN2a (both categories placed in stage IIIC).

with stage III disease, would derive enough benefit to justify the potential toxicities, cost, and inconvenience of adjuvant therapy.[19]

Fluoropyrimidine (FU) Therapy

5-FU therapy remains the backbone for adjuvant chemotherapy for resected colorectal cancer. Although the use of 5-FU therapy has been clearly shown to be beneficial in stage III colorectal cancer based on the NASBP C-03,[21] NCCTG,[22] and IMPACT trials,[23] the benefits in stage II disease remains controversial. The Quick and Simple And Reliable (QUASAR) Collaborative Group aimed to determine the size and duration of any survival benefit from adjuvant chemotherapy for patients with colorectal cancer at a low risk of recurrence, which largely included patients with stage II disease. This trial randomly assigned 3239 patients (91% with stage II disease) after their curative resections of colon or rectal cancer to FU plus leucovorin (LV) with or without levamisole or to observation. As compared to observation, adjuvant chemotherapy was associated with a relative risk of the primary endpoint, all-cause mortality, of 0.82 (95% confidence interval [CI], 0.7 to 0.95; $p = 0.008$), a relative risk of recurrence of 0.78 (95% CI, 0.67 to 0.91; $p = 0.001$), and an absolute improvement in survival of 3.6% (95% CI, 1 to 6). However, among patients with stage II colon cancer, there was only a trend toward improved overall survival (hazard ratio [HR], 0.86; 95% CI, 0.66 to 1.12). Thus, although the QUASAR trial demonstrates that the adjuvant use of FU with LV shows a trend toward improved survival in patients with stage II colon cancer, it does not demonstrate a statistically significant benefit in these patients.[24]

The International Multicentre Pooled Analysis of B2 Colon Cancer Trials (IMPACT B2) trial was also designed to determine whether FU with LV is effective as adjuvant therapy after potentially curative resection in patients with T3N0 colon cancer. This study analyzed the pooled data from 1016 patients enrolled in five separate trials of FU with LV compared to observation. Over the median follow-up duration of 5.75 years, patients receiving FU with LV did not experience a significant improvement in event-free (HR, 0.83; 90% CI, 0.72 to 1.07) or overall survival (HR, 0.86; 90% CI, 0.68 to 1.07). The event-free survival favored chemotherapy (76%) as compared with observation (73%), though the difference was not statistically significant. The 5-year overall survival was similar between those who received chemotherapy (82%) and those who were observed (80%). The lack of support for adjuvant chemotherapy in patients with stage II or Dukes B2 colon cancer may be the result of the size of the trials; to show a survival benefit, an estimated 4000 patients would need to be enrolled, and neither of these trials enrolled this number of patients.

Beyond these two trials, several meta-analyses also evaluated the benefit of adjuvant FU-based chemotherapy in patients with resected colon cancer. An Intergroup analysis included data from 3302 patients with stage II or stage III colon cancer enrolled in seven randomized trials comparing FU with LV or FU with levamisole to surgery alone. T-stage, histologic grade, and nodal status were the only prognostic factors independently significant for both disease-free and overall survival. In a multivariate analysis, adjusting for these three factors, adjuvant therapy was associated with a significant 30% relative reduction in the risk of recurrence and a 26% relative reduction in the risk of death, and these risk reductions were similar for patients with stages II and III disease. Although patients with stage II disease had a statistically significant improvement in 5-year disease-free survival favoring chemotherapy (76% versus 72%), the difference in overall survival was not statistically significant (81% versus 76%).[25]

In comparison, the Cancer Care Ontario Program in Evidence-Based Care's Gastrointestinal Cancer Disease Site Group analysis looked at a subset of 4187 patients in 12 trials that had at least one arm that had an 5-FU–containing chemotherapy and an arm that was a surgery-alone control; it found that chemotherapy was associated with a small but significant absolute improvement in disease-free survival that ranged from 5% to 10%.[26] However, this did not translate into a statistically significant difference in overall survival (risk ratio 0.87; 95% CI, 0.75 to 1.10; $p = 0.07$).

Recently, the use of orally active fluoropyrimidines such as capecitabine has been shown to have similar clinical benefit as compared to 5-FU therapy. The European/Canadian X-ACT randomized patients with resected stage III disease to either capecitabine or 5-FU.[27] This study showed that 3-year disease-free survival (64% versus 61%, $p = 0.05$) and overall survival (81% versus 78%, $p = 0.07$) were similar in both arms. However, more than half of the patients receiving capecitabine required dose reduction secondary to hand-foot syndrome.

The difficulty in interpreting these data is that the majority of these trials included patients with both stage II and stage III disease. Although subgroup analyses have shown a trend toward improved overall survival or significantly improved disease-free survival favoring adjuvant FU-based chemotherapy in stage II disease, these trials were not powered to demonstrate an overall or disease-free survival advantage these patients. To date, no trial has demonstrated statistically significant data supporting the use of routine adjuvant FU-based therapy in patients with stage II colon cancer. An expert panel convened by the American Society of Clinical Oncology concluded that evidence from randomized trials does not support the routine use of adjuvant chemotherapy for these patients.[19]

Oxaliplatin

Although the standard adjuvant treatment for colon cancer used to be 5-FU alone, the addition of oxaliplatin to 5-FU has been found to improve the efficacy of this combination in the adjuvant setting. The MOSAIC trial evaluated the efficacy of treatment with 5-FU and oxaliplatin in the adjuvant setting for patients with stages II or III disease.[28] In this trial, 2246 patients who had undergone curative resection for stage II or III colon cancer were randomly assigned to receive either 5-FU or 5-FU with oxaliplatin for 6 months. After a median follow-up of 37.9 months, 5-FU with oxaliplatin led to fewer cancer-related events (HR 0.77, $p = 0.002$). The rate of disease-free survival at 3 years was also higher in the 5-FU with oxaliplatin group (78.2% versus 72.9%, $p = 0.002$).

A follow-up study confirmed an improved disease-free survival rate of 73.3% in the group given oxaliplatin as compared to 67.4% in the group given 5-FU alone (HR, 0.8; 95% CI, 0.68 to0.93; $p = 0.003$).[29] The secondary endpoint of 6-year overall survival was significantly improved at 78.5% in patients who received oxaliplatin, as compared to 76% in the patients who did not (HR, 0.84; 95% CI, 0.71 to 1.00; $p = 0.046$). In the analysis of patients with stage III disease, the 6-year overall survival rate was 72.9% with oxaliplatin and 68.7% without (HR, 0.8; 95% CI, 0.65 to 0.97; $p = 0.023$). However, no difference in 6-year overall survival was seen in patients with stage II disease.

Like the MOSAIC trial, the National Surgical Adjuvant Breast and Bowel Project C-07 (NSABP C-07) was a Phase III trial that evaluated the impact on disease-free survival of adding oxaliplatin to bolus weekly FU as adjuvant therapy for stages II and III colon cancer.[30] In this study, 2207 patients with stage II or III colon cancer were randomly assigned to bolus 5-FU or bolus 5-FU plus weekly oxaliplatin. Oxaliplatin resulted in a significant improvement in 4-year disease-free survival (73.2% versus 67%; HR for recurrence, 0.8; 95% CI, 0.69 to 0.93). In the subgroup analysis based on stage, patients with stage II disease had less of a disease-free survival benefit from the addition of oxaliplatin (4-year disease-free survival 84% versus 81%, which was not statistically significant).

The benefit of oxaliplatin in stage II disease remains unclear, despite the data from the MOSAIC and NSABP-07 trials. Though each trial had a suggestion of a rather small benefit on disease-free survival in the stage II population, the identical 6-year survival in the MOSAIC trial suggests that even if oxaliplatin is shown to increase survival in patients with stage II disease, the effect is likely to be minimal.

Irinotecan

Irinotecan is not a standard approach in the adjuvant setting based on negative results from three separate trials. In the CALGB 89803 study, 1264 patients were assigned to either weekly bolus FU with LV or weekly bolus irinotecan plus FU with LV. There was no difference in overall survival or disease-free survival.[31] In the PETACC-3 trial, patients with stages II and III colon cancer were randomized to receive 5-FU with LV with or without irinotecan. In 2094 treated patients with stage III disease and a median follow-up of 66.3 months, the 5-year disease-free survival was 56.7% with irinotecan and 54.3% without irinotecan ($p = 0.106$). The addition of irinotecan did not significantly improve overall survival, but it was associated with an increased incidence of grade-3 to grade-4 gastrointestinal toxicity and neutropenia.[32] Finally, the ACCORD trial randomized 400 patients with postoperative N1 or N2 disease to 5-FU with LV or 5-FU with LV plus irinotecan for 12 cycles with no improvement in disease-free or overall survival.[33]

Bevacizumab

Whereas bevacizumab has been shown to improve the outcomes in patients with metastatic disease, the National Surgical Adjuvant Breast and Bowel Project C-08 trial was designed to investigate the safety and efficacy of adding bevacizumab to modified FOLFOX6 (infusional/bolus 5-FU, LV, and oxaliplatin) for the adjuvant treatment of patients with stages II and III colon cancer.[34] In this trial of 2672 analyzed patients with a median follow-up of 35.6 months, the addition of bevacizumab did not result in a significant improvement in disease-free survival (HR, 0.89; 95% CI, 0.76 to 1.04; $p = 0.15$). A second multicenter trial, the European AVANT trial, assessed the use of bevacizumab in combination with oxaliplatin-based chemotherapy in the adjuvant treatment of patients with resected stage III or high-risk stage II colon cancer.[35] In this Phase III, randomized trial, patients with curatively resected stage III or high-risk stage II disease were assigned to receive FOLFOX4, FOLFOX4-bevacizumab, or XELOX (capecitabine/oxaliplatin)-bevacizumab in the adjuvant setting. After a median follow-up of 48 months, 25% in the FOLFOX4 group, 29% in the FOLFOX4-bevacizumab group, and 27% in the XELOX-bevacizumab group had relapsed, developed a new colon cancer, or died. The overall survival hazard ratios favored the no bevacizumab arm with FOLFOX4-bevacizumab compared to FOLFOX4 was 1.27 (95% CI, 1.03 to 1.57; $p = 0.02$), and for XELOX-bevacizumab compared to FOLFOX4 was 1.15 (95% CI, 0.93 to 1.42; $p = 0.21$). Serious adverse events were more common in the bevacizumab-containing groups than in the FOLFOX4 group. Therefore, this study demonstrated that bevacizumab does not prolong disease-free survival when added to adjuvant chemotherapy in resected stage III colon cancer, and the overall survival data even suggest a potential detrimental

effect with bevacizumab plus oxaliplatin-based adjuvant therapy. Bevacizumab use in the adjuvant setting is not recommended.

Cetuximab

Cetuximab is not indicated for any group of patients with resected colon cancer. The N0147 trial randomized 2686 patients (1863 patients with wild-type KRAS, 717 patients with mutated KRAS, and 106 patients with indeterminate KRAS) to mFOLFOX6 with or without cetuximab, but it was closed prematurely when an interim analysis demonstrated no benefit in terms of disease-free survival in any group with cetuximab.[36] Among all patients, grade-3 or higher adverse events and failure to complete the prescribed 12 cycles was significantly higher with cetuximab.

Adjuvant Irradiation with or without Chemotherapy

Rationale: Patterns of Relapse and Surgery Alone

Because of the documented efficacy of adjuvant chemotherapy as well as the perception by many oncologists that colonic (as opposed to rectal) cancer is much more likely to relapse distantly than locally, there has been little evaluation of the efficacy of postoperative irradiation with chemotherapy. The potential indications for adjuvant radiation therapy in colon cancer are based on analyses of patterns of failure following resection[37,38] (Table 50-4). Advanced stage predicts for local failure in both colon and rectal cancer; however, local failure in colon cancer also depends on anatomic origin. The ascending and descending colon are considered "anatomically immobile," and their close proximity to the retroperitoneal tissues often limits wide surgical resection (Figure 50-3). Limitations in achieving satisfactory circumferential margins increase the risk of residual disease and consequently local failure. In contrast, the midsigmoid and midtransverse colon are relatively "mobile" with a wide mesentery permitting the surgeon to obtain wide margins regardless of extent of disease invasion into the mesentery. Unless there is adjacent organ adherence or invasion by tumor, local failure at these sites is uncommon. Local failure rates for cecal, hepatic or splenic flexure, and proximal or distal sigmoid tumors are variable depending on the amount of mesentery present, tumor extension, and the adequacy of radial margins. When colon cancers adhere to or invade adjacent structures, local failure rates exceed 30% following surgery alone.

Adjuvant Irradiation, Single Institution

Most of the data evaluating the use of adjuvant radiation therapy in patients with high-risk colon cancer is from single-institution retrospective analyses.[39-43] To summarize, these studies have suggested that operative bed failures in high-risk patients undergoing resection alone are at least 30% and that the risk of local failure is reduced by the administration of adjuvant radiation therapy. These are discussed in detail here.

TABLE 50-4 Five-Year Actuarial Local Control and Relapse-Free Survival after Surgery Plus Postoperative Radiotherapy versus Surgery Alone, According to Stage: Massachusetts General Hospital Series

	Surgery Alone			Surgery + Postoperative Radiation Therapy		
TNM Stage	No. Patients	LC (%)	RFS (%)	No. Patients	LC (%)	RFS (%)
T3N0	163	90	78	23	91	72
T4N0	83	69	63	54	93	79*
T3N+	100	64	48	55	70	47
T4N+	49	47	38	39	72	53*

LC, *Local control;* RFS, *relapse-free survival.*
*$p < 0.05$.

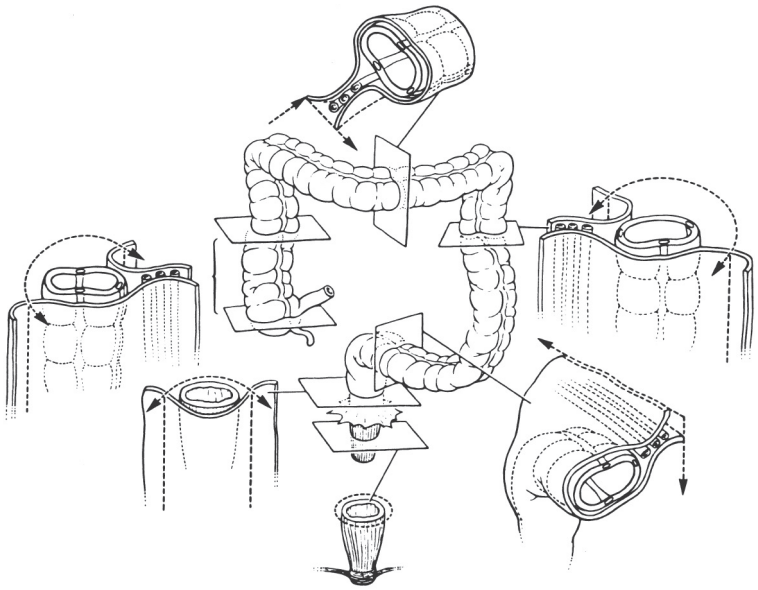


Figure 50-3 Idealized depiction of peritoneal relationships in the colon and rectum. The transverse and sigmoid colon are intraperitoneal, with a complete peritoneal covering (serosa) and mesentery. The ascending and descending colon are retroperitoneal, lack a true mesentery, and usually do not have a peritoneal covering posteriorly or laterally. The upper rectum begins above the peritoneal reflection and has peritoneum anteriorly and laterally. The lower half to two thirds of the rectum is below the peritoneal reflection (infraperitoneal). *Reproduced with permission from Gunderson LL, O'Connell MJ: Postoperative chemotherapy/irradiation adjuvant strategy. In Cohen AF, Winawer SJ, Friedman MA, et al, editors: Cancer of the colon, rectum, and anus, New York, 1995, McGraw-Hill, pp 631–645.*

A report from the Massachusetts General Hospital (MGH) evaluated outcomes in high-risk patients undergoing resection followed by adjuvant radiation therapy and compared these to a similar cohort of patients treated over the same period undergoing surgery only. Irradiated patients included those with T4N0/N+, T3N+ disease (excluding midsigmoid and midtransverse colon), and T3N0 patients with margins of less than 1 cm. A total of 171 patients received postoperative radiation therapy, with 63 patients receiving concurrent chemotherapy, usually with bolus 5-FU (500 mg/m^2/d) for three consecutive days during the first and last weeks of radiation therapy. Radiation treatment was administered through parallel opposed or other multifield techniques to treat the tumor bed with an approximate 3-cm to 5-cm margin to a total dose of 45 Gy, followed by reduced fields to a total dose of 50.4 Gy to 54 Gy. Draining nodes were included if thought to be at high risk for involvement. This cohort was compared to 395 patients with T3-4N0/N+ tumors undergoing surgery alone during the same time period.

Table 50-4 shows 5-year actuarial local control and relapse-free survival in the adjuvant group compared to patients undergoing surgery alone. Local control rates in T4N0 and T4N+ patients treated with radiation therapy were 93% and 72%, respectively, compared to 69% and 47%, in patients undergoing surgery alone. Similarly, relapse-free survivals were 79% and 53%, respectively, in T4N0/T4N+ patients undergoing adjuvant radiation, compared to 63% and 38%, after surgery alone. No significant outcome differences were observed in patients with T3N0 and T3N+ lesions; however, there may be an element of selection bias in the radiation group given most patients were referred because of concerns of adequacy of local control following surgery alone. There was a trend toward improved local control in patients receiving 5-FU (Table 50-5). The rate of acute enteritis in patients receiving irradiation and 5-FU was 16% compared with 4% in patients undergoing irradiation only. This rate of enteritis is similar to data from studies of concurrent 5-FU and radiation therapy in rectal cancer. Late bowel complication rates were not increased by concomitant 5-FU administration. The conclusion was that patients with T4 tumors or tumors with abscess or fistula formation or margin positive resection may benefit from postoperative radiation.[39]

In an updated analysis from MGH, 152 patients with T4 tumors received adjuvant irradiation. On pathological examination, 42 patients had tumors with positive margins. For patients with negative margins the 10-year actuarial local control in T4N0 and T4N+ patients was 78% and 48%, respectively. In patients with node negative tumors, the 10-year actuarial local control and relapse-free survival rates were 87% and 58%, respectively, compared to 65% and 33% in patients with node-positive tumors. For patients with one involved lymph node, local control and relapse-free survival rates were similar to those without nodal involvement; however, with increasing numbers of nodes involved, survival steadily decreased.[43]

A report from the Mayo Clinic described a series of 103 patients receiving radiation therapy following surgery for locally advanced colon cancer.[42] Microscopic and gross residual disease was present in 18 and 35 patients, respectively. More than 90% of patients had T4N0/N+ disease. A median dose of 50.4 Gy was delivered through multifield techniques and most patients received concurrent 5-FU–based chemotherapy. Eleven patients received an intraoperative "boost" of 10 Gy to 20 Gy. Five-year actuarial overall local control was 40%. Patients with margin negative tumors had a 5-year local control rate of 90%, compared to 46% for patients with microscopic residual tumor and 21% with gross residual tumor (Figure 50-4). In patients with residual disease, local control rates in patients undergoing intraoperative boost were 89% compared to 18% in patients undergoing external irradiation alone (Figure 50-5). Similarly, 5-year survival rates were improved in patients undergoing margin negative resection (66%) compared to those with microscopic residual (47%) or gross residual (23%) (Figure 50-6). Additionally, patients undergoing intraoperative boost demonstrated improved survival (76% versus 26%) (Figure 50-7).

A report from the University of Florida of patients with locally advanced but completely resected colon cancers receiving adjuvant radiation therapy reported a local control rate of 88%, similar to the 90% reported at the Mayo Clinic in patients who had completely resected tumors.[40] In addition, there appeared to be a dose response relationship to local control. The 5-year rate of local control was 96% for patients receiving 50 Gy to 55 Gy versus 76% for patients receiving less than 50 Gy ($p = 0.0095$).

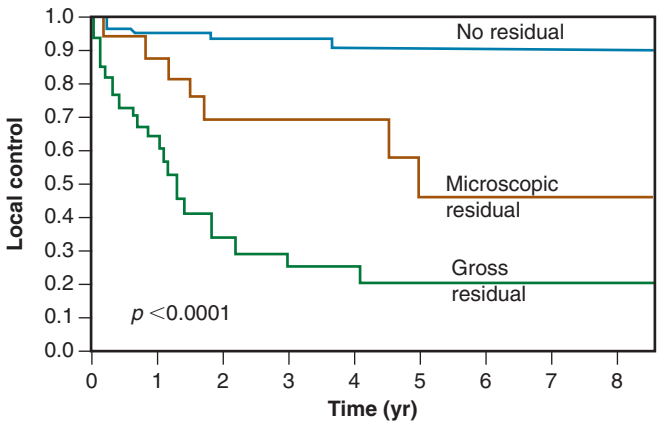


Figure 50-4 Local control by extent of residual disease after maximal resection in a Mayo Clinic series of 103 patients with colon cancer treated with external beam irradiation (EBRT) with or without chemotherapy (concomitant with or without maintenance) with or without intraoperative electron irradiation (IOERT).

TABLE 50-5 Five-Year Actuarial Local Control and Relapse-Free Survival of Adjuvantly Irradiated Patients Based on Administration of 5-Fluorouracil: Massachusetts General Hospital Series

	Without 5-FU			With 5-FU		
TNM Stage	No. Patients	LC (%)	RFS (%)	No. Patients	LC (%)	RFS (%)
T3N0	16	87	69	7	100	80
T4N0	37	94	78	16	100	83
T3N+	41	69	48	14	70	43
T4N+	24	67	53	15	79	52

LC, *Local control;* RFS, *relapse-free survival.*

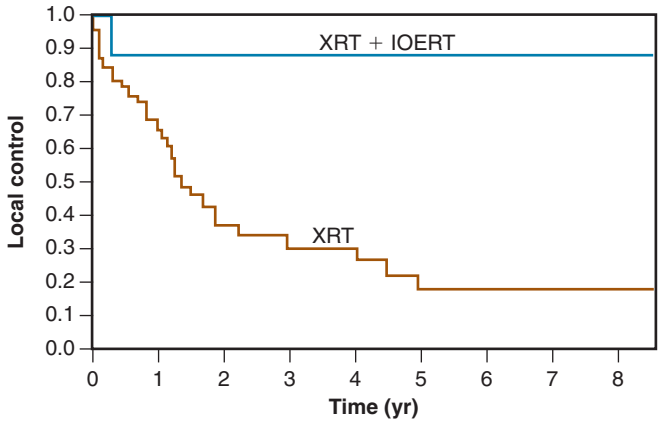


Figure 50-5 Local control by administration of IOERT after maximal resection in a Mayo Clinic series of 103 patients with colon cancer with residual disease treated with external beam irradiation (EBRT) with or without chemotherapy (concomitant with or without maintenance).

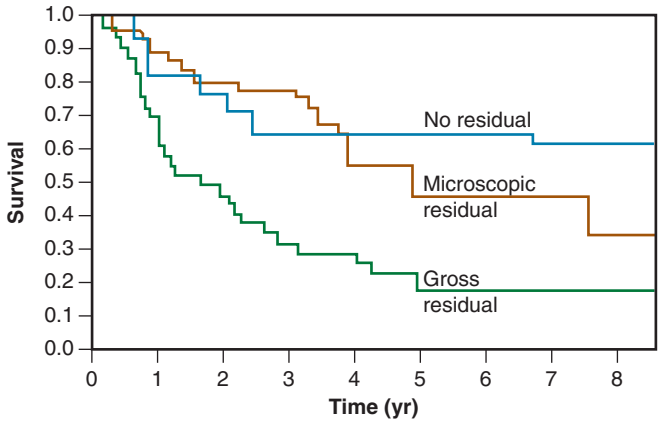


Figure 50-6 Survival results by amount of residual disease after maximal resection in a Mayo Clinic series of 103 patients with resected colon cancer treated with external beam irradiation (EBRT) with or without chemotherapy (concomitant with or without maintenance) with or without intraoperative electron irradiation (IOERT).

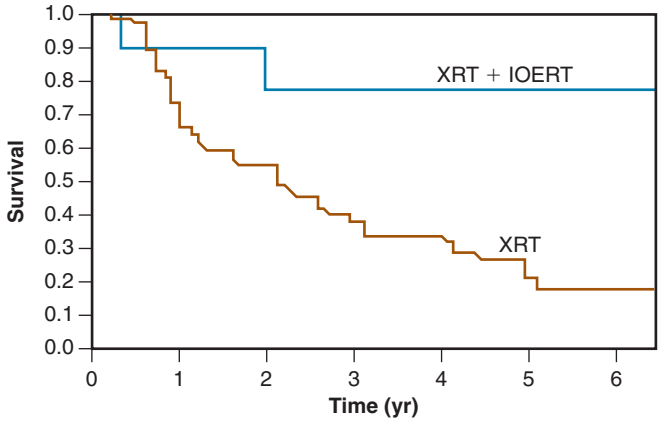


Figure 50-7 Survival results by intraoperative electron beam irradiation (IOERT) administration after maximal resection in a Mayo Clinic series of 103 patients with resected colon cancer treated with external beam irradiation (EBRT) with or without chemotherapy (concomitant with or without maintenance).

A review from the University of Toronto evaluated 33 patients with potentially resectable but locally advanced, adherent colon cancer. Of the 33 patients, 22 had undergone prior laparotomy and surgical exploration without resection given that an R0 resection was not deemed achievable. Patients received neoadjuvant radiation therapy with concurrent infusional 5-FU. All patients then underwent follow-up resection and achieved negative margins. One patient had pathologic complete response and 3 patients had microscopic residual disease only, with approximately two thirds demonstrating ypT4b disease. Three-year overall and disease-free survivals were 86% and 74%, respectively, with two patients developing local recurrence. The authors concluded that neoadjuvant chemoradiotherapy with en bloc multivisceral resection may result in high rates of R0 resection and excellent local control with acceptable morbidity and mortality.[41]

Phase III Intergroup Trial

In 1992 the US GI Intergroup initiated a randomized, prospective trial to assess whether the addition of radiation therapy to adjuvant chemotherapy would result in superior survival and lower locoregional failure rates in patients who were resected with high-risk colon cancer. Eligibility criteria included margin negative tumors with adherence to or invasion of surrounding structures (i.e., T4N0 or N+ disease, excluding peritoneal invasion) or tumors arising in the ascending or descending colon with metastatic regional nodes (T3N+). Patients were randomized to receive weekly 5-FU combined with levamisole for 12 months duration or 5-FU and levamisole for 12 months with combined radiation therapy and chemotherapy beginning 1 month after the first 5-FU administration. The recommended total radiation dose was 45 Gy in 25 fractions over 5 weeks with an optional 5.4 Gy boost.

The initial trial accrual goal was 700 patients; however, the study was closed in 1996 because of poor accrual (222 patients; 189 evaluable) resulting in a decreased statistical power to detect any differences between the groups. No difference in overall or disease-free survival was seen. Five-year overall survival of patients receiving chemotherapy only was 62% compared to 58% for patients randomized to chemoradiation ($p > 0.50$). Local recurrence rates were identical in both arms (18 patients each). Grade-3 and grade-4 hematologic toxicity was higher in patients receiving radiation therapy.[44] Interpretation of the study results was limited by decreased statistical power, high ineligibility rates, and lack of surgical clips or preoperative imaging to assist the definition of appropriate EBRT fields in a high percentage of patients. No definitive conclusions can be made regarding the efficacy of routine postoperative irradiation with 5-FU and levamisole based on this study; however, this study provides no data supporting its routine use.

A subsequent SEER database analysis evaluating patients with colon cancer diagnosed in the United States between 1988 and 2005 showed that tumor location, age, gender, stage, time of diagnosis, and geographic location were significantly associated with radiation therapy use in this disease. Patients diagnosed in 1988 were 2.5 times more likely to receive radiation that those diagnosed in 2005. The authors concluded that radiation therapy is infrequently used for colon cancer and use varies according to patient and tumor characteristics, and that although radiotherapy use had declined markedly since the 1980s, it continued to be used for nonmetastatic disease in a highly individualized manner.[45]

Our current policy is to consider adjuvant tumor bed irradiation in patients with tumors (1) invading adjoining structures, (2) complicated by perforation or fistula, and (3) where incomplete excision is performed. Patients are generally given continuous fluoropyrimidine-based chemo-

therapy 5 days per week throughout the course of radiation therapy.

LOCALLY ADVANCED DISEASE, METASTATIC DISEASE, AND PALLIATION

For patients with metastatic disease, fluoropyrimidine-based chemotherapy is usually administered as a single agent or in combination with oxaliplatin or irinotecan. Prospective randomized trials have shown that multiple agents improve survival in patients with metastatic colorectal cancer. Saltz et al reported the results of a three-arm randomized trial comparing (1) irinotecan, 5-FU, and leucovorin (IFL); (2) 5-FU with IFL; or (3) irinotecan alone. Patients receiving IFL had an improved survival (median survival 14.8 months versus 12.6 months, $p = 0.04$) and response rate (39% versus 21%, $p < 0.001$) compared to 5-FU and IFL alone. The incidence of grade-3 or higher diarrhea was significantly higher with the three-drug regimen.[46]

A study by Goldberg et al randomized 795 patients with previously untreated, metastatic colorectal cancer to receive (1) irinotecan, 5-FU, and IFL; (2) oxaliplatin, 5-FU, and IFL; or (3) irinotecan and oxaliplatin. Patients receiving oxaliplatin, 5-FU, and IFL had an improved median survival compared to those receiving irinotecan, 5-FU, and IFL or irinotecan and oxaliplatin (19.5 months versus 15 months versus 17.4 months; $p < 0.05$ for oxaliplatin-containing regimens versus irinotecan only regimen). Response rates in patients receiving 5-FU, IFL, and oxaliplatin were significantly higher than those receiving irinotecan, 5-FU, and IFL or irinotecan with oxaliplatin (45% versus 31% versus 35%, $p < 0.05$).[47]

Currently, cytotoxic chemotherapy is frequently combined with a targeted agent such as bevacizumab, a monoclonal antibody directed against vascular endothelial growth factor (VEGF), or cetuximab or panitumumab, monoclonal antibodies directed against the epidermal growth factor receptor (EGFR). Cetuximab is a chimeric (mouse/human) antibody and panitumumab is a fully humanized antibody and both are currently only indicated for only tumors without KRAS mutation.

Hurwitz et al reported a randomized trial comparing irinotecan, 5-FU, and IFL with or without bevacizumab. Median survival was significantly improved in the bevacizumab arm (median survival 20.3 months versus 15.6 months, $p < 0.001$). Additionally, response rates were improved in the bevacizumab-containing arm (45% versus 35%, $p = 0.004$).[48] Cunningham et al randomized 329 patients with metastatic colorectal cancer refractory to irinotecan-based chemotherapy regimens to receive cetuximab or cetuximab with irinotecan. Response rates in patients receiving combination therapy were significantly higher (23% versus 11%, $p = 0.007$) as was median time to progression (4.1 versus 1.5 months, $p < 0.001$). No difference in survival was observed.[49] The NO16966 trial evaluated the efficacy and safety of bevacizumab in combination with an oxaliplatin-based regimen. In this trial, 1401 patients were randomly assigned to an oxaliplatin-based therapy, and then to bevacizumab versus placebo, with a primary endpoint of progression-free survival. Although progression-free survival was significantly improved in the bevacizumab group when compared to placebo (9.4 months versus 8.0 months, $p = 0.0023$), the overall survival difference (21.3 months versus 19.9 months, $p = 0.077$) approached but did not reach significance.[50]

In the CRYSTAL trial, 1198 patients with EGFR-positive tumors were randomly assigned to first-line irinotecan-based therapy with or without cetuximab. This trial showed that patients with wild type KRAS had an improvement in overall survival (median 23.5 versus 20 months) and progression-free survival (9.9 versus 8.4 months).[51] Similarly, for oxaliplatin-based therapy, the OPUS trial showed that for patients with KRAS wild-type tumors, the addition of cetuximab to oxaliplatin-based therapy significantly improved response rate (61% versus 37%, $p = 0.0027$) and median progression-free survival (median 7.7 versus 7.2 months, $p = 0.0064$).[52] Finally, in the PRIME trial, a progression-free survival benefit was seen by adding panitumumab to first-line oxaliplatin-based therapy (median progression-free survival 9.6 versus 8 months, $p = 0.02$) and a trend toward improved overall survival (median 24 versus 20 months).[53]

Unfortunately, it remains unclear which targeted agent should be used first. This issue is currently being addressed in two trials; the FIRE-3 trial, in which 735 patients with previously untreated metastatic colorectal cancer are randomly assigned to an irinotecan-based therapy with either bevacizumab or cetuximab, and the US Intergroup C80405 trial, which randomizes patients with KRAS wild-type tumors to cetuximab or bevacizumab with either oxaliplatin- or irinotecan-based therapy. The results of this trial should help to answer the issue of optimal first-line therapy for patients with KRAS wild-type tumors. However, trials evaluating the combination of chemotherapy plus bevacizumab, with or without panitumumab, demonstrated increased toxicity and decreased progression-free survival in patients receiving both anti-VEGF and anti-EGFR therapy, suggesting that dual antibody therapy is not appropriate in these patients.[54] Other novel agents remain the focus of ongoing investigation in both the metastatic and nonmetastatic setting.

Palliative irradiation, sometimes in combination with fluoropyrimidine–based chemotherapy, is considered for patients with specific symptoms referable to metastatic disease—brain, bone, and other sites. Although beyond the scope of this chapter, the use of SBRT is being increasingly used in colorectal cancer patients with oligometastatic disease, including hepatic metastases. The combination of radiation therapy and targeted agents (bevacizumab, cetuximab) remains a topic of investigation.

TECHNIQUES OF IRRADIATION

Treatment field design in colon cancer is based on patterns of failure data. As is true in the treatment of rectal carcinoma, care must be taken in the design of postoperative treatment of adenocarcinoma of the colon. Field arrangement will vary depending on the site of the primary disease as well as areas judged to be at high risk for local recurrence.[55] Patient positioning (supine, prone, decubitus) should be considered in planning. Small bowel is often a dose-limiting structure, and it is often advantageous to position patients in the right or left decubitus position for at least a portion of their treatment, which may facilitate displacement of the small bowel away from the treatment field. Immobilization devices may improve reproducibility. Small-bowel contrast helps define small bowel volume within the treatment field. It may be useful to compare images in both the decubitus and supine positions to determine the actual amount of small bowel displacement. CT-based planning facilitates definition of the tumor bed, determining beam orientation, as well as estimating the volume of small bowel included within the treatment fields. As in other abdominal malignancies, a portion of one kidney may be irradiated. Unilateral renal irradiation results in minimal long-term clinical sequelae, assuming baseline function in the contralateral kidney is normal.[56]

The total radiation dose used in the adjuvant treatment of colon carcinoma depends on the volume of suspected residual disease and tolerance constraints of surrounding normal tissue. Generally, an initial dose of 45 Gy in 25 fractions of 1.8

Gy per fraction is delivered through larger fields to the primary tumor and at risk tissues. Reduced fields may be treated to 50 Gy if only a small portion of small bowel is included. For patient with T4 tumors, the general goal is to treat the tumor bed to a total dose of 54 Gy to 60 Gy. Treatment beyond 50 Gy generally mandates exclusion of all small bowel from the field. Spinal cord dose should generally be limited to 45 Gy. In addition, at least two thirds of one functional kidney should receive no more than 18 Gy to 20 Gy, and at least two thirds of the total liver volume should not receive more than 30 Gy. In a Mayo Clinic analysis, small bowel obstruction rates were lower when more than two treatment fields were used, and attempts should be made to implement multifield techniques, which is aided by CT-based planning.[57] Three-dimensional treatment planning as well as the use of intensity-modulated radiation techniques may facilitate small bowel as well as other normal organ sparing.

Generally, the primary tumor site should be covered with generous margin to cover areas of potential residual disease. The more proximal mesenteric nodal basins beyond the region of the primary tumor are usually not treated if satisfactory margin clearance is obtained in these sites. An exception to this may be right colon tumors where both small bowel and right colon are supplied by ileocolic vessels, limiting the extent of resection. In some instances, treatment of the paraaortic nodes may be indicated, particularly with extensive retroperitoneal involvement by tumor. In many situations, it may be appropriate to exclude treatment of paraaortic nodal basins, based on operative and pathological findings. Treatment of proximal mesenteric nodes may be appropriate if nodes adjacent to the surgical or resection margin are involved. Figures 50-8 and 50-9 show example radiation fields for a cecal as well as sigmoid cancer. Because of improved disease-related outcomes seen in patients with rectal cancer treatment with concurrent radiation therapy and fluoropyrimidine-based chemotherapy, as well as survival benefit seen in node-positive colon cancer receiving 5-FU–based chemotherapy, adjuvant irradiation in patients with resected high-risk colon cancer should be administered concurrently with fluoropyrimidine-based based chemotherapy.

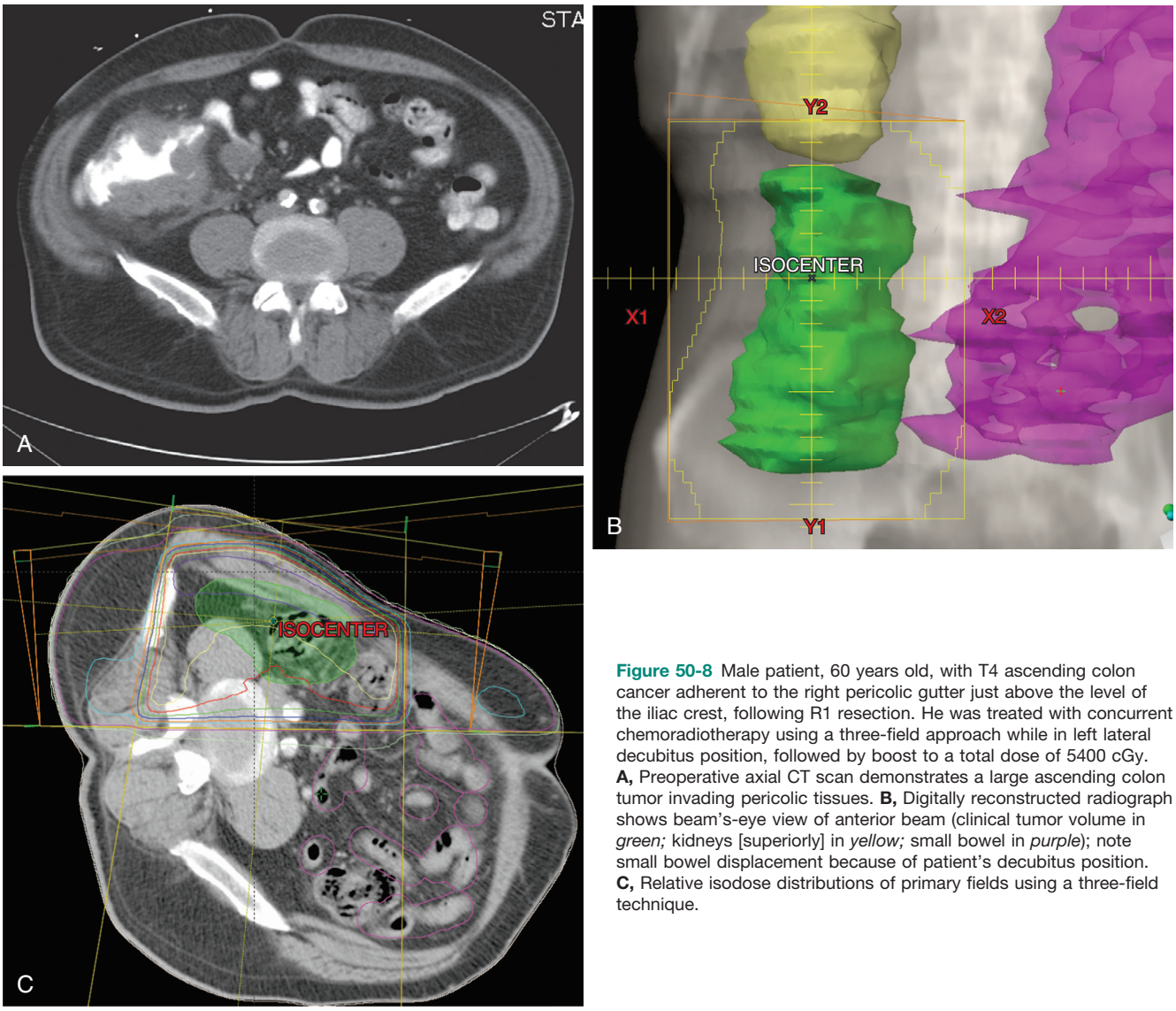


Figure 50-8 Male patient, 60 years old, with T4 ascending colon cancer adherent to the right pericolic gutter just above the level of the iliac crest, following R1 resection. He was treated with concurrent chemoradiotherapy using a three-field approach while in left lateral decubitus position, followed by boost to a total dose of 5400 cGy. **A,** Preoperative axial CT scan demonstrates a large ascending colon tumor invading pericolic tissues. **B,** Digitally reconstructed radiograph shows beam's-eye view of anterior beam (clinical tumor volume in *green;* kidneys [superiorly] in *yellow;* small bowel in *purple*); note small bowel displacement because of patient's decubitus position. **C,** Relative isodose distributions of primary fields using a three-field technique.

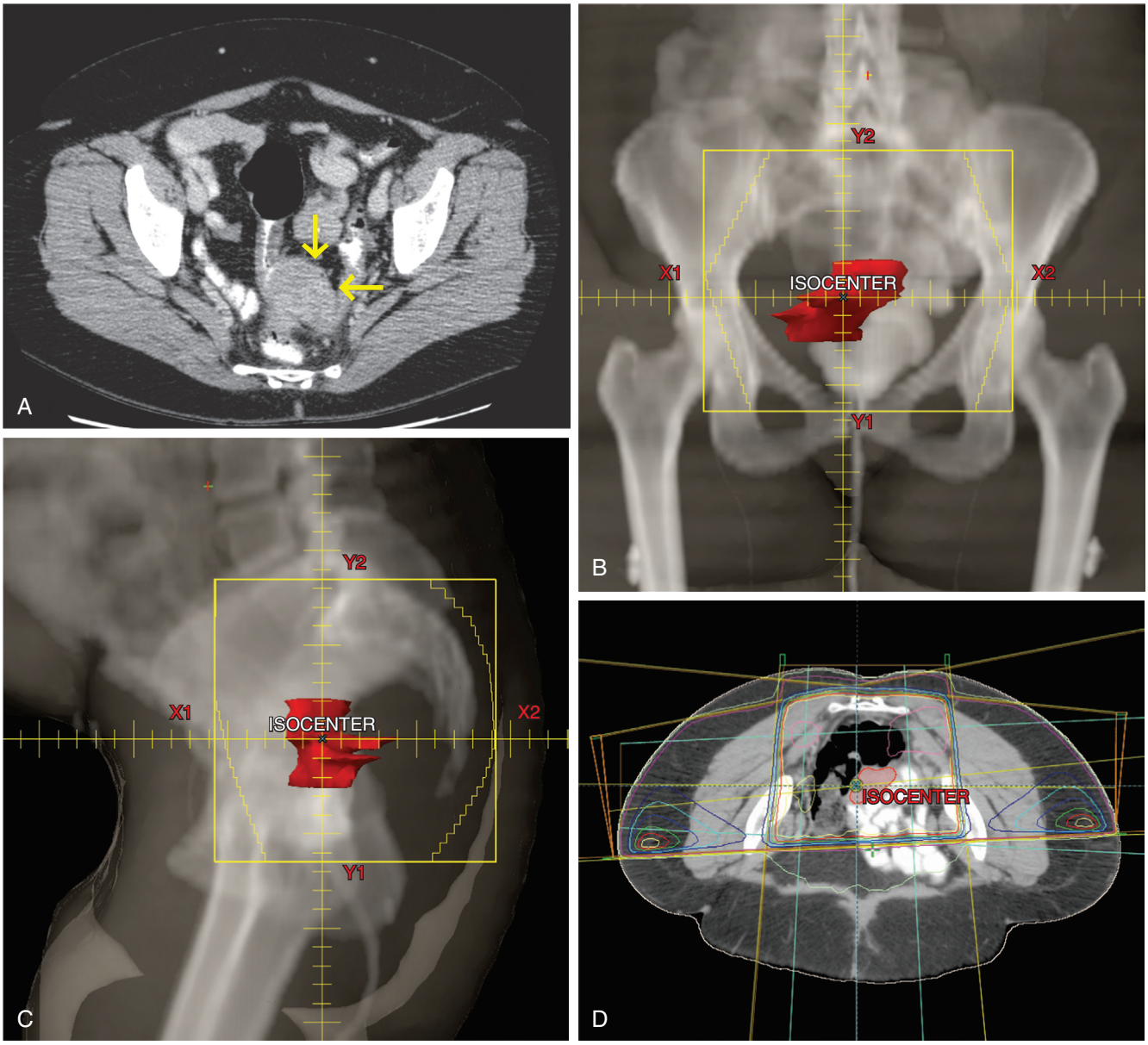


Figure 50-9 Female patient, 54 years old, with nearly obstructing sigmoid lesion at 35 cm from the anal verge. During left hemicolectomy, a perforated sigmoid cancer was found eroding into the proximal rectum with possible vaginal cuff involvement. She was treated with concurrent chemoradiotherapy using a three-field approach, in prone position with false tabletop, to a total dose of 4500 cGy. **A,** Axial CT slice shows sigmoid tumor *(yellow arrows)* invading adjacent rectum. **B,** Digitally reconstructed radiograph shows beam's-eye view of posterior beam (reconstructed gross tumor volume in *red*). **C,** Digitally reconstructed radiograph shows beam's-eye view of lateral beam. **D,** Relative isodose distributions of primary fields.

TREATMENT ALGORITHM, CONCLUSIONS, AND FUTURE POSSIBILITIES

Subsets of patients with colon cancer have local recurrence rates similar to patients with rectal cancer if surgery only is undertaken. Because of encouraging pilot study results with postoperative irradiation with or without 5-FU for patients with resected high-risk colon cancers, and the positive results of 5-FU and levamisole in high-risk adjuvant colon cancer, an Intergroup randomized trial was undertaken, randomizing patients to 5-FU and levamisole or 5-FU and levamisole with tumor bed irradiation in patients at high risk for local recurrence following surgical resection. There was no survival benefit seen in patients receiving adjuvant radiation therapy; however, interpretation of these results is limited by inadequate accrual and significant flaws as previously discussed.

The value of adjuvant postoperative irradiation combined with systemic therapy for patients at high-risk for local relapse is unlikely to be further addressed in a definitive randomized trial. Treatment recommendations should be made on a case-by-case basis with existing data in the setting of an informed consent. A potential treatment algorithm for these patients is shown in Box 50-2 and reflects the personal preference of the chapter authors.

The use of intraoperative irradiation as a supplement to EBRT in certain T4 tumors (i.e., those with uncertain margins) may also be appropriate. For patients with tumors adherent to or invading adjacent structures, the preferred treatment

BOX 50-2 Treatment Algorithm: Approach to the Therapy of Colon Cancer

1. TNM stages T1-2N0: complete resection
2. TNM T3N0: complete resection with consideration of adjuvant chemotherapy
3. TNM T4N0: complete resection with consideration of adjuvant chemotherapy; consider tumor bed/nodal irradiation with fluoropyrimidine-based chemotherapy
4. TNM T1-3N+: complete resection with consideration of adjuvant chemotherapy; for T3N1 tumors arising in immobile bowel with narrow resection margins, consider tumor bed/nodal irradiation with fluoropyrimidine-based chemotherapy.
5. TNM T4N+: complete resection followed by adjuvant chemotherapy; consider tumor bed/nodal irradiation with fluoropyrimidine-based chemotherapy.
6. Patients with fixed tumors: Preoperative irradiation with fluoropyrimidine-based chemotherapy followed by resection with intraoperative irradiation (electrons or brachytherapy) and maintenance chemotherapy.
7. Patients undergoing subtotal resection: External beam irradiation with fluoropyrimidine-based chemotherapy with intraoperative irradiation (electrons or brachytherapy) where possible with maintenance chemotherapy

sequence would be preoperative EBRT plus fluoropyrimidine–based chemotherapy followed by resection with or without IOERT and postoperative systemic therapy, based on excellent results in preliminary IOERT reports from both U.S. and European institutions.[42,57-59] A similar approach would be reasonable for patients with locally recurrent cancers or with regional nodal relapse.[59-62]

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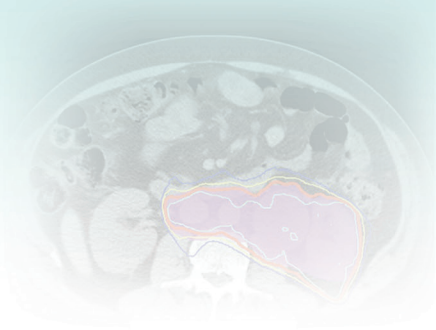
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CHAPTER

51 Rectal Cancer



Bruce D. Minsky, Claus M. Rödel, and Vincenzo Valentini

INCIDENCE

Colorectal cancer is the fourth most common form of cancer worldwide, with an estimated 800,000 new cases diagnosed each year, accounting for roughly 10% of all cancers. Approximately two thirds of cases occur in the colon and one third in the rectum. In the United States, an estimated 39,610 new cases of rectal cancer were estimated to occur in 2015.

BIOLOGIC CHARACTERISTICS

The most important prognostic factor for overall survival is the pathologic extent of disease as determined by the degree of bowel wall penetration by the tumor and the presence or absence of lymph node metastases or distant metastases (TNM stage).

Several biologic markers are now being prospectively evaluated in clinical trials to determine their prognostic utility. At the present time, the TNM staging system is the most reliable.

STAGING EVALUATION

The pretreatment evaluation of a patient with rectal cancer should include a careful history and physical examination. The primary imaging modalities for assessing the extent of the primary tumor are endorectal ultrasound (ERUS), computed tomography (CT), and magnetic resonance imaging (MRI). Both ERUS and high-resolution pelvic MRI are accurate in predicting T category. High-resolution MRI is highly accurate in identifying mesorectal fascial involvement (circumferential resection margin [CRM] positivity). Identifying nodal disease is still a diagnostic problem with CT, MRI, and ERUS, which rely on size criteria for predicting nodal metastases whereas positron emission tomography (PET)/CT does not rely on size criteria and is accurate, when indicated.

PRIMARY THERAPY

The primary therapy for potentially curative rectal cancer is surgery. Identification of radial microscopic lymphatic spread within the mesorectum has led to the use of total mesorectal excision (TME). With this type of surgery, local control rates have markedly increased. However, even with TME, the local failure rate for pathologic node-positive disease is 21% and adjuvant chemoradiation is still necessary.

ADJUVANT THERAPY

The conventional treatment for uT3 to T4 or node-positive clinically resectable rectal cancer is preoperative chemoradiation followed by surgery and postoperative adjuvant chemotherapy. In the German Rectal Cancer Phase III trial, which compared preoperative and postoperative chemoradiation, patients who received preoperative therapy had a significant decrease in rates of local failure, acute toxicity, and chronic toxicity and a significant increase in the rate of sphincter preservation in patients felt to need abdominoperineal resection before treatment. The primary disadvantage of preoperative irradiation or chemoradiation is the possible overtreatment of patients with early-stage (pT1-2N0) disease or undetected metastatic disease. For patients who undergo surgery first, if the tumor is pT3-4N0 or TanyN+, the treatment is commonly postoperative chemoradiation.

LOCALLY ADVANCED DISEASE

With the exception of the uncommon suture line-only recurrence, patients with primary or recurrent unresectable disease should receive preoperative chemoradiation. Although 50% to 90% will be able to undergo resection with negative margins, depending on the degree of tumor fixation, 24% to 55% still develop local recurrence. The addition of intraoperative irradiation decreases the rate of local recurrence.

PALLIATION

Pelvic irradiation offers effective palliation. In most patients, it decreases pelvic pain and bleeding.

Rectal cancer treatment is one of the best examples in oncology of how patients derive benefits from cooperative multimodal treatment strategies. These strategies are as variable as the clinical presentations of the disease. For example, this type of cancer can present as an early tumor suitable for local excision, a locally advanced tumor that requires preoperative therapy plus radical surgery, a tumor invading an adjacent organ or structure with no evidence of distant metastases, or a tumor with distant metastases. Radiation therapy has a well-established role in the treatment of rectal cancer and is used in the definitive, adjuvant, neoadjuvant, and palliative settings. Identifying which patients may benefit most from preoperative, postoperative, or intraoperative radiotherapy and which regimen would be best for which individual patient is undergoing active investigation.

ETIOLOGY AND EPIDEMIOLOGY

The etiology of colorectal cancer appears to be multifactorial and includes both environmental and genetic factors. Approximately 75% of colorectal cancers are sporadic, whereas 15% to 20% develop in those with either a positive family history or a personal history of colorectal cancer or polyps. The remaining cases occur in people with genetic predispositions, such as hereditary nonpolyposis colorectal cancer (HNPCC, Lynch syndrome; 2% to 4%) or familial adenomatous polyposis (FAP; 1%), or in people with inflammatory bowel disease, particularly chronic ulcerative colitis (1%).

The fundamental role of environmental factors is supported by observations in migrant populations. Generally, migrants from low-incidence regions in Africa and Asia who

relocate to high-incidence regions of North America or Australia assume the incidence of the host country within one generation.[1] Specifically, a high-fat, low-fiber diet is associated with the development of colorectal cancer. Conversely, the ingestion of a high-fiber diet is associated with protection against colorectal cancer. Fiber causes the formation of a soft, bulky stool that dilutes out carcinogens; it also decreases colonic transit time, allowing less time for carcinogenic substances to contact the mucosa. The more sedentary lifestyle in Western countries, cigarette smoking, and alcohol consumption also appear to be linked with the risk of colorectal neoplasia.

Most colorectal cancers arise from benign adenomatous polyps lining the wall of the bowel. Those that grow to a large size (>2 cm) and have a villous appearance or contain dysplastic cells are most likely to progress to cancer. This progression from adenoma to carcinoma is associated with an accumulation of genetic alterations, including activation of oncogenes and inactivation of tumor suppressor genes.[2] One of the early steps in this process is the interruption of the APC/β-catenin/TCF-4 pathway, allowing unchecked cellular replication at the crypt surface. This can occur in the germline of patients with FAP, with the second allele being inactivated somatically, or in sporadic cancers, in which both alleles are somatically inactivated.

There are likely three pathways that lead to colorectal cancer: chromosomal instability (CIN), microsatellite instability (MSI), and CpG island methylator phenotype (CIMP).[2] These pathways are not mutually exclusive, with some tumors exhibiting features of more than one pathway. CIN is the genetic reason for tumor formation in 50% to 70% of colorectal cancers and the mechanism operative in FAP. It is characterized by gain or loss of whole chromosomes or chromosomal regions, subsequently resulting in aneuploidy, telomerase dysfunction, or defects in DNA damage response. It is typically coupled with mutations in the APC, KRAS, and TP53 genes, ultimately leading to loss of heterozygosity of TP53 and malignant transformation. MSI is found in more than 90% of HNPCCs that carry a germline inactivation in DNA mismatch repair genes, but it is also found in 15% of sporadic cancers, in which epigenetic hypermethylation silences gene transcription of hMLH1. With MSI, multiple frameshift mutations at microsatellite sequences occur, including those in exon coding sequences of the transforming growth factor-beta receptor II, the proapoptotic BAX gene, and the DNA mismatch repair genes (hMSH3 and hMSH6 genes). The third type, CIMP, is a relatively heterogeneous subgroup and occurs in approximately 10% to 30% of patients, is predominantly associated with KRAS gene mutations but sometimes with BRAF gene mutations, usually lacks chromosomal instability, and has the poorest prognosis of the three types and perhaps a poorer response to chemotherapy. Of the numerous molecular markers examined to date, MSI, 18q, thymidylate synthase, and TP53 overexpression are among those which appear to have the most prognostic significance in colon cancer.[3]

Colorectal cancer is the fourth-commonest form of cancer and the second-leading cause of death in the United States. Approximately two thirds of cases occur in the colon and one third in the rectum. In the United States, annually approximately 132,270 new cases of large bowel cancer are diagnosed, of which 93,090 are colon and 39,610 are rectal cancers.[4] The occurrence of sporadic colorectal cancer increases continuously older than the age of 45 to 50 years for both genders and peaks in the seventh decade. Subgroups of patients, including those with inherited syndromes, such as FAP, HNPCC, or hamartomatous polyposis conditions (e.g., Peutz-Jeghers syndrome), can experience colorectal cancer at a much earlier age.

PREVENTION AND EARLY DETECTION

Primary Prevention

Primary prevention involves the identification and elimination of factors that cause or promote colorectal cancer or interfere with the adenoma-to-carcinoma cascade. Dietary and lifestyle approaches employ higher-fiber, lower-fat components, and increased physical activity to inhibit the carcinogenic process. Prospective studies have suggested that vitamin D deficiency may contribute to the incidence of colorectal cancer.[5] Other dietary components, such as selenium, carotenoids, and vitamins A, C, and E, may also have protective effects by scavenging free oxygen radicals. Folic acid, a component of fresh fruits and green vegetables, supplies methyl groups necessary for nucleotide synthesis and gene regulation. Prospective studies generally support an inverse association between folate intake and colorectal cancer risk.[6]

COX-2 is overexpressed in more than 50% of adenomas and 80% to 85% of adenocarcinomas. Chemopreventive strategies are based on population-based studies that strongly support an inverse relationship between the use of nonsteroidal anti-inflammatory drugs (NSAIDs), such as aspirin, sulindac, or the new selective COX-2 inhibitors, and the risk of colorectal adenomas or carcinomas. Nevertheless, the consumption of NSAID and COX-2 inhibitors may cause serious adverse events to the gastrointestinal, renal, and cardiovascular system. Thus, the optimal dosage and duration, and proper patient selection stills need to be established.[7]

Screening for Early Detection

The process of malignant transformation from adenoma to carcinoma takes several years. The goal of screening is to prevent rectal cancer deaths through the detection and treatment of benign or premalignant lesions and curable-stage cancers. For the average-risk population, screening should begin at age 50 years and should follow one of the following testing options: fecal occult blood testing (FOBT) or fecal immunochemical testing (FIT) every year, flexible sigmoidoscopy every 5 years, double-contrast barium enema every 5 years, CT colonography (virtual colonoscopy) every 5 years, or colonoscopy (preferably) every 10 years.[8]

Some individuals are at increased risk for colorectal cancer. For example, if there is an affected first-degree relative, a family history of FAP or HNPCC, or a personal history of adenomatous polyps, colorectal cancer, or chronic inflammatory bowel disease, screening should begin earlier (at age 40 years) or it should be done more often than in average-risk persons. In some settings such as a personal history of genetic predisposition, screening should be done at an even younger age, as detailed in the NCCN Guidelines for Colorectal Cancer Screening (to view the most recent version, visit www.NCCN.org).

BIOLOGIC CHARACTERISTICS AND MOLECULAR BIOLOGY

The most important prognostic factor for overall survival is the pathologic extent of disease as determined by the degree of bowel wall penetration by the tumor (T category), and the presence or absence of lymph node metastases (N category) or distant metastases (M category). Tumor differentiation (grading) is also prognostically important because poorly differentiated adenocarcinomas are associated with lymph node metastases in more than 50% of cases and also correlate with the likelihood of lymphatic and venous invasion. An elevated

carcinoembryonic antigen (CEA) level at the time of presentation has an adverse impact on survival times independent of tumor stage.[9] Detection of occult metastases in lymph nodes, blood, or bone marrow by molecular techniques may allow further refinement in pathologic staging.

Molecular strategies added to the more traditional histopathologic information may help in the future to identify patients at a lower stage whose tumors are likely to behave like higher-stage lesions, and vice versa. Several biologic markers, including allelic loss of 18q, alteration in KRAS, MSI, thymidylate synthase, thymidine phosphorylase, vascular endothelial growth factor (VEGF), epidermal growth factor receptor (EGFR), P21, P27, BCL2, BAX, and TP53, among others, are now being prospectively evaluated in clinical trials to determine their prognostic utility. At the present time, however, the TNM staging system is the most reliable.

PATHOLOGY AND PATHWAYS OF SPREAD

Histopathology

The majority (>90%) of colorectal cancers are adenocarcinomas. Some adenocarcinomas have mucin, which can be extracellular (colloid) or intracellular (signet-ring cell). Colloid cancer, which occurs in 15% to 20% of adenocarcinomas, is not an independent prognostic factor, whereas signet-ring cell carcinoma, which occurs in 1% to 2% of adenocarcinomas, is an independently poor prognostic factor for survival.[10] Other histologic types are rare and include carcinoid tumors, leiomyosarcomas, lymphomas, and squamous cell cancers. The grading system used for adenocarcinomas refers to the degree of differentiation. Most institutions use a three-grade system (well, moderate, and poor). Despite substantial interobserver and intraobserver variability in tumor grading, poorly differentiated tumors have consistently been found to be associated with a worse prognosis in multivariate analysis.

Anatomy and Pathways of Spread

The rectum is about 15 cm long. In cancer staging, because of differences in treatment and prognosis, the rectum is subdivided into three parts according to the distance of the lower margin of the tumor from the anal verge (assessed by rigid proctoscopy): upper third, 12 to 16 cm; middle third, 6 to 12 cm or less; and lower third, less than 6 cm. When reporting results, it should be stated whether the reference point is the anal verge (i.e., lowermost portion of the anal canal), the dentate line, or the anorectal ring. Distances measured from the anal verge are approximately 2 cm to 3 cm longer than distances from the dentate line. The anorectal ring (also known as the dentate line) is at the level of the puborectalis sling and levators, representing the pelvic floor from within the pelvis. The anterior peritoneal reflexion represents the point at which the rectum exits the peritoneal cavity (approximately 12 cm to 15 cm from the anal verge) and becomes an extraperitoneal structure. Patients entered into postoperative adjuvant rectal trials in the United States were required to have tumors with the inferior aspect at or below the peritoneal reflection. For entry into preoperative trials, most use tumors with a distance of less than 12 cm from the anal verge for eligibility. However, the German trial (CAO/ARO/AIO-94) allowed tumors at a distance of as much as 16 cm.[11,12]

Below the peritoneal reflection, there is a mesorectal fascia (MRF). This layer of visceral fascia encloses both the rectum and mesorectum with the perirectal lymph nodes and thus forms a separate compartment within the pelvis. With TME, the entire specimen is removed by sharp dissection along the mesorectal plane (eFigure 51-1). The CRM is related more to the type and quality of the surgical procedure than to an anatomic landmark. Although distal intramural spread usually extends no more than millimeters beyond the grossly recognizable margin of the tumor, microscopic tumor nodules (satellites) are found in the mesorectum, predominantly in a radial direction but also in a distal one, some centimeters from the lower tumor margin.[13]

The major portion of the lymphatic drainage of the rectum passes along the superior hemorrhoidal arterial trunk toward the inferior mesenteric artery. Only a few lymphatics follow the inferior mesenteric vein. The pararectal nodes above the level of the middle rectal valve drain exclusively along the superior hemorrhoidal lymphatic chain. Below this level (≈7 cm to 8 cm above the anal verge), some lymphatics pass to the lateral rectal pedicle. These lymphatics are associated with nodes along the middle hemorrhoidal artery, obturator fossa, and hypogastric and common iliac arteries. The risk of their involvement increases with tumor stage, presence of mesorectal positive nodes, infiltration of mesorectal fascia, and low location of the primary tumor. Extensive lymphatics are also present in women contiguous with the rectovaginal septum and in men along Denonvilliers' fascia. The venous drainage of the upper rectum is to the inferior mesenteric vein via the superior hemorrhoidal vein and then to the portal system, whereas the lower rectum can, in addition, drain to the internal iliac veins and inferior vena cava. Therefore, liver or lung metastases, or both, can occur with rectal cancers.

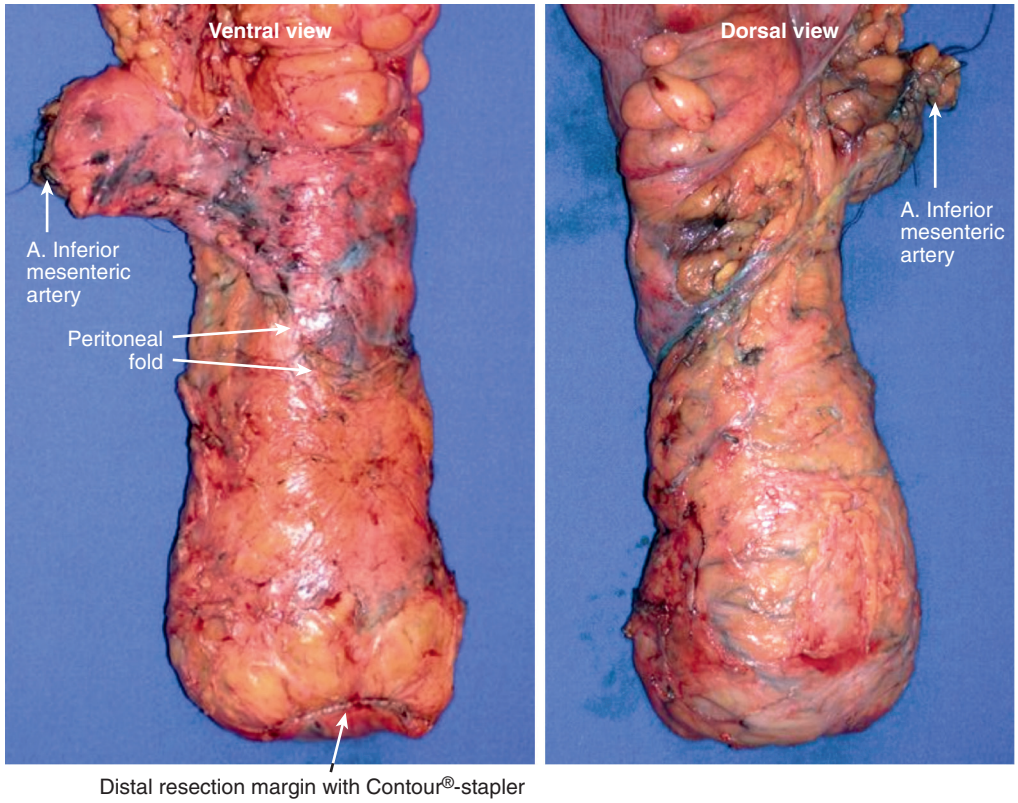
CLINICAL MANIFESTATIONS, PATIENT EVALUATION, AND STAGING

Clinical Manifestations

Rectal cancer is usually symptomatic before diagnosis. Common symptoms include gross red blood (mixed or covering stool, or by itself, sometimes accompanied by the passage of mucus) and a change in bowel habits such as unexplained constipation, diarrhea, or reduction in stool caliber. Hemorrhoidal bleeding should always be a diagnosis of exclusion. Obstructing rectal cancers frequently present with diarrhea rather than constipation. In cases of locally advanced rectal cancer with circumferential growth and extensive transmural penetration, urgency, inadequate emptying, and tenesmus occur. Urinary symptoms and buttock or perineal pain from posterior extension are grave signs. Sciatic pain is indicative of tumor invasion into the sciatic notch, and surgery will likely leave gross disease.

Pretreatment Evaluation and Imaging

The standard diagnostic algorithm for rectal cancer is seen in Table 51-1. The pretreatment evaluation of a patient with rectal cancer should include a careful history and physical examination. By digital rectal examination (the average finger can reach approximately 7 cm to 8 cm), tumors can be assessed for size, ulceration, and fixation to surrounding structures. This examination also permits evaluation of sphincter function, which is critical when determining whether a patient is a candidate for a sphincter-sparing procedure. Rigid proctoscopy allows direct visualization of the lesion and provides an estimation of the size of the lesion and degree of obstruction. This procedure is used to obtain biopsies and gives an accurate measurement of the distance of the lesion from the anal verge. A complete evaluation of the large bowel, preferably by colonoscopy, should be done to rule out synchronous neoplasms.



eFigure 51-1 TME specimen after preoperative chemoradiation and perioperatively performed staining with methylene blue via the inferior mesenteric artery.

TABLE 51-1 Diagnostic Algorithm for Rectal Cancer

History	Including family history of colorectal cancer or polyps
Physical examination	Including assessment of size, minimum diameter of lumen, mobility, distance from anal verge, and cursory evaluation of sphincter function
Rigid proctoscopy	Including assessment of mobility, minimum diameter of lumen, and distance from anal verge. Allows biopsy of the primary tumor.
Colonoscopy	To detect possible synchronous colorectal neoplasm
Endorectal ultrasound*	To assess depth of tumor penetration through the rectal wall and involvement of adjacent mesorectal lymph nodes.
Pelvic MRI*	To assess depth of tumor penetration through the rectal wall, tumor invasion of mesorectum, and involvement of mesorectal and pelvic lymph nodes. Particularly useful for assessment of distance of tumor to mesorectal fascia.
Chest, abdominal, or pelvic CT*	With intravenous and oral contrast; to detect possible metastatic disease.
PET/CT scanning	Not routinely indicated; should only be used if contrast CT or MRI show equivocal findings or in patients with strong contraindications to IV contrast.
CEA levels	To obtain baseline CEA level (a prognostic factor and important for follow-up)
Complete blood count	To check for anemia secondary to bleeding

CEA, *Carcinoembryonic antigen*; CT, *computed tomography*; MRI, *magnetic resonance imaging*; PET, *positron emission tomography*.
**For sensitivity and specificity of endorectal ultrasound, pelvic CT and pelvic MRI for local staging see Table 59.2.*

With the shift to preoperative therapy, clinical staging to accurately identify both T category and N category is critical. The primary imaging modalities to assess the extent of the primary tumor are ERUS, multidetector 4- to 16-slice CT, and phased array MRI. ERUS is an accurate tool in predicting T category of rectal cancers, especially T1 compared to T2 (eTable 51-1, eTable 51-2 and eFigure 51-2). Thus, ERUS has been recommended as the investigation of choice in selection of potentially curative local excision, which should be restricted to patients with T1 tumors without further risk factors (such as G3, L1, sm3), as well as in selection of patients with early T3 tumors (versus T2) for neoadjuvant treatment. ERUS cannot be reliably used in patients with high or stenosing tumors.

Because of limited acoustic penetration by ERUS, invasion of bulky tumors into the perirectal fat, adjacent organs, and pelvic side walls is better evaluated by multislice-CT scan and phased array MRI. The involvement of the anal sphincter and levator ani muscles cannot be truly seen on CT scans, whereas high-resolution MRI techniques using phased-array coils have led to improved spatial resolution and have been shown to identify the anal sphincter, puborectalis, and especially the mesorectal fascia (Figures 51-1, *A* and *B*). This latter finding is an important feature to predict negative circumferential margins between the tumor and the mesorectal fascia, and makes phase array MRI superior to CT especially for lower-third rectal tumors. Moreover, substaging of T3 tumors (T3a/b with tumor spread ≤5 mm into the mesorectal compartment) has been validated prospectively by the MERCURY study group and has shown direct agreement between pretreatment imaging and corresponding pathology.[15]

The identification of positive lymph nodes is more difficult. Involvement is mainly assessed by size criteria (> 8 mm), although enlarged lymph nodes are not pathognomonic of tumor involvement. Morphological features such as the presence of mixed signal intensity and irregularity of the borders of the lymph nodes may be more reliable.[16] In the meta-analysis of Bipat et al, the sensitivity and specificity in detecting positive lymph nodes with the aforementioned techniques were comparable (51-2).[17] However, only CT and MRI can evaluate iliac, mesenteric, or retroperitoneal nodes. Clearly, adequate clinical detection of lymph node involvement remains a challenge that is critically important with the increasing use of preoperative treatment strategies.

Screening for distant metastatic disease is accomplished routinely by chest and abdominal contrast-enhanced CT or abdominal MRI. Bone scan and brain imaging are required for clinical symptoms only. The major advantage of a PET scan is to differentiate between recurrent tumor and scar tissue by measuring tissue metabolism of an injected glucose-based substance. Scar tissue is inactive, whereas tumor generally is hypermetabolic. This test generally is not used in a routine preoperative metastatic workup.

Imaging after Chemoradiation

Although ERUS, CT, and MRI can be used to assess downsizing and staging of the tumor after neoadjuvant multimodal treatment, it is not accurate in distinguishing between ypT0, ypT1, ypT2, or ypT3 residual cancers. Overstaging is common, especially when there is a fibrotic thickening of the rectal wall. A reasonably high level of accuracy has been observed by phased array MRI for differentiating ypT0-2 from ypT3.[18] Diffusion-weighted MRI has been investigated to monitor therapy response and to predict outcome to preoperative therapy; however, further studies are needed.[19] For the identification of responders to neoadjuvant therapy, 18-FDG-PET has a larger role. Many studies have reported a significant decrease in standardized uptake values (SUV) on mid- or post-radiation FDG-PET in responders when compared to nonresponders, but the clinical value of this information remains to be determined.[20]

TNM Staging

The first practical staging system was the Dukes' classification in the 1930s.[21] This system classified colorectal tumors from A to C, with stage A indicating penetration into but not through the bowel wall, stage B indicating penetration through the bowel wall, and stage C indicating involvement of lymph nodes, regardless of the extent of bowel wall penetration. The system has since been modified by many authors to better reflect levels of penetration and nodal metastases. In 1998, the American Joint Commission on Cancer (AJCC) and the Union Internationale Contre le Cancer (UICC) proposed a joint TNM classification staging system.

In the sixth edition of the AJCC staging manual, stage II colorectal cancer was subdivided into IIA (T3N0) and IIB (T4N0) and stage III was subdivided into IIIA (T1-2N1M0), IIIB (T3-4N1M0), and IIIC (any TN2M0), based on improved

eTABLE 51-1 Sensitivity and Specificity of ERUS, Pelvic CT, and MRI in the Staging of Rectal Cancer*

Tumor Extent	Imaging Modality	Sensitivity (%)	Specificity (%)
Muscularis propria invasion	ERUS	94	86
	MRI	94	69
	CT	NA	NA
Perirectal tissue invasion	ERUS	90	75
	MRI	82	76
	CT	79	78
Adjacent organ invasion	ERUS	70	97
	MRI	74	96
	CT	72	96
Lymph node involvement	ERUS	67	78
	MRI	66	76
	CT	55	74

CT, *Computed tomography;* ERUS, *endorectal ultrasound;* MRI, *magnetic resonance imaging*.
**According to Bipat S, Glas AF, Slors FJM, et al: Rectal cancer: local staging and assessment of lymph node involvement with endoluminal US, CT, and MR imaging—a meta-analysis. Radiology 232:773–783, 2004.*

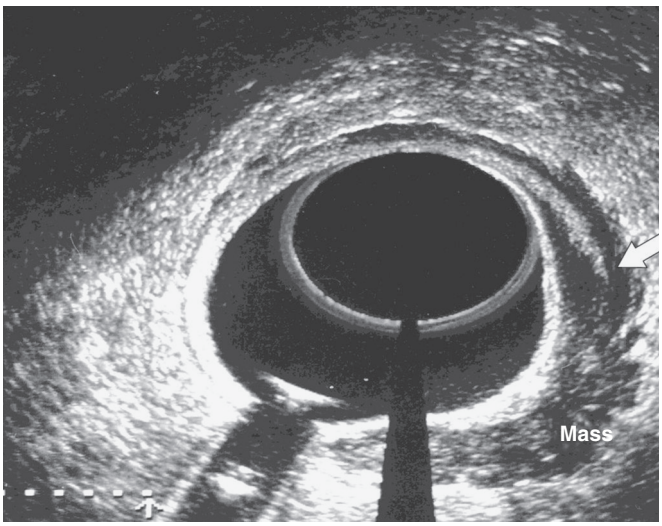
eTABLE 51-2 Grading of Surgical TME Specimen According to Quirke[14]

Good (grade 1): intact mesorectum with only minor irregularities of a smooth mesorectal surface; no defects larger than 5 mm; no coning on specimen; smooth circumferential resection margin on slicing.

Moderate (grade 2): moderate bulk to mesorectum but irregularity of the mesorectal surface; moderate coning of the specimen toward the distal margin; at no site is the muscularis propria visible with the exception of the area of insertion of levator muscles; moderate irregularity of the circumferential resection margin.

Poor (grade 3): little bulk of mesorectum with defects down into muscularis or very irregular circumferential resection margin.

Of note, overestimation of staging with this technique occurs more often than understaging. In the German CAO/ARO/AIO-94 study, 18% of patients in the immediate surgery arm clinically staged by ERUS to have T3 or N+ disease had lymph node negative tumors confined to the rectal wall (pT1/2 pN0) on pathologic assessment of the resected specimen.[12,14] This probably is as a result of the inflammatory and desmoplastic processes caused by the tumor (or by taken tumor biopsy within 1 week before ERUS was performed), but it is also operator dependent. Endorectal coil MRI is an alternative to ERUS but does not appear to be superior to ERUS for T staging.



eFigure 51-2 Endorectal ultrasound (ERUS) visualizes the rectal wall as alternating hyperechoic and hypoechoic layers of tissue. The first layer is the hyperechoic water-filled balloon or mucosal interface, which is bounded by the hypoechoic mucosa and muscularis mucosa, the hyperechoic submucosa, the hypoechoic muscularis propria, and finally, the hyperechoic muscularis propria or perirectal fat interface. Depth of penetration is determined by identifying which of these layers is disrupted by the tumor. The figure shows a mass infiltrating beyond the muscularis propria *(thick arrow)* into the perirectal fat (bright area in the lower part), indicating an uT3-rectal tumor.

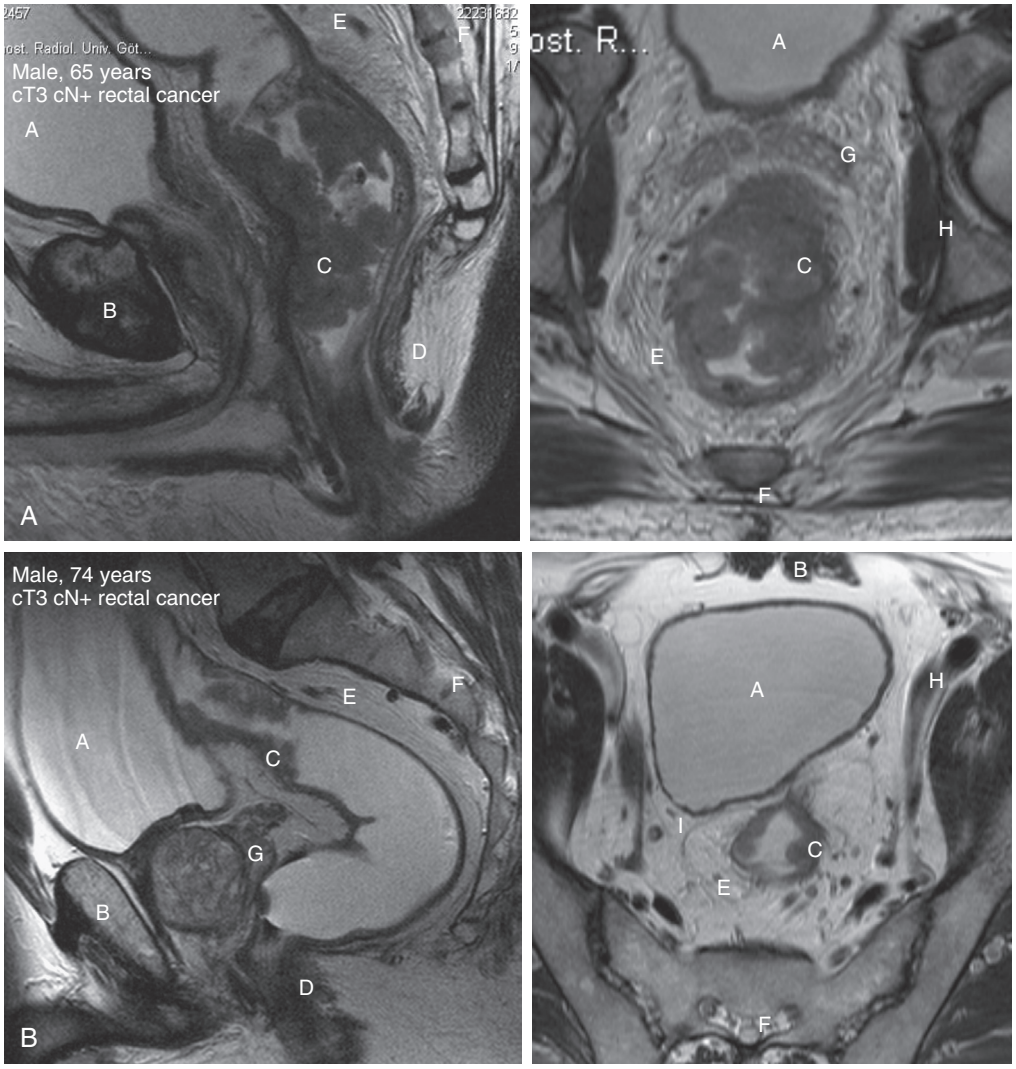


Figure 51-1 **A,** Pelvic MRI scan: Rectal cancer of the lower third of the rectum. **B,** Pelvic MRI: Rectal cancer of the upper third of the rectum A: bladder, B: os pubis, C: rectal cancer lower third **(A)** and upper third **(B)** of the rectum, both uT3 uN+, D: sphincter area, E: mesorectum, F: coccygeus, G: seminal vesicle, H: veins.

outcomes for patients with IIA versus IIB disease and IIIA versus IIIB disease.[22] The prognostic validity of this change was supported by a subsequent pooled analysis of the U.S. GI Intergroup and National Surgical Adjuvant Breast and Bowel Project (NSABP)[23] postoperative trials and the retrospective analysis of the American College of Surgeons National Cancer Database (NCDB).[24] The placement of all TN2 patients into stage IIIC, however, was not based on in-depth outcomes analyses because the impact of depth of bowel wall invasion (T category) in N2 patients had not been evaluated in detail.

Before making substantive changes in the AJCC 7th edition staging manual for colon and rectal cancer (Table 51-2), the AJCC Hindgut Task Force sought population-based validation that depth of invasion and nodal status interact to affect survival rates. Surveillance, Epidemiology, and End Results (SEER) survival data were obtained for patients with invasive colon and rectal cancer and evaluable TN category of disease (35,829 patients with rectal cancer and 109,953 patients with colon cancer).[25] T4N0 cancers were stratified by "tumors that perforate visceral peritoneum" (T4a) versus "tumors that invade or are adherent to adjacent organs or structures" (T4b). N1 and N2 were stratified by number of involved nodes (N+): N1a/N1b (one versus two or three nodes) and N2a/N2b (four to six vs. ≥seven nodes). Rates of 5-year observed and relative survival were obtained for each TN category. The analyses indicated the following information: survival rates are better for T1-2N0 cancers than T3N0 cancers, better for T3N0 cancers than T4N0 cancers, better for T1-2N2 cancers than T3-4N2 cancers, and similar for T4bN1 and T4N2 cancers. In addition, patients with T4a lesions have better survival rates than those with T4b lesions by N category, and the number of positive lymph nodes affects survival for each T category. The SEER population-based colon and rectal cancer analyses supported subdividing T4 (T4a/T4b), N1 (N1a/N1b), and N2 (N2a/N2b) and supported revised substaging of stages II and III (shift of T1-2N2 lesions from IIIC to IIIA/IIIB and T4bN1 lesions from IIIB to IIIC.[25,26]

Clinical staging is designated as cTNM and is based on physical examination, radiologic imaging, and endoscopic, biopsy, and laboratory findings. Pathologic staging is designated as pTNM and depends on data acquired clinically in addition to surgical and pathologic findings. The prescript "y" is used to indicate that the tumor has been treated with neoadjuvant therapy before surgical resection. Recurrent tumors

There are additional descriptors that do not affect the stage grouping but do indicate cases needing separate analysis. The AJCC TNM staging system should be used routinely for staging and treatment purposes. Although CEA has prognostic importance, it was not added to the staging system.[9]

TABLE 51-2 AJCC TNM Staging System for Colorectal Cancer

TNM Category	
Primary Tumor (T)	
Tx	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ: intraepithelial or invasion of the lamina propria*
T1	Tumor invades submucosa
T2	Tumor invades muscularis propria
T3	Tumor invades through the muscularis propria into pericolorectal tissues
T4a	Tumor penetrates to the surface of the visceral peritoneum
T4b	Tumor directly invades or is adherent to other organs or structures†‡
Regional Lymph Nodes (N)	
Nx	Regional nodes cannot be assessed
N0	No regional nodes
N1	Metastasis in 1-3 regional lymph nodes
N1a	Metastasis in 1 regional lymph node
N1b	Metastasis in 2-3 regional lymph nodes
N1c	Tumor deposit(s) in the subserosa, mesentery, or nonperitonealized pericolic or perirectal tissues without regional nodal metastasis
N2	Metastasis in ≥4 regional lymph nodes
N2a	Metastasis in 4-6 regional lymph nodes
N2b	Metastasis in ≥7 regional lymph nodes
Distant Metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis
M1a	Metastasis confined to one organ or site (e.g., liver, lung, ovary, nonregional node)
M1b	Metastases in more than one organ or site or the peritoneum
SUFFIX	**REASON**
M	The presence of multiple primary tumors in a single site and is recorded in parenthesis: pT(m)NM.
y	Cases in which classification is performed during or following initial multimodality therapy. The cTNM or pTNM category is identified by a *y* prefix. The ycTNM or ypTNM categorizes the amount of tumor actually present at the time of the examination. The *y* categorization is not an estimate of tumor before multimodality therapy.
r	Indicates a recurrent tumor when staged after a disease-free interval and is identified by the *r* prefix: rTNM.
a	Designates the stage determined at autopsy: aTNM.
LYMPHATIC VESSEL INVASION (L) AND VENOUS INVASION (V)	
Lympho-vascular invasion not present/not identified *Lympho-vascular invasion present/identified* *Not applicable* *Unknown/indeterminate*	

Stage Groupings			
Stage	**T**	**N**	**M**
0	Tis	N0	M0
I	T1-2	N0	M0
IIA	T3	N0	M0
IIB	T4a	N0	M0
IIC	T4b	N0	M0
IIIA	T1-2	N1/N1c	M0
	T1	N2a	M0
IIIB	T3-4a	N1/N1c	M0
	T2-3	N2a	M0
	T1-2	N2b	M0
IIIC	T4a	N2a	M0
	T3-4a	N2b	M0
	T4b	N1-2	M0
IV	T any	N any	M1

From Edge SB, Byrd DR, Compton C, et al, editors: AJCC Cancer staging manual, ed 7, New York, 2010, Springer.
Additional descriptors: Although they do not affect the stage grouping, additional prefixes are used that indicate the need for additional analysis.
NOTE: A satellite peritumoral nodule in the pericolorectal adipose tissue of a primary carcinoma without histologic evidence of residual lymph node in the nodule may represent discontinuous spread, venous invasion with extravascular spread (V1/2), or a totally replaced lymph node (N1/2). Replaced nodes should be counted separately as positive nodes in the N category, whereas discontinuous spread or venous invasion should be classified and counted in the site-specific factor category tumor deposits (TD).
**This includes cancer cells confined within the glandular basement membrane (intraepithelial) or mucosal lamina propria (intramucosal) with no extension through the muscularis mucosa into the submucosa.*
†Direct invasion in T4 includes invasion of other organs or other segments of the colorectum as a result of direct extension through the serosa, as confirmed on microscopic examination (e.g., invasion of the sigmoid colon by a carcinoma of the cecum) or, for cancers in a retroperitoneal or subperitoneal location, direct invasion of other organs or structures by virtue of extension beyond the muscularis propria.
‡Tumor that is adherent to other organs or structures, grossly, is classified T4b. However, if no tumor is present in the adhesion, microscopically, the classification should be pT1-4a depending on the anatomic depth of wall invasion. The V and L classifications should be used to identify the presence or absence of vascular or lymphatic invasion, whereas the PN site-specific factor should be used for perineural invasion.

are designated with the *r* prefix. If there is uncertainty regarding the appropriate T, N, or M category, the lower (less advanced) category should be used. The role of the pathologist is critical to proper staging. Following surgery alone, a minimum of 12 pelvic nodes must be examined to obtain an accurate pN stage.[27] Tumors treated with preoperative chemoradiation are downstaged, however, and the number of lymph nodes retrieved is significantly less than those treated by surgery alone. Thus, the feasibility and clinical significance of the 12 lymph node threshold guideline in patients who receive neoadjuvant therapy has been challenged.[28]

Posttreatment Assessment

Circumferential Resection Margin

Surgeons identify margins that can be involved by tumor spread at a variety of sites. The completeness of the resection is scored as R0 for negative margins, R1 for microscopic involvement of margins, and R2 for gross residual tumor. The proximal and distal resection margins are involved in only 1% to 2% of cases in randomized trials. The most important margin is that created around the mesorectum (circumferential resection margin or CRM; eFigure 51-3). This margin is under threat by direct involvement but also by the incomplete removal of lymph nodes that lie just under the mesorectal fascia, and any small deviation from the correct surgical plane could enter them, potentially compromising cure. Studies by Quirke and others have shown that local recurrence is greatly increased and survival halved when tumor can be demonstrated at or within 1 mm from the radial surgical plane of resection (CRM+).[14]

Recording of Surgical Quality

Apart from the recording of the surgical CRM, the plane of surgery and the integrity of the total mesorectal excision specimen are key indicators of surgical quality and prognosis. Quirke first introduced the concept of pathological audit of the quality of rectal cancer surgery in the MRC CR07 trial (eTable 51-2).[14] In this trial, the plane of surgery achieved was classified as good (mesorectal) in 52% of 1156 included patients, intermediate (intramesorectal) in 34%, and poor (muscularis propria plane) in 13%. The plane of surgery achieved was significantly associated with the risk of local recurrence both in univariate and multivariate analysis, and therefore should be assessed and reported routinely.

Tumor Regression Grading

Neoadjuvant chemoradiation is able to induce T-level downsizing and UICC- or nodal-downstaging in locally advanced rectal cancers. In approximately 5% to 30% of cases this can lead to complete disappearance of tumor cells (i.e., a pathological complete response [pCR or ypT0N0]). Patients with pCR have consistently been shown to have better outcomes.[29,30] Variation in sampling protocols may explain some of the differences in reporting pCR rates. Moreover, various tumor regression grading (TRG) systems, based on the relative amount of tumor cells and fibrotic reactions, have been proposed. These classifications were often derived from esophageal or gastric cancer, and little information on the extent of inter- and intraobserver variability in defining TRG has been published. The College of American Pathologists Guidelines recently suggest that tumor response should be graded on a scale of 0 (complete response; no viable cancer cells) to 3 (poor response; minimal or no regression, extensive residual cancer).[31] This classification system needs to be prospectively tested on multiple datasets to validate the predictive value in terms of long-term outcome, and its reproducibility in a broader setting.

PRIMARY AND ADJUVANT THERAPY FOR RESECTABLE DISEASE

Adjuvant Irradiation without Chemotherapy

There are two general approaches in which radiation therapy has been used in the adjuvant treatment of resectable rectal cancer: postoperative treatment and preoperative treatment. A third approach known as the sandwich technique includes a short preoperative course of radiation (5 Gy to 15 Gy) followed by surgery, and in patients with pT3-4N1-2 disease, an additional 40 Gy to 45 Gy postoperatively. This technique is no longer used.[32,33]

Postoperative Irradiation

Until 1990, most patients in the United States underwent surgery and, if needed, received postoperative external beam radiation therapy (EBRT). The primary advantage with this approach was pathologic staging and avoiding overtreatment with preoperative therapy. Lastly, if the patient has undergone an APR, the radiation field must be extended to include the perineal scar.

There are five randomized trials examining the use of adjuvant postoperative irradiation without chemotherapy in stage pT3 or N1-2 rectal cancer.[34-38] None have shown an improvement in overall survival (OS). Two reveal a decrease in local failure rates; NSABP trial R-01 (16% versus 25%; $p = 0.06$) and the Medical Research Council (MRC) trial (21% versus 34%; $p = 0.001$).[37] Although there was no survival benefit, it must be emphasized that local control by itself is an important endpoint. Patients with recurrent rectal cancer experience a detriment in quality of life because of pelvic pain.[39]

Preoperative Irradiation

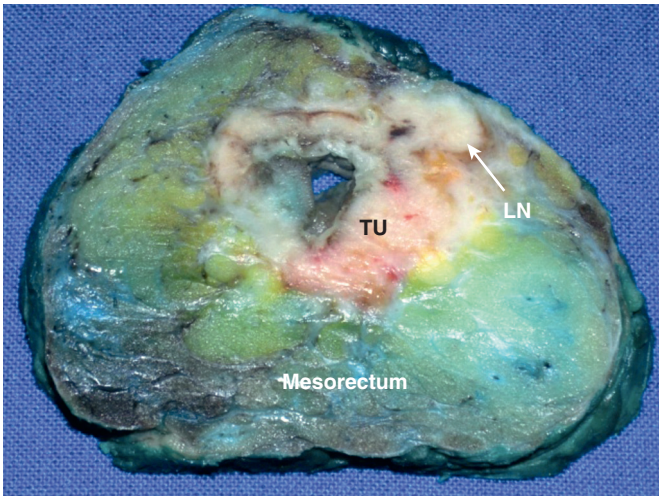
There are two approaches to preoperative therapy. The first, developed in Northern Europe and Scandinavia, is short-course radiation (25 Gy in 5 fractions). In contrast, most other investigators recommend a standard course (50.4 Gy in 28 fractions) combined with concurrent chemotherapy (chemoradiation).

Short-Course Preoperative Irradiation

There are 12 modern randomized trials of short-course preoperative radiation therapy (without chemotherapy).[40] All use low to moderate doses of radiation. Most of the trials showed a decrease in local recurrence rates, and in five of the trials, this difference reached statistical significance. Although in some trials a subset analysis revealed a significant improvement in survival rates, the Swedish Rectal Cancer Trial is the only one that reported a survival advantage for the total treatment group. Two meta-analyses report conflicting results. Although both revealed a decrease in local recurrence rates, the analysis by Camma et al[41] reported a survival advantage, whereas the analysis by the Colorectal Cancer Collaborative Group[42] did not.

In the Swedish Rectal Cancer Trial, patients with cT1-3 rectal cancer were randomized to receive 25 Gy in 1 week followed by surgery 1 week later versus surgery alone.[43] Those who received preoperative irradiation had a significant decrease in local recurrence rates (12% versus 27%; $p < 0.001$) and a correspondingly significant improvement in 5-year OS (58% versus 48%; $p = 0.004$) (see Table 51-5). After 13 years, the OS was still significantly improved (38% versus 30%; $p = 0.008$).[44] The local recurrence rate in patients who are node positive and underwent surgery alone was 46%, illustrating the inferior results of surgery before the adoption of TME.

The Dutch CKVO 95-04 trial randomized 1805 patients with cT1-3 disease to TME or short-course preoperative



eFigure 51-3 Mesorectum and circumferential resection margin (CRM). This margin is under threat by direct tumor *(TU)* involvement but also by the incomplete removal of lymph nodes *(LN)* that lie just under the mesorectal fascia.

Likewise, the assessment of the abdominoperineal excision specimens to measure the amount of tissue removed at the anorectal junction and to determine whether levator muscle is included in the resection is also strongly recommended.

radiation therapy followed by TME.[51] Irradiation significantly decreased the local recurrence rate (8% versus 2%; $p < 0.0001$), but there was no difference in the 2-year survival rate (82%) (Table 51-3). With longer follow-up, the 5-year local failure rate was higher with TME (11%) but was still significantly decreased (to 6%) with preoperative irradiation.[52] A subset analysis of 593 patients with negative margins revealed that although there were 11% fewer deaths resulting from disease in the preoperative radiation compared to TME alone arm (40% versus 51%, $p = 0.01$) there was a corresponding 11% increase in deaths as a result of other causes, including toxicity (51% versus 40%, $p = 0.01$). Therefore, OS was equivalent.

Despite the use of multiple field radiation techniques there was a substantial incidence of acute toxicity including 10% neurotoxicity, 29% perineal wound complications, and 12% postoperative leaks in the radiation arm.[57] It is not clear if the increased toxicity was the result of the learning curve associated with TME, the 1-week interval between the completion of radiation and surgery, or both.

The presence of a positive radial (circumferential) margin is an important negative prognostic sign. In the Dutch CKVO trial, 17% had positive circumferential margins. Although they received 50 Gy postoperatively, this did not compensate for positive margins.[58] MRI is able to identify those patients likely to have close or positive radial margins who undergo initial surgery and therefore, would be better treated by preoperative therapy.[59-61]

Patients selected for treatment with short-course radiation historically have included those with cT1-3 disease, whereas those selected for chemoradiation include T3 or N+ disease. Therefore, a retrospective comparison of trials is not feasible. Two randomized trials of short-course radiation compared to chemoradiation, which have included patients with cT3 or N+ disease and are discussed in another section.

Adjuvant Chemoradiation

Chemoradiation can be delivered preoperatively or postoperatively. For patients with cT1-2N0 disease, the initial treatment is surgery, and if the tumor is pT3-4N0 or TanyN1-2, this is commonly followed by postoperative chemoradiation.[62] For patients with cT3-4N0 or TanyN+ lesions, preoperative chemoradiation is given, followed by surgery (alone or plus intraoperative irradiation therapy [IORT] for T4 lesions) and postoperative adjuvant chemotherapy.

Postoperative Chemoradiation

The National Cancer Institute (NCI) Consensus Conference concluded in 1990 that chemoradiation was the standard postoperative adjuvant treatment for all patients with pT3 or N1-2 disease.[62] This recommendation was based on Phase III trials that compared postoperative chemoradiation arms with control arms of either surgery alone or surgery plus postoperative irradiation (Mayo/NCCTG 79-47-51) and demonstrated improvements in both disease-free survival (DFS) and OS.[63] The standard design in U.S. trials was to deliver six cycles of bolus 5-fluorouracil (5-FU)–based chemotherapy; concurrent irradiation was also given during cycles 3 and 4.

TABLE 51-3 Phase III Trials Testing Preoperative Irradiation versus Surgery Alone, Preoperative versus Postoperative Chemoradiation and Preoperative Radiation Alone or Plus Chemotherapy

		Toxicity						
		Acute	Relapse (%)		Survival (5-yr, %)			
Phase III Trial	Pts	Gr 3-4 (%)	Local	*p* Value	DFS	*p* Value	OS	*p* Value
SURGERY ± PREOP RT								
Swedish[43]	1168							
Surgery alone	585	—	27		65	—	48	
Preop RT (25Gy/5Fx)*	583	—	12	<0.001	74	—	58	0.004
Dutch CVKO[51]						—		
Surgery alone (TME)	937	—	8		—	—	82 (2 yr)	
Preop RT (25/5)*	924	—	2	<0.001	—	—	82 (2 yr)	
PREOP VS. POSTOP CHEMO-RADIATION								
German (RT+5-FU; TME)[53]		(GI/any)						
Postop ChemoRT (50.4/28)*	402	18/40	13		65		74	
Preop ChemoRT (50.4/28)*	421	12/27	6	0.006	68	0.32	76	0.8
NSABP (RT+5FU/Cape)[54]		(GI)						
Postop ChemoRT (50.4/28)*	137	26	9		53		66	
Preop ChemoRT (50.4/28)*	130	34	5	0.5	64	0.08	74	0.14
PREOP RADIATION ± CHEMO								
EORTC†[55]	1011							
Preop RT (45/25)*	252	7.4	17		—		65	
Preop RT + chemo (45/25)*	759	13.9	8-10	<0.001	—		66	0.84
FFCD[56]	742							
Preop RT (45/25)*	367	2.9	16.5		55.5		67.9	
Preop RT + chemo (45/25)*	375	14.6*	8.1	0.004	59.4	—	67.4	0.68

CCT, *Concurrent chemotherapy;* EBRT, *external beam radiation therapy;* GI, *gastrointestinal;* Gr, *grade;* MCT, *maintenance chemotherapy;* Preop, *preoperative;* postop, *postoperative;* pts, *patients;* RT, *radiation therapy;* TME, *total mesorectal excision;* yr, *year.*

**EBRT dose fractions (5 d/wk) bolus 5-FU/Leucovorin in both EORTC and FFCD trials.*

†*Pts were randomized to receive preop RT with or without CCT and with or without MCT: preop RT alone (n = 252), RT/MCT (n = 253), RT-CCT (n = 253), RT-CCT/MCT).*

The U.S. GI Intergroup 86-47-51 trial did not demonstrate an incremental benefit to semustine when it was added to postoperative irradiation plus concurrent and maintenance 5-FU.[64] However, a 2-×2-component of the study demonstrated a positive benefit for giving protracted venous infusion (PVI) 5-FU (also known as continuous infusion 5-FU) rather than interrupted bolus 5-FU concurrently with pelvic irradiation. Patients randomized to receive concurrent PVI 5-FU (225 mg/m²/d, 7 days/week or until intolerance) had improvements in rates of disease control, DFS (at 4 years, 63% versus 53%; $p = 0.01$), and OS (at 4 years, 70% versus 60%; $p = 0.005$).

The successor INT 0114 four-arm trial randomized patients with pT3-4N0 or TanyN+ rectal cancer to postoperative irradiation and bolus 5-FU with or without leucovorin, levamisole, or leucovorin plus levamisole (INT 86-47-51 results were not available before INT0114 study design and completion). There was no significant difference in local control or survival rates among the four arms.[65] With longer follow-up, the study also revealed that local control and survival results continued to deteriorate after 5 years. At 7 years, the local failure rate was 17% and the survival rate was 56%, compared with 14% and 64%, respectively, at 5 years. Patients with high-risk (pT3N+ or T4) disease had a lower survival rate compared with lower-risk (pT1-2N+ or T3N0) disease (45% versus 70%).

The subsequent INT 0144 postoperative adjuvant rectal trial was designed to follow up on the positive results achieved with concurrent PVI 5-FU during irradiation in trial 86-47-51.[66] Patients were randomized to three arms: arm 1, bolus 5-FU/PVI 5-FU + RT/bolus 5-FU (control arm from 86-47-51); arm 2, PVI 5-FU/PVI 5-FU + RT/PVI 5-FU; arm 3, bolus 5-FU–leucovorin(LV)–levamisole/bolus 5-FU–LV–levamisole + RT/bolus 5-FU–LV–levamisole. The concurrent PVI 5-FU arms did not confirm a survival benefit relative to the bolus 5FU/LV/levamisole arm, but arm 2 did report a lower incidence of grade 3+ hematologic toxicity.

Do Patients with Pathologic Node-Negative Rectal Cancer Require Pelvic Irradiation?

The 1990 NCI Consensus Conference recommendation for postoperative chemoradiation was published nearly three decades ago and was based on trials where neither a TME nor an examination of 12 nodes or more was required. Retrospective data suggest that there may be a subset of patients with pT3N0 disease who may not require adjuvant therapy. As noted by Gunderson et al, data in the rectal pooled analysis (U.S. GI Intergroup and NSABP Phase III trials) found that use of trimodality postoperative adjuvant treatment for all patients with intermediate risk T1-2N1 and T3N0 cancers may be excessive treatment because 5-year OS was equivalent with surgery with chemotherapy as a single adjuvant.[24] In the Dutch CVKO Phase III trial 2-year local relapse was 5.7% with TME alone compared to. 1% with preoperative radiation ($p = 0.01$).[51] In a subsequent analysis by Nagtegaal et al, local relapse with TME alone was higher with a radial margin 2 mm or less compared with >2 mm (16% versus 5.8%, $p < 0.0001$).[67] Nissan et al reported results of 100 patients with uT2-3N0 disease who underwent TME alone and had 12 nodes or more examined.[68] In the subset of 49 patients with uT3N0 disease, the overall local recurrence rate was 4%. For the total group, the local recurrence rate was significantly higher in those with lymph vessel invasion tumors (32% versus 6%; $p = 0.006$) and an elevated (>5 ng/mL preoperative CEA level (21% versus 0%).

Patients who undergo high-quality TME, have at least 12 nodes examined, and have pT3N0 disease may not need the radiation component of chemoradiation, dependent on the adequacy of radial and distal margins of resection. The small benefit in local control with irradiation may not be worth the risks, especially in women of reproductive age. However, patients with pT3N0 tumors with adverse pathologic features, who undergo resection without TME, or who have fewer than 12 nodes examined should still receive postoperative chemoradiation.

Preoperative Chemoradiation

Based on the German CAO/ARO/AIO 94 trial, preoperative chemoradiation is standard treatment for patients with cT3-4N0 or TanyN+ disease.[53] The disadvantage of preoperative therapy is the possible overtreatment of patients with either early-stage disease (pT1-2N0) or undetected metastatic disease. A number of questions and issues exist with regard to patient selection for preoperative chemoradiation and optimization of treatment that will be addressed in the following subsections. A subsequent section will also address the question of preoperative chemoradiation compared with short-course radiation.

The Role of Concurrent and Postoperative Chemotherapy

Since INT 0144, most trials of chemoradiation have used preoperative chemoradiation. There has been some debate as to which fluoropyrimidine (PVI 5-FU or capecitabine) is the preferred radiosensitizer. Two trials have examined this question. The NSABP R-04 trial compared preoperative chemoradiation with PVI 5-FU to capecitabine (with or without oxaliplatin). Compared with PVI 5-FU, capecitabine had similar rates of pCR (22% versus 19%), sphincter sparing surgery (63% versus 61%), and grade 3 + diarrhea (11%).[70] Hofheinz et al randomized 401 patients with PVI 5-FU–based chemoradiation compared with capecitabine-based chemoradiation. Patients who received capecitabine had equivalent pCR rates (6% versus 7%) and their 5-year OS was noninferior (76% versus 66%, $p = 0.0004$) compared with PVI 5-FU.[71] Therefore, PVI 5-FU–and capecitabine–based chemoradiation regimens are equivalent.

Almost every randomized trial for the past three decades has confirmed a 10% to 15% survival benefit of a total of 6 months of adjuvant 5-FU–based chemotherapy for patients with lymph node-positive colon or rectal cancer. For patients who receive preoperative chemoradiation and are selected to receive postoperative adjuvant chemotherapy, 4 months (eight cycles) of mFOLFOX6 is recommended. However, two randomized trials question whether postoperative chemotherapy is necessary.[55,56]

The European Organization for Research and Treatment of Cancer (EORTC) trial 22921 was a four-arm randomized trial of 1011 patients who received preoperative irradiation of 45 Gy with or without a concurrent bolus of 5-FU/leucovorin followed by surgery with or without four cycles of postoperative 5-FU/leucovorin.[55] Only 37% had a TME. There was a significant decrease in the local failure rate in those patients who receive chemoradiation compared with irradiation (8% to 10% versus 17%; $p < 0.001$) but no difference in the 5-year OS (65%) (see Table 51-3). An update with 10-year follow-up revealed no significant differences in survival among the four arms.[72] Only 43% of patients received 95% or more of the planned postoperative chemotherapy, which may explain the negative results. Furthermore, a subset analysis of the EORTC trial revealed that patients who responded to preoperative chemoradiation had a survival benefit from postoperative chemotherapy.[73]

A trial by the Fédération Francophone de la Cancérologie Digestive (FFCD 9203) was a two-arm trial of 742 patients randomized to preoperative irradiation of 45 Gy with or

Although the number of nodes is defined in the AJCC staging system, the location of pelvic nodes is not. Leibold et al[69] treated 121 patients with preoperative chemoradiation and found that the incidence of metastatic disease was higher in those patients with positive nodes in the proximal pelvis compared with positive nodes anywhere in the pelvis (46% versus 32%). Of note, the proximal nodes are above the superior border of the typical radiation field (L5/S1) because they are located along the apical and midportion of the inferior mesenteric artery.

without bolus 5-FU/leucovorin.[56] All patients were scheduled to receive postoperative chemotherapy, and 73% received such. The FFCD trial reported a similar decrease in local failure rates (8% versus 17%; $p < 0.05$) and a corresponding increase in pCR (11% versus 4%; $p < 0.05$) with preoperative compared to irradiation alone but no survival benefit (68% versus 67%) (see Table 51-5).

Because most patients did not receive adequate doses of postoperative chemotherapy in the EORTC trial and the FFCD trial only tested the impact of concurrent chemotherapy with preoperative irradiation, preoperative chemoradiation followed by surgery and 4 months of postoperative adjuvant chemotherapy remains the standard practice in most centers. Valentini et al proposed the use of nomograms based on staging and treatment factors to support the decision in multidisciplinary groups. However, there remains considerable controversy in some European countries regarding its use. An international consensus conference failed to reach a definitive recommendation regarding its use.[74] Lastly, because preoperative chemoradiation will decrease the number of nodes harvested from the postoperative specimen, the ypN stage cannot be used to determine the need for postoperative chemotherapy.[75,76]

Selective Use of Radiation

As previously discussed, the risks of chemoradiation (chemoRT) in patients with pT3N0 disease may outweigh the potential benefits.[24,68] Despite advances in preoperative imaging, molecular markers, and clinicopathologic factors, however, none can reproducibly identify patients with pN+ disease more that 70% to 80% of the time.[77]

In the German CAO/ARO/AIO-94 trial, 18% of patients clinically staged as cT3N0 and underwent initial surgery without preoperative therapy had pT1-2N0 disease and would have been over treated if they had received preoperative therapy. Although not ideal, preoperative therapy is still preferred to performing surgery first in this subset of patients. Even after preoperative chemoradiation which downstages tumors, Guillem et al reported that 22% of patients still have ypN+ disease at the time of surgery.[78] In patients who undergo surgery alone this number is as high as 40%.[79]

Given the improvements in systemic chemotherapy there may be an opportunity to use preoperative radiation more selectively. In a prospective pilot trial, Shrag et al treated 32 selected patients with stages uT2N1 or uT3N0-1 mid to upper rectal cancer with neoadjuvant FOLFOX with bevacizumab.[80] Patients who by preoperative assessment required an abdominoperineal resection were not eligible. Pelvic radiation was reserved for patients who progressed preoperatively or, following surgery, had pT4, pN2, or positive margins. Of the 30 patients who underwent surgery none required radiation, the pCR rate was 25%, and 2 required postoperative radiation. This approach remains investigational and is being prospective tested in the ongoing Phase II/III Alliance N1048 trial.

Positive Radial (Circumferential) Margins

Although the distal margin is predictive of both local recurrence as well as the feasibility of a sphincter-preserving operation, the radial (circumferential or CRM) margin also has the most important impact on the local recurrence rate. An analysis of more than 17,500 pathologic specimens by Nagtegaal et al[81] reported inferior survival rates in patients with positive CRMs after neoadjuvant treatment compared with immediate surgery (hazard ratio [HR], 6.3; 95% CI, 3.7 to 16.7 versus HR, 2; 95% CI, 1.4 to 2.9, respectively).

In the Dutch CKVO trial, 17% of patients had positive circumferential margins. In a subset analysis by Nagtegaal et al,[67] patients with positive radial margins who underwent TME alone had a local recurrence rate of 17% after an LAR and 30% after an APR.

In a retrospective analysis reported by Bail et al,[82] despite receiving preoperative chemoradiation, 504 patients with positive radial margins had a higher local recurrence rate (35% versus 11%) and a lower 5-year OS (27% versus 73%) compared with those with negative radial margins. Although high-resolution MRI can help identify patients who will have positive margins,[60,61] not all centers perform the necessary pathologic examination to detect positive circumferential margins.[83]

As reported with preoperative therapy, postoperative treatment has limited ability to control positive radial margins. In the MRC CR-07 trial, patients with positive radial margins who received postoperative chemoradiation had an 11% local recurrence rate.[84] Likewise, in a subset analysis of the Dutch CKVO trial, 50 Gy postoperatively did not compensate for positive margins.[58]

Distance from the Anal Verge

There are no prospective randomized data examining the impact of the distance from the anal verge on local recurrence. The available data are subset analyses from randomized trials that were not stratified by distance.

On univariate analysis, "high" tumors in both the Dutch CKVO and Swedish trials (defined as ≥10.1 cm and ≥11 cm, respectively) had a lower incidence of local recurrence compared with mid and lower tumors (eTable 51-3). Short-course irradiation did not significantly decrease local recurrence rates. By multivariate analysis, tumor location was an independent prognostic variable in the Dutch trial. It is interesting to note that irradiation did significantly decrease local recurrence rates for midtumors in both trials, whereas for lower tumors it was helpful only in the Swedish trial. In contrast, there was no significant difference between mid and upper tumors in the German trial.[86]

In summary, given the conflicting data combined with the report from Guillem et al[78] confirming that the incidence of ypN+ disease following preoperative chemoRT (which are most predictive of local failure) is the same from 0 cm to 12 cm from the anal verge, treatment decisions based solely on the current definitions of low, mid, and high should not be used. However, some women of reproductive age elect to forego radiation with the hope that their nodes are pathologically negative and therefore will not require postoperative radiation.

Patients with cT3N0 tumors should be examined with a straight proctoscope, and if the tumor is 12 cm or less from the anal verge, they should be referred for preoperative chemoRT. If the tumor is more than 12 cm from the anal verge and imaging reveals that the tumor is clearly not adjacent to the presacral hollow, initial surgery is recommended with decisions for postoperative chemoRT based on surgical-pathology findings previously discussed.

Sphincter Preservation with Preoperative Chemoradiation

From the viewpoint of sphincter preservation, the advantage of preoperative therapy is to decrease the volume of the primary tumor. This has relevance only if the surgeon is willing to change the operative technique based on tumor response. When the tumor is located in close proximity to the dentate line, this decrease in tumor volume may allow the surgeon to perform a sphincter-conserving procedure that would not otherwise be possible. However, if the tumor directly invades the anal sphincter, sphincter preservation is unlikely even when a clinical complete response is achieved.

Furthermore, the incidence of positive nodes is not dependent on the distance from the anal verge.[78] In this series, of the 103 patients with tumors from 0 cm to 5 cm from the anal verge, 23% were ypN+, whereas of the 85 patients with tumors 6 cm to 12 cm from the anal verge, the incidence was 20%. These data suggest that up to 12 cm from the anal verge the risk of positive nodes, and likely the corresponding incidence of local recurrence, is similar.

Of the three trials, two used short-course preoperative irradiation and included patients with cT1-2N0 disease (Dutch CKVO and the Swedish Rectal Cancer Trials),[44,52] whereas the German trial used chemoradiation and was limited to patients with cT3N+ disease. The MRC-C07 trial performed a similar subset analysis and measured the distance from the anal verge by rigid sigmoidoscopy. There were additional variables that could have contributed to the differences in local failure rates. For example, TME (and its associated impact on radial margins) was used in the Dutch CKCO and German trials and not in the Swedish trial. All three trials included patients with tumors more than 12 cm from the anal verge in the "upper or high" category. Because the peritoneal reflection varies from 12 cm to 16 cm, some patients with tumors above the peritoneal reflection (colon cancer) were included in the three trials. Most investigators now limit preoperative treatment to tumors less than 12 cm from the anal verge.[78] Lastly, distance measurements using a flexible proctoscope are less accurate than straight proctoscope measurements. Flexible scopes were used in the Dutch CKVO trial. The German trial used a straight scope. In the Swedish trial, proctoscopic information was not mentioned. However, eligibility was limited to tumors "below the promontory as identified by barium enema." The Polish trial is not discussed because all tumors were palpable by digital examination.[85]

eTABLE 51-3 Impact of Distance From the Anal Verge by Univariate Analysis

		Surgery Alone		Preoperative Irradiation (RT)		
Location	**Distance from Anal Verge (cm)**	**#**	**% LF, 5 yr**	**#**	**% LF, 5 yr**	***p*-value**
DUTCH CKVO TRIAL[51]						
High	≥10.1	271	6	262	4	ns
Middle	5.1-10	350	14	372	4	<0.001
Low	≤5	253	12	237	11	ns
SWEDISH RECTAL CANCER TRIAL[43]						
High	≥11	110	12	133	8	ns
Middle	6-10	198	26	185	9	<0.001
Low	<5	146	27	136	10	0.003

LF, *Local failure;* ns, *non-significant;* yr, *year.*

An ongoing controversy is whether the degree of downstaging is adequate to enhance sphincter preservation and, if so, which regimen (short-course radiation or standard-course chemoradiation) is preferred. An analysis of 1316 patients who received short-course preoperative irradiation revealed that downstaging was most pronounced when the interval between the completion of irradiation and surgery was at least 10 days.[87] In the Dutch CKVO 95-04 trial, where the interval was 1 week, there was no downstaging.[88]

When the goal of preoperative therapy is sphincter preservation, standard course chemoradiation with conventional irradiation doses and techniques are recommended. These include multiple-field techniques to a total dose of 45 Gy to 50.4 Gy at 1.8 Gy per fraction. Surgery should be performed 4 to 8 weeks following the completion of chemoradiation. Unlike the short-course irradiation regimen, this conventional design allows for two important events to occur. First is the recovery from the acute side effects of chemoradiation, and second is adequate time for tumor downstaging. Data from the Lyon R90-01 trial of preoperative irradiation suggest that an interval of longer than 2 weeks following the completion of irradiation increases the chance of downstaging.[89] Most series recommend a 4- to 8-week interval.[90-92] However, more recent data suggest that an even longer interval may be helpful. Sloothaak et al reported a retrospective analysis of 1593 patients treated with preoperative chemoradiation by members of the Dutch Colorectal Group.[93] A delay of almost 16 weeks following chemoradiation was needed to achieve the maximum pCR rate of 16% (eFigure 51-4). However, the ultimate impact on outcome is unknown.

Whether increasing the interval between the end of short-course irradiation and surgery to more than 4 weeks will increase downstaging is not known. This question is being addressed in the ongoing three-arm Stockholm III trial. Interim results reveal a significant increase in grade 3+ postoperative complications in patients who received short-course radiation (5 Gy × 5) followed by surgery 1 week later (53 compared to either 5 Gy × 5 (39%) or 2 Gy × 25 (41%) followed by surgery 4 to 8 weeks later.[94]

Preoperative Prospective Clinical Assessment. The most accurate method by which to determine if preoperative therapy increases sphincter preservation is to perform a prospective clinical assessment. The operating surgeon examines the patient before the start of preoperative therapy and declares the type of operation required. The German CAO/ARO/AIO 94 trial reported that this assessment is accurate in 80% of patients.

Clinical Experience with Sphincter Preservation. A valid concern of surgeons is that to perform sphincter preservation in those patients who would otherwise require an APR, the distal resection margin may be suboptimal (<1 cm). Can preoperative therapy compensate for this? Retrospective data from the Memorial Sloan Kettering Cancer Center reveal that with preoperative chemoradiation, the 3-year local control rates were similar regardless of the margins being more than 2 cm, less than 2 cm, more than 1 cm, or less than 1 cm, providing they were negative.[83,95] Similar data have been reported from other investigators.[96]

Sphincter preservation without good function is of questionable benefit. In a series of 73 patients who underwent surgery, Grumann et al[97] reported that the 23 patients who underwent an APR had a more favorable quality of life compared with the 50 who underwent a low anterior resection. However, Krouse et al[98] reported that both men and women with ostomies had significantly worse social well-being compared with those without ostomies.

Preoperative chemoradiation may adversely affect sphincter function.[99] However, the impact is most likely less than postoperative chemoradiation.[100] Most Phase II trials that examine functional outcome report good to excellent results. Functional results continue to improve up to 1 year after surgery.

Is Surgery Needed after Preoperative Chemoradiation?

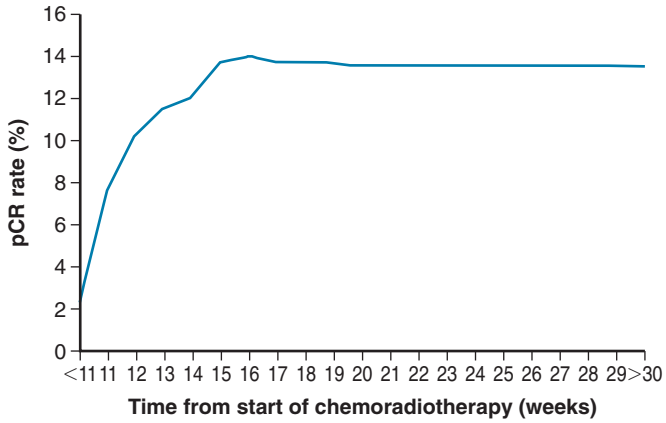
Although the conventional adjuvant treatment for rectal cancer is preoperative chemoradiation there are clinical settings where surgery has not been performed. These include patients with early stage tumors, those with medically inoperable disease, and patients who have refused surgery following a favorable response to preoperative chemoradiation. In these settings, radiation has been delivered by a variety of techniques including endocavitary (contact) treatment, brachytherapy, and pelvic external beam.

Retrospective Series. Treatment of rectal cancer without surgery is not a new concept. Although patients can be cured, the results are inferior to surgery.

A number of modern retrospective series report the use of radiation alone or chemoradiation, most commonly for patients who are medically inoperable or refuse surgery.[101-103] In general, patients received pelvic radiation followed by a boost with either external beam or brachytherapy. Brierley et al from the Princess Margaret Hospital reported the results of pelvic radiation alone (40 Gy to 60 Gy) in patients who refused surgery or had unresectable or medically inoperable disease.[101] The 5-year OS was 27% and by the mobility of the primary tumor was; mobile: 47%, partially fixed: 27%, and fixed: 4%. Gerard et al reported the combination of pelvic radiation, endocavitary, and brachytherapy in 63 patients with uT2-3 tumors.[102] For patients with uT3 disease the 5-year local failure and survival rates were 20% and 35%, respectively. A total of 48 patients with cT3 disease who received radiation or chemoradiation alone because of medical inoperability or patient refusal was reported by Lim et al.[103] The clinical complete response (CR) rate was 56% and, with a median follow-up of 49 months, 37% had progression of disease.

Prospective Series. Five series advocate close observation alone following preoperative chemoradiation (eTable 51-4). The 2004 series by Habr-Gama et al included 265 patients were treated with preoperative 50.4 Gy plus 5-FU and leucovorin.[104] Of those, 27% achieved both a clinical complete response (cCR) and were selected for observation only. Close follow-up was required including frequent exams, biopsy, and abdominal/pelvic CT scans every 6 months. With a mean follow-up of 57 months there was a 3% luminal recurrence rate, 4% distant metastasis rate, and 100% 5-year survival. In an update of 361 patients, the local recurrence rate was 5% and 5-year overall survival was 93% in the 28% who achieved a cCR.[105] It should be emphasized that patients with cT1-3 disease were included and any patient who developed a local recurrence in the first year were excluded from analysis.

In their 2013 series, patients with rectal cancer seen between 2006 and 2010 with tumors located at a maximum of 7 cm from the anal verge underwent high resolution MRI or three-dimensional (3D) transrectal ultrasound and 70 were identified with cT2-4 or N1-2 disease.[109] Chemoradiation included 54 Gy (45 Gy pelvis followed by a 9 Gy cone down) plus three cycles of concurrent chemotherapy (bolus 5-FU/leucovorin at 450/50 mg/m^2 for 3 days every 3 weeks. This was followed by an additional three cycles of chemotherapy. At 10 weeks postchemoradiation repeat staging (various combinations of MRI, TRUS, and PET-CT) was performed. If there was no



eFigure 51-4 A delay of almost 16 weeks following chemoradiation is needed to achieve the maximum pathological complete response (pCR) rate of 16%.
From Sloothaak et al, Br J Surg 2013 {3700}.

eTABLE 51-4 Nonoperative Treatment of Rectal Cancer with the Watch-and-Wait Approach

Series	Patients Treated	Patients Observed	Patients Outcome
Habr-Gama[105] (2004 series)	265	28	5% luminal recurrence 93% 5-yr survival
Mass[106]	192	21	89% 2-yr DFS 100 2-yr survival
Dalton[107]	49	12	50% NED at 26 months
Smith[108]	x	32	21% 2-yr local failure 9% 2-yr distant failure
Habr-Gama[109] (2013 series)	70	47	17% local failure 72% 3-yr DFS, 90% 3-yr survival

DFS, *Disease free survival,* NED, *no evidence of disease,* x, *data not reported;* yr, *year.*

residual abnormality by proctoscopy and staging was negative, patients were staged as initial cCR and placed on the "watch-and-wait" strategy, which included frequent exams and repeat imaging every 2 to 6 months. If at 10 weeks there was a residual abnormality, patients underwent a local excision, and if there was a ypT0 tumor, then they were also placed on the watch and wait strategy. Patients in these two groups who had no evidence of disease at 1 year were staged as sustained cCR. All other patients (defined as incomplete responders) underwent salvage radical surgery. There were 69 evaluable patients with a minimum of 12 months follow-up following the completion of chemoradiation. The overall results were impressive. A total of 68% achieved and initial cCR however 17% developed a local failure. Of the 56% who had a sustained cCR, 4 (10%) developed a local failure. Those four were salvaged with radical surgery and are without evidence of disease at a median follow-up of 26 months. Overall, 51% of patients who completed chemoradiation had a sustained cCR and did not require radical surgery after a median of 56 months. With a total median follow-up of 53 months the 3-year survival was 94%.

Most series suggest an improved outcome in patients who achieve a pCR following preoperative chemoradiation. Patients who are downstaged to ypT0 following chemoradiation have a 5% incidence of positive nodes and a corresponding low nodal recurrence rate.[111] Mass et al reported a pooled analysis of 27 series reporting patients who underwent preoperative chemoradiation and achieved a pCR.[29] There was a significant increase in 5-year DFS compared to those who did not achieve a pCR (83% versus 63%, $p = 0.0001$).

In summary, radical surgery remains a standard component of the treatment of rectal cancer. The wait-and-see approach is encouraging but remains investigational. More accurate methods for postchemoradiation assessment are needed.

Randomized Trials of Preoperative versus Postoperative Chemoradiation

Two randomized trials of preoperative versus postoperative chemoradiation for clinically resectable rectal cancer have been performed, NSABP R0-3[54] and the German CAO/ARO/AIO 94 trial (see Table 51-3).[53] These trials were based on pilot data suggesting that chemotherapy increased the response rate of preoperative radiation,[113] and because of less small bowel in the radiation field,[114] the acute toxicity of preoperative chemoradiation was less then postoperative chemoradiation.[115]

The German trial completed the planned accrual of more than 800 patients and randomized patients with uT3-4 or LN+ rectal cancers less than 16 cm from the anal verge to preoperative chemoradiation (with PVI 5-FU during weeks 1 and 5) compared to postoperative chemoradiation. The trial was stratified by surgeon. Compared with postoperative chemoradiation, patients who received preoperative therapy had a significant decrease in rates of local failure (6% versus 13%; $p = 0.006$), acute toxicity (27% versus 40%; $p = 0.001$), and chronic toxicity (14% versus 24%; $p = 0.012$), and in the 194 patients judged by the surgeon before treatment to require an APR, there was a significant increase in rates of sphincter preservation (39% versus 20%; $p = 0.004$). With a median follow-up of 40 months, there was no difference in 5-year OS (74% versus 76%) In an update with a median follow-up of 11 years, preoperative chemoradiation continued to offer a significantly lower incidence of local failure (7% versus 10%; $p = 0.009$). However, there was no difference in distant failure (28%) or OS (60%).[12] The lack of improvement in distant failure and OS has lead to new trials investigating novel chemotherapy agents and sequencing.

The NSABP R-03 study accrued only 267 of a planned 900 patients with cT3-4 rectal cancers.[54] Patients received induction 5-FU/leucovorin chemotherapy followed by conventional chemoradiation and were randomized to receive it either preoperatively or postoperatively. TME was not required, and some patients underwent local excision. Patients who received preoperative versus postoperative therapy had a significant improvement in 5-year DFS (65% versus 53%; $p = 0.011$) and a borderline significant improvement in 5-year OS (75% versus 66%; $p = 0.065$). There was no difference in 5-year local recurrence rates (11%). There was a correspondingly higher incidence of grade 4+ toxicity, almost all related to early diarrhea (33% versus 23%), but the incidence of grade 3+ toxicity was lower (41% versus 50%). Lastly, based on a prospective office assessment by the operating surgeon, there was no improvement in rates of sphincter preservation (48% versus 39%). The results do not parallel the German trial, likely because of the fact that only 267 of the 900 planned patients were accrued, thereby limiting the statistical power to detect differences.

Given the improved local control rates, acute and long-term toxicity profiles, and sphincter preservation rates reported in the German trial, patients with cT3-4 rectal cancer who require chemoradiation should receive it preoperatively. Although not ideal, this is preferred to performing surgery first because 20% to 40% will have LN+ disease at the time of surgery and require postoperative chemoradiation, which has inferior rates of local control, higher rates of acute and chronic toxicity, and, if a low anastomosis is performed, inferior functional results.[78] Clearly, the development of more accurate methods to identify LN+ disease, including imaging techniques or molecular markers, is essential because more patients are being treated with preoperative chemoradiation.

The UK Medical Research Council trial (MRC C07) randomized 1350 patients with clinical stages I to III rectal cancer to preoperative irradiation of 5 Gy × 5 or selective postoperative chemoradiation (45 Gy with concurrent 5-FU), which was delivered only to patients with a histologic radical margins of less than 1 mm (12% of all patients with immediate surgery).[84] With a median follow-up of 4 years, patients who received preoperative compared with selective postoperative treatment had significantly lower 3-year local recurrence rates (4.4% versus 10.6%; $p < 0.0001$) and higher 3-year DFS (77.5% versus 71.5%; $p = 0.013$).

Preoperative Chemoradiation: Alternate Regimens and Issues

Both cytotoxic and targeted chemotherapeutic agents have been incorporated into preoperative chemoradiation regimens. The most common endpoint of these trials is pCR because, as will be discussed later, most studies suggest that it is associated with improved results.[29] Many of the Phase I/II regimens report higher pCR rates compared with historical rates seen with 5-FU alone.

Concurrent Oxaliplatin Regimens

Five randomized trials have examined the impact of addition of oxaliplatin to 5-FU– or capecitabine-based chemoradiation on response rates and acute toxicity in patients with cT3-4 and/N+ rectal cancer[70,116-119] (eTable 51-5).

Because four of five randomized trials reveal an increase in acute toxicity with no benefit in the pCR rate the current

Mass et al reported their experience of 192 patients with rectal cancer.[110] Patients were staged with diffusion weighted MRI and had cT4, cT3 with threatened margins, or node-positive disease. They received 50.4 Gy plus capecitabine and 6 to 8 weeks later underwent MRI restaging. A strict definition of clinical CR was used that included meeting all of the following criteria: (1) substantial downsizing with no residual tumor or residual fibrosis only, (2) no lymph nodes, (3) endoscopy revealing no tumor or a small residual erythematous ulcer or scar, (4) negative biopsy, and (5) no palpable tumor. A subset of 21 patients had a cCR and, based on patient preference, were included in a wait-and-see policy. Of the 21, 10 had distal tumors, which would have required an APR. The mean follow-up was 25 months. One patient developed an endoluminal local recurrence without nodal recurrence at 22 months and was salvaged with transanal endoscopic microsurgery (TEM) surgery. The cumulative probability of 2-year DFS was 89% and OS was 100%.

Dalton et al from Exeter treated 49 patients with 45 Gy plus capecitabine.[107] Twelve achieved a cCR by MRI and underwent biopsy 6 to 8 weeks later. Patients were then followed closely by PET, CT, MRI, and endoscopy. The 6 who were biopsy negative were all without evidence of disease with a median follow-up of 26 months and 2 of the 6 who were biopsy positive developed distant failure.

The series from Smith et al reported 32 patients with uT2-4 or N+ disease who received 50.4 (45-56 Gy) with 5-FU or capecitabine.[108] A cCR was defined as a negative endoscopy at 4 to 10 weeks. Biopsy and imaging were optional. The local failure rate was 19% crude and 21% 2-year actuarial. The median time to local failure was 11 months and all were salvaged and without evidence of disease at 17 months. Of note 5 of the 6 local failures were endoluminal. The incidence of distant failure was 9%. Their current recommendation for follow-up following chemoradiation is a two-stage process. At 6 to 7 weeks patients undergo and examination and endoscopy. If they have a cCR they are followed. If there is not cCR then it is repeated at 10 to 12 weeks. Patients who have a cCR at 14 months will likely remain in cCR.

Selecting patients for a nonoperative approach based on response is reasonable. The challenge is identifying a surrogate method to surgery to accurately identify patients who have achieved a pCR. Current methods include endoscopy and physical examination, ultrasound, CT, MRI, and PET either alone or in combination. With the exception of the rigorous approach used by Mass et al series,[110] most have not been consistently successful. Glynne-Jones et al reviewed 218 Phase II and 28 Phase III trials of preoperative radiation or chemoradiation and confirmed that clinical or radiologic response does not sufficiently correlate with pathologic response and do not recommend a wait and see approach to surgery following preoperative therapy.[112] However, further refinements in imaging may improve the selection process.

The STAR-01 trial randomized 747 patients to preoperative chemoradiation with 50.4 Gy with PVI 5-FU with or without oxaliplatin (60 mg/m^2 weekly).[116] There was a significant increase in grade 3+ toxicity with oxaliplatin (24% versus 8%; $p < 0.001$) with no improvement in the pCR rate (15% versus 16%).

In the ACCORD 12/0405 PRODIGIE trial, 598 patients were randomized to preoperative chemoradiation with 50 Gy plus capecitabine with oxaliplatin (CAPOX) compared to 45 Gy plus capecitabine.[117] There was a similar significant increase in grade 3+ toxicity with oxaliplatin (25% versus 11%; $p < 0.001$) with no improvement in the pCR rate (19% versus 14%). Oxaliplatin did not improve 3-year local recurrence (6% versus 4%) or survival (88% versus 83%).[118]

The NSABP R-04 trial was a four-arm trial (2 × 2 comparison) of PVI 5-FU compared to capecitabine-based preoperative chemoradiation (50.4 Gy) with or without oxaliplatin.[70] A total of 1606 patients with cT3 and or N+ disease were randomized. The addition of oxaliplatin (to either 5-FU or capecitabine) was associated with a significantly higher incidence of grade 3+ diarrhea (15% versus 7%, $p = 0.0001$) with no improvement in the incidence of pCR (21% versus 19%) or sphincter sparing surgery (60% versus 64%).

The German CAO/ARO/AIO-04 randomized 1265 patients with cT3-4 or N+ disease to the preoperative arm of CAO/ARO/AIO-94 (50.4 Gy + 5-FU) versus 50.4 Gy/5-FU with oxaliplatin (50 mg/m^2 weekly).[119] In contrast with the STAR-01, ACCORD, and NSABP R-04 trials, patient who received oxaliplatin-based chemoradiation had a significant improvement in pCR (17% versus 13%, $p = 0.045$) with no corresponding increase in acute grade 3+ toxicity (23% versus 22%). The preliminary results (published in abstract form at ECCO 2013) of the fifth trial (PETACC-6) did not result in any improvement in tumor downstaging or in anal sphincter preservation.

eTABLE 51-5 Oxaliplatin-Based Preoperative Chemoradiation: Phase III Randomized Trials

Trial/Treatment	Pts	RT (Gy)	pCR (%)	LF (%)	Acute Toxicity Gr 3-4 (*p* Value)
STAR[116]					
CI 5-FU	379	50.3/1.8	16	—	8
CI 5-FU/Oxaliplatin	368	50.4/1.8	15	—	24 (< 0.001)
ACCORD12/[117,118]					
0405 PRODIGIE					
Capecitabine	295	45/1.8	14	6 (3-Yr)	11
Capecitabine/Oxaliplatin	291	50/1.8	19	4	25 (< 0.001)
NSABP R-04[70]					
CI 5-FU or capecitabine	622	50.4/1.8	19	—	7
CI 5-FU or capecitabine	631	50.5/1.8	21	—	15 (0.0001)
+ Oxaliplatin					
CAO/ARO/AIO-94[119]					
CI 5-FU	637	50.4/1.8	13	—	23
CI 5-FU/Oxaliplatin	628	50.4/1.8	17	—	22 (NS)

5-FU, *5-Fluorouracil;* LF, *local failure;* pCR, *pathologic complete response rate;* Pts, *patients;* RT, *radiation dose/fraction size.*

standard is not to include oxaliplatin with 5-FU/capecitabine–based preoperative chemoradiation regimens. However, local control and survival data are not available and this recommendation may need to be modified once these data are reported.

Targeted Biologic Agents

The role of targeted biologic agents such as bevacizumab and cetuximab are being defined. Phase I/II trials using preoperative chemoradiation with CAPOX with bevacizumab reveal pCR rates of 18% to 24%.[120,121] Two recent trials combining bevacizumab with preoperative FOLFOX[106] or capecitabine-based[122] chemoradiation were stopped early because of excessive toxicity. A recent Phase I trial combined the AKT inhibitor nelfinavir with chemoradiation.[123] Although the report from Heidelberg of CAPEIRI-based chemoradiation reported a pCR rate of 25%[124] other trials combining chemoradiation with cetuximab plus 5-FU, capecitabine, or CAPOX have more limited rates of 5% to12%.[125,126]

Patient selection for treatment based on KRAS expression is useful in patients with metastatic disease.[121] The preliminary results from the Phase II EXPERT-C trial (50.4 Gy, CAPOX, Cetuximab) reveal a survival benefit from the addition of cetuximab in the subset of patients with KRAS wild type compared to mutant (96% versus 81% 3-year OS; $p = 0.034$); however the primary endpoint of the trial (pCR) was not changed (11% versus 9%).[127] As an alternative, the SAAK 4/07 trial used panitumumab-based chemoradiation in patients with KRAS wild-type cancers.[128]

RTOG Phase II Randomized Preoperative Chemoradiation Trials

The RTOG had reported two Phase II randomized trials. RTOG 0012 enrolled 106 patients who received preoperative chemoradiation with PVI 5-FU plus twice-a-day irradiation compared to FOLFIRI plus conventional daily fractionated irradiation. There were no significant differences in the rate of pCR (30% versus 26%), local recurrence (16% versus 17%), and a corresponding decrease in 5-year OS (61% versus 75%), respectively.[129] Grade 3+ toxicity rates were 42% and 55%, respectively.

In a more recent trial, the RTOG compared preoperative chemoradiation with CAPEIRI compared to CAPOX in 101 patients with cT3-4 disease (RTOG 0247).[130] Although not statistically significant, patients who received CAPOX had a higher pCR rate (21% versus 10%) with similar hematologic (4% versus 8%) and nonhematologic toxicity rates (29% versus 24%). Neither of these preoperative regimens was moved into Phase III trials.

Impact of Tumor Response to Preoperative Chemoradiation

Most series suggest that there is improved outcome with increasing pathologic response to preoperative therapy.[29,131,132] A retrospective review of 566 patients who achieved a pCR after receiving a variety of preoperative chemoradiation regimens at multiple European centers was reported by Capirci et al.[131] With a median follow-up of 46 months the local recurrence rate was only 1.6% and the 5-year DFS and OS were 85% and 90%, respectively. A pooled analysis of 3105 patients from 14 studies confirmed a significant improvement in local recurrence, distant failure, DFS, and OS for the 16% of patients who achieved a pCR (ypT0N0M0) compared to those without a pCR.[29] Acellular mucin pools are seen in 15% of tumors following chemoradiation and do not have a significant impact on outcome.[133]

Although a number of molecular markers are predictive of outcome in colorectal cancer,[121,134,135] they have had varying success in identifying patients who may respond to preoperative therapy.[136-138]

Konski et al performed pre-treatment and post-treatment 18-FDG PET scans on 53 patients receiving preoperative chemoradiation.[141] By multivariate analysis the percent decrease in SUV was marginally trended in predicting pCR ($p = 0.07$). In contrast, Guillem et al found that neither FDG-PET nor CT can distinguish between a pCR and an incomplete response following preoperative chemoradiation.[142]

Preoperative Short-Course Radiation versus Chemoradiation

Historically short-course radiation has not been recommended for patients with cT3 or N+ disease. This is because of its lack of sphincter preservation, the inability to safely combine it with adequate doses of systemic chemotherapy, and the associated acute toxicity.[145] The KROH 10-01 trial, reported by Yeo et al, treated 73 patients with cT3-4 disease with 5 Gy × 5 (intensity-modulated radiation therapy [IMRT] technique) and concurrent chemotherapy (modified Mayo regimen of 5-FU 400 m^2 and leucovorin 20 mg/m^2) followed by surgery 4 to 8 weeks later.[146] The pCR rate was only 1.4% and the acute grade 3+ toxicity was 38%. However, these shortcomings may be mitigated by increasing the interval between the completion of radiation and surgery as well as delivering chemotherapy sequentially, as opposed to concurrently, with radiation.

Interval between Short-Course Radiation and Surgery

The Stockholm III trial is examining if increasing the interval between radiation and surgery improves sphincter preservation and reduces toxicity. Patients are randomized to 5 Gy × 5 followed by surgery one week later compared with 5 Gy × 5 followed by surgery 4 to 8 weeks later compared with 2 Gy × 25 (50 Gy) followed by surgery 4 to 8 weeks later. An interim analysis has revealed that the pCR rate was 0.8% in arm 1, 12.5% in arm 2, and 5% in arm 3.[147] Final results are pending.

Sequential Chemotherapy

The Dutch Colorectal Group has tested the role of sequential chemotherapy following short-course radiation. A total of 50 patients with primary rectal cancer (8% T2, 76% T3, 16% T4) and synchronous resectable metastasis (84% liver, 10% lung, 6% both) were enrolled on a Phase II trial of short-course radiation followed 2 weeks later by six cycles of CAPOX with bevacizumab.[149] After a 6 to 8 weeks rest they underwent resection of the primary and resection or ablation of the metastasis. For the total patient group, 72% had a R0 resection at all sites however the 2-year relapse rate was 64%. The 2-year OS was 80%. Limiting the analysis to the pelvis, 26% achieved a pCR and with a median follow-up of 32 months the local recurrence rate was 6%.

This approach serves as the experimental arm of the Dutch RAPIDO Phase III trial. Patients with locally advanced but nonmetastatic disease are randomized to short-course radiation followed by CAPOX × 6 and TME compared to standard-course chemoradiation followed by TME. A similar trial is being performed by the Polish Colorectal Cancer Study Group.

In a U.S. pilot trial, 44 evaluable patients were treated with short-course radiation followed by sequential chemotherapy.[150] They received five fractions (25 Gy to the involved mesorectum and 20 Gy to the pelvic nodes), followed by four cycles of mFOLFOX6. Postoperatively, 33 (75%) had ypT0-2 disease including 13 (30%) who were ypT0 and 14 (32%) were ypN0.

Kuremsky et al reviewed 1204 studies examining a total of 36 molecular biomarkers which potentially have predictive value.[139] He et al reported that PIK3CA mutations predict local recurrence after surgery alone.[140] Restricting the analysis to patients treated with preoperative chemoradiation and to gene products examined by five or more studies, only p53, EGFR, thymidylate synthase, Ki-67, p21, and bax/bcl-2 met these criteria. Of these, quantitatively evaluated EGFR or EGFR polymorphisms, thymidylate synthase polymorphisms, and p21 have been identified as promising candidates that should be evaluated in larger prospective trials for their ability to guide preoperative therapy. Because the studies are limited retrospective trials and most do not examined multiple markers, the need for adjuvant therapy should still be based on T and N category of disease.

The pCR rate may provide an alternative endpoint for assessing the efficacy of novel preoperative chemoradiation regimens. Because patients with rectal cancer who receive adjuvant chemoradiation can develop late relapses, however, a minimum follow-up of 7 years is needed.[143] Current intergroup rectal trials prospectively collect tissues for these and other markers.

Short-course radiation (25 Gy in 5 fractions) was established as a standard therapy in the Dutch CKVO and Swedish trials,[51,144] and chemoradiation was established as a standard therapy by the German Rectal Cancer Trial CAO/ARO/AIO-94 (45-50.4 Gy in 25 to 28 fractions plus concurrent chemotherapy).[12,53] These two trials cannot be directly compared because patients selected for treatment with short course included patients with cT1-3 disease, whereas 95% of the patients in the German trial had cT3 and/or N+ disease. Recently, randomized trials of short-course radiation have included patients with stages cT3 or N+ thereby allowing a more relevant comparison between these two approaches.

The sequential approach is based on data from Garcia-Aguilar et al in patients treated with chemoradiation.[148] They reported a randomized Phase II trial of 144 patients with cN+ rectal cancer who received either preoperative chemoradiation (50.4 Gy + continuous infusion 5-FU) followed by surgery 6 weeks later or initial chemoradiation, and if there was a clinical response, mFOLFOX6 followed by surgery 11 weeks later. The pCR rate was increased in the mFOLFOX arm (25% versus 18%) with no associated increase in postoperative complications (40% in each arm). These preliminary data suggested that delivering additional chemotherapy and delaying surgery in patients who respond to preoperative chemoradiation was not detrimental to the response or surgical complication rates.

The Dutch Colorectal Group is also testing the role of postoperative chemotherapy following short-course radiation. In the ongoing SCRIPTS CKTO 2003-16 Phase III trial (Simply Capecitabine in Rectal cancer after Irradiation Plus TME surgery) patients with clinical stage II or III disease located below the level of S1/S2 or the inferior margin within 15 cm of the anal verge receive 5 Gy × 5 followed by TME. Patients are then randomized postoperatively to either capecitabine or observation.

Randomized Trials

Polish Trial

Bujko et al randomized 316 patients with cT3 rectal cancers to preoperative short-course radiation compared to chemoradiation.[85,151] All tumors were above the anorectal ring and TME was performed for distal tumors only. Postoperative chemotherapy was optional. There was no radiation quality control review and TME was performed only for distal tumors. As seen in Table 51-4, compared with short-course radiation, patients who received chemoradiation had a higher pCR rate (16% versus 1%) and a lower incidence of positive radial margins (4% versus 13%, $p = 0.017$). However, there were no significant differences in sphincter preservation (58% versus 61%), crude local recurrence (14% versus 9%), DFS (56% versus 58%) and 4-year OS (66% versus 67%). Of note, the surgeons who participated in this trial were not willing to change surgical techniques from an APR to sphincter preserving based on the response to preoperative therapy. Although acute toxicity was significantly higher with chemoradiation (18% versus 3%; $p < 0.001$), there was no difference in overall postoperative complications.

TROG, AGITG, CSSANZ, and RACS Intergroup Trial

A similar trial from Australia and New Zealand was reported from the Tasman Radiation Oncology Group (TROG).[152] A total of 326 patients with ultrasound or MRI-staged cT3Nany adenocarcinoma located in the lower two thirds of the rectum were randomized to short-course radiation compared to chemoradiation. In contrast with the Polish trial, all patients received 6 months of postoperative adjuvant 5-FU/leucovorin chemotherapy. The median potential follow-up time was 5.9 years and the primary endpoint was 3-year local recurrence.

Compared with short-course radiation, patients who received chemoradiation had a 3% lower cumulative local recurrence rate at 3 years (4.4% versus 7.5%; p = NS), and 2% at 5-years (5.7% versus 7.5%; p = NS). Likewise, there were no significant differences in distant failure, OS, or late radiation toxicity. A subset analysis of the 79 patients with distal tumors revealed a cumulative incidence of local recurrence of 12.5% for short-course radiation and there were no failures with chemoradiation.

Alternative Methods for Sphincter Preservation

Early localized tumors (3% to 5% of rectal cancers) include small, exophytic, mobile tumors without adverse pathologic factors (e.g., high grade, blood vessel invasion, lymphatic vessel invasion, colloid histologic type, or penetration of tumor into or through the bowel wall) and are adequately treated with a variety of local therapies such as local excision or endocavitary irradiation.

Endocavitary Irradiation

Endocavitary irradiation alone[153-155] has been used for early, noninvasive tumors. For more advanced tumors (cT2-3 or LN+), it is combined with a temporary iridium-192 (^{192}Ir) implant or pelvic irradiation.[156-158] This technique is also known as the *Papillion technique.* Before delivery, the anus is dilated and a 4-cm proctoscope is introduced. A low-energy x-ray unit is placed through the scope almost against the tumor. Generally, 50-kV x-rays are delivered at 30 Gy per fraction in three or four fractions over 1 month. Patients who develop local failure can successfully undergo surgical salvage.[159]

Clinical outcomes with endocavitary irradiation alone or combined with pelvic radiation have been reported. At the Mayo Clinic, 29 patients were treated with curative intent with endocavitary irradiation alone to a total dose of up to 155 Gy in one to five fractions. The local control rate was 76% at 10 years, and OS was 65% at 5 years and 42% at 10 years, respectively.[153] At Washington University, patients received pelvic irradiation (20 Gy in 5 fractions for those with cT1; the remainder received 45 Gy in 25 fractions) followed 6 to 7 weeks later by two endocavitary treatments of 30 Gy each.[160] Results by T-category were uT1, 100% DFS; uT2, 85% local control rate; and uT3 (patients with uT3 tumors were not optimal candidates for surgery) or tethered uT2, 56% local control rate (67% after salvage surgery). Gerard et al[159] have reported a similar experience in 44 patients. Because the 50-kVp radiation machine is not currently available, there are limited centers that continue to treat patients with contact irradiation.

Local Excision with or without Radiation Therapy

Given the morbidity of standard surgery as well as the frequent need for adjuvant therapy, the use of a more

TABLE 51-4 Randomized Trials of Preoperative Short-course Radiation versus Chemoradiation

	Polish Trial[85,151]		TROG[152]	
Patients	316		326	
Clinical stage	T3-4		T3Nany (56% N0)	
SCRT	5 Gy × 5		5 Gy × 5	
ChemoRT	50.4 Gy + bolus 5-FU/LV		50.4 Gy + PVI 5-FU	
Postoperative chemotherapy	Not required		Bolus 5-FU/LV (4-6 cycles)	
RESULTS (%)	**CHEMORT**	**SCRT**	**CHEMORT**	**SCRT**
pCR	16	1*		
SP	58	61		
CRM+	4	13*		
Compliance	69	98		
Local failure	14	9 (4-yr)	4	8 (3-yr)
Survival	66	67 (4-yr)	70	74 (3-yr)
Gr 3-4 late toxicity			9	8

ChemoRT, *Chemoradiation;* CRM+, *positive circumferential radial margins;* Gr, *grade;* LV, *leucovorin;* pCR, *pathologic complete response;* PVI, *protracted venous infusion;* RT, *radiation therapy;* SCRT, *short-course radiation therapy.*
**Statistically significant.*

Although a well-designed and performed trial, there were two criticisms of the trial. First, although patient numbers were slightly larger than the Polish trial they still were relatively small. Second, rather than powered to show equivalence it was designed to have an 80% power to detect a difference in the projected 3-year local recurrence rate of 15% for short-course radiation compared with 5% for chemoradiation. Although the 3% lower incidence of local recurrence with chemoradiation compared to short-course radiation did not reach statistical significance ($p = 0.24$), the 95% CI for the difference included an 8% difference in favor of (i.e., 10% versus 2%). Overall, the data suggest a small local control advantage for chemoradiation, especially for distal tumors.

In summary, the most common treatment for T3 or N+ rectal cancer is preoperative chemoradiation. Emerging data are challenging the chemoradiation approach. Randomized trials comparing short-course radiation with chemoradiation are encouraging; however, longer follow-up is needed. The addition of sequential chemotherapy following short-course radiation is feasible and is being tested prospectively. The impact on outcome, acute and chronic toxicity, and sphincter preservation need to be determined.

conservative approach such as local excision plus adjuvant therapy (radiation or more commonly chemoradiation) as primary therapy for selected cases of rectal cancer has been investigated. Unfortunately, the data reported confirm that this approach is a compromise treatment, and in patients with long-term follow-up (>5 years), the local recurrence rates are substantially higher than with radical surgery, even with the addition of chemoradiation. Local recurrences occur both in the primary excision site and the pelvic nodes.

The results of local excision depend on a number of factors such as the type of surgery (full-thickness compared to piecemeal excision) and clinicopathologic factors such as tumor size, T category, grade, margins, and lymphatic and perineural invasion.

Local excision has been performed both before and after radiation therapy. The advantage of performing a local excision before irradiation is that pathologic details can be well characterized. Highly selected patients with pT1 tumors without adverse pathologic factors have local failure rates of 5% to 10%. However, once adverse pathologic factors are present (high grade, vascular invasion, or signet-ring cells) or the tumor invades into or through the muscularis propria, the local failure rate is at least 17% and the incidence of positive mesorectal or pelvic nodes is at least 10% to 15%.[161]

Local Excision Alone

Local excision alone is recommended only for selected patients with pT1 tumors. Nash et al performed a retrospective analysis of patients with cT1N0 disease who underwent a local excision (137 patients) or radical surgery (145 patients) and were found to have pT1Nx disease.[164] With a median follow-up of 5 years, there was a significantly lower local recurrence rate (3% versus 13%; $p < 0.05$) and a higher 5-year disease-specific survival rate (96% versus 87%; $p < 0.05$) in those who underwent radical surgery compared to a local excision. By multivariate analysis, both local excision and perineural invasion were independent prognostic factors associated with lower DFS.

Local Excision Followed by Postoperative Therapy

When all series are combined, the average crude local failure rate after local excision followed by postoperative radiation increases with T category: pT1, 5%; pT2, 14%; and pT3, 22%.[165-175] However, when the analysis is limited to the series with a minimum of 4 years of follow-up,[169,172,175,176] the incidence of local recurrence for pT2 disease is 14% to 24% (eTable 51-6). Therefore, patients who are treated with local excision and postoperative adjuvant therapy require close follow-up beyond 5 years. Surgical salvage is possible, with most series reporting that approximately half of the patients who undergo an APR can be cured.[177]

The CALGB performed a Phase II trial of local excision and selective postoperative chemoradiation (CALGB 8984).[180] A total of 91% underwent a full-thickness local excision. Patients with pT1 disease were observed, and pT2 patients received postoperative treatment with 54 Gy plus concurrent 5-FU. With a median follow-up of 4 years, the local recurrence rate in 59 patients with pT1 disease was 5% and with pT2 disease was 14%.

Sphincter Function

Prospective assessment of functional results after local excision and radiation therapy is limited. The groups from the Memorial Sloan Kettering Cancer Center[173] and Gemelli Hospital in Rome[170] report rates of 94% and 100%, respectively, for good to excellent function. Using a different scale, investigators from the Fox Chase Cancer Center[171] reported an 82% rate of good to excellent function; the University of Pennsylvania[168] reported a 92% rate of satisfactory function; and the M. D. Anderson Cancer Center[167] reported that all patients were continent. In the preoperative setting, sphincter function was reported as good to excellent in 88% to 91%.[181,182]

Preoperative Therapy Followed by Local Excision

Experience with preoperative chemoradiation followed by local excision is more limited.[181-188] Most series selected patients with cT3 disease who were either medically inoperable or refused radical surgery. Local recurrence rates ranged from 0% to 20% and 5-year OS ranged from 78% to 90%. Borschitz et al[187] reported local recurrence rates by pathologic stage as ypT1, 2%, and ypT2, 6% to 20%. Rates were as high as 43% in ypT3 tumors that did not respond to chemoradiation.

This approach was being prospectively tested in the ACOSOG 06031 trial. In this Phase II trial, 77 patients with uT2N0 disease received preoperative CAPOX and radiation therapy. After local excision, if patients have ypT0-2 tumors with negative margins, they undergo observation only. If the pathology extent is ypT3 or if the margins are positive, patients undergo radical surgery. The pCR rate was 44%.[188]

LOCALLY ADVANCED DISEASE AND PALLIATION

Locally advanced rectal cancer is a heterogeneous group of diseases. Based on digital examination it can vary from a tethered or "marginally resectable" cancer to a fixed cancer with adherence to or direct invasion of adjacent organs or vital structures. With the introduction of MRI staging the definition has broadened. Additional radiological features including the proximity to or involvement of the mesorectal fascia (MRF) that surrounds the mesorectal fat outside the rectum and involvement of the sphincter are now considered locally advanced rectal cancers.

The diagnostic workup must evaluate the local spread and the presence and location of pelvic nodes and of metastases. The choice of one or more imaging studies should include pelvic MRI, abdomen with thorax CT scan, or PET depending on the patient's presenting symptoms. Involvement of the sciatic notch indicated by symptoms or scans predicts a situation unlikely to be helped by surgery alone. This has prognostic implications because patients with gross invasion of tumor into vital pelvic structures may be approached in a palliative rather than a curative fashion.

Standard Treatment (Preoperative Chemoradiation and Resection)

With the exception of the uncommon suture line-only recurrence, patients with locally unresectable or MFR with primary or recurrent disease should receive preoperative chemoradiation. Braendengen et al[190] randomized 207 patients with locally nonresectable T4 primary rectal carcinomas or local recurrence from rectal carcinomas to chemotherapy (5-FU/leucovorin) concurrent with 50 Gy plus postoperative adjuvant therapy for 16 weeks compared to 50 Gy alone. Patients who received chemoradiation had a higher R0 resection rate (84% versus 68%; $p = 0.009$), pCR rate (16% versus 7%), and 5-year local control rate (82% versus 67%; $p = 0.03$) but a nonsignificant improvement in the OS (66% versus 53%; $p = 0.09$).

Given the high probability of distant metastatic disease in this group of patients it is reasonable to develop treatment programs, which maximize the amount and duration of systemic therapy, while still delivering pelvic radiation. In this setting, short-course preoperative radiation is an attractive approach. Bujko et al randomized patients with unresectable

eTABLE 51-6 Local Excision Plus Postoperative Therapy: Selected Series

Series		T3 (%)	CT (%)	Survival
Massachusetts General Hospital[169]	47	0	55	74% 5-yr disease free
Catholic University[170]	21	0	0	81% 5-yr actuarial
University of Florida[165]	45	2	4	88% cause specific
NE Deaconess[166]	48	10	54	94% crude
MD Anderson[167]	46	33	17	—
University of Pennsylvania[168]	16	32	0	94% 3-yr actuarial 77% 3-yr colostomy free
Fox Chase[171]	21	19	10	77% 5-yr actuarial
CALGB 8984[178]	51	0	100	—
CALGB 8984[179]	110*	0	100	T1: 85% 10-yr actuarial T2: 66% 10-yr actuarial
Memorial Sloan Kettering[173]	39	21	51	70% 5-yr actuarial 87% colostomy free
Vancouver[174]	23	9	0	81% 5-yr disease free 77% cause specific
Princess Margaret Hospital[175]	73	11	0	67% 5-yr actuarial 82% 5-yr colostomy free

CT, *Concurrent chemotherapy;* yr, *year.*
**Analysis is limited to the 110 patients (T2-2 disease) who met the full eligibility criteria (4 cm, full-thickness local excision, and negative margins).*

Most series include some patients who have undergone suboptimal surgery such as a piecemeal excision or have positive or unassessable margins. Because few of the published series have adequate numbers to perform a meaningful multivariate analysis, it is difficult to determine the influence of these selected clinicopathologic features on one another.

There are a variety of surgical approaches, including transanal local excision, posterior proctotomy, and transsphincteric excision. TEM has emerged as another option for local treatment of rectal cancer, either alone for T1 tumors or combined with irradiation for selected patients with T2-3 disease.[162] Regardless of the technique, the excision should be full thickness and nonfragmented and should have negative margins.[163]

A separate analysis of the 110 patients who met the full eligibility criteria in CALGB 8894 was reported by Greenberg et al.[179] The criteria were limited to tumors less than 4 cm, full-thickness excision, and negative margins. Patients with pT1Nx tumors underwent local excision alone, and those with pT2Nx received postoperative chemoradiation. With a median follow-up of 7.1 years, the rates of local recurrence and 10-year actuarial survival were T1, 8% and 84%, and T2, 18% and 66%, respectively. The median time to failure was T1, 4 years, and T2, 2 years.

A similar trial in France (GRECCAR 2) is designed to accrue 300 patients with cT2-3 disease. They receive 50 Gy with concurrent CAPOX. If the clinical T category following chemoradiation is cT1-2, patients are randomized to undergo local excision versus radical surgery. If the clinical extent is cT3, all have radical surgery.

Bujko et al reported 89 patients with unfavorable cT1N0 or cT2-3N0 rectal cancer who received preoperative therapy with either 5Gy × 5 followed by a 4-Gy boost or chemoradiation. Patients then underwent a local excision and if there was ypT0-1 disease they were observed and if there was less of a response they underwent surgery. A total of 63 patients underwent a local excision and the local failure was 12% in those who received short-course radiation compared with 6% for chemoradiation.[189]

This was based on data from the mid-1980s reporting that involvement of the CRM (also known as lateral or radial margins) was not only the most important factor for the risk of local recurrence following rectal cancer surgery but considerably more relevant than the distal or proximal resection margins.[13] A positive CRM refers to the presence of tumor in the margin or in close proximity to the MRF, irrespective of whether that distance is 1 mm or 2 mm. A positive CRM is predictive not only for local failure but also for distant failure.[81] The ability to obtain a negative CRM depends to the extent of the operation the surgeon is able to perform and ultimately the associated loss of function the patient is willing to accept.

or locally recurrent tumor involving or abutting adjacent organs or structures (cT4) or palpably fixed cT3 disease to receive either preoperative 5-×5-Gy irradiation over 5 days and consolidative chemotherapy with three cycles of FOLFOX4 (schedule I) versus long-course chemoradiation (50.4 Gy in 28 fractions of 1.8 Gy over 5.5 weeks) concomitantly with oxaliplatin, 5-FU, and leucovorin (schedule II). The interval between the start of radiation and surgery was 12 weeks in both groups. The primary endpoint of the study was microscopic negative margins and the accrual goal is 540 patients.

Extended surgery to include the infiltrated organs should be considered if there is a favorable response after preoperative therapy. Even in patients who do not respond adequately to preoperative therapy, surgery should still be considered, balancing the benefits and risks.[191] Given the limitation of the total EBRT dose that can be delivered to the bulky tumor in the pelvis[192] and the frequent problem of local recurrence, the surgeon should be aggressive.[193] Overall, approximately 10% of rectal cancers require extensive surgery such as a pelvic exenteration to obtain negative margins.[194] These include tumors invading the prostate, the base of the bladder, or the uterus and vagina where the disease can be resected en bloc with negative margins. Midline posterior tumors adherent to or invading the distal sacrum may be resectable for cure with APR extended to include the lower sacrum. The 5-year OS ranges between 33% and 50%, with significant rates of morbidity and mortality up to 6%.[192] Improvements in perioperative care, patient selection, and surgical technique, such as vascularized tissue flaps to facilitate the healing of pelvic and perineal wounds, have improved the results[195] In IORT institutions, an excellent alternative to pelvic exenteration is marginal gross total resection (R0 or R1) plus IORT (see subsequent section).

Although sphincter preservation is a major goal for patients with primary resectable disease, this should be a lesser goal for patients with locally recurrent cancers. In view of the extensive surgery required for patients with local recurrence and the likelihood of high-dose EBRT, patients may have a better functional outcome with a permanent colostomy than with coloanal anastomosis or a low anterior resection.

In general, patients with local recurrence have an unfavorable prognosis. Common symptoms include pain, hemorrhage, pelvic infection, and obstructive symptoms. Patients with local recurrence should receive preoperative chemoRT if feasible. However, some patients who present with locally recurrent disease series have had prior adjuvant EBRT and can receive only a limited or no dose.[196]

Intraoperative

The primary advantage of IORT is that radiation can be delivered at the time of surgery to the site with the highest risk of local failure (the tumor bed) while decreasing the dose to the surrounding normal tissues. IORT can be delivered by two techniques: electron beam or brachytherapy. Brachytherapy is most commonly delivered by the high-dose-rate technique, and the dose rate is similar to that used for electron beam IORT.[197-199] The results (and recommended dose) of IORT depend on whether the patient has primary unresectable or recurrent disease and on whether the margins of resection are negative or there is microscopic or gross residual disease. In general, series have used 10-Gy to 20-Gy IORT depending on the volume of residual disease and the dose of EBRT that can be safely delivered with concurrent chemotherapy, preferably before the attempted resection. For example, at the Mayo Clinic, patients with locally unresectable primary cancers receive preoperative chemoRT (45 Gy to 50.4 Gy/25 to 28 fractions) plus an IORT dose of 10 Gy after R0 resection with narrow margins, 10 Gy to 12.5 Gy after R1 resection, and 15 Gy to 20 Gy after R2 resection.[49]

It is difficult to clearly separate treatment-related complications from disease-related complications in patients with unresectable primary or recurrent rectal cancers. The total incidence ranges from 15% to 50% in most series and is highest in patients with the most advanced disease (recurrent unresectable tumors). Complications such as delayed healing, an increase in infection, fistula formation, and neuropathy may be the result of recurrent tumor, aggressive surgery, radiation therapy, or a combination of these.[49,200,201] The incidence of IORT-related peripheral nerve toxicity appears to increase with IORT doses of 15 Gy to 20 Gy. In a series from the Netherlands, 79 patients surveyed reported fatigue (44%), perineal pain (42%), sciatic pain (21%), walking difficulties (36%), and voiding dysfunction (42%).[200] In addition, functional impairment consisted of requiring help with basic activities (15%), sexual inactivity (56%), the loss of former lifestyle (44%), and the loss of professional occupation (40%). The University of Navarra reported peripheral neuropathy up to 5 years after IORT.[201] These consequences must be weighed against the chance of cure if the patient is treated and the disability eventually caused by uncontrolled tumor progression if the patient is not treated.

The long-term morbidity in the Mayo Clinic IORT series of 146 patients with locally unresectable colorectal cancers was 53% and included neuropathy (in 28 of 146 patients, or 19%), small bowel obstruction (14%), and ureteral obstruction (12%).[49] Severe toxicity (grade 3 or 4) was evident in 32 of 146 patients (22%), with small bowel obstruction in 14 patients (9.5%) and severe neuropathy in only 3 (2%).

Primary Unresectable Disease

Results of selected series with or without IORT are seen in Table 51-5. The results of the series from Rotterdam,[47] Madrid,[202] Eindhoven,[203] and Montpellier[204] include patients with both cT3 and cT4 disease and do not report the data separately. The Rotterdam and Eindhoven series examined outcome and did not find a significant difference. However, indications for IORT with T3 primary rectal cancers are questionable, unless used to replace a portion of the EBRT dose in patients with node negative disease. The overall incidence of local failure is approximately 10% to 15%, and central failure in the IORT field is uncommon (i.e., 2% in the Mayo Clinic IORT series of 146 patients with locally unresectable T4 colorectal cancer).[49]

A French multiinstitutional randomized trial performed with 142 patients, T3-4 or N+, M0 stages, has not demonstrated an improvement in local control and DFS in the context of 40-Gy preoperative irradiation with or without 18-Gy IORT pelvic boost.[204] The 5-year local control rates were 92% compared with 93%, and postoperative complications incidence were 30% (IORT) compared to 19% ($p = 0.15$). Topography of pelvic recurrences and technical characteristics of IORT boosting were not reported.

The most favorable results are obtained in patients with gross total resection and negative margins (R0 resection) or microscopically positive margins (R1 resection). The 5-year local recurrence and OS in the Eindhoven IORT series were R0, 8% and 73%, and R1-2, 38% and 31%, respectively.[145] Valentini et al[205] treated 100 patients with primary, clinical, T4M0, extraperitoneal rectal cancer with preoperative chemoRT with or without IORT. The R0 resection rate was 78%; 5-year local control in R0 patients was 90%, better in the IORT group (100%). The 5-year OS was 59% and was better after an R0 versus an R1-2 resection (68% versus 22%). Although the numbers are small, in the Rotterdam series, the 5-year local

Bujko reported outcomes of 49 patients—reported outcome of 49 patients treated according to schedule I, and 48 according to schedule II. Grade 3+ acute toxicity was observed in 26% of patients in group I and in 25% in group II. There were two toxic deaths, both in group II. The microscopically radical resection (primary endpoint) rate was 73% in group I and 71% in group II. Overall and severe postoperative complications were recorded in 27% and 9% of patients compared to 16% and 7%, respectively. Pathological complete response was observed in 21% of the patients in group I and in 9% in group II. Final outcome data are pending.

A similar randomized trial (RAPIDO Trial) is ongoing in Sweden and the Netherlands. Eligibility includes at least one of the following criteria on pelvic MRI: overgrowth to an adjacent organ or structure, cT4b, extramural vascular invasion (EMVI+). N2, MRF+, enlarged lateral nodes, or >1 cm (lat LN+). Patients are randomized between short course 5-×5-Gy followed by six cycles of CAPOX chemotherapy and surgery compared with long-course chemoradiation followed by surgery and eight cycles of postoperative CAPOX. The primary endpoint is 3 years DFS and data are expected for 2016.

TABLE 51-5 Primary Locally Advanced/Unresectable Rectal Cancer ± Intraoperative Radiation: Selected Series

Series	No. Pts	F/U (mo.)	Preoperative Treatment* (Gy)	IORT	Local Failure by Margin Status					Survival by Margin Status		
					# Pts	Negative	# Pts	Positive	Total	Negative	Positive	Total
MGH[45]	145	41M Median	45-50.4 ± 5-FU ± 10-20 IOERT	Yes	45	11% 5-yr	(m) 21 (g) 7	32% 5-yr 43% 5-yr	— —	63% 5-yr DFS	32% 5-yr DFS	—
				No	66	18% 5-yr	6	83% 5-yr	—			
Memorial Sloan Kettering[46]	18	18M Median	50.4 + 5-FU/LV 10-20 HDR IORT	Yes	—	8% 2-yr	—	62% 2-yr	19% 2-yr	77% 2-yr DFS	38% 2-yr DFS	69% 2-yr DFS
Rotterdam[47†]	123	25 M Median	50.0 10 HDR IORT	Yes No	19 85	28% 5-yr 29% 5-yr	11 8	42% 5-yr 100% 5-yr	35% 5-yr —	66% 5-yr 56% 5-yr	38% 5-yr 0% 5-yr	50% 5-yr
Madrid[48†]	123	37 M Median	45-50.4 + 5-FU 12.5 IOERT	Yes	—		—		6% 3-yr	—	—	74% 3-yr
Mayo[49‡]	146	44 M Median	50.4 ± 5-FU 12.5 IOERT[§]	Yes	—		—		14% 5-yr	R0/R1(n = 128) 56% 5-yr	R2 (n = 18) 22% 5-yr	52% 5-yr
Eindhoven[50†]	290	45 M Median	45-50.4 + 5-FU 10-17.5 IOERT	Yes	279	8% 5-yr	9	38% 5-yr	13% 5-yr	73% 5-yr	31% 5-yr	67% 5-yr

5-FU, *5-Fluorouracil;* BID, *twice a day radiation;* DFS, *disease-free survival;* HDR IORT, *high-dose rate intraoperative radiation;* IOERT, *intraoperative electron irradiation;* MGH, *massachusetts general hospital;* NED, *no evidence of disease;* yr, *year.*

**In most patients.*

†Includes patient with all stages (not just T4 disease), 5-FU, or Tegafur with EBRT; of patients in "margins" columns reflect of pts at risk, not with local failure.

‡Includes 40 pts with colon cancer, preoperative RT in 86%.

§Median IORT dose.

recurrence rate was lower in the 11 patients with positive margins who received IORT compared with the 8 who did not (58% versus 100%; $p = 0.016$).

In the Mayo Clinic IORT series of 146 patients with colorectal cancer with T4 lesions, R0-1 resection was accomplished in 128 patients and R2 resection in 18. Those with IORT after R0-1 resection had better 5-year OS than those with R2 resection (56% versus 22%; $p = 0.0006$. Patients who received preoperative chemorRT ($n = 124$) had improved survival compared with those who received postoperative chemoRT ($n = 20$) with 5-year OS of 55% versus 38% ($p = 0.02$).

In the Massachusetts General Hospital (MGH) series of 145 patients with rectal cancer,[45] local failure in patients with negative margins decreased from 18% without IORT to 11% with IORT. In patients with positive margins, local failure was 83% without IORT versus 43% with IORT for gross residual disease and 32% with IORT for microscopic residual disease. For all patients in the series (with or without IORT), the 5-year DFS was 63% for patients with negative margins and 32% for patients with positive margins.

The results in both MGH and Mayo series underscore the importance of delivering preoperative therapy to help achieve negative margins. If negative margins cannot be obtained, then microscopic residual disease is preferable to gross residual disease. Reports from other centers are similar.

At the MGH, of the 95 patients with T4 disease who received preoperative irradiation and underwent complete resection, 40 patients had an IORT boost and 55 did not because it was not indicated secondary to either a favorable response or it was not technically feasible.[206,207] Regardless of the response to preoperative therapy, higher local failure rates were seen in patients not receiving IORT (responders, 0% versus 16%; nonresponders, 12% versus 27%) these data suggest that IORT should be delivered independent of the extent of tumor downstaging.

Locally Recurrent Disease

Recurrences can be heterogeneous, and the pattern of extension is more infiltrative within the operative bed compared with primary rectal cancers. Localized pelvic recurrences may be classified according to the tumor location within the pelvis. At the Mayo Clinic, 106 patients with local recurrence, treated by subtotal resection alone or with IORT (42 patients) or EBRT, were stratified during the surgical procedure according to no pelvic infiltration of the tumor (F0) or infiltration of the tumor to one pelvic site (F1), two pelvic sites (F2), or more than two pelvic sites (F3).[208] This classification system significantly correlated with survival. At the Catholic University of the Sacred Heart, Rome, 47 patients with locally recurrent, nonmetastatic rectal carcinoma were treated by preoperative chemoradiation plus IORT and were classified by CT scan according to the Mayo Clinic system.[209] A further (F4) class was added when tumor infiltrated small bowel or bone structures. The classification system significantly predicted R0 resectability ($p = 0.01$) and survival ($p = 0.008$).

Results in selected series with or without IORT are seen in Table 51-6. As seen in patients treated for primary unresectable disease, the margin status and delivery or nondelivery of IORT have an impact on outcome for patients with locally recurrent disease.

In the MGH IORT series of 49 patients, the 5-year local control rate was 35% and was higher with negative versus positive margins (56% versus 13%).[207] The 5-year OS for the total group was 27%; higher in patients with negative versus positive margins (40% versus 12%).

Kusters et al[217] from Eindhoven treated 170 patients with locally recurrent rectal cancer with preoperative irradiation with or without chemotherapy followed by surgery (154 patients received IORT). The local recurrence rate in patients with negative margins was 32% and with positive margins was 71%. The 154 patients selected to receive IORT had a local recurrence rate of 47%. Patients with posterior (presacral) recurrences were more likely to have positive margins than those with anastomotic recurrences (72% versus 23%) and the 5-year OS was lower than with relapse in other pelvic sites at 19% ($p = 0.03$).

The most recent Mayo Clinic Rochester analysis included 607 patients with recurrent colorectal cancer receiving IOERT as a component of treatment (colon, 180 patients; rectum, 427 patients).[134] Survival at 5 years was 30% for the total group of patients. On multivariate analysis, complete resection, no prior chemotherapy, and treatment after 1996 were associated with improved survival rates. In patients with an R0 resection (227 patients) compared to an R1 resection (224 patients) or R2 resection (156 patients), 5-year OS were 46%, 27%, and 16% ($p < 0.0001$, multivariate analysis), respectively.

Investigators at the M. D. Anderson Cancer Center (MDACC) and in Oslo reported no benefit of IORT for patients with positive margins.[218] In the report from Oslo, 107 patients with isolated pelvic recurrence received 46 Gy to 50 Gy preoperatively followed by resection alone or plus IORT.[214] Regardless of the volume of residual disease, there was no significant difference in local recurrence or survival rates whether or not patients received IORT.

To evaluate disease control, OS and prognostic factors in patients with locally recurrent rectal cancer after IORT-containing multimodal therapy Röder et al analyzed 97 patients with locally recurrent rectal cancer treated with surgery plus IOERT.[219] IOERT was preceded or followed by EBRT in 54 previously untreated patients (median dose 41.4 Gy) usually combined with 5-FU–based chemotherapy (89%). Median OS was 39 months. Estimated 5-year rates for central control (inside the IOERT area), local control (inside the pelvis), distant control, and OS were 54%, 41%, 40%, and 30%, respectively. Resection margin was the strongest prognostic factor for OS (3-year OS of 80% [R0], 37% [R1], 35% [R2]) and LC (3-year LC 82% [R0], 41% [R1], 18% [R2] in the multivariate model. OS was further significantly affected by clinical stage at first diagnosis and achievement of local control after treatment in the univariate model.[220]

In summary, it is unclear in some series if those with R2 resection benefit from aggressive therapy in contrast to patients with R0 or R1 resection. Although the Oslo study reported no long-term survivors for patients with R2 resection, U.S. IORT series report 10% to 18% 5-year OS in this subset of patients which includes those with prior EBRT.

Reirradiation Followed by Surgery

The combination of chemoradiation and TME has significantly decreased the incidence of local recurrence. However, there is a subset of patients who present with local recurrence only who have received previous pelvic irradiation. In these patients, the recurrence is often not resectable with clear margins and reirradiation would be expected to be associated with a high risk of late toxicity.

Few studies have analyzed the role of radiation retreatment in pelvic recurrence. Data from Mohiuddin et al[221] suggest that reirradiation with doses of 30 Gy (and if the small bowel can be excluded from the irradiation field, 40 Gy) can be used for limited volumes. A total of 103 patients with recurrent disease underwent reirradiation with concurrent 5-FU–based chemotherapy. The initial radiation dose to the pelvis ranged from 30 Gy to 74 Gy, with a median dose of 50.4 Gy. Irradiation techniques consisted of two lateral fields with or without a

Calvo et al analyzed prognostic factors associated with survival in patients after IORT for locally recurrent rectal cancer in 60 patients. Overall, 47% also received EBRT (range, 30.6 Gy to 50.4 Gy). The median follow-up time was 36 months (range, 2 months to 189 months), and the 1-year, 3-year, and 5-year rates for locoregional control and OS were 86%, 52%, and 44%; and 78%, 53%, 43%, respectively. EBRT improved the ability to achieve a radical resection and to avoid fragmented resection specimens and in these settings, was associated with improved local regional control. Patients who underwent a R1 resection and no tumor fragmentation showed a significant lower OS after adjustment for other covariates.[219]

TABLE 51-6 Locally Recurrent Rectal Cancer: The Role of Intraoperative Radiation, Selected Series

Series		FU (mo.)	Preop Treatment/IORT dose	Local Failure Rates by Margin Status					Survival Rates by Margin Status		
				No.	Negative	No.	Positive	Total	Negative	Positive	Total
Eindhoven[200]	170	35 Median	50.4 Gy EBRT 10 Gy-17 Gy IORT (154pts)	93	32%	77	71%	—	—	—	40% 5-yr CSS
Mayo, colorectal[210] (no prior RT)	123	—	50.4 Gy-54 Gy 7 Gy-20 Gy IORT	1/17	6% 3-yr	R1, 7/40 R2, 16/65	19% 3-yr 32% 3-yr	25% 3-yr	44% 3-yr	R1 24% 5-yr R2 18% 5-y	20% 5-yr
Mayo, colorectal[211] (prior RT)	51	—	25.2Gy median 15 Gy-20 Gy IORT	4/13	45% 3-yr	R1, 10/21 R2, 4/17	65% 3-yr 57% 3-yr	55% 3-yr	25% 5-yr	R1 27% 3-yr R2 21% 3y	12% 5-yr
Mayo, colorectal[212]	607	—	EBRT/IOERT (Gy)	—	16% 3-yr	—	26% 3-yr	28% 3-yr	R0 49% 5-yr	R1 26%, R2 16%	30% 5-yr
No prior EBRT	359	—	50.4/12.5 median	22/136	12% 3-yr	R1, 25/121 R2, 32/102	21% 3yr 30% 3y	17% 3-yr	R0 47% 5yr	R1 33%, R2 17%	32% 5-yr
Prior EBRT	248	—	27.5/17.5 median	19/91	25% 3-yr	R1, 43/103 R2, 17/54	50% 3yr 44% 3yr	31% 3-yr	R0 43% 5-yr	R1 20%, R2 12%	26% 5-yr
MDACC[213]	43†	26 Median	45 Gy/5-FU ± CDDP 10 Gy-20 Gy IORT	—	—	—	—	36%	—	—	37% 5-yr DFS
MSKCC[46]	46	18 Median	50.4 Gy ± 5-FU 10 Gy-20 Gy HDR IORT (16 pts) 10 Gy-20 Gy IORT alone (25pts)	—	18% 2-yr	—	81% 2-yr	37% 2-yr	71% 2-yr DFS	0% 2-yr DFS	47% 2-yr DFS
MGH[207]	69	31 Median	50.4 Gy ± 5-FU 10 Gy-20 Gy IORT (49 pts) Some prior EBRT	25	44% 5-yr	24	83% 5-yr (R1+R2)	65% 5-yr	40% 5-yr	14% 5-yr	27% 5-yr
Catholic University[209]	47	80 Median	45 Gy-47 Gy + 5-FU/MMC 10 Gy-15 Gy IORT (11 pts)	—	—	—	—	68% 5-yr 21% 5-yr (IORT)	—	—	22% 5-yr 41% 5-yr (IORT)
Oslo[214]	107	26 Median	46 Gy-50 Gy 12 Gy-18 Gy IORT (59pts)	18	30% 5-yr	29 (R1) 12 (R2)	54% 5-yr —	— —	50% 5-yr	R1 25% 5-yr R2 0% 5-yr	30% 5-yr
French IORT Group[215]	73	30 Median	39 Gy ± 5-FU 10 Gy-15 Gy IORT (30 pts) 10 Gy-15 Gy IORT alone (43 pt)	—	—	—	—	69% 3-yr 57% (R0)	—	—	31% 3-yr
Heidelberg[216]	31	28 Median	41.4 Gy (22 pts preop) Mean 13.7 Gy IORT	14	22% 4yr	9 (m) 8 (g)	39% 4yr 40% 4yr	29% crude crude	71% 4yr DFS	29% 4yr DFS	48% 4yr DFS 58% 4yr DFS

DFS, *Disease-free survival;* EBRT, *external beam pelvic irradiation;* g, *gross positive margins;* HDR-IORT, *high dose rate intraoperative radiation therapy;* IOERT, *intraoperative electron irradiation;* IORT, *intraoperative radiation therapy;* m, *microscopic positive margins;* MDACC, *MD Anderson Cancer Center;* MGH, *massachusetts General Hospital;* MMC, *mitomycin C;* MSKCC, *Memorial Sloan Kettering Cancer Center;* preop, *preoperatively;* yr, *year;* mo., *months;* pre-op, *preoperative;* CSS, *cause-specific survival.*

**In most patients.*

†*Excluding 10 patients with multifocal or extrapelvic disease.*

posterior pelvic field to include recurrent tumor with a margin of 2 cm to 4 cm. Doses ranged from 15 Gy to 49.2 Gy (median, 34.8 Gy). After reirradiation, 34 underwent surgical resection for residual disease. For the total group, median survival was 26 months and 5-year OS was 19%. Patients who underwent resection had significantly higher median survival (44 months versus 14 months) and 5-year OS (22% versus 15%; $p = 0.001$). Late complications were seen in 22 patients and were unrelated to radiation dose.

A multicenter Italian trial of 59 patients with recurrent disease who had received less than 55 Gy were retreated preoperatively with concurrent PVI 5-FU plus 30 Gy (1.2 Gy twice daily) to the gross tumor volume (GTV) plus a 4-cm margin.[222] A boost was delivered, with the same fractionation schedule, to the GTV plus a 2-cm margin (10.8 Gy). Grade 3+ toxicity was 5% for acute toxicity and 12% for late toxicity. The prior median radiation dose was 50.4 Gy. The pCR rate was 9%, and 83% of those with pelvic pain before treatment had a symptomatic response. With a median follow-up of 36 months, the rate of local failure was 48%, median survival was 42 months, and 5-year OS was 39% (R0, 67% versus R1-2, 22%). Multivariate analysis confirmed the impact of a longer DFS on local control ($p = 0.016$) and DFS ($p = 0.002$). Patients who underwent an R0 resection had improved local control and DFS ($p = 0.016$).

In the recent Mayo Clinic IORT analysis of 607 patients with locally recurrent colorectal cancer, 248 had received prior EBRT.[134] Additional EBRT was given in 228 patients (median, 27.5 Gy; range, 5 Gy to 39.6 Gy). Prior in-field EBRT versus none was associated with an increased risk of local relapse (3-year rate, 31% versus 17%; $p < 0.0001$) and trends for decreased 5-year OS that did not reach significance (26% versus 32%; $p = 0.07$), Table 51-12. Mayo Clinic investigators prefer to give preoperative EBRT (25 Gy to 30 Gy in 1.8-Gy fractions) plus concurrent CI 5-FU or oral capecitabine before resection and IOERT in this group of patients.

At the MDACC 50 patients with a history of prior pelvic radiotherapy were treated with hyperfractionated accelerated radiotherapy for primary ($n = 2$ patients) or recurrent ($n = 48$ patients) rectal adenocarcinoma.[196] Patients were treated with 1.5 Gy fractions twice daily, with a total dose of 39 Gy ($n = 47$ patients) if the retreatment interval was >1 year or 30 Gy ($n = 3$) if the retreatment interval was <1 year. Concurrent chemotherapy was administered to 48 (96%) patients. Eighteen (36%) patients underwent surgical resection following radiotherapy. The 3-year rate of grade-3 to grade-4 late toxicity was 35%. The 3-year rate of freedom from local progression was 33% (47% in patients undergoing surgery and 21% in those with no surgery, $p = 0.057$). The 3-year OS was 39% for the total group, 66% compared with 23% in patients undergoing surgery compared to not ($p = 0.003$) and 53% compared to 21% in patients with a retreatment interval of >2 years compared with < 2 years ($p = 0.001$).

Irradiation Alone for Locally Unresectable or Recurrent Disease

Some investigators have advocated the use of radiation therapy alone, most commonly in patients who are medically inoperable or refuse surgery.[102,157,223] A variety of techniques have been used, including various combinations of EBRT, brachytherapy, and intracavitary irradiation. In most series, patients received pelvic radiation therapy followed by a boost with EBRT or brachytherapy.

Wang et al[224] from the Princess Margaret Hospital (PMH) reported the results of EBRT alone (40 Gy to 60 Gy) in 227 patients who refused surgery or had unresectable or medically inoperable disease. The 5-year OS was 27% for all patients; if the primary tumor was mobile, the rate was 47%; if partially fixed, 27%; and if fixed, 4%. These data suggest that patients with mobile or partially fixed rectal cancers who are medically inoperable should be treated aggressively with pelvic irradiation as a component of their therapy.

Gerard and et al[102] reported the combination of EBRT, intracavitary therapy, and brachytherapy in 63 patients with uT2-3 tumors. For patients with uT3 disease, the 5-year local failure and survival rates were 20% and 35%, respectively.

Pelvic irradiation offers effective palliation. A recent review the efficacy and toxicity of palliative pelvic radiotherapy of symptomatic rectal cancer and to evaluate different fractionation schedules, based on systematic literature searches of Medline, Embase, and Cochrane databases showed large variations in applied radiotherapy regimens. Pooled overall symptom response rate was 75%, and positive responses were reported for pain (78%), bleeding and discharge (81%), mass effect (71%), and other pelvic symptoms (72%). Toxicity and quality-of-life results were not evaluable.[225] In a subset of 80 patients with metastatic disease who received pelvic irradiation, Crane et al[226] reported that 94% had complete resolution of pelvic symptoms and the 2-year pelvic symptom-free control rate was 82%. The PMH series reported similar palliative benefits.[101] In the subset of 84 patients who received more than 45 Gy, the following presenting symptoms were palliated by 6 to 8 weeks following the completion of radiation therapy: pain, 89%; bleeding, 79%; neurologic symptoms, 52%; mass effect, 71%; discharge, 50%; urologic symptoms, 22%; and other symptoms, 42%. In the Thomas Jefferson University series, complete plus partial symptomatic relief was achieved in the following categories: pain (65% + 28%), bleeding (100%), and mass effect (24% + 64%), respectively.[221] The duration of palliation was 8 to 10 months. In patients who are unable to receive irradiation, laser treatment or stenting[227] offers some palliative benefit.

Treatment of Patients with Metastatic Disease

With the development of more effective systemic chemotherapy, the median survival of patients with metastatic colorectal cancer is greater than 2 years.[228] Aggressive techniques to address liver metastasis with surgery and nonsurgical ablative techniques such as radiofrequency ablation, cryosurgery, microspheres, and EBRT have further improved median survival.[229] Innovative radiation techniques such as stereotactic body radiotherapy of liver metastases are under active investigation.[230]

With these advances, the historical notion that chemoRT is not necessary because patients die before developing a local recurrence is being challenged. In the setting of disease presentation with distant metastasis, there is no standard of care and treatment should be decided on a case-by-case basis with the help of a multidisciplinary tumor board. In general, patients who respond to chemotherapy and have a risk of developing local recurrence should be considered for treatment consolidation with chemoradiation.

Approximately 2% to 5% of colorectal cancers are diagnosed with one or a few synchronous metastases in one organ, usually liver. These patients are staged as having oligometastatic disease and can be treated in a potentially curative fashion. The treatment strategy synchronous oligometastatic rectal cancer should be based on the possibility to achieve R0-resection, either initially or after induction treatment for both the systemic disease and the primary tumor in a multidisciplinary team discussion.[231] It has been shown that surgical resection of colorectal liver and lung metastases is a potentially curative treatment, with reported 5-year survival rates

ranging from 30% to 50%.[232,233] The ideal timing for the surgery of the primary, either concomitant with resection of the metastases or delayed until after chemoradiation, remains controversial. It should be based on the individual patient by a multidisciplinary team discussion.

IRRADIATION TECHNIQUES AND TOLERANCE

Patterns of Relapse That Define Radiation Portals

The design of pelvic radiation therapy fields is mainly based on the pattern and incidence of local recurrence after surgery. For locally advanced disease, recurrences in the soft tissues may arise from tumor extension to the pelvic sidewall, the bladder, the prostate in men, the vagina in women, and the presacral space in all patients. This is especially true for tumors penetrating the mesorectal fascia or those with involved or close (<1 mm) circumferential margins. Incomplete mesorectal excision also has a higher risk of leaving residual microscopic tumor cells behind.

The major lymphatic spread is in a cephalad direction contained within the perirectal fascia and along the mesenteric system, which is commonly dissected by standard TME surgery. Outside the mesorectum is a space containing vessels, nerves, and lymphatics, which is not usually dissected. Tumors at or below the peritoneal reflexion tend to spread laterally along the internal iliac and obturator chains. The external iliac nodes only become at risk with anterior tumor extension and adjacent organ involvement. Lesions that extend to the anal canal or the lower third of the vagina can spread to the inguinal nodes. In this setting, the bilateral inguinal nodes should be considered for inclusion in the pelvic radiation fields.

The relative frequency and sites of pelvic failures were delineated by the seminal work of Gunderson and Sosin.[234] In this reoperative series of 75 patients (initial APR), locoregional failures occurred in the soft tissue of the pelvis or the anastomotic site in 69%, pelvic lymph nodes in 42%, and perineum in 25%. A more contemporary series of 269 patients studied by Hruby et al[235] confirmed that the majority of local failures occurred in the posterior central pelvis (47%) or at the anastomosis (21%), whereas anterior recurrences (11%) were mainly restricted to T4 tumors. Perineal recurrences occurred in 16% of patients who underwent APR.

At the University of Wurzburg, sites of failure were analyzed in 155 patients.[236] The incidence of failure sites was similar for APR compared to LAR: local plus nodal disease, 61% versus 66%; isolated lymph node disease, 4% versus 5%; internal iliac and presacral node disease, 47% versus 59%; and external iliac disease, 7% versus 2%. Local recurrence was most commonly seen in the presacral pelvis and in patients who underwent an LAR; the anastomosis was involved in 93%.

A study to evaluate local recurrences fully in three dimensions in patients treated in the Dutch TME trial, comparing preoperative short-course radiation plus TME with TME alone, showed that the most cranial recurrences were located a few centimeters caudal of the promontory, irrespective of whether radiation was delivered.[237]

Two-dimensional Irradiation Field Design

The whole-pelvic radiation field should adequately cover the primary tumor and tumor bed as well as the primary nodes at risk. The intent of the boost is to treat the primary tumor and tumor bed and not to include the nodes. The exact size is determined by the size and location of the primary tumor.

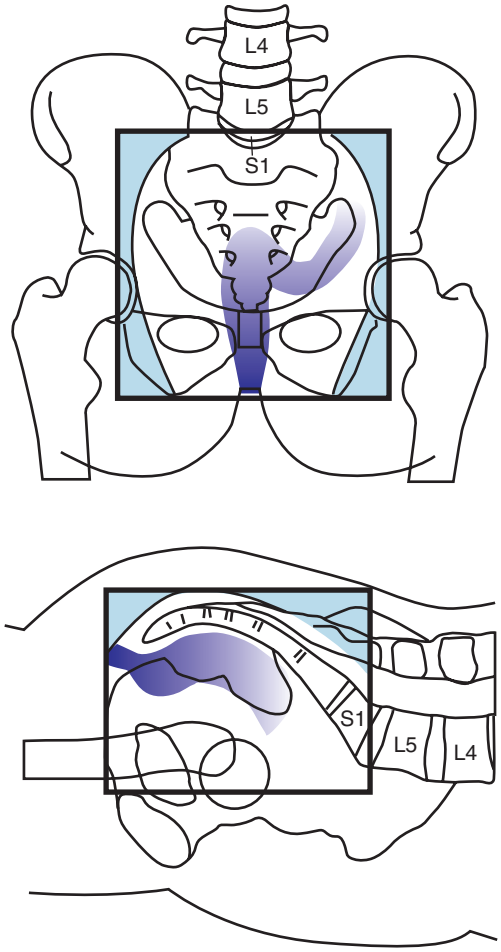


Figure 51-2 Treatment fields following a LAR for a T3N1M0 rectal cancer at 8 cm. Angle is from the anal verge. In this example, the distal border is at the bottom of the obturator foramen and the perineum is blocked. Because the tumor was a T3, the anterior field is at the posterior margin of the symphysis pubis (to treat only the internal iliac nodes).

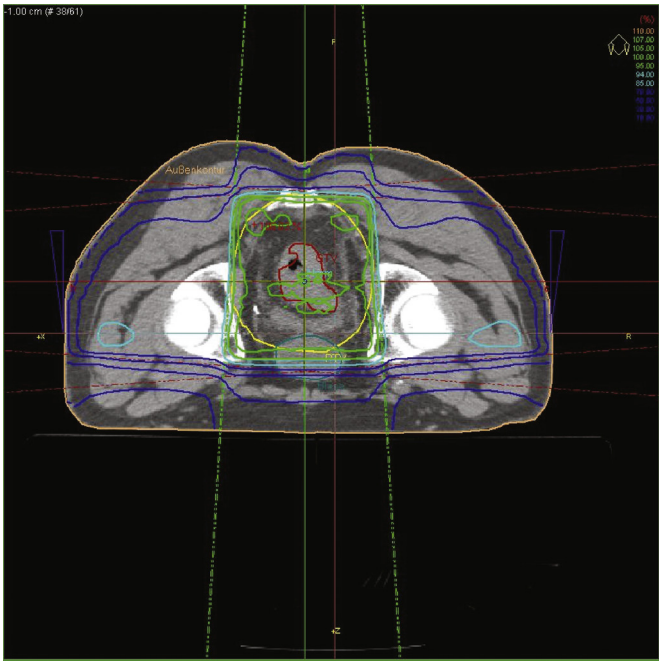
Whole pelvic and boost fields are usually treated with a three-field (posterior-anterior and laterals) or four-field technique. Field shaping by blocks is used to spare additional small intestine anteriorly and superiorly, the posterior muscle and soft tissue behind the sacrum, and the region inferior to the symphysis pubis. General guidelines for the design of two-dimensional (2D) fields as well as specific examples of field arrangements with conventional techniques for a variety of presentations are seen in Figures 51-2 to 51-4.

Three-dimensional Treatment Planning and Delineation Recommendations

Techniques using CT-based 3D treatment planning have replaced fluoroscopy-based simulators (eFigure 51-5). Using a 3D planning system, Koelbl et al[238] found that in patients receiving postoperative EBRT, the use of the prone position plus a belly board decreased the small bowel volume treated versus the supine position. Guidelines for the definition and delineation of the clinical target volumes (CTVs) are now available from a number of investigators.[239,240]

After the introduction of conformal radiotherapy, a number of investigators published recommendations for contouring.[239-242] The goal of guidelines is to standardize the

Interestingly, a CRM+ does not necessarily mean that the recurrence appears at the same level as the primary tumor. The most cranial recurrences were presacral, with the highest recurrence halfway to the level of S1, which was easily covered by the radiation field. Interestingly, the most cranial recurrences originated from tumors less than 5 cm from the anal verge. In addition, these cranial recurrences originated from patients with primary nodal involvement and a positive CRM. The most cranial recurrence for patients who are N0 and CRM- was found at the junction between S2 and S3 in the group that received radiation and at the level of S3 in the group that did not receive radiation. Recurrences in patients following a LAR were found mainly in the presacral and anastomotic regions, whereas in patients with an APR of Hartmann resection, recurrences were found in all regions.



eFigure 51-5 Three-dimensional treatment plan for rectal cancer.

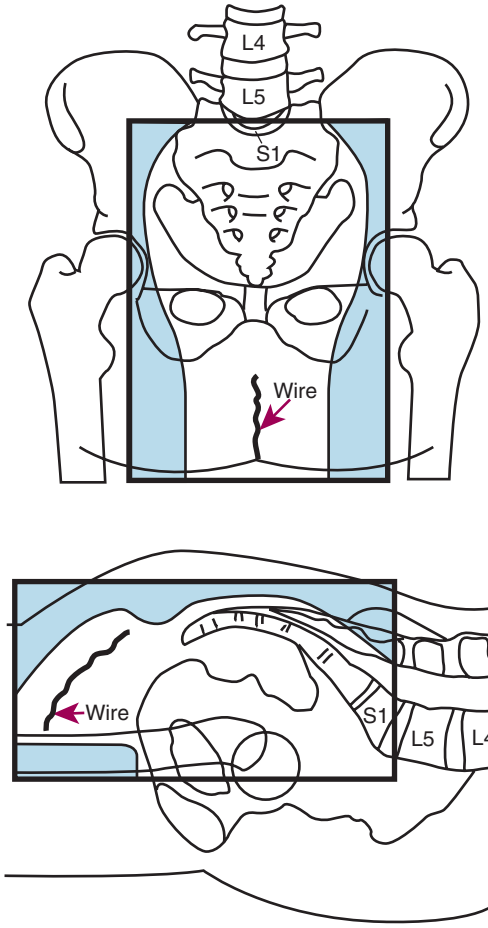


Figure 51-3 Treatment fields following an APR for a T3N1M0 rectal cancer 2 cm. Angle is from the anal verge. In this example the distal border is extended to include the perineal scar. Because the distal border is being extended only to include the scar, the remaining normal tissues can be blocked.

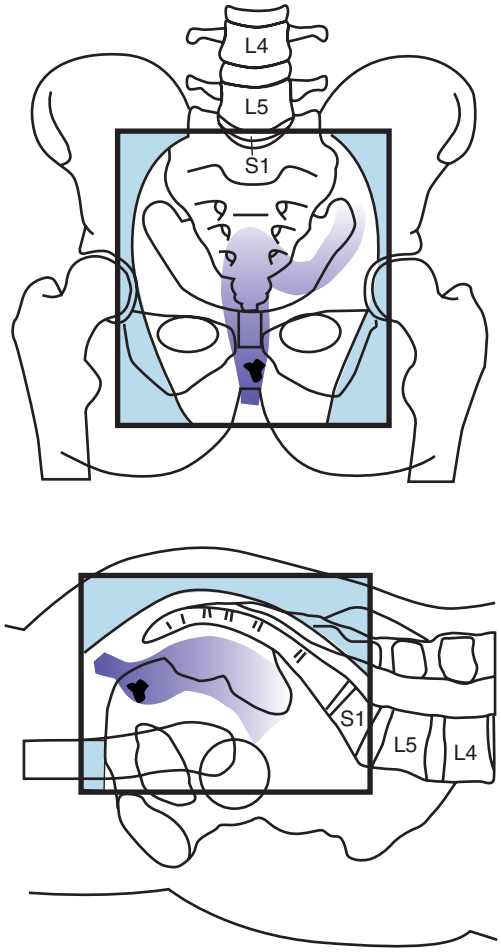


Figure 51-4 Treatment fields for preoperative radiation therapy for a low lying T3NXM0 (or following a LAR for a T3N1M0) rectal cancer. In this example the distal border is extended 3 cm beyond the primary tumor and the perineum is blocked. Because the tumor was a T3, the anterior field is at the posterior margin of the symphysis pubis (to treat only the internal iliac nodes).

target volume delineation; however, some uncertainties still remain and a uniform approach has not yet been reached.[242] The sites of recurrence and the involvement of lymph nodes in the lateral spaces of the pelvis reported by Japanese surgeons who systematically removed them have identified different pelvic subsites.[243-249] There are a number of subsites in common with mostly of these guidelines. First is the mesorectum. It is easy to identify in the mid to low pelvis in relation to the location of the pelvic organs (bladder, uterus/vagina, prostate). However, in the superior pelvis, the anterior part of the mesorectal subsite does not have an anatomical boundary. In the presacral subsite space is small and it is often not visible on CT scan. It is usually delineated together with the mesorectum as only one subsite. Lastly, the internal iliac node area is represented by a triangular lymphovascular fat area located between the pelvic wall and the mesorectum behind the external iliac vessels. In some guidelines the obturator nerve is used to split it into two subsites: the obturator subsite encompassed by the external iliac vessels and the obturator nerves and the internal iliac subsite, posterior to the obturator nerve. The external iliac subsite is the easiest to identify, because of the external iliac arteries and veins, which are well visualized on CT scan.

The inclusion of lateral nodes in the pelvic target volume for preoperative radiotherapy should be personalized according to tumor stage, tumor site, and lymph node location.[241] This is illustrated in Figure 51-5, *A-C* (eFigure 51-5, *A-B*). For cT3 tumors the primary tumor, the entire mesorectum, presacral space, and internal iliac nodes should be included. In addition, the obturator nodes should be added in case of low and medium rectum MRF+, clearly positive internal iliac nodes, and posterior cT4 disease. In cT4 tumors with anterior organ invasion, or for cT3 tumors with clear obturator node involvement, the addition of the external iliac nodes is recommended.[240,250] The lower edge of the CTV may be modified according to tumor extension and invasion based on the following criteria: (1) for tumors located at >1.5 cm above the anal-rectal ring, the lower border should be limited at the end of the mesorectum; (2) for tumors located <1.5 cm from the anal-rectal ring, the lower border should extend to encompass 1 cm of the anal canal; (3) for tumors extending through the anal canal, the entire anal canal and the sphincter complex should be included—although in published literature, adding a margin around the sphincter complex is not indicated, it is recommend to contour 5 mm to 10 mm of fat around it—and (4) when the rectal fossa is directly infiltrated by the tumor, both ischiorectal fossae should be included. Inguinal nodes generally are not targeted in rectal cancer. However, when most of the anal canal or the ischiorectal fossa is infiltrated, they should be part of the CTV.

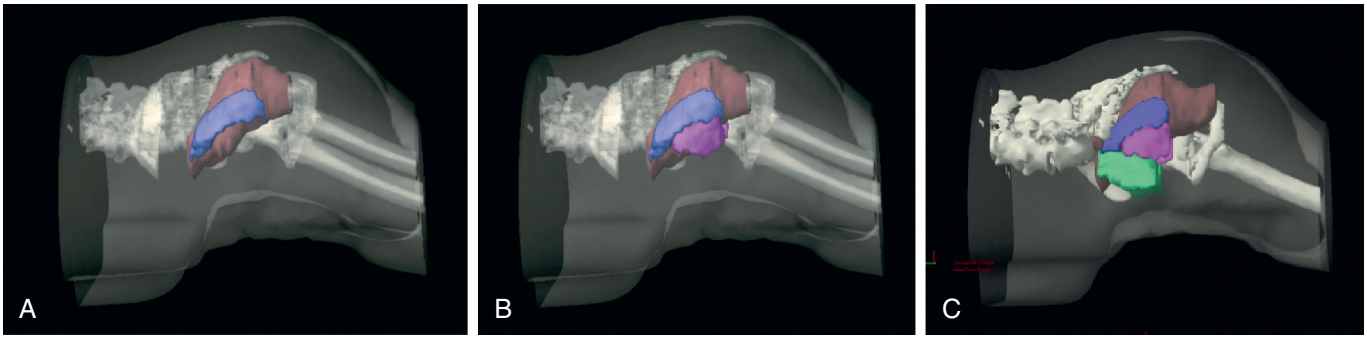


Figure 51-5 Contouring clinical target volumes in rectal cancer delineation (patient in prone position on an up-down table): **(A)** Mesorectum with internal iliac nodes; cT3 MRF (-). mid/high rectum. **(B)** Mesorectum with internal iliac and obturator nodes: cT3 low/mid rectum, MRF(+) or internal iliac positive node(s). **(C)** Mesorectum with internal iliac, obturator and external iliac nodes: cT4 for anterior infiltration or obturator positive node(s).

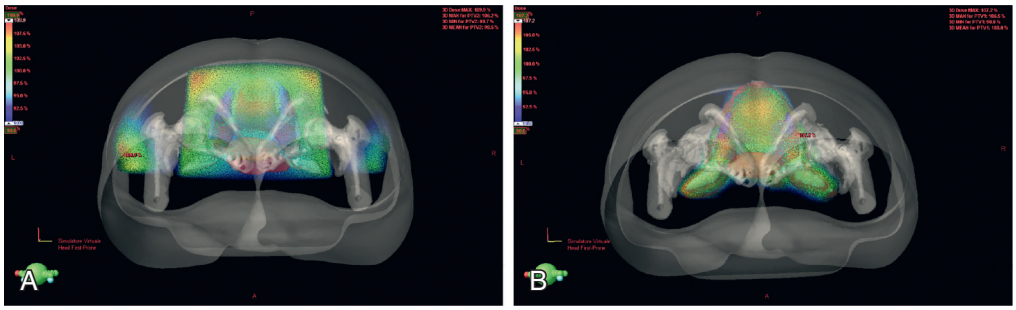


Figure 51-6 Comparison of three-dimensional **(A)** compared with intensity-modulated radiation therapy **(B)** plans in a patient with clinical target volume including mesorectum with internal iliac, obturator, and external iliac nodes (see Figure 51-5, *C* for corresponding clinical target volumes).

Introduction to IMRT and IGRT

With IMRT, the conformality and homogeneity of the dose to the planning target volume (PTV) are further improved.[251] In addition to having a limited number of beam angles (step and shoot), the IMRT can also be delivered in a continuous fashion during which the collimator, rotation speed and intensity can be modulated (intensity-modulated arc therapy [IMAT]).[252] The required PTV margin is based on geometrical uncertainties, which describe the differences between how the radiation was planned and the actual treatment situation. With the introduction of image-guided radiotherapy (IGRT), geometrical uncertainties can be measured and corrected during treatment, allowing for a reduction of the PTV margin. The acquired IGRT images also enable visualization of the target volume during treatment, for example, with cone beam CT scans, enabling better understanding of the treatment delivery.

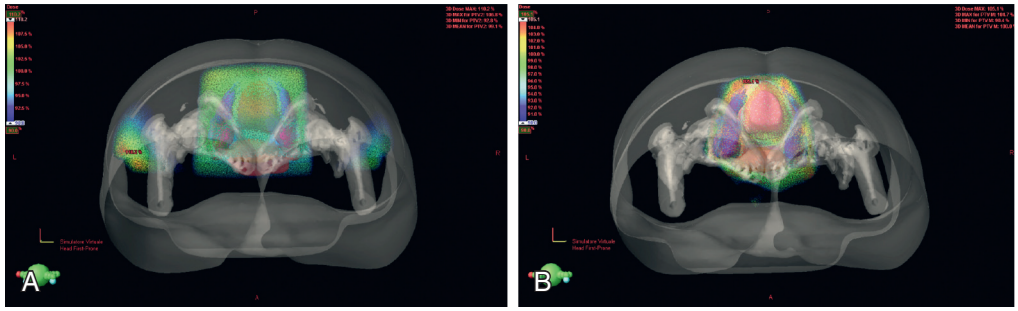
In current clinical practice, 3D conformal three- or four-field dose delivery techniques are used most often but IMRT can be of great value if external iliac lymph nodes needed to be included in the CTV. For each field, the shape of the beam is adapted to the shape of the target volume using a multileaf collimator, while using a uniform intensity for the field. With this type of treatment, it is impossible to fully conform to the "horseshoe" shape of the CTV, resulting in delivery of dose to the organs at risk anterior of the CTV, especially the small bowel (Figure 51-6, *A-B* and eFigure 51-6, *A-B*). With IMRT, it is possible to deliver more concave dose distributions, which also have a more uniform dose distribution. However, these often have less homogeneity with IMRT. Important parameters for prediction of acute and late bowel toxicity, such as the volume of small bowel receiving 15 Gy or more (V15) are significantly reduced using IMRT.[253-255]

The clinical utility of routine 3D and IMRT treatment planning techniques is being investigated.[256,257] An analysis of 3D treatment planning techniques at the MGH suggests that the volume of small bowel in the radiation field is decreased with protons as compared with photons.[258] IMRT treatment planning techniques can also decrease the volume of small bowel in the field when compared with 3D conformal techniques.[259] However, the clinical benefit of IMRT compared with 3D or conventional treatment delivery remains to be determined.[257]

Samuelian et al[259] compared 92 consecutive patients of which 61 were treated with conformal radiation and 31 were treated with IMRT. In the IMRT group, significantly fewer patients (32%) experienced acute grade-2 or higher GI toxicity compared with 62% in the conformal radiation group, primarily with differences in diarrhea (23% versus 48%) and enteritis (6% versus 30%). Although these findings were not based on randomized data, they do indicate that the theoretical dosimetric benefit of IMRT does translate into a clinical benefit.

IMRT has also shown to be an ideal technique to deliver a boost to the GTV, simultaneously delivering the standard dose to the CTV[260] without compromising the organ at risk dose. The boost dose can be used to increase downstaging, improve the ability to have an R0 resection and increase the percentage of pathologic complete responders.[261] However, IMRT cannot be safely implemented without careful attention to details unique to IMRT (e.g., monitoring target volume during treatment with cone beam CT scans).

Apart from the aforementioned CTV and delineation uncertainties, geometrical uncertainties as inter- and intrafraction set-up errors and inter- and intrafraction target volume variation need to be compensated for to ensure safe application of IMRT in rectal cancer. All these factors together will



eFigure 51-6 Comparison of three-dimesional **(A)** compared with intensity-modulated radiation therapy **(B)** plans in a patient with clinical target volume including mesorectum with internal iliac and obturator nodes.

finally result in a CTV-PTV margin that ensures sufficient coverage of the clinical target volume. The introduction of the cone beam CT has made a reliable estimate of these uncertainties possible.

Few data are available concerning the shape variation of the CTV in patients with rectal cancer. Nuyttens et al described the movement of the anterior border of the CTV, ranging from 0.4 cm SD at the level of the anus to 1.0 cm SD at 10 cm from the anus.[266] In a recent repeat CT study, Nijkamp et al investigated the shape variation of the entire CTV, both for short- and long-course radiation.

Correcting for shape variation errors using IGRT is more complex than adjusting for set-up errors. Online shape variation correction would involve on-site treatment planning or choosing the most appropriate plan out of a library of plans. Although these strategies seem promising, they have not been translated into general clinical practice.

Irradiation Fractionation, Modality, and Dose

At Vejle Hospital (Denmark), Appelt et al examined the radiation dose-response curves for various grades of tumor regression in 222 patients after preoperative chemoradiation.[268] Radiation therapy consisted of a combination of EBRT and brachytherapy. Response at the time of operation was evaluated from the histopathologic specimen and graded on a 5-point scale (TRG1-5). The radiation dose-response relationship for a specific grade of histopathologic tumor regression was defined in terms of the dose required for 50% response, D50, and the normalized dose-response gradient, γ50. A highly significant dose-response relationship was found ($p = 0.002$). Both tumor size and N category had a significant effect on the dose-response relationships. The study confirmed a significant dose-response relationship for tumor regression after preoperative chemoradiation for locally advanced rectal cancer for tumor dose levels in the range of 50.4 Gy to 70 Gy, which is higher than the dose range usually considered.

A meta-analysis concluded that biologically effective preoperative doses above 30 Gy resulted in a statistically significant reduction in locoregional recurrence rates.[42] With conventional fractionation, the doses necessary to treat microscopic disease with a high level of local control are in the range of 45 Gy to 50.4 Gy in 5 to 6 weeks.[269] A retrospective comparison of 143 patients treated in three Phase II trials of chemoradiation with 40 Gy, 46 Gy, and 50 Gy revealed a significant improvement in 2-year OS for those receiving 46 Gy and 50 Gy (94% and 92%, respectively) compared with 40 Gy (72%; $p = 0.03$).[270]

A meta-analysis of individual patients included in European randomized trials published after 2000, showed that a radiation dose of more than 50 Gy improved local control and survival.[271] The association between higher dose and improved local control but inferior sphincter function has been well recognized, although the impact of either factor such as concomitant chemotherapy continues to be debated.[272]

After the dose level of 45 Gy in 25 fractions over 5 weeks, a boost of 5.4 to 9 Gy may be delivered to the primary tumor or tumor bed may be delivered if the small bowel is excluded from the high-dose field. Higher preoperative doses up to 60 Gy are associated with increased pCR rates; however, they may also significantly increase acute and long-term morbidity rates. The RTOG R-0012 Phase II randomized trial compared twice-daily preoperative chemoradiation of up to 60 Gy (1.2 Gy to 45.6 Gy, with a boost of 9.6 Gy to 14.4 Gy) with conventional fractionation (1.8 Gy to 45 Gy, with a boost of 5.4 Gy to 9 Gy) plus 5-FU/irinotecan.[129] Both regimens resulted in a 28% pCR rate but were also associated with a more than 40% rate of grade-3 to grade-4 acute toxicity.

Hyperfractionated radiation has been examined in Phase I and II trials.[273] In general, the pCR rates may be improved but at the expense of increased acute toxicity.

In the postoperative setting, if there is incomplete resection (R1 or R2 resection), radiation doses of more than 60 Gy are required. EBRT is limited by normal tissue tolerance, and results for patients with residual disease who received postoperative EBRT alone are disappointing.[279] As previously discussed, IORT may help to overcome this problem by direct visualization and irradiation of the persistent tumor.

Methods to Reduce Acute and Chronic Toxicity

Complications of pelvic radiation therapy are a function of the volume of the radiation field, overall treatment time, fraction size, radiation energy, total dose, technique, and sequence of radiotherapy.[114]

Acute side effects such as diarrhea and increased bowel frequency (small bowel), acute proctitis (large bowel), and dysuria are common during treatment.[280] These conditions are usually transient and resolve within a few weeks following the completion of irradiation. The symptoms appear to be a function of the dose rate and fraction size rather than the total dose. Symptoms are usually more severe if concurrent chemotherapy is given during EBRT. The mechanism is primarily the depletion of actively dividing cells in what is otherwise a stable cell renewal system. In the small bowel, loss of the mucosal cells results in malabsorption of various substances, including fat, carbohydrate, protein, and bile salts. Examination during treatment frequently reveals an inflamed, edematous, and friable rectal mucosa. The bowel mucosa usually recovers completely in 1 to 3 months following irradiation. Management usually involves the use of antispasmodic or anticholinergic medications. Small bowel-related complications are proportional to the volume of small bowel in the radiation field.[254] In patients receiving combined irradiation and chemotherapy, the volume of small bowel in the radiation field limited the ability to escalate the dose of 5-FU.[114]

Delayed complications occur less frequently but are substantially more serious. The initial symptoms commonly occur 6 to 18 months following completion of irradiation. Complications may include persistent diarrhea and increased bowel frequency, proctitis and strictures at the anastomotic site, small bowel obstruction, perineal and scrotal tenderness, delayed perineal wound healing, urinary incontinence, and bladder atrophy and bleeding. Injury to the vascular and supporting stromal tissues is the presumed pathophysiology. Analysis of pooled patients from 1599 patients treated in Swedish rectal cancer trials revealed a 1.5% increase in in-field secondary tumors for those treated with irradiation compared with those not receiving irradiation.[281] However, irradiation still had a positive effect on local control rates.

The most common delayed severe complications result from small bowel damage and include small bowel enteritis, adhesions, and small bowel obstruction requiring surgery. The incidence of small bowel obstruction requiring surgery following postoperative pelvic irradiation for rectal cancer is 4% to 12% in historical series. In the MGH series, the incidence of small bowel obstruction with conventional postoperative radiation therapy was 6% as compared with 5% with surgery alone.[282] It was 2% in the preoperative chemoradiation arm of the German CAO/ARO/AIO-94 trial.[53]

Even with appropriate doses and techniques of irradiation, approximately 1% of patients will have significant long-term toxicity of pelvic organs. Active inflammatory bowel disease is a relative contraindication to pelvic irradiation, although there are some reports of such patients who have tolerated

Set-up errors are measured at the treatment machine using electronic portal imaging devices,[262] cone beam CT,[263] or tomotherapy CT.[264] Corrections for set-up errors can be applied directly before treatment, by applying a table shift. These online corrections use daily imaging and come with increased imaging dose and treatment time. Corrections can also be applied in an offline setting, using statistical models such as shrinking action level or no action level protocols.[265]

For 33 patients receiving short-course radiotherapy, daily repeat CT scans were acquired.[267] In 30 patients receiving preoperative chemoradiation, daily repeat CT scans were acquired, followed by weekly scans. On a total of 482 CT scans, the CTV, bladder and rectum were delineated and the CTV shape variation was determined. The heterogeneous shape variation as shown by Nuyttens et al was confirmed.[266] A negative time trend in rectal volume was present, which translated in a group mean error of approximately 0.5 cm at the upper anterior border of the mesorectum.

Current IGRT is effective in minimization of the set-up errors, but not as effective for the other uncertainties. Additional research in online adaptive replanning or plan selection needs to be performed to really utilize IGRT for rectal cancer.

Coucke et al[274] treated 250 assessable patients with cT3-4 or N+ disease with 41.6 Gy at 1.6 Gy twice daily and reported a 92% actuarial 5-year local control rate but a survival rate of only 60%. The rate of acute grade 3+ toxicity was 42% in the 5-FU plus twice-a-day radiation arm of RTOG R-0012 (1.2 Gy to 45.6 Gy, with a boost of 9.6 Gy to 14.4 Gy). Hyperfractionated and accelerated fractionated radiation, especially in combination with chemotherapy, remains investigational. Other investigational approaches such as neutrons,[275] carbon ions,[276] and hyperthermia[277,278] have been examined. None have shown a clear advantage compared with conventional pelvic EBRT.

EBRT.[283,284] Although historic data suggested that pelvic fractures are rare a more recent retrospective analysis of imaging from 492 patients revealed an incidence of 7.1% with a median follow-up of 3.5 years.[285] Independent risk factors included osteoporosis, female gender, and age older than 60. However, it should be emphasized that most fractures were asymptomatic and did not require any intervention. Testosterone levels are decreased when the testicles are near or in the radiation field.[286,287] Radiation, alone or in combination with surgery can have a negative impact on sexual function.[288,289] In the Dutch CKVO trial, patients experienced new or worsening sexual dysfunction following treatment (men, 76%, and women, 62%).[290] By multivariate analysis, independent factors included irradiation in men and the psychological presence of a stoma in both men and women. The authors concluded that despite the additional effect of irradiation, sexual dysfunction was mainly caused by surgery.

Randomized trials have investigated the use of sucralfate enemas to decrease acute radiation proctitis, olsalazine and mesalazine to decrease acute enteritis, and butyric acid to decrease chronic radiation proctitis.[291] All of these trials have been negative. The radioprotector WR-2721 did not reduce toxicity in early trials, but there is a suggestion of a benefit in a more recent study.[292,293] Rectally administered amifostine is well tolerated. However, its efficacy remains to be determined.[294] Other trials of amifostine have not shown clear benefits.[295]

TREATMENT ALGORITHMS, CONTROVERSIES, PROBLEMS, CHALLENGES, AND FUTURE POSSIBILITIES

Treatment Algorithms

The treatment of rectal cancer is multidisciplinary. It is important to develop treatment algorithms using a balanced approach with representation from all medical specialties, including radiation, medical, and surgical oncology as well as radiology, gastroenterology, and pathology. Treatment algorithms developed by representatives of a single modality or institution may be biased.

The National Comprehensive Cancer Network (NCCN) clinical practice guidelines for rectal cancer current guidelines can be found at www.nccn.org/professionals/physician_gls/f_guidelines.asp#site.

Recently, a European coalition of oncology societies plus allied disciplines (radiology, pathology, biology, epidemiology, and patient groups) proposed recommendations for the diagnosis and treatment of rectal cancer.[233] These are seen in Figure 51-7 (Figure 51-7, and eFigure 51-7, *A-H*). The goal of the European Registration of Cancer Care (EURECCA) is to reduce variance and improve cancer care in Europe through registry, feedback, and definition of core treatment strategies. It supports the development of a European audit structure to improve the quality of care for all patients with colon and rectal cancer.

Decision Supportive Tools

Clinical decision making for a single patient has become more complex because of the increased amount of data from genetics, proteomics, and diagnostic imaging. Human cognitive capacity is limited and this increase in decision-making complexity requires decision support systems and computational support on different levels and steps in the treatment process. Several applications of data sharing for cancer-related data have been initiated in the last decade: EUROCAT (www.eurocat.info); MISTIR (www.mistir.info); RODA (www.elekta.com); Oncospace (www.hopkinsmedicine.org); caBIG (cabig.nci.nih.gov); and CancerData (www.cancerdata.org).

A more public approach is to make prediction models available on the Internet; some of them also have applications also for rectal cancer. A prediction website that focuses more on decision support for radiotherapy was recently set up by MAASTRO Clinic (http://www.predictcancer.org). Also, the

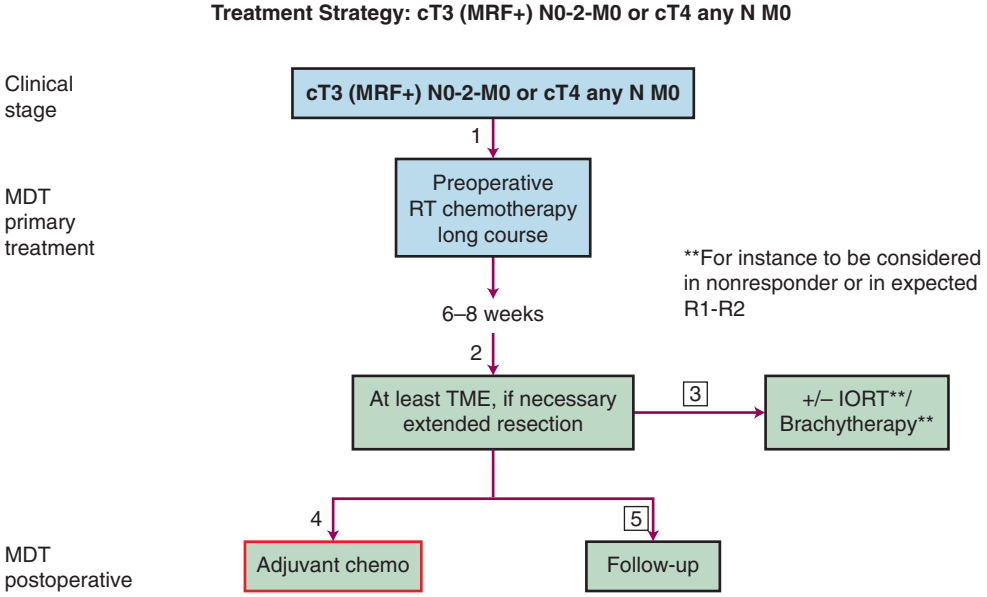
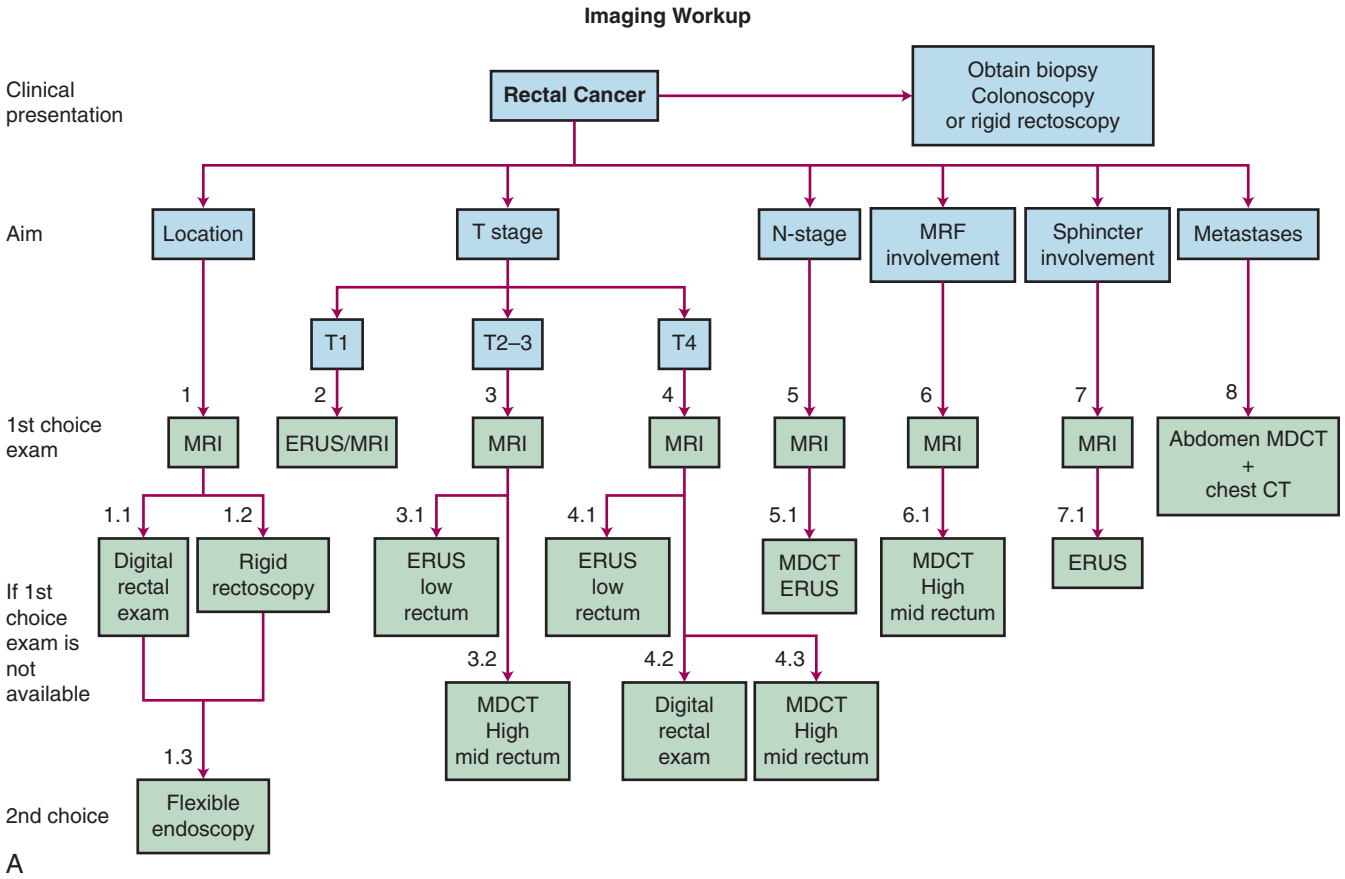
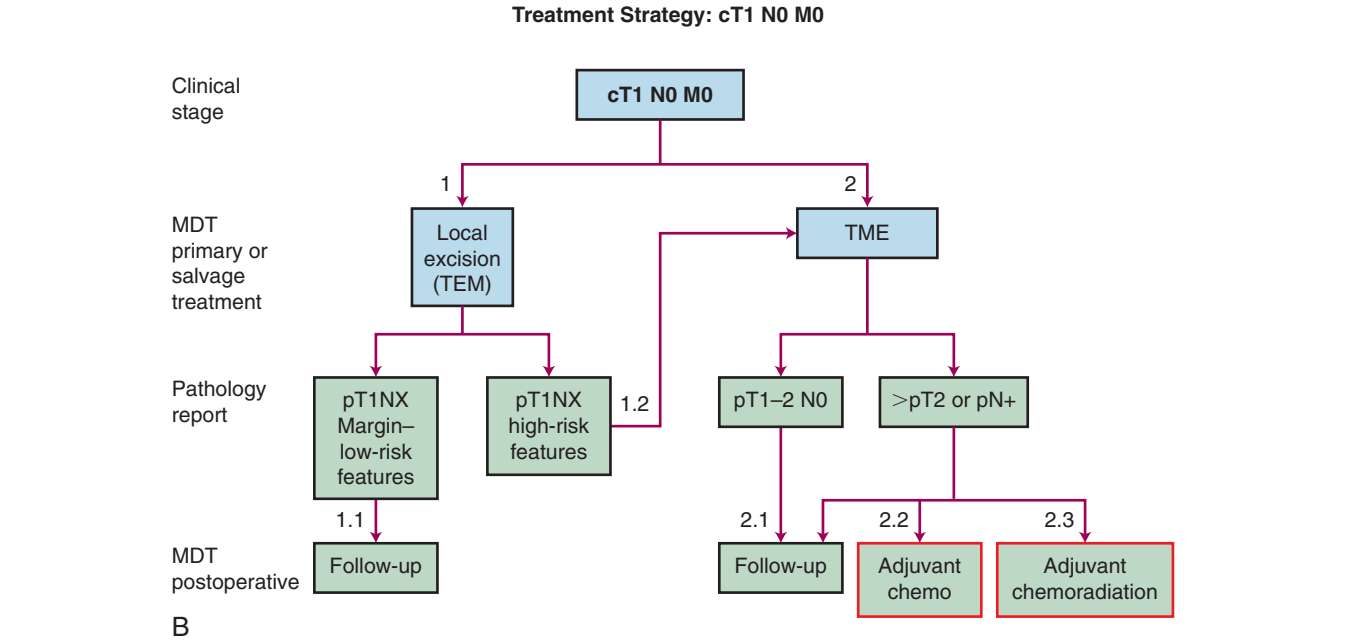


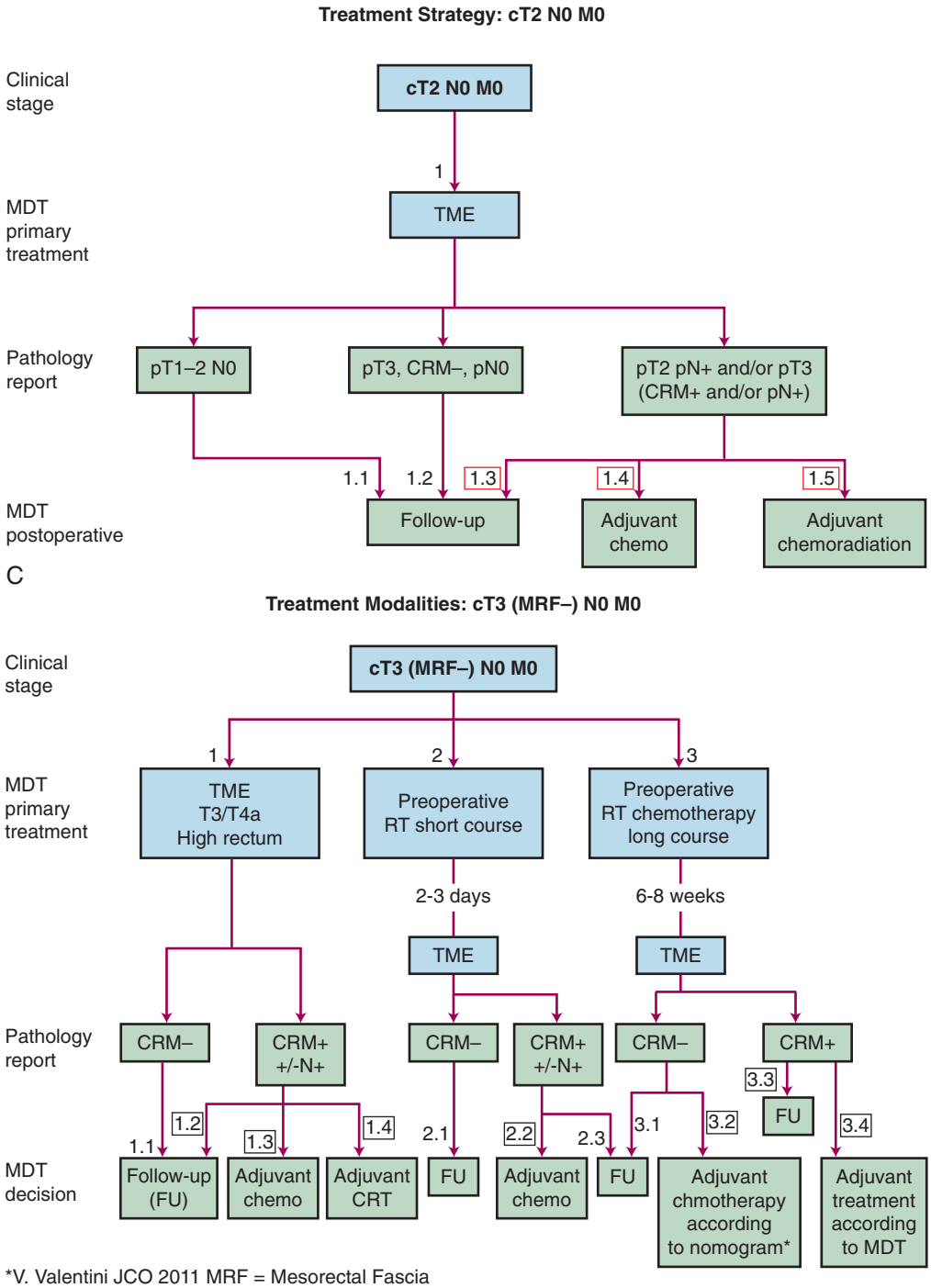
Figure 51-7 European treatment algorithm for rectal cancer based on multidisciplinary consensus conference. Treatment modalities: cT3 (MRF+) anyN M0 or cT4 any N. Moderate consensus was achieved for step 3 and 5, minimum consensus indicated with red borders was achieved for step 4 in the decision making. *IORT,* intraoperative radiation therapy; *MDT,* multidisciplinary team; *MRF,* mesorectal fascia; *TME,* total mesorectal excision.

Treatment algorithms can be based on evidence, consensus, or both. Although purely evidence-based algorithms are the most rigorous, there are a variety of clinical settings where prospective trials do not specifically address a treatment controversy. Therefore, multidisciplinary panels that use evidence from randomized trials as well as lower-level sources such as clinical experience reports offer a more practical approach. The National Comprehensive Cancer Network (NCCN) has published clinical practice guidelines for rectal cancer based on multidisciplinary panels that use evidence from randomized trials as well as lower-level sources such as clinical experience reports.



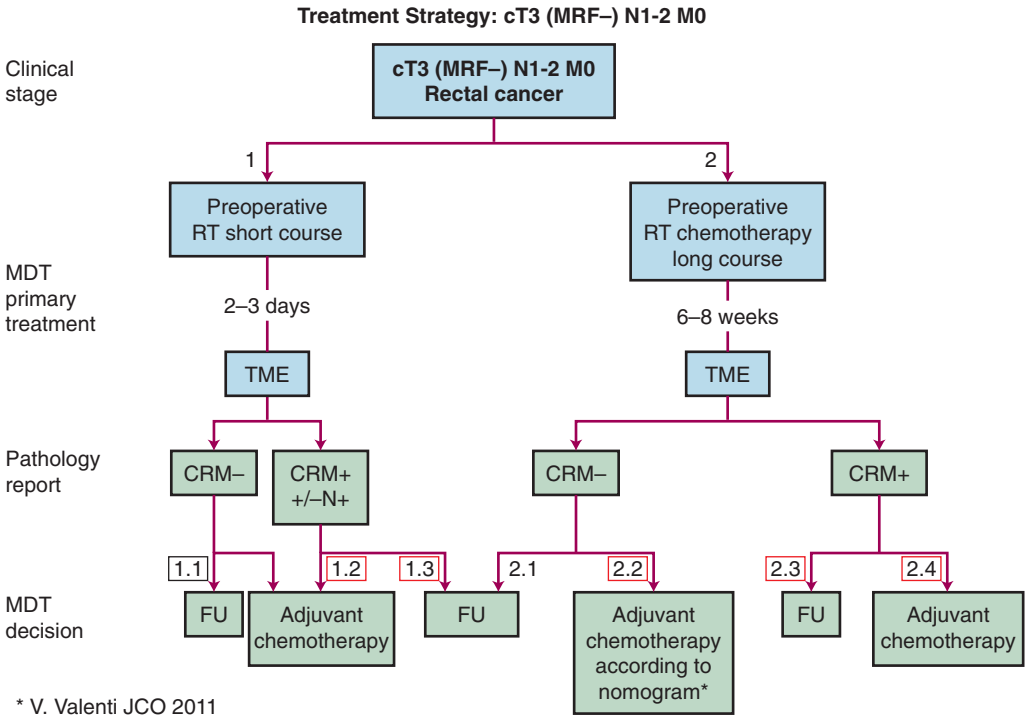


eFigure 51-7 A-H, **European workup and treatment algorithms for rectal cancer** based on multidisciplinary consensus conference. **A, Elective imaging workup algorithm for rectal cancer.** Almost all imaging decisions achieved large consensus with exception of the two lesser choice examination decisions. Moderate consensus was achieved on imaging step 1.1 and moderate consensus on step 3.1. **B, Treatment strategy rectal cancer: cT1N0M0.** Two decisions in the clinical T1 rectal treatment algorithm did not achieve large consensus, indicated with red border; being minimal consensus for step 2.2 to give adjuvant chemotherapy after primay TME or salvage TME after TEM; and no consensus was achieved on step 2.3 to decide on postoperative chemotherapy and radiation.

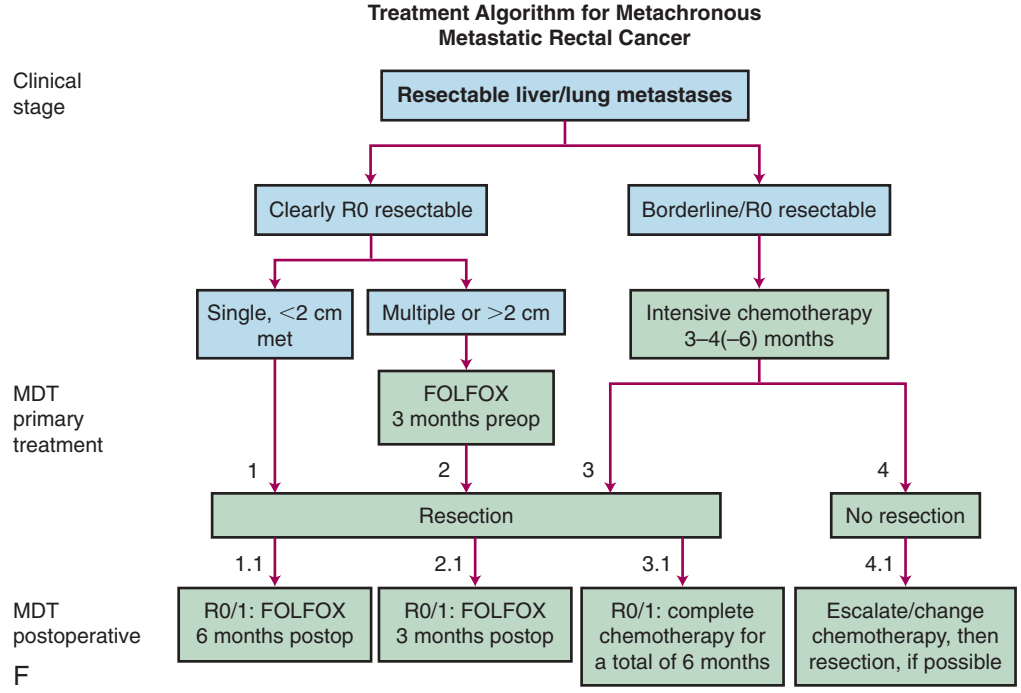


eFigure 51-7, cont'd **C, Treatment strategy: cT2N0M0 rectal cancer.** Three decisions in the clinical T2 treatment algorithm did not achieve large consensus, indicated with red lining; being minimum consensus for step 1.3 to go to follow up in case of positive nodal stage, positive CRM or pT3; and no consensus was achieved on step 1.4 and 1.5 to decide on postoperative chemotherapy and chemoradiation in these patients. **D, Treatment strategy: cT3 N0M0 rectal cancer.** Nine decisions in the algorithm did not achieve large consensus. Indicated with red lining is the "no consensus" for decision 1.3 and 3.2; and "minimum consensus" for 1.2, 1.4 and 3.4. With moderate consensus it was agreed to decide on steps 2, 3, 2.2, and 3.3.

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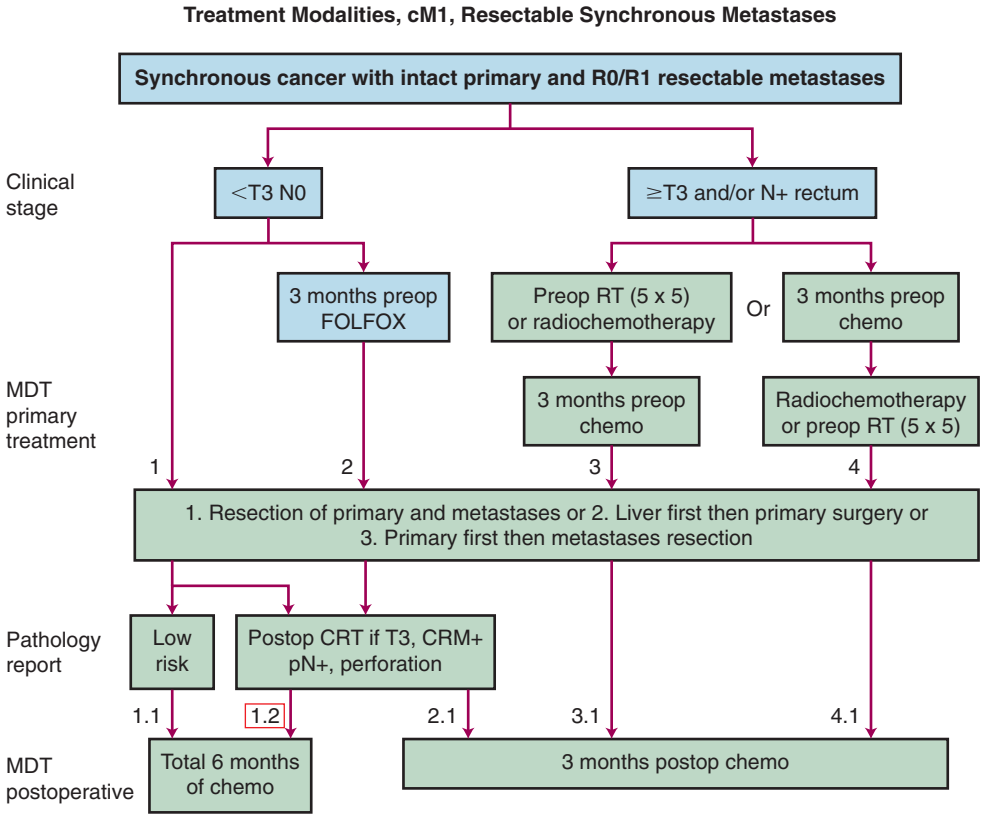


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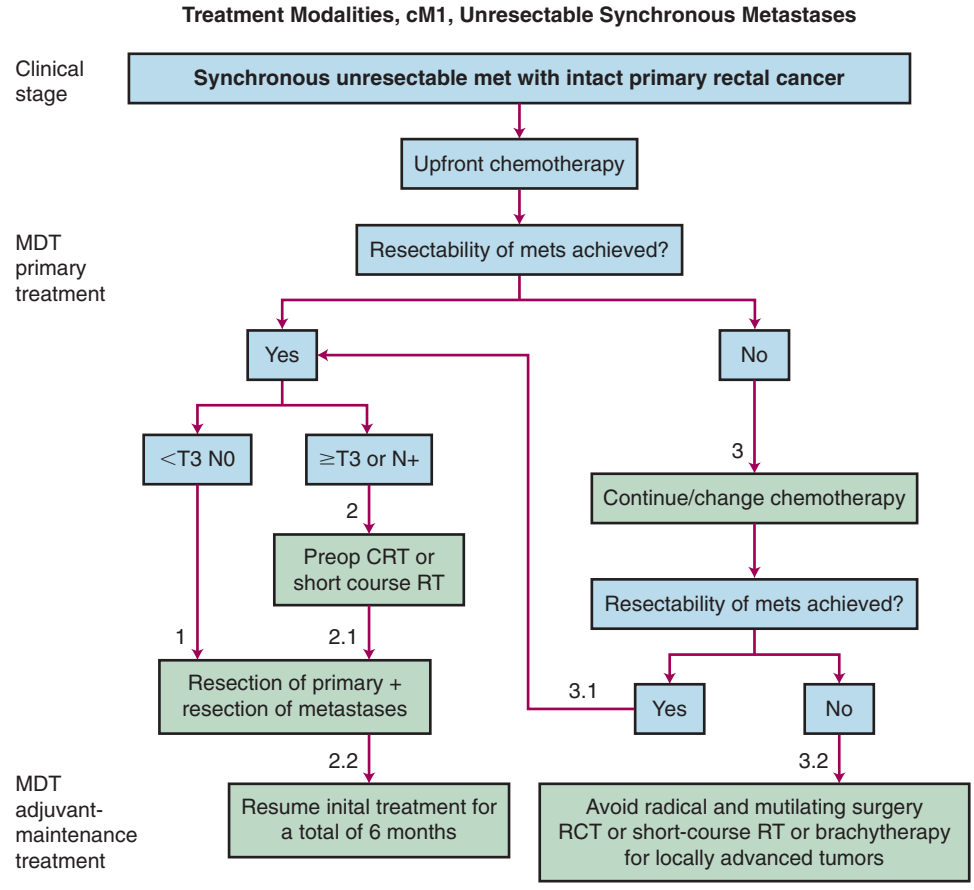


F

eFigure 51-7, cont'd **E, Treatment strategy: cT3 N+ M0 rectal cancer.** Six decisions in the algorithm did not achieve large consensus, indicated with red lining; being no consensus for decision 2.2 adjuvant chemotherapy according to the nomogram; minimum consensus for decision 1.2, 1.3, 2.3, and 2.4. There was moderate consensus for decision 1.1. The large variation in agreement illustrates that there is little evidence for adjuvant chemotherapy in rectal cancer. **F, Treatment modalities: metachronous metastatic rectal cancer.**



G



H

eFigure 51-7, cont'd **G, Treatment modalities, cM1, resectable synchronous metastases.** For patients with resectable synchronous colorectal metastases, with moderate consensus it was agreed on decision 4; decision 1.2 agreed with the mimimum consensus indicated by red borders. **H, Treatment modalities, cM+, unresectable synchronous metastases.** All decisions were agreed with large consensus. *CRM,* Circumferential resection margin; *CT,* computed tomography; *ERUS,* endorectal ultrasound; *FU,* follow-up; *MDCT,* multidetector computed tomography; *MDT,* multidisciplinary team; *MRF*, mesorectal fascia; *MRI,* magnetic resonance imaging; *postop,* postoperative; *preop,* preoperative; *RCT,* radio-chemo therapy; *RT,* radiation therapy; *TEM,* transanal endoscopic microsurgery; *TME,* total mesorectal excision.
Modified from Van de Velde CJ, et al, EURECCA colorectal: Multidisciplinary management: European consensus conference colon and rectum. Eur J Cancer 2013, [Epub ahead of print].

Finally, two caveats. All treatment guideline recommendations should be interpreted with caution. Radiation oncology, like other medical specialties, is both an art and a science. Therefore, guidelines should serve as a "guide" rather than a "cookbook." Lastly, the ideal management for patients with rectal cancer is in a clinical trial, and participation in these is encouraged.

Multidisciplinary Teams

Cancer management using the multidisciplinary team (MDT) approach has been implemented in cancer care systems throughout much of Europe, the United States, and Australia, and forms a core component of guidelines in all cancer care services. There is almost universal approval for this strategy, which indeed some consider crucial, despite the fact that there is little evidence for its effectiveness in improving outcomes.[296] This is particularly relevant in rectal cancer, in which preoperative radiotherapy and chemoradiation are often delivered according to clinical findings and staging (particularly in terms of the MRI) and many different surgical options are available with varying levels of radicality and implications for future quality of life in the patient. For example, an international survey of 173 colorectal surgeons (of whom 123 responded) showed that working in regular MDTs made the use of MRI for staging more likely and hence significantly influenced the use of neoadjuvant chemoradiation (RR = 5.67, $p = 0.03$) for a threatened circumferential margin on MRI.[297]

Memorial Sloan Kettering Cancer Center has prediction tools for different cancer types (http://www.mskcc.org/mskcc/html/5794.cfm).

Controversies and Future Directions

Significant progress has been made in the three conventional modalities used to treat rectal cancer: surgery, irradiation, and chemotherapy. Identification of radial microscopic lymphatic spread within the mesorectum has led to the use of TME. With this type of surgery, local recurrence rates have appeared to decrease. However, in patients with pN+ disease there is still a 21% local recurrence rate and adjuvant chemoradiation remains standard. The use of short-course radiation has increased as the techniques to integrate it with chemotherapy have improved. Technical advances in irradiation planning and delivery techniques as well as refinements in the sequencing of radiotherapy, chemotherapy, and surgery will likely lead to further improvements. Moreover, cytotoxic chemotherapeutic agents as well as novel targeted therapies, such as bevacizumab and cetuximab, which have improved results of patients treated in the adjuvant or metastatic setting, are currently being studied in chemoradiation programs. Clinicopathologic and molecular features as well as the development of more accurate preoperative imaging and staging methods will also play an important and integrative part in the multimodality treatment of rectal cancer. Lastly, more selective approaches to the use of surgery (watch-and-wait approach) as well as radiation (PROSPECT trial) are being investigated.

Recent data from Phase III trials are helping to clarify some of the issues about both the benefit and type of concurrent/maintenance chemotherapy in chemoradiation regimens. In NSABP RO4, chemoradiation regimens using PVI 5-FU and capecitabine had similar pCR rates and tolerance. In three separate Phase III trials, the addition of oxaliplatin to either PVI 5F-U or capecitabine did not improve pCR but added toxicity. Accordingly, the current standard is not to include oxaliplatin in preoperative chemoradiation regimens, pending longer-term outcomes of local control and survival. Additional text is found on the Expert Consult website with regard to the benefit of concurrent chemoradiation, sequencing with surgery, and the impact of type of concurrent chemotherapy on outcomes.

There are many controversies remaining, which lead to the following questions: Should patients receive short-course irradiation (i.e., 25 Gy in 5 fractions in 1 week) or standard-course preoperative chemoradiation (i.e., 45 Gy to 50.4 Gy in 25 to 28 fractions over 5 to 5.5 weeks)? Is postoperative adjuvant chemotherapy necessary for all patients? Should the type of surgery following chemoradiation be based on the response rate? Can we develop more accurate imaging techniques or molecular markers to identify patients with positive pelvic nodes to reduce the chance of overtreatment with preoperative therapy? Will more effective systemic agents improve the results of chemoradiation as well as modify the need for pelvic irradiation in some TN categories of disease? These questions and others remain active areas of clinical investigation.

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A full list of cited references is published online at www.expertconsult.com.

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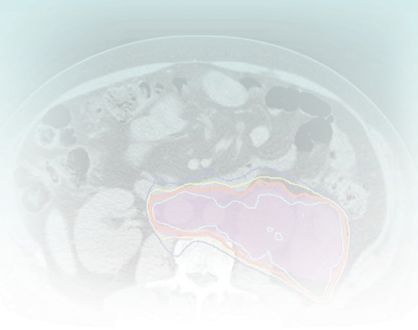
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CHAPTER

52 Anal Carcinoma



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INCIDENCE

In 2015, there were an estimated 7270 new cases and 1010 deaths attributable to anal squamous cell carcinoma,[1] representing approximately 2% of gastrointestinal malignancies in the United States.[2]

BIOLOGIC CHARACTERISTICS

Prognostic factors predictive for local control and survival are size, extent of the primary tumor, and regional lymph node involvement.

STAGING EVALUATION

Staging should generally include a complete history and physical examination, anoscopy with biopsy, complete blood cell count, liver function tests, serum creatinine levels, chest radiograph, and computed tomography (CT) scanning of the abdomen and pelvis. Positron emission tomography (PET) imaging should be considered.

Endoscopic ultrasound may be used to evaluate the depth of invasion.

PRIMARY THERAPY

Definitive radiotherapy and concomitant 5-fluorouracil (5-FU) and mitomycin-C are appropriate treatment for most patients with anal cancer. Five-year survival rates range from 40% to 80%.

Local control with anal preservation is achieved in more than 95% of patients with tumors less than 2 cm in size and in 60% to 75% of those with larger tumors.

ADJUVANT THERAPY

Adjuvant radiotherapy and concurrent chemotherapy are indicated for those rare patients who are managed initially with abdominoperineal resection but have primary tumor extension beyond the anal sphincter or metastases to regional lymph nodes.

Approximately 60% of patients with persistent or recurrent local disease after radiotherapy plus chemotherapy may still be cured with abdominoperineal resection.

LOCALLY ADVANCED DISEASE

Radiotherapy and concurrent chemotherapy are effective in patients with large primary cancers with or without invasion of adjacent organs. Two thirds of patients with locally advanced primary tumors maintain sphincter function.

Patients with positive nodes have a 5-year survival of 40% to 60%.

PALLIATION

Palliative chemotherapy with 5-FU and mitomycin C in patients with metastatic disease is associated with a 50% response rate.

Brain and osseous metastases may be effectively palliated with hypofractionated radiotherapy.

Carcinoma of the anal canal accounts for about 1.9% of all malignant tumors of the digestive system in patients in the United States.[1] Despite the rarity of anal cancer, it is a model for successful oncology research, both in the laboratory and in the clinic. Epidemiologic observations about the increased incidence of anal cancer in some populations, along with advances in molecular biology that have allowed the identification of human papillomavirus (HPV) DNA in most anal tumors, have provided the initial clues to the mechanism of anal carcinogenesis. Retrospective studies have provided important information about the natural history and patterns of spread of anal cancer, as well as hypotheses to test in prospective trials. Prospective randomized trials have been completed successfully and have led to the adoption of a combination of radiotherapy and chemotherapy as the standard of care for patients with anal cancer. Questions remain, however, about the most effective and least toxic regimens of radiotherapy and chemotherapy.

This chapter focuses on the biologic characteristics of anal cancer, the rationale for patient evaluation, treatment recommendations, and results of treatment. Radiotherapy techniques for patients with anal cancer will also be discussed.

ETIOLOGY AND EPIDEMIOLOGY

Anal cancer occurs much less frequently than other types of cancer of the digestive tract. In 2015, there were an estimated 7270 new cases and 1010 deaths attributable to anal cancer,[1] representing approximately 2% of gastrointestinal malignancies in the United States.[2] In the United States, the annual incidence is 0.47 per 100,000 white men and 0.69 per 100,000 white women.[3] The annual incidence among African Americans is higher: 0.57 per 100,000 men and 0.78 per 100,000 women.[3] Overall, 87% of patients diagnosed with anal cancer are non-Hispanic whites, 5% are African American, and 3% are Hispanic.[4] The median age at diagnosis is 62 years.[4] Thus, the typical American patient with anal cancer is a white woman in her seventh decade of life.

Epidemiologic studies from the United States, Europe, and Australia have reported an increased incidence of anal cancer in the past 30 to 40 years.[5-7] Within the United States, the incidence of anal cancer in the general population has increased over the last 30 years, from 10 to about 20 per million.[5] In a review of the Surveillance, Epidemiology, and End Results (SEER) database from 1973 to 2000, the incidence of anal

cancer in men and women was found to have risen from 1.06 and 1.39 per 100,000 persons to 2.04 and 2.06 per 100,000 persons.[5] In particular, the incidence of squamous cell anal carcinoma has increased dramatically after 1997 for men and women, consistent with the impact HIV has had on the acquisition and persistence of HPV.[8] In England, between 1990 and 2010, there has been a 69% increase in squamous cell anal carcinoma from 0.43 per 100,000 population in 1990–1994 to 0.73 in 2006 to 2010, with effect more marked in women than men.[9] Similarly, the number of new cases of anal cancer in Denmark has doubled in men and tripled in women.[10]

The incidence of anal cancer is higher in urban than in rural populations, and increases in the incidence of anal cancer have been greater in urban than in rural populations.[3,10] In the United States, the increased incidence of anal cancer has been predominantly limited to densely populated regions. Young men account for a substantial proportion of this increase.[8] In Denmark, the median age at diagnosis in men has decreased from 68 to 63 years, whereas in women, it has remained constant at 66 to 67 years.[10]

Association with HIV Infection

At least part of the increased incidence in young men can be explained by the observation that men who have sex with men (MSM) are at increased risk for the development of both anal intraepithelial neoplasia (AIN) and anal cancer, particularly among patients with HIV.[11-15] The population at highest risk for anal cancer appears to be MSM (odds ratio [OR], 17.3),[16] and in particular in the subset of these men who are HIV-positive. A meta-analysis of 53 studies found that prevalence of anal cancer (45.9 versus 5.1 per 100,000 men) was significantly higher among MSM who were HIV-positive as compared to HIV-negative.[11]

With the introduction of highly active antiretroviral therapy (HAART), although the incidence of some AIDS-associated cancers, including Kaposi's sarcoma and non-Hodgkin's lymphoma, have decreased in incidence, the incidence of anal cancer has not declined.[21-24] Two large cohort studies from England and France recently demonstrated no significant difference in the standardized incidence ratio (SIR) for development of invasive anal cancer with the introduction of HAART.[23,24]

The incidence of anal cancer is markedly increased in both men and women who have AIDS. The relative risk (RR) estimated from a linkage analysis of cancer registries and AIDS registries is 63, and it is higher for homosexual men (RR, 84) than for heterosexual men (RR, 38). The increased risk is also apparent during the 5-year period before an AIDS diagnosis. The absolute risk of anal cancer in patients with AIDS is 1 per 1000.[25]

Risk Factors

The pathogenesis of anal cancer is multifactorial. A diagnosis of anal cancer represents the result of an interplay of multiple environmental and host factors. Patients with epidermoid anal cancer are more likely than control patients to have had a previous diagnosis of malignant disease, including cancers of the vulva, vagina, or cervix and lymphoma or leukemia. Patients with anal cancer who are diagnosed before age 60 years are at higher risk of subsequent development of malignant diseases of the respiratory system, bladder, vulva, vagina, and breast, but they are not at increased risk for subsequent development of colon or rectal cancers.[26] Overexpression of the c-*myc* oncogene has been implicated in the pathogenesis of both anal squamous cell neoplasia and breast cancer.[27,28] This finding, along with an observed pattern of second malignant diseases and prior malignant diseases in patients with anal cancer, suggests a multifactorial pathogenesis and common oncogenetic risk factors. These factors may include sexually transmitted viruses, environmental carcinogens such as cigarette smoke, immunosuppression, and genetic susceptibility.[26]

Anal cancer and cancers of the female genital tract share a common pathogenesis.[29] In the embryo, the anal and cervical canals are both derived from closely related anlagen.[30] Women patients with anal cancer are more likely than women with colon or stomach cancer to have had a prior diagnosis of cervical intraepithelial neoplasia.[29] An association between anal cancer and the number of lifetime sexual partners has been reported in women.[31] Case-control studies have also found an association between anal cancer and some sexually transmitted diseases.[17,31-33] This association, along with the increased incidence in young homosexual men, strongly suggests an etiologic factor for anal cancer associated with increased sexual activity.[3]

Among sexually transmittable infectious agents, HPV has been the most thoroughly studied potential causative agent. Although there are more than 60 types of HPV, those most commonly associated with benign genital condylomata acuminata are HPVs 6 and 11, whereas HPVs 16, 18, 31, 33, and 35 are associated with malignancy or high-grade dysplasia.[34] Several investigators have also reported an association between genital warts and anal cancer in men and women.[32-36] The development of anal warts in both sexes has been linked with the practice of anal intercourse.[32]

The likelihood of finding HPV DNA in specimens of anal cancer varies according to patient demographics and laboratory technique. Patients with HPV-associated anal cancer are 10 years younger on average than patients with reportedly HPV-negative cancers.[37] In addition, HPV-associated anal cancer has been reported more frequently in Europe and South America than in South Africa and India.[38] When in situ hybridization techniques are used to analyze biopsy specimens of anal cancer, the rate of HPV DNA detection ranges from 17% to 73%.[34,37]

Exposure to HPV may be a risk factor even for patients in whom HPV DNA is not detected in the carcinoma specimen. Serum IgA antibodies to a peptide antigen from the E2 region of HPV 16 have been found in 89% of patients with anal cancer compared with only 24% of controls.[37] In another study, antibodies to HPV 16 capsids were elevated in 55% of patients with anal cancer compared with 3% of controls. Antibodies to HPV-capsid antigen were detected in an equal number of cancer specimens from patients whose HPV DNA was negative or positive (as assessed by in situ hybridization), which suggests that some patients presumed to be HPV-negative had been exposed to HPV.[40]

HPV infection and anal cytologic abnormalities are common in patients with HIV infection.[12] Patients who are HIV-positive with HPV DNA found in anal biopsy specimens seem to have a high rate of cytologic abnormalities. In one study of 12 patients who are positive with HIV without AIDS, 11 patients (92%) with normal cytologic findings but with HPV DNA found in anal mucosa later had cytologic abnormalities at 17-month follow-up.[41]

Although the true influence of HPV in anal carcinogenesis is uncertain, some laboratory findings point to the involvement of the HPV E6 and E7 proteins. These findings include the observation that the *E6* and *E7* oncogenes are consistently expressed in tumor cells but that normal E6 and E7 regulatory mechanisms are absent.[43] In addition, the E7 protein of HPV 16, in cooperation with the E6 protein, is able to transform mammalian cells in vitro while blocking *E6* and *E7* gene function, which results in reversal of the malignant

HPV DNA is more likely to be detected with polymerase chain reaction analysis. Studies comparing both techniques have found that polymerase chain reaction techniques detect HPV DNA in 78% to 85% of patients, whereas in situ hybridization techniques find HPV DNA in only 17% to 50% of the same patients.[34,39]

Additionally, recently published data of 34,189 individuals infected with HIV and 114,260 individuals not infected with HIV in the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD) from 1996 to 2007, the unadjusted anal cancer incidence rates were 131 for MSM who were infected with HIV, 46 for other men who were infected with HIV, and 2 for men who were uninfected with HIV per 100,000 person-years.[15] Although in most areas of the world, anal cancer is more common in women than in men of all age groups,[17,18] in areas with a relatively high proportion of MSM, however, anal cancer may be more common in men. For example, in San Francisco, the incidence of anal cancer in white men more than doubled from 0.53 per 100,000 in 1975 to 1.2 per 100,000 in 1989,[3] and in Los Angeles, anal cancer has become more common in men than in women younger than age 35.[19] A study of Danish MSM living in registered "marriage-like partnerships" identified an incidence of cancer double what was expected, which could be accounted for by HIV-related cancers, including Kaposi's sarcoma, non-Hodgkin's lymphoma, and anal cancer. The relative risk ([RR] of anal cancer in this population was 31, and anal cancer appeared to be associated with a positive HIV status.[20]

Many patients with AIDS most likely die of opportunistic infections before anal cancer is manifested. Although the impact of effective antiretroviral therapy on the incidence of anal cancer is not yet clear,[42] further increases in the incidence of anal cancer may be observed in patients with AIDS as survival time is prolonged.[41]

phenotype.[43,44] Interactions of HPV oncoproteins with known tumor suppressor gene products have been reported. The E6 protein of HPV 16 and HPV 18 forms stable complexes with the p53 protein product of the *P53* tumor suppressor gene.[45-47] The cellular p53-E6 protein complex results in a lack of appropriate G1 arrest and subsequent genomic instability. The E7 protein also forms complexes with the retinoblastoma gene product and with p107, p130, p33, cdk2, and cyclin A. E7 also activates the cyclin-A promoter and overrides two inhibitory functions that restrict the expression of cyclin A and cyclin E.[44]

Some evidence suggests that infectious agents other than HPV may contribute to anal carcinogenesis. Associations have been found between the development of anal cancer and a history of syphilis or gonorrhea in men[33,48] and between anal cancer and *Chlamydia* and herpes simplex virus type 2 in both sexes.[31,32] In a study of patients in and around San Francisco, herpes simplex virus DNA was detected in 3 of 15 patients with invasive anal cancer and in 3 of 4 patients with high-grade intraepithelial neoplasia.[39] No Epstein-Barr virus or cytomegalovirus DNA was found in the tumor specimens of the 15 patients with anal cancer. Further studies are needed to determine whether these and other sexually transmitted agents are involved in anal oncogenesis or are merely surrogate markers for probable HPV infection.

Chronic immunosuppression is associated with an increased risk for anal malignant disease. Renal transplant recipients have an increased incidence (as high as 100-fold) of carcinoma of the vulva or anus.[49,50] These cancers occur at an earlier age than they do in the general population.[49] Renal transplant patients also have an increased incidence of cutaneous neoplasia and viral warts. Those with a high susceptibility to cutaneous malignant disease (four or more skin cancers) are more likely to have HPV DNA-associated skin cancer and are more likely to have an anogenital malignant tumor.[51] The increased incidence of anal malignant disease in patients who are HIV-positive is most likely caused in part by chronic immunosuppression.

A number of authors have reported an association between anal cancer and cigarette smoking.[31,32,35,52] When compared with a control group of patients with colon cancer, both men and women smokers were found to have an increased risk of anal cancer.[32]

Although in the past, chronic inflammation or irritation from benign anal conditions (e.g., hemorrhoids, anal fissure, fistula, or inflammatory bowel disease) had been associated with anal cancer,[18,53-55] recently published case controlled series have failed to demonstrate an association between benign anal conditions and anal cancer.[35,56] A Danish population-based study found that patients with anal fissure, fistula, perianal abscess, or hemorrhoids were at increased risk for anal cancer; however, the RR for invasive anal cancer was highest in the year immediately after a diagnosis of benign anal pathology, and it declined from a high of 12 the first year to 1.8 after 5 or more years. Thus, despite a temporal association between the diagnosis of benign anal lesions and the diagnosis of anal cancer, this suggests that a so-called benign anal condition is often a symptom or misdiagnosis rather than a cause of anal cancer.[56]

PREVENTION AND EARLY DETECTION

Prevention of anal cancer should include educational efforts about the causal link of sexually transmitted HPV infection with malignant diseases of the anogenital tract. Recommendations of the 1996 National Institutes of Health Consensus Panel on cervical cancer prevention are also applicable to anal cancer and include encouragement to delay onset of sexual intercourse.[58] Barrier methods, such as condoms, do not prevent HPV transmission.[59] The panel also recommended development of an effective vaccine to prevent transmission of HPV, and a subsequent Phase III clinical trial provided encouraging results in this regard.[60-62]

In a randomized trial of 4065 healthy males 16 to 26 years of age, a quadrivalent vaccine was effective in preventing infection with HPV types 6, 11, 16, and 18 and prevented the development of external genital lesions. In the per-protocol population, efficacy against lesions related to HPV types 6, 11, 16, or 18 was 90.4%.[63] A planned substudy of that trial analyzed the impact of HPV vaccine on the development of anal squamous intraepithelial lesion (SIL) in 602 MSM who had a history of five or fewer lifetime sexual partners. Participants with a history or evidence of anal lesions were excluded, as were participants who were HIV positive at enrollment on the protocol. The primary endpoint of the trial was the development of anal SIL associated with HPV types 6, 11, 16, or 18. In the per-protocol population, which included 402 of the 598 men (67%) who received all three doses of vaccine, the incidence of anal SIL associated with HPV 6, 11, 16, or 18 was decreased by 78 percent in those receiving vaccine compared with placebo (1.3 versus 5.8 events per 100 person years at risk). Additionally, there was a 75% decrease in the incidence of high-grade squamous intraepithelial lesion (HSIL) with vaccine (0.8 versus 3.1 events per 100 person-years at risk).[64] As a result of these promising results, in October 2011, the Advisory Committee on Immunization Practices (ACIP) recommended the routine use of quadrivalent vaccine in males aged 11 or 12 years.[65]

Additional preventive efforts should be focused on the treatment of HPV infection, including the development of antiviral agents, targeting of E6 and E7 to block transforming activities, and vaccines to prevent progression of HPV infection.[51,58] Education is also required about the causal role of cigarette smoking in anal and other cancers.

Because of the rarity of anal cancer, efforts at early detection through widespread screening are not feasible. However, screening may be feasible in certain high-risk subsets. Anal intraepithelial neoplasia is a common finding in people who are infected with HPV.[12,41] Analogous to the situation with cervical cancer, where cervical SILs may progress to cervical carcinoma, HSIL may be a precursor to invasive anal cancer.[66-68] Anal cytologic smears have been used to diagnose HSIL in high-risk patients. Because the specificity of anal cytology for the detection of HSIL is low, anoscopy with biopsy is required to differentiate anal condylomata acuminata from HSIL.[66] However, the colposcopic criteria to distinguish low-grade squamous intraepithelial lesions (LSIL) from cervical HSIL have been used to distinguish LSIL from HSIL of the anus in homosexual and bisexual men.[69] This information may allow for a targeted biopsy of suspected HSIL, resulting in increased sensitivity for detection. One study of anal cytology in homosexual and bisexual men reported the sensitivity and specificity for detection of HSIL to be 69% and 59%, respectively, in men who are HIV-positive and 47% and 92%, respectively, in men who are HIV-negative.[68]

BIOLOGIC CHARACTERISTICS

Unlike most gastrointestinal tract malignant diseases, anal cancer is predominantly a locoregional disease, and distant metastasis is relatively rare. Most relapses after curative therapy are located in the pelvis, perineum, or inguinal regions.[70] Only 5% to 10% of patients will have cancer that has spread beyond the pelvis at diagnosis,[53,59,71] and 10% to 30% of patients will have disease relapse at distant sites after curative local therapy.[60,70,72,73] Although chemotherapy is considered a

In a population-based case-control study of patients with anogenital cancers in the Pacific Northwest, 60% of patients with newly diagnosed anal cancer were current smokers compared with 25% of the controls. The risk of anal cancer was positively correlated with both the number of cigarettes smoked per day and the number of years the patient had been a smoker.[52]

Supporting evidence for this view is found in a study of patients treated for benign anal conditions at U.S. Veterans Affairs hospitals. The elevated RR for anal cancer in these patients was most pronounced in the first year after the benign pathologic condition was diagnosed, and it decreased rapidly thereafter until there was no increased risk of anal cancer between year 5 and year 22.[57]

component of standard therapy for anal cancer, its addition has not decreased the number of patients with distant metastases.[71,74,75] As the number of metastatically involved regional nodes increases, so does the risk of distant metastasis.[76] The most common site of distant metastasis is the liver, followed, in variable order, by the lungs, extrapelvic lymph nodes, skin, or bones.[71,75,77-80]

Characteristics of anal cancer that have consistently been correlated with local control and survival are the size and extent of the primary tumor and the status of the inguinal and pelvic lymph nodes.[81-83] The 5-year survival for patients with tumors 2 cm or less in diameter that are treated surgically is about 80% but declines to 55% to 65% when the tumor is 2 cm to 5 cm or to 40% to 55% when the tumor is more than 5 cm.[76,84] The depth of invasion and the size and extent of the primary tumor are prognostic for response to treatment, local control, and survival when patients are treated nonsurgrically with radiotherapy and chemotherapy.[70,75,80,85-88]

The survival for patients with regional lymph node metastases who are treated primarily with surgical procedures with or without adjuvant therapy is about half that observed in similar patients without nodal metastases.[84,89] Similarly, 5-year survival after radiotherapy alone in patients with inguinal lymph node metastases range from 0% to 36% compared with 5-year survival of more than 50% in patients without lymph node involvement.[89-91]

There is relatively little information in the medical literature about the prognostic significance of regional nodal metastases in patients who receive combined radiotherapy and chemotherapy. In a retrospective, recursive, partitioning analysis of patients treated at Princess Margaret Hospital (PMH), patients who are node-positive at 5-year follow-up were found to have a trend toward lower cause-specific survival (CSS) (57% versus 81%; $p = 0.07$).[74] In the European Organization for Research and Treatment of Cancer (EORTC) randomized trial of radiotherapy alone versus concurrent chemoradiation, regional nodal metastases were associated with significantly worse local control ($p = 0.004$) and survival ($p < 0.001$).[82] However, in node-positive patients, the number of involved nodes (≥1), their size (<2 cm or >2 cm), and the extent of involvement (N1, N2, or N3 category) added no further prognostic information.[82] Similarly, in a secondary analysis evaluating the impact of TN category on outcomes for RTOG 98-11, the best outcomes were found among patients with T2-3N0 disease, and the worse outcomes were in patients with T4N0, T3N+, and T4N+ disease. Outcomes for T2N+ patients were intermediate between T3N0 and T4N0.[73]

Patient-related variables that have been evaluated as potential prognostic factors for local control and survival in patients with anal cancer include age, gender, race, performance status, hemoglobin levels, and white blood cell counts. Age probably does not have independent prognostic significance for any endpoint. A retrospective Canadian study found that older patients were treated with less aggressive chemotherapy and were less likely to be offered salvage surgery for recurrence; therefore patients older than 65 years of age were found to be at higher risk for death from anal cancer.[92] An Australian study reported that although requirement for treatment break was higher in elderly patients, chemoradiation was safe and tolerable in elderly patients and provides equivalent disease control rates compared to the younger age group.[93] Conflicting data exist about the impact of gender on prognosis. Several studies have reported no difference in outcome by gender in patients treated with radiotherapy or combined radiotherapy and surgery.[74,91,92,94] However, a trend toward higher survival in women has been reported in some surgical series,[76,84] and in the EORTC randomized trial, female sex was associated with better survival ($p = 0.12$) and local control ($p = 0.05$).[82] Similarly, in recently published analyses of the Radiation Therapy Oncology Group (RTOG) 98-11 and United Kingdom Coordinating Committee on Cancer Research (UKCCCR) study respectively, male sex was significantly associated with poorer locoregional control,[83] disease-free survival (DFS),[81] disease-specific survival,[83] and overall survival (OS).[81,83] Lower survival has been reported in patients with a lower performance status, in nonwhite patients, and patients with higher white blood cell count with anal cancer who received combined-modality therapy.[83,95] A lower hemoglobin level has also been suggested to have an adverse effect on disease-specific survival.[83]

Several histopathologic variables have been evaluated as potential prognostic factors in patients with anal cancer. The histologic subtype (squamous cell cancer versus cloacogenic subtype), tumor cell morphology, extent of differentiation or keratinization, cell size, architecture, and pleomorphism are of no prognostic significance.[74,91,92,94,96] The extent of differentiation may be associated with tumor stage because patients with advanced-stage cancer tend to have tumors that are less differentiated.[76] The depth of invasion of the primary tumor has been reported to have prognostic significance in patients treated primarily with surgical resection.[96] DNA ploidy has also been associated with prognosis in surgically treated patients with DNA aneuploid tumors predictive of an inferior outcome.[96] In a Mayo Clinic study of surgically treated patients, those with aneuploid tumors had inferior survival compared with patients with DNA diploid or tetraploid tumors on univariate analysis. On multivariate analysis, however, DNA ploidy was not a significant predictive variable.[97]

There are currently no clinically useful tumor markers. Despite negative liver imaging, patients with elevated alkaline phosphatase or lactate dehydrogenase are at increased risk for subsequent liver metastases.[98] In one study, reduced expression of $p21^{waf1}$, a cyclin-dependent kinase inhibitor, was associated with shorter OS.[99] Preliminary information suggests that serum antibodies to HPV proteins may eventually be useful as prognostic markers. Elevated serum IgA antibodies to HPV 16 E2:9 peptide have been associated with lower survival rates independent of tumor size.[37] In another study, patients who died of anal cancer were found to have higher levels of IgG against HPV E7:5 peptide than did patients with anal cancer in complete remission or patients who died of other causes.[40]

PATHOLOGY AND PATHWAYS OF SPREAD

The World Health Organization (WHO) classification of malignant epithelial tumors of the anal canal includes squamous cell carcinoma, adenocarcinoma, small cell carcinoma, and undifferentiated carcinoma. Most cases of adenocarcinoma of the anus are actually distal rectal adenocarcinomas with extension into the anal canal. True primary anal canal adenocarcinoma is rare, as is small cell carcinoma of presumed neuroendocrine origin.[18,76] Subsets of squamous cell carcinoma in the WHO system include large-cell keratinizing carcinoma, large-cell nonkeratinizing or transitional carcinoma, and basaloid carcinoma.[100] Although basaloid carcinomas have historically been considered to be nonkeratinizing tumors, most basaloid carcinomas exhibit keratinization and should be considered squamous cell carcinomas.[67]

Although most anal canal malignant tumors are squamous cell carcinomas or squamous cell variants, marked morphologic heterogeneity is characteristic.[67] Classification of epidermoid anal cancers on the basis of morphologic appearance has led to the use of several potentially confusing terms. These include transitional cell carcinoma, basaloid carcinoma, and mucoepidermoid carcinoma. These tumors all arise from the

anal transition zone and are often grouped together as *cloacogenic carcinoma. Mucoepidermoid carcinomas* contain mucous microcysts and are histologically dissimilar to mucoepidermoid carcinomas of the salivary glands. The natural history is identical to that of squamous cell carcinoma of the anus without microcysts. Although sometimes considered to be distinct lesions in the medical literature, cloacogenic carcinoma, transitional cell carcinoma, basaloid carcinoma, and mucoepidermoid carcinoma are all subtypes of squamous cell carcinoma because patients with these various tumor subtypes have similar clinical characteristics and the tumor subgroups do not differ in natural history or response to therapy[18,53,70,101]

Primary anal melanoma is a rare tumor that accounts for only 1% of all anal cancers. Anal melanoma is similar to melanoma of the skin in that it rarely affects African Americans and is characterized by the distant spread of disease.[102] Outcome is poor after wide local excision or abdominoperineal resection, with just a 10% survival in most series at 5-year follow-up.[103]

Pathways of Tumor Spread

Anal cancer tumors spread by direct extension to surrounding tissues, lymphatic dissemination to pelvic and inguinal lymph nodes, or hematogenous spread to distant viscera.[104] At diagnosis, about half of all anal cancers have been found to invade the anal sphincter or surrounding soft tissue. Although Denonvilliers fascia is usually an effective barrier to prostatic invasion in men, direct extension to the rectovaginal septum is a common occurrence in women.[105]

The anal canal has several potential lymphatic drainage pathways. The superficial inguinal nodes are the primary drainage basin for that part of the anal canal distal to the dentate line.[106,107] Lymphatic drainage around the dentate line occurs to perirectal lymph nodes and along the pathway of the inferior and middle hemorrhoidal vessels to obturator and hypogastric lymph nodes. Lymphatic connections also join the anus to presacral, external iliac, and deep inguinal nodes.[108]

Metastatic involvement of pelvic lymph nodes has been reported in 25% to 35% of patients treated primarily with abdominoperineal resection.[53,76] Inguinal node metastases are found in about 10% of patients at diagnosis; the risk depends on the size and extent of the primary tumor.[71,77] The incidence of inguinal node metastases may be as high as 20% for tumors more than 4 cm in diameter and as high as 60% when there is direct invasion of adjacent pelvic organs.[77] Relapse in undissected inguinal nodes has been reported in 13% of surgically managed patients with clinically negative inguinal lymph nodes.[76] Cumulative rates of inguinal relapse among patients treated with definitive chemoradiation without prophylactic inguinal irradiation has been reported in 30% of T3-T4 patients[109] and 7% to 12% of T1-T2N0 patients.[109,110] Prophylactic irradiation may significantly reduce the rate of inguinal recurrence.[109]

CLINICAL MANIFESTATIONS, PATIENT EVALUATION, AND STAGING

Rectal bleeding is the most common symptom of anal malignant disease. Perineal pain, mass sensation at the anus, and a change in bowel habits are also frequently reported.[18,53,108,111-113] Many patients with symptoms of early anal cancer are diagnosed initially with a benign anal condition, such as hemorrhoids, anal fissures, or fistulae.[18,53]

Most patients with anal cancer are diagnosed at an early stage. A national survey of such patients found that 73% were diagnosed with stage 0 to II cancer, whereas only 8% were diagnosed with stage IV cancer.[4] The interval from the onset of symptoms to diagnosis may be quite prolonged, however, exceeding 1 month in 80% of patients and 6 months in 33%. A study of Norwegian patients with anal cancer found that nearly one third of them had a delay of more than 6 months from onset of symptoms to diagnosis.[91,113] This finding emphasizes the importance of a thorough digital rectal examination in patients with anal symptoms.[56,57,113]

Patient Evaluation

Evaluation of the patient with known or suspected anal cancer should begin with a thorough history and physical examination. The patient should be questioned about anal sphincter function and any history of risk factors (sexual or drug abuse) for HIV infection.

In addition to a complete general physical examination, a detailed examination should be conducted of the abdomen, inguinal region, anus, and rectum. The extent of circumferential involvement of the anal canal should be noted, and documentation should be made of the size, extent, and location of the primary tumor. The size, location, and mobility of palpable inguinal lymph nodes should be noted. Perirectal lymph nodes may be involved metastatically, but these are rarely palpable by digital rectal examination.[91]

Laboratory studies should include a complete blood cell count, measurement of serum creatinine levels, and liver function studies of bilirubin, alkaline phosphatase, lactate dehydrogenase, and glutamic-oxaloacetic transaminase. For patients with HIV risk factors, a determination of HIV status should be made before the initiation of therapy. Although concentrations of serum carcinoembryonic antigen (CEA) are elevated in 20% of patients with anal cancer, posttreatment CEA values have not been found to correlate with clinical outcomes and have not proven useful in patient management.[114] There are no other clinically useful tumor markers for anal cancer.

Radiographic evaluation should include chest radiographs and CT scanning of the abdomen and pelvis. The CT scan is generally inferior to the physical examination for the characterization of primary tumors, but it is useful for the evaluation of the liver and the perirectal, inguinal, pelvic, and paraaortic lymph nodes. Magnetic resonance imaging (MRI) has not yet been proven to be more clinically useful than CT scanning. The depth of invasion of the primary tumor may be evaluated with ultrasonography.[115]

PET imaging is useful in further evaluating the extent of the primary tumor and the presence of regional lymph node metastases and distant metastases, as well as in evaluating the response to therapy.[116-121] A retrospective evaluation of the sensitivity of PET/CT imaging compared with physical examination and CT scanning alone among 41 patients with anal cancer showed that PET/CT imaging detected the primary tumor in 91% of patients compared with only 59% by CT scanning alone.[122] In addition, PET/CT identified positive inguinal nodes in 17% of patients who were found to be clinically negative by CT and physical examination. Another series reports that use of PET during initial staging led to a change in stage in 23% of patients and radiotherapy field changes in 13% of patients.[123] Furthermore, a posttherapy PET scan showing resolution of metabolic activity was reported to be highly associated with improved progression-free survival (PFS) (95% at 2 years versus 22%; $p < 0.0001$).[124] Posttreatment PET/CT demonstrating resolution of metabolic activity performed 3 months compared to 1 month after completion of treatment may yield higher sensitivity (100% versus 66%) and specificity (97.4% versus 92.5%) with respect to predicting outcomes.[120]

Staging

Anal cancer should be staged according to the TNM staging system of the American Joint Committee on Cancer (AJCC)[125] (Table 52-1). Tumors are classified according to their maximum diameter and their invasion of adjacent structures, as determined by the physical examination and any imaging studies.

The AJCC staging system for anal canal cancer is applicable to all carcinomas that arise from the anal canal. Cancers of the anal margin (distal to the anal verge) are staged as skin cancers, but melanoma of the anal canal is excluded. For staging purposes, the regional lymph nodes in the AJCC system are the anorectal, perirectal, lateral sacral, internal iliac (hypogastric), and superficial and deep inguinal lymph nodes.[126]

TABLE 52-1 TNM 7th Edition Staging System of the American Joint Committee on Cancer, 2010

Stage	T*	N†	M
0	Tis	N0	M0
I	T1	N0	M0
II	T2	N0	M0
	T3	N0	M0
IIIA	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
	T4	N0	M0
IIIB	T4	N1	M0
	Any	N2	M0
	Any	N3	M0
IV	Any	Any	M1

**Tumor category:* Tis, *carcinoma in situ;* T1, *tumor 2 cm or less in greatest dimension;* T2, *tumor more than 2 cm but 5 cm or less in greatest dimension;* T3, *tumor more than 5 cm in greatest dimension;* T4, *tumor of any size invades adjacent organs, for example, vagina, urethra, bladder (Note: direct invasion of the rectal wall, perirectal skin, subcutaneous tissue or the sphincter muscle is not classified as T4).*

†Nodal category: N0, *no regional lymph node metastases;* N1, *metastasis in perirectal lymph node(s);* N2, *metastasis in unilateral internal iliac or unilateral inguinal lymph node(s);* N3, *metastasis in perirectal and inguinal or bilateral internal iliac or bilateral inguinal lymph node(s).*

PRIMARY THERAPY

Surgery Alone

Before the establishment in the 1980s of sphincter-sparing therapy as the standard of care for epidermoid anal cancer, most patients with anal cancer in North America were treated surgically with abdominoperineal resection. Reported 5-year OS after abdominoperineal resection for anal cancer ranged from 25% to 70% (average, 50%).[76,84,127] Locoregional recurrence developed in 25% to 35% of patients and distant metastasis in 10%.[76,84,127] Patients at highest risk for local recurrence (range, 36% to 48%) after abdominoperineal resection are those with extension of the primary tumor beyond the anal sphincter or metastases to inguinal or pelvic lymph nodes.[76] A component of locoregional disease is present in as many as 84% of patients with relapse after abdominoperineal resection.[76] When the inguinal lymph nodes are metastatically involved, 5-year OS after primary surgical therapy is only 10% to 20%.[127] Although abdominoperineal resection is now rarely used initially, it is still useful for treatment of patients with local recurrence after conservative therapy and for management of complications after conservative therapy.[127]

Irradiation Alone or Plus Chemotherapy

High-dose radiotherapy without surgical resection or other adjuvant therapy is an effective treatment for small stage T1 tumors without inguinal adenopathy. Table 52-2 summarizes the local control and survival results from retrospective series of radiotherapy alone for small anal cancers. For patients with anal cancers of 2 cm or less in diameter, 100% local control 5 years after radiotherapy without chemotherapy has been reported in several small series of less than 10 patients each.[74,75,128] In a larger French retrospective series, however, among 66 patients treated with T1 tumors ≤1 cm, 6 developed local recurrence at a median interval of 50 months.[129] Local control rates at 5 years are lower (57% to 76%) in patients with 2- to 5-cm tumors.[74,75,130]

TABLE 52-2 5-Year Disease Control and Survival after Radiotherapy Alone for Early-Stage Anal Cancer

First Author/ Reference	No. Pts.	Total RT Dose (Gy)	Tumor Size	Local Control (%)	Overall Survival (%)
Allal[75]	5	60-65[a]	≤2 cm	100	100
	37	60-65[a]	2-5 cm	76	63
Cummings[74]	6	45-55[b]	≤2 cm	100	NR
	23	45-55[b]	2-5 cm	57	NR
Martenson[128]	18	55-67	≤5 cm[c]	100	94
Schlienger[91]	63	60-65	T1-T2, UICC[d]	71	85
Doggett[77]	35	45-76	≤5 cm	77	92
Papillon[130]	63	45-50[d]	≤4 cm	87	76
Eschwege[90]	27	60-65	T1-T2, UICC[e]	90	72
Ortholan[129]	69	35-70	Tis, T1	91	89

No. pts, *number of patients;* NR, *not reported;* UICC, *Union Internationale Contre le Cancer.*

[a]*Usually, 40 Gy of external beam radiation therapy (EBRT) plus 20 Gy to 25 Gy with interstitial implant.*

[b]*Overall 4-week treatment period.*

[c]*One patient with tumor >5 cm.*

[d]*Equivalent to 30 Gy in 10 fractions, followed by 15 Gy to 20 Gy with interstitial implant.*

[e]*1979 UICC staging: T1, less than one third length and circumference of anal canal; T2, more than one third length or circumference of anal canal or infiltration of external sphincter.*

In previous editions of the staging system of the Union Internationale Contre le Cancer (International Union Against Cancer [UICC]),[91] primary tumors were classified not by size but rather according to the length and extent of their circumferential involvement with the anal canal. Tumors involving less than one third of the length and circumference of the anal canal were classified as T1 category of disease, whereas those that involved more than one third of the length or circumference or that invaded the external sphincter were classified as T2. T3 tumors involved the rectum or perianal skin, and T4 tumors invaded adjacent structures.

Radiation Alone or Plus 5-FU and Mitomycin C

The only prospective randomized trial to compare radiotherapy alone with the combination of radiotherapy and chemotherapy in patients with node-negative anal cancers 5 cm or less in diameter (T1 to T2, N0) was carried out by the UKCCCR Anal Cancer Trial Working Party.[131] In this trial, 223 of 585 patients had T1 or T2, N0 anal cancer and were randomized to receive 40 Gy to 45 Gy of external beam radiotherapy (EBRT) to the pelvis, followed by a 15-Gy to 25-Gy boost with a perineal field or interstitial implant with or without two 4- or 5-day infusions of 5-FU and a single bolus injection of mitomycin C. Using local control as the endpoint, subset analysis showed a statistically significant advantage for combined-modality therapy for patients with T1N0 or T2N0 anal cancer.[132]

Combined-modality therapy with radiotherapy and chemotherapy is appropriate for most patients with anal cancer and has become the standard of care. Statistics from the U.S. National Cancer Data Base for 1988 and 1993 show that the use of chemotherapy has increased and the use of resection as the primary treatment has declined.[4]

The initial studies that led to the adoption of combined-modality therapy with nonsurgical treatment were conducted at Wayne State University. Before scheduled surgical resection, 30 Gy of radiation in 15 fractions was delivered to the true pelvis, medial inguinal nodes, and anal canal in conjunction with concomitant 5-FU 1000 mg/m^2 every 24 hours for 4 days as a continuous infusion and mitomycin C (MMC) in a single bolus injection of 15 mg/m^2. After five of the first six patients were found to have no residual tumor in the abdominoperineal resection (APR) specimen 4 to 6 weeks after the completion of radiotherapy, surgical resection was subsequently reserved for locally persistent or recurrent disease after radiotherapy and concurrent chemotherapy.[80] Overall, 86% of patients (24 of 28) had a clinical complete response to chemoradiation, and 7 of the 12 patients (58%) who had an APR had a complete pathologic response.[133]

Table 52-3 summarizes the disease control and survival results with concomitant chemoradiation from several series. Local failure after radiation doses of 45 Gy to 60 Gy with concomitant chemotherapy occurred in 11% to 40% of patients, and 5-year OS was 65% to 80%.

Two randomized studies comparing radiotherapy alone with concomitant radiotherapy plus 5-FU and MMC have been performed by the EORTC[82] and the UKCCCR Anal Cancer Trial Working Party.[131] For patient eligibility, the EORTC trial required a locally advanced primary tumor (T3 or T4 category) or involvement of regional lymph nodes, whereas the UKCCCR trial enrolled patients with any stage of disease, including distant metastases. Initial radiotherapy was similar in both trials and consisted of 45 Gy to the pelvis over 4 to 5 weeks. In the EORTC trial, partial responders at 6 weeks after induction therapy were boosted with an additional 20 Gy and complete responders received 15 Gy. In the UKCCCR trial, a 15-Gy to 25-Gy boost was administered to patients with more than a 50% tumor response; patients with less than a 50% response had radical surgery. Concurrent chemotherapy in the EORTC trial consisted of 5-FU 750 mg/m^2 every 24 hours on days 1 to 5 and days 29 to 33 with a single 15-mg/m^2 dose of MMC on day 1. Chemotherapy in the UKCCCR trial consisted of 5-FU 1000 mg/m^2 every 24 hours on days 1 to 4 and days 29 to 32 or 750 mg/m^2 every 24 hours on days 1 to 5 and days 29 to 33, with a single MMC dose of 12 mg/m^2 given on the first day of radiotherapy.

Results of the EORTC[82] and UKCCCR[131] trials are summarized in Table 52-4. The complete response rate 6 weeks after boost radiotherapy was significantly improved with the addition of chemotherapy to radiotherapy (80% versus 54%; p = 0.02) in the EORTC trial. A nonstatistically significant trend toward a higher complete response rate was also reported in

TABLE 52-3 Disease Control and Survival Rates after Irradiation and Chemotherapy for Anal Cancer in Selected Series

First Author/ Reference	No. Pts	Median FU (mo)	Total RT Dose (Gy)	Tumor Extent	Chemo Agent	Local Failure No. (%)	Overall Survival (%)
Rich[134]	39	54	45-66	T0-T4	5-FU[a]	13/39 (33)	74
Cummings[74]	66	24	48-50	T1-T4	5-FU	26/65 (40)	64
Hughes[135]	25	30	45-66	T0-T4	5-FU[b]	8/24 (33)	96 (2-year)
Martenson[95]	50	NR	50-53	T1-T4	5-FU, MMC	(20)[c]	58
Allal[75]	68	48	50-55[d]	T1-T4	5-FU, MMC	22/68 (32)	65
Doci[136]	56	49	54-56	T1-T3	5-FU, MMC	12/49 (24)	81
Tanum[78]	86	>36[e]	50	T0-T4	5-FU, MMC	—	72
Cummings[74]	69	36 (min)	48-60	T1-T4	5-FU, MMC	10/69 (14)	76
Sischy[85]	26	32	40.8	<3 cm	5-FU, MMC	4/26 (15)	85 (3-year)
	50		40.8	≥3 cm	5-FU, MMC	18/50 (36)	68 (3-year)
Rich[134]	19	20	54-60	T2-T4	5-FU, CCDP	2/19 (11)	85 (3-year)
Doci[137]	35	37	54-58	T1-T3	5-FU, CDDP	4/35 (11)[f]	97[f]
Defoe[138]	78	16	45-67.6	T1-T4	5-FU, MMC	7/78 (9.8)	87 (2-year)
Eng[138a]	201	103	34-69.9	T1-T4	5-FU, CDDP	22/201 (11)	86 (5-year)

5-FU, *5-Fluorouracil;* CDDP, *cisplatin;* Chemo, *chemotherapy; cm, centimeters;* FU, *follow-up;* Gy, *Gray;* min, *minimum;* MMC, *mitomycin C;* mo, *months;* No. Pts, *number of patient;* NR, *not reported* RT, *radiotherapy.*

[a]*5-FU, 250-300 mg/m^2/day, by infusion 5 days or 7 days weekly throughout radiotherapy.*

[b]*5-FU, 300 mg/m^2/day throughout radiotherapy.*

[c]*Kaplan-Meier estimate at 5 years.*

[d]*Usually, 30 Gy of external beam radiation therapy (EBRT) in 10 fractions plus 20 Gy with interstitial implant.*

[e]*Investigators monitored for more than 3 years.*

[f]*Crude.*

TABLE 52-4 3-Year Disease Control and Survival in Phase III Studies Comparing Radiotherapy Alone with Radiation and Chemotherapy

Study	Pt No.	Median FU (mo)	Complete Response*		Local Control†		Distant Mets, Crude (%)	Overall Survival	
			%	*p* Value	%	*p* Value		%	*p* Value
EORTC	103	42							
RT	52		54		55		21	64	
RT plus 5-FU, MMC	51		80	0.02	69	0.02	18	69	0.17
UKCCCR	577	42							
RT	285		30		39		17	58	
RT plus 5-FU, MMC	292		39	0.08	61	<0.001	10	65	0.25

5-FU, *5-Fluorouracil;* EORTC, *European Organization for Research and Treatment of Cancer;* Mets, *metastases;* MMC, *mitomycin C;* mo, *months;* Pt. No., *patient numbers;* RT, *radiotherapy;* UKCCCR, *United Kingdom Coordinating Committee on Cancer Research.*

**Assessment of complete response was 6 weeks after 45 Gy (before radiotherapy boost) in UKCCCR trial and 6 weeks after completion of 60 Gy to 65 Gy in EORTC trial.*

†Patients who had surgery to achieve local control at the completion of radiotherapy were considered locally controlled in the EORTC trial; in the UKCCCR trial, patients who had surgery at the completion of radiotherapy were considered local treatment failures, as were all patients who had surgery for treatment morbidity.

TABLE 52-5 4-Year Disease Control, Survival, and Toxicity after Radiotherapy and 5-FU Alone or Plus Mitomycin C: Results of RTOG 8704/ECOG 1289 Phase III Trial[104]

Treatment Arm	N	Total Radiotherapy Dose (Gy)	Negative Biopsy		Local Control		Colostomy Rate		Colostomy-Free Survival		Disease-Free Survival		Overall Survival		Grades 4-5 Toxicity	
			%	*p* Value	%	*p* Value	%	*p* Value	%	*p* Value	%	*p* Value	%	*p* Value	%	*p* Value
RT plus 5-FU	145	45-50.4	85		66		22		59		51		67		8	
RT + 5-FU/MMC	146	45-50.4	92	0.135	84	0.0008	9	0.002	71	0.014	73	0.003	76	0.31	26	≤0.001

5-FU, *5-Fluorouracil;* ECOG, *Eastern Cooperative Oncology Group;* Gy, *Gray;* MMC, *mitomycin C;* RT, *radiotherapy;* RTOG, *Radiation Therapy Oncology Group.*

the UKCCCR trial. However, this endpoint was measured 6 weeks after the initiation of therapy compared with 6 weeks after the completion of all therapy in the EORTC trial. In both studies, local control was significantly improved with the addition of concurrent chemotherapy. Local control with radiotherapy alone was surprisingly low (39% at 3 years) in the UKCCCR study. The definition of local failure included tumor reduction of less than 50% 6 weeks after 45 Gy of irradiation, surgery for morbidity, and failure to close a pretreatment colostomy for any reason. Conversely, EORTC investigators considered patients locally controlled even if they had to undergo surgery to achieve a complete response at the completion of radiotherapy. Neither study reported any significant impact of chemotherapy on the incidence of distant metastases or on OS, although absolute survival at 3 years slightly favored the chemoradiation arms numerically in both trials.

The EORTC and UKCCCR trials established combined-modality therapy as the standard of care for patients with anal cancer. Further refinement in the understanding of optimal therapy is provided by the results of a Phase III study conducted by RTOG and the Eastern Cooperative Oncology Group (ECOG). In the RTOG/ECOG study (Table 52-5), patients were treated with radiotherapy (45 Gy to 50.4 Gy in 25 to 28 fractions) and 5-FU and were randomized to receive or not receive MMC.[139] The addition of MMC was associated with fewer colostomies, higher local control, and better DFS. The addition of MMC also significantly increased the risk of major toxicity. Survival was slightly higher in the MMC arm of the study, but the difference was not statistically significant. The chemotherapy regimen in this trial differed from that of the European trials because two doses of MMC 10 mg/m^2 were delivered on day 1 and day 29 instead of a single dose. Two of the four treatment-related deaths in the MMC arm were felt to be caused by a failure to follow protocol dose-reduction guidelines for the second MMC dose.

The biologic basis for improved outcome with the addition of chemotherapy to the treatment regimen is not known. However, the fact that several studies have reported no significant reduction in distant failure with chemotherapy suggests that the effect is predominantly locoregional, possibly because of an interaction with irradiation.[74] For example, in the PMH experience, distant failure occurred in 18% of patients treated with radiotherapy alone, in 17% of those who received MMC and 5-FU, and in 10% of those receiving 5-FU alone.[74,140] Synergistic interactions between irradiation and 5-FU or MMC and between 5-FU and MMC have been demonstrated in mammalian tumor cell lines in vitro.[141] Hypoxic mammalian tumor cells also have an increased sensitivity to mitomycin C in vitro, although whether the hypoxia has any effect when anal cancer is treated with fractionated radiotherapy is not known.[142] Laboratory studies have also shown increased cytotoxicity associated with continuous infusion 5-FU compared with 5-FU delivery by intermittent bolus.[143]

It cannot be assumed that sequential therapy will duplicate the excellent results achieved with concomitant chemoradiation. Complete pathologic response rates 6 weeks after 50 Gy of irradiation, 5-FU, and MMC are in the range of 85% to 95%.[80,144,145] In contrast, only 45% of 42 patients who received

TABLE 52-6 5-Year Disease Control and Survival after Radiotherapy and 5-FU Plus Mitomycin C or Cisplatin: Results of RTOG 98-11 and ACT II Phase III Trials

		Colostomy-Free Survival		Disease-Free Survival		Overall Survival	
Study	**Pt. No.**	**%**	***p* Value**	**%**	***p* Value**	**%**	***p* Value**
RTOG 98-11[*152]	649						
RT plus FU/MMC	325	71.9 (5-year)	0.05	67.8 (5-year)	0.006	78.3 (5-year)	0.026
RT plus FU/CDDP	324	65		57.8		70.7	
ACT II[†153]							
RT plus FU/MMC	472	68 (3-year)	0.94	69 (3-year)	0.63	79 (3-year)	0.7
RT plus FU/CDDP	468	67		69		77	

5-FU, *5-Fluorouracil;* CDDP, *cisplatin;* MMC, *mitomycin C;* mo, *months;* Pt. No., *patient numbers;* RT, *radiotherapy;* RTOG, *Radiation Therapy Oncology Group.*
**5-year outcomes reported for RTOG 98-11.*
†3-year outcomes reported for ACT II Study.

sequential 5-FU and MMC, followed by radiotherapy, had a complete pathologic response.[111]

Radiation Plus 5-FU and MMC versus 5-FU and Cisplatin

In addition to the concurrent use of MMC and 5-FU during radiotherapy, multiple single institutions[134,136,146,147] and prospective Phase II trials[148-150] have reported favorable results with concurrent cisplatin (CDDP) and 5-FU, with or without an induction chemotherapy phase of treatment. A U.S. Gastrointestinal Intergroup Phase III trial (RTOG 9811) was conducted to compare the efficacy of concurrent cisplatin-based therapy with standard MMC-based therapy.[151,152] Six hundred forty-four patients with T2 category or higher (any N category) carcinoma of the anal canal were randomized to two cycles of induction CDDP (75 mg/m^2) and 5-FU (1000 mg/m^2 for 4 days) followed by 45 Gy to 59 Gy of irradiation with two concurrent cycles of the same regimen versus MMC (10 mg/m^2) and 5-FU (1000 mg/m^2 for 4 days) given twice concurrently during radiotherapy (no induction phase). For the cisplatin- and MMC-based arms, 5-year OS was 70.7% and 78.3%, respectively ($p = 0.026$), and 5-year DFS was 57.8% and 67.8%, respectively ($p = 0.006$) (Table 52-6). There was a trend toward statistical significance for colostomy-free survival (CFS), locoregional failure (LRF), and colostomy failure (CF) ($p = 0.05$, $p = 0.087$, and $p = 0.074$, respectively).[152] Based on this trial, a regimen of MMC and 5-FU given concurrently with radiotherapy remains the standard of care for anal cancer. It is unclear whether the delayed use of radiotherapy or difference in radiosensitization of cisplatin compared with MMC played a role in the inferior colostomy rate observed in the experimental arm of this study.

In contrast, the largest Phase III trial, the UK ACT II study, was theoretically a direct comparison of CDDP versus MMC (gave two doses of CDDP versus only one of MMC) and also examined the role of maintenance (adjuvant) treatment. The ACT II trial enrolled 940 patients in a 2 × 2 randomized trial with a control arm of 5-FU (1000 mg/m^2, days 1-4, 29-32) and MMC (12 mg/m^2, day 1) versus an experimental arm of + 5-FU (1000 mg/m^2, days 1-4, 29-32) and cisplatin (60 mg/m^2, day 1 and 29) with a primary endpoint of 6-month response rate.[153] Patients were subsequently randomized to receive either no maintenance versus maintenance therapy of 5-FU (1000 mg/m^2, days 1-4, 29-32) and CDDP (60 mg/m^2, days 1 and 29) to be initiated 4 weeks after the completion of radiotherapy, with a primary endpoint of relapse-free survival (RFS). With a median follow-up of 5.1 years, 90.5% (391/432) patients in the MMC group compared to 89.6% (386/431) in the CDDP group had a complete response at 26 weeks ($p = 0.64$). Overall, toxic effects were similar in each group, although there were more grade-3 and grade-4 hematological toxicities in the MMC arm (26% versus 16%, $p = < 0.001$).[153] Maintenance chemotherapy (chemo) was not associated with an improvement in 3-year PFS (Table 52-6; 74% with maintenance chemo versus 73% without maintenance; HR, 0.95; 95% CI, 0.75 to 1.21; $p = 0.70$). Based on the results of this study, the largest in anal cancer to date, the authors concluded that administration of MMC, in combination with 5-FU and 50.4 Gy RT in 28 daily fractions without maintenance chemo, should remain standard practice because of similar efficacy and toxic effects, fewer cycles of chemo, fewer nonchemotherapy drugs, less time in the chemo suite, less expense, and no risk of neuropathy compared with cisplatin.[153]

Role of Dose Intensification

In patients with locally advanced anal cancer, based on the promising results of a Phase II trial of induction chemotherapy,[149] the role of induction chemo and dose intensification of the radiation boost was evaluated in the UNICANCER ACCORD 03 study.[154] In this study, 307 patients with tumors ≥4 cm or <4 cm and N1-3M0 were randomly assigned by 2 × 2 randomization to receive one of the following: (1) 2 cycles of induction 5FU-CDDP (5-FU 800 mg/m^2, day 1-4, 29-32) and CDDP (80 mg/m^2 intravenously, days 1 and 29), with EBRT (45 Gy in 25 fractions over 5 weeks, 5-FU–CDDP during weeks 1 and 5), and standard-dose boost (SD: 15 Gy); (2) 2 cycles of induction chemo, chemoRT, and high-dose boost (HD, 20 Gy to 25 Gy); (3) chemoRT and standard-dose boost; or (4) chemoRT and HD boost. With a median follow-up of 50 months, neither induction chemo nor dose intensification of the RT boost was associated with improvements in 5-year CFS (76.5% versus 75.0%, $p = 0.37$ for induction versus no induction, and 73.7% versus 77.8%, $p = 0.067$ for SD versus HD, respectively).

Although the primary study endpoint was negative, given the trend toward improved CFS in this study, further dose intensification studies, either with new drugs or new radiation techniques, may be warranted.[154]

Treatment Tolerance

Anal function is preserved in 65% to 80% of patients after sphincter-sparing therapy.[74,75,94,135] The most common indication for abdominoperineal resection is local recurrence or disease persistence because 90% of patients for whom local control is achieved can be expected to maintain a functional anus.[74] Late treatment complications may result in the loss of anal function, and a colostomy may be required to manage complications in 2% to 10% of patients whose cancer is locally controlled.[74,75,77,91,94,128,137,155,156] A Danish multicenter cohort study of 235 patients reported a 5-year cumulative incidence

of therapy-related colostomy of 12%. Of the 12 patients who received therapy-related colostomies not part of an APR, indications included chronic anorectal ulcer, fecal incontinence, bowel obstruction, rectovaginal fistula, perianal skin injury, and anal canal fibrosis.[156]

LOCALLY ADVANCED DISEASE AND PALLIATION

Tumor size appears to have a moderate impact on treatment outcome when combined-modality therapy is used. In the RTOG/ECOG study, 17% of patients with primary tumors 5 cm or more in diameter had positive biopsy findings 6 weeks after completion of therapy compared with 7% of those with a tumor less than 5 cm in diameter ($p = 0.02$). Preservation of anal function was also more likely in patients who had smaller tumors; 11% of patients with T1 or T2 cancer required a colostomy compared with 21% of those with T3 or T4 cancer.[139] Differences in local control have also been reported using tumor diameter cutoffs of less than 5 cm. In a previous RTOG study, local control at 3 years was 84% among patients with tumors smaller than 3 cm and 62% among those with tumors 3 cm or larger.[85] Similarly, local control among patients treated at PMH was 94% for those with tumors of 2 cm or less and 72% for those with larger tumors. No difference in local control was reported between the subgroups of patients with tumors of 2 cm to 5 cm or with larger tumors (>5 cm), unless invasion of adjacent structures was discovered, in which case local control was 62%.[74]

Secondary analyses of the U.S. Gastrointestinal Intergroup RTOG 9811 Phase III trial have been performed to further define prognostic factors for outcomes in patients treated with concurrent chemoradiation. The initial analysis found that a tumor size of more than 5 cm was the only pretreatment characteristic that independently predicted a subsequent need for colostomy (hazard ratio, 1.85; $p = 0.008$).[151]

A subsequent analysis of RTOG 98-11 was performed to determine if the TN category of disease (T2N0, T3N0, T4N0, T2N+, T3N+, T4N+) has an impact on DFS and OS, LRF, distant metastasis, or CF.[73] All endpoints showed statistically significant differences between the 6 TN categories of disease, including OS ($p < 0.0001$), DFS ($p < 0.0001$), LRF ($p < 0.0001$), distant metastasis ($p = 0.0011$), and CF ($p = 0.01$). The best outcomes for OS, DFS, and LRF were found with T2N0 and T3N0 categories of disease (5-year OS, 82% and 74%; DFS, 72% and 61%; and LRF, 17% and 18%). The poorest outcomes were with the T3N+ and T4N+ disease categories (5-year OS, 57% and 42%; DFS, 38% and 31%; and LRF, 44% and 60%). The 5-year CF was best for patients with T2N0 (11%) or T2N+ (11%) disease and worst for patients with T4N0 (26%), T3N+ (27%) and T4N+ (24%) disease.[73]

Preservation of anal function is possible in two thirds to three fourths of patients with locally advanced disease in both RTOG 98-11 (see earlier mention)[73] and PMH series.[74] In the PMH experience, two thirds of patients with tumors that invaded adjacent structures maintained anal function after radiotherapy and chemotherapy, as did two thirds of patients with tumors that involved more than 75% of the circumference of the anal canal.[74] Locally advanced disease is not an indication for abdominoperineal resection in patients who retain some measure of anal function at diagnosis.[74]

Node Involvement

Involvement of the inguinal lymph nodes at diagnosis is associated with a worse prognosis. In the EORTC randomized trial, patients with involved lymph nodes had inferior local control and survival. However, the extent of nodal involvement did not add any prognostic information.[82] In a report from PMH, the 5-year cause-specific survival for patients who were clinically node-positive was 57% compared with 81% patients who were node-negative ($p = 0.07$). Combined-modality therapy was effective in the treatment of patients with involved nodes. In such patients, control of cancer in metastatically involved lymph nodes was achieved 87% of the time.[74] In an RTOG 9811 secondary analysis, 5-year DFS was 64% for patients who were node-negative and only 35% for patients who were node-positive ($p \leq 0.0001$).[157] As noted in the prior section, in a subsequent secondary analysis of RTOG 98-11, the poorest rates of OS, DFS, and LRF were with T3-4, N+ disease.[73]

Radiotherapy without chemotherapy has been used for patients with metastatically involved inguinal lymph nodes, with control of nodal disease reported in 60% to 70% of patients.[77,94] However, survival is poor for these patients with radiotherapy alone (range, 0% to 36% at 5 years), and combined-modality therapy with radiotherapy and concurrent chemotherapy is preferred.[89-91,94]

Salvage Therapy

Patients with local failure after radiotherapy and chemotherapy should be considered for abdominoperineal resection. Local control can be achieved with abdominoperineal resection in as many as 60% of these patients.[74,75,77,88,91,94] Ultimate local control is obtained in more than 90% of patients with anal cancer, including patients who require surgery after radiotherapy for locally persistent or recurrent disease.[77,94]

Patients who have locally advanced recurrent disease that is not surgically resectable for cure may benefit from low-dose reirradiation plus concurrent chemo followed by surgical resection of gross disease and intraoperative radiotherapy (IORT). This aggressive combined-modality treatment approach may result in successful salvage as seen in a recent Mayo Clinic Rochester analysis.[158] Salvage surgical resection and IORT were used in a series of 32 patients between 1993 and 2012 who had either residual ($n = 9$) or recurrent ($n = 23$) disease following primary chemoradiation. Those with recurrent disease received low-dose preop chemoRT before resection or IORT. Five-year OS and DFS were 23% and 17%, respectively.

Palliation

Although anal cancer is predominantly a locoregional disease, 5% to 10% of patients will have disease beyond the pelvis at diagnosis and distant metastases will develop in 10% to 20% after locoregional therapy.[71,74,75] The most common site of distant metastases reported in most series is the liver; metastases to the lungs, lymph nodes, skin, bones, and brain have also been reported.[71,75,77-80] Palliative chemotherapy with 5-FU plus either mitomycin C or cisplatin is associated with a 50% response rate and a median survival of 12 months.[71] Patients with brain metastases, symptomatic osseous metastases, or other localized symptomatic metastases should receive hypofractionated radiotherapy for palliation.

IRRADIATION TECHNIQUES AND TOLERANCE

Traditional Field Design

Radiotherapy field design should be based on an understanding of the spread of anal cancer. Historical results in patients treated by APR show that 35% to 46% had involvement of

pelvic lymph nodes and that 13% to 16% had a relapse in the inguinal lymph nodes.[76,84] Therefore, the pelvic and inguinal lymph nodes should be included in the radiotherapy fields.

A portion of the inguinal lymph node chain is superficial to the femoral head and neck. It is important to use radiotherapy fields that decrease the radiation dose to these structures. Large anteroposterior/posteroanterior (AP/PA) fields that include the inguinal lymph nodes will deliver the full radiation dose to the femoral head and neck. Patients treated in this way may be at risk for radiation-induced fracture.[159] Radiotherapy techniques that treat the lateral inguinal lymph nodes only through anterior fields will minimize the dose to the femoral head and neck. One method is to treat the primary tumor, pelvic nodes, and inguinal nodes with an anterior photon field that encompasses all these structures. The posterior field is designed to treat only the primary tumor and the pelvic lymph nodes. Electron fields are used to supplement the dose to the lateral superficial inguinal nodes that are not included in the posterior photon field (Figure 52-1). Another technique is to use CT-based simulation for optimal delineation of the inguinal lymph nodes and then to use this information to minimize the volume of the femur included within the radiotherapy field.

Target Volumes and Normal Structures

Accurate target and normal structure identification is crucial to advanced treatment planning with three-dimensional radiotherapy or intensity-modulated radiation therapy (IMRT). The gross tumor volume (GTV) represents the maximal extent of the primary tumor and clinically involved lymph nodes based on the combined consideration of the physical examination, endoscopic findings, and diagnostic imaging studies. The clinical target volume (CTV) includes all

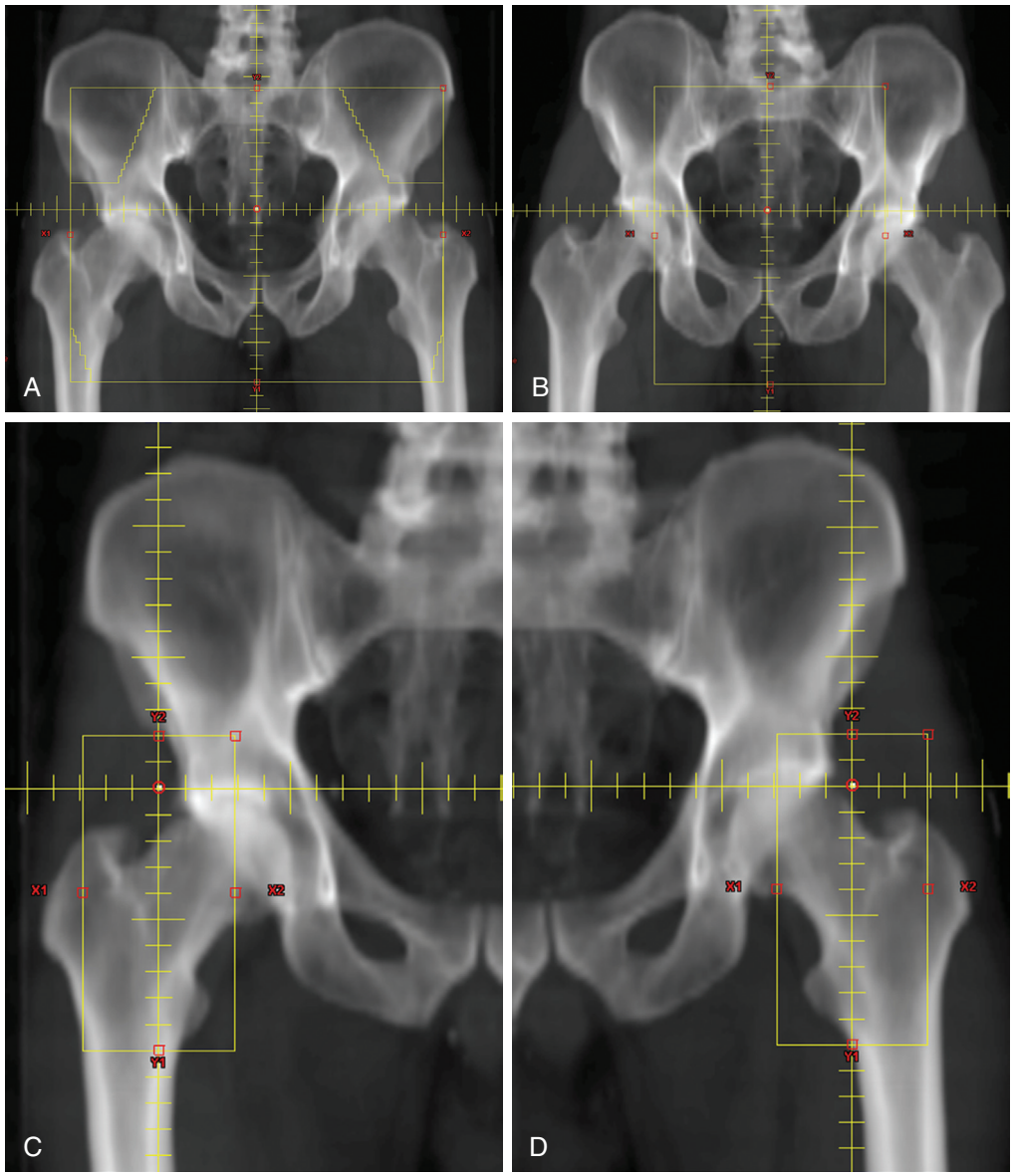


Figure 52-1 Anal cancer fields: Wide anterior **(A)** and narrow posterior **(B)** photon fields. Electron fields are used to give a supplementary radiation dose to lateral inguinal nodes not included in the narrow posterior photon field **(C** and **D)**. The medial border of each electron field is placed at the posterior photon field's lateral exit point on the anterior abdominal wall.

tissues at risk of longitudinal or radial microscopic extension of the primary tumor as well as nodal areas at risk. These nodal regions include the perirectal nodes (including all of the mesorectum to the pelvic floor), inguinal nodes, presacral nodes, and internal and external iliac nodes. Multiple CTVs may be constructed based on differences in planned dose delivery to elective regions of treatment. The superior extent of the elective nodal coverage is generally at least to the iliac bifurcation or to the sacral promontory.

A retrospective review of 167 patients treated at the M. D. Anderson Cancer Center with definitive chemoradiation reported that all regional pelvic failures (21% of relapses) occurred among patients whose superior field border was placed at the bottom of the sacroiliac joint. The authors concluded that a superior field or target border at vertebrae L5/S1 may reduce such recurrences.[160]

In 2009, an RTOG panel reported consensus contouring guidelines and an atlas for elective CTV demarcation in anorectal cancer.[161] This reference serves as an excellent template and resource for lower gastrointestinal cancer treatment planning. Key normal structures that should be identified in the planning process and avoided include the femoral head and neck, bladder, and bowel. Excessive skin exposure should also be avoided in the perineum and groin.

Intensity-Modulated Radiotherapy

Given the close proximity of the bladder, small bowel, femoral heads, and possibly pelvic bone marrow to target regions in the management of anal cancer, the improved conformality of IMRT compared with traditional techniques presents an opportunity for toxicity reduction[162,163] (Figure 52-2). A retrospective review of 53 patients treated at multiple institutions has reported favorable acute toxicity and efficacy rates with early follow-up among 53 patients treated with IMRT and concurrent chemotherapy.[164] More than 92% of patients had a complete clinical response, and acute grade-3 or higher gastrointestinal (GI) or dermatologic toxicities were observed in only 15% and 38% of patients, respectively. RTOG 0529, a Phase II trial of 52 patients treated with dose-painted IMRT and concurrent mitomycin C and 5-FU also shows favorable patient tolerance rates.[165] In this study, patients with T2-4N0-3M0 anal cancer received 5-FU and MMC on days 1 and 29 of dose-painted IMRT, prescribed per stage as follows: T2N0: 50.4 Gy to the anal primary PTV, 42 Gy to elective nodal PTV in 28 fractions; for T3-4, N0-3: 54 Gy to the anal primary PTV, 54 Gy to >3 cm metastatic nodal PTV, 50.4 Gy to ≤3 cm metastatic nodal PTV, and 45 Gy to elective nodal PTV. Compared with the historical benchmarks of RTOG 9811, there was significantly less grade 2+ hematologic toxicity (73% versus 85%; $p = 0.032$), grade 3+ GI or genitourinary toxicity (21% versus 36%; $p = 0.0082$) and grade 3+ dermatologic toxicity (23% versus 49%; $p < 0.0001$), with a favorable early clinical response reported.[165] Treatment interruptions because of toxicity were significantly less with dose painted IMRT with median treatment duration of 43 days compared with 49 days ($p < 0.0001$). Integration of IMRT requires rigorous quality assurance, however, to ensure appropriate target volume coverage, minimize marginal misses, and maximize normal tissue sparing with accurate identification of normal tissue structures. This was evidenced in RTOG 05-29, in that 81% of treatment plans required dose-painted-IMRT replanning on initial review and 46% of plans required multiple resubmissions.[165] Preliminary efficacy outcomes of RTOG 05-29 demonstrated similar 2-year outcomes to RTOG 98-11 (2-year LC: 20% versus 19%, 2-year OS: 88% versus 91%, 2-year DFS: 77% versus 76%, for RTOG 05-29 and RTOG 98-11, respectively).[166] Because of the associated acute toxicity sparing, DP-IMRT will be used as the platform and may allow for radiation dose escalation in future RTOG anal canal trials.

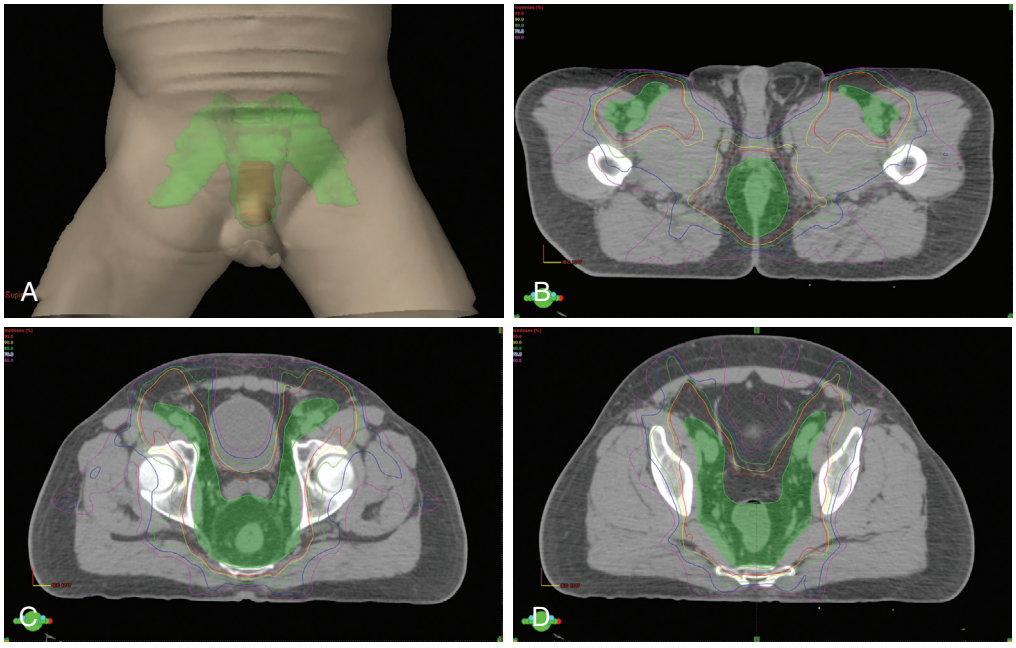


Figure 52-2 Three-dimensional rendering **(A)** of the clinical target volume *(green)* and gross tumor volume in a 65-year-old male with T2N0M0 squamous cell carcinoma of the anal canal. Axial dosimetry using an eight-field intensity-modulated radiation therapy plan in the lower **(B)**, mid **(C)**, and upper pelvis **(D)**. *Red, yellow, green, blue,* and *purple lines* represent the 95%, 90%, 80%, 70%, and 60% isodose lines, respectively. (The planning tumor volume is not shown.)

Radiation Dose and Fractionation

The RTOG/ECOG Phase III clinical trial provided useful information about the most favorable combination of radiation dose and chemotherapy agents.[139] The best local control rates resulted from an aggressive regimen of concurrent chemoradiation (5-FU, 1000 mg/m^2/d on days 1 to 4 and days 29 to 32 of EBRT; MCC, 10 mg/m^2 on day 1 and day 29 of EBRT). The primary tumor, pelvic lymph nodes, and inguinal lymph nodes received a total dose of 36 Gy of EBRT in 20 fractions, followed by a field reduction to include the primary tumor. An additional 9 Gy was administered in 5 fractions, for a total dose to the primary tumor of 45 Gy in 25 fractions. Patients who had residual tumor after 45 Gy received an additional dose of 5.4 Gy in 3 fractions, for a total cumulative primary tumor dose of 50.4 Gy in 28 fractions. The medial inguinal lymph nodes received 45 Gy if clinically negative or 50.4 Gy if clinically positive. This combination of radiotherapy plus 5-FU and MMC resulted in 4-year local control of 84%, which was significantly better than 4-year local control of 66% in patients randomized to receive an identical dose of irradiation plus 5-FU alone ($p < 0.001$).

In the RTOG/ECOG study, 26% of the patients treated with radiation therapy plus 5FU-MMC experienced life-threatening or fatal toxicity, including a 3% treatment-related death rate. It is not yet known whether increasing the radiation dose to more than 50.4 Gy in conjunction with 5-FU and mitomycin C chemotherapy will improve the therapeutic ratio of local control to treatment tolerance. In the subsequent U.S. Gastrointestinal Intergroup clinical trial RTOG 98-11, the recommended final boost dose was 55 Gy to 59 Gy for patients with T3 to T4 disease, positive nodes, or T2 disease with residual disease after 45 Gy.[151,152] Locoregional relapse continued to be a problem even with these slightly higher radiotherapy doses, as noted previously (5-year LRF range of 17% [T2N0] to 60% [T4N+] by TN disease category).[73] In RTOG 05-29 with dose-painted IMRT, recommended final doses were 54 Gy in 30 fractions for patients with T3 to T4 or node positive disease and 50.4 Gy in 28 fractions for patients with T2N0 disease.[165] Preliminary outcomes demonstrate equivalent rates of 2-year local control with this dose fractionation schema compared to RTOG 98-11.[166]

The hypothesis that there will be fewer local failures when the irradiation dose is increased to more than 50.4 Gy with concurrent 5-FU and mitomycin C has not been tested in prospective trials. Three retrospective series have contributed to the formation of this hypothesis. At the University of Texas M. D. Anderson Cancer Center, patients with anal cancer who were treated with radiotherapy and continuous infusion 5-FU 300 mg/m^2 during the entire radiotherapy course had better local control with radiation doses of 55 Gy to 66 Gy (9 of 10 patients) than with lower doses of 45 Gy to 49 Gy (7 of 14 patients).[135] Researchers at the University of Kansas evaluated treatment with or without chemotherapy and found local control of 92% for radiation doses of more than 55 Gy, 77% for 45 Gy to 55 Gy, and 64% for 45 Gy or less.[167] Similarly, a retrospective review from the Medical University of Vienna demonstrated 14% local recurrence with doses of 54 Gy or more compared with 70% with doses of less than 54 Gy among patients with T3 or T4 tumors.[168]

In contrast to dose escalation for locally advanced tumors, more moderate doses of irradiation with chemotherapy may be adequate for early tumors or after local excision of a small tumor. In addition to the original experience with complete responses to 30 Gy reported by Nigro et al,[133] at least two other institutions have reported local control of over 95% with 30 Gy and concurrent chemotherapy among a limited number of patients with early tumors or after local excision.[169,170] Such a strategy has not been evaluated in a prospective clinical trial.

EBRT alone is appropriate for a few patients who are not candidates for combined-modality therapy because of clinically significant comorbid illness or other reasons. A high rate of tumor control has been found in patients with small tumors treated with a radiation dose of 45 Gy in 25 fractions to the pelvis, inguinal lymph nodes, and primary tumor, followed by a boost dose to the primary tumor, for a total cumulative dose of 60 Gy to 70 Gy in 33 to 35 fractions.[86,128]

Nearly all patients who receive concomitant chemoradiation for anal cancer will have perineal skin reactions, and more than half will have confluent moist desquamation. The severity of such acute reactions is influenced by the radiation fraction size and treatment technique. In a PMH study of 50 Gy in 20 fractions (2.5 Gy per fraction), the acute and late toxicities were considered unacceptably high.[74] Less severe toxicity was reported with the same fractionation schedule and a break in treatment or with a fractionation schedule of 48 Gy in 24 fractions.[74] The use of IMRT appears to decrease both severity and volume of perineal skin reactions, hematologic suppression, and gastrointestinal toxicity in single institution and group studies. Improvement in acute treatment-related toxicities with IMRT may lead to decreased requirement for treatment break and shorter overall treatment times.

The overall treatment time may affect the outcome of radiotherapy or chemoradiation. In an RTOG pilot study evaluating 59.4 Gy with 5-FU and MMC that included a planned treatment break, 30% of patients required a colostomy by year 2 compared with only 7% in the RTOG/ECOG randomized trial, which did not use planned treatment breaks.[171] Pooled data analysis of RTOG 8704 and 9811 determined that each increase in treatment duration by 14 days was associated with a 9.4% increase in risk of failure requiring colostomy.[172]

Tumor Regression

Tumor regression may be slow after radiation therapy alone or chemoradiation, with the time to complete regression ranging from 2 to 36 weeks (median, 12 weeks).[74] Preliminary results from a secondary analysis from the ACT II study evaluating optimal time to assess clinical complete response (CCR) found that 29% of patients not in CCR at 11 weeks achieved CCR at 26 weeks. As early surgical salvage would not have been appropriate for these patients, CCR at 26 weeks has been recommended as the optimal timing of response for future trials.[173]

An alternate approach in patients with high risk of local persistence or relapse (T4N0, T3-4N+) would be to use PET-CT response instead of CCR to determine when surgical salvage is indicated. This may lead to better rates of surgical salvage and allow the possibility of local excision instead of APR in select patients.

Most recurrences at the primary site manifest within 2 years of treatment.[74] When concurrent chemotherapy is not used, tumor regression may be even more prolonged. In a French study of 193 patients with anal cancer treated with radiation therapy alone, the mean time to a complete response was 3 months after the completion of therapy, and some patients required as long as 12 months for a complete response.[91] However, the rapidity of the clinical response to therapy may also be prognostic. Another institution from France reported that patients with T3 to T4 tumors who had a tumor reduction of 80% or less at the completion of the first phase of radiotherapy (30 Gy to 45 Gy of EBRT) had 5-year CFS of only 24.8% compared with 65% among patients with a response of more than 80% ($p = 0.002$).[174]

Although routine biopsies have been required 4 to 6 weeks after the completion of therapy in several studies,[80,144,145] routine biopsies should not be performed on patients with regressing or clinically absent tumors. Treatment with 30 Gy to 50 Gy plus 5FU-MMC is associated with negative biopsy findings in 85% to 90% of patients 4 to 6 weeks after completion of radiotherapy.[80,144,145] Because of accelerated repopulation in surviving clonogens, a low-dose radiation boost after a 6-week break is unlikely to provide any benefit. The purported benefit of additional therapy for 7 of 22 patients in the RTOG/ECOG study is more likely a result of continued slow tumor regression after initial therapy than the result of the addition of 9 Gy of irradiation and cisplatin chemotherapy.

Treatment Tolerance

The acute toxicity associated with therapy for anal cancer may depend in part on the radiation fraction size and schedule and how chemotherapy is used. Investigators at PMH reported a decrease from 75% to 40% in acute grade-3 toxicities when the fraction size was reduced from 2.5 Gy to 2 Gy or when a planned treatment break was used.[74] Acute toxicity is markedly higher when MMC is added to 5-FU and radiotherapy. In the RTOG/ECOG trial, 26% of patients who received 5-FU and MMC together experienced grade-4 or grade-5 toxicity (3% treatment-related deaths), compared with only 7% of patients receiving 5-FU (0.7% treatment-related deaths).[139] As noted previously, IMRT appears to decrease the incidence of grade-3 or higher treatment intolerance.[165]

For patients receiving both MMC and 5-FU, the most common life-threatening toxicity is bone marrow suppression resulting in neutropenic sepsis. In addition, essentially all patients will experience a perineal skin reaction.[85] In the RTOG/ECOG study, confluent moist desquamation was reported in 55% of patients treated with this combination.[171] Mild to moderate diarrhea may be experienced by two thirds of patients, and nausea and vomiting by 25% and 15%, respectively.[85]

Late treatment-related complications are usually diagnosed within 2 years of treatment.[90] Asymptomatic or minimally symptomatic perineal fibrosis, telangiectasia, and minor intermittent bleeding from the anorectal region or bladder may be observed.[175] Severe late effects that affect a patient's social life or require surgical intervention have been reported in as many as 15% of patients.[74,78,91] These effects include anal incontinence, intestinal obstruction, chronic diarrhea, chronic pelvic pain, fistula, or bladder dysfunction.[78] Elderly women may be at increased risk for fractures of the femoral head and neck, especially if the radiotherapy fields encompass the entire femoral head and neck in both anterior and posterior treatment fields.[128,159] Late complications may necessitate colostomy for management in 2% to 10% of patients.[74,75,77,91,94,128,156] Whether the use of IMRT will reduce late toxicity remains to be seen.

Late complications of radiotherapy may be more likely when treatment is delivered with fraction sizes larger than 2 Gy.[74] Late complications are also more common in patients with locally advanced tumors; one series reported late effects in 23% of patients with T3 or T4 tumors compared with only 6% of patients with T1 or T2 tumors.[90]

Some investigators have reported that patients who are positive for HIV with anal cancer have reduced tolerance for combined chemoradiation regimens.[176,177] Compared with patients who are HIV-negative, patients who are HIV-positive are more likely to require treatment breaks, hospitalization for acute reactions, and chemotherapy dose reductions.[176,178] In addition, survival of patients with HIV is often limited; one report found a 29% 2-year survival for patients who are HIV-positive compared with 71% at 4 years for patients who are HIV-negative.[176] Although the best treatment strategy is unknown, low-dose chemoradiation in a small series of patients has been reported to result in a satisfactory tolerance and response in patients who are HIV-positive and in patients with AIDS without major opportunistic infections.[178]

The advent of highly active antiretroviral therapy (HAART) in the management of patients who are HIV-positive appears to have led to improved tolerance and treatment outcomes among patients who are HIV-positive. A pooled retrospective analysis from four institutions of 121 patients with anal cancer treated in the HAART era revealed similar clinical complete response rates (≥92%) and OS among patients who are HIV-positive and HIV-negative.[179] However, patients who are HIV-positive were much more likely to fail locally by 5 years (62% versus 13%; $p = 0.008$) and had increased dermatologic and hematologic acute toxicity with therapy. Other institutions have reported successful treatment and acceptable toxicity with standard anal cancer chemoradiation regimens among patients who are HIV-positive in the HAART era,[180-184] but some have also noted inferior long-term local control rates despite excellent initial response rates.[185]

TREATMENT ALGORITHM AND FUTURE DIRECTIONS

Figure 52-3 is a diagnostic and treatment algorithm for patients with newly diagnosed anal cancer.

Future investigations in the clinical management of anal cancer should be focused on improving efficacy among patients with locally advanced disease but also reductions in acute and long-term morbidity from therapy. The continued advances in treatment target definition, radiation conformality (e.g., IMRT), and accuracy of radiotherapy delivery through image-guided radiation therapy (IGRT) afford the opportunity for the prospective study of dose escalation among patients with locally advanced disease at presentation. In addition, these technologies provide opportunity for reducing treatment toxicity by limiting the dose to the genitalia, femora, bladder, bowel, and bone marrow, as has been demonstrated with early clinical experience.

Though RTOG 9811 demonstrated a reduction in severe acute hematologic toxicity with the experimental cisplatin-based arm, there is an opportunity for study of newer cytotoxic, radiosensitizing agents in an attempt to improve efficacy or reduce chemotherapy-related side effects. In addition, the incorporation of biologic agents with treatment has the potential to improve efficacy. There is no role for maintenance chemotherapy after definitive chemoradiation at this time.

Advances in imaging may also improve therapy and medical decision making in the management of anal cancer. As discussed, PET/CT imaging improves the initial staging of anal cancer and may aid in evaluation of the response. The value of early reimaging with PET as a predictor of response to therapy and possibly to guide selection of the total radiotherapy dose and earlier surgical salvage (local excision, APR) has not yet been investigated.

Despite the rarity of anal cancer, major advances in the laboratory and clinic have led to an increased understanding of anal neoplasia that has improved treatment outcomes. As pathways leading to anal carcinogenesis are more fully described and the influences of HPV and other infectious agents are better defined, expanded research efforts focusing on prevention will be possible. However, further advances in the prevention and treatment of anal cancer will require continued commitment to prospective trials.

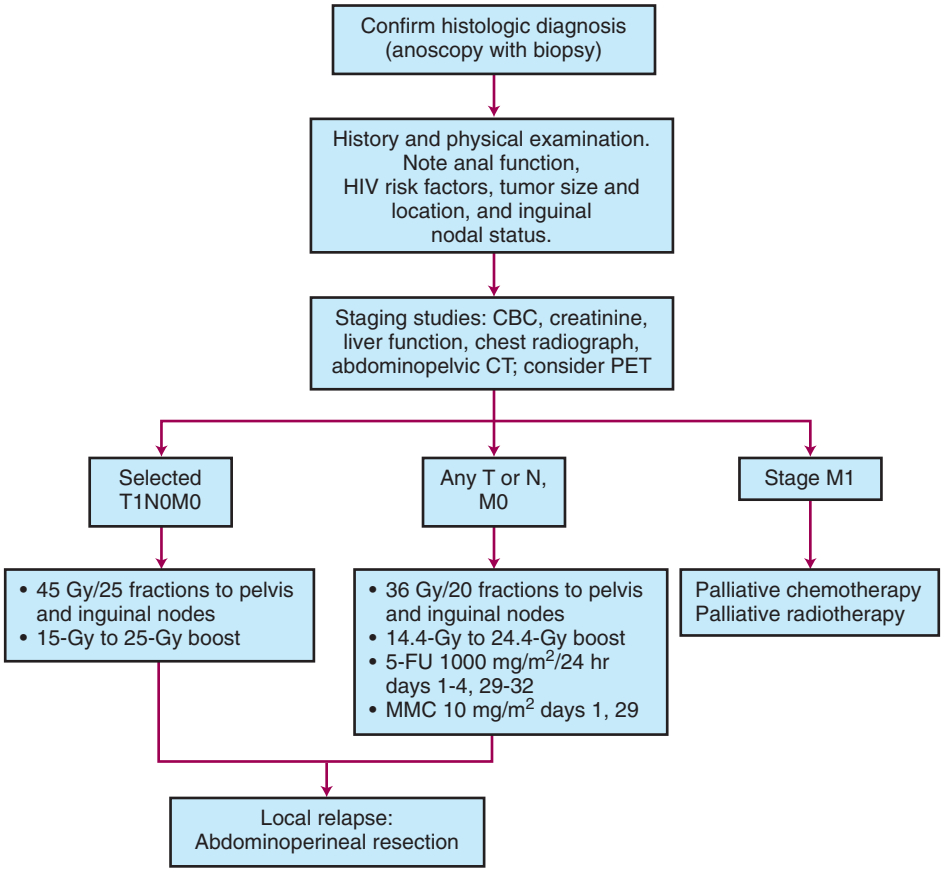


Figure 52-3 Diagnostic and treatment algorithm for newly diagnosed anal cancer. *5-FU*, 5-fluorouracil; *CBC*, complete blood count; *HIV*, human immunodeficiency virus; *MMC*, mitomycin C; *PET*, positron emission tomography.

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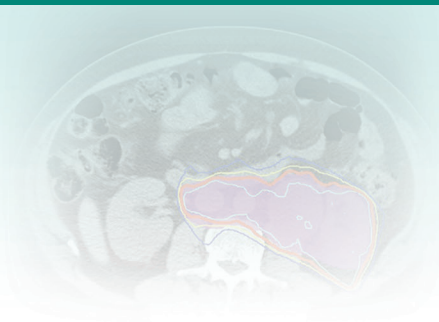
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Overview

Anthony L. Zietman

Since the publication of the last edition of this textbook, the field of genitourinary oncology has continued to change dramatically. It has truly become a field that is intensely multidisciplinary, and radiation oncologists, often substantially outnumbered in the multidisciplinary clinic, must be masters of the published data. Genitourinary oncology has become one of the areas in which practicing radiation oncologists are likely to spend a substantial proportion of their time and one that they cannot choose to ignore.

Developments in genitourinary oncology illustrate the best and some of the more problematic aspects of contemporary medicine. There is much research in areas of spectacular technologic advance, but too much has been widely adopted without sufficient and rigorous scientific evaluation. New drug therapies are being rapidly added to practice but how best to incorporate them with existing therapies and radiation remains an urgent need. Randomized trials are being performed, but they often struggle to overcome decades of therapeutic prejudice. This overview provides highlights of the field that are reviewed in greater detail by the authors of the following chapters.

PROSTATE CANCER

Prostate cancer, along with breast and lung cancers, continues to be the most common type of cancer seen by practicing radiation oncologists. This situation reflects the explosion in early case detection through the widespread use of the prostate-specific antigen (PSA) blood test and the successes of therapy. The incidence peaked in the early 1990s, a few years after the introduction of PSA because the prevalence of the disease in the previously unscreened population was reduced. As predicted, the rate fell, but never to baseline levels. It now holds steady at more than twice the original annual incidence, and the detection rates far exceed the death rates.

It is becoming clear that prostate cancer is being detected in many more men than require treatment.[1] Because we still struggle to sort the "tigers" from the "pussycats," radiation oncologists and urologists have been erring on the side of caution and treating most patients who are diagnosed with prostate cancer.[2] This will change in the near future because of widely expressed concerns by patients, physicians, and policy makers about overtreatment to the point that prostate cancer has come to be regarded as the "bad boy" of the U.S. healthcare system. Randomized trials are being published that call into question many of our assumptions of the last 30 years.

In the years ahead, biomarkers and radiologic advances will likely evolve that, combined with PSA testing and Gleason grading, will be able to determine who does and who does not require treatment. When that happens, the caseload will decline, and oncologists will be able to concentrate their energies and their effective therapies on the patients who need them. Active surveillance for low-risk prostate cancer is now a mainstream approach that is gathering advocates. What the role of radiation oncologists will be in following these patients is yet to be determined and will, in part, define the way we practice in the future. Will this role default to us, to the urologists, or back to primary care? More than one third of patients who elect for active surveillance end up requiring therapy and many of these, being older patients, choose radiation. Thus, it is incumbent on radiation oncologists to remain involved.

Whether patients require treatment at the time of diagnosis or at some later stage one question that remains central is: Which is the most effective therapy? External beam radiation therapy (EBRT) has progressed substantially over the last two decades. In 1999, the Patterns of Care Study showed that most radiation oncologists in the United States were using three-dimensional conformal techniques. These, in turn, have been replaced by other forms of EBRT, such as intensity-modulated radiation therapy (IMRT), and more recently, by proton beam and stereotactic techniques.

Prospective trials have shown that increased radiation doses yield higher cure rates and that highly conformal techniques are the only safe ways to give these doses.[3,4] This is a superb example of practice changing on the basis of strong evidence. Whether the more recent evolutions in delivery systems offer dosimetric gains that are of significance remains controversial, but the now-routine use of patient-reported outcomes in radiation therapy trials will answer the question. The use of image guidance has gained widespread acceptance, and few centers currently deliver prostate treatment without it. The next decade will be spent evaluating the patient-reported benefits of these technical advances and integrating them with advances in anatomic and functional imaging to develop boost techniques for subtotal prostate irradiation.

The substantial technical improvements have made EBRT a much more lengthy and expensive process. As a result, alternative approaches have been proposed in an attempt to reduce the social and economic burdens. One such method is hypofractionation. In the past, proponents of its use were considered "heretics," but evidence now suggests that hypofractionation may be beneficial because prostate cancer may have a low α/β ratio.[5] Better targeting may now even allow for extreme, and thus patient friendly forms of hypofractionation. These concepts are being tested in randomized trials in the United States, Canada, and Europe. Such investigations are vital because many centers are using this approach without a clear understanding of its biologic implications and risks. Uncertainties remain about the most appropriate doses particularly at the extremes of hypofractionation. Also popular

has been low-dose-rate and high-dose-rate (HDR) brachytherapy, which have many proponents and a body of favorable evidence. Despite this, these therapies are sliding out of favor in competition with other novel radiation and nonradiation approaches.

Patients with early prostate cancer have a disease that is so likely to be cured that quality-of-life issues become important for survivors. Appropriate instruments are being used to report on such issues at an increasing rate, and it is evident that effects on quality of life will become one of the important factors influencing patients and physicians in choosing therapy in the years ahead.[6]

For locally advanced disease, there have been tremendous efforts by the large U.S. and European cooperative groups to perform trials, answer questions, and determine standards of practice. The role of androgen therapy combined with EBRT has become better defined. Results with radiation alone for low-risk disease are sufficiently good that these patients probably do not need androgen therapy[7]; intermediate-risk disease probably does require androgen therapy but only a short neoadjuvant course[7,8]; and high-risk prostate cancer certainly needs it for years in a manner akin to breast cancer.[8,9] The role of pelvic lymph node irradiation in locally advanced disease is one that will not go away. RTOG 94-13 has suggested that there may be a small disease-specific survival advantage when it is given, and newer technology is being used to treat the lymph nodes in a fashion that results in less severe side effects than in the past.[10] Active trials are addressing the use of high-dose irradiation in addition to androgen deprivation, and now with novel forms of androgen deprivation also chemotherapy. These represent a brave new frontier in the management of men with a disease that indisputably needs more effective therapy.

Despite the now stable incidence of prostate cancer and the increase in active surveillance the number of patients managed surgically continues to increase, in large part, riding a wave of enthusiasm for robotic technology. A significant proportion of these patients experience a subsequent failure and postoperative radiation is now a large part of the contemporary radiation oncologist's practice. Large randomized trials have clearly shown that irradiation has a role in the postoperative management of prostate cancer. It is becoming widely accepted not only in salvage treatment but also in adjuvant treatment.[11,12]

Prostate cancer now joins breast and testicular cancers and lymphoma as an exemplary field for clinical research. One trial builds on the "shoulders" of the next, and piece-by-piece, knowledge is accumulated to create a clearer picture of management. Prostate cancer also has become a model in its multidisciplinary approach. Through brachytherapy and combined-modality treatment, radiation oncologists, urologists, and medical oncologists have developed a new and productive spirit of cooperation.

BLADDER CANCER

Bladder cancer is a disease for which substantial gains have been made. A growing body of supportive evidence has made the multimodality approach to bladder preservation a recognized alternative to radical cystectomy.[13] The Radiation Therapy Oncology Group (RTOG) continues to refine treatment techniques in a series of trials optimizing the doses of irradiation and chemotherapeutic agents. In the United Kingdom and northern Europe, there has been much work on better defining the treatment volume, and randomized trials are answering questions about nodal treatment and the value of whole bladder versus partial bladder irradiation. There is interest in daily image guidance for this highly mobile tumor because the most severe side effects of bladder cancer treatment are gastrointestinal rather than genitourinary complications. Any method radiation oncologists can find to tighten target volumes and reduce the volume of small bowel treated will be a step forward for patients with bladder cancer. Several new studies look at improving the tolerance of chemoradiation through altered fractionation and gentler chemotherapy.

Several molecular markers and potential molecular targets have emerged in bladder cancer and are creating new avenues for clinical research. Future trial group research will likely be focused on using markers to better select patients for bladder preservation and on the interaction of targeted therapies with chemoradiation.

With all the progress, why is multimodality treatment with organ conservation not more popular with patients and urologists? The urologists have traditionally been the gatekeepers, and their belief that the bladder must be removed rapidly to maximize the chance for cure is strong, as is the belief that an irradiated bladder functions poorly and that superficial and invasive local failures are common and difficult to manage. The section of this chapter on bladder cancer summarizes the data that may be used by radiation and medical oncologists to argue for organ conservation as an alternative to immediate cystectomy for the willing patient. Recent high-profile randomized trials from the United Kingdom and the United States looking at radiation therapy with and without chemotherapy will likely strengthen the argument of those proposing organ preservation.[14,15]

TESTICULAR CANCER

Seminoma is one of the most radiation sensitive of all tumors, and radiation oncologists take particular pride in being able to promise a high probability of cure. There are few cancers for which cure rates exceed 95%, as they do in stage I to II seminoma. For 40 years, adjuvant irradiation has been the principal player alongside orchiectomy, but more recently, there has been a stepwise retreat in its use. Large volume irradiation has a long-term legacy in the treatment of young male patients. Long ago, the mediastinal field was dropped because of concerns about cardiac toxicity and because improved chemotherapy offered effective salvage in cases in which it was needed. Recent concerns revolve around radiation-induced tumors.[16] Conformal techniques are now routinely used to spare some normal tissue, and in a series of British and Canadian randomized trials, substantial reductions in target volume and dose have been tested and validated.

Since the first edition of this book appeared, the standard adjuvant treatment in Europe has shrunk from a full "dog-leg" field treated to 30 Gy down to a paraaortic field alone treated to only 20 Gy.[17] Trials have looked at single-agent carboplatin as an alternative to irradiation, and it has been found to be effective, although its long-term effects are unknown.[18] In Canada, recognizing that most men with small tumors were disease free after orchiectomy, a policy of surveillance became commonplace, with treatment deferred and given only to those who ultimately prove to have stage II disease. In Chapter 55, Warde documents these changes and the discussions that the contemporary radiation oncologist must have with any newly diagnosed patient. The recent story of irradiation in seminoma mirrors that of irradiation in Hodgkin's disease in that the search for the dose that is "as low as we can go" has been driven by the success of the treatment.

KIDNEY AND URETERAL CANCERS

Renal cancer, cancer of the renal pelvis, and cancer of the ureter have traditionally been the preserve of the surgeon.

There has been a tremendous stage shift in renal cancer with the routine discovery of small, incidental tumors on abdominal computed tomography (CT) scans performed for other reasons. Development of partial nephrectomy, laparoscopic nephrectomy, and percutaneous ultrasound ablation has provided effective therapy that cannot be matched by any medical or radiation therapy alternative.

Although renal cell cancer is recognized to be relatively insensitive to radiation, irradiation has a role to play in locally advanced or metastatic disease. It may be considered as an option after resection of disease with positive margins or after resection of an isolated local recurrence. Intraoperative irradiation may be used as a supplement to EBRT to deliver the high doses required for local tumor control without causing excessive bowel toxicity. In metastatic disease, irradiation to a high dose has an important role in maintaining the quality of life of patients who may live for many years. Stereotactic irradiation has become commonplace for the treatment of brain metastases, and this technique allows for the delivery of the high doses needed to ablate disease in this common site of spread. Because patients are now living longer with the development of effective targeted agents, it is likely that these techniques will be in high demand for the management of metastases outside the central nervous system (CNS).

Cancers of the renal pelvis and ureter are different from renal cell adenocarcinomas. Because they are transitional cell in origin, they behave more like bladder cancer and are more sensitive to irradiation and cisplatin-based chemotherapy. Organ-sparing approaches are not used, however. There is little gain in function or quality of life for preserving a kidney or ureter when another exists, and surgery is the mainstay of treatment. Chemoradiation may offer some assistance when the disease is locally advanced or has spread to nearby lymph nodes.

PENILE CANCER

Penile carcinoma is another cancer for which organ conservation may be expected to be popular. In Chapter 57, Crook and Mazeron demonstrate that penile cancer may in many ways be regarded like any other skin cancer but in one way it stands apart, and that is in its high propensity for nodal spread. They also show that effective organ-sparing radiation treatment is possible. Treatment is technically challenging, and in the United States, where men are circumcised and the disease is rare, there is little accumulated experience. However, treatment by brachytherapy or EBRT follows simple first principles, and it is not beyond the reach of any skillful radiation oncologist.

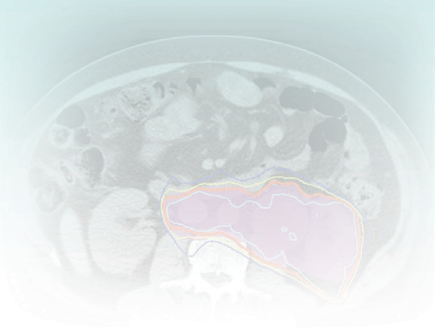
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CHAPTER

53 Prostate Cancer

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INCIDENCE

There was an estimated 220,800 new cases of prostate cancer in the United States in 2015 and 27,540 deaths. Although the incidence of new cases has been relatively stable since 1994 because of prostate-specific antigen (PSA) screening, the rate of death has been declining as a result of earlier diagnosis and treatment. One in six American men will develop prostate cancer during their lifetime.

BIOLOGIC CHARACTERISTICS

PSA, clinical tumor stage, and tumor grade are predictive of extraprostatic tumor extension, lymphatic and hematogenous metastasis, and therapeutic outcome. These factors may be combined to improve the accuracy of predicting disease-related survival.

STAGING

The tumor (T), nodes (N), and metastasis (M) (TNM) classifications may be determined by clinical examination, diagnostic imaging, and pathologic examination of prostatectomy and lymphadenectomy specimens.

Digital rectal examination (DRE), with or without ultrasound, Gleason score of the biopsy, and PSA form the basis of the clinical staging workup. Total body bone scan and pelvic imaging with either computed tomography (CT) or magnetic resonance imaging (MRI) are selectively used in high-risk patients.

PRIMARY THERAPY

The selection of radiation therapy (RT) and radical prostatectomy as primary therapeutic modalities is based on life expectancy, comorbidity, tumor-related characteristics, and patient expectation with regard to quality of life issues.

In clinically localized disease, several years of observation are required to measure the impact of a particular treatment on the natural history of the disease. RT provides outcomes for patients with organ-confined disease that compare favorably with expected survival duration and is an alternative to radical prostatectomy.

Three-dimensional and intensity modulated external beam RT allow radiation dose to conform to the target, while minimizing exposure of nontarget (e.g., rectal and bladder) tissues.

Transperineal ultrasound guided brachytherapy provides a means for accurate radioactive source placement. Long-term cancer control and survival are comparable to radical prostatectomy.

ADJUVANT THERAPY

Risk factors for postprostatectomy local tumor recurrence include tumor involvement of surgical margins, seminal vesicles, or pelvic lymph nodes. Adjuvant RT improves local tumor control, disease-free, metastasis-free, and overall survival (OS).

LOCALLY ADVANCED DISEASE

External beam radiation therapy (EBRT) is considered the preferred primary treatment modality. The addition of neoadjuvant androgen deprivation (AD) to EBRT improves local tumor control and progression-free survival (PFS) rates. AD as adjuvant therapy to EBRT diminishes the risk for local tumor recurrence and metastatic disease relapse. Improved survival duration may also be observed, particularly for patients with high-grade tumors.

PALLIATION

EBRT effectively relieves symptoms resulting from locally progressive disease or metastases. Systemic radiotherapy with radium-223 (^{223}Ra) improves survival and reduces the risk of skeletal fractures, spinal cord compression, and other adverse skeletal events.

Prostate cancer is an important health issue that provokes considerable debate among healthcare professionals, agents of the healthcare policy, patient advocates, insurers, and other third-party payers. The high prevalence of prostate cancer coupled with the variable natural history and multiple treatment approaches encourages deliberation as to the appropriate approach to the population of men that may confront this illness. In this context, the radiation oncologist may engage in discussion with primary care physicians, urologists, and other healthcare professionals concerned for the welfare of patients with prostate cancer.

EPIDEMIOLOGY AND ETIOLOGY

Epidemiology

In 2015, an estimated 220,800 Americans were diagnosed with prostate cancer, accounting for 28% of all newly diagnosed cancers in men.[1] It appears that one in six American men will develop a clinically recognized invasive prostate cancer during his lifetime. Ninety percent of cases are expected to be diagnosed with local or regional stage disease for which the 5-year relative survival rate approaches 100%.

A broad base of knowledge relevant to multispecialty interaction and detailed information regarding the current controversies is essential for a productive dialogue. Furthermore, the clinician should interpret existing medical literature with a critical view and should strive to contribute to clinical research efforts that will ultimately improve the care of patients with this disease.

The age-adjusted annual incidence rate increased 66% overall between the periods of 1975 to 1979 and 1987 to 1991.[2] This change largely reflected the increased detection of localized, rather than regionally advanced or metastatic, prostate cancer cases. In recent years, the incidence of newly diagnosed cases has dropped 1.9% per year from 2001 to 2009.[1] The recent decrease in the incidence of prostate cancer may reflect stabilization related to PSA screening. Prostate cancer remains the second-leading cause of cancer death in men with an estimated 29,720 deaths in 2013. As with the incidence of newly diagnosed cancers, there has been a 40% drop in prostate cancer death rates over the past two decades. The annual death rate from prostate cancer was 38.56 in 1990 compared to 23.6 deaths per hundred thousand men during the years 2005 to 2009.[1]

Etiology

Cohort and case-control studies are the two principal methods used to ascertain the etiology of cancer.[6] Several reports describe various host-related and environmental factors that appear associated with prostate cancer (eBox 53-1), but it is not yet understood which factors directly initiate or promote prostate carcinogenesis. As discussed by several authors,[7,8] long-term androgen exposure, which is required for normal prostatic development and for cancer growth and maintenance, advanced age,[9] race/ethnicity,[10-12] and familial history of prostate cancer[13,14] are presently viewed as the most likely risk factors. Other associations such as diet, body mass index, energy balance, and physical activity are becoming more suspect.[15-19]

Hormonal Factors

Although several lines of investigation suggest the importance of hormones in the promotion of prostate cancer, their mechanism of action and interactions are not clearly understood. Animal studies indicate that chronic testosterone exposure markedly enhances the effects of carcinogens on prostatic tissues.[20] Furthermore, both benign prostatic hyperplasia (BPH) and prostate cancer simultaneously develop under androgen stimulation, and some reports suggest that men with benign hyperplasia are at increased risk for development of prostate cancer.[21,22] Various authors also report that men with prostate cancer have alterations in serum androstenedione, dihydrotestosterone (DHT), sex hormone–binding globulin, or testosterone,[23-26] which was also noted to vary according to race and ethnicity.[25,26] Despite these associations, circulating androgens do not fully explain the development of prostate cancer and downstream effects in target tissue may be more relevant.[27] Testosterone is the main circulating androgen, but it is converted to DHT in prostate and other peripheral tissues by 5α-reductase. DHT binds the androgen receptor leading to nuclear translocation and activation of transcriptional and androgen responsive genes. The activity of 5α-reductase is different in various ethnic groups and may partially explain the variable incidence and aggressiveness of prostate cancers by race.[26,28]

Age

Age may be the single most important factor associated with prostate cancer because most elderly men have histologic evidence of cancer in the prostate gland,[4] and the rate of clinical detection is a direct function of age.[1] Although several causes may be invoked such as senescence of the immune system, higher levels of oxidative stress, prolonged exposure to carcinogens, and impaired response to DNA damage, an exact explanation for this association is lacking.

Hereditary Factors

Twin studies suggest that heritable factors account for a proportion of prostate cancer risk.[29] Several investigators observed familial clustering of prostate cancer and suggested that genetic constitution may increase susceptibility to the disease.[13,14] It has been estimated that as many as 5% to 15% of prostate cancer cases are hereditary or familial,[30,31] and they are typically diagnosed at an earlier age than sporadic cases.[30] Carter et al describe an increased risk of the disease, a greater number of affected relatives, and an earlier age of onset with the familial type compared with the sporadic form.[13] The age-adjusted risk of developing prostate cancer in the setting of a familial predisposition is approximately twice that of the general population but may be greater (i.e., 5- to 11-fold), depending on the number of affected first-degree relatives.[13,32]

Racial and Ethnic Variations

Prostate cancer incidence is characterized by marked racial and ethnic variation that is dependent on geographic factors.[1] For example, a 30- to 50-fold difference in the incidence of the disease is observed between black men and native Asians.[34] In the Health Professionals Follow-up Study, African American race was strongly associated with a risk of developing prostate cancer.[35] However, a complex interaction between race and ethnicity and environment exists. For example, the incidence of cancer in a particular racial or ethnic group (e.g., Japanese) tends to shift toward that of the population in the geographic area to which that group immigrates (e.g., the United States) as the group assimilates to its new environment and culture.[36] Furthermore, certain racial and ethnic groups (e.g., blacks) present with more-advanced prostate cancer and appear to have a stage-adjusted outcome that is worse than for other members of their society (e.g., whites).[37,38] Racial variations of hormonal, dietary, genetic, and perhaps socioeconomic factors may account for such findings,[10,26,28,39,40] but definitive evidence in this regard is lacking, and further research is necessary to clarify the association between race and ethnicity and prostate cancer risk.

Dietary Factors

The role of dietary factors in prostate cancer pathogenesis is difficult to discern because research in this area is confounded by complex interactions with other potential risk factors. There are striking racial or ethnicity and geographic variations in prostate cancer incidence that may have a dietary basis. In particular, a high-fat diet appears to correlate with prostate cancer incidence and mortality,[8,15,39,41] whereas ingestion of retinol,[42] certain carotenoids (e.g., lycopene),[8,43] phytoestrogens,[44] and vitamin D may be protective.[45] The influence of other vitamins (e.g., vitamin E) and minerals (e.g., zinc) is uncertain.[8] In a large prospective cohort study of American men, Sinha reported an association of processed and red meat with the total prostate cancer incidence and the incidence of locally advanced disease.[46] Other dietary factors such as α-linolenic acid are associated with increased risk of prostate cancer, whereas tomato-based products containing lycopene have been associated with reduced risk.[35,47] It has been suggested that a diet high in fruit and vegetable intake is associated with a lower rate of prostate cancer.[48] The Health Professionals Follow-up study demonstrated and association for tomato sauce, the primary source of bioavailable lycopene, and a lower risk of prostate cancer.[47] In the Selenium and Vitamin E Cancer Prevention Trial (SELECT) investigators identified an association of high serum levels of long chain omega-3 polyunsaturated fatty acids and the development of prostate cancer.[49]

The incidence of incidental (or latent) prostate cancer observed at autopsy examination and the incidence and prevalence of clinically manifest prostate cancer increase substantially with age.[1,3,4] Information from the Surveillance, Epidemiology, and End Results (SEER) Program indicates that approximately 1.8% of American men between ages 40 and 59 years had a clinical diagnosis of prostate cancer, whereas 15% of men 60 to 79 years old would have prostate cancer by the time they attained this age. Although the prevalence of incidental carcinoma does not exhibit marked geographic variation, the regional disparity in the antemortem clinical expression of the disease and the cancer mortality rate of prostatic carcinoma is noteworthy.[3,5] North America, Australia/New Zealand, Western and Northern Europe, and the Caribbean have a much higher incidence of this disease than Asia.[5]

eBOX 53-1 Potential Risk Factors for Prostate Cancer

Advanced age
Benign prostatic hyperplasia
Diet (e.g., fat intake)
Familial history of prostate cancer
Histologic precursors (e.g., prostatic intraepithelial neoplasia)
Hormonal factors (e.g., serum testosterone)
Occupational exposure (e.g., cadmium)
Race or ethnicity (e.g., black)
Sexual behavior (e.g., multiple partners)
Sexually transmitted disease (e.g., herpes virus)
Tobacco use
Vasectomy

A meta-analysis of 13 case-control and cohort studies determined a relative risk in first-degree relatives of 2.5 (95% confidence interval [CI], 2.2 to 2.8).[14] The highest risk was in relatives of cases diagnosed before 60 years of age. The risk of developing prostate cancer was 3.5-fold greater in men with two affected relatives.[14] Candidate susceptibility genes like *RNASEL*, *ELAC2*, and *MSR1* have been identified in cases of heritable prostate cancer,[31] whereas mutations in these genes are rare in the more common sporadic forms of the disease.[33]

Some vitamins, minerals, and other micronutrients have been implicated as having a protective role in prostate cancer. An association between low levels ultraviolet light exposure and prostate cancer mortality rates led to the hypothesis that vitamin D insufficiency may play a role in prostate cancer risk.[50] In contrast, the European Prospective Investigation into Cancer and Nutrition (EPIC) showed no significant association between circulating levels of 25-hydroxyvitamin D and risk of prostate cancer.[51] Giovannucci hypothesized that high dairy and meat consumption increase risk of prostate cancer by lowering 1,25(OH)2D.[52] Indeed, there may be important interactions with vitamin D and calcium that may influence the risk of developing prostate cancer. In the Health Professionals Follow-up study a high dietary calcium intake was associated with an increased risk of prostate cancer.[19] Halthur suggests that high serum levels of calcium in young overweight men may be a marker for a decreased risk of developing prostate cancer.[53] EPIC reported an increase risk of prostate cancer with dairy proteins and dairy calcium.[17] The Nutritional Prevention of Cancer Study Group tested selenium supplementation as a preventative agent for a number of cancers. Clark reported a 63% reduction in the incidence of prostate cancer with oral selenium supplementation.[54] Similarly, a secondary analysis of the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study showed a 32% reduction in the incidence of prostate cancer.[55]

Body Habitus

Although studies have failed to consistently show that obesity is related to prostate cancer incidence, a study of more than 400,000 men (Cancer Prevention Study II) showed that men with higher body mass index (weight versus height) had an increased risk of prostate cancer death as compared to men with a lower body mass index.[15,16] The mechanism through which obesity might cause prostate cancer or a higher mortality from prostate cancer is complex but is thought to be related to a state of hyperinsulinemia that leads to higher levels of insulin-like growth factor and available sex steroids (androgens).[56]

Precancerous Lesions

Certain atypical epithelial lesions may be precursors of prostate cancer, and their presence in a prostatic biopsy may serve as a risk factor for this condition. These lesions may now be classified into two categories: prostatic intraepithelial neoplasia (PIN) and atypical adenomatous hyperplasia.

Of the two categories, PIN represents the putative precancerous end of the morphologic continuum of cellular proliferation and is more strongly associated with prostate cancer.[76] Two grades (low and high) are recognized, with high-grade PIN considered a precursor of invasive carcinoma.[76,77] Studies suggest that PIN predates prostate cancer by 10 years or more, with low-grade PIN first emerging in the third decade of life.[78] PIN is often found in proximity to carcinoma, and its presence warrants search for invasive carcinoma.[79] Davidson et al[80] noted that 35% of patients with PIN had prostate cancer identified on subsequent biopsy, which is consistent with the results of other studies.[81] These results suggested that PIN was a likely and strong risk factor for prostate cancer that warrants close surveillance and follow-up.[82,83] However, in the Prostate Cancer Prevention Trial the incidence of a new cancer diagnosis on repeat prostate biopsy was as high as 35% even in the absence of high-grade PIN.[84] Specific molecular findings associated with high grade PIN may be able to predict which men may have invasive cancer on repeat biopsies. In a study of biopsy specimens expressing Alpha-methylacyl-CoA racemase (AMACR), there was a 5.2 times greater incidence of cancer on repeat biopsy compared to high-grade PIN without AMACR positivity.[85] AMACR overexpression was also more often identified in high-grade PIN adjacent to cancer than high-grade PIN lesions distant from cancer in prostatectomy specimens.[86]

PREVENTION AND EARLY DETECTION

Prevention

Prostate cancer is an androgen-dependent tumor with a prolonged latency between initial malignant transformation and clinical expression, features well-suited to disease prevention efforts.[3] Progression from tumor inception to invasive carcinoma often takes decades, allowing sufficient time for intervention.[87] Chemoprevention strategies that use high-risk target populations have the greatest potential to identify promising agents in a time-efficient manner.[88] The results of focused studies such as these can then be confirmed in large-scale trials applied to the general population. The ability to alter the hormonal environment of the host provides an excellent opportunity to interrupt the multistep process that results in clinical expression of the disease.[3] Advances in our understanding of the process of carcinogenesis and the availability of promising new chemopreventive agents, including those producing reversible AD, have the potential to favorably affect the morbidity and mortality of prostate cancer in the foreseeable future.

Luteinizing hormone–releasing hormone analogs (e.g., goserelin, leuprolide) reduce luteinizing hormone and (secondarily) testosterone levels. The long-term use of these agents may cause anemia, atrophy of reproductive organs, diminished muscle mass, loss of libido, and vasomotor instability, which limits the utility of these agents for chemoprevention in the general population. Nonsteroidal antiandrogens (e.g., flutamide, bicalutamide) competitively bind to androgen receptors in target tissues. These agents are tolerated in patients, although adverse effects may include gastrointestinal (GI) disturbance, gynecomastia, hot flushes, and a metabolic syndrome.

Intracellular 5α-reductase converts testosterone to DHT, the hormone responsible for prostate epithelial proliferation. DHT has greater affinity for the androgen receptor and is the primary agonist leading to prostate maintenance and growth. Three isoforms of 5α-reductase have been identified with various levels in different tissues. Type 1 is expressed in BPH and its expression is greatly increased in prostate cancer, especially high-grade tumors.[89] Type 2 5α-reductase expression is decreased in PIN and some early cancers but is increased in metastatic and recurrent prostate cancer.[89] The role of type 3 5α-reductase is less defined. Competitive inhibitors of 5α-reductase (e.g., finasteride and dutasteride) suppress intraprostatic DHT to castrate levels. The Prostate Cancer Prevention Trial (PCPT) was initiated to test the efficacy of finasteride as a chemoprevention agent in men at low risk of having prostate cancer.[90] This placebo-controlled Phase III trial randomized 18,882 eligible men (older than 55 years, normal DRE, and PSA levels <3 ng/mL) to finasteride (5 mg daily) or placebo for 7 years. There was a 25% reduction in the prevalence of prostate cancer over this 7-year period from 30.6% in the placebo group to 18.6% in the finasteride group.[90] Of note, however, is that more aggressive tumors, Gleason score 7-10, were more common in patients who took finasteride, 37% of all tumors and 6.4% of all men on the finasteride arm versus 22% of all tumors and 5.1% of all men on the placebo arm. The increase incidence of high-grade cancers seen in the PCPT trial has been a topic of great debate. The investigators have argued that the increase in high-grade cancers is a result of a detection-bias related to the reduced volume of prostate tissue and therefore a greater ratio of cancer to benign tissue. Furthermore, there was no dose effect from the finasteride with no significant increase in worse cancers with higher cumulative doses of the drug.[91] The PCPT study was not designed or powered to detect differences in cancer-specific survival or OS. Finasteride did reduce urinary symptoms compared to placebo, but there were also significantly more adverse sexual side effects.[90] A reduced volume of ejaculate, erectile dysfunction, loss of libido, and gynecomastia were more common in the finasteride group ($p < 0.001$), but urinary urgency, frequency, retention, urinary tract infection, and prostatitis were less common with finasteride ($p < 0.001$).[90]

The Reduction by Dutasteride of Prostate Cancer Events (REDUCE) trial, a Phase III study testing inhibition of 5α-reductase with dutasteride.[92] Dutasteride blocks both types I and II 5α-reductase suggesting it may be more effective at preventing the development of prostate cancer. The REDUCE trial is a randomized trial of placebo compared with dutasteride 0.5 mg administered daily to evaluate it as a chemopreventive agent for prostate cancer. The use of dutasteride was associated with a 22.8% lower risk of being diagnosed with prostate cancer 4 years after study entry. However, like the PCPT trial, the REDUCE trial has not shown a decrease in the incidence of prostate cancer death nor all-cause mortality. It may be that these medications decrease the likelihood of detecting clinically insignificant cancers but do not reduce the incidence of potentially fatal disease.

Different factors may be at play in the carcinogenesis of nonagressive cancers and the evolution of disease to an aggressive form.[57] Taller height was associated with in increased risk of fatal prostate cancer in the Health Professionals Follow-up study.[35] Height may be a surrogate for dietary and hormonal influences that may affect the risk of prostate cancer.

Other Lifestyle Factors

Research regarding other lifestyle factors such as tobacco use, alcohol consumption, physical activity level, sexual behavior, and sexually transmitted diseases has provided mixed findings with regard to the importance of these factors in prostate cancer pathogenesis.[15,16,18,35,58-67] Previous infection with *Trichomonas vaginalis* has been associated with an increase risk of aggressive prostate cancer.[67] Vigorous physical activity was associated with a lower risk of fatal prostate cancer in the Health Professionals Follow-up study.[35] In a meta-analysis including more than 88,000 cases, Liu reported a reduction in the incidence of prostate cancer with physical activity, particularly occupational activity.[68] Likewise, the EPIC study showed that only occupational and not leisure activity was associated with a reduction in prostate cancer risk.[18] Although the results of these studies may be affected by the fact that several lifestyle factors may be simultaneously interacting and difficult to separate, nevertheless, this research increasingly suggests that there may be an effect for at least some of these etiologic factors.

Environmental Exposure

A link between environmental or occupational exposure to carcinogens and development of prostate cancer has also been explored, but establishing a correlation and identifying a causative agent(s) have been difficult. For example, laborers in heavy industry, rubber manufacturers, and newspaper printers may have a somewhat higher incidence of prostate cancer,[69] but this association is weak, and its significance remains uncertain. Exposure to cadmium, as from cigarette smoke, nickel-cadmium batteries, or certain paints, has been implicated as a carcinogen because cadmium workers have more aggressive prostate cancers and an increased cause-specific mortality.[70] A clear association between these factors, environmental or occupational exposure, and prostate cancer is conjectural, and further study is required before firm conclusions can be formed.

Vasectomy

Some investigations suggested that vasectomy increases androgen levels[71] or produces an immunologic reaction[72] that might promote prostate carcinogenesis. However, John et al[73] and Sidney et al[74] could not confirm this association in large cohort studies. Furthermore, the National Institutes of Health determined that information regarding a putative association between vasectomy and prostate cancer was not convincing and that a causative relationship had not been established.[75] Therefore, vasectomy should not be considered a prostate cancer risk factor.

The association of dietary consumption or serum levels of selenium and α-tocopherol and a low rate of prostate cancer has suggested that dietary supplements of these nutrients may protect men from the development of this disease.[55] Despite this association, two prospective Phase III clinical trials did not show a reduction in the incidence of prostate cancer with vitamin or selenium supplementation. In the SELECT trial, there was no significant reduction in prostate cancer incidence related to either selenium or vitamin E supplementation.[93] The SELECT enrolled 32,400 participants to a Phase III randomized, double-blind, placebo-controlled trial with a 2×2 factorial design. The study was designed to determine the efficacy of selenium, vitamin E, or a combination of the two to prevent prostate cancer. In this trial, an increase of 1.17 relative risk of developing prostate cancer was associated with taking vitamin E, although there was no significant change in the risk when taking selenium or the combination. The Physicians' Health Study II enrolled 14,641 male physicians and randomized them to receive vitamin E and C supplements daily. Neither vitamin E nor C supplementation reduced the risk of prostate or other cancers.[94]

Early Detection

Considerable controversy surrounds the use of early detection programs for prostate cancer. Some argue that early detection efforts are too costly and will lead to the recognition of an increased number of clinically insignificant tumors because autopsy studies demonstrate a high prevalence of incidental tumors in older men.[5,87] Likewise, a study of prostate cancer discovered in organ donors found incidental prostate cancer in one third of men age 60 to 69, and 46% in men older than age 70.[95]

Contributing further to the arguments against prostate cancer screening are the limited sensitivity and specificity of PSA, DRE, and ultrasound in diagnosing cancer. Although DRE has high specificity for prostate cancer, it has a low sensitivity profile and is not considered an effective detection tool on its own.[96] In contemporary series, PSA testing with a threshold of 4.0 ng/mL has a sensitivity of only about 20%.[97] Although the sensitivity of PSA testing could be improved by lowering the threshold value for all men this would compromise the specificity and increase the detection of clinically insignificant cancers. Early detection strategies have also been criticized for exaggerated improvements in cancer-specific survival related to an early detection bias. In an early report, the use of PSA resulted in a diagnostic lead time of approximately 5 years[98,99] and longer in the detection of earlier-stage and lower-grade tumors.[100] Data from the European Randomized Study of Screening for Prostate Cancer (ERSPC) and SEER registry suggest the lead-time bias could range from 5.9 to 7.9 years.[101] Included in the debate over prostate cancer screening are the risks of overdetection and overtreatment. Overdetection occurs when men are found to have disease that would have remained silent and contributed no morbidity in his lifetime. Overtreatment occurs when an intervention plays no role in extending a patient's life or preventing morbidity from the illness. The real challenge for clinicians involved in the management of prostate cancer is the identification of clinically significant disease.

Arguments in support of prostate cancer screening include the 36% reduction in prostate cancer deaths seen between 1990 and 2005.[1] This trend began shortly after the introduction of PSA testing and statistical models suggest that PSA testing contributed to this decline.[102,103] Furthermore, PSA testing is responsible for the migration of prostate cancer diagnoses to earlier and more curable stages.[1] These findings, as well as data from studies suggesting a survival benefit to treatment for early cancers support a role for early detection and treatment. The Swedish randomized trial of surgery versus watchful waiting demonstrated an improvement in disease-specific and overall mortality in men undergoing radical prostatectomy for early stage disease.[104] In the United States, an observational cohort of 44,630 men from the SEER data suggests a survival advantage with active treatment for low- and intermediate-risk prostate cancer in men age 65 to 80 years.[105] Countering those arguments are the results of the randomized Prostate Cancer Intervention versus Observation Trial (PIVOT) that failed to show a survival benefit to early surgical treatment for early stage prostate cancer in the PSA screening era.[106] In that trial of 731 men with localized prostate cancer, the 10-year survival rate was 53.0% in men assigned to radical prostatectomy and 50.1% in those assigned to observation ($p = 0.22$). Furthermore, the prostate cancer specific death rate was not significantly different between the two arms.

Early data from three prospective randomized trials seeking to measure the benefit from prostate cancer screening contribute to this screening controversy.[107-110] The U.S. Prostate, Lung, Colon and Ovary (PLCO) Screening Trial registered 76,685 men at 10 study centers to determine the impact of annual PSA and DRE on the cause-specific mortality for cancers in each of these organ sites.[110] The primary exclusion criteria were a history of a PLCO cancer, current cancer therapy, and more than one PSA blood test in the 3 years before study enrollment. Subjects in the screening group were offered annual DRE for 4 years and annual PSA testing for 6 years. A PSA of more than 4.0 ng/mL or a DRE with nodularity or induration were considered suspicious for prostate cancer and patients with these findings were advised to seek diagnostic evaluation. With a median follow-up of 13 years, although there were 12% more cancers diagnosed in the screened group, there was no reduction in prostate cancer mortality.[110] The cumulative mortality rates from prostate cancer were 3.7 and 3.4 deaths per 100,000 person-years in the screened and control arms, respectively. The European Randomized Study of Screening for Prostate Cancer (ERSPC) recruited 182,160 men between the ages of 50 and 74 years from seven European countries.[109] They were randomized to undergo PSA screening once every 4 years or to a control group that did not get PSA screening. There was country-to-country variability in enrollment criteria and screening regimens: age of eligibility, case selection criteria, thresholds for PSA, and the inclusion of DRE in the screening assessments. PSA values as low as 3.0 ng/mL were considered abnormal and would prompt referral for further testing. Of 162,388 eligible men enrolled 6693, prostate cancers were diagnosed in the study group compared to 5396 (20% fewer) in the control group. With a median follow-up of 11 years, the adjusted rate ratio of prostate cancer death in the screened arm was 0.79 (95% CI, 0.68 to 0.91, $p = 0.001$).[109] This represents a relative risk reduction of 21% in favor of screening. In this trial, the number of men that would need to be screened to prevent one prostate cancer death is 1055. More importantly, 37 men would need to be treated to prevent each prostate cancer death.[109] A population-based screening trial was conducted in Sweden.[111] The Goteberg trial prerandomized 20,000 men born between 1930 and 1940 before inviting half of them to participate in PSA screening. PSA was drawn at time of study entry in the invited group and every 2 years thereafter up until the age of 70. In the men invited to screen, 7758 of 9952 (76%) had at least one PSA drawn. Unlike the PLCO trial where as many as 44% of enrollees had prior PSA testing, the Goteberg population had fewer than 3% previously screened. This trial showed a greater reduction in prostate cancer mortality compared to either the ERSPC or the PLCO trials. The relative risk of prostate cancer death in the screened population was 0.56 in the Goteberg study compared to 0.80 in the ERSPC and no reduction in the PLCO trials. Finally, the Prostate testing for cancer and Treatment (ProtecT) trial in the United Kingdom and its companion screening trial has enrolled hundreds of primary care centers and 225,000 patients to help address the value of screening and treatment for early-stage prostate cancer.[112] Primary results of these studies are expected in 2016 with a median follow-up of 10 years.

There are important differences in these screening trials that help explain to apparent differences in conclusions. The U.S. PLCO trial enrolled a group of men in whom as many as 42% of cases underwent previous screening effectively reducing the prevalence of cancer relative to that of a completely unscreened population. This prescreening allowance is emphasized when looking at the Goteburg study where nearly a quarter of the patients were diagnosed at their first screening visit. In addition, over the period of the PLCO trial 52% of nonscreened men had PSA testing, contaminating the control group. The follow-up of 11 years for prostate cancer mortality is relatively short for a group of men with screened cancers. The heterogeneity of eligibility and screening criteria in the ERSPC trial make it challenging to determine the exact

population that would benefit from screening. The Goteberg study included younger men, had a lower PSA threshold, an interval of 2 years between testing, a higher rate of biopsy for men with a positive screen PSA, and less contamination because of prior or ongoing PSA testing in the control arm. This trial may be more indicative of the true value of unbiased PSA screening. The ProtecT trial has also seen less than 10% of the men in the nonscreened arm having their PSA tested making this also a "clean" study for determining the benefits, or otherwise, of screening.

One criticism of published trials of PSA screening is the use of singular thresholds to prompt further diagnostic evaluation. Because serum PSA levels directly correlate with age in men without prostate cancer, several investigators sought to improve the diagnostic accuracy of PSA by defining the normal test range as a function of age and race (eTable 53-1).[113-118] El-Galley et al[118] studied the clinical impact of age-specific reference ranges in 2657 men who underwent prostatic biopsy. Analysis of the sensitivity, specificity, and positive predictive value profiles supported use of age-specific reference ranges because of increased detection sensitivity in younger men and increased specificity in older men.

Newer biomarkers are currently being explored to complement or replace PSA for screening. Prostate Cancer Antigen 3 (PCA3) is a noncoding RNA whose expression is restricted to the prostate and is not expressed in any other normal human tissue or tumor.[130] PCA3 RNA is highly overexpressed in 95% of tumors compared to normal or BPH tissue with up to 66-fold upregulation of PCA3 in cancer compared with normal prostate tissue. Because cancer cells with high PCA3 levels are shed from the prostate into urine, PCA3 RNA can be measured not only in prostate tissue specimens but also in urine and in urine sediments after a DRE. In a correlative biomarker study conducted in the control arm of the REDUCE prevention trial, elevated urinary PCA3 scores were associated with positive biopsy rate ($p = 0.0001$) and correlated with biopsy Gleason score ($p = 0.0017$).[131] In recent studies gene alterations involving androgen regulated *TMPRSS2* and *ERG* transcription factor genes were identified in patients diagnosed with prostate cancer.[130] *ERG* is regarded as a key prostate cancer oncogene. Similar to PCA3, *TMPRSS2-ERG* gene rearrangement can be detected in urine after a DRE. The detection of *TMPRSS2-ERG* fusion in urine has greater than 90% specificity and 94% positive predictive value for prostate cancer detection. Given the high specificity of the test, fusion status in men who are ERG-positive may serve as a viable biomarker to establish disease presence or absence.

Screening Recommendations

The controversy in prostate cancer screening is evident when the current recommendations from various professional societies are reviewed. The American Cancer Society (ACS) previously recommended annual DRE and PSA testing in men older than 50 years of age with a life expectancy of at least 10 years. In 2009, following the publication of the interim results of the PLCO and ERSCP trials, the ACS no longer supports routine testing for prostate cancer. The ACS does support healthcare professionals discussing the potential benefits and limitations of early detection with an *offer* to test with annual PSA and DRE beginning at age 50 in men who are at average risk of prostate cancer and a life expectancy of more than 10 years[132] (http://www.cancer.org/cancer/prostatecancer/detailedguide/prostate-cancer-detection). In African American men and men who have a first-degree relative diagnosed with prostate cancer the discussion should take place at age 45. In men with more than one first-degree relative with prostate cancer the process could begin at age 40. If no prostate cancer is detected as a result of screening the interval for PSA testing can be extended to once every 2 years if the PSA is less than 2.5 ng/mL. The American Urological Association (AUA)[133] strongly recommends shared decision making for men age 55 to 69 years that are considering PSA screening and proceeding based on a man's values and preferences. The AUA discourages PSA screening in men age older than 70 years or who have less than a 10- to 15-year life expectancy. Based largely on the findings of the PLCO and ERSCP studies, the U.S. Preventative Services Task Force (USPSTF) concluded that the benefits of screening for prostate cancer are uncertain and the balance of benefits and harms cannot be determined.[134] The USPSTF does not recommend screening for high risk or other specific populations as none of the trials were powered to detect differences in these subgroups.

PATHOLOGY AND PATHWAYS OF SPREAD

Anatomy

Prostatic anatomy is readily understood by using the urethra as a reference point. The verumontanum is a major anatomic landmark and protrudes from the posterior prostatic wall at the midpoint of the urethra. Most prostatic ducts and the ejaculatory ducts empty into the urethra in this region, whereas the periurethral glands empty throughout the length of the urethra. Immediately proximal to the verumontanum is the müllerian remnant, the utricle, an approximate 0.5-cm length of epithelium-lined cul-de-sac. A circumferential sleeve of muscle surrounds the entire urethra and is composed of the proximal preprostatic smooth muscle sphincter, which prevents retrograde ejaculation, and a distal sphincter of striated and smooth muscle at the apex that is essential for urinary control.

The prostate is composed of three zones: peripheral, central, and transition. The peripheral zone includes approximately 70% of the prostatic volume and is the most common site of PIN and carcinoma. DRE often includes a description of the prostatic lobes based on palpation of the median furrow, which divides the peripheral zone into the right and left halves. The central zone is a cone-shaped area that includes the base of the prostate and encompasses the ejaculatory ducts; it represents approximately 25% of the volume of the prostate. The transition zone is the smallest component of the normal prostate, accounting for approximately 5% of the gland, but it usually enlarges as men age as a result of BPH and may grow to dwarf the remainder of the prostate.

The prostatic capsule consists of an inner smooth muscle layer and an outer covering of collagen, with marked variability in the relative amount of each in different areas. At the apex, acinar elements are sparse and the capsule is ill-defined. As a result, the prostatic capsule cannot be regarded as a well-defined anatomic structure with constant features.

The nerve supply of the prostate is furnished by paired neurovascular bundles along the posterolateral edge of the prostate. Autonomic ganglia are clustered near the neurovascular bundles, and small nerve trunks arising at this site penetrate the capsule to form an extensive network within the gland.

The primary blood supply of the prostate is furnished by the internal iliac artery, and the venous drainage is directly into the prostatic plexus, which eventually empties into the internal iliac vein. This route may account for hematogenous metastases, most often in osseous sites.

The lymphatics of the prostate and the seminal vesicles were detailed through anatomic dissections described by Rouvière.[135] Lymphatic drainage of the prostate originates in an extensive intraprostatic network that coalesces to form a subcapsular system and henceforth coalesces into a periprostatic lymphatic network and the four pedicles of the collecting

eTABLE 53-1 Upper Normal Age-Specific Limits for Prostate-Specific Antigen in Men without Prostate Cancer

		Prostate-Specific Antigen Limits By Age Group*			
Study	**No. of Patients**	**40-49 Years**	**50-59 Years**	**60-69 Years**	**70-79 Years**
Anderson et al[117]	1,716‡	1.5	2.5	4.5	7.5
Dalkin et al[113]	728‡		3.5	5.4	6.3
DeAntoni et al[119]	77,890‡	2.4	3.8	5.6	6.9
El-Galley et al[118]	2,657‡		3.5	5.0	7.0
Morgan et al[116]	1,693†	2.0	4.0	4.5	5.5
Oesterling et al[114]	471‡	2.5	3.5	4.5	6.5
Oesterling et al[115]	286‡	2.0	3.0	4.0	5.0

**Prostate-specific antigen values expressed in ng/mL.*
†Black men only.
‡Japanese men only.

Additional attempts to improve the screening accuracy of PSA measurements are based on the observation that serum PSA level depends on cancer volume, tumor differentiation, and the amount of benign prostatic tissue.[120] To account for coexistent BPH, the concept of PSA density (PSAD) was introduced by Benson et al.[121] PSAD is the total serum PSA value divided by the volume of the prostate gland, as determined by transrectal ultrasound (TRUS). PSAD appears most useful for patients with a total serum PSA level in the range of 4 ng/mL to 10 ng/mL, particularly when palpable prostatic abnormalities are absent. In this setting, it is believed a PSAD of 0.15 ng/mL/cm^3 or more best identifies men in whom prostatic biopsy should be considered.[122,123]

Because the proportion of PSA complexed to α_1-antichymotrypsin is greater in patients with prostate cancer than in men with benign prostatic disease, the ratio of free-to-total (i.e., percent free) PSA will be lower in men with prostate cancer and may help discriminate between benign and malignant prostate conditions.[124-128] Although the free-to-total PSA ratio can be applied to any serum PSA level, performing a free PSA determination improves the specificity for prostate cancer detection when the total serum PSA range is approximately 3 ng/mL to 10 ng/mL.[126,129] To determine the optimal cutoff point that may warrant prostatic biopsy, various free-to-total PSA ratios were examined for their association with prostate cancer.[128,129] A multicenter clinical performance study demonstrated that a free-to-total PSA ratio of less than 7% was highly suspicious for cancer, whereas a free-to-total PSA ratio of above 25% was rarely associated with malignancy.

trunks: the external iliac, hypogastric (or internal iliac), and posterior and inferior pedicles that terminate in the external iliac (including the obturator), presacral, and hypogastric lymph nodes, respectively. The lymphatics of the seminal vesicle originate in the mucous and muscular networks and give rise to the superficial plexus, which culminates in the lymph nodes of the external iliac system. Modern surgical series of extended pelvic lymph node dissections report involved lymph nodes commonly in the obturator fossa, external and internal iliac regions.[136,137] These sites account for nearly 85% of lymph node metastases in prostate cancer.[137] Another 15% of involved nodes can be identified in the presacral, paravesicular, and pararectal sites.[137]

Histology

The prostatic epithelium consists of three main histologic types: secretory, basal, and neuroendocrine cells. Despite having the lowest proliferative activity of the epithelial elements, secretory cells produce PSA, prostatic acid phosphatase (PAP), acid mucin, and other secretory products. The basal cells form a flattened layer of cells surmounting the basement membrane at the periphery of the glands. These cells possess the highest proliferative activity of the prostatic epithelium and are thought to act as stem or "reserve" cells that repopulate the secretory cell layer.[138] Basal cells, selectively labeled with antibodies to high-molecular-weight keratin (e.g., 34βE12), are used to differentiate benign acinar processes from adenocarcinoma, which lacks a basal cell layer. Neuroendocrine cells are the least common epithelial cell type and are often not identified in routinely stained sections.

The seminal vesicles have a variable anatomic distribution, portions of which may occasionally be found within the prostatic capsule where they may be mistaken for prostatic nodularity or induration on examination. The cells of the epithelial component have large, irregular hyperchromatic nuclei with coarse chromatin and prominent nucleoli that often show nuclear abnormalities.

Pathology of Prostate Cancer

Prostatic Intraepithelial Neoplasia

PIN represents the putative precancerous end of the morphologic continuum of cellular proliferation within prostatic ducts, ductules, and acini.[76,139] The histologic diagnosis requires both cytologic and architectural abnormalities, and lesions displaying some but not all such changes are considered atypical. PIN is designated as low grade or high grade, based on relative nuclear and nucleolar enlargement. The continuum culminating in high-grade PIN, and henceforth in early invasive cancer, is characterized by basal cell layer disruption, loss of markers of secretory differentiation, nuclear and nucleolar abnormalities, increased proliferative potential, and variations in DNA content (i.e., aneuploidy).[140-142] Rubin described *TMPRSS2-ERG* fusion genes in PIN intermingled with invasive cancer carrying the same fusion pattern. Using antibodies specific for ERG rearrangements, they observed ERG oncogene overexpression in high-grade PIN but not in adjacent benign prostate tissue.[143] Virtually all measures of phenotype and nuclear abnormality by computer-based image analysis reveal similarities between PIN and invasive cancer, in contrast with normal and hyperplastic epithelium.[77] The recognition of PIN should serve as an indication for a thorough search for invasive cancer because of their close association.[76,139]

Histologic Appearance

Gross identification of prostate cancer may be difficult or impossible, and definitive diagnosis requires microscopic examination. In radical prostatectomy specimens, cancer is often multifocal, with a predilection for the peripheral zone. Tumor foci must be at least 5 mm in greatest dimension to be grossly apparent and appear yellow-white with a stony-hard consistency caused by stromal desmoplasia or inflammatory processes.

The minimal criteria necessary to establish a diagnosis of prostate cancer in biopsy material are described by Algaba et al.[144] Approximately 99% of prostatic cancers are adenocarcinomas that have a microscopic appearance consisting of a proliferation of small acini with multiple patterns. Evaluation of small acinar proliferation of the prostate can be a diagnostic challenge, particularly when the suspicious focus is small. Diagnosis relies on a combination of architectural and cytologic findings that may be enhanced by ancillary studies such as immunohistochemistry. Architectural features include irregular glandular contours that deviate from the smoothly rounded contours of normal prostatic glands. The fact that glands are usually regular in shape is useful because malignancies often exhibit an irregular and haphazard arrangement. Noting variations in gland size can also be of value, and comparison with adjacent normal prostatic glands may be useful. Atypical cytologic features are also important for the diagnosis of cancer because nuclear and nucleolar enlargement is seen in the majority of cells suspicious for cancer.

The basal cell layer is critical to the diagnosis of adenocarcinoma because an intact basal cell layer is present at the periphery of benign glands, whereas a basal cell layer is entirely lacking in carcinoma. However, small foci of adenocarcinoma clustered around larger glands, which have an intact basal cell layer, may occasionally compound diagnostic difficulty, and it may be useful to employ monoclonal antibodies against high-molecular-weight keratin (HMWK) to evaluate the basal layer. Alpha-methylacyl-CoA racemase (AAMCR) is preferentially expressed prostate cancer[145] and P63 is an important marker for basal cells[146] that aid in the immunohistochemical diagnosis of prostate cancer. Other ancillary histologic features that may aid in diagnosis include acidic mucin in the acinar lumen, eosinophilic crystalloids, and microvascular invasion. Inflammation should be noted when evaluating small glandular proliferation because reactive atypia may result or may be seen in the setting of prior RT, infarction, or other conditions.

Morphologic Variants

Several unusual morphologic variants (e.g., mucinous, prostatic duct, small cell, and transitional cell carcinomas) of prostatic carcinoma have been identified but account for less than 10% of cases. These tumors are usually associated with typical acinar adenocarcinoma and rarely occur in pure form. It is important to recognize the special variants and to understand the criteria that distinguish them from benign mimics. Although data are limited, the clinical behavior and prognostic significance of the morphologic variants may differ from typical prostatic adenocarcinoma.[147]

Grading

The Gleason system, based on a Veterans Administration study of more than 4000 patients, has become the global standard for grading prostate cancer (Figure 53-1). The Gleason system is based on the degree of glandular differentiation and an overall pattern of tumor growth at relatively low microscopic magnification.[148] Five patterns of growth are recognized and numbered in order of increasing aggressiveness. Because tumors may display variable histology, two patterns are recorded for each case: a primary or predominant pattern (Gleason 1-5) and a secondary or lesser pattern (Gleason 1-5). The Gleason score is the sum of the primary and secondary

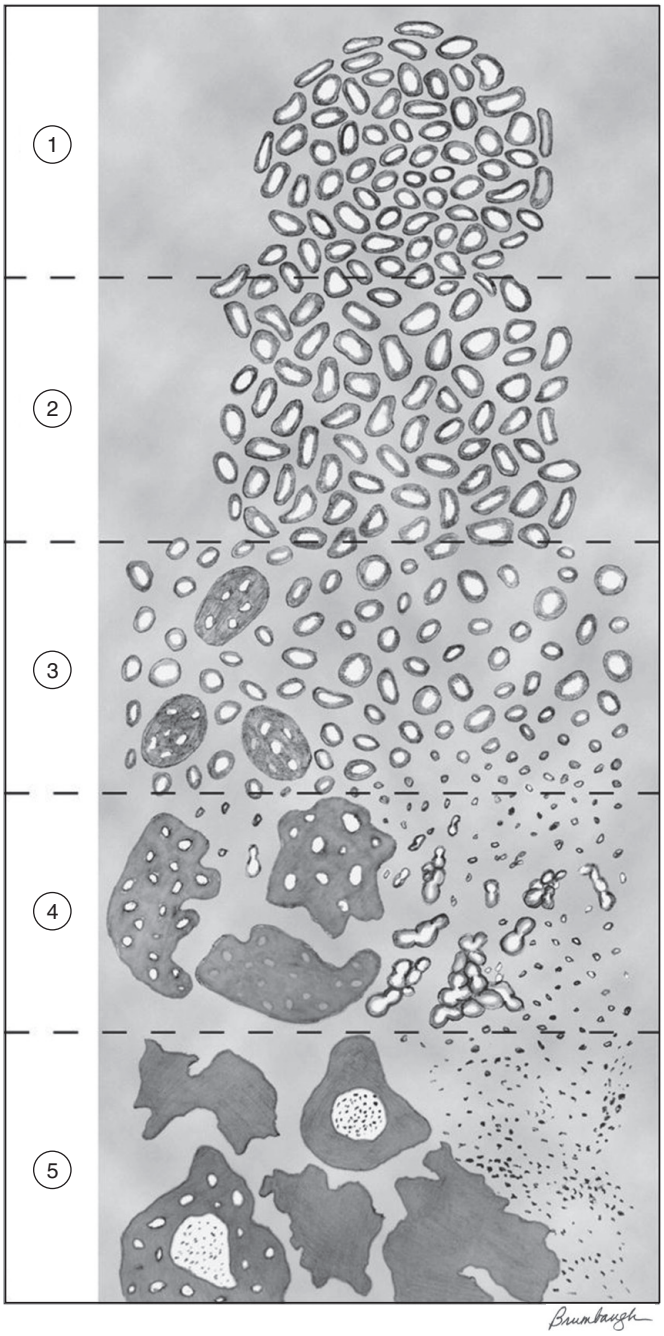


Figure 53-1 Schematic drawing of modified Gleason grading system. *From Epstein JI, et al: The 2005 International Society of Urological Pathology (ISUP) Consensus Conference on Gleason Grading of Prostatic Carcinoma. Am J Surg Pathol 29:1228–1242, 2005.*

patterns and ranges from 2 to 10. If only one pattern is present, the primary and secondary patterns receive the same designation. Gleason noted that more than half of prostate cancers contain two or more patterns,[149] and Aihara et al[150] found an average of 2.7 different Gleason grades in a series of prostatectomy specimens. Interobserver and intraobserver variability has been reported with the Gleason and other grading systems, and Gleason noted exact reproducibility of score in 50% of needle biopsies, and >1 score in 85% of cases.[149]

In 2005, the International Society of the Urological Pathologists held a consensus conference to update the guidelines for Gleason scoring.[151,152] The modifications were felt to be necessary because of the evolving roles of PSA screening and TRUS-guided biopsy techniques on the diagnosis and identification of cancer in needle core specimens. For example, the Gleason scoring system predated the use of immunohistochemical staining for basal cells. Many of the grade 1 + 1 = 2 adenocarcinomas diagnosed in the past would now be considered adenosis because of an intact basal layer. Furthermore, it was made clear that Gleason score 3 or 4 should rarely be applied to ultrasound-acquired biopsies because these are rarely present in the peripheral zone but more typically found by transurethral resection of the prostate (TURP) of the transition zone. In addition, the finding that a cribriform pattern is more aptly included as a Gleason grade-4 pattern has shifted some Gleason score 6 cases to Gleason score 7. These changes have resulted in a grade migration over the past decade that has paralleled the stage migration witnessed as a result of PSA screening.[153] In a review of 1240 radical prostatectomy specimens, the modified Gleason scoring system resulted in upgrading of patients with classic Gleason 6 cancers 34% of the time. Patients with tumors upgraded to Gleason 7 indeed had worse biochemical and metastatic disease progression than patients whose tumors remained Gleason 6.[154]

Although a correlation exists between the needle biopsy tumor grade and that found in the prostatectomy specimen, a higher grade (i.e., more poorly differentiated) is identified in approximately one third of cases.[148,155,156] The correlation is strongest for the primary Gleason pattern, but the secondary pattern also provides useful predictive information, particularly when used to create the Gleason score.[148] The incidences of undergrading and understaging are decreasing related to stage migration as well as the elimination of Gleason scores 2 to 4 biopsy specimens.[157,158] In a series of 1455 men undergoing radical prostatectomy at Johns Hopkins, Fine and Epstein reported 80.0% accuracy of biopsy Gleason scores of 6 or less on final surgical pathology.[158] For patients with biopsy Gleason scores of 7 or greater, 25% were less than Gleason score 7 on final pathology. Whereas in the past downgrading of high grade cancers was uncommon at radical prostatectomy, one quarter to one half high-grade cancers are now downgraded at surgery.[158-163]

Pathologic Staging

The criteria for assigning pathologic classification and stage were developed by the American Joint Commission on Cancer (AJCC) and the International Union Against Cancer (Tables 53-1 and 53-2).[164,165] Currently, the AJCC 7th edition is in use.[164] The details of handling, processing, and recording histologic findings of biopsy, radical prostatectomy, and nodal dissection tissue specimens are described in detail by the Association of Directors of Anatomic and Surgical Pathology.[166] Thorough examination of radical prostatectomy (RP) specimens is critical for tumor classification and should allow accurate determination of pathologic stage, Gleason score, tumor volume, and surgical margin status. Pathologic stage is assessed by determining the presence or absence of extraprostatic extension (EPE), seminal vesicle invasion (SVI), and lymph node involvement (LNI).

Extension of cancer beyond the edge or capsule of the prostate is diagnostic of EPE. The identification of tumor cells in fat is the only reliable way to diagnose EPE on needle biopsy specimens.[166] In radical prostatectomy specimens, designation of EPE requires identification of tumor cells admixed or abutting fat or extending beyond the dense smooth muscle of the prostate to involve the loose connective tissue or less compact smooth muscle outside the prostate.[166] Difficulty is occasionally encountered in the presence of a dense desmoplastic response in extraprostatic tissue, particularly in cases treated

TABLE 53-1 American Joint Commission on Cancer TNM Staging Classification

Classification		Definition
PRIMARY TUMOR (T)		
Clinical		
Tx		Primary tumor cannot be assessed
T0		No evidence of primary tumor
T1		Clinically inapparent tumor neither palpable nor visible by imaging
	T1a	Tumor incidental histologic finding in 5% or less of tissue resected
	T1b	Tumor incidental histologic finding in more than 5% of tissue resected
	T1c	Tumor identified by needle biopsy (for example, because of elevated PSA)
T2		Tumor confined within prostate[a]
	T2a	Tumor involves one-half of one lobe or less
	T2b	Tumor involves more than one-half of one lobe but not both lobes
	T2c	Tumor involves both lobes
T3		Tumor extends through the prostate capsule[b]
	T3a	Extracapsular extension (unilateral or bilateral)
	T3b	Tumor invades seminal vesicle(s)
T4		Tumor is fixed or invades adjacent structures other than seminal vesicles, such as external sphincter, rectum, bladder, levator muscles, or pelvic wall
PRIMARY TUMOR (T)		
Pathologic (pT)[c]		
pT2		Organ confined
	pT2a	Unilateral, one-half of one side or less
	pT2b	Unilateral, involving more than one-half of side but not both sides
	pT2c	Bilateral disease
pT3		Extraprostatic extension
	pT3a	Extraprostatic extension or microscopic invasion of bladder neck[d]
	pT3b	Seminal vesicle invasion
REGIONAL LYMPH NODES (N)		
Clinical		
Nx		Regional lymph nodes were not assessed
N0		No regional lymph node metastasis
N1		Metastasis in regional lymph node(s)
Pathologic		
pNx		Regional nodes not sampled
pN0		No positive regional nodes
pN1		Metastases in regional node(s)
DISTANT METASTASIS (M)[e]		
M0		No distant metastasis
M1		Distant metastasis
	M1a	Nonregional lymph node(s)
	M1b	Bone(s)
	M1c	Other site(s) with or without bone disease

[a]*Tumor found in one or both lobes by needle biopsy, but not palpable or reliably visible by imaging, is classified as T1c.*
[b]*Invasion into the prostatic apex or into (but not beyond) the prostatic capsule is classified not as T3 but as T2.*
[c]*There is no pathologic T1 classification.*
[d]*Positive surgical margin should be indicated by an R1 descriptor (residual microscopic disease).*
[e]*When more than one site of metastasis is present, the most advanced category is used. pM1c is most advanced.*

TABLE 53-2 American Joint Commission on Cancer Stage Grouping for Prostate Cancer

Anatomic Stage/Prognostic Groups*					
Group	**T**	**N**	**M**	**PSA**	**Gleason**
I	T1a-c	NO	MO	PSA < 10	Gleason ≤ 6
	T2a	NO	MO	PSA < 10	Gleason ≤ 6
	Tl-2a	NO	MO	PSA X	Gleason X
IIA	T1a-c	NO	MO	PSA < 20	Gleason 7
	T1a-c	NO	MO	PSA ≥ 10 < 20	Gleason ≤ 6
	T2a	NO	MO	PSA ≥ l0 < 20	Gleason ≤ 6
	T2a	NO	MO	PSA < 20	Gleason 7
	T2b	NO	MO	PSA < 20	Gleason ≤ 7
	T2b	NO	MO	PSA X	Gleason X
IIB	T2c	NO	MO	Any PSA	Any Gleason
	T1-2	NO	MO	PSA ≥ 20	Any Gleason
	T1-2	NO	MO	Any PSA	Gleason ≥ 28
III	T3a-b	NO	MO	Any PSA	Any Gleason
IV	T4	NO	MO	Any PSA	Any Gleason
	AnyT	N1	MO	Any PSA	Any Gleason
	Any T	Any N	M1	Any PSA	Any Gleason

**When either PSA or Gleason is not available, grouping should be determined by T stage and either PSA or Gleason as available.*

by AD. Perineural invasion may exist in the absence of EPE. The anterior muscle is an uncommon site for EPE; this is observed only with large tumors involving the transition zone. Reporting EPE at the apex is challenging because of the vague boundaries of the capsule in this region. Most patients (57% to 81%) with EPE have involved surgical margins,[167] which predicts a worse prognosis.

Positive surgical margins are defined as cancer cells touching the inked surface of the prostatectomy specimen. Care must be taken to avoid interpreting ink within tissue crevices created by postoperative handling of the specimen as margin positivity. It is important to note that the status of the surgical margin is not explicitly included in pathologic staging, and pathologists and clinical investigators should describe surgical margin status separately from EPE. Positive surgical margins can be present in the absence of EPE because of capsular incision (pT2+ disease).

Seminal vesicle invasion is a pathologic finding associated with an increased risk for disease relapse[168,169] and occurs when tumor extends into the region where vas deferens and seminal vesicle converge at the prostatic base.[170] Direct tumor growth from this location along the ejaculatory duct complex or through the prostatic capsule may result in seminal vesicle invasion. This mechanism accounts for the observations that tumor volume is often greatest at the prostatic end of the seminal vesicle in the vicinity of the vas deferens,[170] that involvement of both seminal vesicles is a common finding,[169] and that isolated deposits of prostate cancer remote from the ejaculatory duct complex are observed in only one eighth of seminal vesicle specimens involved with tumor.[169] Microscopic involvement of the bladder neck is not a pT4 designation. Patients with microscopic bladder neck invasion have a prognosis similar to those with seminal vesicle invasion and should be designated pT3a.[164,171]

Postirradiation Histology

For approximately 18 to 24 months after EBRT, and perhaps longer for interstitial implantation, needle biopsy of the prostate in the absence of clinical disease progression is of limited value because of delayed and continuing tumor cell death.[172]

After this period, needle biopsy is associated with a lower level of diagnostic error that is minimized by obtaining multiple specimens.[173-175] Histologic changes of prostatic radiation injury include acinar atrophy, shrinkage and distortion, marked cytologic abnormalities of the epithelium, basal cell hyperplasia, stromal fibrosis, and a decreased ratio of acini to stroma.[172] Vascular sclerosis is also prominent and may involve small and large vessels. Although a definitive method to assess tumor viability after RT does not exist, PSA and PAP expression persists,[176] suggesting that tumor cells capable of protein production retain the potential for cell division and spread.[177,178] Keratin 34αE12 expression also persists and is often of value in separating treated adenocarcinoma from some of its mimics. AMACR staining may be lost in nonneoplastic epithelium but can persist in residual tumor cells. Proliferative cell nuclear antigen (PCNA) may improve the sensitivity and specificity of a postirradiation biopsy. Negative PCNA staining in an otherwise positive biopsy predicts (83% to 97% for eventual resolution of tumor, whereas positive PCNA staining is correlated with a local failure in 49% to 79% of cases.[177] Grading of cancer following RT can be problematic.[179,180] Squamous metaplasia is common and the acini have nuclei that are large and hyperchromatic with conspicuous nucleoli. The tumor may show loss of architectural features suggestive of higher grade. Cancer grading after RT has yielded conflicting results: some observers noted no difference in pretherapy grade or behavior,[172,181] whereas others found increased grade.[182] There is better success at applying a postirradiation Gleason score in cases where the radiation treatment effect is minimal. If considerable treatment effect is seen, then grading is problematic.[179,180]

Effects of Androgen Deprivation

AD of normal, hyperplastic, and dysplastic epithelial cells causes acceleration of programmed cell death (i.e., apoptosis), with fragmentation of tumor DNA, emergence of apoptotic bodies, and inhibition of cell growth. Global glandular atrophy can be seen but it tends to be more prominent in the peripheral zone.[179] Furthermore, there is reduced nuclear size, loss of nucleoli, chromatin condensation, nuclear pyknosis, and cytoplasmic vacuolation.[183,184] However, grading may be misleading and is to be avoided.[184] AMACR, PSA, PAP, and keratin 34αE12 immunohistochemistry are useful in identifying carcinoma because AMACR, PSA, and PAP are retained and 34αE12 remains negative. Expression of neuroendocrine differentiation markers (e.g., chromogranin, neuron-specific enolase), remains unaltered, whereas proliferative activity, as measured by Ki67 (MIB-1) or PCNA immunoreactivity, is reduced after AD.[179,184]

BIOLOGIC CHARACTERISTICS AND MOLECULAR BIOLOGY

Molecular Biology

As our understanding of the molecular biology of prostate cancer grows, it is conceivable that treatment can become personalized with agents that specifically target the genomic or metabolic characteristics of a particular patient's cancer. Increasing focus is given to the role of the androgen receptor (AR) in the tumorigenesis, treatment, and prognosis of prostate cancer.[187] Androgens, along with multiple coregulatory factors, activate the AR leading to transcription of AR target genes promoting the growth of normal and neoplastic prostate tissue. The ETS family of genes is transcription factors that are involved in a variety of functions including cellular differentiation and cell cycle control. Several ETS factors have been implicated in carcinogenesis through gene rearrangements. Tomlins et al have identified recurrent gene fusions of two ETS transcription factors, ERG and ETV1, to the *TMPRSS2* gene.[188] In their initial series, the *TMPRSS2-ERG* gene rearrangement was identified in 47% of clinically localized prostate cancers. *TMPRSS2* is expressed in normal luminal epithelial and neoplastic prostate tissue and is strongly induced by androgen in androgen-sensitive prostate cell lines. *TMPRSS2-ERG* fusion gene can be detected in a proportion of high-grade PIN lesions and that this molecular rearrangement may be an early event that precedes chromosome-level alterations in prostate carcinogenesis.[189] The importance of the TMPRSS2-ERG fusion as an early event in the development of prostate cancer is supported by the homogenous distribution of the fusion gene in a prostate cancer, the absence of the fusion in benign prostate tissue, and the association of *TMPRSS2-ERG*–positive cancers associated with the same fusion in high-grade PIN lesions.[190] Mutation or changes in AR expression may account for the development of androgen-independent prostate cancer. ERG overexpression, mediated through *TMPRSS2-ERG* fusion, contributes to development of androgen-independence through disruption of AR signaling. Yu found that ERG inhibits AR expression and activity and induces repressive epigenetic programs that contribute to AR and cancer progression.[191] Unfortunately, early clinical data has not shown the TMRPSS2-ERG status to be predictive of response to radiation therapy.[192]

As acknowledged, slightly less than half of all prostate cancers harbor rearrangements of the ETS transcription factor family. Other common genome rearrangements include SPOP mutant and the serine peptidase inhibitor Kazal type 1 (SPINK1) overexpressing subtypes. The SPOP gene encodes for the substrate-recognition component of an ubiquitin ligase. This protein affects a variety of pathways, including hedgehog, c-Jun-N-terminal kinase, and components of steroid receptor signaling. Inhibitors of these pathways are being tested for prostate cancer activity. Likewise, the fact that epidermal growth factor receptor (EGFR) mediates part of the oncogenic properties of SPINK1 provides a rationale for EGFR inhibition in these tumors.

Predictive Factors

Pathologic Endpoints

The therapeutic efficacy of RT and RP depends on the accurate determination of tumor burden and the risk of subclinical disease. Despite the clinical impression of disease confined to the prostate gland, occult tumor extension through the prostatic capsule or involvement of seminal vesicle(s) or regional lymph nodes is common at the time of diagnosis. Compared with surgical-pathologic stage, the clinical staging of prostate cancer frequently underestimates disease extent, and many patients are "upstaged" after RP with pelvic node dissection.[193] Among patients thought to have prostate confined disease by clinical assessment, variable proportions of patients will be found to have extracapsular extension (ECE), SVI, or lymph node involvement at the time of prostatectomy with the likelihood of these findings correlated with pretreatment characteristics such as T category, Gleason grade, and PSA level[194] (eTable 53-2). Because these findings may have considerable importance for selection of an appropriate therapeutic strategy (e.g., radioactive seed implantation or RP versus EBRT), several investigators studied the association between readily available pretherapy factors and the pathologic endpoints of extraprostatic tumor extension, SVI, and pelvic LNI.

Extraprostatic Extension

EPE is a pathologic feature that is associated with a worse outcome following RP.[196-200] Several pretherapy tumor-related

The PCPT has provided important information about the impact of 5α-reductase inhibitors on the histological appearance of prostate cancer. The initial report of the PCPT suggested that the rate of high-grade tumors was increased with the use of finasteride. Subsequent reports suggest that the drug may have reduced the volume of benign prostate tissue and low-grade cancer thereby increasing the likelihood of identifying higher grade disease.[185,186]

eTABLE 53-2 Clinical Staging Nomogram (Partin Tables) for Prostate Cancer

PSA	Pathological Stage	Biopsy Gleason Score 6	3 + 4	4 + 3	8	9-10
CLINICAL STAGE T1C (*n* = 4380)						
0-2.5	OC (*n* = 289)	93 (91-95)	83 (78-87)	80 (74-85)	79 (72-85)	74 (61-83)
	EPE (*n* = 21)	7 (5-8)	15 (11-20)	17 (12-22)	18 (12-24)	20 (12-29)
	SV + (*n* = 4)	0 (0-1)	2 (0-3)	3 (1-6)	3 (1-6)	5 (1-12)
	LN + (*n* = 0)	0 (0-0)	0 (0-1)	0 (0-2)	0 (0-2)	2 (0-6)
2.6-4.0	OC (*n* = 751)	87 (85-89)	71 (67-75)	66 (60-71)	65 (57-72)	56 (44-67)
	EPE (*n* = 133)	12 (10-14)	25 (22-29)	27 (22-32)	28 (22-34)	29 (20-40)
	SV + (*n*.= 10)	0 (0-1)	2 (1-4)	4 (2-7)	4 (2-8)	7 (3-12)
	LN + (*n* = 4)	0 (0-0)	1 (0-2)	3 (1-5)	3 (1-6)	8 (3-16)
4.1-6.0	OC (*n* = 1439)	84 (83-86)	66 (63-69)	60 (55-65)	59 (51-66)	50 (38-60)
	EPE (*n* = 371)	15 (13-16)	29 (26-33)	31 (26-36)	32 (25-38)	32 (23-42)
	SV + (*n* = 37)	1 (0-1)	4 (2-5)	6 (4-9)	6 (4-10)	10 (5-16)
	LN + (*n* = 11)	0 (0-0)	1 (0-2)	3 (2-5)	3 (1-6)	8 (4-15)
6.1-10.0	OC (*n* = 686)	80 (78-82)	59 (55-63)	53 (47-58)	52 (44-59)	42 (31-52)
	EPE (*n* – 226)	18 (16-20)	34 (30-38)	35 (30-40)	36 (29-43)	36 (26-46)
	SV + (*n* = 36)	1 (1-2)	6 (4-8)	9 (6-13)	9 (5-14)	14 (8-21)
	LN + (*n* = 8)	0 (0-0)	1 (0-2)	3 (1-5)	3 (1-6)	8 (4-14)
>10.0	OC (*n* = 191)	69 (64-74)	42 (36-48)	34 (28-40)	33 (26-40)	23 (15-32)
	EPE (*n* = 121)	27 (22-31)	42 (36-47)	28 (32-45)	39 (31-47)	33 (24-44)
	SV + (*n* = 28)	3 (2-5)	13 (9-18)	20 (14-27)	20 (12-28)	25 (15-36)
	LN + (*n* = 14)	0 (0-1)	3 (1-5)	8 (4-14)	8 (3-14)	18 (9-30)
CLINICAL STAGE T2A (*n* = 897)						
0-2.5	OC (*n* = 140)	90 (87-92)	76 (70-81)	72 (65-79)	71 (62-79)	65 (51-76)
	EPE (*n* = 23)	10 (7-13)	22 (17-28)	24 (17-30)	24 (18-33)	27 (18-39)
	SV + (*n* = 1)	0 (0-1)	2 (0-4)	3 (1-7)	3 (1-7)	6 (1-13)
	LN + (*n* = 1)	0 (0-0)	0 (0-1)	1 (0-49	1 (0-3)	2 (0-9)
2.6-4.0	OC (*n* = 139)	82 (78-84)	61 (56-66)	56 (48-62)	54 (46-63)	45 (33-56)
	EPE (*n*.= 52)	18 (15-21)	34 (29-39)	35 (29-42)	36 (29-44)	36 (26-49)
	SV + (*n* = 5)	1 (0-1)	3 (1-5)	5 (2-8)	5 (2-9)	7 (3-14)
	LN + (*n* = 5)	0 (0-0)	1 (0-3)	4 (1-8)	4 (1-10)	11 (4-23)
4.1-6.0	OC (*n* = 183)	78 (74-81)	56 (51-60)	49 (43-56)	48 (40-56)	39 (28-50)
	EPE (*n* = 9l)	21 (18-24)	38 (34-43)	39 (33-46)	40 (32-48)	39 (28-50)
	SV + (*n* = 8)	1 (1-1)	4 (3-6)	7 (4-10)	7 (4-11)	10 (5-16)
	LN + (*n* = 3)	0 (0-0)	2 (1-3)	4 (2-7)	4 (2-8)	11 (4-21)
6.1-10.0	OC (*n* = 104)	73 (68-77)	48 (43-54)	42 (36-49)	41 (33-50)	32 (23-43)
	EPE (*n* = 72)	26 (22-30)	44 (39-49)	44 (37-50)	45 (36-52)	43 (31-54)
	SV + (*n* = 10)	1 (1-2)	6 (4-9)	10 (6-15)	10 (5-16)	14 (7-22)
	LN + (*n* = 4)	0 (0-0)	1 (1-3)	4 (2-7)	4 (1-8)	10 (4-20)
>10.0	OC (*n* = 22)	60 (53-66)	32 (26-39)	25 (20-31)	24 (18-32)	16 (10-24)
	EPE (*n* = 22)	36 (30-42)	50 (43-56)	44 (36-53)	45 (35-55)	37 (25-49)
	SV + (*n* = 10)	4 (2-6)	14 (8-20)	20 (12-29)	20 (11-30)	24 (13-38)
	LN + (*n* = 2)	1 (0-2)	4 (2-7)	10 (4-18)	10 (4-20)	22 (10-37)
CLINICAL STAGE T2B OR T2C (*n* = 352)						
0-2.5	OC (*n* = 26)	82 (76-87)	61 (52-70)	55 (45-66)	54 (44-66)	45 (32-60)
	EPE (*n* = 13)	17 (12-23)	33 (25-42)	34 (25-44)	35 (24-46)	35 (23-48)
	SV + (*n* = 0)	1 (0-2)	5 (1-10)	8 (2-16)	8 (2-16)	13 (3-24)
	LN + (*n* = 0)	0 (0-0)	1 (0-3)	2 (0-9)	3 (0-9)	7 (0-21)

Continued

eTABLE 53-2 Clinical Staging Nomogram (Partin Tables) for Prostate Cancer

PSA	Pathological Stage	Biopsy Gleason Score				
		6	3 + 4	4 + 3	8	9-10
2.6-4.0	OC (*n* = 27)	70 (63-75)	44 (37-51)	36 (29-44)	35 (27-44)	24 (16-35)
	EPE (*n* = 30)	28 (22-35)	46 (39-53)	43 (35-51)	44 (34-53)	37 (26-51)
	SV + (*n* = 3)	2 (1-3)	6 (3-10)	10 (5-16)	10 (5-17)	13 (6-23)
	LN + (*n* = 2)	1 (0-2)	4 (2-8)	11 (5-20)	11 (4-21)	25 (12-42)
4.1-6.0	OC (*n* = 52)	64 (58-70)	38 (32-44)	30 (24-37)	30 (22-37)	20 (13-29)
	EPE (*n* = 45)	32 (27-39)	49 (42-56)	45 (38-52)	46 (37-55)	38 (26-51)
	SV + (*n* = 14)	2 (1-1)	9 (6-13)	14 (9-20)	13 (8-21)	17 (9-28)
	LN + (*n* = l2)	1 (0-2)	4 (2-8)	11 (5-17)	11 (5-19)	24 (12-40)
6.1-10.0	OC (*n* = 25)	58 (50-65)	31 (25-37)	24 (19-31)	24 (18-31)	16 (10-23)
	EPE (*n* = 36)	38 (32-15)	52 (46-59)	47 (40-55)	48 (39-57)	40 (28-52)
	SV + (*n*.= 7)	4 (2-6)	12 (8-18)	19 (12-25)	18 (10-26)	23 (12-34)
	LN + (*n* = 5)	1 (0-2)	4 (2-7)	10 (5-16)	10 (5-18)	22 (10-35)
>10.0	OC (*n* = 8)	42 (34-50)	17 (13-23)	12 (8-16)	11 (8-16)	6 (4-11)
	EPE (*n* = 21)	47 (39-55)	50 (41-59)	39 (30-49)	40 (28-51)	27 (18-40)
	SV + (*n* = 18)	9 (5-14)	23 (15-33)	30 (20-41)	29 (18-42)	30 (17-45)
	LN + (*n* = 8)	2 (0-4)	9 (4-16)	20 (10-31)	20 (9-32)	36 (20-53)

From Eifler JB, Feng Z, Lin BM, et al: An updated prostate cancer staging nomogram (Partin tables) based on cases from 2006 to 2011. Br J Urol 111:22–29, 2012.[195]

EPE, *Extraprostatic extension;* LN+, *lymph node involvement;* OC, *organ confined;* PSA, *prostate-specific antigen;* RP, *radical prostatectomy;* SV+, *seminal vesicle involvement.*

factors are associated with EPE, and these include clinical tumor stage,[193] pretherapy serum PSA value,[193] prostatic biopsy tumor grade,[193] microvessel density (i.e., neovascularity),[201] and percent of biopsy containing cancer.[201] Although any of these factors may be individually used to estimate the likelihood for EPE, the accuracy of such estimates is enhanced by combining those factors that independently contribute to the predictive model.[193,194,202] The extent of EPE is associated with the risk of clinical failure. Epstein reported significantly worse rates of progression with established ECE compared to pathology specimens that had just a few malignant glands outside the capsule.[198] Wheeler defined extensive EPE as tumor extending more than one high-power field outside the capsule on more than two separate sections.[197] Both focal and extensive EPE were significantly associated with other adverse findings such as seminal vesicle involvement and lymph node metastases as well as a lower progression-free probability (73% and 42%) compared to no progression in the absence of any capsular invasion.[197]

In the PSA era, Partin et al[203] were among the first to use multivariate statistical analysis to identify pretherapy variables associated with EPE in patients who underwent RP and demonstrated that clinical tumor stage, Gleason score of the diagnostic biopsy, and serum PSA level independently correlate with this finding. The combination of these factors was used to develop probability estimates, which were displayed as a nomogram and later incorporated into clinical practice guidelines for patient management. Kattan et al[202] conducted a separate validation study that confirmed that the nomogram discriminated well between men with organ-confined disease and those in whom the disease extended beyond the prostate gland. The updated Partin nomogram eTable 53-2 may be useful for predicting the probability of organ-confined status,[195] but any estimation should consider the confidence of the prediction, as indicated by the associated 95% confidence intervals, for the combination of factors relevant to the new patient under consideration.

Seminal Vesicle Invasion

SVI is a pathologic finding associated with an increased risk for disease relapse.[168,169,196,204] The adverse prognostic impact of SVI is exceeded only by lymph node metastases.[205] In a multiinstitutional study of 6740 patients undergoing RP, Baccala reported 10-year biochemical relapse-free survival of 77.2% without SVI compared to 25.6% with SVI.[204] Several investigators have correlated pretherapy tumor-related factors with SVI as a means to identify patients with a high likelihood for this condition.[169,193,202,204,206-209] These studies demonstrate that clinical tumor stage, tumor grade of the diagnostic biopsy specimen, percentage of cancer in the biopsy, and serum PSA level are associated with SVI in a statistically significant manner.

Although serum PSA level was the best single predictor, Partin et al[193] noted that clinical tumor stage and Gleason score contributed to SVI risk estimation and so were among the first to combine these factors to develop nomograms for clinical use. Thereafter, Diaz et al used this information to create a prediction equation.[210] However, Kattan et al[202] applied the original SVI nomogram of Partin et al[193] to an independent data set and concluded that the nomogram was suspect, particularly in the areas of high predicted probability, and ill-suited to clinical application. In the RP series reported by Baccala, the biopsy Gleason score and clinical stage T3 were more predictive of SVI than PSA.[204]

In response to Kattan et al, Partin et al performed a multiinstitutional analysis in which updated nomograms were developed and validated.[211] Although this provides useful information, patients were only assigned to the most advanced and mutually exclusive pathologic category based on the findings of the RP and PND specimens for the analysis. Furthermore, all these data are derived from patients selected for radical prostatectomy and may underestimate the true extent of disease in men not considered suitable for surgery. Although these nomograms may be appropriate for the surgical candidate, the risk of SVI may be underestimated with this approach, and caution is necessary in using the revised nomogram for other purposes (e.g., RT target volume definition).

Nodal Involvement

Clinical T category, prostatic biopsy tumor grade, and serum PSA level are also associated with pelvic LNI, and a combination of these factors may be used to predict the probability of LNI in the patient with a new diagnosis of clinically localized prostate cancer.[193,206,212,213] Partin et al[193,203] incorporated these factors in a LNI predictive nomogram. Kattan et al[202] were not able to validate the LNI nomogram in a separate group of patients and suggested that the nomograms were not broadly applicable. As a result, Partin et al[211] used a different mathematical method to analyze a larger and more diverse study population and provided revised nomograms to estimate the probability of LNI.[193,194]

Clinical Endpoints

Factors predictive of clinical endpoints may be grouped according to whether they are patient related, are intrinsic to the neoplasm (i.e., tumor related), or are treatment related. It is essential to recognize that a factor may have importance only in certain patient subsets (e.g., those with clinically localized disease) but not in other settings (e.g., metastatic disease). Furthermore, different endpoints may be considered (e.g., local tumor control, metastatic relapse, biochemical relapse [BCR], cause-specific or overall mortality), and a particular factor may have significance for some, but not all endpoints.

Patient-Related Factors

Patient age had been identified as a prognostic factor in older series of patients managed with surgery, RT or expectant management.[215-219] These reports have offered conflicting results suggesting that younger patients did better with expectant management in some series[216,220] whereas older patients fared worse in others.[215] Similarly, some series suggest a worse prognosis with surgery or radiation therapy for younger patients[217,219,221-223] whereas others do not.[224-230] A meta-analysis of 34 studies with more than 27,000 patients did not show an association between age and outcome in the PSA era.[231] Parker speculated that PSA screening may have eliminated the impact of age on prognosis because of less delay in diagnosis, improved measures of outcome, a screening related age-specific lead-time bias, and an interaction between age and tumor grade.[231]

Racial and ethnic disparities for the outcome of patients after diagnosis and treatment exist for many malignancies, including prostate cancer. African Americans are more likely to be diagnosed with advanced stage and higher grade prostate cancer than whites or non-African American minorities.[1] The survival rate of African American men is inferior to that of non-Hispanic white men with localized prostate cancer.[38,232] The reason for these disparities are unclear and may be related to variations in genetics, nutrition, socioeconomic status, clinical and surgical staging procedures applied to different races, or access to care or inherent differences in cancer biology. SEER data has shown a difference in the rate of radical prostatectomy and surgical staging being performed in African American men with localized prostate cancer.[233]

The presence of coexistent medical ailments (e.g., ischemic heart disease) in a patient with prostate cancer may have a significant impact on treatment decisions. These comorbidities

In a series of 588 men undergoing RP with an extended pelvic lymph node dissection, Briganti identified the percentage of positive biopsy cores as being the single-most important factor predicting LNI.[214] In a multivariate analysis, clinical T-category, primary biopsy Gleason grade and percentage of positive cores were independent predictors of LNI. They developed a nomogram that could identify men who could be spared an extended pelvic lymph node dissection.

In a secondary analysis of RTOG clinical trial data where eligibility and treatment guidelines were prescribed according to study specifications, Roach reported that the observed inferior survival of black Americans was likely related to their presentation with more advanced disease and not resulting from inherent biological differences in their cancer.[234] In a review of SWOG trials, the survival of African American men with advanced stage prostate cancer was worse than all other patients, even when corrected for differences in socioeconomic status.[235] Two other studies suggest that even when effects of age, presenting PSA, Gleason score, and stage are controlled, a difference in PFS persists.[236,237] Moul demonstrated differences in outcome in men treated with radical prostatectomy in an "equal access" medical system (i.e., the U.S. military).[238] There is recent evidence for differences in presentation and outcome for Hispanic men with localized prostate cancer,[239] but few to no reliable estimates exist for the Native American, Native Alaskan, Asian or Pacific Islander populations. Therefore, it appears that some evidence suggestive of biologic differences in patient subgroups is emerging.

may determine whether or not a patient is a candidate for an aggressive surgical intervention or whether the patient should be treated at all. These nonprostate cancer–related treatment selection criteria have a profound impact on outcome reporting that are unrelated to the effectiveness of any specific treatment strategy. Several instruments are available to quantify the severity of comorbidity.[240] The selection of a particular management approach based on overall health status has important implications in interpreting and comparing outcomes, because OS and, perhaps, CSS estimates will be influenced.[240-243] The selection of a particular management approach based on overall health status has important implications in interpreting and comparing outcomes, because OS and, perhaps, CSS estimates will be influenced.[240-243] A nomogram has been described that may allow estimation of life expectancy and aid physicians and patients in choosing treatment strategies.[240]

Tumor Category

The anatomic extent of prostate cancer is an important tumor-related factor predictive of patient outcome. Studies consistently demonstrate the association of primary tumor category with several endpoints in patients with localized disease. Cause-specific survival (CSS) and OS are directly related to the extent of the primary tumor in both RT[244-246] and expectant management[216,247,248] series. The probability of local tumor control[249] and the risk of clinical,[245,250] metastatic,[249,251] and biochemical relapse[225,227,228,246] are influenced in a similar manner. Increasingly T category is combined with other prognostic factors (e.g., initial PSA, tumor grade) to define prognostic groups and report outcomes. Despite this, T-category remains an important factor in selecting optimal local therapy.

Surgical Margins

Modifications to surgical technique have resulted in an improvement in the rate of positive margins with an open prostatectomy technique[252]; however, even with laparoscopic and robot-assisted procedures the rates of positive margins remain as high as 50% and 28%, respectively.[253] In a systematic review and meta-analysis, Tewari abstracted data from more than 400 articles representing 286,876 RPs. After adjusting for preoperative variables, robot-assisted RPs had lower rates of positive margins compared to nonrobot-assisted RPs but not open RPs.[254] Positive margins are typically located at the apex (48%), rectal and lateral surfaces (24%), bladder neck (15%), and posterior pedicles (10%).[167,255] The presence of a positive surgical margin (PSM) increases the likelihood of biochemical relapse, local recurrence, and the need for salvage therapies.[256-258] In a series of 11,729 men undergoing radical prostatectomy between 1990 and 2006, Boorjian reported PSMs in 31% of cases.[256] Patients with positive margins had a biochemical relapse-free survival (bRFS) rate of only 56% compared to 77% ($p < 0.0001$) and a local RFS of 89% compared to 95% ($p < 0.0001$) in patients with negative margins. In some series, patients with PSMs also had a significantly worse systemic RFS, CSS, and OS. In a pooled series of 7816 patients from eight academic urology centers, the presence of a PSM increased the risk of biochemical relapse by 3.7-fold.[258] When combined with risk factors such as high Gleason score or initial PSA, the presence of positive margins is more predictive of clinical failure.[259,260]

It had been suggested that an apical positive margin may actually represent an artifact in the processing of prostatectomy specimens and it may not carry as great a prognostic significance as margins involved elsewhere.[261,262] Analyses of randomized trials evaluating the role of adjuvant radiation therapy failed to show any differences in outcome by site of surgical margin involvement.[263,264]

The extent of surgical margin involvement has been reported to carry prognostic significance.[265-269] In a series of 2468 patients, Lake reported that even focally positive margins (≤3 mm) in patients with organ-confined disease conferred a significant decrease in disease free survival (DFS).[267] The 10-year DFS for patients with organ confined disease was 84%, 64%, and 38% with negative, focally positive, and extensively positive margins (>3 mm), $p < 0.0001$.[267] The data argue strongly that the presence of a PSM has a profound impact on patient prognosis and such patients should be considered for adjuvant therapy.

Nodal Involvement

Tumor spread to regional lymph nodes is associated with a particularly poor outcome following radiotherapeutic or surgical management alone.[268-273] The prognostic significance of the number of involved nodes was identified in some.[273-277] In a series of more than 10,000 patients treated with radical prostatectomy, Boorjian reported that the risk of systemic cancer progression was three-fold greater with one positive node, and another two-fold greater with two or more. One positive node increased the risk of cancer-related death four-fold and when two or more were involved the risk was another two-fold higher.[273] Briganti reported a significantly better 15-year CSS in patients with one or two positive nodes (84%) compared to patients with more than two positive nodes (62%).[277] Schmid et al[275] found that patients with micrometastasis (i.e., ≤5 mm in largest dimension) had significantly better PFS and OS compared with patients with more extensive nodal involvement. In contrast, Srignoli et al[278] found no difference in the risk of subsequent distant metastasis. Cheng et al[279] reported that the risk of distant metastasis in patients with regional nodal involvement was directly proportional to nodal cancer volume, and it was the best predictor of 5-year metastasis-free survival.

Tumor Grade

Long-term case series of EBRT,[227,245,280,281] brachytherapy,[282-284] RP,[285-288] and expectant management[216,247] uniformly identify tumor grade as a strong predictor of disease relapse and mortality in clinically localized prostate cancer. Studies consistently demonstrate that patients with a poorly differentiated tumor (i.e., grades 4 to 5 or Gleason score ≥7) have an increased risk of metastatic disease progression and reduced OS and disease-specific survival (DSS).[247,249,281,289] For the patient with clinical T1 or T2 disease, tumor grade has greater predictive value than does the distinction between T1 and T2 categories.[216,227,249,282,284,288] The association of tumor grade with metastatic relapse[227,249,250] and OS[249] is preserved when pretherapy serum PSA level is considered. Although tumor grade is also associated with DFS and freedom from clinically evident disease relapse,[217,227,290,291] its impact on local tumor control after EBRT is less certain, as some reports noted an association,[244,249] whereas others did not.[290] PSA level (i.e., biochemical control) following local therapy is impacted by tumor grade. Multivariate analysis of pretherapy tumor-related factors for in RT[227,228,249] and surgical[287,289,292] series confirms the significance of tumor grade as a predictor for biochemical relapse.

The relative amount of high-grade cancer in biopsy and surgical specimens predicts for clinical and biochemical outcomes.[293,294] In patients with Gleason score 7, a primary component of Gleason grade 4 (4 + 3) has been associated with a higher rate of metastatic, biochemical, and clinical progression than a primary Gleason grade 3 component (3 + 4) in both surgical[295-298] and RT series.[299] However, although some series demonstrate that the presence of the higher primary Gleason grade is correlated other adverse prognostic factors such as tumor volume, SVI, or positive surgical margins,[297,300] it is not

Albertsen et al applied three comorbidity assessment instruments (i.e., the Kaplan-Feinstein and Charlson indices and the index of coexistent disease) to a cohort of men with localized prostate cancer to assess the impact of comorbidity on patient survival. Although the index of coexistent disease had a marginally better predictive value, each instrument was predictive of age-adjusted survival when corrected for the effect of Gleason score.[240] The risk of death from causes other than prostate cancer (i.e., competing causes) strongly correlated with the severity of comorbidity, and a weak association with prostate cancer–related (i.e., cause-specific) mortality was also noted. Additional research is essential to quantify the confounding effect of comorbidity in the setting of prostate cancer outcomes reporting.

Van Oort reported a higher rate of biochemical relapse in patients when the length of a PSM was more than 10 mm compared to smaller margins.[265] In a series from the Mayo Clinic, Kausik did not detect a difference in relapse rates in patients with EPE and one versus more than one positive margins.[266] In a series of 1712 RP patients, Mauermann reported 10-year bRFS rates of 82% for patients who are margin-negative, 72% for patients with single positive margins, and 59% for patients with multiple positive margins ($p < 0.0001$).

independently associated with a worse outcome in some surgical[297] or RT series.[301-303] Increasingly it is being recognized that tertiary patterns of high-grade adenocarcinoma (Gleason grade 4 or 5) negatively impact prognosis.[294,304-306] Gleason score 7 cancers with any higher grade tertiary pattern have a prognosis following radical prostatectomy that is indistinguishable from patients with a Gleason score 8.[304]

Prostate-Specific Antigen

An abundant literature attests to the importance of the pretherapy serum PSA level as an independent and highly significant predictor of therapeutic outcome.[227,230,249,285,287,307,308] In general the pretreatment PSA level is a measure of tumor volume, although one must also consider the relative PSA contribution from the normal prostate tissue and the fact that some tumors, especially the poorly differentiated ones, may not produce PSA commensurate with the tumor burden. In assessment of post-RT outcome, Landmann and Hunig[309] were the first to draw attention to this association, which was confirmed by the detailed statistical analysis of larger study populations.[227,230,250,251,310,311] Furthermore, the prognostic significance of PSA is not limited to patients treated with RT because similar observations appear in surgical reports.[285,287,289,312,313]

Pretreatment PSA is one of the strongest individual predictors of biochemical relapse.[249,282,285,287,307,314] The effect of pretreatment PSA on outcome increases in a continuous fashion.[228,249] Zagars et al described a relationship between pretherapy PSA and clinical or biochemical relapse after RT.[249] In this series, there was a significant difference in the risk of relapse for pretherapy PSA categories of 4.0 or less, 4.1 to 10.0, 10.1 to 20.0, and more than 20 ng/mL, which was 16%, 34%, 51%, and 89% at 6-year follow-up, respectively. D'Amico described a risk grouping based on pretreatment PSA, Gleason score, and clinical stage.[315] A slightly modified risk group category has been adopted by the National Cancer Center Network and is used for reporting outcomes and to assist in treatment decision making (Table 53-3).[316] Most institutional and other large series now report outcomes by risk stratification group.

The rate of change of the PSA over time may have important diagnostic and prognostic implications. Carter et al reviewed the outcomes of men participating in the Baltimore Longitudinal Study of Aging for up to 39 years. PSA velocity measured 10 years to 15 years before a diagnosis of prostate cancer was correlated with prostate cancer-specific survival 25 years later.[322] The prostate cancer specific survival was 92% in men with a PSA velocity of 0.35 ng/mL per year or less compared to 54% with a PSA velocity of more than 0.35 ng/mL per year ($p < 0.001$). D'Amico reported that the risk of prostate cancer death in men undergoing radical prostatectomy[323] or EBRT[324] because localized prostate cancer was higher if the PSA velocity was more than 2.0 ng/mL per year. Against these observations are the prospective data from the large screening and prevention trials. The ERSPC trial found that PSA velocity did not improve cancer detection and the PLCO model for cancer detection was not significantly affected when velocity was excluded from the algorithm.[325,326] The PCPT found that velocity did not contribute independent prognostic information and the Scandinavian SPCG4 trial determined that PSA changes before diagnosis were not predictive of fatal prostate cancer.[84,327]

PSA doubling time (PSADT) is as a useful tool to estimate prognosis and guide treatment decisions. Derived from the same data as PSA velocity (PSAV), which measures the absolute rate of change, PSADT is calculated as the slope of PSA measurements over time. PSADT represents the relative rate of PSA change over time and is the time needed for the PSA value to double. PSADT takes into account the exponential nature of prostate cancer growth and requires logarithmic conversion using the formula:

$$PSADT = \frac{\log 2x(T2 - T1)}{\log PSA2 - \log PSA1}$$

A number of PSADT calculators are available for use on handheld computing devices or from web pages (www.nomograms.org, www.nomogram.org). Klotz has proposed that PSADT be used as a factor in the selection of patients for active surveillance.[248] A PSADT of 3 years or less is associated with an 8.5-fold greater risk of biochemical failure after definitive treatment than longer PSADT. Hanks et al[328] used PSADT as a pretherapy predictive factor in patients treated with EBRT and found that a PSADT of less than 12 months adversely affected therapeutic outcome. Most reports have focused on posttreatment PSADT to predict the clinical outcome of patients with biochemical relapse after RT[229,290,329-333] or surgery.[332-335] Although there is considerable individual variation, a local tumor recurrence tends to correlate with a longer PSADT (median, 12 to 14 months), whereas a shorter PSADT (median, 4 to 6 months) is observed for metastatic relapse.[311,336] The posttreatment PSADT in patients that have failed treatment with RT is similar to that observed in surgical patients.[337]

After RT, residual prostatic epithelial cells may produce PSA under androgenic stimulation, and serum levels of PSA may be detected even in the absence of prostate cancer.[338] The post-RT nadir PSA (nPSA) level is considered to be a predictive variable similar to pretherapy factors.[227,331,339-341] The nPSA correlates with pretherapy PSA level, tumor grade, and clinical T category[341,342] but is an independent predictor associated with biochemical or clinical relapse,[311,339,340,343] and with local and metastatic tumor control.[317,331,340] Alcantara reported a 10-year distant metastasis rate of 4% versus 19% in men with a 12-month nPSA of ≤2 ng/mL versus >2 ng/mL, $p < 0.0001$.[342] Zelefsky reported the incidence of distant metastases was 10.3% and 17.5% at 10 years in men that had a 2-year nadir

TABLE 53-3 National Cancer Center Network Prostate Cancer Risk Grouping

Relapse Risk	T Category	Grade	PSA (ng/mL)	Comments
Very low risk	T1a	GS ≤ 6	<10	Fewer than 3 biopsy cores positive, ≤ 50% cancer in each involved core, PSA density < 0.15 ng/mL/g
Low risk	T1-2a	GS = 2-6	<10	All three factors
Intermediate risk	T2b-2c	GS = 7	10-20	Any one of the three factors
High risk	T3a	GS = 8-10	> 20	Any one of the three factors
Very high risk	T3b-T4	Any	Any	
Metastatic	Any T	Any grade	Any PSA	N1M0 or NanyM1

Although numerous studies relate pretherapy PSA level to biochemical relapse, reports using clinical endpoints are not as abundant.[249,250,317] Nonetheless, Crook et al[318] affirmed that local tumor recurrence correlated with pretreatment PSA in patients in whom serial post-RT prostatic biopsies were performed. Zagars et al[249] reported a similar finding in a study population in whom post-RT prostatic biopsies were generally obtained to identify an otherwise unknown source for biochemical relapse. Studies with long enough follow-ups to document clinical disease relapse, local and distant, are now being reported and correlate clinical endpoints with pretreatment PSA levels.[227,285,291]

In an effort to improve the prognostic accuracy of pretherapy serum PSA many investigators have examined derivatives of the serum PSA including PSAD (a correction for benign prostate gland volume) or PSA kinetics (velocity of rise or doubling time). Zentner et al[317] evaluated PSAD (i.e., the PSA value divided by prostatic volume) in patients treated with EBRT. Patients with a PSAD of 0.3 ng/mL/cm^3 or less had a 100% DFS probability at 30 months, whereas the estimate for patients with PSAD of more than 0.3 ng/cm^3 was significantly worse (62%). Others have not shown this association and PSAD does not appear to add significantly to the utility of serum PSA level as a predictor of outcome after EBRT, and it is not routinely used as a prognostic factor.[319-321]

value of ≤1.5 ng/mL versus >1.5 ng/mL, $p < 0.002$).[340] Although nadir level can be used to predict the relative likelihood of failure after radiation, there is no absolute level which can determine success or failure after this therapy. Kuban et al in a multiinstitutional study of 4839 patients treated by EBRT for prostate cancer demonstrated that progressively lower nadir levels were associated with incremental improvement in PSA DFS with an 8-year rate of 75% with a nadir <0.5 compared to only 12% with a nadir ≥4.0.[227]

PSA Failure Definitions after Local Therapy

PSA is commonly being used to assess outcome after local therapy because clinical failure, especially following treatment of localized disease, takes years to develop. In evaluating new treatment methods and techniques, it is desirable to obtain comparative efficacy information as soon as possible. Therefore, a consistent, reliable, and accurate method of using PSA as a marker for failure is necessary.

PSA failure definitions following surgery or radiation therapy must use different criteria because of the inherent effect on the prostate by each of these modalities. Because the goal of radical prostatectomy is to remove all prostatic tissue, a detectable PSA level after surgery has been correlated with outcome. Although an undetectable PSA is desirable, the possibility of residual benign glands capable of producing low levels of serum PSA has been suggested. The PSA level is very low, in the 0.1 ng/mL to 0.4 ng/mL range, and is representative of a small amount of prostate tissue left behind.[312,344,345] Although these levels have been correlated to postoperative relapse, further proof of progressive disease is evidenced by a subsequent rising PSA. Cutpoints of 0.2 ng/mL and 0.4 ng/mL have been proposed to report biochemical failure following surgery. In each case, patients with PSA values greater than the cutpoint have higher rates of subsequent rising PSA or clinical failure.[312,344,345] The AUA has recommended defining biochemical relapse as an initial serum PSA ≥0.2 ng/mL with a confirmatory PSA >0.2 ng/mL.[346] For irradiated patients, a rising PSA is the criteria for relapse that is often used because a low target PSA value, especially soon after treatment is not specific in predicting clinical failure.[347,348] This is because the prostate remains intact in irradiated patients and it takes a median of nearly 2 years for the PSA to reach the nadir, or lowest level.[349] Simultaneous with this gradual declining process, a PSA "bounce" can occur, mimicking failure because the bounce is a PSA rise but one secondary to a benign cause, likely prostatitis.[350-352] Therefore, the definition of PSA relapse after radiation must take both of these factors into account to minimize false-positive failure reporting.

The American Society of Radiation Oncology (ASTRO) held a Consensus Conference in 1996 for the purpose of devising a PSA-based failure definition after EBRT, which would standardize outcome reporting. The ASTRO definition for biochemical failure is characterized by three consecutive PSA rises with the time of failure backdated to halfway between the PSA nadir and the first PSA rise.[353] After several additional years experience in the PSA era and more sophisticated statistical analysis, criticisms of the ASTRO definition were brought forward and alternative definitions that were more sensitive and specific were advocated.[347,354] Problems with the original PSA definition included biases associated with back-dating and the time necessary to collect three consecutive rises. The original ASTRO consensus also did not consider the use of neoadjuvant or adjuvant hormone therapy nor did it include data from alternative radiation techniques such as permanent or temporary brachytherapy.

A second Consensus Conference sponsored by both ASTRO and RTOG was held in 2005 at the RTOG's semiannual meeting in Phoenix, Arizona.[355] A panel representing radiation and surgical specialties as well as clinical trials groups formulated a revised consensus statement, commonly referred to as the "Phoenix" or nadir + 2 definition. The revised definition states that a PSA rise of 2 ng/mL or more above the nadir PSA (defined as the lowest PSA achieved) is a biochemical failure. The date of failure is the date at which that PSA value is determined "at call" and not backdated.[355] Patients not meeting these criteria but who undergo salvage therapy such as AD, prostatectomy, brachytherapy, or cryosurgery are considered failures at the time of a positive biopsy or when salvage therapy is initiated. Based on clinical outcomes reported by Kestin, the original ASTRO definition had a sensitivity of 51%, specificity of 78%, positive predictive value of 31%, and a negative predictive value of 88%. The Phoenix definition has a sensitivity of 64%, specificity of 78%, positive predictive value of 36%, and a negative predictive value of 92%.[354,355] Another important point stressed at both consensus conferences is the minimum follow-up necessary to use these definitions. The stated date of control should not be more than 2 years short of the median follow-up time. For example, to report a 5-year biochemical control rate, the median follow-up should be at least 3 years. The original ASTRO definition still has important utility because it can be used to compare results to prior publications. The consensus panel encouraged reporting results using both the Phoenix and ASTRO definitions.[355] The interval to biochemical failure by the Phoenix definition is important in predicting the future development of distant metastases or prostate cancer mortality. Patients experiencing a rising PSA to the nadir + 2 within 18 months of treatment have a significantly higher rate of death from prostate cancer.[356]

Predictive and Prognostic Models

The previous sections on prognostic factors emphasized the interactions many of them have with each other as it relates patient outcomes. Furthermore, comparing treatment between modalities or between institutions and series is complicated by the fact that the patient populations vary considerably between them. It has become increasingly important to use models to account for variable prognostic factors and allow more meaningful comparisons between heterogeneous populations of patients. Models that are predictive describe the likelihood of a finding or event, irrespective of time, whereas prognostic models describe the likelihood of an even over time.

Risk groupings are relatively easy to use and are based on a limited number of clinical variables that allow categorization of patients by their likelihood of recurrence. One of the most commonly used risk grouping was described by D'Amico to estimate the biochemical outcome of men following radical prostatectomy, EBRT, or interstitial brachytherapy.[315] Patients are classified into three categories based on their presenting PSA, Gleason Score, and clinical stage; low risk (stage T1c, T2a, and PSA ≤10 ng/mL and Gleason score ≤6), intermediate risk (stage T2b or Gleason score = 7 or PSA >10 and ≤20 ng/mL) or high risk (stage ≥T2c or PSA >20 ng/mL or Gleason score ≥8). Additional risk groupings have been developed by the National Cancer Center Network (NCCN), University of California–San Francisco (UCSF), and Johns Hopkins University[193,316,358] and are discussed on the Expert Consult website.

Numerous nomograms have been developed to calculate risk of positive biopsies on screening exams, estimate pathological stage, predict biochemical control before surgery,[359] EBRT,[360] or brachytherapy[361] as well as the risk of prostate cancer progression after local therapy.[362,363] Examples of nomograms for predicting biochemical disease-free survival (bDFS) following radical prostatectomy and EBRT are presented in Figures 53-2 and 53-3.

In a multiinstitutional series, Buyyounouski reported a 10-year estimate of prostate cancer death of 26.2% compared to 55.9% if the interval to biochemical failure were more than 18 months compared to less than 18 months, respectively.[357]

Numerous models exist to assist decision making in many aspects of prostate cancer screening, diagnosis, staging, and treatment. These models include nomograms, risk groupings, probability tables, and artificial neural networks. Each of these predictive models vary on their levels of discrimination, calibration, generalizability, and complexity. Discrimination describes the ability to identify patients that will or will not experience the outcome of interest. Calibration refers to the ability to generate predictions that closely approximate observed outcomes. That is, given a risk of x% experiencing an event then close to x% actually experience it. Although there are methods to internally validate them, ideally predictive models should be externally validated by a data set other than that used to create the model. This validation step speaks to the generalizability of the model, how likely the prediction is to be accurate in similar groups of patients at different centers or at different points in time. When using predictive and prognostic models it must be understood that the data is often unique to the population used to derive the model.

The NCCN has adopted a similar classification for treatment recommendations except T2b-T2c is considered intermediate risk and T3a-T4 represent high-risk tumor stages.[316] The UCSF group has described a risk grouping model that includes the percentage of positive biopsy cores and patient age. The cancer of the prostate risk assessment (CAPRA) score is calculated by assigning points to increasing risk factors. Unlike the D'Amico grouping, the PSA is divided into five discrete categories. The CAPRA score may range from 0 to 10 although 0-1 and 7-10 groups are often combined. The CAPRA score has been validated as a useful tool to predict outcomes following radical prostatectomy.[358] One problem with risk groupings is that each category may contain a heterogenous population and continuous variables are converted into categorical variables, thereby removing the information about the actual value. It also assumes each variable carries equal weight in contributing to patient outcome. Probability tables have been used to estimate pathological findings following radical prostatectomy and are commonly used in multidisciplinary settings to estimate the risks of ECE, SVI, or lymph node metastases. Partin popularized the use of probability tables based on a series of more than 5000 men undergoing radical prostatectomy at Johns Hopkins University.[193] The Partin tables combine serum PSA, clinical stage, and biopsy Gleason score to predict the pathological stage in four groups; organ-confined disease, established ECE, SVI, or lymph node involvement. The outcomes are considered mutually exclusive so the tables tend to underestimate the risk of ECE or SVI because a significant proportion of patients with LNI will also have these findings.[193,194] Nomograms are graphical calculation devices that incorporate at least two continuous or categorical variables. Risk points are determined by identifying the value of variables of interest on axes corresponding to a given prognostic factor. The risk points are then summed and used to estimate the combined effect of the predictors on the expected outcome. Nomograms often use Cox proportional hazards or modified logistic regression to correct for variable impact of incremental changes across a broad range of values to predict endpoints.[356] Nomograms can be adapted to web-based or handheld personal data assistant applications to quickly and conveniently calculate predicted outcomes (www.nomograms.org and www.nomogram.org).

Complementary to these models used to predict the likelihood of a staging outcome or clinical endpoint, nomograms have been developed that are used for estimating 10-year life expectancy to gauge the appropriateness for curative therapy in patients that may be better suited for conservative management approaches. Likewise, there are models that can estimate the likelihood of complication-free survival following surgery or radiation therapy.

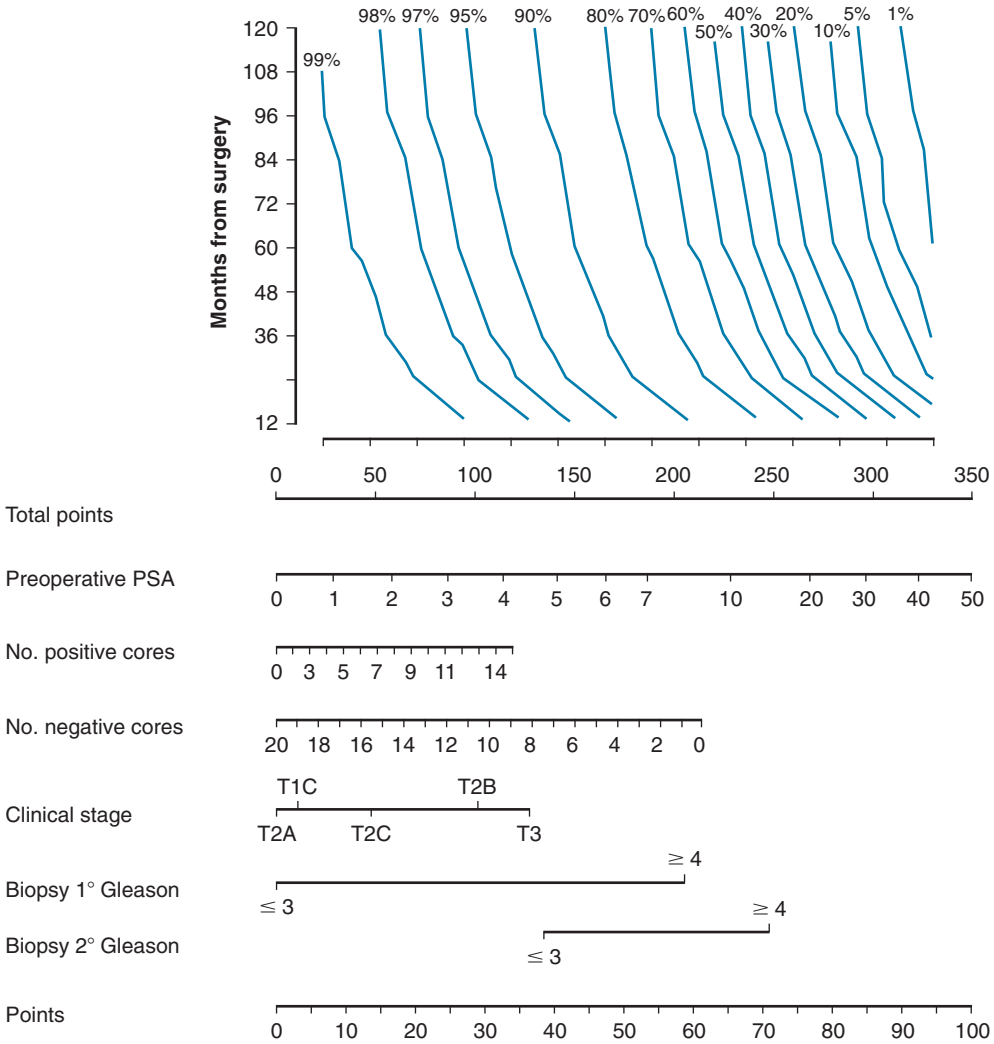


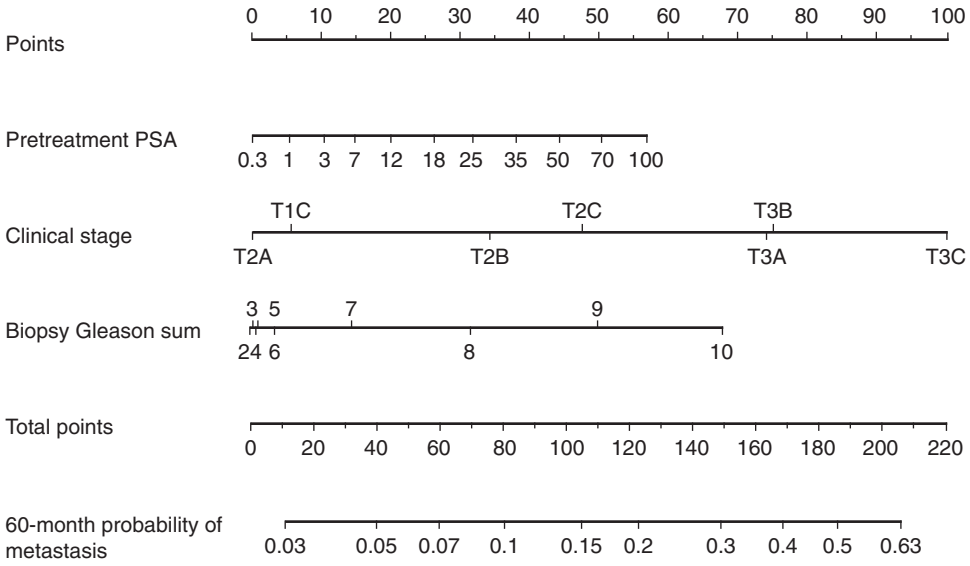
Figure 53-2 Preoperative nomogram estimating the 1- to 10-year progression-free probability after radical prostatectomy alone.
Instructions for physician: Locate patient's preoperative prostate-specific antigen (PSA) on the Preoperative PSA axis. Draw a straight line down to the Points axis to determine how many points toward disease recurrence that patient receives. Repeat this process for each of the remaining variable axes. Sum the points for each predictor and locate this sum on the Total Points axis. Draw a line straight up from the Total Points axis until it intersects with the horizontal line drawn from Months from Surgery, corresponding to the time point in the future within which the risk of recurrence is wished to be calculated. The progression-free probability can be estimated at 12 to 120 months after radical prostatectomy. The slanted vertical line that crosses this intersection point corresponds to the calculated progression-free probability within that point in time after radical prostatectomy.
Instructions for patient: Mr. X, if we had 100 men exactly like you, we would predict <predicted probability from nomogram × 100> percent to remain free of disease progression at <specified months from surgery> following radical prostatectomy alone.
Data from Stephenson AJ, et al: Preoperative nomogram predicting the 10-year probability of prostate cancer recurrence after radical prostatectomy. J Natl Cancer Inst 98:715–717, 2006.

CLINICAL MANIFESTATIONS, PATIENT EVALUATION, AND STAGING

Clinical Symptoms and Signs

Most patients with early-stage prostate cancer are asymptomatic because most cancers arise in the peripheral zone of the gland. However, a tumor may arise in the transition zone or may extend from a peripheral location to encroach on the prostatic urethra and produce obstructive symptoms. The resulting symptoms, commonly referred to as prostatism, initially consist of urinary hesitancy, diminished force of stream, intermittency, and a sense of incomplete voiding. Thereafter, the bladder detrusor muscle may lose compliance, and irritative symptoms such as urgency, frequency, nocturia, dysuria, and incontinence may develop. Although acute urinary retention may ensue, it is no more likely to occur in the patient with prostate cancer than in the general population.[364,365] Indeed, the constellation of obstructive symptoms now referred to as lower urinary tract symptoms (LUTS) are commonplace in the elderly male population[366] and are often associated with BPH or other mechanical or functional disorders of the urinary bladder. Hematuria, which may result from tumor involvement of the prostatic urethra or bladder trigone, and hematospermia are uncommon signs of prostate cancer and should prompt further investigation to identify their etiology.

Local extraprostatic tumor spread is often asymptomatic and may not be apparent on physical or radiologic examination. However, extensive disease involvement of the periprostatic tissues may produce symptoms as a late manifestation of the disease process. Denonvilliers' fascia is a barrier to rectal



Physician instructions: Locate the patient's PSA on the PSA axis. Draw a line straight up to the Points axis to determine how many points toward recurrence the patient receives for his PSA. Repeat this process for the other axes, each time drawing straight up to the Points axis. Sum the points for each predictor and locate this number on the Total Points axis. Draw a line straight down to find the patient's probability of metastasis within 60 months.

Patient instructions: "Mr. X, if we had 100 men exactly like you, we would expect *<predicted percentage from nomogram>* to develop metastasis within 5 years following conformal radiation therapy. This prediction assumes you may need hormonal therapy, and that you might die of another cause first."

Figure 53-3 Nomogram for 60-month *EBRT* probability of metastasis after EBRT, recognizing the potential for death from other causes. *PSA*, Prostate-specific antigen.
Data from Kattan MW, et al: Pretreatment nomogram that predicts 5-year probability of metastasis following three-dimensional conformal radiation therapy for localized prostate cancer. J Clin Oncol 21:4568–4571, 2003.

involvement, but symptoms similar to those of a primary rectal cancer, such as hematochezia, constipation, or intermittent diarrhea, reduced stool caliber, or abdominopelvic pain, may occur. Renal impairment as a result of prolonged bladder outlet obstruction or from tumor involvement of the bladder trigone or periureteral tissues may cause hydronephrosis and symptoms or signs because of fluid retention or electrolyte imbalance. Invasion of the neurovascular bundles, urogenital diaphragm, or penile corporeal bodies may result in impotence, perineal pain, or priapism, respectively.

The pelvic, axial, and proximal regions of the appendicular skeleton are the most common sites of metastatic disease spread. Based on the distribution of uptake on radionuclide bone scan, the vertebral column (74%), ribs (70%), pelvis (60%), femora (44%), and shoulder girdle (41%) are the prevailing sites of involvement in patients with osseous metastases.[367] Although approximately one third to one half of those with bone metastases may be asymptomatic, pain in these areas is commonly described or may be elicited through examination of the skeletal system. The extent of osseous metastasis and the presence of symptoms[368] are associated with responsiveness to therapeutic intervention and survival. Pathologic fractures are uncommon but may affect the femora, humeri, and vertebral column. Extension of tumor into the epidural space or compression of nerve rootlets or peripheral nerves may cause neurologic deficits. Spinal cord compression is characterized by motor weakness, sensory changes, and bladder and bowel dysfunction. Its presence is considered an oncologic emergency that requires prompt recognition and treatment to avoid permanent disability.

Tumor involvement of pelvic or paraaortic lymph nodes is usually asymptomatic, and clinical signs, such as edema of the abdominal wall, genitalia, and lower extremities, are rarely apparent unless bulky nodal disease is present. Although metastases to other anatomic sites (e.g., adrenal glands, liver, lung, and skin) are described,[369] symptoms or signs resulting from functional compromise are uncommon. Paraneoplastic syndromes, including Cushing's syndrome, the syndrome of inappropriate antidiuretic hormone secretion and abnormalities of serum calcium levels, and hematologic manifestations (e.g., anemia, disseminated intravascular coagulation) may also be present in the patient with advanced metastatic disease.[370]

History and Physical Examination

A thorough history and physical examination are fundamental components of patient evaluation and may be instrumental in directing further diagnostic and staging procedures. In particular, detailed inquiry regarding urinary status, sexual function, and skeletal symptoms identifies the patient's baseline condition and may prompt further investigation and therapy. Assessment of comorbid illness may have relevance to therapeutic decision making, and the family medical history may identify other family members at high risk for developing prostate cancer.

A complete physical examination is essential and may reveal metastatic disease or other clinically important conditions. Careful DRE of the prostate forms the cornerstone of the physical examination and is instrumental in tumor staging. The examination may be performed in the lithotomy, knee-chest, lateral prone (Sims), or standing position with a well-lubricated, gloved index finger. The examiner should measure the craniocaudad and transverse dimensions of the gland and determine its overall consistency, sensitivity, and mobility, as well as the presence and size of any firm or elevated areas. Typically, an area of prostate cancer is quite hard, may or may not be raised above the surface of the gland, and is surrounded by compressible prostatic tissue. However, an area of prostatic induration per se is not pathognomonic of cancer because induration may be the result of prostatic calculi, infection, infarction, granulomatous prostatitis, or nodularity as a result of BPH. Although DRE is important in staging, it is not particularly accurate in screening. In a meta-analysis of 13 prostate cancer screening studies, the pooled sensitivity, specificity, and positive predictive value for DRE were 53.2%, 83.6%, and 17.8%, respectively.[371] The lateral rectal sulci and the urogenital diaphragm are also examined to determine whether extraprostatic tumor extension is present. Although the normal seminal vesicles are too soft to be palpated as discrete structures, firmness extending superior to the prostate gland suggests SVI, and further investigation may be warranted.

Staging

Whitmore[372] is credited with developing the first widely accepted stage groupings for prostate cancer, and the general concepts set forth were later incorporated into the AUA system.[373] Subsequently, the Organ Systems Coordinating Center of the National Cancer Institute initiated a process to align the Whitmore-based groupings and the TNM system. This and other efforts led to development of the AJCC TNM classification and stage groupings,[374] which were unified with the Union Internationale Contre le Cancer in 1987.[165] This system retains the general organizational scheme of prior systems and conforms to the TNM rules applied to tumors originating in other sites.

The AJCC TNM classifications and the stage groupings for prostate cancer are shown in Tables 53-1 and 53-2, respectively. Clinical staging involves primary tumor assessment with DRE, complete general examination to determine disease extent, serum PSA determination, and diagnostic imaging (including TRUS). The regional lymph nodes are defined as those confined to the true pelvis (i.e., those lying below the bifurcation of the common iliac arteries) and include the obturator, external and internal iliac, and sacral lymph node groups. All information available before definitive therapy may be used for clinical staging. Pathologic staging requires histologic examination of the prostatoseminovesiculectomy and pelvic lymph node specimens; presence of EPE, SVI, and margin status, as well as the extent and location of involved lymph nodes should be specified.[151]

Diagnostic Imaging

Ultrasonography

TRUS is an important tool in prostate cancer diagnosis and may be used to identify abnormalities of the prostate gland and seminal vesicles for staging purposes. Although the typical sonographic appearance of prostate cancer is an area of diminished echogenicity (hypoechoic) in the peripheral zone of the gland, between 14% and 29% of patients with prostate cancer have an isoechoic tumor that cannot be reliably distinguished from normal prostatic tissue.[375-377] Furthermore, among prostate cancer screening participants with a hypoechoic finding on TRUS that prompts further evaluation, only 17% to 31% have a diagnosis of cancer established by needle biopsy of the prostate.[375-377] Color or contrast-enhanced Doppler TRUS improve the sensitivity and specificity of prostate cancer detection.[378]

Several investigations address the ability of TRUS to detect extraprostatic tumor extension, which may affect tumor stage, by correlating ultrasound observations with the findings from histologic examination of the prostatoseminovesiculectomy specimen.[379-383] In a series of 200 patients with clinical T3a disease, TRUS was not remarkably different than DRE in detecting EPE.[380] Histopathological examination of prostatectomy specimens confirmed unilateral T3a disease in 49.5% of cases detected by DRE and 55.7% detected by TRUS.

Despite limitations, tumor extension into the seminal vesicles may be appreciated by TRUS as echogenic abnormalities and by anterior displacement and enlargement of this structure. TRUS-guided biopsy may be appropriate if predicted rates of SVI by preoperative nomograms are high and a treatment decision would change based on this finding. TRUS is also valuable in assessing patients for prostate brachytherapy. Prostate gland volume and the presence of prominent median lobe tissue are important considerations for radioactive seed implantation.

Computed Tomography

CT imaging has little value in assessing intraprostatic anatomic changes because of the primary tumor because the neoplasm usually has the same attenuation as the normal prostate gland. In the presence of EPE, the periprostatic fat planes may become indistinct, or there may be deformity of the bladder base, obliteration of the normal angle between the seminal vesicle(s) and the posterior aspect of the bladder, or asymmetric enlargement of a seminal vesicle. However, caution must be exerted in interpreting these images because they may be an artifact of biopsy or the plane between seminal vesicles and bladder may be obscured by rectal distention. Furthermore, EPE is often microscopic and cannot be detected with CT scanning. This observation largely accounts for the low sensitivity of this procedure (24%), which limits its utility in staging the primary tumor.[383]

Diagnostic CT scanning of the abdomen and pelvis for lymph node staging of newly diagnosed prostate cancer infrequently yields valuable information. CT imaging can detect only abnormalities in lymph node size that may result from extensive tumor involvement. As a result, the diagnostic sensitivity of this procedure with respect to lymph node assessment is poor (~25%),[383,384] and the routine use of this test is of little value in assignment of regional node stage in low-risk patients.[385-388] The American College of Radiology (ACR) and the AUA restrict their recommendations on the use of abdominal and pelvic CT scans for staging to locally advanced and high-risk patients.[133,389]

Magnetic Resonance Imaging

In staging prostate cancer, T1-weighted (T1WI) sequences provide high contrast between water density structures (e.g., prostate gland, seminal vesicles) and fat and are particularly useful for evaluating the periprostatic fat and veins, neurovascular bundles, perivesical tissues, and lymph nodes. MRI should be obtained at least 4 to 6 weeks after biopsy to prevent biopsy-related hemorrhage from causing artifacts. The T2-weighted image (T2WI) sequences demonstrate the internal zonal anatomy of the prostate and the architecture of the seminal vesicles. Prostate cancer is typically a focal, peripheral region of decreased signal intensity on T2WI surrounded by a normal (high-intensity) peripheral zone. Transition zone

The Radiology Diagnostic Oncology Group prospectively evaluated preoperative TRUS in 219 patients who underwent RP.[379] Among 85 patients considered to have disease confined to the prostate gland, 43 (51%) had extraprostatic tumor extension, whereas 50 of 134 patients (37%) with suspected extraprostatic disease did not have this confirmed by histologic examination. Overall, the sensitivity and specificity of TRUS in identifying extraprostatic disease were 66% and 46%, respectively, and the test accuracy was only 58%. Based on these results, these investigators concluded that TRUS is not sufficiently accurate to assist in staging early-stage prostate cancer, mainly because of its limitations in identifying microscopic extraprostatic disease spread. In a prospective, multiinstitutional study of 263 patients who underwent radical prostatectomy, preoperative clinical staging by TRUS and DRE was compared with pathologic staging.[381] Overall, TRUS was not significantly better than was DRE in predicting ECE.

Terris et al[382] demonstrated the feasibility of obtaining ultrasound-guided preoperative bilateral seminal vesicle biopsies. Among 73 patients with prostate cancer suitable for prostatectomy, biopsy showed tumor involvement adjacent to seminal epithelium (i.e., a pathognomonic finding) in 8 patients; all of these instances were confirmed following examination of the surgical specimen. Eleven of 133 negative preoperative seminal vesicle biopsies had involvement with cancer, resulting in a false-negative rate of 8%.

Huncharek and Muscat[386] analyzed the CT results of 425 patients with newly diagnosed prostate cancer and found that only 12 patients (3%) had radiologic evidence of adenopathy. Because patients with adenopathy had higher serum PSA levels, these authors concluded that CT scanning was not indicated in the patient with a PSA value under 20 ng/mL, wherein fewer than 1% had adenopathy. Other investigators noted a similar association between serum PSA level and radiologic and histologic findings and likewise concluded that CT imaging for nodal assessment should be reserved for patients with higher (>20 ng/mL) PSA values.[384,387] Fine-needle aspiration cytology may further enhance the specificity and accuracy of CT-based pelvic node evaluation, particularly in intermediate- and high-risk patients.[388]

(TZ) cancers are more challenging to detect because the signal characteristics of the TZ and prostate cancer overlap. Occasionally, nodules of BPH may have similar signal characteristics. ECE can be identified by a contour deformity with an angulated margin, an irregular bulge, a breech of the capsule with direct tumor extension, obliteration of the rectoprostatic angle, or asymmetry of the neurovascular bundles. SVI is characterized by contiguous low signal tumor extension from the base of the prostate, tumor extension along the ejaculatory duct, asymmetric decreased signal of the seminal vesicles, or decreased conspicuity of the seminal vesicle wall on T2WI.

Based on a low sensitivity, specificity, and accuracy a 1.5T body-coil MRI alone may not an accurate method for prostate cancer staging.[379] Over the past decade technologic advances and the introduction of high magnetic field (3T) and multiparametric imaging protocols have allowed for higher MRI resolution and improved staging accuracy. Endorectal coil MRI has been shown to have superior spatial resolution and contrast than 1.5T body-coil images. In addition, the simultaneous use of other clinical information in pretreatment nomograms enhances the value of MRI in predicting seminal vesicle invasion and organ-confined disease.[389,390] Therefore, endorectal-coil or 3T MRI may be best applied in conjunction with the DRE, Gleason score, and pretherapy serum PSA findings in select patients with intermediate- or high-risk prostate cancer.

Dynamic contrast enhancement (DCE)-MRI may visualize neovasculature associated with prostate cancer. DCE-MRI shows earlier and more intense enhancement of prostate cancer than normal peripheral zone tissue. Padhani has shown that DCE-MRI could reliably distinguish tumor from noncancerous prostate.[393] Diffusion-weighted imaging (DWI)-MRI capitalizes on tumor cell density restricting the motion of water molecules. DWI-MRI alone may not provide superior localization or staging information than T2WI, but it has shown some utility as a biomarker predictive of histologic grade.[394]

Magnetic resonance spectroscopy (MRS) can assess cellular metabolism and aid in distinguishing prostate cancer from benign intraglandular changes. Loss of a citrate peak and gain in the choline/creatine peak on MRS has been correlated with the presence of prostate cancer (Figure 53-4).[396] Although it has been hoped that MRS would improve the diagnostic accuracy and staging of prostate cancer, a clinical trial by the ACR Imaging Network (ACRIN) showed no benefit to MRS over standard MRI alone.[397]

Multiparametric MR imaging (mp-MRI) includes a high resolution T2WI along with at least two functional MR techniques (DCE-MRI, DWI-MRI, or MRS). Combining these techniques improves both diagnostic and staging accuracy. Both the ACR and the European Society of Urogenital Urology have described mp-MRI as useful tools to characterize tumor stage and biology.[389,390]

As in CT imaging, interpretation of pelvic MRI images for lymph node metastases relies on lymph node size. Pelvic MRI may also identify bone metastases and confirm the malignant nature of abnormalities identified on bone scan.

Nuclear Medicine Imaging

Bone Scans

Clinically apparent metastatic disease is limited to bone in 80% to 85% of patients with prostate cancer metastases and is observed in a pattern that correlates with the distribution of hematopoietic marrow in the adult. Radionuclide bone scan appearance of metastases may range from a solitary focus of radionuclide uptake to the "super scan," wherein the entire skeleton is uniformly affected. Recognition of the latter condition, distinguished by the lack of renal uptake and excretion of the radionuclide, is important because the scan may otherwise be interpreted as normal. Although the bone scan is a sensitive imaging tool, various other conditions, such as arthritis, bone fracture, and Paget's disease, may also result in uptake of the radionuclide. In certain situations, standard bone radiography or tomography, CT, or MRI may be required to determine the nature of the findings noted on bone scan.

Since the advent of serum PSA testing, Chybowski et al[400] were among the first to evaluate the utility of obtaining a routine bone scan in the pretherapy evaluation of the patient with newly diagnosed prostate cancer. These investigators conducted a retrospective evaluation of 521 randomly selected patients and correlated clinical T category, tumor grade of the diagnostic biopsy specimen, acid phosphatase, PAP, and PSA serum levels with bone scan findings. The probability of a bone scan showing metastatic disease was most strongly associated with and was directly proportional to the serum PSA level, as illustrated in Figure 53-5. Only 0.3% of patients with a pretherapy PSA of 20 ng/mL or lower had a positive bone scan at presentation.[400] Based on a retrospective analysis of 853 consecutive patients, Briganti et al developed a classification

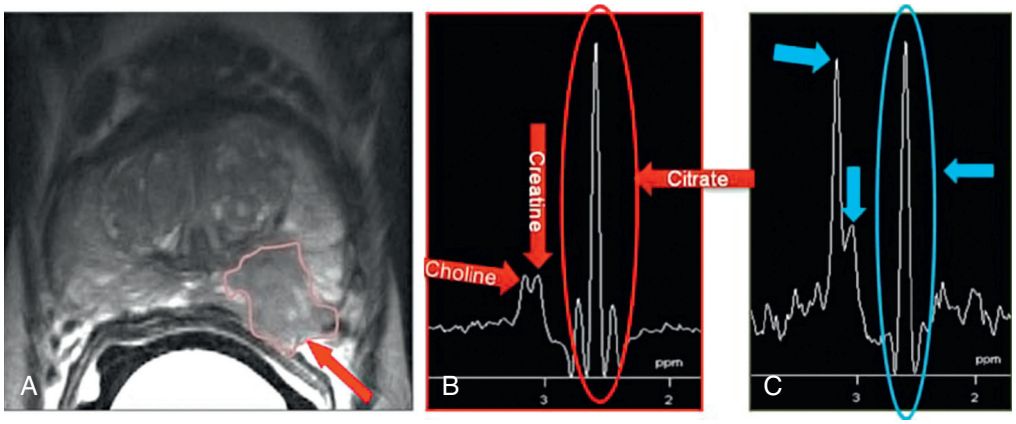


Figure 53-4 A 65-year-old man with stage T3a Gleason 4 + 3 prostate cancer at the left peripheral zone (PZ). **(A)** On the axial T2WI at mid-prostate level in the left PZ there is a low signal lesion *(outlined)* with obliteration of the recto-prostatic angle and extracapsular extension *(arrow)*. **(B)** Magnetic resonance spectroscopic imaging (MRSI) of the normal right side shows low choline + creatine, whereas on **(C)** MRSI of the tumor shows high choline + creatine. The choline peak of tumor is as equally as high as the citrate peak.
From Barentsz JO, Richenberg J, Clements R, et al: ESUR prostate MR guidelines 2012. Eur Radiol 22:746–757, 2012.

In a prospective study of 82 patients, Futterer reported that using an endorectal–pelvic-phased array coil significantly improved anatomical details, staging accuracy, and specificity. Local staging accuracy, sensitivity, and specificity using a pelvic-phased array coil alone were 59%, 54%, and 62%, respectively, although using a combined endorectal–pelvic-phased array coil, local staging accuracy, sensitivity, and specificity were 83%, 65%, and 98%, respectively.[391] High-field (3T) MRI scanners improve the sensitivity and specificity for the nonoperative staging of localized prostate cancer.[392] In a prospective study of 32 patients undergoing 3T endorectal MRI before radical prostatectomy the accuracy, sensitivity, and specificity of local staging were 94%, 88%, and 96%, respectively, for two experienced radiologists, and 81%, 50%, and 92%, respectively, for a less-experienced radiologist.

In a prospective study of 32 patients, Bloch demonstrated a mean sensitivity, specificity, positive-predictive value, and negative-predictive value or 86%, 95%, 90%, and 93%, respectively for predicting ECE by two experienced readers.[395] Although DCE-MRI needs to be validated in larger multiinstitutional studies, it appears to be a promising imaging tool for prostate cancer staging.

Citrate levels in prostate adenocarcinoma appear to be grade dependent. Preliminary data suggest that there is a strong linear relationship between a decrease in citrate levels and the elevation of choline with cancer aggressiveness.[396]

Harisinghani et al have described the intravenous ultrasmall superparamagnetic iron oxide (USPIO) lymphotropic nanoparticles in normal saline to enhance MRI imaging of lymph nodes.[398] Macrophages in lymph nodes involved with cancer do not take up the particles and provide contrast to detect metastases. For lymph nodes that were considered normal by standard MRI criteria, the sensitivity of detecting tumor by this method was 96%. In a meta-analysis of USPIO MRI examinations, the per lymph node sensitivity and specificity were 0.90 and 0.96, respectively. The highest sensitivity and specificity for the studies included in the meta-analysis were for prostate cancer.[399]

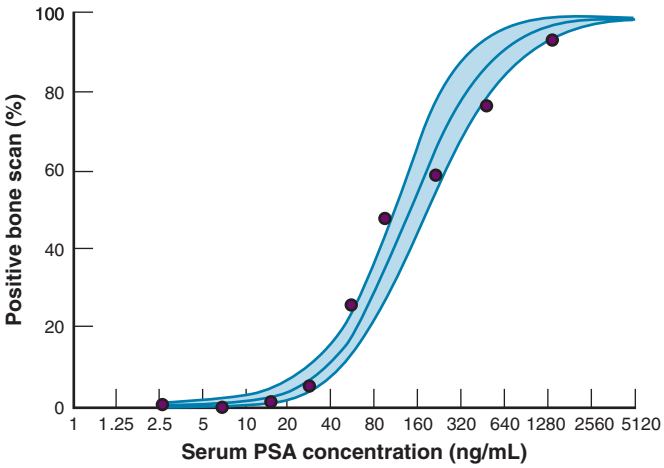


Figure 53-5 Results of bone scintiscan findings as a function of pretherapy serum prostate-specific antigen (PSA) level; 95% confidence intervals are *shaded*.
From Chybowski FM, Larson Keller JJ, Bergstralh EJ, et al: Predicting radionuclide bone scan findings in patients with newly diagnosed, untreated prostate cancer. Prostate-specific antigen is superior to all other clinical parameters. J Urol 145:313, 1991. Copyright 1991, with permission from American Urological Association.

and regression tree model predicts the frequency of a positive bone scan. According to this tool, a staging bone scan should be considered only for patients with a Gleason score >7 or with a PSA >10 ng/mL and palpable disease.[401] A bone scan is not routinely required in the staging evaluation of the patient without skeletal discomfort if the pretherapy serum PSA level is 10 ng/mL or less.

Radionuclide bone scintigraphy may also be of value in the posttherapy assessment of the patient with prostate cancer. The onset of skeletal symptoms, particularly in association with a rising serum PSA profile, should prompt radioscintigraphic investigation. However, posttherapy serum PSA monitoring is apt to identify tumor relapse before the occurrence of symptoms because biochemical relapse may antedate development of bone scan abnormalities by several months.

Monoclonal Antibody Imaging

111-Indium (^{111}In)-labeled capromab pendetide (ProstaScint) is an antibody directed against a prostate-specific membrane antigen.[404] The image performance of ProstaScint has been assessed in the pretherapy evaluation of patients with clinically localized prostate cancer who are considered at high risk for disease spread to regional nodes and in the posttherapy setting when occult residual or recurrent disease is suspected. Surgical series suggest the diagnostic accuracy in the 70% range.[405,406] In the setting of a rising PSA following prostatectomy, ProstaScint imaging has been used to evaluate patients for the presence of local or lymph node recurrence of disease following prostatectomy. The reported value of ProstaScint imaging has been inconsistent with some investigators reporting improved patient selection and outcomes for salvage therapy of a presumed localized recurrence,[407,408] whereas others have reported no difference in outcome in patients with localized versus distant tracer uptake.[409-411]

Positron Emission Tomography (PET) Imaging

PET imaging uses positron-emitting isotopes conjugated to compounds to detect physiological or pathological processes. The most common PET agent used to date is ^{18}F Fluorodeoxyglucose (FDG), a glucose analog that is taken up by upregulated glucose transporters in many cancers. FDG-PET imaging in prostate cancer has been disappointing with poor sensitivity and specificity for local and regional staging.[412,413] Newer PET imaging agents using ^{18}F or ^{11}C labeled methionine, acetate, or choline are showing promise in the primary staging of high-risk prostate cancers and in the evaluation of patients with biochemical relapse.[414] Unfortunately, used as imaging agents to assess disease relapse, the level of PSA associated with the detection of regional or metastatic disease may exceed 2 ng/mL.[415] This high level of PSA makes salvage therapies less useful as the burden or location of disease may exceed that for which radiation therapy could be considered curative.

PET bone imaging with ^{18}F sodium fluoride appears to have superior sensitivity to traditional ^{99m}Tc bone scans. Even-Sapir et al compared Tc-99m planar bone scan, single-photo emission computed tomography (SPECT), F-18 Fluoride PET, and F-18 Fluoride PET/CT in 44 patients with either localized high-risk or metastatic prostate cancer.[416] F-18 Fluoride PET/CT was significantly more sensitive and specific than bone scintigraphy ($p < 0.001$) and more specific than PET alone ($p < 0.001$).

Laboratory Evaluation

Prostate-Specific Antigen

PSA is a serine protease produced by normal prostatic acinar and ductal epithelial cells and by neoplastic cells of prostatic origin.[406,417] It is detectable in the serum in a form immunologically identical to that purified from prostatic tissues and may be elevated in patients with benign (e.g., prostatic hypertrophy, prostatitis) or malignant disorders of the prostate gland.[406] Although PSA exists in several forms in the serum, the PSA–α_1-anti-chymotrypsin complex predominates, whereas the free (noncomplexed) form of PSA is less abundant.[124,418]

Serum PSA levels may exhibit interassay (run-to-run) and physiologic (i.e., intraindividual) variation that must be considered in interpreting serial determinations. Physiologic variation refers to the difference in PSA levels observed when a second sample is obtained from the same patient within a few weeks of the initial sample. For physiologic variation, the ratio difference variation is significantly greater than the interassay variation, is inversely related to the PSA level, and may be as high as 0.298 (95% CI).[419] This means, for example, that a serum PSA of 4 ng/mL can increase to 5.2 ng/mL (4.0 × 1.298) and still remain in the range of physiologic variability.

The serum half-life of PSA is approximately 2.2 (±0.8) to 3.2 (±0.1) days,[420] which means that several weeks are required for serum levels to return to baseline after prostatic manipulation or for a nadir value to be reached after prostatectomy. Although digital examination of the prostate, prostatic massage, TRUS, ejaculation, and cystoscopy have an insignificant effect on the serum PSA level, prostate biopsy causes an immediate PSA elevation (median, 7.9 ng/mL) that requires several weeks to return to baseline.[421-423] TURP also causes PSA elevation (median, 5.9 ng/mL), with a median of 17 days required to arrive at the new baseline value.[423] Because the production and secretion of PSA are androgen dependent, AD therapy often results in a striking reduction in the PSA level,[424] which should be considered in interpreting serum PSA values in this setting.

Acid Phosphatase

Abnormally high serum PAP levels correlate with clinical T3-4 disease, higher tumor grade, and pretherapy serum PSA.[245] However, serum PAP determinations add little to current patient evaluation in either the pretherapy or posttherapy setting.

In a series of 239 patients evaluated with bone scan for biochemical relapse after radical prostatectomy, Dotan et al reported an incidence of bone metastases of 4%, 36%, 50%, and 79% with trigger PSA values of 0-10, 10.1-20, 20.1-50, and above 50 ng/mL, respectively.[402] In a multivariate analysis, PSA slope, PSA velocity, and trigger PSA were all significant factors for predicting a positive bone in the evaluation of biochemical failures after prostatectomy. Using CaPSURE registry data on 292 patients that had failed either radical prostatectomy (66%) or radiation therapy (34%), Choueiri reported that age (<60, 60-69, ≥70), imaging type (bone scan, CT, or MR), trigger PSA (≤5 ng/mL versus >5 ng/mL), and PSADT (<10 months versus ≤10 months) were associated with positive scans. They concluded that followup imaging studies are least useful when the PSA is ≤5 ng/mL and PSADT is ≥10 months.[403]

PET labeled acetate may be a marker for fatty acid synthase, which is upregulated in some prostate cancers. Likewise, PET labeled choline is preferentially taken up by prostate cancer with upregulated choline kinase leading to incorporation of phosphatidylcholine in tumor cell membranes.

The sensitivity and specificity for detection of bone metastases was 70% and 57% for planar bone scan, 92% and 82% for bone SPECT, 100% and 62% for F-18 Fluoride PET, and 100% and 100% for F-18 Fluoride PET/CT, respectively.[416] The authors concluded that F-18 Fluoride PET/CT is a highly accurate imaging modality for the detection of bone metastases in patients with high-risk prostate cancer.

As already stated, pretherapy serum PSA is an important prognostic factor in predicting outcome after treatment for prostate cancer and should play an important role in consideration of treatment options. In general, the higher the PSA level, the more likely that the tumor is outside the capsule and into the seminal vesicles or lymph nodes, which has major impact on the choice of therapy.[227,249,360,425]

Although also produced in nonprostatic tissues, the glandular epithelium of the prostate is the dominant source of acid phosphatase in humans. The prostate-specific form of this enzyme (i.e., PAP) is distinct from other isoenzymatic forms and is influenced by hormonal factors, and its expression is altered in the androgen-deprived state. Since the introduction of assays for serum PSA, acid phosphatase testing has declined in frequency.

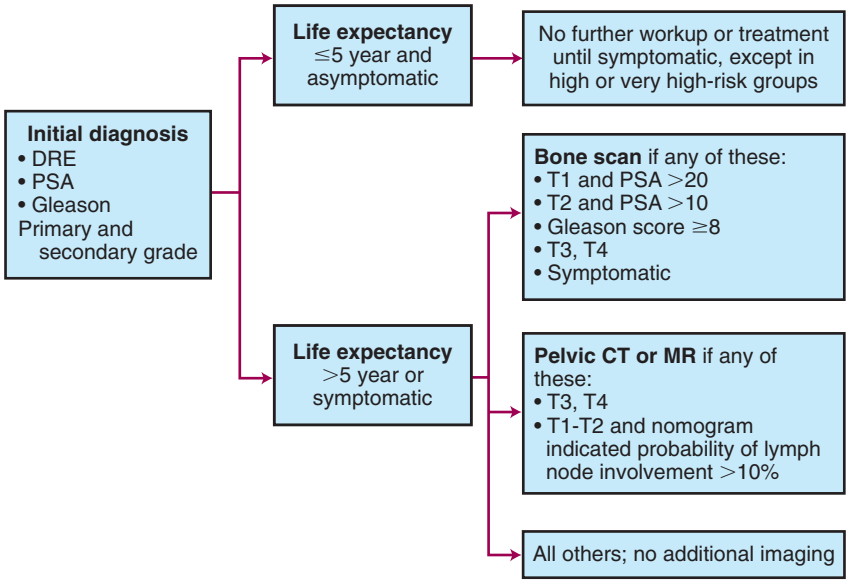


Figure 53-6 Diagnostic Algorithm Guidelines for the initial staging workup. The National Comprehensive Cancer Network (NCCN) guidelines constitute a consensus statement by its authors on the accepted approaches to treatment. Any clinician seeking to apply or consult any NCCN guideline is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment. The NCCN makes no warranties of any kind regarding the guidelines' content, use, or application and disclaims any responsibility for their application or use in any way.*CT*, Computed tomography; *DRE*, digital rectal examination; *MRI*, magnetic resonance imaging; *PSA*, prostate-specific antigen.

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Staging Workup

The ACR[426] and the NCCN have established guidelines for the pretherapy staging of patients with a recently established diagnosis of prostate cancer. The scheme proposed by the NCCN is displayed in Figure 53-6[316] and may be used for guidance. However, individual clinical circumstance may require departure from these guidelines because independent medical judgment is necessary to meet needs unique to a particular situation.

PRIMARY THERAPY

Expectant Management

Expectant management is a clinical strategy wherein immediate therapeutic intervention is not pursued when the diagnosis of prostate cancer is first established. With this approach, treatment is withheld until the time of disease progression or the development of symptoms. Expectant management is used throughout the world, and it is considered a satisfactory alternative to the use of primary RT or RP by its proponents. Under a program of watchful waiting, noncurative treatment would be offered at the time of progression and would consist primarily of hormonal therapy to induce tumor regression and alleviate symptoms.[216,427,428] Increasingly, an alternative expectant management strategy, active surveillance, is replacing watchful waiting. Whereas the goal of watchful waiting is to avoid treatment, the goal of active surveillance is to individualize patient care and treat only those men who have a clinically significant cancer and avoid the risk of treatment related morbidity in men whose cancers are unlikely to progress.

The rationale for expectant management related to the natural history of the condition, the age and comorbidity of the incident population, the perceived need (or lack thereof) for therapeutic intervention, and health-related quality of life issues. PSA screening has resulted in an increased rate of prostate cancer overdiagnosis. Overdiagnosis refers to the lead time bias in establishing a diagnosis of cancer that would otherwise not be detected during a man's expected life span. Overtreatment occurs when an intervention plays no role in extending a patient's life or preventing morbidity from the illness. Furthermore, incidental (or latent) prostate cancer is often found on autopsy examination of the prostate gland, and although particularly common in the elderly,[5,87] is observed in as many as one third of men in their fourth and fifth decades.[4] The key to a successful expectant management strategy is the proper selection of patients who have indolent disease or comorbidities that would impact their expected survival relative to the natural history of the prostate cancer.

The Scandanavian Prostate Cancer Group-4 trial comparing radical prostatectomy to watchful waiting has been updated.[438] Radical prostatectomy was associated with a 12.7% decline in the cumulative incidence of death. At 18 years, 56.1% of patients died in the RP arm compared to 68.9% in the watchful waiting group. The cumulative incidence of prostate cancer death was reduced by 11.0%. The men that had the largest reduction in prostate cancer death related to RP were those younger than 65 years and those with intermediate-risk disease. Even men older than 65 showed a reduction in the incidence of distant metastases with RP.

The North American Prostate Cancer Intervention versus Observation Trial (PIVOT) compared the effectiveness of radical prostatectomy to observation in men with localized prostate cancer detected by PSA screening.[106] Although it fell short of its target accrual of 2000 men, it enrolled 731 patients with T1-2NxM0 adenocarcinoma of the prostate. With a median followup of 10 years, 47.0% of men assigned to surgery

Several studies demonstrate that many localized prostate cancers have an indolent course that may support the use of expectant management for this condition. In particular, the prognosis appears quite favorable for the patient with a small-volume, low-grade tumor identified incidental to transurethral resection (T1a category) for BPH.[429,430] However, the distinction between T1a and T1b is important because the risk of disease progression and disease-specific mortality is highly dependent on tumor volume and grade.[430-432]

One of the largest studies of expectant management was reported by Chodak et al,[216] who collected patient and disease characteristics from several nonrandomized institutional series and from a population-based study to evaluate the outcome of expectant management in patients with localized prostate cancer. The expectant management approach in this study was watchful waiting with no attempt to implement curative local therapy in these patients. The investigators identified 10 studies published during the preceding decade and obtained original data on 828 patients from 6 of them. In this meta-analysis, multivariate regression analysis identified tumor grade as the most significant factor associated with DSS. Based on their observations, the authors concluded that localized prostate cancer is a steadily progressive disorder but that observation with delayed hormonal therapy is a reasonable approach for some men with low-grade disease.

Although single-institution series include patients selected for expectant management on the basis of advanced age or life-limiting comorbidity, population-based studies may minimize this potential source of bias. Johansson et al[427] described a group of 300 consecutive patients diagnosed with T1-2 category prostate cancer at the Örebro Medical Centre, a hospital serving a geographically well-defined population. Among these patients, 223 patients with predominantly low-grade tumors were treated with exogenous estrogen or orchiectomy if symptomatic tumor progression occurred. By the time of last evaluation, extraprostatic tumor extension or metastatic disease had developed in 36% and 17%, respectively. Although the 15-year PFS (45%) and OS (21%) rates were rather low, the high 15-year DSS (79%) appeared consistent with the results of several single-institution investigations.[433,434] However, in an update of this study, the prostate cancer mortality rate increased from 15 per 1000 person-years during the first 15 years to 44 per 1000 person-years beyond 15 years of follow-up.[427] Although most cancers had an indolent course during the first 10 to 15 years after diagnosis, follow-up from 15 to 20 years revealed a substantial decrease in PFS (from 45% to 36%), survival without metastases (from 77% to 51%), and prostate CSS (from 79% to 54%). Therefore, these findings support early curative therapy for patients with an estimated life expectancy of more than 15 years.

Other population-based studies from Sweden have not confirmed the high 10-year to 15-year DSS rate observed in the series from the Örebro Medical Centre.[427] For example, Aus et al[435] identified all patients with an antemortem diagnosis of nonmetastatic prostate cancer treated with primary hormonal (63%) or deferred (36%) therapy who died in Göteborg, Sweden, between 1988 and 1990. Among 301 such patients, the cause of death was related to prostate cancer in 149 (50%), and for those surviving at least 10 years, 63% died from this disease. The initial T-category and grade were associated with the prostate cancer–related death rate. Although only 10% of patients with T1a tumors died of prostate cancer, 47% to 53% of patients with T1b-T3 tumors, and 70% of patients with T4 lesions died secondary to their malignant disease. Forty-three to forty-eight percent of patients with grade-1 and grade-2 tumors and 60% of patients with grade-3 lesions died of prostate cancer. Furthermore, 58% of patients underwent transurethral prostatic resection, 22% underwent an upper urinary tract procedure (e.g., pyelostomy) because of urinary obstruction, and 35% received palliative irradiation.[436] Norlén[437] noted similar findings in an evaluation of 44,300 patients with prostate cancer, representing 99% of all newly diagnosed cases, reported to the Swedish Cancer Registry between 1960 and 1978. Survival rates were adjusted for mortality in the general population and were expressed as relative survival, which estimates the likelihood of dying of prostate cancer. Among patients with prostate cancer, the relative survival was 51%, 34%, and 17% after 5, 10, and 20 years of observation, respectively, representing an excess death rate of approximately 8% per year.

died compared to 49.9% undergoing observation ($p = 0.22$). The death rate from prostate cancer or treatment was 5.8% in the men undergoing surgery compared to 8.4% assigned to observation ($p = 0.09$). Only in the subset of men with a presenting PSA of more than 10 ng/mL was there a significant reduction in all-cause mortality. This study lends support to the position that observation is an acceptable course of managing early stage prostate cancer.

Active Surveillance

Unlike watchful waiting, active surveillance strategies attempt to individualize the decision to recommend treatment based on a patient's risk of cancer progression in his lifetime. The key to a successful active surveillance strategy is the accurate identification of patients with clinically insignificant cancer, a rational follow-up plan, and early intervention criteria. Epstein introduced biopsy criteria to predict an insignificant cancer: Clinical T1c (non-palpable), PSA density <0.15 ng/mL, no Gleason pattern 4 or 5, fewer than three positive cores, and <50% cancer per involved core.[439] In an analysis of 237 patients with nonpalpable (T1c) prostate cancer treated at Johns Hopkins University, the Epstein criteria predicted for organ-confined disease in 91.6% of cases.[440] The other 8.4% that fulfilled the Epstein criteria had evidence of extraprostatic disease. In a European validation study of the Epstein criteria, Jeldres examined a cohort of 366 patients.[441] In that series, 20% of patients that fulfilled the Epstein criteria had unfavorable findings at radical prostatectomy such as Gleason score 7 or nonorgan-confined disease.[441] Consequently, as many as 20% to 25% of patients predicted to have insignificant cancer by the Epstein criteria may be expected to have nonorgan-confined disease.[442] The risk of missing a clinically significant cancer and avoiding necessary treatment in a potentially curative patient is the primary reason that active surveillance has not been more broadly adapted.

To accurately identify truly clinically insignificant cancers, many active surveillance series have included additional selection factors to the Epstein criteria. These have included an absolute PSA <10 ng/mL[443,444] or <15 ng/mL,[445,446] or fewer than 33% positive cores.[443] Although clinical validation has not been established, Shukla-Dave has reported the utility of incorporating MRI and MRS into nomograms to predict for clinical significant disease.[447] The receiver operating characteristic area under the curve for the nomogram was 0.54 compared to only 0.726 for the best clinical nomogram that did not include MR imaging data, $p < 0.0001$.

While on active surveillance, clear criteria need to be described for patient follow-up. All published series to date include repeated DRE, PSA, and repeated prostate biopsies. The interval for DRE varies from every 3 to 6 months for the first 2 years, to every 6 months after 2 years. PSA testing frequency ranges from every 1 to 3 months for the first 1 to 2 years and then every 6 months thereafter. Recommended biopsy intervals vary from every 6 or 12 months during the first year, then annually or biannually thereafter. Likewise, the indications for treatment should be well defined before advising an active surveillance strategy. Common criteria for implementing therapy include a change in PSA kinetics, such as an increase in PSA velocity or a decrease in the PSA doubling time to less than 2 or 3 years.[248] Clinical progression of a palpable or ultrasound detected nodule or a rebiopsy pathology with any Gleason pattern 4 or 5 with more than two cores involved or more than 50% of any core involved with prostate cancer is also used as a trigger to implement treatment.

Several single-institutional studies suggest a role for active surveillance in the management of men with low-risk and low-volume prostate cancer including Toronto Sunnybrook Hospital[250] ($n = 450$), Royal Mardsen[448] ($n = 326$), UCSF[445] ($n = 321$), and Johns Hopkins[449] ($n = 407$). The optimal selection criteria for active surveillance remain to be defined, as well as the frequency of follow-up exams, such as DRE, PSA, and repeat biopsy. The criteria for which to initiate active therapy vary from series to series and the long-term impact on prostate CSS and quality of life remains to be determined. eTable 53-3 summarizes the inclusion criteria for eight series reporting on their results of active surveillance, and eTable 53-4 shows the surveillance protocols practiced at each of these centers. The criteria for moving from active surveillance to treatment vary by series but include rising PSA, accelerated PSA kinetics, progression on DRE, worsening Gleason score, or increase in cancer volume by biopsy.[448] Lately, the change in PSA velocity and PSA doubling time have been questioned as to whether or not they portend a worsening state of disease.[450] In these series of active surveillance, the prostate cancer-free survival approaches 100%.

Increasingly, active surveillance strategies are being endorsed by oncologic specialty societies and networks, including the NCCN and AUA.[316,318,458-461] Currently, three randomized clinical trials are under way in North America, Europe, and the United Kingdom to evaluate the role of active surveillance relative to treatment.

Local Therapy

There are two well established primary modalities to manage patients with localized prostate cancer: RP and RT. There are no modern randomized clinical trials comparing these two modalities. Two older trials that attempted to make this comparison were compromised by methodological flaws.[461,463] Although the trial conducted in the United States suggested an advantage to surgery, the study was underpowered and did not analyze patients strictly by their study randomization.[461] With 10 years of follow-up, a smaller Japanese Phase III trial did not show a significant difference in OS or prostate CSS rates.[463] Neither of these trials took place in the PSA era nor did they employ modern staging and treatment techniques. Recent attempts to complete randomized clinical trials in the United States and United Kingdom comparing surgery to RT or brachytherapy have been unsuccessful.[464,465]

In clinically localized prostate cancer, several years of post-treatment observation are necessary to measure the impact of a particular treatment on outcome. Biochemical endpoints such as a detectable or rising PSA are imperfect surrogates for ultimate cancer control. Many biochemical definitions of failure require prolonged follow-up to ascertain failure and that may precede clinical failure by several years.[291,355] As a result, comparisons of outcomes between modalities and series that use different biochemical endpoints can be problematic. Careful attention must be paid to the specific biochemical or clinical endpoint as well as the length of follow-up when reviewing outcome analyses.

Lacking prospective randomized clinical trials comparing surgery and RT, it is necessary to rely on large single-institution and multiinstitutional studies to compare long-term DFS. In a series that included cases from the Hospital of the University of Pennsylvania and the Joint Center for Radiation Therapy in Boston, D'Amico reported the results of 1872 patients treated with localized prostate cancer by surgery (888 cases), permanent seed brachytherapy (218 cases), or EBRT (766 cases). The 5-year biochemical outcomes (ASTRO definition) were not significantly different by modality for patients with low-risk disease but patients with intermediate- and high-risk disease fared worse with brachytherapy compared to either EBRT or surgery.[315] In a case control study of 490 cases, Fletcher reported that the combination of brachytherapy and EBRT

eTABLE 53-3 Active Surveillance Inclusion Criteria by Institutional Series

Study (Author)	n	Inclusion Criteria				
		PSA Parameters*	Clinical Stage	Gleason Grade	Volume	Cores
Royal Marsden (van As et al)[446]	326	PSA ≤15	cT1-2a, N0-x, M0-x	≤3 + 4	—	≤50% of cores involved
UCSF (Dall'Era et al)[443]	321	PSA ≤10	cT1-2a	≤3 + 3	—	≤33% of cores involved
Multiinstitutional (Eggener et al)[449]	262	PSA ≤10	cT1-2a	≤3 + 3	—	≤3 of cores positive
PASS (Newcomb et al)[451]	233	—	cT1-2,N0-x, M0-x	—	—	—
Toronto (Klotz et al)[248]	450	If age ≤70 y; ≤10 If age >70 y; ≤15	cT1c	If age ≤70 y; ≤3 + 3 If age >70 y; ≤3 + 4	—	—
Miami (Soloway et al)[452]	230	PSA ≤10	cT1a-2	≤3 + 3	≤20% of each involved core	<2 cores positive
Johns Hopkins (Tosoian et al)[453]	769	PSA ≤10 PSAD ≤0.15	cT1c	≤3 + 3	≤50% of each involved core	<2 cores positive
PRIAS (Bangma et al)[454]	>2000	PSA ≤10 PSAD ≤0.2	cT1c-T2	≤3 + 3	—	<2 cores positive

PASS, *Prostate Active Surveillance Study;* PRIAS, *Prostate Cancer Research International: Active Surveillance Study;* PSA, *prostate-specific antigen;* PSAD, *prostate-specific antigen density;* UCSF, *University of California–San Francisco.*
**PSA expressed in ng/mL*

eTABLE 53-4 Active Surveillance Protocols by Institutional Series

Study (Author)	Surveillance Protocols		
	PSA	DRE	Prostatic Biopsy Schedule
Royal Marsden (van As et al[446])	Every 1 mo year 1 Every 3 mo year 2 Every 6 mo > year 2	Every 3 mo years 1 and 2 Every 6 mo > year 2	Between 18 and 24 mo after diagnostic biopsy
UCSF (Dall'Era et al)[443]	Every 3-6 mo	Every 6-12 mo	Between 12 and 24 mo after diagnostic biopsy, then every 6-12 mo
Multiinstitutional (Eggener et al)[449]	Every 6-12 mo	Every 6-12 mo	All had restaging biopsy before going on AS Within 18 mo after enrollment in AS Then every 1-3 years
PASS (Newcomb et al)[451]	Every 3 mo	Every 6 mo	If diagnosed ≤ 1 year before entry: at 6-12 mo & at 24 mo If diagnosed > 1 year before entry: repeat at 24 mo
Toronto (Klotz et al[248])	Every 3 mo years 1 and 2, then every 6 mo	Every 3 mo years 1 and 2, then every 6 mo	Within 12 mo of diagnostic biopsy, then every 3-4 years; more often for those with PSAdt near 3
Miami (Soloway et al)[452]	Every 3-4 mo years 1-2 then every 6 mo > year 2	Every 3-4 mo years 1-2, then every 6 mo > year 2	Between 9 and 12 mo after diagnostic biopsy, then every 12 mo; sooner if dramatic PSA or DRE changes
Johns Hopkins (Tosoian et al[453])	Every 6 mo (total and free)	Every 6 mo	Every 12 mo
PRIAS (Bangma et al)[454]	Every 3 mo years 1-2 Every 6 mo > years 2	Every 3 mo years 1-2 Every 6 mo > years 2	At mo 12, 48, and 84 If PSAdt 3-10: every 12 mo

AS, *Active surveillance;* DRE, *digital rectal examination;* mo, *months;* PASS, *Prostate Active Surveillance Study;* PRIAS, *Prostate Cancer Research International: Active Surveillance study;* PSA, *prostate-specific antigen;* PSAdt, *prostate-specific antigen doubling time;* UCSF, *University of California San Francisco.*

The largest and most mature prospective series of active surveillance to date is that of the Toronto Sunnybrook Hospital with 450 patients and a median follow-up of 6.8 years.[248] The criteria for active surveillance initially included all favorable risk patients (i.e., Gleason score 6 or less, PSA 10 ng/mL or less) and for patients older than 70 years with a PSA up to 15 ng/mL or Gleason scores up to 3 + 4 was allowed. After 2000 the study strictly limited enrollment to favorable-risk patients. The criteria for implementing treatment were PSA doubling time of 3 years or fewer, histological upgrading and repeat biopsy, or clinical progression on DRE. Initially a PSA doubling time of 2 years or fewer was used but was increased to 3 years when it became apparent that only 10% of patients were identified as higher risk necessitating treatment. Patients had a PSA every 3 months for the first 2 years and every 6 months thereafter, as long as the PSA was stable. A repeat biopsy was performed at 6 to 12 months after enrollment and repeated every 3 to 4 years until the patient reached the age of 80 years. Overall 83% of patients had a Gleason score 6 or less and 13% had a Gleason score 3 + 4 = 7 at study entry. The 10-year prostate cancer-free survival rate was 97.2%. Overall 30% of patients had evidence of progression to higher risk categories and were offered therapy. Of 117 patients treated, the PSA failure rate from treatment was 50%, but this represented only 13% of the entire study cohort.[248]

From the Royal Marsden Hospital, Van As reported the results of 326 men managed with active surveillance.[446] Inclusion criteria for their study were clinical T1-T2a, Gleason score <7 (3 + 4), PSA <15 ng/mL, and <50% of biopsy cores positive. Treatment criteria were PSA velocity of >1 ng/mL per year, Gleason score ≥4 + 3 or ≥50% cancer involvement in any involved core on repeat biopsy. With a median follow up of 22 months, they have reported no prostate cancer deaths and 20% of their patients have moved to active treatment.

Dall'Era reported the UCSF experience of 321 men selected as having PSA ≤10 ng/mL, no Gleason pattern 4 or 5, clinical stage T2a or lower, PSA density of <0.75 ng/mL, and fewer than 33% positive cores involved with cancer.[443] Patients were offered treatment if they had a repeat biopsy Gleason score ≥7 or any increase in cancer volume on repeat biopsy or a rising PSA. With a median follow up of 3.6 years, 37% of patients met at least one criterion for treatment. Overall 38% had higher grade cancer on repeat biopsy and 26% had a PSA velocity of >0.75 ng/mL. Seventy-eight of the 321 men (24%) received treatment and there have been no prostate cancer deaths reported to date. They reported that 13% of patients chose therapy despite no evidence of disease progression.

The Johns Hopkins University experience of 407 men with a median age of 65.7 years has been reported by Carter.[455] All patients met the Epstein criteria for clinically insignificant cancers. With a median follow up of 3.4 years, 59% remain on active surveillance and 25% underwent active treatment with curative intent. No patient has died of prostate cancer in that series.

It is worth noting that men often experience anxiety as a result of their diagnosis and fear of disease progression. A randomized clinical trial from Sweden comparing treatment to watchful waiting showed no difference in quality of life in men at 5 years. Worry, depression, and anxiety were equally common in each group.[456] In an early analysis of 129 patients enrolled on the Dutch Prostate Cancer Research International Active Surveillance study (PRIAS), van den Bergh reported that the majority of men scored better than reference values in the domains of decision, depression, generic anxiety, and prostate cancer specific anxiety.[457] These data suggest that when informed, men willingly accept active surveillance as a management strategy.

The NCCN strongly recommends active surveillance for men with a short life expectancy.[316] The NCCN cites the observation by Lu-Yao[462] that the prostate cancer-specific death rate for men on an active surveillance strategy has dropped by 74% in the decade between 1992 and 2002 largely because of earlier diagnosis and the identification of more indolent cancers through PSA screening. The AUA guidelines[458] and the American Cancer Society (ACS)[459] both recommend that patients be informed of active surveillance as an alternative to a curative intervention. The Standard Treatment Against Restrictive Treatment (START)[460] trial in North America, the Prostate Cancer Research Interactive: Active Surveillance (PRIAS)[444] trial in Europe, and the PROstate TEsting for Cancer and Treatment (PROTECT)[112] trial in the United Kingdom are actively following patients. These studies will help bring clarity to the issues surrounding expectant management and early stage prostate cancer.

The North America Phase III Surgical Prostatectomy versus Interstitial Radiation Intervention Trial (SPIRIT) and the Medical Research Council PR06 trials closed prematurely because of poor patient accrual.[464,465] The ProtecT trial[112] randomized patients screened patients diagnosed with cancer to undergo surgery, RT, or active surveillance. Nearly half the men accepted randomization and the first report of this study is expected in 2015.

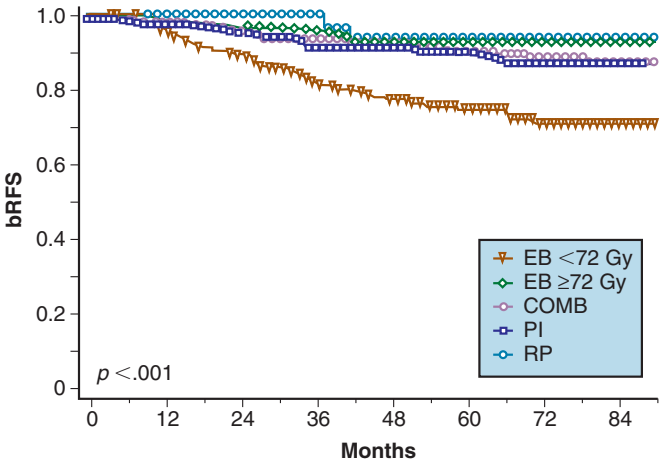


Figure 53-7 Biochemical freedom from recurrence for patients treated with permanent prostate brachytherapy (PI), external beam (EB) radiotherapy by dose (EB <72 Gy and EB ≥72 Gy), radical prostatectomy (RP), and combined methods (COMB).
Data from Kupelian PA, Potters L, Khuntia D, et al: Radical prostatectomy, external beam radiotherapy <72 Gy, external beam radiotherapy > or = 72 Gy, permanent seed implantation, or combined seeds/external beam radiotherapy for stage T1-T2 prostate cancer. Int J Radiat Oncol Biol Phys 58:25, 2004.

yielded statistically superior bDFS (PSA > 0.2) than either brachytherapy alone or RP.[466] Vicini reported the combined results of 6877 men with low- and intermediate-risk prostate cancer treated at seven institutions with a diverse set of modalities including permanent radioactive seed brachytherapy, temporary high-dose rate brachytherapy, EBRT, neutron therapy, and RP. Once corrected for prognostic variables, the 5-year biochemical outcomes were similar between institutions and modalities.[467] Kupelian reported outcomes of 1682 men from the Cleveland Clinic undergoing EBRT (628 cases) or RP (1054 cases).[468] The 8-year bDFS (PSA > 0.2) for the RP patients was 72% compared to 70% for the patients receiving EBRT (ASTRO definition). In a multivariate analysis, while clinical stage, pretreatment PSA, biopsy Gleason Score, year of therapy, and the use of neoadjuvant AD were independent predictors of survival, age, race, prior TURP, and treatment modality (surgery or RT) were not associated with outcome.[468] A pooled analysis of 2991 patients from the Cleveland Clinic and the Memorial Sloan Kettering at Mercy Medical Center showed comparable 5-year bDFS for patients receiving EBRT with doses in excess of 72 Gy, brachytherapy, a combination of EBRT and brachytherapy, or RP (Figure 53-7).[469] A retrospective analysis from the SEER registry of 60,290 men treated for localized prostate cancer found prostate cancer-specific mortality at 10 years was 1.3%, 0.5%, and 3.7% for RP, brachytherapy, and no definitive therapy, respectively.[470] In a multivariate analysis both surgery and brachytherapy resulted in better prostate cancer-specific and all-cause mortality than no definitive therapy. The magnitude of the survival benefits from surgery and brachytherapy were similar.[470]

Two recent series have suggested a higher rate of distant metastases and worse survival in men undergoing RT compared to RP for high-risk prostate cancer.[243,471-473] Each of these series had an imbalance of prostate cancer risk factors and comorbidities that contribute to the observed inferior outcomes with RT. In the Swiss experience, EBRT techniques and total doses were not specified, but the period of the study preceded the availability of both three-dimensional conformal radiation therapy (3DCRT) and intensity-modulated radiation therapy (IMRT).[243] That patients undergoing surgery appear to have better all-cause mortality points to the underlying selection bias in surgical series. Patients with preexisting comorbidities are not routinely selected for radical surgery because of the risk of morbidity and mortality from anesthesia and the operation itself. Attempts to correct for these comorbidities have been problematic. Although no differences in prostate CSS have been identified, no explanation for death from other causes satisfactorily explains the worse OS in men undergoing either EBRT or brachytherapy.[472,473] It is likely that unaccounted health issues such as obesity, smoking, hypercholesterolemia, and hypertension contribute to worse survival in men unable to tolerate RP.[474] Furthermore, as will be discussed later in this chapter, adjuvant hormone therapy, which is considered a standard of care for patients with high-risk disease receiving RT, was not routinely administered to patients in either of those series.

To summarize, RT and surgery must be considered as equal treatments for localized prostate cancer in terms of cancer control. Treatment decisions need to take into account patient health, the impact of treatment on his quality of life, and access to therapy. A thorough discussion of these treatment options, as well as active surveillance if appropriate, needs to be presented to all patients at the time of diagnosis.

Radiation Therapy

General Principles

Radiation therapy has been used as curative therapy for clinically localized prostate cancer for nearly a century. With the advent of megavoltage teletherapy systems in the 1960s, EBRT became a standard therapeutic approach for men with nonmetastatic prostate cancer. Over the past two decades, important advances in EBRT delivery methods such as 3DCRT, IMRT, image guided radiation therapy (IGRT), stereotactic body radiation therapy (SBRT), and proton beam RT have contributed to an improvement in the therapeutic ratio for men with prostate cancer. Similarly, brachytherapy methods improved with advances in imaging modalities, treatment planning software, and delivery methods for localized prostate cancer. At present, the radiation oncologist has several radiotherapeutic options available to apply to the management of men with prostate cancer.

Organ-Confined Disease

The literature contains few prospective, comparative clinical trials relevant to the treatment of patients with clinical T1-2 prostate cancer. Most reports were derived from single-institution observational case series in which a predetermined therapeutic approach and follow-up schedule were not established, and retrospective medical record review was used to assess efficacy and toxicity. Because the interpretation of observational case series presents certain problems,[475] statements about the utility of any treatment method, particularly compared with an alternative strategy, should be viewed with caution. In this context, the ensuing discussion emphasizes the experience from selected centers of urologic excellence and large multiinstitutional studies because these sources present a relatively broad perspective on the results achieved across the spectrum of radiotherapeutic practice.

Conventional External Beam Radiation

Conventional EBRT refers to a treatment planning method wherein the prostate and other target tissues are identified by the anatomy of surrounding structures (e.g., bony landmarks and contrast-enhanced viscera). The availability of modern imaging modalities, particularly CT and MR, coupled with RT treatment planning computers allowed for precise localization

of the prostate gland and other target tissues with respect to the treatment beam. Thus, accurate three-dimensional (3D) target volume definition was made possible, and individualized RT field definitions were devised to conform dose distributions (i.e., conformal RT) to the shape of the target volume(s). Without the benefit of conformal radiation techniques, radiation doses generally could not exceed a prescribed dose of 70 Gy without an associated increase in the rate of bowel or bladder toxicity.[476] Even more importantly, IMRT is a technique that uses multiple beam angles and CT-based computer planning to conform the dose to the prostate as closely as possible, thereby sparing the nearby normal structures. During IMRT a part of the radiation field is blocked or modulated at a specified times and locations to optimize radiation fluence to the target yet limit the dose to adjacent critical structures, in this case, the bladder and the rectum. This modulation can be accomplished with a multileaf collimator or with compensation filters. Image-guidance with in-room CT, x-ray or other methods of tumor localization should accompany IMRT to assure the tight radiation dose distributions are covering the intended target. With dose escalation and treatment intensification with hypofractionation, SBRT methods are being explored.

Results with Conventional EBRT. Before the advent of PSA screening and conformal radiation therapy, the 5-, 10-, and 15-year OS rates associated with definitive RT for T1-T2 prostate cancer were approximately 80%, 60%, and 35%, respectively.[245,478,479] Because significant comorbid illness may reduce life expectancy, CSS is a more appropriate endpoint to assess the efficacy of a particular treatment strategy. CSS probabilities following conventional RT in the pre-PSA era ranged from 55% to 80% at 5 years and 35% to 70% at 10 years.[245,478,479] In general, CSS is higher than OS, which emphasizes the importance of comorbidity in assessment of therapeutic outcome.

Although survival is a crucial and unequivocal endpoint, patient mortality (and, through inference, therapeutic efficacy) is strongly affected by underlying host- (e.g., age, comorbidity) and tumor-related (e.g., tumor grade) factors that may influence selection of a particular management approach. Therefore, complete and permanent eradication of the primary tumor (i.e., local tumor control) may be a more direct measure of radiotherapeutic efficacy. However, local tumor control is not consistently defined in the literature, and definitive evidence regarding the ability of EBRT to attain complete tumor ablation is difficult to obtain. Although most reports defined local tumor control as the absence of a progressively enlarging prostatic abnormality or of signs or symptoms suggesting local tumor recurrence (e.g., hematuria, urinary obstruction), there is considerable disparity between clinical assessment and the results of post-RT prostatic biopsy,[480,481] and few investigations adequately address this issue. Strategies to improve local tumor control in the current era include dose escalation with conformal EBRT, IMRT, proton therapy, SBRT, interstitial brachytherapy with or without EBRT, and the addition of AD therapy.

Relatively few RT series evaluated regional nodal tumor relapse, but fewer than 3% of patients had this identified as a site of disease relapse.[245,478] However, the reported probability of regional nodal relapse was likely an underestimate because serial radiologic imaging was not routinely performed during post-RT patient follow-up. Therefore, the mortality associated with regional nodal relapse has not been defined.

Median life expectancy after appearance of metastatic disease is approximately 2 to 5 years.[245,291] The rate of distant metastasis in men treated with primary RT without long-term androgen suppression ranges from 11% to 28%.[363] A nomogram to predict the rate of distant metastases at 5 years has been constructed and validated.[363] Heightened awareness for the development of metastases may be important in the presence of local tumor recurrence because patients with this condition are at particularly high risk for subsequent metastatic relapse.[482-486] Whether tumor-related factors (e.g., tumor grade) that predispose to local recurrence place patients at risk for harboring subclinical metastases at presentation, or whether persistent disease at the primary site results in secondary tumor dissemination, is uncertain. Yorke et al[487] proposed that more than half of metastases originate in association with local recurrence, and Coen et al[485] reported a late wave of distant metastasis following local failure, suggesting that improved control of the primary tumor may enhance long-term survival. There is increasing evidence that improved local tumor control with aggressive local therapy is having a favorable impact on distant metastases rates.[486,488-490]

Biochemical Relapse. More contemporary studies incorporate both pre- and posttherapy serum PSA into outcome analyses to better define prognostic groups and disease-free status. Serial PSA measurements and the endpoint of PSA RFS have become the new benchmark for assessing treatment efficacy. To study long-term outcome after EBRT in the PSA era, six institutions combined data and used the ASTRO PSA failure definition, defined by the Consensus conference in 1996, as the analysis endpoint.[491] Tumor stage, Gleason score, pretreatment PSA level, and PSA nadir after therapy were all established as important factors in outcome. Five years later, a follow-up study with data from nine institutions was completed and ultimately included 4839 patients with T1-T2 prostate cancer treated from 1986 to 1995 with median 6.3 years follow-up.[227] During this study period a conventional technique (70%) was used in earlier years and conformal therapy (30%) more recently. Prescribed radiation doses were those common for that era as well. Sixteen percent of patients were treated to 60 Gy to 65 Gy, 54% to 66 Gy to 70 Gy, 19% to 70 Gy to 72 Gy, 10% to 73 Gy to 78 Gy, and 1% above 78 Gy. Outcome analysis confirmed the prognostic factors established by the first study: T category, Gleason score, pretreatment PSA, and posttreatment PSA nadir[491] and also established dose and year of treatment as independent prognostic variables.[227] PSA disease-free results for patients treated to at least 70 Gy, shown in eTable 53-5 and Figure 53-8, demonstrate the relationship between nadir and eventual biochemical failure. Because of the long-term follow-up available for these patients, up to 14 years, this analysis also showed that of those patients who were PSA disease-free at 5 years, an additional 17% would develop PSA relapse by 10 years, pointing out the late relapsing nature of this disease. Clinical failure and survival analysis (Table 53-4) showed results more encouraging than those with

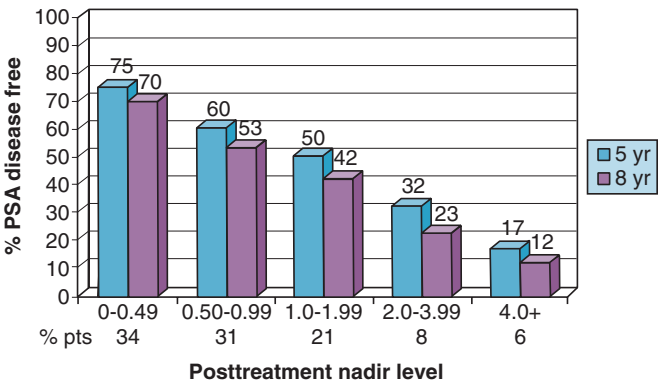


Figure 53-8 The likelihood for long-term local tumor control after external beam radiation is shown as a percentage of all patients determined to be disease free by their PSA nadir level. The percentage of patients achieving each nadir level is given on the *x* axis.

Simultaneous with advances in technology there has been progress in outcome reporting, staging, and risk assessment. Currently, outcome reporting mainly uses PSA after treatment to determine relapse but also uses PSA as a pretreatment factor to classify the disease burden and to categorize patients into prognostic risk groups. Because diagnostic imaging has improved markedly over the last several years, stage migration has also occurred. In fact, there is evidence that the year that treatment was delivered is an independent predictor of outcome in addition to all the other well-known prognostic factors such as T category, grade, RT dose, and technique.[477]

eTABLE 53-5 Five- and 8-Year Disease-Free Survival by PSA Level and Prognostic Factor* Treated to ≥ 70 Gy

		Initial PSA (ng/mL)			
		0-3.99	4-9.99	10-19.99	≥20
Category	Gleason Score	5 y/8 y	5 y/8 y	5 y/8 y	5 y/8 y
T1B-C					
	2-4	100/—	75/75	70/70	36/24
	5-6	89/—	83/75	70/70	40/29
	7	100/100	63/59	53/47	17/—
	8-10	—/—	33/—	47/—	40/—
T2					
	2-4	93/84	80/74	78/69	16/16
	5-6	73/73	70/67	60/51	42/30
	7	68/54	64/57	53/45	12/—
	8-10	71/—	59/54	28/21	—/—

From Kuban DA, Thames HD, Levy LB, et al: Long-term multi-institutional analysis of stage T1-T2 prostate cancer treated with radiotherapy in the PSA era. Int J Radiat Oncol Biol Phys 57(4):915–928, 2003.[227]

PSA, *Prostate-specific antigen;* y, *year.*

**Prognostic factors: T category, Gleason score.*

TABLE 53-4 Clinical Outcomes for Patients with T1-2 Prostate Cancer

		OS (%)		LRFS (%)		MRFS (%)		CDFS (%)		CSS (%)	
Risk Category	**No. of Patients**	**5 Y**	**8 Y**	**5 Y**	**8 Y**	**5 Y**	**8 Y**	**5 Y**	**8 Y**	**5 Y**	**8 Y**
All	4839	87	72	93	89	95	92	89	83	98	93
Low	1237	92	81	97	93	99	99	97	92	100	99
Intermediate	2191	86	72	94	90	96	94	91	84	99	95
High	1109	82	64	87	84	88	84	77	71	97	87

From Pisansky TM, Thames HD, Levy LB, et al: Clinical outcomes and prognostic factors in 4839 patients treated with external radiotherapy for stage T1-T2 prostate cancer [abstract 63]. Proceedings of the 46th annual ASTRO meeting. Int J Radiat Oncol Biol Phys 60:S167, 2004.[492]

CDFS, *Clinical disease-free survival;* CSS, *cause-specific survival;* LRFS, *local recurrence-free survival;* MRFS, *metastatic relapse-free survival;* OS, *overall survival;* Y, *years.*

PSA relapse as the endpoint.[492] In studying the relationship of PSA relapse to clinical relapse, this multiinstitutional effort reported that 49% to 78% of patients were clinically disease free at 5 years and 46% to 58% were clinically disease free at 10 years after PSA failure, depending on risk group.[227] bDFS is being investigated as a surrogate endpoint in clinical trials of local therapy because it may fulfill the Prentice Criteria for predicting clinical DFS and possibly OS.[493,494]

Dose Escalation. With PSA outcome reports showing more room for improvement in treatment efficacy than was previously believed, effort was directed toward more conformal treatment techniques, 3DCRT, IMRT, and proton beam therapy to increase the prostate dose while avoiding adjacent nontarget tissues. Several single institutional series have reported outcomes for doses ranging from less than 70 Gy to more than 86.4 Gy.[246,486,489,495,496] Improvement in PSA-DFS and a significant impact on distant metastatic rates have been attributed to dose escalation.[246,486,490,495]

Table 53-5 summarizes five randomized trials that demonstrate a significant improvement in bDFS with EBRT dose escalation.[496-503] Although each of these studies employed conventional or conformal EBRT photon therapy for part or all of the treatment course, the boost treatment in one trial employed a proton beam boost.[501]

It is difficult to draw broad conclusions about the scope of benefit of dose escalation from these prospective Phase III trials. The eligibility criteria were different and the use of AD therapy was required in one trial,[496] allowed by physician discretion for high-risk patients in another trial[497] and not allowed in the others.[498-501] The follow-up duration and the total doses used in the studies also varies. In each of the modern EBRT dose escalation trials,[496-498,501] dose escalation has unequivocally improved bDFS for the populations of patients enrolled in the trials. Within each study, subgroup analyses suggest that some populations benefit more than others. In the MRC trial, all NCCN subgroups benefited from dose escalation.[496] In the Dutch trial, only patients with intermediate- and high-risk disease had improved outcome with higher doses.[497] In the M. D. Anderson trial, the benefit was limited to patients with an initial PSA of more than 10 ng/mL.[498] The Proton Radiation Oncology Group trial showed a significant benefit to both low- and intermediate-risk groups.[501] There were insufficient high risk patients (<5%) to determine the value of dose escalation in that trial. The MRC trial showed an improvement in clinical DFS, 69% compared with 61% (p = 0.03).[496] With a median follow-up of 8.7 years, Kuban reported a significant reduction in the clinical failure rate from 15% to 7% (p = 0.014) with 78 Gy as compared to 70 Gy.[498] Although distant metastases were infrequent, dose escalation improved the distant metastasis-free survival rate from 95% to 99% (p = 0.059). In the patients with NCCN high-risk disease, the reduction in distant metastatic rate from 96% to 83% was significant (p = 0.035). The French trial reported ASTRO biochemical relapse rates of 39% and 28% with 70 Gy and 78 Gy, respectively (p = 0.36).[503] Like the others, there was no clinical or OS improvement.

With a median follow up of 10 years, the MRC trial has not shown a difference in OS. The OS is 71% in both arms despite there being a significant difference in biochemical and disease progression outcomes. Clearly, many patients that develop biochemical or clinical progression will receive long-term AD and other recently approved agents that may prolong survival. Whether the avoidance of the cost and morbidity associated with these salvage systemic therapies is worth the trade off of slightly higher GI side effects will require further examination. RTOG has completed a trial of dose escalation in intermediate-risk prostate cancer that is also powered to demonstrate a survival difference.[504] Follow-up from this and the other randomized trials may help understand the impact that dose escalation has on OS and specific patient subsets. In a systematic review of 38 published studies from 1990 to 2003, an OS benefit to dose escalation in the range of 70 Gy to 80 Gy was demonstrated.[505] In a pooled analysis of four RTOG trials from 1975 to 1992, Valicenti demonstrated that higher radiation dose was a significant predictor for improved DFS and OS for patients with Gleason scores 8 to 10 ($p < 0.05$).[506] After adjusting for other known clinical prognostic factors, a higher radiation dose was associated with a 29% lower relative risk of death from prostate cancer and a 27% reduced mortality rate ($p < 0.05$).

Hypofractionation and Treatment Duration. Preclinical and clinical data have suggested that radiation therapy of prostate cancer may be improved with hypofractionation (higher dose per fraction with a shortened overall course of therapy). Unlike other epithelial cancers, it has been speculated that the alpha-to-beta ratio of prostate cancer is lower than that of its surrounding normal tissues. A low alpha-to-beta ratio would imply a tumor's sensitivity to fraction size and therefore a fraction size of more than the common 1.8 Gy to 2.0 Gy would offer a therapeutic advantage. The early use of hypofractionation was motivated by concerns of cost and resource availability and not related to an expectation of a biological advantage.[507-509] The early suggestion that the alpha-to-beta ratio for prostate cancer is approximately 1.5 came from a computational analysis of patient outcomes that compared men treated with permanent seed prostate brachytherapy to a dose of 145 Gy to a group of men treated with EBRT and conventional fractionation to doses of 70 Gy to 74 Gy.[510,511] Fowler calculated a similar estimate of an alpha-to-beta ratio of 2 Gy with men treated using EBRT and prostate brachytherapy with either iodine-125 (^{125}In) or palladium-103 (^{103}Pd) monotherapy.[512] Brenner completed another alpha-to-beta estimation with a group of men treated on a dose escalation trial using high-dose-rate (HDR) brachytherapy with doses

In their series, irrespective of NCCN risk group, Zelefsky et al reported a 5-year PSA-DFS of 61% with a dose of >70.2 Gy, 74% with 75.6 Gy, 85% with 81 Gy, and 82% with 86.4 Gy.[246] In their highest dose level of 86.4 Gy, they reported exceptional biochemical controls rates of 98%, 85%, and 78% for NCCN low-, intermediate-, and high-risk groups, respectively.[495] In their patients with intermediate- and high-risk disease, high radiation dose was an important and statistically significant predictor for improved distant metastases-free survival.[246] In a multivariate analysis, the Fox Chase Cancer Center group reported that high T category, Gleason score, initial PSA, and low radiation dose were all significant variables associated with the development of distant metastases.[490] In another series of 919 patients treated at the Cleveland Clinic, Kupelian reported that the 7-year distant metastatic rate was 9%, 6%, and 1% for patients treated to a dose less than 72 Gy, 72 Gy to 82 Gy, and 82 Gy or more, respectively ($p = 0.008$).[486]

TABLE 53-5 Outcomes of Randomized Trials Evaluating Radiation Dose Escalation for Localized Prostate Cancer

Author	N	Hormones	Report Interval	bDFS (ASTRO Definition)	Clinical DFS	Overall Survival	Risk Subgroup Benefit	Grade ≥ 2 GI Toxicity	Grade ≥ 2 GU Toxicity
				High Dose vs Standard Dose (*p* Value)					
Kuban (2008)	301	None	8 years	78% vs 59% $p = 0.004$	93% vs 85% $p = 0.014$	78% vs 79% $p = 0.32$	PSA > 10	26% vs 13% $p = 0.001$	13% vs 8% $p = 0.69$
Zietman (2010)	393	None	10 years	83% vs 68% $p < 0.001$	Not reported	83% vs 78% $p = 0.41$	All (low, Intermediate)	24% vs 13% $p = 0.09$	29% vs 25% $p = 0.79$
Al-Mamgani (2008)	669	0, 6, or 36 months per participating institutional guidelines	7 years	54% vs 47% $p = 0.04$	Not reported $p = 0.68$	75% vs 75% $p = 0.45$	Intermediate, high	35% vs 25% $p = 0.04$	40% vs 41% $p = 0.6$
Dearnaley (2014)	843	All patients, 3-6 months before start of RT	10 years	71% vs 60% $p = 0.0003$	90% vs 87% $p = 0.03$	71% vs 71% $p = 0.96$	All subgroups	33% vs 24% $p = 0.005$	11% vs 8% $p = 0.14$
Beckendorf (2011)	306	None	5 years	72% vs 61% $p = 0.036$	Not reported	Not reported	iPSA ≥ 15	20% vs 14% $p = 0.22$	18% vs 10% $p = 0.046$

bDFS, *Biochemical disease-free survival;* RT, *radiation therapy.*

per fraction ranging from 5.5 Gy to 10.5 Gy.[513] Patients treated with dose escalated hypofractionated HDR brachytherapy had better biochemical control with a calculated alpha-to-beta ratio of 1.2 Gy (95% CI, 0.03 Gy to 4.1 Gy).

An oft-cited criticism of the preceding analyses are the uncertainties associated with retrospective studies in general, as well as the use of data pooled from multiple institutions and the inclusion of brachytherapy where dose heterogeneities are substantial.[515] Furthermore tumor clonogen repopulation[516] and tumor hypoxia[517] may further confound the calculation of accurate alpha-to-beta ratios. Recently, a provocative hypothesis has been put forth suggesting that overall treatment time is an important biological factor related to prostate cancer disease control. Although older, pre-PSA–era series did not show a time factor, an analysis of clinical outcomes from several analyses suggest that a longer overall treatment time was associated with a worse biochemical failure for patients with low-risk prostate cancer.[518,519] Their data raise the question that the benefit of hypofractionation may be partly explained by the shorter overall course of treatment (eTable 53-6).[520]

Prospective randomized trials evaluating hypofractionation for early stage prostate cancer are summarized in Table 53-6. Two older Phase III trials compared standard fractionation to hypofractionation but neither showed an advantage to the shorter course of therapy.[521,522] The short-course regimens were selected for reduced resource utilization and not for radiobiological considerations. The biological equivalent doses chosen for were relatively low and therefore would not have been expected to yield improved outcomes. Several modern Phase III trials were designed on the principle that the alpha-to-beta ratio for prostate cancer is lower than surrounding tissues and that hypofractionation could deliver biologically equivalent doses (EQD2) in the range of 77 Gy to 84 Gy to the tumor.[523-526] These hypofractionation arms were compared to conventional fractionation in 1.8-Gy to 2-Gy daily doses to total doses of 70 Gy to 76 Gy. The first trial from Regina Elena, Italy, was designed to show comparable bDFS but with lower rates of late toxicity.[523,524] Initially reported in 2010, the trial showed a result opposite to what was expected with no difference in 2-year GI toxicity but an unanticipated improvement in bDFS. With further follow up, the differences in biochemical control were no longer significant. A Phase III trial from the Fox Chase Cancer Center compared 76 Gy in 38 fractions of 2 Gy/day to a hypofractionated regimen of 70.2 Gy in 26 fractions of 2.7 Gy/day.[525] It had been hypothesized that the shorter course of treatment would improve the bDFS from 70% to 85% at 5 years. The results from that trial showed no difference with 81% and 85% 5-year bDFS in the short and conventional arms, respectively ($p = 0.745$). Although there were no differences in GI toxicity, patients that had prior urinary obstructive symptoms with an International Prostate Symptom Score (IPSS) score of more than 12 experienced more late genitourinary (GU) toxicity. The authors concluded that there is no disease control advantage with hypofractionation, but fewer healthcare resources would be consumed with hypofractionation, as long as it was limited to patients without prior urinary obstructive symptoms. Finally, early results from a trial at M. D. Anderson Cancer Center (MDACC) compared 75.6 Gy in 42 fractions of 1.8 Gy/day to 72 Gy in 30 fractions of 2.4 Gy/day. Cancer control or PSA outcomes were not reported, but they reported near doubling in the rate of grade-2 or worse GI toxicity from 5.1% to 10.0% and similar rates of grade-2 or greater GU toxicity with 16.5% and 15.8% with conventional versus hypofractionated RT, respectively. Neither difference was statistically significant.[527]

Each of these studies was based upon the premise that the biochemical control rates would be improved with hypofractionation or that the toxicity would be equal or better. Although it appears the short courses of radiation therapy are comparable, noninferiority trials need to establish that this strategy will not result in inferior outcomes over time. Three large Phase III noninferiority trials (Table 53-6) have been completed accrual with more than 5000 cases registered among them. Results from these trials should shed light and inform radiation oncologists about the merits, or lack thereof, of short-course hypofractionated radiation therapy.

Several groups have explored even more aggressive hypofractionation schedules using image guided IMRT or SBRT methods with fraction sizes ranging from 6.7 Gy to 10 Gy. eTable 53-7 summarizes the treatment schedules and 2 Gy equivalent doses.[528-533] The results from these trials show that this extreme fractionation is feasible with rates of bDFS of 90% or better, albeit with short median follow up (Table 53-14). Late toxicity with these ultra-hypofractionated schedules will require long-term follow up to reassure treating physicians that these regimens are both safe and effective.

TABLE 53-6 Prospective Trials Evaluating Moderate and Extreme Hypofractionation for Localized Prostate Cancer

Study and Institution	No. Patients	Dose/Fraction Size/No. Fractions	Total Equivalent Dose in 2-Gy Fractions (EQD2) $\alpha/\beta = 1.5$ (Tumor)	Total Equivalent Dose in 2-Gy Fractions (EQD2) $\alpha/\beta = 3$-5 (Late Effects)	Median Follow-up (mo)	5-year% bDFS	≥Grade 2 Late Toxicity (%) GI	≥Grade 2 Late Toxicity (%) GU
PHASE III TRIALS, LOW EQD2 (2D CONVENTIONAL OR 3D CONFORMAL RADIATION THERAPY)								
Lukka et al (NCIC)	466	52.5/2.625 Gy/20	61.9 Gy	59.1 Gy	68	40%	1.3%	1.9%
	470	66 Gy/2 Gy/33	66 Gy	66 Gy		47%		
Yeoh et al (Adelaide)	109	55 Gy/2.75 Gy/20	66.8 Gy	63.2 Gy	48	57.4%	NR	NR
	108	64 Gy/2 Gy/32	64 Gy	64 Gy		55.5%		
PHASE III SUPERIORITY TRIALS, HIGH EQD2 (3D CONFORMAL RADIATION THERAPY OR IMRT)								
Arcangeli (Regina Elena)	83	62 Gy/3.1 Gy/20	80 Gy	75 Gy	70	85%	17%	16%
	85	80 Gy/2 Gy/40	80 Gy	80 Gy		79%	14%	11%
Pollack (Fox Chase) NCT00062309	151	70.2 Gy/2.7 Gy/26	84.4	77.2 Gy	68.4	81%	18%	22%
	152	76 Gy/2 Gy/38	76 Gy	76 Gy		85%	23%	13%
Hoffman (M. D. Anderson) NCT00667888	102	72 Gy/2.4 Gy/30	80.2 Gy	77.8 Gy	56.5	NR	10.0%	15.8%
	102	75.6 Gy/1.8 Gy/42	71.3 Gy	72.6 Gy		NR	5.1%	16.5%

2D, *Two-dimensional;* 3D, *three-dimensional;* GI, *gastrointestinal;* GU, *genitourinary;* IMRT, *intensity-modulated radiation therapy;* ISRCTN, *International Standard Randomised Controlled Trial Number;* NCT, *National Clinical Trial number;* NR, *not reported.*

In a series of 3756 patients treated with EBRT that included 185 patients receiving a HDR brachytherapy boost, Williams et al estimated the alpha-to-beta ratio was 2.6 Gy. There was, however, a wide CI of 0.9 to 4.8 Gy.[514]

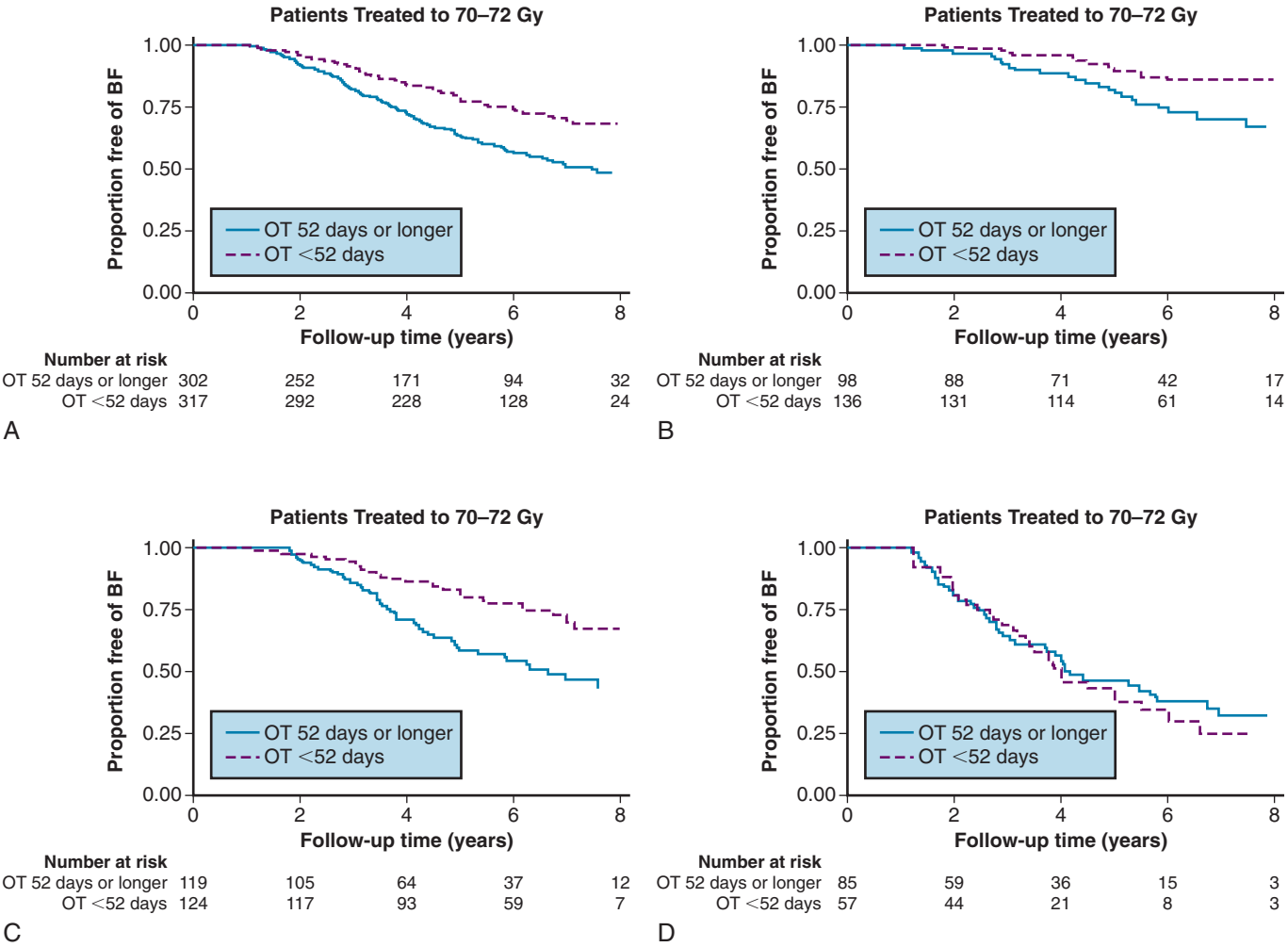
The Fox Chase Cancer Center defined a nontreatment day ratio (NTDR) as the number of nontreatment days divided by the total elapsed days of the RT course. The larger the NTDR, the more days off or interruptions in treatment were experienced by the patients. The 10-year bDFS of patients with low-risk disease was 82% for patients with a NTDR of <33% compared to only 57% if the NTDR was more than 33% (p = 0.0019).[518] Thames et al confirmed the importance of overall treatment time in a retrospective analysis of 4338 men treated at nine institutions.[519] Overall treatment time was not a factor in biochemical disease control in patients who were treated with EBRT doses less than 70 Gy. However, men with NCCN low- and intermediate-risk prostate cancer who received 70 Gy or higher had 6% loss of bDFS for each additional week increase in overall treatment time. Some of this loss of tumor control could be overcome with an increase in EBRT dose with a 15% decrease in biochemical failure for each 6 Gy increase in dose.[519]

eTABLE 53-6 Prospective Trials Evaluating Moderate and Extreme Hypofractionation for Localized Prostate Cancer, Outcomes Pending

Study and Institution	No. Patients	Dose/Fraction Size/No. Fractions	Total Equivalent Dose in 2-Gy Fractions (EQD2) α/β = 1.5 (Tumor)	Total Equivalent Dose in 2-Gy Fractions (EQD2) α/β = 3-5 (Late Effects)	Comments
PHASE III NONINFERIORITY TRIALS, HIGH EQD2 (3D CONFORMAL RADIATION THERAPY OR IMRT)					
Lee (RTOG 0415) NCT00331773	1067	70 Gy/2.5 Gy/28 73.8 Gy/1.8 Gy/41	80 Gy 69.6 Gy	77 Gy 70.9 Gy	Accrual completed, no results reported
Dearnaley CHHiP (MRC) ISRCTN97182923	3216	60 Gy/3 Gy/20 57 Gy/3 Gy/19 74 Gy/2 Gy/37	77.1 Gy 73.3 Gy 74 Gy	72 Gy 68.4 Gy 74 Gy	Accrual completed, no results reported
Catton PROFIT (OCOG) ISRCTN43853433	1204	60 Gy/3 Gy/20 78 Gy/2 Gy/39	77.1 Gy 78 Gy	72 Gy 78 Gy	Accrual completed 2012, no results reported
PHASE IIR OR PHASE III SUPERIORITY TRIALS, ULTRAHIGH EQD2 (SBRT OR IMRT)					
Lukka (RTOG 0938) NCT01434290	174	36.25 Gy/7.25 Gy/5 51.6 Gy/4.3 Gy/12	90.6 Gy 85.5 Gy	74.3 Gy 75.3 Gy	Accrual completed 2014, no results reported. Phase IIR, endpoints are toxicity and patient reported outcomes
Incrocci HYPRO (Netherlands) ISRCTN85138529	800	64.6 Gy/3.4 Gy/19 78 Gy/2 Gy/39	90.4 Gy 78 Gy	82.7 Gy 78 Gy	Accrual completed 2011, no results reported
Widmark (SPCG) ISRCTN45905321	592	42.7 Gy/6.1 Gy/7 78 Gy/2 Gy/39	92.7 Gy 78 Gy	77.1 Gy 78 Gy	Accrual ongoing, expected completion 2015
Abramowitz (Miami) NCT01794403	75	70.2 Gy/2.7 Gy/26 36.25 Gy/7.25 Gy/5	84.4 90.6 Gy	77.2 Gy 74.3 Gy	Accrual ongoing, expected completion 2018

3D, *Three dimensional;* bDFS, *biochemical disease-free survival;* GI, *gastrointestinal;* GU, *genitourinary;* IMRT, *intensity-modulated radiation therapy;* ISRCTN, *International Standard Randomised Controlled Trial Number;* NCT, *National Clinical Trial number;* SBRT, *stereotactic body radiation therapy.*

Thames et al analyzed the outcomes of 4839 men treated with EBRT for prostate cancer. In patients that received 70 to 72 Gy, there was a significant improvement in biochemical control if their treatment was completed in fewer than 52 days (eFigure 53-1). This improvement was limited to low and intermediate risk subgroups.



eFigure 53-1 Biochemical failure (isolated clinical failure and BF time <12 months excluded) for patients treated to 70-72 Gy, compared for OTP52 days vs. OT < 52 days using the Wilcoxon test. **A,** All patients ($p < .0005$, 193 events/619 at risk); **B,** low-risk patients ($p = .011$, 40 events/234 at risk); **C,** intermediate-risk patients ($p = .0005$, 76 events/243 at risk); **D,** high-risk patients ($p = 0.90$, 77 events/142 at risk). *(Modified from Thames HD, Kuban D, Levy LB, et al: The role of overall treatment time in the outcome of radiotherapy of prostate cancer: An analysis of biochemical failure in 4839 men treated between 1987 and 1995. Radiother Oncol 96:6–12, 2010.)*

eTABLE 53-7 Ultrahypofractionation Trials: Schedules and Equivalent Total Doses in 2-Gy Fractions

References	No. Pts	Dose/Fx Size/No. Fxs	Total Equivalent Dose in 2-Gy Fractions (EQD2)		Med. F/U (mos)	≥Grade 2 Late Toxicity (%)	
			$\alpha/\beta = 1.5$ (Tumor)	$\alpha/\beta = 3$ (Late Effects)		GI	GU
Madsen et al[528] Virginia Mason	40	33.5 Gy/6.7 Gy/5 fx	78 Gy	64.9 Gy	41	7.5	20
King et al[529] Stanford	41	36.25 Gy/7.25 Gy/5 fx	90.6 Gy	74.3 Gy	33	15	29
Tang et al[534] University of Toronto	30	35 Gy/7 Gy/5 fx	85.1 Gy	70 Gy	12	13	13
Katz et al[530] Wintrop University	50	35 Gy/7 Gy/5 fx	85.1 Gy	70 Gy	30	0	2
	254	36.25 Gy/7.25 Gy/5 fx	90.6 Gy	74.3 Gy	17	2.9	6.3

Adapted from Ritter M, et al: Hypofractionation for prostate cancer. Cancer J 15(1):1–6, 2009.[535]
Fx, *Fraction;* F/U, *follow-up;* GI, *gastrointestinal;* GU, *genitourinary;* mos, *months.*

The first Phase I/II trial of SBRT for early stage prostate cancer was reported by Madsen in 2007.[528] Forty men with low-risk prostate cancer received 33.5 Gy in 5 fractions of 6.7 Gy with daily localization had a Phoenix biochemical DFS of 90%. The incidences of late grade-2 or greater GU and GI toxicities were 20% and 7.5%, respectively. Katz reported the largest single-institutional series of SBRT with 304 predominantly low-risk patients.[530] Their first 50 patients received 35 Gy in five 7 Gy fractions and the next 254 patients received 36.25 Gy in five 7.25 Gy fractions. With a median follow up of 30 and 17 months for the low-dose and high-dose cohorts respectively, they reported a low rate of 5% late grade-2 GU toxicities and 2% late grade-2 GI toxicities. Biochemical failure was not reported but they did note that more than 80% of patients achieved a PSA nadir of <1 ng/ml. A PSA bounce of more than 0.2 ng/ml was seen in 16% of their patients. In a pooled series of 1100 patients from eight institutions, King reported a 5-year biochemical DFS of 93% for all patients with a median follow up of 36 months.[536] In a subset of 135 patients with a minimum follow-up of 5 years, the 5-year bDFS was 99% and 93% for low- and intermediate-risk cases, respectively. King reported a significantly lower rate of late rectal toxicity if the therapy was delivered every other day rather than 5 consecutive days (0% versus 38%, $p = 0.0035$).[529] In the series from the University of Texas, Southwestern reported by Boike et al, 1 of the 15 patients treated to a dose of 50 Gy in 5 fractions of 10 Gy suffered a grade-4 toxicity that required a diverting colostomy.[533] Several prospective trials are under way comparing these ultra-hypofractionation schedules to more traditional courses of radiation therapy. In an analysis of Medicare claims, Yu reported that 15.6% of patients receiving SBRT had GU toxicity compared to 12.6% of those that received IMRT.[537] It appeared that urethritis, incontinence, and urinary obstruction were more common in the patients treated with SBRT.

Complications. Complications that occur during or after EBRT can be grouped into four major categories: intestinal, urinary, sexual, and other. Intestinal toxicity occurring during RT manifests as an acute enteritis resulting from the effect of irradiation on the small and large intestine. The severity of this side effect is proportional to the volume of bowel included in the treatment fields but is usually well controlled with antidiarrheal medications and local steroidal type preparations for proctitis. After treatment, any such symptoms typically return to the baseline state within 2 to 4 weeks. However, long-term injury may occur in a small proportion of patients, and this may manifest as persistent diarrhea, tenesmus, rectal/anal strictures, or hematochezia; bowel ulceration, obstruction, or perforation is more uncommon. The RTOG system for late (>90 days after completion of RT) morbidity is shown in Table 53-7 along with a more detailed LENT-RTOG modification used in some studies. A recent review led by the Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC) group addressed the time, dose, and volume relationships associated with radiation related toxicity in the management of a broad spectrum of malignancies. The normal tissue dose constraints recommended by this group are summarized in Table 53-8. Of note, most normal tissue constraints are derived from common fractionation and 3D conformal techniques. The use of hypofractionation and techniques that are more conformal than 3DCRT such as IMRT or proton therapy may require modification of these constraints.

Most patients experience some degree of urinary toxicity during EBRT. The symptoms of cystitis/urethritis are characterized by urinary frequency, urgency, hesitancy, decreased force of stream, and dysuria. These symptoms are usually mild to moderate and resolve 2 to 4 weeks after treatment is completed. Significant long-term urinary sequelae are uncommon, but may take the form of cystitis, hematuria, urethral stricture, or bladder contracture.

Although long-term rectal complications were typically acceptable for lower doses of radiation (<5% ≥ Grade 2 for the 64-Gy to 70-Gy dose range), the use of higher EBRT doses without modification in radiation technique led to an unacceptable level of long-term complications.[476,539,540] Storey et al, using data from the MDACC randomized dose response study with 3DCRT, evaluated the amount of rectum that could be treated to a dose of 70 Gy while still keeping the rectal and bladder complication rates at a reasonable level.[541] This analysis showed that grade-2 and grade-3 rectal complications, which were mainly grade 2, increased with 78 Gy as compared to 70 Gy. According to the latest update, 26% of patients treated to 78 Gy developed complications as compared to 12%

TABLE 53-7 Grading System According to the Radiation Therapy Oncology Group Criteria

Grade	Criteria or Symptoms
RTOG GRADING SYSTEM FOR LATE RADIATION THERAPY MORBIDITY	
1	Minor symptoms requiring no treatment
2	Symptoms responding to simple outpatient management, lifestyle (performance status) not affected
3	Distressing symptoms altering patient's lifestyle (performance status) Hospitalization for diagnosis or minor surgical intervention (e.g., urethral dilatation) may be required
4	Major surgical intervention (e.g., laparotomy, colostomy, cystectomy) or prolonged hospitalization
5	Fatal complication
MODIFIED LENT-RTOG COMPLICATION GRADING SYSTEM FOR LATE RECTAL TOXICITY[538]	
1	Excess bowel movements twice baseline Slight rectal discharge or blood
2	>2 antidiarrheals/wk; ≤2 coagulations; occasional steroids or dilatation; intermittent pad use; regular non-narcotics or occasional narcotics
3	>2 antidiarrheals/d; >2 coagulations; ≤1 transfusion; prolonged daily steroid enemas; hyperbaric oxygen; regular dilatation; daily pads; regular narcotics
4	Dysfunction requiring surgery; perforation; life-threatening bleeding
5	Fatal toxicity

LENT, *Late Effects Normal Tissue Task Force;* RTOG, *Radiation Therapy Oncology Group.*

TABLE 53-8 Quantec Organ-at-Risk Dose Recommendations

Organ	Endpoint	Dose (Gy) or Dose/Volume Parameters	Rate (%)	Notes on Dose/Volume Parameters
Rectum	Grade ≥ 2 late rectal toxicity	V50 < 50%	<15	
	Grade ≥ 3 late rectal toxicity		<10	
	Grade ≥ 2 late rectal toxicity	V60 < 35%	<15	
	Grade ≥ 3 late rectal toxicity		<10	
	Grade ≥ 2 late rectal toxicity	V65 < 25%	<15	
	Grade ≥ 3 late rectal toxicity		<10	
	Grade ≥ 2 late rectal toxicity	V70 < 20%	<15	
	Grade ≥ 3 late rectal toxicity		<10	
	Grade ≥ 2 late rectal toxicity	V75 < 15%	<15	
	Grade ≥ 3 late rectal toxicity		<10	
Bladder	Grade ≥ 3 late bladder toxicity	V65 ≤ 50% V70 ≤ 35% V75 ≤ 25% V80 ≤ 15%		Based on RTOG 0415 dose guidelines
Penile bulb	Severe erectile dysfunction	Mean dose to 95% of penile bulb < 50 Gy	<35	
		D90 < 50 Gy	<35	
		D60-70 < 70 Gy	<55	

treated to 70 Gy.[542] However, it was also shown that this complication rate could be minimized by decreasing the amount of rectum treated above 70 Gy. If ≤26% of the rectal volume was treated to ≥70 Gy, grade-2 and grade-3 complications occurred in 13% of patients as compared to 51% of patients if more than 26% of the rectal volume was treated to this dose level. In patients treated with 3DCRT, grade-3 rectal complications, still mainly rectal bleeding but more severe, occur much less frequently (1% to 7% of treated patients).[538,540,541,543] In a preliminary analysis of toxicity in patients enrolled on the high-dose (79.2 Gy) arm of the RTOG randomized trial, Michalski reported significantly higher rates of rectal toxicity if the volume of rectum receiving more than 70 Gy (Rectal V70) or 75 Gy (Rectal V75) exceeded 15% and 10%, respectively (Figure 53-9).[544] In an analysis of patients treated on the Dutch dose escalation trial, Peeters reported an association of fecal incontinence with dose delivered to the distal 3 cm of the anal canal wall, whereas rectal bleeding and high stool frequency were associated with dose to the anorectal wall.[545] Clinical factors associated with complication risk include

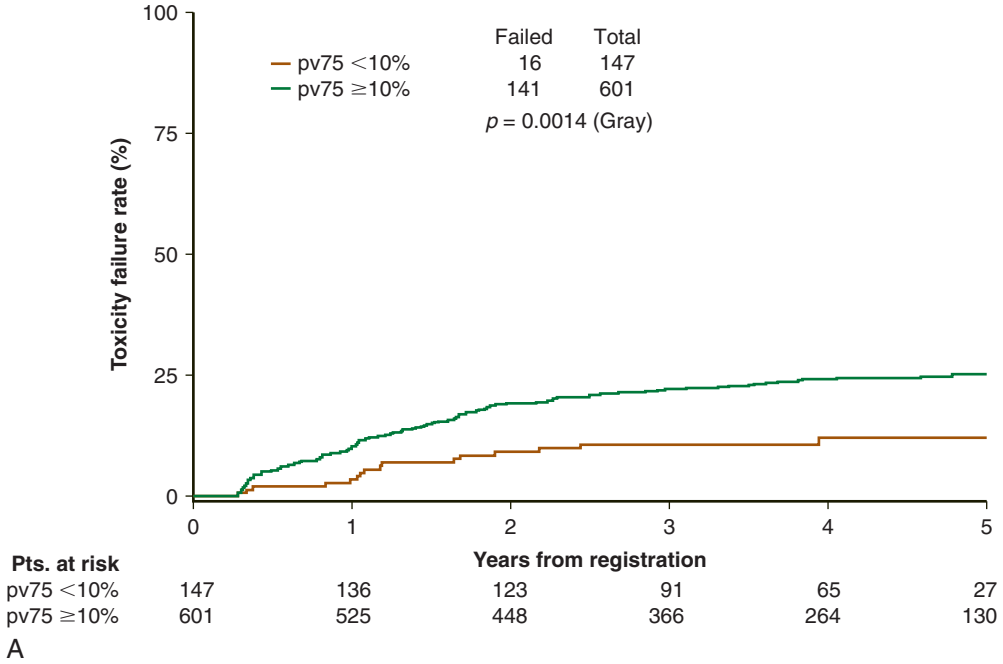


Figure 53-9 Actuarial time to the development of grade 2+ late GI toxicity by dose-volume metrics in patient treated on RTOG dose escalation trial: **(A)** pV70 < 15% or **(B)** pV75 < 10%.
From Michalski, et al: Int J Rad Biol Phys 87:932–938, 2013.

diabetes mellitus, hemorrhoids, inflammatory bowel disease, advanced age, AD therapy, rectum size, prior abdominal surgery, and severe acute rectal toxicity.[546]

A high rate of acute rectal toxicity is now recognized as associated with late RT proctopathy.[544,547-549] In the Dutch randomized dose trial for localized prostate cancer, acute toxicity was an independent significant predictor for late GI toxicity. Zelefsky reported a similar association of acute toxicity to late toxicity in the Memorial Sloan Kettering dose escalation experience.[550] The risk of grade-4 complications, those requiring a major surgical procedure, and grade-5 incidents, those causing the death of the patient, is practically zero and usually related to comorbid conditions.[539,543] In the RTOG dose escalation trial, the incidence of grade-3 or greater late rectal toxicity was significantly greater in patients experiencing grade-2 or greater acute toxicity.[544]

IMRT consistently produces a conformal dose distribution, decreasing the dose to surrounding organs. This has translated into the clinical benefit of decreased toxicity rates despite the delivery of significantly higher doses to the tumor. With a median of 10 years of follow-up, Zelefsky reported that the risk of GI toxicity dropped from 13% with 3DCRT to 5% with IMRT, $p < 0.001$).[550] In the analysis of 748 patients enrolled on the 79.2-Gy arm of the RTOG Phase III dose escalation trial, Michalski reported a significant reduction in grade-2 or worse GI toxicity with IMRT compared to 3DCRT. In the multivariate analysis, IMRT was associated with a 27% reduction in grade-2 late GI toxicity.[544]

The correlation between dose-volume histogram (DVH) and bladder complication risk has not been as straightforward.[551] With 3DCRT, Pollack et al did not see a difference in complication rates when increasing dose from the 70-Gy to the 78-Gy level.[499] In the RTOG dose escalation study, Michalski et al saw a correlation between late bladder complications and the percentage of bladder receiving radiation doses greater than or equal to the defined reference doses of 60 Gy and 65 Gy.[543] In general, the greater the percentage of bladder receiving higher doses, the higher the complication rate. However, there was no dose-volume cut-off above which a complication was more expected as has been seen in rectal DVH analyses. Even more unexpectedly, a higher mean dose to the bladder was a predictor for a lower relative risk of bladder toxicity. An explanation for this might be that bladder complications occur late, as they did in the Massachusetts General Hospital (MGH) proton boost dose escalation study, and the full incidence may not yet have been realized in more recent studies.[552] With 10 years of follow-up, Zelefsky reported that patients receiving a prescribed dose of 81 Gy had a 20% rate of late grade-2 or greater GU toxicity compared to 12% in patients receiving lower doses.[550] There was little difference in the urinary complication rate for 3DCRT versus IMRT. This is likely explained by the fact that much of the toxicity is related to the urethra, which cannot be avoided with either technique. The lack of consistent correlation may be the result of the relative proportion of bladder irradiated, which can change substantially as the treatment course proceeds. As irritative symptoms develop, the frequency of urination increases, which decreases bladder filling and, therefore, total bladder size. This has a direct effect on the percentage of bladder within the treatment field that may differ substantially from that predicted by the initial treatment plan, which is done with a desirably full bladder. In a subsequent series of 268 patients treated to 86.4 Gy, the incidence of grade-2 and grade-3 late GU toxicity was 20% and 1%, respectively.[553] In nearly half the cases, the toxicity resolved with further followup. A DVH analysis demonstrated that hot spots in the bladder trigone were significantly associated with worsening urinary symptoms.[553] They recommended keeping the maximal dose to the bladder trigone to <86.3 Gy with a prescribed dose of 80 Gy in 2 Gy fractions.

Assessment of sexual function after EBRT is complex and may be fraught with difficulty. Potency typically begins to diminish 1 to 2 years after radiation and actuarial analysis appears similar to the natural aging process. Additionally, some patients have compromised potency as a result of concurrent illnesses such as diabetes or arteriosclerosis or as a result of medications taken for comorbid conditions. According to single-institution reports and a meta-analysis, it appears that 50% to 60% of potent patients remain so after EBRT.[554] The specific target tissue for loss of erectile function is unclear, but it has been suggested that either the periprostatic neurovascular bundles or the penile components just inferior to the prostate may be responsible. As part of the QUANTEC project, Roach summarized the risk of erectile dysfunction and the association with mean doses to the penile bulb in excess of 50 Gy.

Other complications including leg or genital edema and osteonecrosis are rare with contemporary techniques. With more conformal radiation, complications appear to be localized.

Of concern, however, are the recent reports on second malignancies associated with radiation for prostate cancer. Although there is a long latency period (5 years to 15 years), this is becoming a more significant consideration because of the younger age at diagnosis, presentation at earlier stages, improved treatment efficacy, and longer average life expectancy. Using SEER data from 1973 to 1993, Brenner et al compared the risk of second malignancy in 51,584 irradiated men to 70,539 who had prostatectomy. There was a fairly small but significant excess risk of solid tumors in men who underwent prostate radiation: 1 in 290 (all years), 1 in 125 for ≥5-year survivors, and 1 in 70 for ≥10-year survivors.[555] The most significant contributors to this increased risk were carcinomas of the bladder, rectum, lung, and sarcomas within the treatment field. Using SEER data from 1973 to 1994 Baxter et al[556] found a hazard ratio of 1.7 for the development of rectal cancers at the irradiated site that did not occur in the remainder of the colon. This 70% increased risk may appear more alarming than it actually is because it translates into 1.4 more rectal cancers per 1000 irradiated men, the same approximate order of magnitude as the risk of having a first-degree relative with colorectal cancer or adding 10 years to ones age. Abdel-Wahab compared the risk of second primary cancers following patients treated with no radiation, EBRT, or brachytherapy.[557] Although the patients who underwent brachytherapy initially had no higher risk of second cancers compared to patients who underwent no radiation, with follow-up beyond 5 years the relative risk of second cancers was similar to patients treated with EBRT.

Particle Beam Therapy

Proton Therapy

Technical Issues. The technical aspects of proton and carbon ion therapy are reviewed in greater detail in the chapters devoted to those technologies. The unique dosimetric feature of the Bragg peak allows relative dose intensity to be applied at deep targets while sparing organs at risk distal to it. Because entrance dose contributes dose to organs proximal to the Bragg peak, most radiation plans for prostate cancer use opposed lateral beams. Just as with IMRT, margins must allow for prostate motion and set-up error. Additionally, because protons are more sensitive to tissue density, extra margin (smearing) must be allowed for inconsistent attenuation in the beam path, such as more bone versus soft tissue, and uncertainties in CT scan densities at planning. Two parallel-opposed lateral beams are typically used for prostate radiation. Range

Historical Perspective. Particle beam therapy has been explored in the treatment of prostate cancer over the last 30 years. In general large, cumbersome, expensive equipment was required to produce the particle beam, set-up and delivery time was lengthy, the process was labor-intensive, and the dosimetry was not tumor conformal, leading to high complication rates with dose escalation because of nearby critical organ tolerance. From the late 1970s through the early 1990s a series of trials were conducted with mixed neutron-photons, proton-photons, and neutrons alone all of which served to study outcomes, both tumor and toxicity, for dose-escalation with particle beam therapy.[500,558,559] Especially for neutron therapy, the increase in dose was largely related to a higher RBE estimated at 4 for the tumor and 3 for normal tissue, which also led to a steep dose-response function for late sequelae.[560] So although mixed photon-neutron therapy showed a survival benefit in one study (RTOG 77-04),[558] and a mixed photon-proton approach produced better local control in poorly differentiated tumors in the MGH trial,[500] the associated toxicity was such that options for dose-escalation with better normal tissue avoidance were preferentially explored. 3DCRT and IMRT with more readily available photons, as well as the application of hormonal therapy to address not only the local but also the metastatic components of treatment failure were applied and refined. As tumor/organ imaging and targeting improved and treatment technology advanced, enthusiasm for particle therapy once again resurged with the hope of decreasing the size of the treatment field and the amount of the nearby normal tissue irradiated. Thus in the current era, proton therapy for prostate cancer is being increasingly more commonly applied and studied and heavy ion treatment with carbon-12 nuclei is being explored. Although data on the comparative efficacy and complications of proton and carbon ion therapy is lacking, several theoretical advantages have been offered. Likewise, there are associated technical trade-offs and concerns that must also be understood.

(depth) uncertainties requiring adequate margin and the slightly higher RBE at the distal end of the Bragg peak prevent using an anterior beam aimed at the rectum. At depth, however, proton beams exhibit significant penumbra affecting the rectum from laterally directed beams.

Studies comparing dosimetry with IMRT with 3D conformal proton therapy have been reported (Figure 53-10).[561,562] The amount of rectum and bladder in the high-dose area are quite similar with both modalities by DVH analysis, allowing for plan optimization and variations in patient anatomy[561,562] There is an advantage for proton therapy for rectal and bladder doses of 30 Gy to 40 Gy or less and for diminished total body doses in the LDR because proton therapy avoids multiple entrance and exit beams (Figure 53-11).[561] (6) The hip dose is 10% to 20% higher with proton therapy, however, because of the use of only two laterally directed beams. The high-dose volume may actually be larger than photons as a result of the need to account for beam attenuation uncertainties and the wide lateral penumbra.

Radiobiology and Second Malignancies. Because protons do not have a much higher linear energy transfer (LET) than photons, the relative RBE is approximately 1.1. Therefore, effects on tumor and normal tissue are assumed to be related to dose and fractionation much the same as for photon treatment. To date, doses and fractionation schedules with proton therapy for prostate cancer have been similar to IMRT. Theoretical benefit in reducing the risk of second malignancy with proton therapy has been proposed.

Clinical Outcomes. To date, outcome reports on proton therapy are sparse, and there are no randomized trials comparing proton therapy to 3DCRT or IMRT. Two randomized trials contained proton therapy as a boost, but the trials were designed as dose comparison studies, and the more recent study included proton therapy in both arms.[500,501] A retrospective review with 10 years follow-up from Loma Linda University contained patients treated with a combination of photons and protons as well as patients treated with protons alone.[564] The dose level was 74 Gy to 75 Gy and the PSA disease-free results were similar to those seen with equivalent doses of photon therapy. Complications to date do not appear to be reduced with proton therapy at comparable dose levels. Preliminary results of a single-arm trial using proton therapy to 82 Gy in 2 Gy fractions showed a grade-2 GI complication rate of 10% and a grade-3 rate of 1%, whereas the respective GU rates were 22% and 7%. There was, in fact, one patient with grade-4 GI and GU toxicity.[565] What this suggests is that unless the urethra and bladder neck are spared, GU toxicity may increase with further dose escalation. Mendenhall reported the early results of three prospective trials of image-guided proton therapy in 211 men treated at the University of Florida.[566] With doses from 78 CGE to 82 CGE, the 5-year cumulative incidences of grade-3 or worse late GI and GU toxicity were 1% and 5%, respectively. The incidence of grade-2 toxicity was not reported but in the previous report it was 4% and 20% at 2 years, respectively.[567] The five year bDFS rates were 99%, 99%, and 76% for the low-, intermediate-, and high-risk NCCN categories. However, in a retrospective study of 27,647 Medicare beneficiaries, Yu reported that compared to IMRT, proton therapy offered no significant difference in the rate of GI or GU toxicity 12 months following treatment.[568]

Future Applications. Pencil beam scanning technology has paved the way for intensity-modulated proton therapy (IMPT). Although most proton centers around the world still use the passive scatter method, which is a 3D conformal approach, it is thought that IMPT holds the key to better directed therapy, possibly to include focal boosting, and the ability to avoid more normal tissue (Figures 53-10 and 53-11).

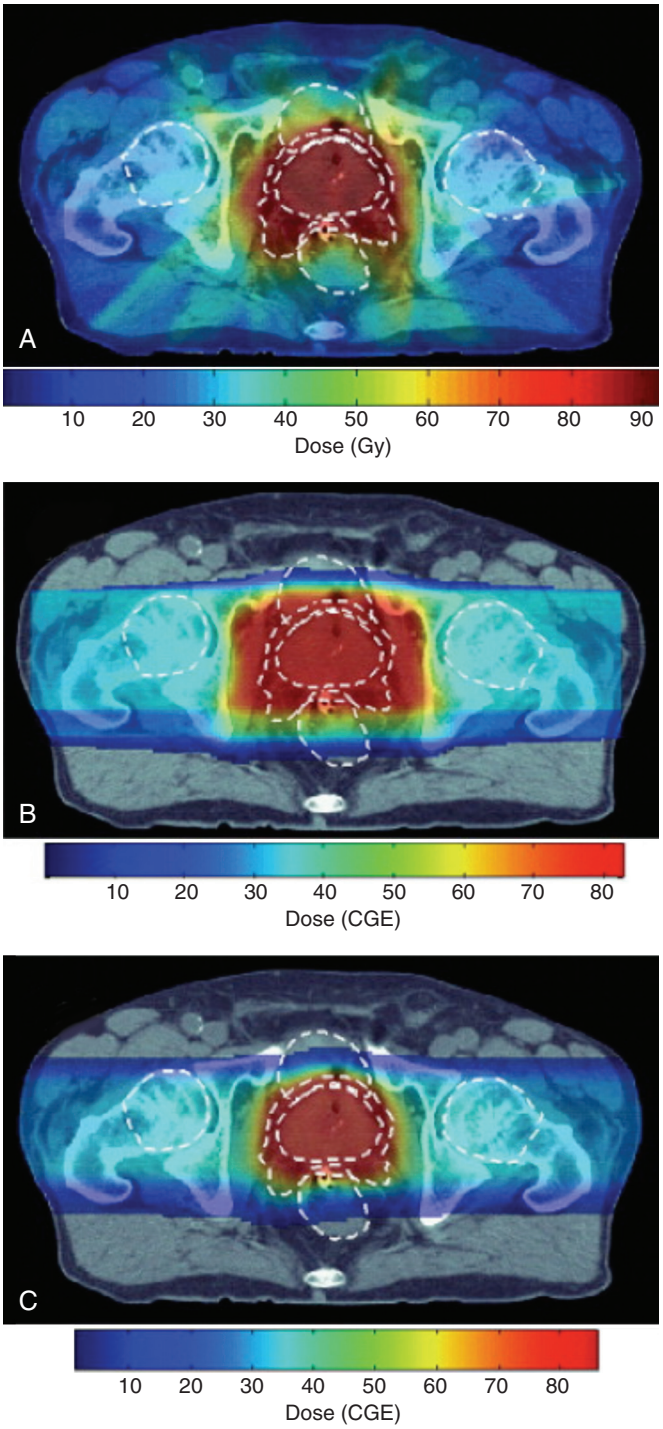


Figure 53-10 Dose distribution in the transversal isocenter section for **(A)** intensity-modulated radiation therapy, **(B)** 3D conformal proton therapy, and **(C)** intensity-modulated proton therapy plans.
From Trofimov A, et al: Radiotherapy treatment of early-stage prostate cancer with IMRT and protons. A treatment planning comparison. Int J Radiat Oncol Biol Phys 69:444-453, 2007.

Studies modeling the risk of second malignancy have suggested that the in-field contribution to this risk is considerably greater than the out-of-field risk from stray radiation and that the in-field risk may be reduced with proton therapy.[563] Of note, however, is the neutron component, which is greater with protons produced by the passive scatter process as compared to 6 MV photons used for IMRT. There is considerable debate over how much more to weight the effect of the neutron component on carcinogenesis. Therefore, the resulting second malignancy rate of one modality versus the other remains debatable because no comparative clinical studies have been reported to date. The impact of patient age is no doubt also a factor in view of the long latency period associated with radiation induced second cancers versus the expected survival of the elderly prostate cancer cohort.

Because the benefit of proton therapy for prostate cancer has been more hypothetical than evidenced-based thus far, cost has become a widely debated issue. Typical proton therapy centers with multiple gantrys carry price tags in the $150- to $200-million range, although single-gantry units may become available for $20 to $30 million. Currently, reimbursement for proton therapy is nearly twice that paid for IMRT. Cost analysis models have not shown proton therapy to be cost-effective by the usual measures even when unproven assumptions are made that this modality will have superior tumor control. Proton therapy proponents argue that as we become technologically more adept with this modality, complication rates will decrease as compared to state of the art photon treatment.

Carbon Ion Therapy. At least one other charged particle is being explored for prostate cancer radiation, the carbon ion. This particle has the advantage of a low LET of approximately 1 in the entrance channel as compared to a LET of 3-4 at the Bragg peak. Accurate targeting is essential for a radiation beam with a high relative biological effectiveness. High LET radiation does have several benefits such as a lower oxygen enhancement ratio making hypoxic tumors more sensitive, less cell cycle dependence, and possible deleterious effects on the microenvironment particularly angiogenesis. Early results from carbon ion trials in Japan show good tolerance and promising 5-year bDFS rates[569,570] With hypofractionated schedules of 66.0 GyE/20 fractions, 63.0 GyE/20 fractions, or 57.6 GyE/16 fractions the cumulative incidences of grade-2 or worse GI and GU toxicities were 1.9% and 6.3%, respectively. The 5-year biochemical and local DFS rates were 91% and 98%, respectively.

Interest in brachytherapy reemerged in the 1970s when Whitmore et al at Memorial Sloan Kettering Cancer Center (MSKCC) in New York established an open, retropubic approach using iodine-125 (^{125}I) seeds.[572] However, trying to uniformly implant the exposed gland did not prove to be the best way to achieve homogenous dose coverage. The 15-year outcomes were disappointing, with only 21% of patients reported controlled. Nonetheless, a retrospective analysis of 110 patients from the original retropubic Yale series with modern, 3D CT-based dosimetric parameters provides insight into the retropubic experience.[573] Several dosimetric parameters were evaluated to determine "cutoff" points that statistically separated these factors by local RFS. When separated by favorable and unfavorable dosimetry parameters, there was a twofold increase in 10-year RFS. More importantly, a comparison of Yale's "inadequate" implants identified a group of patients with local control rates similar to other series from this era that have reported poor outcomes. The experience with the open, free-hand approach suggests that optimal results could be achieved if accurate source placement was accomplished, if dose homogeneity and total dose were adequate, and if patients were appropriately selected.[574]

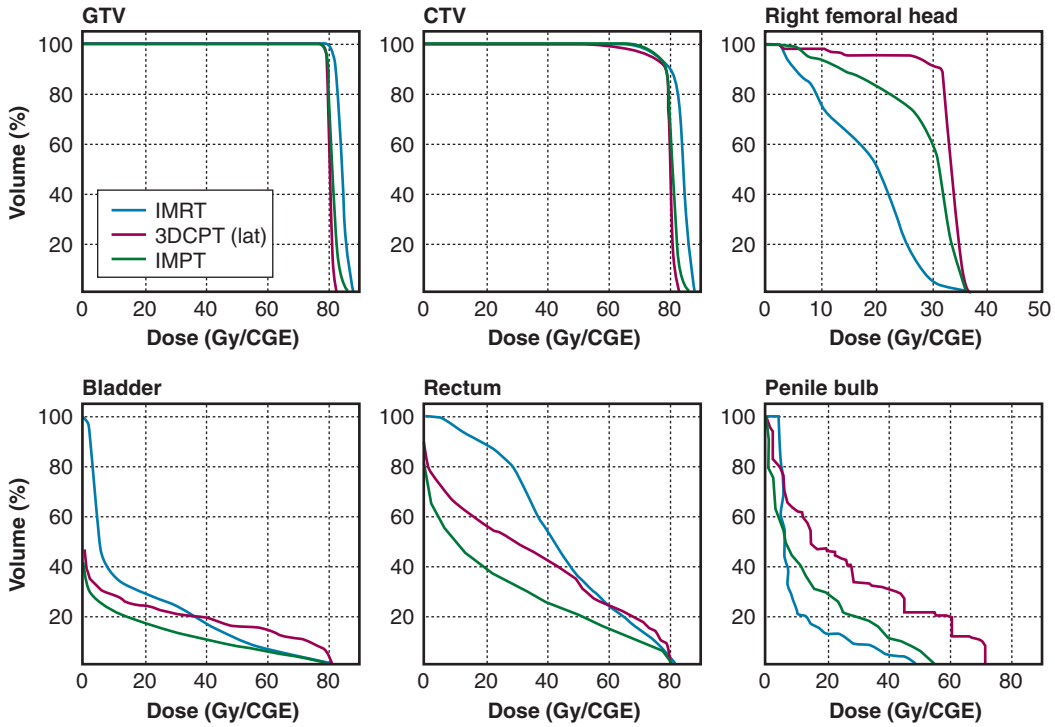


Figure 53-11 Dose-volume histograms for intensity-modulated radiation therapy (IMRT), 3D conformal proton therapy (3DCPT), and intensity-modulated proton therapy (IMPT) plans.
Data from Trofimov A, et al: Radiotherapy treatment of early-stage prostate cancer with IMRT and protons. A treatment planning comparison. Int J Radiat Oncol Biol Phys 69:444–453, 2007.

As always, the goal is to increase the dose while reducing complications.

Brachytherapy

Prostate brachytherapy predates radical prostatectomy, having been introduced in the 1920s with radium needle implants. Later, in the 1960s, radioactive gold seeds were used to treat prostate cancer.[571] Outcomes were poorly reported in the pre-PSA era and, given the complexity of working with radioactive isotopes, its acceptance as a treatment modality was hampered.

A resurgence of prostate brachytherapy occurred in the 1980s because of the transperineal approach developed by Holm et al.[575] This approach adopted in Seattle used a "preplan" to account for the seed placement, whereas in New York a more conservative approach was developed to limit the morbidity of the procedure by peripherally placing seeds to limit central hot-spots.[576] Given the ability for real-time image guidance of implant in situ, excellent results have been obtained with brachytherapy, and both approaches remain active to this day.

Patient Selection. Implantation of the prostate is an attractive option because it concentrates treatment on the prostate and minimizes radiation exposure and morbidity to nearby organs, including the bladder, rectum, and small bowel. Prostate brachytherapy is an outpatient procedure after which the patient may resume 100% of physical activity within 24 hours. The implant serves as the delivery mode of the isotopes, which decay over time and deliver the actual radiation treatment. Prostate brachytherapy can be accomplished with LDR, permanently implanted low-energy, short half-life isotopes such as ^{125}I, ^{103}Pd, and cesium-137 (^{137}Cs) or with high-energy, HDR isotopes such as iridium-192 (^{192}Ir).

The selection of patients for prostate brachytherapy is generally reserved for patients with clinically confined prostate cancer. Similar to other modalities, risk stratification and assessment of pathologic, clinical, and radiographic features best combine to predict for a high probability of organ-confined disease[194]

The selection of brachytherapy as monotherapy versus brachytherapy as a boost with supplemental EBRT has primarily been based on pathologic risk factors. Risk stratification of disease by initial PSA value and Gleason score better predicts outcome and allows for treatment modification to account for those men with high-risk disease. When the risk of extraprostatic disease is high there is the need to combine prostate brachytherapy with EBRT.

The American Brachytherapy Society (ABS) recommends monotherapy for patients with clinical T1-T2a, PSA 10 ng/mL or less and Gleason score 6 or less with the addition of supplemental EBRT for all with higher risk features.[577,578] However, the role for combined EBRT and brachytherapy for patients with intermediate-risk disease remains controversial with some data suggesting that supplemental EBRT may be omitted depending on implant quality and seed placement philosophy.[579]

Brachytherapy is associated with urinary morbidity that may be mild or may be protracted and quite bothersome to the patient. Indwelling catheterization has been reported between 2% and 20% after prostate brachytherapy. Higher rates of acute urinary obstruction date back to older techniques that failed to spare high doses centrally within the prostate. But other factors associated with increased postimplant urinary bother include a high initial International Prostate Symptom Score (>7 to 10) and an enlarged prostate volume.[580] Patients with either or both these factors need to be coached carefully before undergoing permanent brachytherapy. Although it is customary to offer men with enlarged prostates a 3-month course of androgen ablation to reduce the prostate volume, data from Princess Margaret Hospital (PMH)

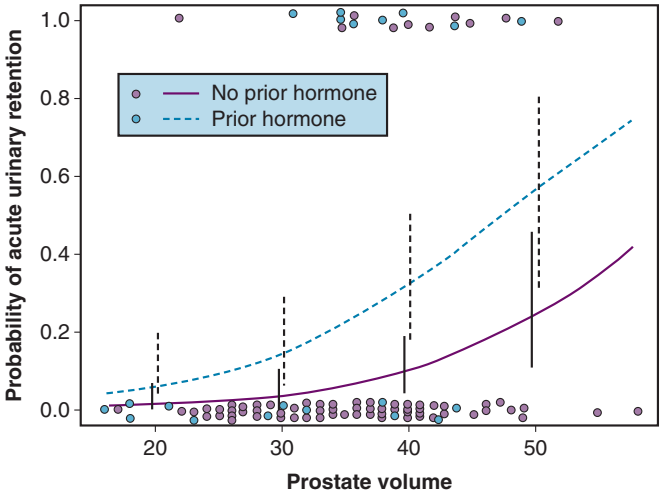


Figure 53-12 Risk of urinary retention according to prostate volume for patients treated with or without hormonal therapy.
Data from Crook J, McLean M, Catton C, et al: Factors influencing risk of acute urinary retention after TRUS-guided permanent prostate seed implantation. Int J Radiat Oncol Biol Phys 52:453, 2002.

suggest that, by doing so, postimplant urinary morbidity is not reduced.[581] Furthermore, the long-term impact on potency of even a 3-month course of androgen ablative therapy needs to be considered. Patients with enlarged prostates and high IPSS values may want to consider EBRT as definitive treatment.

Large prostate size is widely believed to be a relative contraindication to brachytherapy because of technical concerns and the perception that such patients are at higher risk for urinary morbidity. However, contrary to popular perception, several studies have reported that appropriately selected patients with a large prostate can be implanted with acceptable morbidity and with good dosimetry.[582,583] Pubic arch interference may represent a technical problem regardless of prostate size depending on the implant technique used. With the preloaded needle technique, the extended lithotomy position may be difficult to achieve during the planning phase, which may limit needle placement at the time of the implant. With intraoperative planning, patient positioning can be achieved at the time of implant under anesthesia without pubic arch interference.

There appears to be a direct relationship between preimplantation IPSS values and postimplantation urinary obstruction in men undergoing prostate brachytherapy, whether downsized with hormones or not[581] (Figure 53-12). The use of prophylactic α-adrenergic blockers may diminish the impact of a high initial IPSS value.[584] Nonetheless, patients with urinary symptoms should be informed of their risk of urinary retention after implantation.[580,585]

Patients who have been treated for BPH with TURP pose potential problems when treated with permanent prostate brachytherapy. A fresh TURP defect may lead to excessive morbidity and inadequate seed geometry.[586] In general, a preimplant ultrasound evaluation is required for these patients to assess the TURP defect relative to the planned seed locations. Furthermore, it has been reported that patients with a previous TURP may experience prolonged postimplant dysuria and are at risk of urethral necrosis.[587] Current protocols for permanent prostate brachytherapy that place seeds peripherally in the prostate gland do not cause the high rates of urethral necrosis originally reported.[588]

Therefore, past TURP, prostate size, and history of inflammatory bowel disease, all relative contraindications in the past, need to be considered on an individual basis. Patients must also have a patent anus to allow for ultrasonography.

At present, an age-related bias exists within the urologic community, with younger patients being referred more often for radical prostatectomy than either radiation or no therapy. In a recent study from Shapiro et al,[589] men younger than 60 years of age had identical biochemical outcomes at 5 and 10 years compared with patients older than 60 years of age, suggesting that age should not bias prostate brachytherapy as an option in younger men. However, the risk of second primary cancers (SPC) is an important consideration when offering prostate brachytherapy and should be discussed with each patient.

Isotope Selection. Radiobiologic data suggested that isotope dose-rate may be an important factor for treating prostate cancer because different grades of disease with different cell doubling times may have specific sensitivities to either ^{125}I or ^{103}Pd.[592-594] Nevertheless, there have been no data to date to suggest that isotope choice should be based on tumor grade or prostate cancer doubling time.[577] A recent study found that ^{125}I compared to ^{103}Pd brachytherapy followed by EBRT both had an equivalent impact on morbidity and biochemical outcome for patients with clinically localized prostate cancer.[594]

Role of EBRT. The reasons for combining EBRT and permanent prostate brachytherapy are based on the statistical risk of having extracapsular disease associated with Gleason score, PSA, and stage.[193] A prostate implant only provides dose to the prostate with perhaps a 3-mm to 5-mm margin and may include just the base of the seminal vesicles.[595] The "field" effect of EBRT to encompass the seminal vesicles and a larger prostatic margin will potentially encompass the areas at risk for extracapsular disease not treated by the implant.

Patients with T2b cancer or Gleason score 8-10 or PSA >20 ng/mL are recommended to undergo EBRT and implant rather than implant alone.[577] Nonetheless, a review of the literature is not helpful to delineate whether there is a biochemical control difference between these approaches because many centers do not stratify their patients accordingly (Table 53-9).[578,596] Further, detailed pathology studies indicate that the radial extent of extraprostatic cancer extension is almost always 5 mm or less, which is within the confines of a monotherapy brachytherapy dose distribution.[597] If the prostate gland is implanted with a generous periprostatic margin, supplemental EBRT may not improve the outcome in low-, intermediate-, or even high-risk cases.[577,582,598,599]

Results with brachytherapy alone or plus EBRT have been evaluated in several series. In an update of the Long Island experience, Potters et al have shown little difference in PSA-RFS with combined EBRT and brachytherapy versus monotherapy brachytherapy,[579] provided that implant dosimetry is acceptable. Likewise, Blasko et al have identified excellent 10-year BCR in all risk patients undergoing monotherapy brachytherapy. In their study, 230 patients were treated with Pd-103 monotherapy and they reported a 9-yr PSA-RFS of 83%.[283] Forty percent of these patients presented with a Gleason score ≥7 and 24% of the patients had a pretreatment PSA value of >20 ng/mL. These long-term results are as good as any series that routinely use combined EBRT and permanent brachytherapy.[469,598,603] Recently, Shilkrut et al found that EBRT and brachytherapy versus EBRT alone resulted in better outcomes for biochemical failure and prostate cancer specific mortality in patients with high-risk prostate cancer, suggesting that combined modality treatment has a greater impact on CSS and FFBF than EBRT alone in patients with high-risk prostate cancer.[604] Another study found that EBRT with HDR

To that end, it is recognized that radiation exposure is associated with second primary cancers. Several studies have shown an increased risk of bladder and colorectal cancer in men who were treated with radiation for prostate cancer.[556,590] However, these studies were in patients treated EBRT. Brachytherapy, which is highly conformal therapy, appears to have lower SPC risk than EBRT.[557,591]

At the time of the Whitmore implants, ^{125}I was the isotope used and continues to be used for prostate brachytherapy. In the early 1990s, palladium-103 (^{103}Pd) was introduced. With a shorter half-life, it was postulated that ^{103}Pd would be the preferred isotope for higher Gleason score tumors because of their faster tumor doubling time.[593] In 2003, cesium-131 (^{131}Cs) was introduced as a third isotope for prostate brachytherapy; ^{131}Cs has even a shorter half-life than ^{103}Pd, which can offer the advantage of a reduced period to monitor radiation exposure precautions following the implant.

TABLE 53-9 Review of the Literature on Permanent Prostate Brachytherapy Performed as Monotherapy or Combined with External Radiotherapy

Study	No. of Patients	Median Follow-up (mo)	Biochemical Control	Definition	Comments
Ragde et al[600]		93		ASTRO†	High-risk patients treated with CMT; no analysis performed comparing groups
CMT	75		79%		
Monotherapy	144		66%		
Critz et al[601]					
CMT	689	48	88%	Nadir < 0.2 ng/mL	
Dattoli et al[598]					
CMT	73	36	79%	PSA < 1.0 ng/mL	All high-risk patients
Zelefsky et al[602]				ASTRO	CT-based ^{125}I implants; includes patients with clinical T3 disease
Monotherapy	248	48	71%		
Low risk*	112		88%		
Intermediate risk*	92		77%		
High risk*	22		38%		
Blasko et al[603]		58		ASTRO	
CMT	403		88%		
Monotherapy	231		79%		
Low risk*					
CMT	279		94%		
Monotherapy	75		79%		$p = 0.06$
Intermediate risk*					
CMT	111		85%		
Monotherapy	104		84%		$p = 0.86$
High risk*					
CMT	11		62%		
Monotherapy	13		54%		$p = 0.53$
Potters et al[596]		45		ASTRO	
CMT	314		81.5%		
Monotherapy	1162		82.1%		$p = 0.54$
Low risk* (matched)					
CMT	38		87.7%		
Monotherapy	40		93.4%		$p = 0.54$
Intermediate risk* (matched)					
CMT	174		84.8%		
Monotherapy	191		79.7%		$p = .064$
High risk* (matched)					
CMT	102		68.6%		
Monotherapy	84		60.5%		$p = 0.49$

From Potters L, Fearn P, Kattan M: The role of external radiotherapy in patients treated with permanent prostate brachytherapy. Prostate Cancer Prostatic Dis 5:47–53, 2002.[596]

ASTRO, *American Society for Radiation Oncology;* CMT, *combined-modality permanent prostate brachytherapy and external radiation therapy;* CT, *computed tomography;* PSA, *prostate-specific antigen.*

**National Comprehensive Cancer Network (NCCN) Risk Category.*

†Three consecutive elevations with the failure date backdated to half-way between the PSA nadir and the first PSA elevation.

brachytherapy boost compared to EBRT alone in the treatment of localized prostate cancer resulted in a 31% reduction in risk of recurrence and a significant improvement in RFS with comparable GI and GU toxicity.[605] There is currently a study by Zelefsky et al (in press) that likewise found improved PSA-RSF and distant metastasis free survival (DMFS) of combination therapy but with EBRT and LDR brachytherapy, instead of HDR, compared to EBRT alone in the treatment of intermediate-risk prostate cancer.[606] The study also found comparable late GI and GU toxicity between the two different treatment modalities.

RTOG 0232 is a Phase III clinical trial that recently closed and sought to compare permanent implants alone to permanent implants plus EBRT in men with intermediate-risk prostate cancer.[607] The results of this study are expected to clarify the role of EBRT in men receiving permanent seed brachytherapy.

Brachytherapy and Androgen Ablative Therapy. With the development of real-time ultrasound permanent prostate brachytherapy in the mid 1980s, the role of combining neoadjuvant androgen deprivation (NAAD) and permanent prostate brachytherapy was to reduce the prostate size if it exceeded 60 grams. This decreases the total isotope activity required and decreases pelvic arch interference.[608] Although this practice has continued, there is data to suggest prostate size is less relevant to implant quality than originally suspected.[583] While some prospective data indicates an improvement in DSS when combining NAAD and EBRT in patients with locally advanced and metastatic prostate cancer,[609] there is no prospective data to support the concept of NAAD as a radiosensitizer for early-stage prostate cancer.[610]

Although Stock et al[611] initially reported on a potential role for combined permanent prostate brachytherapy and hormone therapy, they have subsequently identified that any advantage

TABLE 53-10 Recommendations for Postimplantation Dosimetric Analysis

All patients require postimplant analysis
CT-based dosimetry is recommended (minimum)
Plain radiographs (to verify seed count)
Consistent post implant interval for performing dosimetry
Isodose displays for 50%, 80%, 90%, 100%, and 200%
D90 dose from the dose volume histogram
Additional doses should be reported: D80, D100, V80, V90, V100, V150, V200*
URETHRAL DOSES
Anatomy
1. Contour a volume, not a point or line
2. Catheter or fusion with ultrasound to delineate the urethra
3. Estimation is not accurate
Dosimetric parameters
1. Ur150: (volume in mL of urethra receiving 150% Rx dose)
2. UrD5 (in cGy)
3. UrD30 (in cGy)
RECTAL DOSES
Anatomy
1. Inner and outer wall contour on all CT slices where seeds are identified
2. Dose-percent parameters are too subjective
Dosimetric parameters:
1. R100: (volume of rectum in mL receiving 100% of recommended dose)
2. R150: (volume of rectum in mL receiving 150% of recommended dose)
ERECTILE RECOMMENDATIONS
1. Cannot make recommendations: Weight of evidence toward NVB dose No consensus on location and ability to contour the NVB on CT or ultrasound
2. Recommend study on NVB dosing and contouring
3. Could not support penile bulb dose measurements

From Crook J, Potters L, Stock R, et al: Critical organ dosimetry in permanent seed prostate brachytherapy: Defining the organs at risk. An American Brachytherapy Society Consensus Statement. Brachytherapy 4:186–194, 2005.[616]

CT, *Computed tomography;* D80, D90, and D100, *dose to the respective volume percent of the prostate (D90 represents the minimum dose to 90% of the prostate volume);* NVB, *neurovascular bundle.*

**V80, V90, V100, V150, and V200, volume of the prostate that received the respective dose percent.*

of hormones is negated when postimplant dosimetry is acceptable. Likewise, in the 12-year experience of Potters et al,[282] the addition of hormonal therapy with prostate brachytherapy failed to significantly affect biochemical freedom from relapse when including the impact of the postimplant dosimetry.[282]

Postimplant Dosimetry. Postimplant analysis is an important process and needs to be performed on all patients undergoing permanent prostate brachytherapy (Table 53-10). Single plane pelvic x-rays are insufficient because they do not accurately assess the spatial relationship of the prostate dose and surrounding tissues. Therefore, CT-based dosimetry appears to be the best approach for postimplant dosimetry at this time.[615]

Despite these recommendations, there are several problems with postimplant CT studies that can limit permanent prostate brachytherapy dosimetry. The timing of the study is important because prostate edema may develop acutely following the traumatic insult associated with needle insertion.[618] Early CT scans following the implant may underestimate the prostate dose by up to 10% to 20%.[599] The reported edema half-life is approximately 10 to 14 days so the best time to obtain this study may be 30 days postpermanent prostate brachytherapy.[619] Also, CT scans, may by virtue of pixel size and the location of pelvic and periprostatic muscles, overestimate the prostate size.[620] Lastly, there is tremendous individual variability in drawing the prostate margin, which may overestimate or underestimate the delivered dose.[615] A difference of 1 mm to 2 mm can affect the prostate volume by as much as 30%. Therefore, each clinic needs to set up quality controls to assure that prostate volumes are being appropriately drawn.

These problems aside, Stock et al were able to define the D90 dose as the critical variable to assess permanent prostate brachytherapy (the D90 represents the minimum dose to 90% of the prostate volume). Patients with a D90 dose greater than 140 Gy had a 4-year PSA RFS of 92%, whereas those with a D90 dose less than 140 Gy had a 4-year PSA RFS of 68% (p = 0.04). In a 12-year study, Potters et al[282] identified that the D90% (the D90 dose reflecting the percent of the prescribed dose) was an independent predictor of biochemical freedom from relapse.

Standards have been suggested for postimplant dosimetric analysis of implant quality for the reporting of morbidity.[621] However, many diverse methods of defining the critical organs for morbidity, and of reporting the dose to these organs, are currently evident in the literature. This nonuniformity of approach makes it difficult, if not impossible, to combine data from different centers to establish guidelines for minimizing toxicity.

An expert panel reached a consensus regarding dose parameters that should be tracked to normal tissue(s) when performing prostate brachytherapy. It is hoped that collecting outcomes based on these parameters betters the understanding of normal tissue tolerances and side effects.[616] At this time, there is too little data to make any sound conclusions on any specific data points that will predict the risk of complications and with the advent of real-time, dynamic implants, the role of postimplant dosimetry assessment may become unnecessary.[622]

High-Dose Rate Brachytherapy. HDR remote afterloaded brachytherapy, as an alternative to permanent prostate implants, has been successfully used to treat prostate cancer, but the preponderance of data using HDR for prostate cancer is in men with locally advanced disease. Generally, HDR treatments are combined with EBRT although its application as a monotherapy in patients with low-risk and selected patients with intermediate-risk disease is growing. The ABS recently published consensus guidelines for HDR brachytherapy as a definitive treatment for localized prostate cancer and stated that HDR brachytherapy is an excellent option for the definitive treatment of prostate cancer in any risk category.[613] The consensus statement further recommended that although HDR monotherapy is more established in its role in the treatment of low and intermediate risk prostate cancer, HDR monotherapy for high-risk prostate cancer should still be considered investigational.[613] A recent Phase II study has shown some promising results for HDR as salvage therapy for patients who develop local recurrence in the prostate after definitive EBRT.[623] The study found that in the 42 patients with locally recurrent prostate cancer, with prior EBRT definitive treatment, the treatment with HDR monotherapy as salvage therapy resulted in CSS of 94%.[623]

A recent study found that pretreatment planning with MRI guidance allowed the increased delivery of boost dose to focal tumor volume. This was accomplished by increasing D90 and V150 to the tumor volume using HDR brachytherapy without violating GI or GU constraints.[624]

In patients with high-risk disease treated with EBRT and hormone therapy on the RTOG-9413 study, an improvement was noted when hormones and full pelvic EBRT were used with an EBRT prostate boost.[612] A recent prospective Phase II clinical trial found that the combined effect of EBRT, hormone therapy, and brachytherapy resulted in excellent FFBF.[613] Future studies using permanent prostate brachytherapy may be worthwhile to incorporate a similar approach with adjuvant therapies. Nonetheless, a review of the literature does not appear to demonstrate any synergy based on current practices of combined use of hormones and permanent prostate brachytherapy.[596,614]

Postoperative CT based dosimetric analysis provides detailed information regarding the coverage and uniformity of an implant, affords the ability to compare various intraoperative techniques, and provides a sound basis for future improvement. Although CT determination of prostate volume is widely accepted for EBRT planning, the use of CT for brachytherapy purposes is controversial. The accurate delineation of prostate contours on postimplantation CT may be difficult because of postoperative edema, degradation of the image as a result of implanted metallic seeds, and a possible tendency to overestimate prostate volume from CT compared with transurethral ultrasound. However, a close correlation has been demonstrated for CT and ultrasound determined prostate volumes.[617]

Based on the unpredictable nature of prostatic edema during permanent prostate brachytherapy and its impact on dosimetry, dynamic real-time intraoperative treatment planning systems may ultimately improve the consistency of the D90 dose. Future studies with CT-ultrasound or CT-MRI spatial coregistration (fusion) may better define the prostate margin to determine the delivered dose. In addition, studies on dose heterogeneity will better identify areas within the prostate based on dose that prove to be an independent predictor for toxicity or outcomes.

Modern HDR brachytherapy systems use computer planning programs and robotic delivery systems. During the treatment, a single, high-activity ^{192}Ir source is moved through the implant catheters at 2.5-mm to 5.0-mm intervals. The programmable delivery system controls the amount of time the source stops at a particular location. This is also called the "dwell time." By changing the combination of dwell times, an infinite variety of isovolume dose distributions can be generated. The brachytherapy treatment planning systems can optimize the dwell times based on their location in the implant using computer algorithms. This allows a more homogeneous dose within the implant volume and better coverage of the target volume. Recent advances in treatment planning may provide further refinement of dosimetry by using inverse planning and other dose optimization algorithms. The pretreatment optimization of HDR offers a unique dosimetric advantage over LDR brachytherapy.

In a series of patients receiving either LDR or HDR brachytherapy, Wang reported superior prostate coverage, improved heterogeneity and lower doses to the rectum and urethra with optimized HDR brachytherapy compared to a similar group of men who had permanent LDR implants.[625] HDR brachytherapy dose and fractionation may be an advantage in the treatment of prostate cancer with its hypothetically low α/β ratio.[514] The slow proliferation rate of prostate cancer may be more sensitive to large fraction size and higher dose rates. Indeed, much of the clinical data supporting the low α/β ratio for prostate cancer has been derived from HDR brachytherapy experience.[513,514]

Beside the dosimetric advantages, there are other practical advantages of HDR brachytherapy compared with traditional LDR brachytherapy. Because the HDR source has high activity (typically 10 Curie), a treatment is delivered in a few minutes, similar to EBRT, and is always carried out in the shielded, controlled environment of the HDR treatment room. Between treatments the patient does not need to be isolated and can stay in an unshielded room with other patients. There is no radiation exposure to hospital personnel or to the patient's family members. Because HDR implant is a closed system, there is no risk of seed migration. The effect of postimplant edema can be accounted for by performing dose calculation after the implant.

Brachytherapy Outcomes. Studies reporting long-term outcomes after permanent prostate brachytherapy are mature with more than 10-year outcomes in many men. Without randomized data it is difficult to compare permanent prostate brachytherapy with EBRT or RP. However, by using PSA surrogates to define a successful outcome it appears that permanent prostate brachytherapy is at least equivalent to RP and perhaps slightly better than EBRT.

Long-term data in excess of 10 years support the use of permanent prostate brachytherapy in the definitive treatment of low-risk prostate cancer. Potters et al[282] have reported a 12-year biochemical control rate (bNED) of 81% from a cohort of 1449 patients. Freedom from biochemical recurrence for patients with low-risk disease was 91%. Similarly, Grimm et al showed that the PSA RFS at 10 years was 87% for patients with low-risk disease.[627] Taira recently reported 12-year OS, CSS, and biochemical survival of 72.6%, 98.2%, and 95.6%, respectively out of 1656 men.[628] They also note that for men experiencing biochemical progression, the median time to biochemical failure was 1.9 years compared with 2.4 years for men with a Gleason score of ≤7 and a Gleason score of ≥8 ($p = 0.231$). Although younger patients look for longer-term outcomes, it must be remembered that for permanent prostate brachytherapy, RP and EBRT, outcomes that exceed 10 years to 15 years are pushing against the early experience of PSA screening. Stage and grade migration over time may make long-term data less relevant to the current patient.

Outcomes for men with low-risk disease are excellent, with bNED rates > 90% at 8 years to 12 years.[282] In several studies, implant quality as measured by the D90 dose (the radiation dose that covers 90% of the prostate volume) correlates with outcome. Therefore, the importance of implant quality needs to be emphasized.

For patients with intermediate-risk prostate cancer, Blasko et al[603] identified that the addition of EBRT and permanent prostate brachytherapy was no better than permanent prostate brachytherapy as monotherapy; 5-year biochemical success rate was 85% compared with 84%, respectively. Potters et al[282] also failed to identify an advantage of adding EBRT on Cox regression analysis of intermediate-risk patients. One hypothesis is that poor implant quality, as measured by the D90 dose, can be compensated by the addition of EBRT.

A predictive model for a postimplant nomogram for prostate cancer relapse at 9 years has recently been reported from a large multiinstitutional analysis of 5889 patients who underwent permanent prostate brachytherapy.[629] This study further confirmed the significance of implant dosimetry for predicting outcome. Unique to predictive models, this nomogram may be used a priori to calculate a D90 dose that likely achieves a desired outcome with further validation. Thus, a personalized dose prescription can be calculated for each patient.

In high-risk prostate cancer there appears to be both a dose and radiation field effect associated with permanent prostate brachytherapy. In a multicenter analysis of 3928 patients, Stone et al[630,631] found that patients with high-risk prostate cancer benefited the most from an escalation in the biologically effective doses (BED) compared with the dose typically prescribed to those patients with low-risk prostate cancer.

Long-term biochemical freedom from relapse is reported for permanent prostate brachytherapy from several other centers.[282,283,600,611,633] Although there is little data to correlate clinical outcomes with biochemical outcomes, several studies have compared treatment outcomes between surgery, EBRT, and prostate brachytherapy (alone or combined with EBRT).[469,634] Treatment selection was not a significant factor to predict biochemical outcome except with EBRT doses <72 Gy (Figure 53-7).

Brachytherapy Complications. Many of the side effects associated with brachytherapy are associated with radiation exposure of the urethra, bladder, and rectum. These side effects can have serious quality of life implications and require informed consent from the patient.

In a prospective analysis of the quality of life of patients undergoing primary treatment for their prostate cancer, Sanda et al[635] found that patients undergoing brachytherapy had a significant detriment in urinary irritation or obstruction scores compared with baseline. As noted, factors associated with a greater detriment in urinary irritation or obstruction included a large prostate size and a high IPSS score. In the Sanda study, these factors were not controlled for, suggesting that patient selection remains important.

Similar to patients treated with EBRT and RP, brachytherapy patients were found to have detriments in the domains of sexual function, urinary incontinence, bowel or rectal function, and vitality compared with baseline. Changes in these domains were found to have a subsequent impact on the patient's satisfaction with the overall outcome of the treatment. Yet, for the sexual domain, permanent prostate brachytherapy patients performed better than EBRT and RP.[635]

Treatment-related morbidities following prostate brachytherapy may be acute, subacute, or chronic and affect most commonly the urinary, lower GI, and sexual functions. Many factors have been shown to influence the likelihood of incurring complications and may allow physicians to better select patients suitable for this approach.[580,621,636,637] These reports have also exposed the difficulties in evaluating morbidity due, in part, to the lack of standard assessment methods and potential biases. However, an updated consensus statement of the ABS has outlined standard data points from postimplant dosimetry studies that may better allow the study of dose and normal tissue toxicity (Table 53-10).[616]

Urinary Morbidity and Management. In the immediate postoperative period, patients will likely develop symptoms such as dysuria, frequency, and hematuria (Figure 53-13).[580] The inflammation in the prostate and adjacent tissues may result in weak stream or urinary retention.[637,638] Phenazopyridine is often helpful with dysuria and alpha-blockers, such as tamsulosin, terazosin, and doxazosin, can be prescribed for irritative urinary symptoms such as frequency and weak stream. Hematuria generally improves spontaneously but

Disadvantages of HDR brachytherapy are primarily related to the fractionation schedule. Patients often require an overnight hospitalization in which they are confined to their bed while the transperineal catheters remain in place. In some cases, multiple implant procedures are required to meet the treatment schedule with more than three or four fractions. The HDR procedure may also place a higher demand on healthcare personnel, including the physician, medical physicist, dosimetrist, and nurse, while the implant procedure, treatment planning and optimization, and treatments take place on the same day.

To delineate outcomes in men treated with radiation, a recent study from the UCSF compared endorectal magnetic resonance spectroscopy imaging (eMRSI) responses between permanent prostate brachytherapy and EBRT. For each parameter assessed, permanent prostate brachytherapy outperformed EBRT in both the median time to spectroscopic evidence of disease ablation (24.8 and 32.2 months, respectively) and median time to nadir PSA (38.0 and 52.4 months, respectively).[626]

With new techniques such as dynamic-adaptive permanent prostate brachytherapy, the D90 dose can be controlled intraoperatively. This further negates the need for combined therapy, especially in patients with low- and intermediate-risk disease.

A radiation field effect was also suggested in RTOG 9413. This study demonstrated an advantage in outcomes to whole pelvic radiation plus a cone-down or boost to the prostate, but longer follow-up questions whether nodal radiation is truly beneficial.[632]

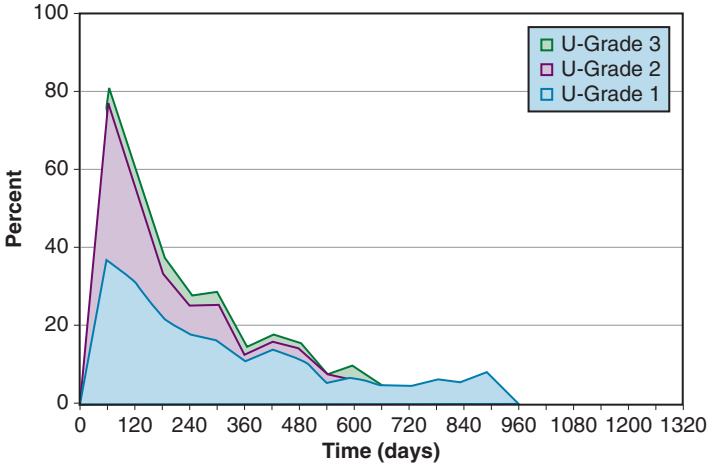


Figure 53-13 Cumulative reported urinary toxicity (i.e., frequency of urination or nocturia) for all patients using the modified Radiation Therapy Oncology Group (RTOG) toxicity scale. U-Grade 1 indicates dysuria, urgency, or bladder spasm requiring no or minimal medical intervention, such as phenazopyridine. U-Grade 2 indicates frequency with urgency and nocturia associated with early obstructive symptoms requiring other α-adrenergic blocker–type therapy. U-Grade 3 indicates obstructive symptoms requiring an indwelling catheter or posttreatment transurethral resection of the prostate (TURP) for symptom relief.
Data from Gelblum DY, Potters L, Ashley R, et al: Urinary morbidity following ultrasound-guided transperineal prostate seed implantation. Int J Radiat Oncol Biol Phys 45:59, 1999.

may cause urine retention requiring bladder irrigation. Patients who develop urinary retention may require catheter placement for an indefinite period of time. Local trauma to the prostate and seminal vesicles can result in hematospermia and orgasmalgia during the first few ejaculatory episodes and may persist for several weeks.

Subacute urinary morbidity develops 1 to 2 weeks after the implant and lasts for several weeks (6 weeks to 12 weeks). Symptoms generally peak approximately 4 weeks to 6 weeks after implant for both ^{125}I and ^{103}Pd.[639] Although these symptoms generally resolve over time, many patients will benefit from alpha-blocking agents.

Any surgical manipulations of the prostate to correct for retention should be considered only after all medical options have been exhausted. Transurethral incision or a transurethral resection of the prostatic urethra for relief of obstructive symptoms can be performed after two to three half-lives of the isotope but is associated with up to a 26% incontinence rate.[641]

Chronic urinary morbidity can occur after 6 months and may include urinary frequency, incontinence, urethral strictures, and urethral necrosis.[642] In addition, improvements in technique that avoid high peri-urethral radiation doses with peripheral seed placement have resulted in fewer severe long-term urinary side effects.[643,644]

A paradox associated with postimplant toxicity is the use of hormonal therapy to reduce the prostate volume for brachytherapy. As noted, Crook et al examined the rate and predictors of acute urinary retention in 150 patients undergoing implant and multivariate analysis showed large prostate volume and prior hormone therapy to be independent predictors of urinary retention. The explanation for this observation may be that cytoreduction of the prostate leaves mainly fibrous tissue as opposed to glandular tissue, which does not allow the gland to accommodate to the acute implant reaction.

Lower Gastrointestinal Morbidity and Management. During the weeks following the implant, there may be changes in bowel habits in the form of diarrhea, constipation, tenesmus, or rectal pressure.[636,647,648] These symptoms generally respond to conservative symptomatic management.

Late injury includes proctitis, rectal ulceration, fistula formation, and incontinence.[648-650] The most common of these is proctitis, which often presents as a painless bleeding that is usually self-limited. Bleeding from proctitis presents late, about 1 to 2 years after implantation and may be exacerbated by constipation. Conservative management is recommended with stool softeners, local steroid creams, or foams. Aggressive measures such as biopsies and laser treatments may precipitate ulceration and fistula formation and should be avoided whenever possible.

The incidence of proctitis has been reported to range from 1% to 12%.[651] Although the 12% proctitis rate reported by Wallner et al represents the early experience with CT-based implants, subsequent refinements of the technique indicate that proctitis rates have decreased to 2% to 6%.[652,653] Synder et al reporting on grade-2 proctitis following ^{125}I implants concluded that the incidence of proctitis was volume dependent for each dose studied.[654] The 5-year actuarial risk of grade-2 proctitis was 5% if 1.3 mL or less of the rectal volume received the prescription dose of 160 Gy, and 17% for >1.3 mL ($p = 0.001$). Others have tried to correlate the risk of proctitis relative to the delivered dose and volume of the rectum with less success.[648] Although there appears to be the suggestion of a dose response, the lack of conformity in the literature makes it difficult to recommend a specific dose to a certain volume of rectum. Further, intraoperative planning systems allow the operator to measure and limit the rectal dose during the case.[655]

Sexual Function Morbidity and Management. Given the impact of erectile dysfunction on quality of life in an ever-younger cohort of patients with newly diagnosed prostate cancer, discussing the impact of sexual function is vital with each patient.

Acute changes in sexual function following permanent prostate brachytherapy include pain with ejaculation and hematospermia. These symptoms generally dissipate over time and correlate with the acute prostatitis that the patient experiences. Erectile dysfunction (ED) following brachytherapy may be multifactorial, as a result of changes to the patient's neurologic, vascular, or psychologic makeup. Zelefsky et al have identified a potential vascular mechanism for impotence following radiation, whereas Merrick et al has examined and tried to correlate the radiation dose to the penile bulb as a mechanism for impotence.[658,659] Other confounding factors include comorbidities such as diabetes, hypertension, and smoking.

There are no prospective data looking at sexual potency following permanent prostate brachytherapy. However, retrospective data indicate a wide range of potency rates following brachytherapy, with as many as 80% to 85% of men younger than age 60 years old remaining potent[628] when treated with implant only versus 29% remaining potent following combination therapy with EBRT, AD, and an implant (Figure 53-14).[660] In a study on 416 patients treated with implant only, Stock et al reported that preservation of potency was 79% at 3 years and 59% at 6 years.[661] In multivariate analysis,

Locke et al reported prospectively on urinary retention in 62 consecutive patients undergoing permanent prostate brachytherapy with or without EBRT.[640] At 1 week, the retention rate was 34% and predictors for retention included prostate size >36 g and the preimplant AUA symptom score >10. The median duration of retention was 70 days with a range of 0 days to 469 days. Others have reported lower retention rates but noted that similar predictors, such as prostate size and preimplant symptoms, affected the overall chance of developing retention.[580,581,637]

The widespread use of the AUA score allows for standardization of certain morbidities and provides an outline of the severity and course of these symptoms. Desai et al reported on urinary toxicity in 117 patients and found a mean doubling of the baseline AUA score, peaking at 1 month following implant and returning to baseline by about 24 months.[645] In a later study from the same institution, Terk et al showed that the pretreatment IPSS was an independent factor to predict urinary retention in a multivariate analysis.[637] Gelblum et al reported urinary toxicity using a modified RTOG scoring system from a large cohort of 693 patients undergoing permanent prostate brachytherapy with or without EBRT.[580] The IPSS scores 1 month after implant were about three times that of the baseline scores. There was no significant difference in AUA scores between ^{125}I and ^{103}Pd at 60 days and 120 days post-implant.

There is much published on the urethral sparing technique to help decrease acute urinary morbidity. Surprisingly, urinary toxicity is greatest in those with large prostates where peripheral seed placement has the greatest impact on lowering the central prostatic dose.[646]

The addition of EBRT to permanent prostate brachytherapy may be a risk factor for increased rectal toxicity. A study by Zeitlin et al reporting a 2.3% fistula rate raises concern that combination therapy may be associated with more rectal injury.[656] This observation was also identified by Brandeis et al in a study comparing quality of life indicators between implant alone and when combined with EBRT.[657] In that study rectal intolerance was significantly higher in those patients treated with combination therapy.

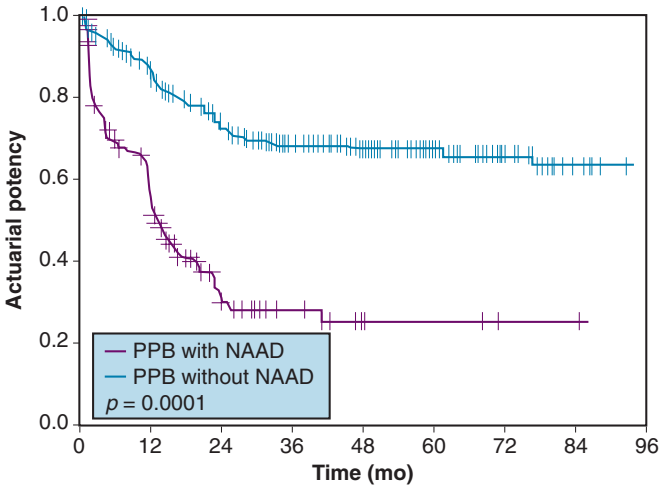


Figure 53-14 Actuarial potency of patients treated with or without neoadjuvant androgen ablation. *NAAD*, Neoadjuvant androgen deprivation; *PPB*, permanent prostate brachytherapy. *Data from Potters L, Torre T, Fearn PA, et al: Potency after permanent prostate brachytherapy for localized prostate cancer. Int J Radiat Oncol Biol Phys 50:1235, 2001.*

pretreatment potency and the implant dose were significant factors for ED post-therapy.

The use of sildenafil and similarly acting agents to treat impotence showed a 62% response rate with patients never having been treated with AD responding more often. Recently, Merrick et al have reported their 7-year actuarial rate of potency preservation of 55.6%.[628] Potent patients were statistically younger ($p = 0.014$), had a higher preimplant International Index of Erectile Function (IIEF) ($p < 0.001$), were less likely to be diabetic ($p = 0.002$), and were more likely to report nocturnal erections ($p = 0.008$).

HDR-Brachytherapy Outcomes. The technique of HDR prostate brachytherapy has been in clinical practice since the 1980s.[662-664] Kovacs et al reported one of the earliest experiences using HDR brachytherapy boost at University of Kiel.[665] Patients selected were mostly those with high-grade.

T2b-T3 lesions who were treated with a combination of split-course EBRT and two 15-Gy HDR treatments. The positive biopsy rate was 18% at 18 months post-treatment. The result was updated at 10 years and 78% of 171 patients remained free of disease at a median follow-up of 55 months. Mate et al at Swedish Medical Center reported their experience with HDR brachytherapy.[666] This group used a more moderate hypofractionated schema with four HDR treatments of 3 Gy to 4 Gy each combined with 45 Gy to 50 Gy EBRT. Pretreatment patient characteristics were stage T1b to T3c, mean initial PSA of 12.9, and Gleason grade range of III to IX. The 5-year bDFS was 84%. In a pooled analysis of 611 patients from the University of Kiel, the Seattle Prostate Institute and the William Beaumont Hospital, Galalae reported 5- and 10-year bDFS rates of 77% and 73%, respectively.[667] Of note, more than half the patients in this multicenter analysis had two or more high-risk features.

Vargas et al at the William Beaumont Hospital reported results of a prospective dose escalation trial using increasingly larger fractions of HDR from 5.5 Gy to 6.5 Gy × 3 to 8.25 Gy to 11.5 Gy × 2 combined with 46 Gy of EBRT in patients with intermediate- and high-risk disease.[668] Assuming an α/β ratio of 1.2, the calculated biologically equivalent doses ranged from 80.2 Gy to 94.2 Gy for the low dose, three fraction group and 99.9 Gy to 136.3 Gy for the high dose, two fraction group. Although the rate of mild grade-1 and grad-2 dysuria was significantly higher with the high-dose group, there were no other significant differences in toxicity for the two groups. The 11.5 Gy × 2 regimen was considered a tolerable regimen. Despite a high frequency of poor prognostic factors, the 5-year actuarial biochemical control rate was 67% and 86% for the low-dose and high-dose groups, respectively. The 5-year clinical DFS was 75.5% and 91.7% for the low- and high-dose arms, respectively.[668]

Early results of HDR implant monotherapy in the management of low risk prostate cancer have been reported.[669,670] The rates of acute urinary and rectal toxicities were reported to be less frequent than with permanent seed implantation using Pd-103 and the rates of chronic urinary frequency and urgency were also less common.[670] bDFS appeared good but the follow-up was too short to claim equivalence to other RT methods.[669,670]

Postirradiation Prostate Biopsy

Although prostatic biopsy had been considered the "gold standard" for determining local tumor control after RT, there is considerable doubt that a positive post-RT biopsy always indicates persistent or recurrent tumor.[318,480,481,484,671-673] Crook et al[671] performed serial prostatic biopsies in a consecutive and unselected group of patients treated with EBRT. TRUS and prostatic biopsy were initially performed 12 months after RT and at 6-month intervals thereafter if the preceding biopsy result was positive or local tumor recurrence was suspected. These investigators concluded that complete post-RT tumor clearance may require more than 2 years, that many patients (more than one third) with an initially tumor-positive or indeterminate biopsy converted to negative on subsequent biopsy. The proportion of indeterminate biopsies decreased over time with 33% at first biopsy to 7% at the fourth biopsy. Positive staining for proliferative markers was associated with an increase in both local and other clinical failures.

Several investigators have found that biopsy results correlated very well with PSA level after radiation,[174,673] and subsequent work on the predictive value of PSA nadir and rising PSA after therapy proved this to be a reliable, noninvasive means of establishing tumor recurrence. Because a rising trend in PSA may herald not only local failure but distant disease as well, situations that call for the documentation of local disease specifically, such as consideration of aggressive local therapy, still necessitate biopsy confirmation.

A few general conclusions about post-RT prostatic biopsy may be made: (1) routine biopsy is justified only in a research setting; (2) the tumor-positive biopsy rate is inversely related to the post-RT interval and appears to plateau at about 3 years; (3) tumor-positive biopsy results more than 2 or 3 years after RT are associated with reduced DFS; (4) tumor-positive biopsy in an asymptomatic patient, particularly in the patient with normal DRE findings and a slowly rising PSA (doubling time at least 10 months to 12 months), is not a mandate for intervention because the disease may take a slow, indolent course.[333]

Surgical Therapy

General Principles

Conventional open radical prostatectomy begins with a low midline incision and mobilization of the peritoneum. Bilateral pelvic lymph node dissection (PLND) precedes RP in patients with sufficient risk of nodal involvement.[193]

Minimally invasive techniques have become popular over the past decade and are largely replacing open prostatectomy in most large U.S. centers. Laparoscopic radical prostatectomy (LRP) follows the same oncological principals as radical retropubic prostatectomy (RRP) with PLND, when indicated, followed by removal of the prostate and seminal vesicles.

During the past few decades, a considerable range of post-RT positive biopsy rates were reported (19% to 93%),[318,480,481,484,671-673] which likely reflected issues relevant to patient selection, interval from RT, biopsy extent, and therapeutic approach. The probability of obtaining a positive biopsy was related to pretherapy T-category, tumor grade, and post-RT clinical examination findings. However, there are potential pitfalls in histologic interpretation of the post-RT biopsy, and the distinction between RT-induced epithelial atypia and residual neoplasm must be established to avoid erroneous histologic diagnosis. A positive biopsy following radiation therapy may be an independent predictor of outcome but in many circumstances these will evolve over time to become negative.

The early history of RP can be traced to Hugh Hampton Young, who first performed the procedure through a perineal approach in 1904 at the Johns Hopkins Hospital. Although initially introduced for BPH some 40 years later, the retropubic technique was later modified for prostate cancer therapy. However, the procedure was accompanied by unacceptable morbidity (e.g., urinary incontinence, erectile dysfunction, and blood loss) until redefined by Walsh et al,[674] Myers et al,[675] and others. Refinements in the procedure gave the retropubic RP certain advantages over the perineal approach and set the stage for broader application and acceptance of this therapeutic modality.[676]

As described by Morgan and Lieber,[677] a "standard" or extended PLND may be performed. Increasingly, extended PLND is recommended to improve staging. Some studies have even suggested a survival advantage although this may be more related to selection of appropriate adjuvant therapies than it is to the removal of micrometastases.[276,316,678] Its margins of dissection are lateral, junction between external iliac artery and vein; inferior, femoral canal; posterior, obturator nerve and vasculature; and superior, bifurcation of the common iliac vessels. Frozen-section histologic examination is performed, and the procedure may be terminated in the presence of nodal disease.

Thereafter, the preprostatic adipose tissue is removed from the prostate to expose the endopelvic fascia, which is incised to separate the levator ani musculature from the prostate. The puboprostatic ligaments are transected to facilitate mobility of the prostatic apex, and the dorsal venous complex and anterior membranous urethra are transected in a manner to preserve the entire distal continence mechanism. The dissection continues by transecting the "pillars of the prostate" and the rectourethralis muscle, and a plane between the prostate and the anterior rectal wall is developed. If the nerve-sparing procedure is performed, the lateral pelvic fascia is incised, and the neurovascular bundles are allowed to fall away posterolaterally. After transecting and securing the pedicles to the prostate, Denonvilliers' fascia is incised to expose the vasa deferentia and seminal vesicles, and the vasa deferentia are transected. The seminal vesicles are dissected from the surrounding tissues, and the plane between prostate and bladder is developed until the longitudinal fibers of the bladder neck are identified. The bladder neck and proximal prostatic urethra are dissected from the prostatic parenchyma, the urethra is transected, and the prostate is removed. Attention is then turned to approximating the distal urethral stump and the proximal urethra at the bladder base to create the urethrourethral anastomosis. The bladder is brought down into the pelvis, the fascia is approximated in the midline, and the skin is closed.

Rather than a large suprapubic incision, LRP methods make use of abdominal insufflation with transabdominal trocars used to introduce laparoscopes and surgical instruments to accomplish the dissection of the pelvic tissues and reanastomosis of the bladder neck to the urethra. LRP is a demanding technique with a considerable learning curve to develop the skills necessary to complete the procedure in a reasonable time with optimum oncological outcomes.[679]

Robot-assisted laparoscopic radical prostatectomy (RARP) gives the surgeon better operative site visualization and more natural hand motions to control the surgical instruments. In a review of insurance and Medicare claims data of 14,727 men undergoing radical prostatectomy between 2003 and 2005, Hu reported the use of minimally invasive techniques rose from 5.4% to 24.4%.[680]

In a similar comparison using SEER data, Hu reported shorter length of stay, fewer surgical complications and strictures with RARP.[681] However, there was an increase in incontinence, ED, and the need for additional cancer therapies such as adjuvant hormones or radiation therapy.

In a systematic literature review and meta-analysis of 79 published reports on the use of RARP between 2008 and 2011, Novara reported a mean positive surgical margin rate of 15% (range 6.5% to 32%).[682] Surgical margins were most commonly present at the prostate apex (5%) followed by the posterolateral margin (2.6%) or multifocal (2.2%). The need for adjuvant therapies was variably reported with series ranging from 0.5% to 23% with a mean value of 4%. There were no significant differences in the rates of positive surgical margins or biochemical relapse by type of prostatectomy, be it RARP, LRP, or RRP.[254,682] RARP was also associated with reduced blood loss and a shorter convalescent period.

Organ-Confined Disease

For patients with a life expectancy exceeding 10 years, RP is generally thought to be an appropriate option if disease is clinically confined to the prostate gland (i.e., stages I to II), although consideration is given to Gleason score and PSA level.[316] However, approximately one half (range, 41% to 64%) of patients thought to have organ-confined disease by clinical assessment have this confirmed by pathologic examination of the surgical specimen,[193,196,202,285] and one third of patients primarily treated with RP undergo additional cancer-directed therapy (i.e., radiation or AD therapy) within 5 years.[683]

Disease outcome after RP is derived from retrospective analysis of study populations from single academic medical centers,[196,285,288,289,684,685] pooled analysis from selected centers,[686] or population-based cohorts[687,688] but is subject to the limitations of observational case series reports as described by Green and Byar.[475] The endpoints of OS, CSS, and metastasis-free survival likelihood from contemporary series of RP (with or without adjuvant or salvage therapy) for patients with clinical stages I to II disease are displayed in Table 53-11. Recent reports indicate that biochemical and clinical failure rates are highly dependent on pretreatment prognostic factors such as T-category, Gleason score, and PSA level as well as surgical findings such as margin status and seminal vesicle and lymph node involvement.[285,684,685,689-691] As an example the series reported by Han et al is shown in Table 53-12. In a series of 1384 patients treated by RARP at the Vattikuti Urology Institute, Menon reported 3-, 5-, and 7-year bDFS of 90%, 87%, and 81%, respectively.[692] Stephenson reported 15-year outcomes of 12,677 patients treated at four academic medical centers. The 15-year prostate cancer specific and all cause mortality rates were 12% and 38%, respectively.[693] It was acknowledged that the exceptionally low rate of prostate cancer mortality may be related to the inclusion of men without a lethal prostate cancer phenotype as well as the effectiveness of modern radical prostatectomy.[285]

Complications

Advances in surgical and anesthetic techniques and in postoperative care reduced intraoperative and postoperative complication rates. The anatomic approach to RP improved hemostasis and visualization during surgical dissection, which reduced the transfusion rate from 77% to approximately 16%.[697,698] Frank rectal injury is uncommon (~0.5%),[697,698] and most patients do not require diverting colostomy because primary closure of a small defect may suffice. Furthermore, myocardial infarction (0.7%), deep vein thrombosis (0.8%), and pulmonary embolism (1%) are uncommon, and less than 0.5% of patients die in the perioperative period.[697,698]

Urinary incontinence is an often-cited complication of RP that typically improves during the first year. Although its precise etiology is not fully understood, the remaining functional length of urethra and preservation of the muscular fibers about the bladder neck are probably critical factors. Depending on the severity of incontinence, it may be managed with protective pads, Cunningham clamp, transurethral collagen injection, or placement of an artificial genitourinary sphincter. Approximately one third (range, 6% to 63%) of patients experience a significant amount of postoperative urinary incontinence,[699-703] and most patients (97%) report some degree of voiding dysfunction.[704] The variation in incontinence rates may result from differences in patient characteristics (e.g., age), surgical technique, and the method through

TABLE 53-11 Radical Prostatectomy for Clinical Stages I-II Prostate Cancer

Study	Study Period	No. of Patients	BCR-Free (%)	Met-Free Survival (%)	CSS (%)	OS (%)	End Point
Amling et al[690]	1987-1993	2782	60	—	—	—	10-y actuarial
Gerber et al[686]	1970-1993	2758	—	70	85	—	10-y actuarial
Han et al[285]	1982-1999	2494	79	82	—	—	15-y actuarial
Hull et al[685]	1983-1998	986	75	84	98	87	10-y actuarial
Kupelian et al[289]	1987-1993	423	58	91	—	94	5-y actuarial
Lu-Yao and Yao[687]	1983-1992	21,222	—	—	89	54-77*	10-y actuarial
Pound et al[684]	1982-1995	1621	68	≈92	—	—	10-y actuarial
Trapasso et al[196]	1972-1992	725	47		94	86	10-y actuarial
Roehl et al[287]	1983-2003	3478	68	—	83	97	10-y actuarial
Yossepowitch et al[694]	1985-2005	5022 Low, Int†	—	96	98	—	10-y actuarial
		938 High†	—	78	92	—	
Zincke et al[288]	1966-1991	3170	52	82	90	75	10-y actuarial

BCR, *Biochemical relapse;* CSS, *cause-specific survival;* Met, *metastasis;* OS, *overall survival;* y, *year.*
**Outcome determined by histologic subgroup within specified range.*
†NCCN risk categories.

Complications by technique were compared in Hu's Medicare claims analysis. Men undergoing minimally invasive or perineal radical prostatectomy experienced significantly fewer 30 day complications (14.2% and 14.9% versus 17.5%), anastomotic strictures (6.8% and 8.5% versus 12.9%), required fewer blood transfusions (2.2% and 3.6% versus 9.1%), and had shorter hospital stays (1 and 2 days versus 4 days).[680]

In a contemporary series of 741 patients treated at Yale by Colberg et al, the 5-year bDFS for patients undergoing surgery or brachytherapy were identical for the favorable-risk group (93% versus 92%), intermediate-risk group (70% versus 70%), and the high-risk group (50% versus 52%).[691]

Although to date randomized trials comparing contemporary therapies for definitive treatment of prostate cancer have been nearly impossible to complete, available data suggests that both radiation, either EBRT to current doses or radioisotopic implant, and prostatectomy result in similar outcome for patients with equivalent prognostic factors.[469] Other comparisons by modality are complicated by case selection, intercurrent and comorbid conditions, or lack of appropriate adjuvant therapies.[243,471] Unfortunately, physician bias toward treatment options has been shown to be specialty related.[695,696] Many institutions have attempted to solve this problem through multidisciplinary clinics where patients have the benefit of obtaining consultation from multiple specialists.

TABLE 53-12 Actuarial 5-, 10-, and 15-Year Relapse-Free Rates Following Anatomic Radical Retropubic Prostatectomy in Relation to Clinical T category, Preoperative Prostate-Specific Antigen Level, and Gleason Score

	Actuarial Percentage (95% CI)		
Variable	**5 Year**	**10 Year**	**15 Year**
TNM			
T1a	100	100	100
T1b	90 (83-95)	85 (76-91)	75 (58-86)
T1c	91 (88-93)	76 (48-90)	76 (48-90)*
T2a	86 (83-88)	75 (71-79)	66 (59-72)
T2b	75 (70-79)	62 (56-68)	50 (41-58)
T2c	71 (61-79)	57 (45-68)	57 (45-68)
T3a	60 (45-72)	49 (34-63)	67 (34-86)
SERUM PSA (ng/mL)			
0-4.0	94 (92-96)	91 (87-93)	67 (34-86)
4.1-10.0	89 (86-91)	79 (74-83)	75 (69-80)
10.1-20.0	73 (68-78)	57 (48-64)	54 (44-63)*
>20.0	60 (49-69)	48 (36-59)	48 (36-59)*
POSTOPERATIVE GLEASON SCORE			
2-4	100	100	100
5	98 (96-99)	94 (90-96)	86 (78-92)
6	95 (93-97)	88 (83-92)	73 (59-82)
7 (All)	73 (69-76)	54 (48-59)	48 (41-56)
7 (3 + 4)	81 (77-84)	60 (53-67)	59 (51-65)
7 (4 + 3)	53 (44-61)	33 (22-43)	33 (22-43)
8-10	44 (36-52)	29 (22-37)	15 (5-28)
PATHOLOGIC STAGE			
Organ confined	97 (95-98)	93 (90-95)	84 (77-90)
EPE+, GS < 7, SM–	97 (94-98)	93 (89-96)	84 (70-92)
EPE+, GS < 7, SM+	89 (80-94)	73 (61-82)	58 (41-71)
EPE+, GS ≥ 7, SM–	80 (75-85)	61 (52-68)	59 (50-67)
EPE+, GS ≥ 7, SM+	58 (49-66)	42 (32-52)	33 (23-44)
SV+, (LN–)	48 (38-58)	30 (19-41)	17 (5-35)
LN+	26 (19-35)	10 (5-18)	0

From Han M, Partin AW, Pound CR, et al: Long-term biochemical disease-free and cancer-disease-free and cancer-specific survival following anatomic radical retropubic prostatectomy. Urol Clin North Am 28:555, 2001.[285]

CI, *Confidence interval;* EPE, *extraprostatic extension;* GS, *Gleason score;* LN+, *micrometastases to pelvic lymph nodes;* PSA, *prostate-specific antigen;* SM, *surgical margins;* SV+, *(LN–), involvement of seminal vesicles, negative lymph nodes;* TNM, *tumor-node-metastasis staging system;* –, *negative;* +, *positive.*

**Fourteen-year data.*

which information was obtained. In systematic review and meta-analysis that included 51 articles published between 2008 and 2011, Ficarra reported the incidence of urinary incontinence (control requiring no pad) following RARP ranged from 4% to 31% with a mean of 16%.[705] Patients with advanced age, large body mass index, comorbidities, lower urinary tract symptoms, and larger prostate volumes were more likely to experience incontinence. Several reports suggest that physician-based assessments underestimate the presence and severity of incontinence,[699,704,706] as patients were hesitant to mention difficulties of this nature to their physician. Bladder neck or anastomotic stricture occurs in approximately 12% (range, 5% to 20%) of patients[699] and may require dilatation or incision to improve urinary flow.

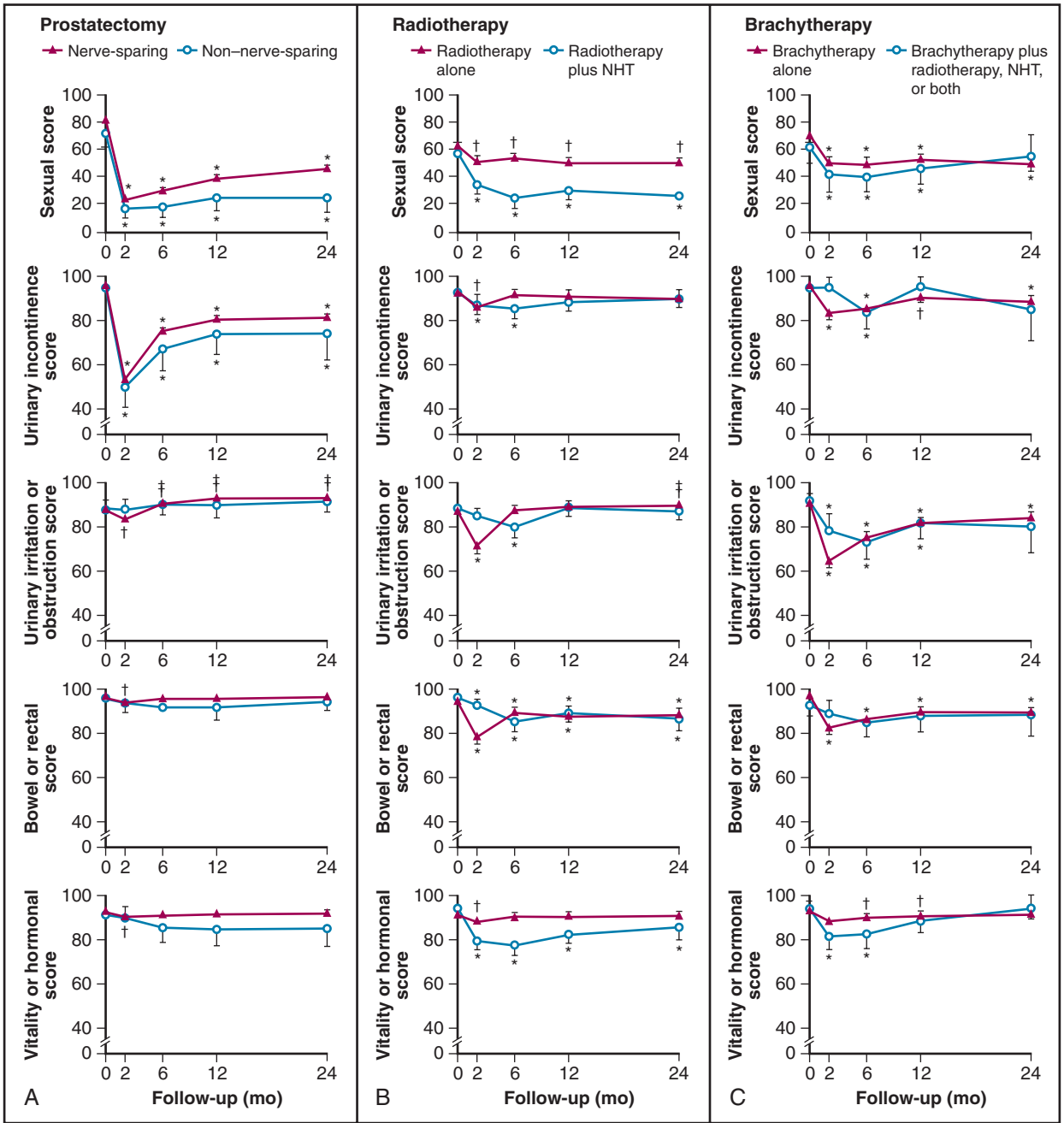
Until recently, there was little awareness of bowel dysfunction as a possible postoperative complication. However, health-related quality of life instruments indicated that one third of patients had impaired bowel function (e.g., diarrhea, rectal urgency),[704] and one in five experienced fecal incontinence.[703] These difficulties often were not appreciated through physician inquiry and reporting[704] and were substantially greater than the expected incidence in a similar age group. Additional research is necessary to determine the cause of this problem so that modifications of surgical technique may be sought to reduce the risk of this complication.

Before introduction of the nerve-sparing procedure, ED was uniformly encountered. However, it was possible to preserve potency once the autonomic innervation of the corpora cavernosa was delineated and the nerve-sparing modification of the RP was made. Walsh et al[701] reported that 68% of men retained potency, which was confirmed by Catalona et al (59%).[707] Patient age, T category, and excision or preservation of one or both neurovascular bundles correlated with the return of sexual function.[700] Population-based studies indicated that 21% (range, 11% to 27%) of patients were potent after RP,[699,701] and 97% of patients reported sexual dysfunction in a survey conducted by Litwin et al.[704] In systematic review and meta-analysis that included 31 articles published between 2008 and 2011, Ficarra reported the incidence of retained potency following RARP ranged from 54% to 90% at 12 months and 63% to 94% at 24 months.[708] Recovery of potency was influenced by age, baseline potency, comorbidities, and the extent of nerve sparing. RARP did appear to have a significant advantage in sparing potency compared to RRP.

Quality of Life

Following the development of validated instruments, such as the UCLA Prostate Cancer Index and the Expanded Prostate Cancer Index Composite (EPIC), quality of life (QOL) assessment has become an important component of posttreatment evaluation.[709,710] Litwin et al[711] were among the first to evaluate QOL in men treated for localized prostate cancer compared men with an age-matched population. Since that time, investigators have generally found that bowel dysfunction is worse following EBRT than after radioisotopic implant or RP.[712-714] This is typically evidenced by urgency, frequency, and bleeding. Urinary function is worse after RP, especially incontinence, although urinary morbidity following implant may be greater than EBRT during the first 12 months.[713,714] Sexual function was similar for RP and EBRT, mainly because of the increasing dysfunction 2 years to 5 years after EBRT, but better for implant patients.[713,714] Additionally, age and comorbidities affected QOL as did the delivery of multiple therapies, especially hormonal therapy. Patient report surveys appear to give a more accurate assessment as compared to physician or chart-based reporting.[704,706]

In a prospective series of 1201 men with localized prostate cancer, Sanda characterized the changes in QOL associated with RP, EBRT, and prostate brachytherapy (BT).[635] Each treatment modality had a negative impact on a man's QOL with a distinct pattern of change in the domains of urinary, sexual, bowel, and hormonal function. After RP, the frequency and severity sexual dysfunction was less severe when a nerve-sparing procedure was used. Urinary incontinence was common after RP with some recovery over time. Likewise, BT was associated with longer lasting urinary morbidity. Figure 53-15 illustrates the time course of onset and recovery for the various QOL domains following each treatment modality. In a French series of 435 patients undergoing RP (n = 127) or brachytherapy (n = 308), Buron described a similar time course of changes in QOL following primary therapy.[715] Impotence



Patient interview–completion rates

	Before treatment	Follow-up (mo)			
		2	6	12	24
No. patients	1201	1201	1201	1181	834
No. patients who completed the interview	1201	1133	1125	1088	730

D

Figure 53-15 **A** to **D,** Changes in quality of life after primary treatment for prostate cancer. The graphs show unadjusted changes in mean quality-of-life scores over time for each domain, stratified according to study group. Scores on the Expanded Prostate Cancer Index Composite domains range from 0 to 100, with higher values representing a more favorable health-related quality of life. In the prostatectomy group, non–nerve-sparing procedures consisted of wide excision of both neurovascular bundles. In the radiotherapy group, patients received either external radiation alone or external radiation with neoadjuvant hormone therapy (NHT). In the brachytherapy group, patients received either brachytherapy alone or brachytherapy in combination with NHT, radiotherapy, or both. *Asterisks* designate time points at which scores differed from those at pretreatment baseline by more than half a standard deviation and the comparison was significant ($p < 0.01$, to account for Bonferroni adjustment). *Daggers* designate time points at which differences from baseline were significant but were below the threshold of clinical relevance. *Double daggers* designate mean scores that showed improvement over pretreatment levels. Error bars represent 95% confidence intervals; confidence intervals were symmetric, but error bars are shown as one sided to avoid overlap with mean scores. **D,** Shown are the number of patients for whom sufficient time had elapsed after treatment to enter each follow-up period (including patients who were lost to follow-up) and the corresponding number who completed their prescribed follow-up interview at each time point.

From Sanda MG, et al: Quality of life and satisfaction with outcome among prostate-cancer survivors. N Engl J Med 358:1250–1261, 2008.

and urinary incontinence were more pronounced after RP whereas urinary urgency, frequency, and dysuria were more common after BT. In the Sanda report, patient satisfaction was associated with the change in symptom scores relative to baseline.[635] In a similar prospective study of 435 patients treated by RP, EBRT, or BT in Spain, Pardo reported greater sexual and urinary continence deterioration in patients undergoing RP however patients treated with BT or EBRT had significantly worse urinary irritative-obstructive scores and bowel symptoms.[716] These studies emphasize the importance of patient education and counseling before treatment decisions are made.

LOCALLY ADVANCED DISEASE

Surgery for Locally Advanced Prostate Cancer

Surgery is often more technically difficult in men with locally advanced disease. Among men with very high-risk factors such as a PSA >100 ng/mL, hydronephrosis or pelvic side wall fixation, the perioperative morbidity was much higher than men without these adverse features.[721] In carefully selected individuals and in the hands of experienced surgeons, the complication rate in series of patients with high-risk disease does not appear to be significantly worse than patients with lower risk disease.[722,723] Oftentimes, nerve sparing cannot be achieved leading to higher rates of impotence and urinary incontinence. Nearly 50% of patients will have findings indicating a need for postoperative RT or hormone therapy. In a pooled multiinstitution series of 1366 patients with high-risk disease from eight European centers, Briganti reported that only 505 (37%) had specimen confined disease at RP.[724] Half of the patients received either adjuvant hormone therapy, RT, or both following the RP.

Radiation Therapy

Locally advanced adenocarcinoma of the prostate includes clinical T3 or T4 and bulky T2c tumors. Because these patients have disease that is unlikely to be completely removed surgically the preferred treatment is radiation therapy.

Unfortunately the clinical outcome for such patients with radiation alone is poor with more than half of the patients developing clinically overt metastases by ten years.[245] In addition, given the ability of serum PSA posttherapy to monitor assessment of disease, data shows that the results of RT alone are poor with only approximately one third of the patients showing no biochemical failure at 5 years and approximately 10% at 10 years.[250]

Understanding the poor results of radiation alone, a number of clinical investigators have looked at approaches such as particle beam therapy with neutrons or protons (see the section on particle therapy), EBRT plus HDR brachytherapy with ^{192}I (see brachytherapy section), use of AD with radiation, and chemotherapy in addition to radiation. We will look at these approaches individually.

Androgen Deprivation Plus Radiation

It has been shown that reducing intracellular concentrations of dihydrogen testosterone through the use of AD can induce apoptotic regression of androgen-responsive prostate cancers.[725] Apoptotic regression of androgen-responsive prostate cancers thus, in the context of locally advanced prostate cancer, could help to reduce the primary tumor volume (i.e., cytoreductive therapy), which could improve local control and, therefore, decrease metastatic disease. It may also be helpful in the primary prevention of metastatic disease if used in the adjuvant setting. Extensive work has been done in the arena of AD for locally advanced disease. Although data was emerging showing the addition of estrogen therapy to radiation therapy improved tumor control, the first clinical study to evaluate this in a randomized way was RTOG study 83-07. This study evaluated the efficacy and toxicity of megestrol and diethylstilbestrol (DES) in a Phase II randomized study where patients were assigned to either agent for 2 months prior to and during EBRT.[726] Both the megestrol and DES in addition to radiation resulted in a high likelihood of clearance of the primary tumor (94% to 97%) and local regional tumor control (93% and 94%). Unfortunately there were significant side effects especially in regards to the DES with cardiovascular events. With the development of luteinizing hormone-releasing hormone (LHRH) agonists and nonsteroidal anti androgens, the focus of the investigations within the RTOG changed to these agents.[727] RTOG study 85-19, which used these agents for patients with locally advanced disease, found them to be well tolerated and still resulting in a high rate of tumor clearance (100%).[727]

With a clear indication of a potential benefit by AD therapy to radiation for locally advanced cancers, a number of prospective randomized trials were developed both in the United States through the RTOG and in western Europe through the EORTC. These trials addressed two questions with regard to the use of androgen suppression and radiation. The first question evaluated was the adjuvant question; could radiation therapy and adjuvant AD result in a decrease in distant metastases and increase OS? This question was addressed by RTOG 85-31 (Table 53-13).[728] In this trial patients with locally advanced disease were randomized to EBRT plus indefinite goserelin (started immediately after RT was complete) versus EBRT alone. Treatment included whole pelvis irradiation to 44 Gy to 46 Gy and a boost of 20 Gy to 25 Gy bringing the total prostate dose to 65 Gy to 70 Gy. Ten-year results (Table 53-13) show a benefit across all endpoints including OS. During the same time frame the EORTC performed their own adjuvant trial (22863)[729,730] for locally advanced patients and a small RT and immediate goserelin for 3 years (goserelin started with initiation of RT). The RT included whole pelvis irradiation to 50 Gy with a boost of 20 Gy at 2 Gy per fraction. Results of this trial also showed a benefit to all endpoints including bNED, DFS, CSS, and OS[730] (Table 53-13).

During this same time frame the RTOG addressed the neoadjuvant question with trial 86-10.[731] Could neoadjuvant total androgen suppression (TAS) decrease the tumor burden and thus increase local control with RT? In this trial, patients with locally advanced nonmetastatic disease were randomized to RT alone versus neoadjuvant TAS (flutamide 250 mg three times a day and goserelin acetate monthly for 4 months)[731] for 2 months before and 2 months during RT. Radiation therapy volumes used whole pelvis RT to 45 Gy and a boost of 20 Gy to 25 Gy delivering 65 Gy to 70 Gy to the prostate. Results of this trial have shown statistical improvements in bNED, DMFS and CSS (Table 53-13), but no OS benefit to date.[9]

Another attempt to address the neoadjuvant AD question was performed by the Trans-tasman Radiation Oncology Group (TROG) with protocol 96-01. Patients on this trial had locally advanced disease and were randomized to RT alone (66 Gy in 33 fractions to the prostate and seminal vesicles only) versus 3 months of TAS with goserelin and flutamide 250 mg three times a day starting 2 months before RT versus 6 months of total androgen suppression starting 5 months before RT.[732,733] Five year results revealed a benefit to the six months of total androgen suppression plus RT over RT alone in terms of bDFS, DMFS, CSS and local control. (Table 53-13) The three months of total androgen suppression showed a benefit in terms of bNED and local failure, but not DMFS or CSS.[732,733]

Although there exists a large body of class I evidence to support the routine use of combined EBRT and AD in locally advanced and high-risk prostate cancer, there is scant prospective evidence to support the role of RP. Despite this, there is growing enthusiasm for RP in the management of high-risk disease. One challenge in making comparisons between surgery and RT for locally advanced disease is the ever-increasing use of risk groupings to classify patients. The high-risk category of disease is more commonly determined by Gleason score and less frequently clinical T-category.[717] Furthermore, the specificity of the DRE for clinical staging is low with an approximate 20% to 25% rate of downstaging in RP series.[718] In carefully selected men, the risk of complications is low with RP[718,719]; however, the frequency with which patients will need additional therapies such as adjuvant EBRT is high.[719,720]

TABLE 53-13 Phase III Trials of External Beam Radiation Therapy with or without Adjuvant Hormone Therapy for Locally Advanced Prostate Cancer

Trial	Arms	Median F/U	bNED 5 yr	bNED 10 yr	DMF Survival 5 yr	DMF Survival 10 yr	CSS 5 yr	CSS 10 yr	OS 5 yrs	OS 10 yrs
RTOG 85-31	I: RT + Goserelin	7.6 years (11 yrs	62%	31%	85%	76%	91%	84%	76%	49%
n = 977	(indefinite)	living patients)	44%	23%	71%	61%	87%	78%	71%	39%
	II: RT alone		*p* = <.0001		*p* = <.0001		*p* = .0052		*p* = .002	
EORTC 22863	I: RT + 3 yrs GnRH	9.1 years	76%	38%	90%	51%	94%	89%	78%	58%
n = 415	II: RT alone		45%	18%	71%	30%	79%	69%	62%	40%
			p < .0001		*p* = <.0001		*p* = .001		*p* = .0004	
RTOG 86-10	I: 4 mo TAS + RTII.	8.7 years*	36%	35%	66%	65%	85%	23%	73%	43%
n = 456	RT alone	7.3 years	15%	20%	59%	53%	80%	36%	71%	34%
			p = <.0001		*p* = .006		*p* = .01		*p* = .12	
TROG 96.01	I: RT alone	10.6 years	38%	26%	81%	79%	91%	78%	__	58%
n = 818	II: 3 mo TAS + RT		52%	40%	78%	82%	92%	81%	__	63%
	III: 6 mo TAS + RT		56%	47%	87%	89%	94%	89%	__	71%
			p = .0009, 3 mo. *p* < .0001, 6 mo.		*p* = .0006, 6 mo.		*p* = .0002, 6 mo.s)		*p* = .0005, 6 mo.	

bNED, *Biochemical no evidence of disease;* DMF, *distant metastasis free;* CSS, *cause specific survival;* NS, *not specified;* OS, *overall survival.*
**11.9 years living.*

Given the evidence of the benefit of AD and radiation therapy in controlling locally advanced adenocarcinoma of the prostate, at least three cooperative trials have examined the optimal duration of AD. The RTOG, the EORTC, and the Canadian PCS IV trial posed this question in three different phase III randomized trials (Table 53-14). RTOG protocol 92-02 randomized locally advanced patients to 4 months TAS (flutamide 250 mg three times a day plus goserelin), 2 months neoadjuvantly and 2 months concurrently with whole pelvis RT (WPRT) 44 Gy to 46 Gy and a boost to the prostate delivering 65 Gy to 70 Gy to the prostate verses the same treatment plus 2 years of additional goserelin.[734,735] Ten-year follow-up is now available for this trial and shows a benefit to the long-term androgen deprivation (LTAD) in bNED, DMFS, and CSS, but not OS except for patients with Gleason Scores of 8 to 10 who did show an OS benefit. The EORTC trial 22961 also looked at the question of duration of AD. In this trial patients were randomized to RT (WPRT to 50 Gy plus a 20-Gy boost totaling 70 Gy to the prostate) and 6 months of Total Androgen Suppression (TAS) (flutamide 250 mg three times a day or bicalutamide 50 mg) and an Luteinizing Hormone Releasing Hormone (LHRH) agonist starting with RT versus the same treatment and an additional 2.5 years of LHRH therapy.[736] Five-year OS and CSS were both statistically improved with the addition of the 2.5 years of LHRH therapy (Table 53-14). Subsequently the Canadian PCS IV trial examined 18 months compared with 36 months in patients with locally advanced disease.[737] In this trial, patients received 1 month of neoadjuvant TAS (bicalutamide and goserelin) then concurrent and adjuvant goserelin for a total of 18 compared with 36 months in addition to RT (44 Gy in 4.5 weeks "whole pelvis" and a prostate dose of 70 Gy in 7 weeks). With a median follow up of 6.4 years, there was no significant difference in prostate CSS or OS between the two arms.[737]

Based on the available data to date, patients with locally advanced nonmetastatic adenocarcinoma of the prostate should receive neoadjuvant and concurrent AD and long-term AD of an additional minimum of 14 months (totaling 18 months of AD).

Toxicity of Androgen Deprivation Therapy

With the need to add AD to RT for patients with locally advanced prostate cancer clearly established, the question of toxicity has to be addressed. Virtually all patients placed on LHRH therapy will have hot flushes, sexual dysfunction, and decreased libido as a result of the decrease in testosterone. In addition with longer duration LHRH therapy, patients can develop increased fat mass, decreased lean body mass, and increased waist circumference.[738] Understanding concerns about weight gain and resultant health issues such as diabetes and cardiovascular disease, several authors have looked at the large randomized trials to understand whether there is truly an increase risk of fatal cardiovascular events with RT and LHRH therapy.[730,731,739] None of these trials, which include RTOG 85-31, 86-10, and the EORTC trial 22863, have shown an increase in fatal cardiovascular events for the RT and AD arm. The follow-up in these trials is long (approximately 10 years on average for living patients) and represent close to 2000 randomized patients. Thus, if there was a significant risk of increased fatal cardiovascular events, it should have been detected. Furthermore, the EORTC protocol 22961 and the RTOG protocol 92-02 showed no difference in fatal cardiac events between the short-course AD versus the longer-term AD arms.[15] Yet some authors have challenged these results.[740,741]

Careful analysis of metabolic changes that occur with 12 months of LHRH therapy has been performed by at least one group.[738] This data reveals a "metabolic syndrome" for LHRH therapy that consists of increased subcutaneous fat, increased serum high-density lipoprotein (HDL), increased adiponectin levels, no change in C-reactive proteins, and insulin sensitivity. This is different than "the metabolic syndrome,"[738] which is characterized by increased visceral fat, decreased serum HDL, decreased adiponectin levels, increased C-reactive proteins, and insulin resistance.

Although there are unquestionably metabolic changes that occur with AD therapy, the LHRH drugs do not appear to cause changes that lead to a significant increase in cardiovascular deaths. Yet, given the weight gain and other changes

TABLE 53-14 Phase III Trials of Duration of Adjuvant Hormone Therapy with External Beam Radiation Therapy for Locally Advanced Prostate Cancer

Trial	Arms	Median F/U	bNED 5 Years	bNED 10 Years	DMF Survival 5 Years	DMF Survival 10 Years	CSS 5 Years	CSS 10 Years	OS 5 Years	OS 10 Years
RTOG 92-02	I: 4 mos TAS + RT	11.3 years (living pts)	44.5%	31.9%	83%	77.2%	91.2%	83.9%	78.5%	51.6%
n = 1554	II: 4 mos TAS + RT + 2 yrs GnRH	11.3 years (living pts)	72%	48.1%	88.5%	85.2%	94.6%	88.7%	80.0%	53.9%
			p = <.0001		*p* = <.0001		*p* = .0042		*p* = .3590	
EORTC 22961	I: RT + 6 mos TAS	6.4 years	—	—	—	—	95.3%	—	81%	—
n = 1113	II: RT + 6 mos TAS + 2.5 yrs GnRH		—	—	—	—	96.8%	—	84.7%	—
							p = .002		*p* = <.05	
Canadian PCS IV	I: 1 month TAS + RT + 35 months GnRH	6.4 years	—	—	—	—	97.6%	87.2%	92.1%	63.6%
n = 630	II: 1 month TAS + RT + 17 months GnRH		—	—	—	—	96.4%	87.2%	86.8%	63.2%
							p = .838		*p* = .429	

bNED, *Biochemical no evidence of disease;* DMF, *distant metastasis free;* CSS, *cause specific survival;* NS, *not specified;* OS, *overall survival.*

caused by LHRH therapy, caution is the best approach when considering these therapies in patients with preexisting serious cardiovascular medical histories. Consultation with the patient's cardiologist should be considered.

The other major metabolic concern of LHRH therapy is changes in bone density. Bone loss and the need for baseline bone mineral density (DEXA) scanning is well accepted.[742] Recommended treatment for this potential bone loss includes vitamin D supplements (800 to 1000 IU daily) and calcium supplements (≥1200 mg/day). DEXA scanning should be repeated at 1 year while on LHRH therapy and then every 2 years or as clinically indicated subsequently.[742] Bisphosphonate therapy should be seriously considered for patients going on LHRH therapy if their baseline DEXA scan is consistent with osteoporosis.[742]

Scope of Radiation Therapy

Treatment volumes for locally advanced prostate cancer have included the prostate and seminal vesicles plus a margin along with the pelvic lymph nodes. The vast majority of the large randomized trials have treated in this fashion using doses to the lymph nodes of 45 Gy to 50 Gy (four-field box technique and dose prescribed to isocenter) with a boost to the prostate totaling approximately 70 Gy (isocenter dose).[728,729,731,735,736] Today there is little doubt that the prostate/seminal vesicle dose was too low in these trials because multiple data sets have shown a benefit from dose escalation for these patients.[743] The bigger question regarding the scope of the radiation therapy for this population is whether one needs to treat the pelvic lymph nodes? RTOG 94-13 was designed to answer this question. This trial randomized 1323 patients to whole pelvis radiation therapy (WPRT) versus prostate only radiation therapy (PORT) and neoadjuvant 4 months of TAS verses adjuvant 4 months TAS.[632] Results of this trial showed no difference in WPRT verses PORT and no statistical difference between neoadjuvant TAS versus adjuvant TAS. Unfortunately this trial did show an unexpected interaction between the timing of the TAS and the scope of the radiation therapy.[632] PFS was better with the WPRT and neoadjuvant TAS arm versus the other three arms. But this trial was unable to answer, in a definitive way, the WPRT-versus-PORT question because of the unexpected interactions. Therefore, the question of WPRT versus PORT still needs to be evaluated in a prospective trial. Currently the RTOG is examining the pelvic lymph node radiation question in RTOG 09-24.[744] Until we have more data, WPRT with neoadjuvant and concurrent TAS, and long-term LHRH therapy for at least 14 additional months, remains the standard of care for patients with locally advanced disease.[728,729,735-737,744]

Given the data showing a significant advantage to RT and AD, many practitioners argued that the benefit seen was solely the result of the AD and perhaps RT was not needed. This question has been addressed by two Phase III randomized trials (SPCG-7/SFUO-3) and the Canadian Intragroup Trial. Forty-seven Scandinavian centers participated in the SPCG-7/SFUO-3 trial accruing patients with locally advanced prostate cancer. Patients were randomized to TAS for 3 months followed by AD with flutamide indefinitely versus the same AD plus RT.[745] The addition of the radiation statistically increased the 10-year prostate CSS compared to the AD-alone arm and statistically increased OS with acceptable toxicity rates.[745] The Canadian Intergroup Trial looked at the same question in more than 1000 patients with T3 or T4 tumors or T2 tumors with either PSA >40 ng/mL or PSA >20 ng/mL and Gleason Score 8 disease. All patients received lifelong LHRH agonist or orchiectomy. They were then randomized to RT ("whole pelvis" to 45 Gy in 25 fractions and subsequent boosting to the prostate to 65 Gy to 69 Gy total) or no other treatment.[746] This data also showed a statically significant OS and DSS advantage to AD and RT over AD alone with minimal toxicity.[747] Thus, there should be no question as to the value of radiation therapy in addition to AD therapy for these patients.

Designing the treatment of nodal volumes in addition to the prostate/seminal vesicle volumes has been an area of some confusion, especially in light of the use of IMRT. Even RTOG GU (genitourinary) radiation oncology "experts" had trouble agreeing on such volumes.[748] In an effort to standardize the correct anatomical pelvic lymph nodes to be covered for locally advanced patients, RTOG GU radiation oncologists developed a consensus on the clinical tumor volume (CTV) for pelvic lymph nodes.[749] The nodal groups to be included extend from the L5-S1 interspace (i.e., low common iliac lymph nodes) to the top of the pubic symphysis (obturator lymph node region). Presacral lymph nodes (subaortic only, S1-S3) are also included.

These volumes correlate well with the nodal volumes typically treated with the four-field "box" technique used in all the randomized trials previously mentioned.[749]

Toxicity of Radiation Therapy

Treatment of the pelvic lymph nodes and boosting the primary (the prostate with or without seminal vesicles) is not without toxicity. A review of late sequelae of RTOG protocols 85-31, 86-10, and 92-02 evaluating almost 3000 patients with a median follow-up of 10.3 years for living patients has been reported.[750] All patients received WPRT to approximately 45 Gy and a prostate boost to approximately 70 Gy plus or minus short-term androgen suppression or long-term androgen suppression. The risk of late GI grade-3 or higher toxicity was 4%, 1%, and 3% for RT alone, short-term AD and RT, and RT plus long-term AD, respectively. Late GU grade-3 or higher toxicity was 9%, 5%, and 6% for RT alone, short-term AD plus RT, and RT plus long-term AD, respectively.[750] Grade-5 (lethal) toxicity occurred in 3 patients out of 2906 treated for a risk of approximately 0.1%. Data on late toxicity has been reported for the Phase III Canadian Intergroup Trial (AD versus AD plus RT) showing minimal additional toxicity via the use of radiation in patients with locally advanced prostate cancer.[746,747] These data reinforce the safety of radiation for locally advanced patients and are consistent with other randomized trials of RT plus AD.[730,736]

Role of Adjuvant Chemotherapy

Two randomized trials have shown statistical improvements in survival for patients with metastatic hormone refractory prostate cancer[751,752] with the addition of docetaxel-based chemotherapy. Given these results the RTOG embarked on a randomized trial (99-02) for patients with high-risk nonmetastic prostate cancer. Patients were randomized to RT with long-term AD compared with RT with long-term AD with paclitaxel, estramustine, and oral etoposide.[753] The trial was closed early because of toxicity particularly estramustine-based increased thromboembolic events.[753] Subsequently RTOG protocol 05-21 was opened to test the chemotherapy question. This trial randomized patients with "high-risk" nonmetastatic prostate cancer to RT with long-term AD compared with RT with long-term AD with docetaxel and prednisone. This trial has met accrual and we anxiously await the results. Until we have these results, there is no defined role for cytoxic chemotherapy in addition to RT with long-term AD for patients with locally advanced prostate cancer.

Regional Lymph Node Positive Disease (pN+)

Positive regional (i.e., pelvic) lymph nodes in patients with prostate cancer is a negative prognostic indicator.[754] Although some authors have reported significant long-term survivors from aggressive surgery or radiation approaches,[755,756] the majority of these patients will develop metastatic disease. This fact suggests that occult systemic metastasis likely exist at the time of diagnosis and supports the concept of systemic treatment in addition to any local or local regional therapy. Two data sets are now mature and help the treating oncologist to select appropriate treatment for such patients. The first is a subset analysis of RTOG protocol 85-31.[271] This trial discussed previously, randomized patients with locally advanced adenocarcinoma of the prostate plus or minus pN+ to RT alone (WPRT + a boost to the prostate) versus RT with LHRH indefinitely.[728] One hundred and seventy three patients in this trial had pN+ disease (98 received RT and LHRH and 75 received RT alone). An update of this trial with a median follow up of 6.5 years (9.5 years for living patients) showed a statistical improvement in OS, DSS, and freedom from distant metastasis in favor of RT with LHRH therapy.[757]

The Eastern Cooperative Oncology Group (ECOG) conducted a Phase III trial for patients with pN+ disease, following radical prostatectomy. They were randomized to observation versus immediate hormone therapy (indefinite LHRH or bilateral orchiectomy). The trial closed because of poor accrual, but 98 patients were entered and randomized.[758] At a median follow up of 7.1 years patients receiving immediate hormone therapy had an increase in OS.

Neither of these clinical trials provides the type of level I data necessary to know for certain which is the best approach for pN+ patients. Yet both point to the need for systemic therapy. RTOG protocol 96-08 (which randomized pN+ patients to AD alone versus AD with RT) closed because of poor accrual so the question of the additional benefit of pelvic RT over AD alone remains unclear. It is likely not answerable with a prospective randomized trial. Therefore, given the data available, patients with pN+ disease should be seriously considered for AD in addition to local or regional therapy with radiation or surgery.

Postoperative Radiotherapy

Approximately one third of men with prostate cancer undergo prostatectomy as initial therapy.[759,760] Among patients treated at high-volume academic centers, one quarter to one third are at risk for treatment failure within the ensuing 10 years.[761-764] Postoperative RT is usually administered in three curative situations: the presence of adverse risk factors after complete surgical resection, subclinical disease identified solely by an elevated postoperative serum PSA, or clinically apparent tumor recurrence in the prostatic fossa. When strictly applied, the term *adjuvant* refers to treatment administered to reduce the risk of recurrence when all clinically detectable disease was removed surgically, and this term should be reserved for patients with an undetectable postoperative PSA level.[765] When there is a detectable PSA level after surgery or there is clinical evidence of disease confined to the fossa, the therapeutic goal changes to one of eradicating residual or recurrent cancer, and treatment administered under this condition is referred to as *salvage* therapy.[765]

Adjuvant Radiotherapy

The rationale for adjuvant RT is based on the premise that residual disease in the prostatic fossa is the principal cause of treatment failure,[766] that a substantial number of cancer cells may be present before serum PSA is detectable, and that the greatest opportunity for cure exists when they are fewest in number and localized. Prostate cancer may become more aggressive over time,[767] and this implies that earlier intervention may improve local tumor control and prevent subsequent metastases. Consensus-derived clinical principles encourage preoperative education of patients about adverse pathology findings that increase the risk of cancer relapse and provide indication for postoperative therapy.[765]

Certain factors are associated with a greater risk of disease relapse after prostatectomy. These include higher preoperative PSA,[762,768-770] greater Gleason score,[761,762,768-771] a positive surgical margin,[762,768-770] tumor extension through the prostatic capsule (i.e., EPE),[761,762,771] SVI,[762,768,769,771] and pelvic LNI.[762,768,771] Traditionally, EPE, SVI, or a positive surgical margin are the factors on which a recommendation for adjuvant RT is made.[765,772,773] These risk factors may be combined to provide more individualized estimates for postoperative disease relapse.[761,762,768]

There is an abundant literature of adjuvant RT observational series, and Table 53-15 summarizes outcomes from selected reports.[774-780] It is generally acknowledged that RT improves local tumor control compared to prostatectomy alone,[774,776,778,779] which is reported in ~99% and ~92% of patients with adverse risk factors at 5 and 10 years after RT,

TABLE 53-15 Selected Case Series of Radical Prostatectomy with or without Adjuvant RT

	Local Control, %		Disease-Free Survival, %		Metastasis-Free Survival, %		Overall Survival, %		
Author	**RP**	**RP + RT**	**RP**	**RP + RT**	**RP**	**RP + RT**	**RP**	**RP + RT**	**Endpoint**
Schild[774]	83	100*	40	57*	~92	~92	~92	~92	5-yr actuarial
Valicenti[775]	92[C]	100[C]	55	89*	100[C]	100[C]	100[C] †	100[C] †	5-yr actuarial
Leibovich[776]	≥84	100*	59	88*	≥84	100*	93	97	5-yr actuarial
Petrovich[777]	—	—	46	53	—	—	74	81	10-yr actuarial
Cozzarini[778]	63	93*	31	69*	75	88*	80†	93†*	8-yr actuarial
Anscher[779]	53	89*	30	50	55	62	48†	63†	15-yr actuarial
Boorjian[780]	82	97*	45	63*	91	93	84	87	10-yr actuarial

C, *Crude rate;* NS, *specific value not stated;* RP, *radical prostatectomy;* RT, *radiotherapy;* yr, *year.*
**Statistically significant improvement with RT.*
†*Cause-specific.*

TABLE 53-16 Randomized Clinical Trials of Radical Prostatectomy with or without Adjuvant RT

			Freedom from Biochemical Relapse, %		Local Control, %		Clinical Disease-Free Survival, %		Metastasis-Free Survival, %		Survival, %		
Trial	**Patients**	**Accrual**	**RP**	**RP + RT**	**RP**	**RP + RT**	**RP**	**RP + RT**	**RP**	**RP + RT**	**RP**	**RP + RT**	**Endpoint**
ARO 9602[769]	268	1997-2004	54	72*	NS	NS	NS	NS	NS	NS	95[c]	97[c]	5-yr actuarial
EORTC 22911[788,789]	1005	1992-2001	53	74*	85	95*	81	91*	94	94	93	92	5-yr actuarial
			41	61*	83	93*	65	70	89	90	81	77	10-yr actuarial
SWOG 8794[766,784,786]	425	1988-1997	44	72*	78[c]	92[c] *	70	84*	82	87	90	91	5-yr actuarial
			25	51*	78[c]	92[c] *	49	70*	61	71*	66*	74*	10-yr actuarial

ARO, *Arbeitsgemeinschaft Radiologische Onkologie;* [c], *crude rate;* EORTC, *European Organisation for Research and Treatment of Cancer;* NS, *specific value not stated;* RP, *radical prostatectomy;* RT, *radiotherapy;* SWOG, *Southwest Oncology Group.*
**Statistically significant improvement with adjuvant RT.*

respectively.[774-780] The 5-year and 10-year local control after RP alone is ~85% and ~61%.[774-780] Clinical and biochemical relapse-free rates are also improved with adjuvant RT,[774-776,779-781] which generally reduces the relative risk of relapse by 43% to 88%.[775,776,780] Nonetheless, an estimated one quarter of patients with biochemical relapse only after adjuvant RT has persistent cancer in the prostatic fossa,[782] and this suggests that improved target definition, localization, or dose escalation may improve outcomes.

The impact of adjuvant RT on metastasis-free, OS, and CSS is not clear from the observational studies, because inconsistent findings are reported (Table 53-15).[774,775,777-780] However, this may be the result of differences in patient selection, time trends in disease presentation and therapeutic approach, inadequate patient numbers for conclusive statistical analysis, insufficient follow-up, and the confounding effect of androgen suppression therapy. Nonetheless, reduced metastases and death as a result of prostate cancer rates were observed in some studies with longer follow-up.[778,779,783]

Three randomized clinical trials evaluated adjuvant RT (Table 53-16), and these studies provide the highest level evidence on outcomes. Southwest Oncology Group (SWOG) trial 8794 was the first trial conducted among patients at increased risk of disease relapse (i.e., those with EPE, SVI, or positive surgical margin).[766,784-787] This trial was designed primarily to determine whether adjuvant RT improved metastasis-free survival. Long-term follow-up demonstrated that adjuvant RT improved metastasis-free and OS compared to RP alone with therapy at physician discretion at disease relapse.[784,786] Analysis of metastasis-free survival according to various patient subsets provided no evidence that any particular type of patient should not receive RT.[786] For patients assigned to adjuvant RT, the relative risk of death was reduced by 28% and median survival duration was extended by nearly 2 years.[786] This observation supported the hypothesis that locally persistent cancer contributes to delayed metastatic spread as proposed in the context of primary RT.[787] Additionally, adjuvant RT in this trial was associated with improved freedom from biochemical and local tumor relapse, and reduced use of salvage androgen suppression.[784]

EORTC trial 22911[788-790] enrolled patients with the same characteristics as those of SWOG 8794.[784,786] However, this trial was designed primarily to assess Biochemical Progression Free Survival (bPFS) which was improved in patients assigned to immediate adjuvant RT compared to treatment delayed until disease relapse (Table 53-16). A statistically significant difference favoring adjuvant RT was also noted for locoregional tumor control, and for use of salvage therapy (22% versus 48% by 10 years).[789] Adjuvant RT improved b-PFS in all patient subsets,[789] which did not support a previous conclusion of lack of benefit in margin-negative patients.[790] Although between-group differences in death from prostate cancer or from other causes, or in the incidence of metastases were not observed, the trial lacked a sample size sufficient to identify any such differences.

Although patients with a detectable postoperative PSA level were included in SWOG 8794 (34%) and EORTC 22911 (29%), only patients with an undetectable PSA were evaluated

in the German Cancer Society Arrbeitsgemeinschaft Radiologische Onkologie (ARO) trial 9602 (Table 53-16).[769] As with EORTC 22911, this trial was designed to determine whether adjuvant RT improved b-RFS compared to initial observation. The risk of biochemical relapse was reduced from 46% at 5 years to 23% in patients treated with adjuvant RT, which met the test of significance for the primary endpoint. The trial was not designed to evaluate clinical RFS and OS, so it is unlikely that longer patient follow-up will identify differences in these endpoints.

Studies of adjuvant RT include patients with varied characteristics, so a natural line of inquiry is whether RT benefits all patient subsets. It appears that patients with positive surgical margins,[769,778,779,784,789,790] extraprostatic tumor extension,[769,778,779,784,789,790] SVI,[779,784,789] and possibly pelvic node involvement[778,791,792] derive the greatest benefit. A beneficial effect exists irrespective of Gleason score[769,789,790] and postoperative PSA level,[766,789] or when margins are negative[784,789] or EPE or SVI is absent.[769,789] Inconsistent conclusions from the literature are likely explained by variations in pathology interpretation,[790] patient selection bias, and the small number of patients or events under study. An inability of statistical analysis to identify a significant effect in some studies should not be interpreted necessarily as lack of benefit.

The role of androgen suppression with adjuvant RT is not adequately studied. RTOG 8531 included a subset of prostatectomy patients who were assigned to adjuvant RT or RT with long-term androgen suppression.[793] Improved outcomes were observed with androgen suppression, but such a subset analysis might be considered exploratory rather than definitive. An attempt to study this further was made in RTOG trial P-0011, but it closed prematurely because of inadequate patient accrual. Nonetheless, this issue is being addressed in ongoing trials conducted by the Medical Research Council PR10[794] and the EORTC trial 22043-33041. Androgen suppression alone is the mainstay of adjuvant therapy for pelvic node-positive disease,[795] whereas the addition of RT remains controversial.[778,791,792] An attempt by RTOG randomized trial 9608 to investigate this did not meet with successful accrual, so definitive evidence of benefit is lacking.

Several organizations provide guidelines for postoperative management.[765,772,773,796,797] NCCN (www.nccn.org) and ASTRO/AUA guidelines[765] support adjuvant RT when adverse pathology findings are noted. This view is endorsed by some,[773] and others recommend a discussion between patient and physician,[772,796] or do not advise its routine use.[797]

Salvage Radiotherapy

Biochemical Relapse. The serum half-life of PSA is 3.1 days, so PSA should be undetectable ≥4 weeks after successful prostatectomy. The AUA defines biochemical relapse as PSA ≥0.2 ng/mL with a subsequent value >0.2 ng/mL.[800] Biochemical relapse should prompt a thorough discussion of salvage therapy,[765] yet some suggest that two successive values ≥0.4 ng/mL more strongly correlates with clinically significant disease progression.[801] It is important to note that the efficacy of salvage RT is greatest when PSA is the lowest,[802] and this may help inform the discussion.

The natural history of biochemical relapse varies, and this contributes to discussions about its prevention (e.g., adjuvant therapy) and management. Based on PSA response to salvage RT[766,804-810] and observations from MRI, most such patients have residual cancer in the prostatic fossa.

The kinetics of postoperative PSA (e.g., the PSA doubling time [PSAdt]) has been investigated as a predictor of clinical relapse and mortality.[814-817]) The PSA Working Group provided guidelines for PSAdt calculation, and these include using ≥3 PSA values that are ≥0.2 ng/mL during the past 12 months, values that are increasing only, and values obtained in a setting where testosterone is stable (i.e., not recovering from prior androgen suppression).[818] The relationship of postoperative PSAdt to clinical relapse and mortality exists on a continuum, which may account for the various prognostic groupings that appear in the literature.

Biochemical relapse often prompts a desire to identify the site of disease relapse, despite a typically normal digital rectal examination.[819] Conventional gray-scale TRUS has limited diagnostic accuracy,[820,821] so it should not be used routinely. Although it may be useful to direct prostatic fossa biopsy, biopsy results do not influence significantly the outcome of salvage RT[822-824] because a negative biopsy does not exclude local recurrence and a positive biopsy does not necessarily improve RT outcome. Color and power Doppler TRUS and intravascular microbubble contrast improves accuracy,[825,826] but its role in diagnosis and decision making remains undefined.

Conventional pelvic with or without abdominal computed tomography findings are often non-specific or normal until PSA is substantially elevated.[827-832] Dotan et al constructed a predictive nomogram that may be used to select patients in whom the yield is greatest.[833]

PET uses various radiotracers for cancer imaging, integrated with CT to enhance anatomical localization. 18F-FDG may be used,[834] but 11C-choline may be a more promising agent.[835-838] Radiotracer avidity is most common in nodal, prostatic fossa, and osseous sites, with greater detection rates at higher PSA levels (>1.4 ng/mL),[835-838] and in patients with larger (>1 cm) volume recurrence,[836] or with prior seminal vesicle or pelvic node involvement.[837]

MRI with external and endorectal coil is a useful method to identify postoperative intrapelvic tumor recurrence. A prostatic fossa tumor mass appears iso-intense on T-1 sequences, hyper-intense on T-2, and is early-phase gadolinium enhancing. Endorectal MRI has excellent diagnostic sensitivity (84% to 95%), specificity (89% to 100%), and accuracy (86% to 94%)[841-845] that directly correlates with serum PSA level and prostatectomy histopathology.

Salvage RT Outcomes after Biochemical Relapse. The outcome of salvage RT is described in more than one hundred observational case series reports[765] and a systematic review,[848] but randomized clinical trial results are largely lacking. These series (Table 53-17) provide some insight into outcomes,[780,804-810,816,822,849-855] but cautious interpretation is needed because RT was not administered under ideal conditions (i.e., low PSA level) in all cases. Nonetheless, a substantial proportion of patients had an initial biochemical response,[804,806,809] which suggests that incomplete surgical excision of the cancer is the source of biochemical relapse in most patients. Improved diagnostic evaluation (e.g., endorectal MRI) and IMRT to higher than conventional doses yields promising results[854,856,857] that may be enhanced further with IGRT localization.[858,859] Therefore, the results observed previously may not reflect outcomes expected at present.

Gleason score,[805,807,809,810,816,849,853,854,860] tumor DNA ploidy,[853] persistently detectable postoperative PSA,[805,850] PSA level before RT,[804,806,809,810,816,822,852,853,855,860] PSAdt postoperatively,[806,810,816,822,860] surgical margin status,[810,816] SVI,[804,806,808,816,850,853] pelvic nodal involvement,[810] and delay in initiation of RT[860] are closely associated with the success of salvage RT.

Prognostic factors may be combined to estimate the likelihood that sustained RFS will follow salvage RT.[810,853] Stephenson et al used prognostic factors in a proportional hazards regression to develop a nomogram predictive of RT outcome (Figure 53-16).[810]

Androgen suppression may be given before, during or after salvage RT, but it has been used typically for 2 to 3 months before and then concurrent with RT. Outcomes are presented

Consensus recommendations regarding the selection of adjuvant RT compared with observation with early salvage RT does not exist presently. Some case-controlled series support the notion that adjuvant RT yields improved outcomes,[798] and this gains some support from SWOG 8794.[786] However, these conclusions are not definitive, so the Medical Research Council study PR10,[794] Trans-Tasman Radiation Oncology Group #08.03, Groupe d'Etude des Tumeurs Uro-Genitales, and the Federation Nationale des Centres de Lutte Contre la Cancer are conducting randomized clinical trials to address this issue.

Further guidance may be derived from more individualized estimates of relapse risk in association with male life expectancy.[768,799] The GPSM scoring algorithm (Score = [prostatectomy Gleason score] + [+1 if preoperative PSA 4-10, +2 if PSA 10.1-20, +3 if PSA > 20] + [+2 if seminal vesicle or node involvement] + [+2 if positive surgical margin]) sets out categories of PFS and CSS estimates after prostatectomy.[768] Patients with GPSM score ≥10 are at greater risk for early biochemical relapse and for death from prostate cancer, so patients with greater life expectancy (e.g., ≥10 years) may also benefit most greatly from adjuvant RT. This context may be used to frame a discussion with the patient that balances competing perspectives and uncertainties.

There is the suggestion that low PSA levels result from residual benign prostatic tissue. This does not appear to contribute significantly to biochemical relapse.[803]

Biochemical relapse, however, does not translate universally into clinical expression of disease or excess mortality. A persistently elevated PSA after prostatectomy,[811] shorter interval from surgery to biochemical relapse,[812-814] shorter PSA doubling time,[812-816] higher Gleason[812-815] and GPSM scores,[815] and nondiploid tumor DNA content[815] are associated with progression to metastatic disease and prostate cancer mortality.

Ward et al found that PSAdt was strongly associated with subsequent clinical relapse,[815] with one half to three quarters of patients with PSAdt <12 months having clinical relapse within 10 years. Freedland et al identified PSAdt, Gleason score, and interval from surgery to biochemical relapse as important factors associated with development of metastases and prostate cancer-specific mortality.[814] Most deaths (90%) were attributed to prostate cancer when PSAdt was <15 months, whereas one third of deaths were the result of prostate cancer when PSAdt was ≥15 months. As also noted by Zhou et al,[817] life expectancy was shortest in those with PSAdt <3 months.[814] Although definitive guidelines on its use are lacking, these observations suggest a role for PSAdt when considering salvage therapy.

Postoperative changes may give the false impression of a tumor mass or of retained seminal vesicles.[827] Although a particular PSA level or PSA kinetic parameter does not have sufficient predictive value to trigger an imaging recommendation,[830] an abnormal CT is rare with PSA ≤5 ng/mL to 10 ng/mL or PSA doubling time ≥6 to 10 months.[830,831] Whole-body bone scan is often normal in the asymptomatic patient, particularly with a PSA level ≤10 ng/mL,[830,832] or when the PSA doubling time is >6 months.[831]

Because a normal PET-CT does not preclude a favorable response to salvage RT,[836] best use of this modality requires further study.[836] [111]In capromab prostate-specific membrane antigen monoclonal antibody imaging (ProstaScint) is another nuclear medicine technique. However, it has low sensitivity for detection of local recurrence or metastases, and its results do not predict the outcome of salvage RT.[839,840] Therefore, its use is not recommended routinely.

Studies of multiparametric MRI suggest that combined T2-weighted and dynamic contrast-enhanced images have the highest sensitivity, whereas diffusion-weighted and spectroscopic images do not add greatly to detection.[845] The most frequent sites of recurrence are the vesicourethral anastomosis (50%), retrovesical space (24%), and seminal vesicle region (26%).[841-846] Miralbell et al[847] noted that an approximate 4 cm (length) × 3 cm (diameter) cylindrical volume centered 0.5 cm posterior and 0.3 cm inferior to the vesicourethral anastomosis defined the "ideal" CTV when adapted to exclude nontarget structures (e.g., bladder, rectum, bone). However, tumor recurrence beyond this volume (e.g., at vas deferens transection) may occur,[846] so caution is warranted.

Some studies evaluated pre-RT PSA level using various cutoff values. However, there is a continuous risk of relapse as PSA rises,[810,853] such that each doubling of PSA increases the relative risk of biochemical relapse by approximately 40%. Therefore, an ideal PSA "trigger" for intervention has not been identified.

This nomogram is meant for the patient yet to receive salvage RT, but it is important to note that the results reflect techniques used during the past. Although surgical findings and the postoperative PSAdt represent intrinsic and fixed determinants of prognosis, their contribution to an adverse outcome is lessened when RT is initiated at lower PSA levels.

TABLE 53-17 Selected Case Series of Salvage RT for Biochemical Relapse after Prostatectomy

Author	Pt. No.	RT Dose, Median (Gy)	Biochemical Response, %*	BCR-Free, %	Endpoint
Chawla[805]	54	64.8	76	35	5-yr actuarial
De Meerleer[854]	87	75.0	—	67	5-yr actuarial
Do[804]	60	64.8	92	55	5-yr actuarial
Goenka[816]	285	≥70.0	—	39	5-yr actuarial
Leventis[822]	49	66.0	—	24	5-yr actuarial
Neuhof[809]	171	~63.0	83	35	5-yr actuarial
Peyromaure[849]	62	65.0	—	42	5-yr actuarial
Quero[855]	59	66.0	—	41	5-yr actuarial
Taylor[850]	71	70.0	—	66	5-yr actuarial
Ward[806]	211	64.0	90	48-66	5-yr actuarial
Brooks[807]	114	64.0	69†	33	6-yr actuarial
Stephenson[810]	1540	64.8	59†	32	6-yr actuarial
Maier[852]	170	68.0	—	44	7-yr actuarial
Buskirk[853]	368	64.8	—	35	8-yr actuarial
Tsien[851]	57	64.8	—	30	8-yr actuarial
Pazona[808]	223	63.0	73†	25	10-yr actuarial

BCR, *Biochemical relapse;* RT, *radiotherapy;* yr, *year.*
**Observed rate.*
†Complete response (i.e., undetectable PSA).

in only a few observational case series,[810,816,850,861] where criteria for its use were not consistently prescribed. Although its role is controversial,[765] several ongoing clinical trials address its use.

Consensus-based guidelines provide general direction for use of salvage RT.[765,772,773,797] These guidelines state that prescribed dose to the prostatic fossa should be ≥64 Gy,[765,773] but some observational series suggest that a higher dose is beneficial.[854,856,857]

Clinically Apparent Local Recurrence. The distinction between biochemical relapse only and clinically apparent local recurrence has become less clear with the advent of more sensitive diagnostic imaging. Endorectal MRI demonstrated that local recurrences are often located beyond the reach of digital rectal examination and may be of substantial size.[841-845] Thus, clinical detection is a function of tumor location, PSA level, and the frequency and intensity of surveillance.

The efficacy of salvage RT specifically in this setting has been evaluated by relatively few investigators,[822,823,862-868] whose reports often include a heterogeneous and small study cohort. The results of RT (eTable 53-8) suggest that clinically based local tumor control is achieved in ~85% of patients,[862-864,866-868] but the likelihood of bDFS 5 years after RT is considerably less (~25%).[822,823,862,864-868] These observations suggest that DRE lacks sufficient sensitivity to prompt intervention in lieu of a strategy primarily based on PSA monitoring.

More extensive radiological evaluation and fusion of complimentary imaging modalities (e.g., MR and CT) may be needed to provide optimal identification of the mass' complete extent. IGRT[858,859] and highly conformal IMRT may also allow for a significant dose differential in the target volume, and this can be exploited to administer a higher dose within the tumor than in the remaining prostatic fossa. The results of RT achieved to date suggest also a role for neoadjuvant with or without adjuvant androgen suppression to supplement RT.

Adverse Effects

Adverse effects of postoperative RT are similar to those with primary RT and result from incidental irradiation of the bladder, rectum, femoral heads, and erectile tissues, and patients should be informed of these in concert with the potential benefits.[765] Early effects are those that occur during or within 90 days of RT completion, and late effects are those that occur or persist thereafter; the term *chronic* should be avoided because most late effects resolve spontaneously or with minimal intervention. Several observational series[856,878,879] and clinical trials[769,784,788] describe these effects and incidences (not prevalence), but these reports do not necessarily reflect current RT techniques.[856,880] The RT planning and treatment techniques, dose-volumetric parameters, imaging and localization methods, and antecedent surgery influence the incidence and severity of adverse effects. It is essential to document baseline status before RT (e.g., number of daily stools), investigate causation (e.g., proctoscopy), assign attribution correctly (i.e., RT versus not), and monitor the course of these events.

Early adverse effects are limited typically to GU and GI systems, and these tend to be irritative in nature and self-limited. A causal relationship between early and late effects is suggested but not yet irrefutably proven.

The cumulative incidence of late grade-2 or higher (that is, moderate or severe) adverse events likely attributable to postoperative RT is <20% at 5 years[769,878,879]; many adverse effects are not chronic. The 5-year incidence of late grade-2 or higher GI events is <5%,[769,784,856,878] and severe events are less common still (<1%).[769,788,878,879]

It may be difficult to accurately attribute late GU effect causality because both surgery and RT may contribute and their cause is often evaluated incompletely. The incidence of grade-2 or higher late effects is approximately 10%[769,856,878,879] with severe events not likely to arise from RT.[788]

Patient-reported QoL was studied by Moinpour et al in a longitudinal assessment of prostatectomy with or without adjuvant RT.[785] More patients assigned to RT reported urinary frequency throughout the 5-year study period, and bowel symptoms were more common during the first 2 years. This contributed to reduced global QoL during the initial 2 years, but the adjuvant RT group fared better than the surgery only group thereafter.

RTOG trial 9601 assigned patients to prostatic fossa RT with bicalutamide compared with placebo for 2 years, and RTOG 0534 is a three-arm trial of prostatic fossa RT alone versus short-term androgen suppression given before and during prostatic fossa with or without elective pelvic nodal RT. The Japan Clinical Oncology Group 0401 compares bicalutamide to RT with bicalutamide, and the Medical Research Council PR10 includes a comparison of RT compared with RT with 6-month androgen suppression compared with RT with 2-year androgen suppression.[794]

The NCCN (www.nccn.org) supports offering RT in all men with a detectable PSA. This recommendation is provided also by the ASTRO/AUA, the European Association of Urology,[773] the Australian and New Zealand Radiation Oncology Genito-Urinary Group,[772] and the European Society of Medical Oncology (endorsed by the Japanese Society of Medical Oncology).

Acute treatment related dysuria, urgency or frequency, proctalgia, increased daily stools, and (infrequently) hematuria or hematochezia may occur.[788,856] Rectal dose, pelvic nodal RT, diabetes mellitus, hemorrhoids, and androgen suppression or anticoagulant use contributes to acute GI adverse effects, and these factors may be used in a predictive nomogram.[881]

The use of adjuvant (verus salvage) and nonconformal RT and of androgen suppression is associated with increased adverse late effects.[856,878] Late GI adverse events may include increased or urgent stools/tenesmus, proctalgia, hematochezia, mucous discharge, rectal stricture, or fecal incontinence (0.2%).[878]

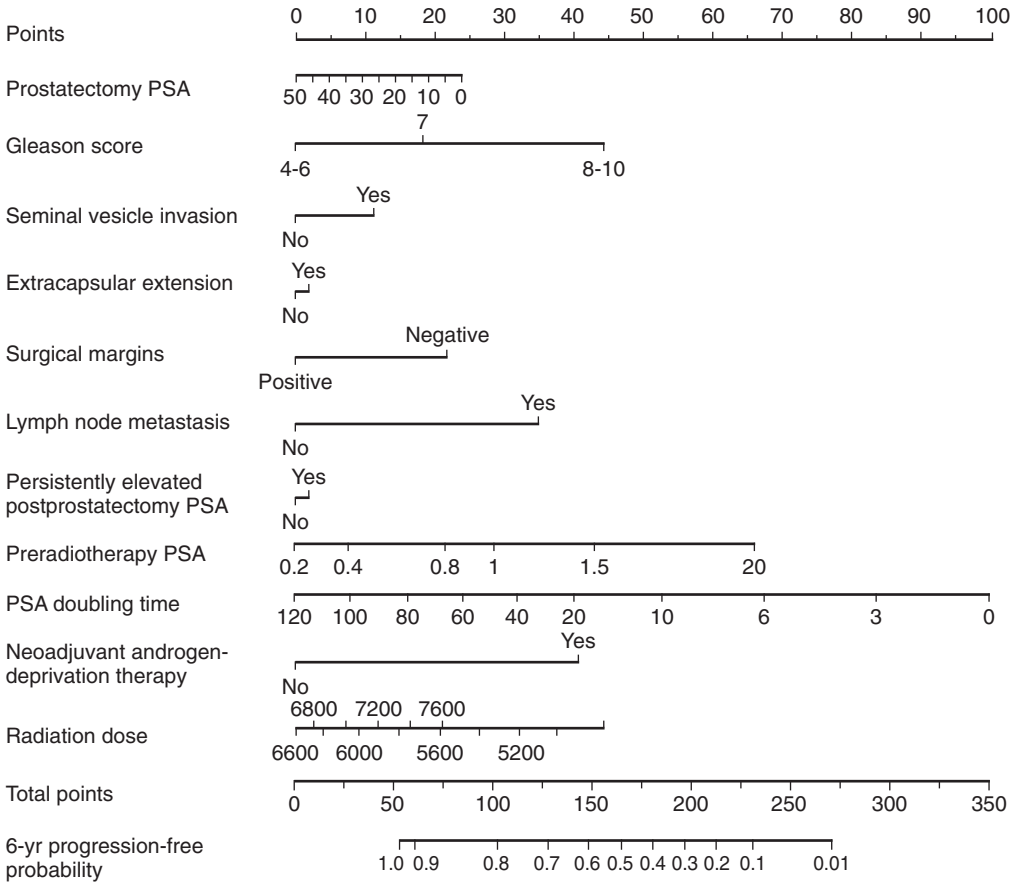
Late GU events may include bladder neck contracture or urethral stricture (5%),[809,878,879] urgency or frequency, dysuria, or transient hematuria (5%).[809,878,879] Urinary continence is comparable to that which follows surgery alone,[774,777,804,805,866,882] and is typically of a mild stress-induced nature when it occurs.[777] It does not appear that RT diminishes erectile function in men who undergo nerve-sparing prostatectomy,[883] but more comprehensive research is required to address this issue.

Functional and health perceptions did not differ between the groups. Although this study is informative, conformal RT was not used, so it is not certain that these findings can be extrapolated to present-day practice. The experience of Pinkawa et al is perhaps more relevant,[884] because it used a broadly accepted QoL instrument and more modern salvage RT techniques. Reduced urinary function and bother was evident only at end of RT, and reduced bowel function and bother was reported through 2 months, but not thereafter. Lesser bladder distention, bladder D90 ≥ 28% and D50 ≥ 45% was associated with urinary bother at RT end, D90 ≥ 28% was associated with urinary incontinence function and bother subscores at RT end, and D50 ≥ 45% was associated with urinary function and urinary incontinence function score at 12 months. An association between rectal dose-volumetric parameters and QoL endpoints was not identified.

eTABLE 53-8 Salvage RT for Clinically Apparent Local Recurrence after Prostatectomy

Author	Pt. No.	RT Dose, Median (Gy)	Local Control, %	BCR-Free, %	Endpoint
Koppie[869]	34	68.4†	—	39	3-year actuarial
Cadeddu[870]	25	64.0†	—	14	5-year actuarial
Catton[871]	16	60.0	60	0	5-year actuarial
Choo[872]	44	63.0	97*	11	5-year actuarial
Leventis[873]	15	66.0	—	18	5-year actuarial
Macdonald[874]	42	68.4	95*	27	5-year actuarial
Wiegel[875]	20	65.0	95*	68	5-year actuarial
vander Kooy[876]	35	64.0	97*	56	8-year actuarial
Syndikus[877]	26	52.0†	54	—	10-year actuarial

BCR, *Biochemical relapse;* No, *number;* Pt., *patient,* RT, *radiotherapy.*
**Observed (crude) rate.*
†*Mean. Mean daily fraction size was 2.76 Gy in Syndikus et al.*[877]



Instructions: Locate Gleason score on the Gleason axis. Draw a line straight up to the Points axis to determine how many points toward disease recurrence the patient receives for his score. Repeat this process for the other 10 disease and treatment axes, each time drawing straight up to the Points axis. Sum the points and locate this number on the Total Points axis. Draw a straight line down to find the patient's probability of remaining free of disease progression.

Figure 53-16 Pretreatment nomogram predicting 6-year progression-free probability after salvage RT.
Data from Stephenson AJ, et al: Predicting the outcome of salvage radiation therapy for recurrent prostate cancer after radical prostatectomy. J Clin Oncol 25:2035-2041, 2007.

Postirradiation Local Salvage Therapy

Surgery for a biopsy proven locally recurrent prostate cancer is an appropriate intervention for selected patients. Because there can be considerable morbidity, an extensive preoperative evaluation to assess surgical feasibility and to exclude clinically overt metastatic disease is warranted. Thus, cystoscopy, examination under anesthesia, CT or MRI of abdomen and pelvis, chest radiography, and radionuclide bone scintigraphy (with or without supplemental skeletal radiography or MRI) may be used to complement the history and clinical examination. Furthermore, the general health condition (i.e., comorbidity) and life expectancy of the patient and the patient's expectations should be considered in concert with the efficacy and morbidity of the procedure. The decision between prostatectomy, anterior exenterative surgery (e.g., cystoprostatectomy), or less invasive procedures (e.g., cryoablation, brachytherapy, or high-intensity focused ultrasound) requires careful preoperative and intraoperative evaluation. A cystoprostatectomy may be indicated in the presence of biopsy-proven bladder neck or seminal vesicle tumor invasion, incontinence from a noncompliant low-capacity bladder, severe RT-induced cystopathy, or pelvic adhesions.[885,886]

Several observational case series described disease outcome after surgical resection for post-RT locally recurrent prostate cancer. The most extensive modern experience was reported by Ward et al who demonstrated that salvage surgery (with or without AD) provided encouraging tumor control and survival rates.[887]

Another alternative to postradiation prostatectomy is cryosurgery, which is the killing of cells via the application of very cold temperatures.[890-895] Several retrospective series have shown reasonable PSA control rates of 30% to 70% at 12 to 20 months with major complications in the 10% range in patients treated with cryosurgery post-RT local failure.[890,892-895]

Brachytherapy has been used as an effective salvage therapy for men who have experienced a local recurrence following either EBRT or brachytherapy.[316,899-905] Second biochemical DFS of 34% to 53% at 5 years[900,902,904] and 54% at 10 years[901] have been reported with permanent seed LDR brachytherapy.

METASTATIC DISEASE

In the past decade several new classes of drugs have been developed to treat prostate cancer. These include

In their experience, there has been a shift away from radical cystoprostatectomy to radical prostatectomy after 1990 such that 82% of salvage procedures are prostatecomies only compared to 54% before that era. The 10-year CSS was 65%.[887] Tumor ploidy, Gleason grade, and pathological stage were strong predictors for outcome. Bianco reported 100 consecutive patients undergoing salvage RP with an overall 5-year PFS of 55%. The 5-year control rate was highly depended on preoperative PSA values with progression free rates of 86%, 55%, and 37% for PSA levels of <4, 4-10, and >10 ng/mL, respectively.[888]

Because RT-induced fibrosis tends to obliterate the usual tissue planes used to establish surgical lines of resection, the increased technical difficulty and morbidity of the procedure result in a general reluctance to perform salvage surgery. The utilization of conformal radiation or brachytherapy techniques appears to make the surgical approach less challenging than older series of salvage prostatectomy.[889] In a series of 100 patients, Stephenson reported a major complication rate of 13% compared to 33% with the rectal injury rate falling to 2% compared to 15% prior to 1993.[886] The rectal injury rate was 5% for prostatectomy patients and 10% for cystoprostatectomy. In the largest published series, the most common complications were urinary extravasation (15%) or bladder neck contracture (22%).[887] Ward noted a decreased need for blood transfusion and a reduced complication rate in patients treated with RP during more recent years, which highlights the importance of the anatomic approach and extent of surgical experience with this situation.[887]

Cryosurgery was first used for prostate cancer in the 1960s and 1970s, but incontinence, urethral necrosis, and fistula were common in because of lack of controlled urethral warming. Subsequently, TRUS guidance and urethral warming were developed.[896,897] Just as for salvage prostatectomy, patients should have biopsy proven locally recurrent disease without evidence of distant metastasis.[890,891] Additionally for patients whose PSA is >5 ng/mL, evaluation of the pelvic lymph nodes via a CT, MRI, or pelvic lymph node dissection is reasonable because salvage radical prostatectomy series report between 20% and 40% of patients as having metastatic disease to the pelvic lymph nodes in this setting.[890,891] In one large series comparing salvage RP to cryosurgery, the cancer control and survival rates were superior for RP over cryosurgery.[898] Cryosurgery remains an option in patients that are not suitable for RP, although properly selecting candidates for this procedure remains a challenge.

Presalvage PSA values of less than 6 ng/mL[901] or less than 10 ng/mL[900] have been associated with better biochemical control rates. Grade-3 or greater GI or GU toxicity rates range from 0% to 47%.[901,902,904-906] The most common late toxicities are urinary incontinence, stricture, or rectal ulcer. An interval from primary RT to salvage brachytherapy of less than 4.5 years has been associated with a greater rate of late complications.[905] HDR brachytherapy has also successfully salvaged patients with local tumor recurrences, although follow-up with this technique has been limited.[903,907]

antiandrogenic agents, cytotoxic chemotherapies, immunotherapies, bone-targeted agents, vaccines, and radiopharmaceuticals. Because many of these new therapies were developed along parallel tracks, the precise impact and timing each of these may have on patients with metastatic disease remains under considerable discussion and investigation. The order with which these drugs have been approved have more to do with regulatory and funding concerns than they have with the ideal sequence of treatment. In the next decade, the optimum combination and timing of these agents will be explored.

Hormonal Therapy

Androgens play a critical role in the health and survival of both normal prostate epithelium as well as prostate cancer. Over the past decade a we have gained a clearer understanding of the role of androgens, the androgen receptor (AR), and the molecular biology of both endocrine and intracrine regulatory processes in the growth of prostate cancer.

Several classes of AD agents are available for medical (versus surgical) castration and include estrogens (e.g., diethylstilbestrol, estramustine), progestational agents (e.g., cyproterone, medroxyprogesterone, megesterol), LHRH agonists (e.g., goserelin, leuprolide, triptorelin, buserelin, histrelin), LHRH antagonists (aberelix, degarelix), and steroidal (e.g., cyproterone, medroxyprogesterone, megestrol) and nonsteroidal (e.g., bicalutamide, flutamide, nilutamide) antiandrogens. There are new classes of antiandrogen agents that specifically target downstream conversion of testosterone to the potent DHT or block its interaction with the AR. Although ~80% of patients with metastatic disease respond to AD,[910] this response is often transient.[911,912] In men with metastatic disease, prostate cancer becomes castrate resistant within 16 months whereas in patients with strictly biochemical progression or failure the time to castrate resistance may be as long as 10 years.[913,914]

Estrogenic therapy lowers LH concentration and thereby reduces serum testosterone levels. Continuous administration of LHRH agonists cause inhibition of LH and FSH release and suppression of testosterone, which reaches castrate levels after 3 weeks. However, LHRH agonists initially produce a significant increase in testicular androgen production, known as the "flare" reaction, which can be inhibited with the administration of antiandrogens. The major side effects of the LHRH agonists include impotence, loss of libido, atrophy of the reproductive organs, and hot flashes. As discussed previously, they can also be associated with metabolic changes that may predispose patients to diabetes, dyslipidemia, or osteopenia. Antiandrogens competitively bind to androgen receptors at the target cell level. This class of drugs blocks the effects of testicular and adrenal androgens.[915,916] Antiandrogens may offer a quality of life advantage over other AD methods because they do not reduce serum testosterone and therefore do not have the marked inhibitory effect on libido and potency apparent with other agents. However, because antiandrogens increase estrogen levels, gynecomastia is a common complication and can occur in as many as 70% of patients. Either prophylactic breast radiation or an anti-estrogen such as tamoxifen is recommended.[917,918]

The role of total androgen suppression (TAS) (i.e., LHRH agonist or orchiectomy and an antiandrogen) has been the subject of considerable investigation. Although Crawford et al[911] and Janknegt et al[919] demonstrated that PFS and OS were improved with TAS, the Prostate Cancer Trialists' Collaborative Group performed a systematic overview, or meta-analysis, of 22 clinical trials and concluded that survival duration was not enhanced with TAS.[912]

There is growing support for the use of intermittent androgen deprivation (IAD) rather than continuous AD. At least three arguments support this strategy over continuous AD including improved QOL because of a reduction in hormone-related adverse events, lower treatment costs, and the possible delay in the development of castrate insensitive disease. In a Phase III trial of continuous versus intermittent AD, Crook reported a median OS of 8.8 years with intermittent AD compared to 9.1 years with continuous AD. The rates of prostate cancer deaths were not significantly different between the two arms. The QOL for patients receiving intermittent AD was improved in the domains of hot flashes, sexual desire, urinary symptoms, and fatigue.[914,920] The optimal duration of treatment while on hormone therapy and the specific triggers for when to reinitiate treatment remain to be defined.

New antiandrogenic agents are undergoing clinical investigation including abiraterone, enzalutamide, and orteronel.[921-923] These drugs appear to have activity in patients previously treated with AD therapies. Several mechanisms for castrate resistance (eBox 53-2) have been identified that may suggest specific strategies to overcome disease progression.[923]

Both abiraterone and enzalutamide have been evaluated in a series of trials for castrate resistant prostate cancer (CRPC) both before and following prior treatments with systemic chemotherapy. The COU-AA-301 trial was a Phase III comparison of abiraterone and prednisone versus placebo and prednisone in men with CRPC that had previously progressed on chemotherapy.[924,925] The median overall survival was significantly increased with abiraterone by 3.9 months (14.8 months compared to 10.9 months). A similar Phase III trial in CRPC patients that had not received prior chemotherapy (COU-AA-302) showed nearly doubling in median survival from 8.3 months to 16.5 months with abiraterone and prednisone compared to prednisone alone.[926] The AFFIRM trial compared enzalutamide to placebo in a similar population of CRPC patients who had progressed following chemotherapy. Enzalutamide was associated with a statistically significant 4.8-month improvement in median survival from 13.6 months with placebo to 18.4 months with enzalutamide.[927] Enzalutamide has also been evaluated in CRPC in the prechemotherapy setting. The PREVAIL study was a double-blind, placebo-controlled trial that demonstrated a 29% increase in survival.[928]

Chemotherapy

Mitoxantrone and prednisone had been approved for CRPC on the basis of improvement in QOL and symptoms related to metastatic disease.[929] Although that combination improved patient reported outcomes, it had no impact on OS. For nearly a decade, little progress had been made in the systemic management of metastatic CRPC. Today, docetaxel-based chemotherapy is considered a standard option for CRPC.[751,752] In a randomized trial of 1006 patients who are castrate-resistant, docetaxel plus prednisone showed a 2.4-month advantage in median survival as compared to mitoxantrone plus prednisone.[752] A similar randomized trial in 770 men with CRPC comparing docetaxel and estramustine to mitoxantrone showed an improvement of time to progression from 3.2 months with mitoxantrone to 6.3 months with docetaxel and estramustine.[751] Additionally a meta-analysis of three randomized trials comparing docetaxel to mitoxantrone showed a reduction in death risk of 8% to 21% with docetaxel which persisted 3 years after the start of therapy.[930] Cabazitaxel is a novel tubulin binding taxane that shows activity in patients previously exposed to docetaxel. In the TROPIC trial, 755 men with CRPC who had progressed on docetaxel were randomized 1 to 2 to receive either mitxantrone or cabazitaxel. In this heavily pretreated patient population, cabazitaxel was associated with a 2.4-month prolongation in median survival (12.7 months versus 15.1 months).[931]

The clinical importance of androgens was established in the early 1940s by Huggins et al,[908] who demonstrated the therapeutic benefit of AD in the context of metastatic disease. The principles and efficacy of AD therapy for patients with advanced and metastatic prostate cancer were well summarized by Schulman et al.[909]

Sex hormone production is regulated by the hypothalamic-pituitary axis. Gonadotropin-releasing hormone is synthesized by the hypothalamus and transported to the anterior lobe of the pituitary gland, where it controls the synthesis and secretion of the gonadotropic hormones, luteinizing hormone (LH), and follicle-stimulating hormone (FSH). The predominant means of controlling FSH and LH levels involve a closed-loop negative-feedback mechanism in which gonadal steroids have the capacity to inhibit FSH and LH secretion. The interaction of circulating LH with its receptor in the target cell results in production of circulating androgens through the following biosynthetic pathway:

Cholesterol → Pregnenolone → 17α-Hydroxypregnenolone → Dehydroepiandrosterone (DHEA) → Androstenediol → Testosterone → Dihydrotestosterone

Under normal physiologic conditions, Leydig's cells account for 95% of testosterone production in adult men, with approximately 5% derived from adrenal androgen production (i.e., androstenedione) and its conversion in peripheral tissues to testosterone. After its diffusion into its target tissue, testosterone is converted to the more potent androgen DHT by 5α-reductase. In turn, DHT forms an intracellular complex with the androgen receptor that targets specific DNA sequences. It is the androgen-responsive genes that determine the balance between cellular proliferation, cell death, and differentiation of the prostatic epithelial cell.

eBOX 53-2 Proposed Mechanisms for Continued AR Signaling in Castrate Resistant Prostate Cancer

Intracrine synthesis of androgens
Amplification and/or overexpression of AR
Overexpression or polymorphism of steroid transporters
Mutation of the AR gene
Constitutively active AR splice variants
Alteration in AR coregulators
Cross-talk between AR and other signaling pathways
Posttranslational modifications of AR
Distinct AR-mediated transcriptional programs

AR, *Androgen receptor.*

Antiandrogens are currently approved for use in combination therapy with an LHRH analogue to provide complete androgen blockade. Their use as a sole means of AD has been investigated.[915,916] At 150 mg/d, bicalutamide appeared to be equivalent to an LHRH agonist or castration in patients with locally advanced but nonmetastatic disease.[915]

Abiraterone is a pregnenolone analog that inhibits CYP17A1 (17 alpha-hydrolase/C17,20 lyase complex) preventing the formation of DHEA and androstenedione thereby lowering the levels of circulating androgen produced by the testes and adrenal glands without causing adrenal insufficiency.[921] The drug is administered with a low-dose corticosteroid to prevent secondary mineralocorticoid excess as a result of an increase in upstream steroids. Orterenol is another testosterone synthesis inhibitor currently being evaluated in clinical trials. Enzalutamide, an androgen receptor antagonist, blocks testosterone binding to the androgen receptor, slows nuclear translocation of the androgen receptor, and inhibits receptor binding to DNA.[922] Like abiraterone, it has shown activity in castrate-resistant prostate cancer suggesting a sustained role of the androgen receptor in castrate-resistant disease. Some studies have shown an upregulation of steroidogenic enzymes leading to an increase in androgen synthesis. In some cases, the Castrate Resistant Prostate Cancer (CRPC) cells can bypass the dominant pathway of the conversion of androstenedione to testosterone and DHT by alternative routes. Enhanced transport of androgen through the cell membrane has been identified. Most importantly, changes in AR expression by mutation or genomic amplification and overexpression may enhance the activity of diminished quantities of intracellular androgen.

Immunotherapy

There are multiple approaches to evoke the host's immune system to respond to metastatic cancer. Sipuleucel-T is an autologous cellular immunotherapy that has prolonged survival a median of 4 months in men with CRPC compared to placebo.[932] This treatment involves obtaining autologous cells by leukopheresis and culturing them in vitro with a protein that couples the vaccine target (prostatic acid phosphatase) to granulocyte-macrophage–stimulating factor. The activated leukocytes are then reinfused into the patient. Approved by the FDA in 2010, Sipuleucel-T represents the first immunotherapy vaccine for the treatment of metastatic cancer.

Systemic Radiotherapy

For the patient with multiple sites of painful osseous metastases, the administration of systemic radioisotopes may be considered. ^{223}Ra is an isotope of radium with a half-life of 11.4 days. It decays by the emission of high energy alpha particles with a short range (<100 μm).

The ALSYMPCA trial was a Phase III placebo controlled randomized trial of ^{223}Ra in CRPC patients with no visceral metastases.[937] Visceral metastases, except lymph nodes <3 cm, were excluded because the agent is not taken up by prostate cancer cells. Patients either previously received docetaxel or were unfit or declined to receive it previously. Radium was administered intravenously at a dose of 50 kBq/kg every 4 weeks for six injections. With 921 patient randomized to ^{223}Ra or placebo in a 2:1 ratio, patients who received ^{223}Ra had a 2.6-month improvement in median overall survival (14.9 months versus 11.3 months). ^{223}Ra significantly prolonged the time to the first symptomatic skeletal event (median, 15.6 months versus 9.8 months).

Strontium-89 (^{89}Sr) is a calcium analogue that is absorbed by the newly forming bone. Approximately 80% of patients experience reduced pain with ^{89}Sr, but only about 10% of patients become pain free.[938]

A prospective randomized trial by Sartor et al has shown samarium-153 (^{153}Sm) to be both safe and effective in the treatment of painful bony metastasis in patients with hormone refractory prostate cancer.[941]

Bone-Directed Therapies

Another option for managing skeletal metastasis in metastatic prostate cancer is the use of bisphosphonates. They bind to exposed bone mineral and diminish the availability of hydroxylapatite crystals for osteoclast mediated resorption. Bisphosphonates can directly inhibit osteoclasts and their precursors. In a Phase III trial of zoledronic acid or placebo in men with asymptomatic or minimally symptomatic CRPC, patient receiving the 4 mg or 8 mg of zoledronic acid every 3 weeks had significantly fewer skeletal related events than men in the placebo group (33.2% versus 44.2%).[942] It also significantly delayed the median time to onset of the first skeletal event to 546 days compared to 464 days. A slight survival benefit accompanied the use of zoledronic acid, but this was not statistically significant. A potential benefit of bisphosphonate therapy is the prevention of osteoporosis caused by prolonged AD use in patients with metastatic disease. Osteoporosis associated with AD causes an increase in skeletal fractures[943] and bisphosphonates could reduce such fractures.

Denosumab is a human monoclonal antibody against the receptor activator of nuclear factor kappa-B ligand (RANKL). RANKL is a tumor necrosis factor cytokine which functions as a key factor for osteoclast differentiation and activation. Denosumab inhibits osteoclast-mediated bone destruction and has been evaluated in men receiving androgen deprivation who are at risk of developing osteoporosis as well as patients with bone metastases. In a double-blind placebo-controlled Phase III trial, Smith et al reported a 5.6% increase in the bone mineral density of men receiving denosumab 60 mg every 6 months compared to a 1.0% loss of density in men receiving placebo.[944] They also experienced a significant reduction in new vertebral fractures (1.5% versus 3.9%) at 36 months. In a double-blind Phase III trial of 1904 men with CRPC, Fizazi compared denosumab 120 mg or zoledronic acid 4 mg, every 4 weeks.[945] Denosumab was better than zoledronic acid for the prevention of skeletal related events. The median time to first skeletal related event was 20.7 months with denosumab compared to 17.1 months with zedronic acid. The rates of adverse events were comparable between the two groups.

Radiation Therapy

EBRT has an important role in the palliative care of patients with symptomatic metastatic disease. Painful osseous metastases are successfully palliated in more than 80% of patients.[946] Dose and fractionation schemes vary, but 30 Gy in 10 fractions or 8 Gy in one fraction are commonly used.[947-949] For patients with multiple sites of osseous pain, hemibody RT may provide pain relief. Either a single fraction or multiple treatments may be given.[950] This treatment technique is gradually being replaced by systemic radionuclides and chemotherapy.[951]

IRRADIATION TECHNIQUES

Primary Therapy

External Beam Irradiation

Before starting EBRT, a comfortable and reproducible (supine or prone) position is established during simulation that allows radiologic imaging to define the appropriate treatment volumes. A prone position may allow greater rectal sparing, particularly in patients with large seminal vesicles.[952] However, the prone position appears to be associated with greater prostate motion from breathing. In the prone position, prostate motion (cranial-caudal) ranged from 0.9 mm to 5.1 mm,[953] and deep breathing resulted in movements of 3.8 mm to 10.5 mm. In the supine position prostate movements during normal breathing were less than 1 mm in all directions. In a randomized study of patient positioning, the supine position was found to be more comfortable and reproducible.[954]

According to current standards, treatment simulation incorporates the use of a patient immobilization device and is done with CT imaging.[955] Immobilization devices reduce variation in daily patient position, thereby improving the accuracy of treatment delivery.[956,957] In the past contrast material may have been instilled into the bladder and rectum to localize the position of the prostate and adjacent organs on planar simulation radiographs; this is unnecessary with CT simulation. A urethrogram can help localize the urogenital diaphragm and, therefore, the apex of the prostate. The prostatic apex is 3 mm to 13 mm above the most proximal aspect of the urogenital diaphragm as defined by the urethrogram.[958,959] Care should be taken not to over inflate the urethra with iodinated contrast as this may distend or move the prostate from its relaxed position.[960,961] Because bladder and rectal filling can cause positional changes in target organs as well as affect the amount of normal tissue irradiated, the amount of bladder and rectal distention should remain as consistent as possible throughout the course of therapy. This is typically accomplished by simulating patients with a full bladder and an empty rectum. In some clinics patients are instructed to modify their diet and consume mild laxatives to minimize rectal distention. A

Other immune therapy approaches include the insertion of cancer cell antigens into viral vectors such as a Pox virus.[933] PROSTAVAC is a vaccine that has three costimulatory molecules that stimulate the immune system and has shown some benefit in delaying progression but has no impact on survival.[934] T-cell function augmentation using anti cytotoxic T-lymphocyte antigen-4 (CTLA-4) antibody may increase T-cell activation, proliferation, and infiltration into tumors, leading to cancer cell death.[935] Ipilimumab is a human monoclonal antibody against CTLA-4 currently being evaluated in clinical trials for CRPC.[936] Ipilimumab has been approved for the treatment of metastatic melanoma. In the randomized Phase II trial of CRPC, patients received ipilimumab with or without radiation therapy to sites of metastatic disease. One objective of the study is to determine whether or not local radiation therapy could augment the immune response through release of circulating tumor antigens following a tumoricidal dose.

^{233}Ra is a calcium mimetic, bound to newly formed bone stroma within the microenvironment of osteoblastic and sclerotic metastases. The large charged alpha-particle causes double-stranded DNA breaks, which result in a highly cytotoxic effect. ^{233}Ra is eliminated primarily in the GI tract and has a favorable safety profile with mild myelotoxicity.

Recent data suggests an improvement in QOL for those patients who have a decrease in pain after ^{89}Sr.[939] The major toxicity of this agent is myelosuppression, so adequate bone marrow reserve is required to safely use this form of RT. Other radionuclides, such as ^{153}Sm, have somewhat less hematologic toxicity.[940]

In the Phase III trial, 152 men with hormone refractory prostate cancer and painful bony metastasis were enrolled in a prospective randomized double-blinded trial comparing radioactive ^{153}Sm versus nonradioactive ^{153}Sm. Randomization was 2:1 to the radioactive agent. The results of this trail demonstrated that 1 mCi/kg of ^{153}Sm is both safe and effective for palliation of painful bony metastases in patients with hormone refractory prostate cancer.[941]

distended rectum may introduce a systematic error in the treatment planning process by compressing the prostate and pushing the posterior wall of the gland forward. Subsequently, during the course of radiation the rectum will empty more completely because of radiation proctitis resulting in a posterior shift of the prostate outside the planning target volume.[962] Three studies have shown an increase rate of biochemical failures in men simulated with a distended rectum.[962-964]

MR imaging complements the delineation of the prostate and seminal vesicles. CT may over estimate the volume of the gland by 27% to 32% and the localization of the prostatic apex is more accurate identified with MR.[958,965,966] The use of MR and CT visible fiducial markers implanted in the prostate before imaging for treatment planning may facilitate and improve the registration of images for treatment planning.

Clinical Target Volumes

Defining the volumes requiring an adequate therapeutic dose of radiation is a fundamental step in the RT planning process. The radiation oncologist must define the treatment volumes, which consist of the primary tumor and its clinically or radiographically evident extensions (i.e., gross tumor volume [GTV]), and regional tissues (e.g., seminal vesicle, lymph nodes) at risk of harboring subclinical tumor deposits (i.e., CTV). The GTV is the prostate gland and any extension of the primary tumor, as determined by clinical or radiologic examinations. The CTV includes GTV and regional sites to which the tumor may spread but that are beyond the limits of clinical detection (i.e., subclinical disease). Determination of CTV should consider pretherapy tumor-related factors correlated with histological findings from surgical experiences (see "Predictive Factors"; "Pathologic Endpoints"). Nomograms and risk categories are helpful to decide whether adjacent uninvolved tissue should be included in the CTV. Margin for possible EPE has been recommended by several authors. In a study of radical prostatectomy specimens, Davis et al demonstrated that EPE was present in 28% of 376 patients.[967] The average radial EPE distance from the prostate capsule was 0.8 mm with a range of 0.04 mm to 4.4 mm. The average radial EPE distance from the prostate capsule was 0.8 mm with a range of 0.04 mm to 4.4 mm. Sohayda reported EPE in 35% of 265 cases extending posterolateral in 53%, lateral in 24%, and posterior in 13%.[968] The 90th percentile of EPE distance was 3.3 mm for patients with clinical T1-2, pretreatment PSA of ≤10 ng/mL and biopsy Gleason score of 6 or less and 3.9 mm for less favorable tumors.

The seminal vesicle(s) may be a site of subclinical tumor extension in patients with clinically localized prostate cancer. The likelihood of SVI may be estimated from predictive models or nomograms.[193,202,210,969] Ultrasound-guided biopsy[382] or endorectal-coil MRI[209,970,971] may be used in the pretherapy evaluation. The role of elective RT of the seminal vesicles in patients with low-risk disease is controversial.[972,973] Nonetheless, the seminal vesicles may be included in the CTV if the risk of SVI is 15% or greater.[202,210,213,612] Exclusion of the seminal vesicles in patients with a low likelihood of SVI reduces the volume of, and RT dose to, nontarget normal tissues (e.g., rectum).[210,973]

Because the extent of SVI is generally within 1 cm of the junction of the seminal vesicles with the prostatic base,[170] inclusion of the entire seminal vesicle within the high-dose target volume may not be routinely required for intermediate-risk disease. In patients with intermediate-risk disease, the proximal 1 cm of seminal vesicle tissue may be included in the high-dose volume. This may be increased if the patient has multiple risk factors. Patients with high-risk disease may require treatment of the entire the seminal vesicles in the high-dose volume, particularly if there is clinical or radiographic evidence of extraprostatic extension or SVI.

The regional lymphatic tissues may be considered a CTV in high-risk situations. Several observational case series suggested that elective nodal irradiation (ENI) contributed a therapeutic benefit for certain patient subsets.[975-978] The RTOG conducted a prospective, randomized trial that evaluated ENI in the pre-PSA era and no improvement in outcome was observed.[979] Results of a contemporary trial, RTOG 94-13, show a higher bDFS rate in patients with a risk of LNI greater than 15%, provided that hormonal therapy was given neoadjuvantly.[612,632] At present, some feel it is appropriate to use models that estimate the risk of pelvic nodal involvement[193,213] and consider ENI when the risk of LNI reaches or exceeds 15%.[612] Whether or not to irradiate pelvic lymph nodes remains a controversial issue. Two additional trials testing the value of ENI are under way by the RTOG. One of them is in the definitive setting with lymph node risk assessed by the clinical factors of PSA, Gleason Score, and clinical stage. The other study is in the salvage setting for men that have a rising PSA following radical prostatectomy.

The goal of ENI of the pelvis is to include the obturator and internal and external iliac lymph nodes. This is often accomplished with a four-field beam arrangement that consists of AP, posteroanterior (PA), and opposed lateral fields or IMRT with five to nine beams. In the past, field margins were typically established through their relationship with certain bony landmarks as follows: (1) superior: L5-S1 interspace; (2) inferior: bottom of ischial tuberosities; (3) lateral: 2 cm lateral to pelvic inlet; (4) anterior: approximately 1 cm anterior to anterior projection of pubic symphysis; and (5) posterior: S3-4 interspace.

The nodal groups to be included extend from the L5-S1 interspace (i.e., low common iliac lymph nodes) to the top of the pubic symphysis (obturator lymph node region) (Figure 53-17). Presacral lymph nodes (subaortic only, S1-S3) are also included. These volumes correlate well with the nodal volumes typically treated with the four-field "box" technique used in all the randomized trials previously mentioned.[749] Complex blocking to shield portions of the small intestine and rectum is recommended. Alternatively, IMRT can be used. A dose of 45 Gy to 50.4 Gy is recommended and is often administered in 1.8-Gy once-daily fractions.[316]

Planning Target Volumes

The planning target volume (PTV) is determined by adding margin to the CTV to account for internal target volume and patient motion, and the field margins are set to conform to the PTV with allowance for the RT beam penumbra and dose build-up effect. These uncertainties can exist day to day (interfraction) and during a single fraction (intrafraction).

Internal movement of prostate, seminal vesicles, and surrounding tissues (e.g., bladder, rectum) throughout the course of EBRT is a well-recognized phenomenon that is a function of bladder and rectal distention and has particular relevance to the design and dosimetric consequences of a tight conformal dose distribution.[980-985] With real time monitor and intrafraction position correction, displacements can be corrected during treatment. Various methods to assess the setup and internal organ localization uncertainty are available including transabdominal ultrasound, in-room cone-beam CT, in-room conventional CT, in-room megavoltage CT, and x-ray imaging of implanted fiducial markers. Some systems are able only to detect prostate position at the start of a treatment whereas others, such as implanted electromagnetic radiofrequency transponders, can monitor position during a treatment session.[986] Chandra et al showed that the prostate would be outside the PTV approximately one third of the time when using a 5-mm margin without daily ultrasound to correct for interfractional prostate movement.[982] Studies have compared

When involved, the extent of involvement of the seminal vesicles may extend as far as 2 cm away from the insertion in the prostate gland.[969,974] Kestin found an excellent correlation between the prognostic features and the probability of seminal vesicle involvement. In 81 patients with positive SVI, the median length of tumor involvement was 1 cm. However, in their entire reported population only 7% of patients had SVI beyond 1 cm.[974]

Defining appropriate lymph node volumes for conformal ENI varies considerably among radiation oncologists.[748] In an effort to standardize the correct anatomical pelvic lymph nodes to be covered for locally advanced patients, RTOG GU radiation oncologists developed a consensus on the CTV for pelvic lymph nodes.[749]

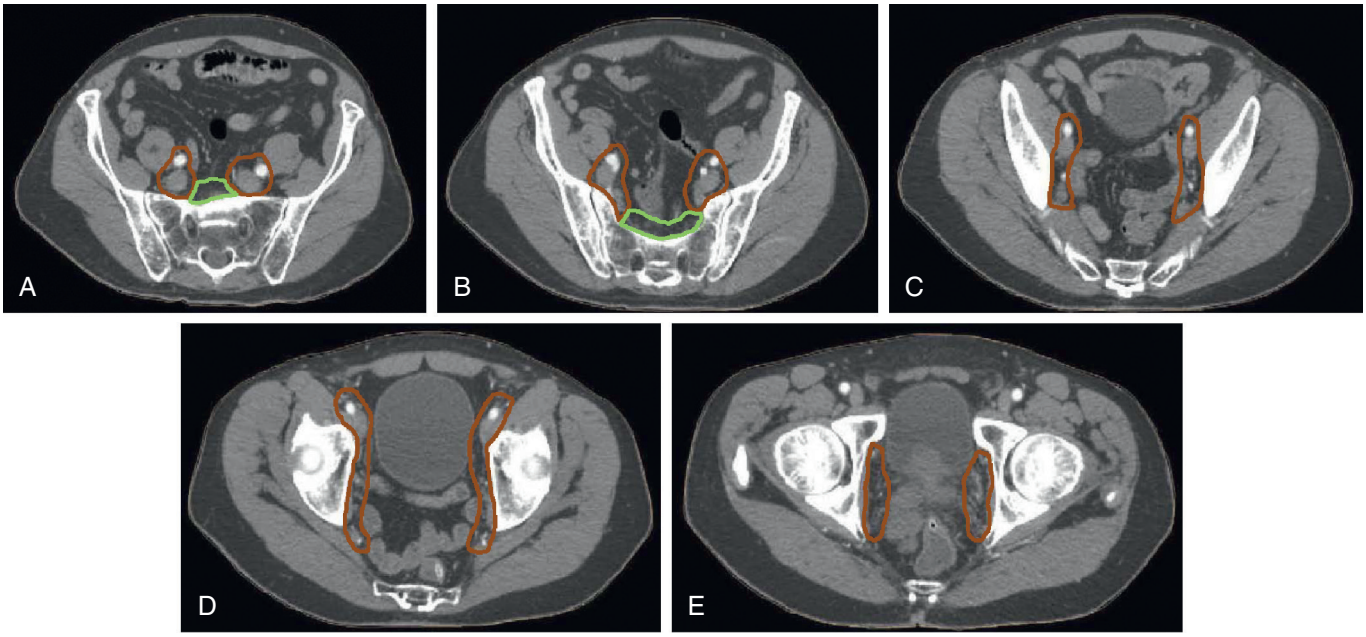


Figure 53-17 Representative pelvic lymph node clinical target volume (CTV) contours from RTOG consensus computed tomography. **A,** Common iliac and presacral CTV lymph node volumes (L5/S1). **B,** External, internal, and presacral CTV lymph node volumes (S1-S3). **C,** External and internal Iliac CTV lymph node volumes (below S3). **D,** End of external iliac CTV lymph node volumes (at top of femoral head, boney landmark for the inguinal ligament). **E,** Obturator CTV lymph node volumes (above the top of the pubic symphysis).

ultrasound to other methods of prostate localization such as cone beam CT (CBCT), megavoltage CT, and fiducial markers with port films.[982,987] Although transabdominal ultrasound systems offer the appeal of being less invasive, fiducial-based systems appear to offer an advantage over ultrasound with respect to the ease of use and the magnitude of residual error.[987] Results tend to vary by approximately 5 mm to 7 mm such that margins of this magnitude are still necessary even when using a method for prostate localization more accurate than port films. Like conventional CT scans, both megavoltage tomographic CT (e.g., tomotherapy) and CBCT offer cross-sectional views of internal anatomy and registration of daily targets to the original simulation CT. Image quality for both these volumetric imaging systems is inferior to simulation CT scans because of the physics of radiation interactions in the Megavoltage (MV) range, a limited field of view or organ motion during image acquisition.[988,989] Despite these deficiencies the images are of sufficient quality to allow daily anatomy-based target localization.[990] The concurrent use of implanted fiducial markers along with MV CT provides a more objective and reproducible determination of target localization.[991] Implanted electromagnetic radiofrequency transponders offer the opportunity to track prostate target position real time. Compared to other imaging techniques, the implanted transponders have a high temporal resolution, which can be used to monitor prostate position continuously during treatment delivery.

Variation in the shape, size, and position of the CTV in relation to the internal fixed point and the position of patient and RT beam in relation to external fixed points are accounted for as the internal motion and set-up margins to establish the PTV; these margins are typically in the range of 0.5 cm to 1.0 cm. Seminal vesicle motion can be greater and more variable than the prostate and may require more PTV margin.

Meijer analyzed serial CT scans on 30 prostate cancer patients and employed deformable image registration techniques to calculate the margin that would be used in the absence of daily imaging and with CT-based methods aligning to boney anatomy or implanted fiducial markers.[993] Without setup correction margins of 11 mm and 15 mm around the prostate and seminal vesicles would be required, respectively. With daily imaging and alignment to bony anatomy the margins could be reduced to 8 mm and 13 mm. With implanted fiducial markers, margins of 3 mm and 8 mm around the prostate and seminal vesicles, respectively, maintained adequate dosimetric coverage to the clinical target volumes.[993] They recommended larger margins at the prostatic apex due to difficulties identifying the inferior border of the prostate.

When using proton beam therapy the thickness of some implanted fiducials may create shadows or artifacts that could lead to underdosing tissue adjacent to the markers. Thin gold fiducials and placement away from known disease in the gland are advised.[994]

Caution should be exercised when reducing margin with improved treatment localization methods. Engels et al reported an increase rate of biochemical failure in a group of men treated with implanted fiducial markers and a margin of 3 mm laterally and 5 mm anterior, posterior, and craniocaudal.[963] This narrow margin, coupled with prostate deformation and dose uncertainty in the penumbra, may have contributed to tumor underdosing. They recommend a PTV margin of 6 mm when using fiducial markers without intrafraction monitoring.

Use of an endorectal balloon during daily treatment may stabilize the position of the gland. Air in the balloon decreases the rectal surface dose by decreasing the electronic equilibrium and buildup at the air–soft-tissue interface. Teh et al reported results of 100 consecutive patients treated with IMRT and an endorectal balloon.[995] Eighty percent had no rectal complaints and 11% and 6% had grade-1 or grade-2 acute toxicity, respectively.

In proton therapy the endorectal balloon is generally filled with water to minimize dosimetric uncertainties related to the lateral penumbra at the prescription depth.

A study conducted at five centers positioned 41 patients over a full course of therapy.[992] The study found that the continuous motion of the prostate was unpredictable and varied from persistent drift to transient rapid movements. Displacements >3 mm and >5 mm for cumulative durations of at least 30 sec were observed during 41% and 15% of treatment sessions.

Techniques for prostate localization prior to each treatment fraction are now available; however, such that margins have been decreased substantially to increase dose and limit normal tissue complications. The magnitude of the margin used for EBRT should be a function of immobilization, localization technique, and the frequency of treatment monitoring.

With air in the balloon, the dose at the air-tissue interface is approximately 15% lower than the dose at the same point without air. The dose builds up rapidly so that at 1 mm and 2 mm away from the interface, the dose is only approximately 8% and 5% lower. The dose to the posterior rectal wall is reduced with the use of an endorectal balloon during the prostate RT. A fluid-filled endorectal balloon is commonly used in patients receiving proton beam therapy because it does not introduce dosimetry uncertainties like fiducial markers can.

Treatment Planning and Delivery

Various EBRT beam arrangements may be used, the most current of which include (1) six-field (right and left anterior oblique, right and left posterior oblique, opposed lateral) 3DCRT techniques and (2) five to nine beam IMRT techniques (Figure 53-18)[251,996,997] or arc-based IMRT methods.

Modern treatment-planning computers also allow display of DVHs to graphically display RT dose to target (i.e., prostate) and nontarget (e.g., bladder, rectum) tissues, and "idealized" treatment plans may be derived through analysis of DVHs and computerized beam optimization. The QUANTEC project has provided DVH parameters that serve as treatment planning guidelines for limiting rectal and bladder toxicity or erectile dysfunction (Table 53-8).[546] In a preliminary analysis of the RTOG Phase III trial of dose escalation for intermediate prostate cancer stricter dose constraints for rectal dosimetry have been identified. Patients with rectal V70 of less than 15% and a V75 of less than 10% were less likely to have grade-2 or greater late rectal toxicity.[544]

The randomized clinical trials demonstrating a bDFS advantage for localized prostate cancer prescribed radiation doses ranging from 74 Gy to 79.2 Gy in conventional fraction sizes of 1.8 Gy to 2 Gy per day.[497,498,501,998] Although each study improved bDFS, there was also an increase in grade-2 or greater late bowel or bladder toxicity. Of note, other than the proton trial, each of these trials employed 3DCRT and not IMRT. It is expected that IMRT will allow safe escalation of dose above 75 Gy without an increase in late GI or GU toxicity.[550,999,1000] Most of the dose escalation trials prescribed treatment to the isocenter, which will deliver approximately 4% lower dose as a minimum to the PTV. In the RTOG dose escalation and hypofractionation trials, the minimum dose to ≥98% of the PTV (V98) was intended to be the study prescription

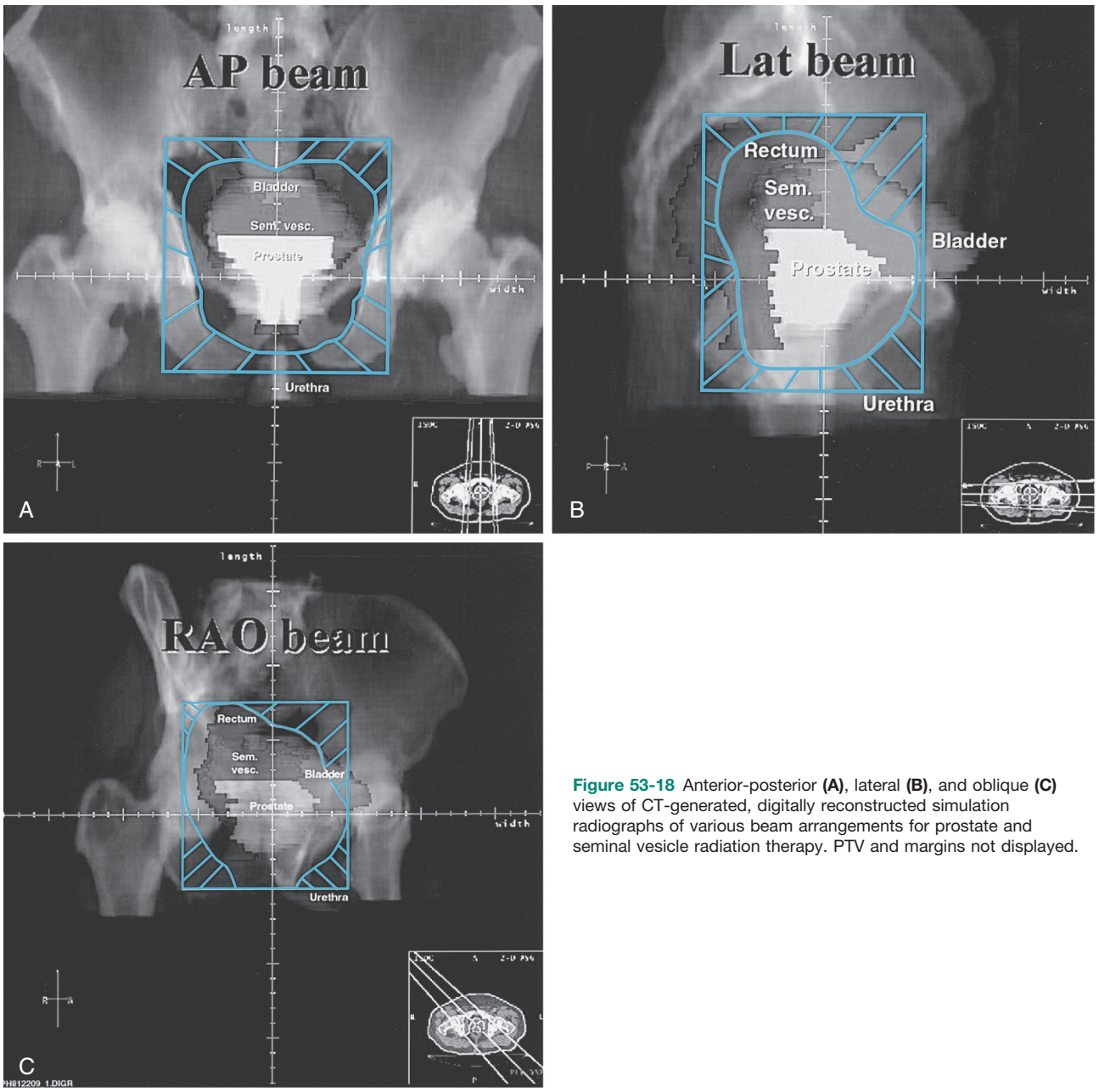


Figure 53-18 Anterior-posterior **(A)**, lateral **(B)**, and oblique **(C)** views of CT-generated, digitally reconstructed simulation radiographs of various beam arrangements for prostate and seminal vesicle radiation therapy. PTV and margins not displayed.

dose. In other words, no more than 2% of the PTV[504,1001] received less than the prescribed study dose.

Brachytherapy

Several techniques for permanent seed brachytherapy have been developed based on prostate imaging. The CT-based method, initially used by Wallner et al, was associated with high rectal and urinary complications, and has largely been discontinued as it does not offer direct intraoperative visualization.[1002]

Most permanent prostate brachytherapy incorporates real-time ultrasonography to visualize the prostate (Figure 53-19). The probe is placed on a fixed stepping device that allows its independent movement relative to the transperineal template. With or without the addition of fluoroscopy, the use of a biplane ultrasound probe allows prostate visualization in sagittal and axial mode for accurate prostate imaging. Others are using real-time MRI techniques to perform permanent prostate brachytherapy.[1003] Most centers use real-time ultrasonography imaging with various techniques. The "Seattle" technique employs the use of a preplan-based on serial axial TRUS performed in lithotomy position in advance of the implant.[586] Based on an approved plan, needles are loaded with I-125 or Pd-103 and spacers, and used in the operating room to correspond with the plan. Needle placement follows the plan with deposition of each successive needle's seeds. Use of fluoroscopy may assist to assure that the needles are positioned against a "zero" plane as a reference position. Several vender specific products have been developed to mimic this process with seed links or strands. An advantage of this approach is that it allows for multiple plans to be developed in advance of the case and that needle placement in the operating room is generally easy and can be performed in a timely manner. The disadvantage of this process is that it remains difficult to achieve the exact position of the prostate relative to the preplan, and that there is no ability to compensate for discrepancies during the case, except to add additional sources at the discretion of the physician.

With advances in software treatment planning systems, Potters et al have reported on a dynamic intraoperative technique that achieves dose conformality based on set parameters for minimum and maximum prostate dose with inverse planning.[655] Using treatment planning software in the operating room, seed location can be determined on actual needle placement, and then followed by dynamic assessment of the dosimetry during the case. Final intraoperative dosimetry appears to correlate to the CT-based dosimetry, with the advantage of using 8% less isotope activity per case (Figure 53-20). Others are using like techniques as the integration of intraoperative computerization and seed planning allows greater flexibility during the case to achieve the implant quality with fewer seeds.[1004-1006]

HDR Brachytherapy

Generally reserved for patients with locally advanced cancers, HDR brachytherapy offers a boost treatment option to EBRT. By placing HDR afterloading needles directly into the prostate gland under real-time ultrasound guidance, a steep dose gradient between the prostate and adjacent normal tissues can be generated that is unaffected by organ motion and edema or treatment setup uncertainties. The ability to control the amount of time the single radioactive source dwells at each position along the length of each brachytherapy catheter further enhances the conformity of the dose. Recent data from several groups performing HDR brachytherapy in patients with locally advanced disease suggest similar tumor control as 3D-conformal EBRT with the added advantages of reduced treatment times, less acute toxicity, and no additional technological requirements to account and correct for treatment setup uncertainties and organ motion.[1007-1009] The issues that remain unresolved with this technique (as with other methods of dose escalation) revolve around the amount of additional dose required to provide optimal tumor control,

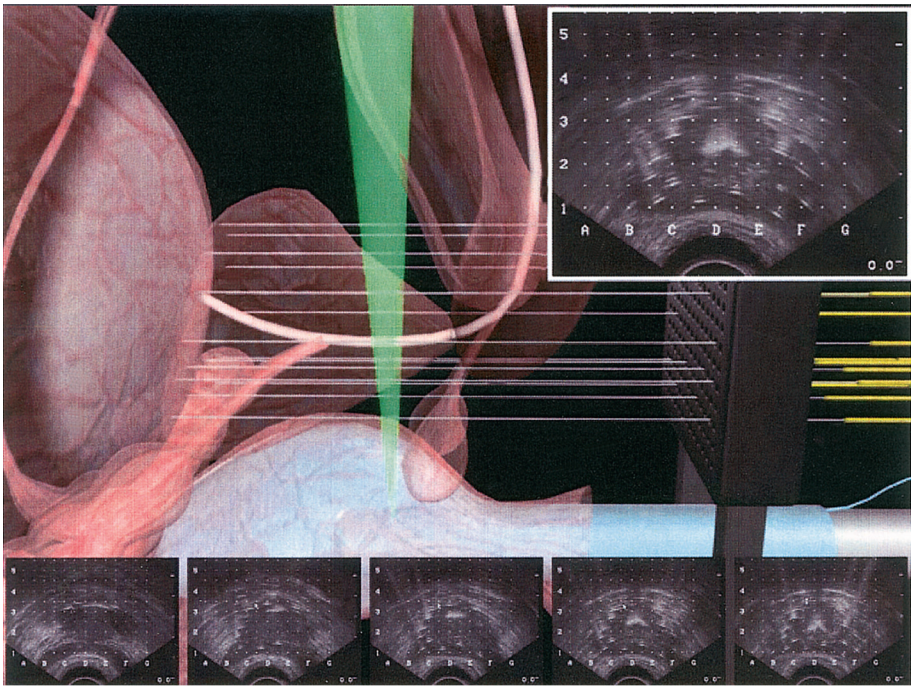


Figure 53-19 Axial-view image of permanent prostate brachytherapy.
Courtesy of Louis Potters, MD, Memorial Sloan Kettering Cancer Center at Mercy Medical Center, Rockville Center, NY.

An alternative technique, originally developed at Mount Sinai, uses an interstitial gun to place each seed individually.[1004] The interstitial gun can be used with a preplan, but is more commonly utilized for a real-time implant, where needle positions can be adjusted as needed. Likewise, use of the interstitial applicator is operator dependent and requires a higher degree of dexterity and ultrasound skills.

There are no studies that have directly compared these techniques. However, it is generally understood that implant quality is similar between the real-time and preplanned techniques.[614]

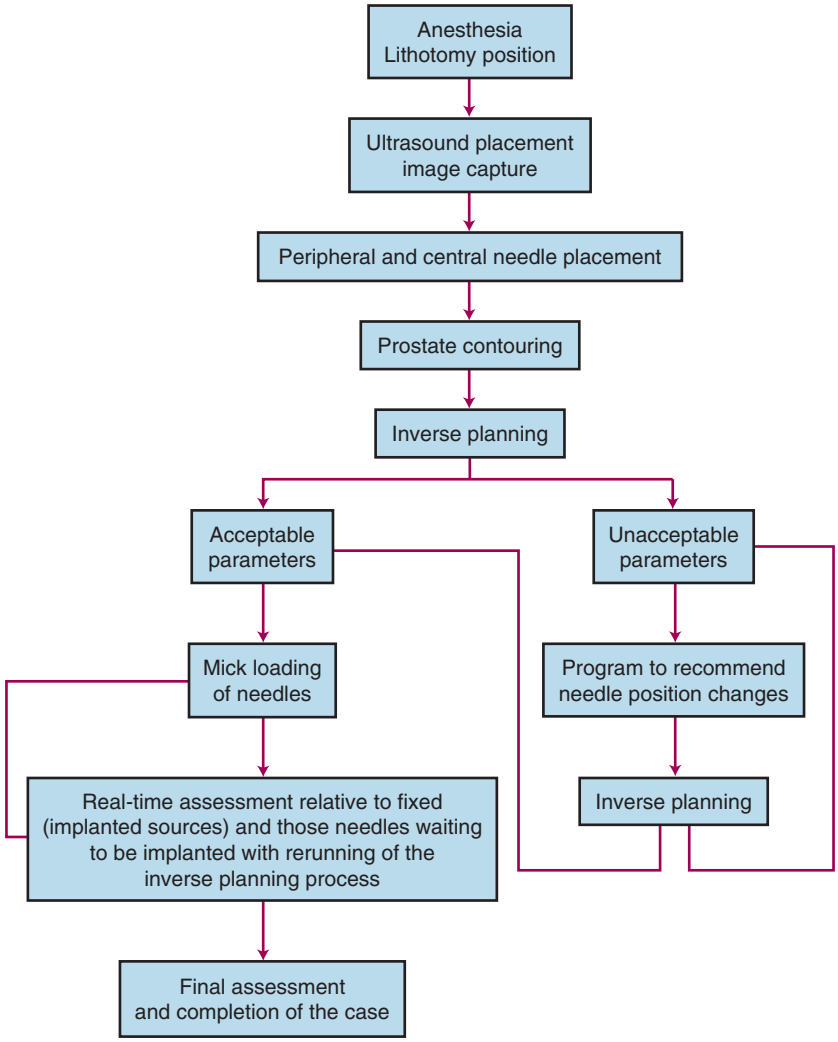


Figure 53-20 Dynamic prostate implant algorithm using treatment planning systems that employ inverse planning techniques.
From Potters L, Calguaru E, Thornton B, et al: Toward a dynamic real-time intraoperative permanent prostate brachytherapy methodology. Brachytherapy 2:172–180, 2003, with permission of the American Brachytherapy Society.

the role of AD in the management of patients with locally advanced disease, and whether the regional lymphatics should be irradiated. Real-time, conformal techniques control for dose to normal tissues while boosting the prostate, usually in 3 fractions, and better eliminate problems associated with catheter movement between fractions, when performed as a single needle implant.[1010]

Postoperative Irradiation

Treatment Technique

Adjuvant RT typically begins two to four months after surgery when urinary control is improved, and there is wound healing without urinary extravasations or anastomotic stricture. Evidence-based recommendations for pre-RT evaluation are unavailable, but it is prudent to obtain a serum PSA level to assure it is <0.2 ng/mL. Radiological or urological (e.g., cystoscopy) evaluations are seldom warranted, and should be performed only to pursue specific symptoms or clinical signs.

Pelvic nodal RT may be used in the node-positive setting,[1011] but recent series[1012-1015] and clinical trials[488,996,1016] otherwise defined the CTV as the prostatic fossa, and this is the current standard. CT simulation in supine position at ≤ 0.3-cm acquisition spacing with a protocol to assure the bladder is comfortably full and bowels are evacuated is recommended. Bladder contrast may facilitate identification of the vesicourethral anastomosis (VUA), and retrograde urethrography may aid localization of the urogenital diaphragm. However, urethrography may displace tissues superiorly,[961] so this should be accounted for in target delineation. Immobilization of the hips or legs should be considered.

Although guidance may be obtained from preoperative imaging and operative and pathologic findings (e.g., sites of margin involvement), the CTV is determined by the anatomic boundaries of the prostatoseminovesiculectomy as defined by CT or MRI postoperatively (Table 53-18 and Figure 53-21).[1017-1020] The prostatic fossa inferiorly is typically 0.5 cm to 0.8 cm below the VUA,[1018] but the penile bulb is not exposed surgically, so the CTV inferior margin need not extend into it. The superior dissection boundary is the superior surgical clips (if present) or approximately 0.5 cm above the ligation of the vasa deferentia. The anterior surgical plane is along the posterior symphysis pubis and the posterior bladder wall more

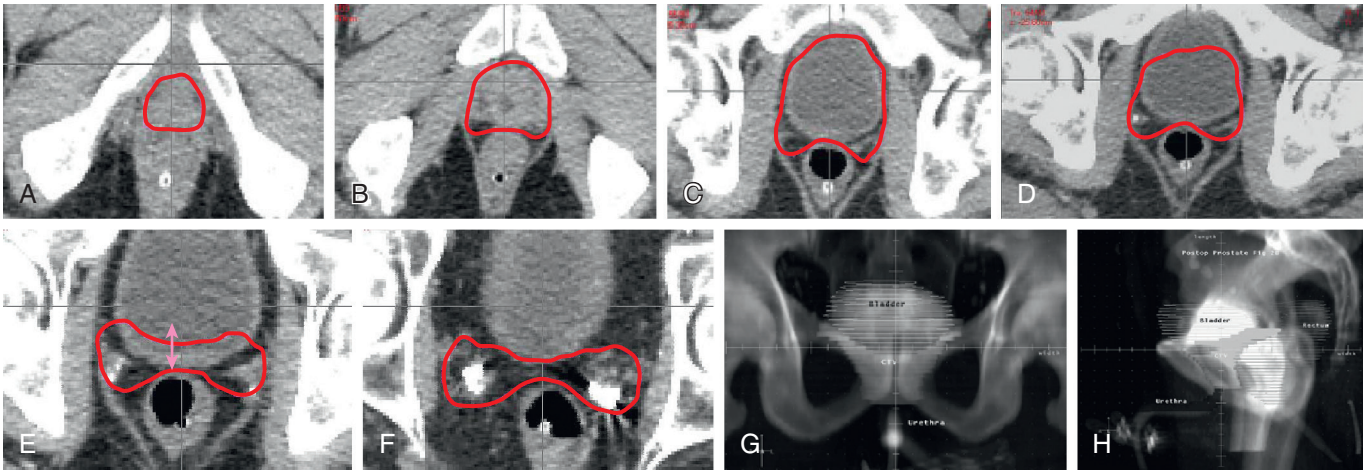


Figure 53-21 Axial CT simulation images from pelvic floor to level of distal vasa deferentia **(A-F)** with delineation of clinical target volume (CTV) and anterior-posterior and lateral radiographs **(G-H)** of CTV for postoperative RT.

TABLE 53-18 Anatomic Boundaries for Postoperative CTV Definition

	Below Superior Aspect of Symphysis Pubis	Above Superior Aspect of Symphysis Pubis
Anterior	Posterior aspect of symphysis pubis	Posterior 1.5 cm of bladder wall
Posterior	Anterior (outer) rectal wall • may form concavity laterally	Mesorectal fascia
Lateral	Obturator internus or levator ani	Sacrorectogenitopubic fascia • obturator internus, if + EPE
Inferior	0.8 cm inferior to VUA or immediately superior to penile bulb • encompass all prostatic fossa clips	—
Superior	—	Seminal vesicle bed as demarcated by clips or distal vas deferens • include residual seminal vesicles (if any), if + SVI

CTV, *Clinical target volume;* EPE, *extraprostatic extension;* SVI, *seminal vesicle invasion;* VUA, *vesicourethral anastomosis.*

superiorly. The posterior plane follows the anterior rectal wall and levator ani inferiorly and is anterior to the mesorectal fascia superiorly. The mesorectal fascia is the disruption in MRI fat signal or the CT hypodensity anterior to the rectum. Lateral dissection extends along the pelvic fascia, which is visualized as a disruption in MRI fat signal or CT hypodensity medial to the obturator muscle. More superiorly, the boundary is the sacrorectogenitopubic fascia.

The critical normal structures are rectum, bladder, femoral heads, and penile bulb, which are typically defined as solid structures for treatment planning. The outer rectal wall is outlined from the rectosigmoid flexure to the ischial tuberosities, and the femoral heads are delineated through the lesser trochanter. The bladder and bulb are outlined in their entirety. Dose-volumetric constraints on critical normal structures are sufficiently defined for prostate in situ RT,[1021] but are less well defined for postoperative RT. The etiology of RT-induced erectile dysfunction is vasogenic, but a dose-volume relationship has not been reported for postoperative RT. With primary RT, mean penile bulb dose > 52.5 Gy or D_{60} >42 Gy.[1022,1023]

The PTV encompasses the CTV with margins for set-up variation and internal displacement of target tissues. The *x*-(right:left), *y*-(superior:inferior), and *z*-axis (anterior:posterior) margins are derived from daily positional variations of prostatic fossa gold markers or surgical clips.[1024,1025] The standard deviation (SD) of the set-up variation is within 0.6 cm (*x*-axis) and 0.7 cm (*y*- and *z*-axes), and for internal displacement it is within 0.2 cm (all axes). If daily localization methods are not used, the SD of set-up variation and of internal displacement is combined in quadrature, and two SD are used so the CTV is covered in > 95% of treatments. Therefore, the PTV margins are 0.9 cm to 1.2 cm (*x*-axis), 1.0 cm to 1.6 cm (*y*-axis), and 0.9 cm to 1.1 cm (*z*-axis), but they may be reduced with daily image-guidance.[1024,1025]

The observational series (Table 53-15) and randomized clinical trials (Table 53-16) typically prescribed 60 Gy to 64 Gy. However, dose-response analysis suggested that ≥70.2 Gy yielded improved outcomes[1026] when a conformal approach with critical normal structure dose-volumetric constraints are met.[1027,1028] Although more study is needed, provisional dose-volumetric guidance is provided in Table 53-19.

The principles of salvage RT are similar to the adjuvant setting because the prostatic fossa only was treated in most reports (Table 53-17). The CTV is constructed in the same manner (Table 53-18, Figure 53-21), margins are added to define the PTV, and the same dose-volumetric constraints (Table 53-19) may be used in planning. Consensus guidelines recommend that ≥64 Gy should be prescribed to the PTV.[1029,1030] However, more recent literature supports ≥66.6 Gy to 70.2 Gy,[1024,1026] and 75 Gy has been delivered safely with IMRT.[1031]

TABLE 53-19 Dose Volumetric Constraints for Critical Normal Structures in Postoperative RT*

	Rectum	Bladder	Femurs	Comments
RTOG 0534	$V_{40} \leq 45\%$ $V_{65} \leq 25\%$	$V_{40} \leq 60\%$ $V_{65} \leq 40\%$	$V_{50} \leq 10\%$	Rectum: rectosigmoid junction → ischium; bladder: entire; Femurs: head → intertrochanter
Cozzarini[1027]	$V_{50} < 63\%$ $V_{55} < 57\%$ $V_{60} < 50\%$	—	—	Rectum: rectosigmoid junction → anal verge
Fonteyne[1028] †	$V_{40} < 84\%$ $V_{50} < 68\%$ $V_{60} < 59\%$ $V_{65} < 48\%$	—	—	Rectal wall: 0.6 cm superior to target volume → inferiorly
Sidhom[1019]	$V_{40} \leq 60\%$ $V_{60} \leq 40\%$	—	—	Rectum: rectosigmoid junction → 1.5 cm inferior of CTV

CTV, *Clinical target volume;* RT, *radiotherapy;* RTOG, *Radiation Therapy Oncology Group;* V_n, *volume receiving ≥ nGy.*
**These guidelines are preliminary, as more studies are needed.*
†*To avoid grade-2 or higher adverse events.*

TREATMENT ALGORITHM AND FUTURE DIRECTIONS

Practice guideline development methods were set forth by the Agency for Healthcare Research and Quality.[1032] Multidisciplinary efforts of this nature are centered on analysis of existing scientific outcome and technology assessment studies in an environment of consensus building. Clinical practice guidelines so derived are meant to apply to most, but not all, patients with the specified condition. Nonetheless, it is essential that patient evaluation and management decisions are made in light of all circumstances present in an individual case. In this context, the ACR,[1020,1033-1036] the AUA,[458] the ACS,[459] and the NCCN[316] provided management pathways relevant to pretherapy evaluation, radiotherapeutic care, posttherapy surveillance, and salvage therapy for patients with prostate cancer. Application of these guidelines will not necessarily ensure optimal outcome, so the clinician must exercise independent medical judgment to determine an individual patient's best care program. Likewise, as new studies are reported and more current information emerges, this must drive diagnostic and treatment decisions because formal guidelines are only updated periodically. There has been a rapidly advancing technological revolution in diagnostic imaging and radiation treatment secondary to computer-driven applications which can quickly make adopted guidelines and recommendations obsolete.

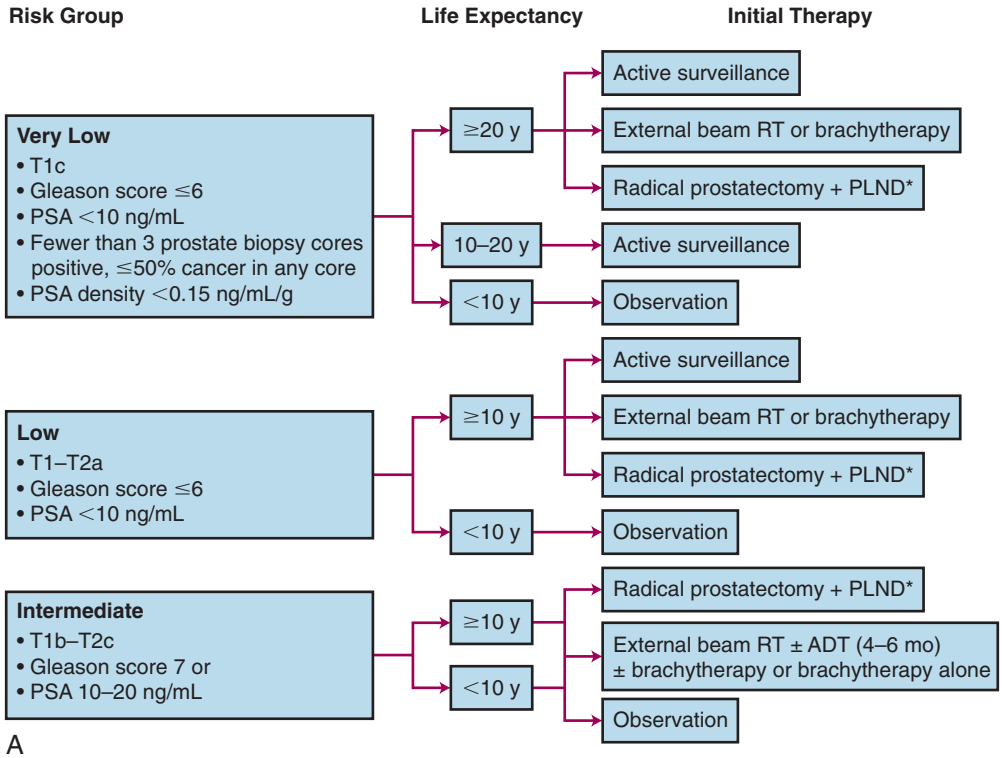
The most recent NCCN recommendations are presented in Figure 53-22.[316] In recent years the trend has been toward evidence-based medicine tailored as much as possible for the individual patient. This is especially pertinent in cancer care where studies, both prospectively randomized and retrospective, often provide generalized information for a disease, which can have significantly diverse variables in select populations and individuals. An emphasis has been placed on recommending active surveillance for patients with very-low and low-risk disease, especially those with limited life expectancies. Observation is now recommended for those patients with life expectancies shorter than 10 years with the intent to offer noncurative treatment in the event of a patient developing symptoms or there is a change in the patient's examination or PSA that would suggest symptoms are imminent. Patients with clinically significant disease should be counseled about all their management options. In high-risk and very-high-risk disease, radiation therapy with ADT is recommended over surgical options, which are appropriate only in carefully selected individuals.

Future Directions

The large gap in the rate of prostate cancer death compared to the high incidence of new prostate cancer diagnoses speaks to a significant heterogeneity in the biology of this disease. Understanding which individuals harbor clinically significant disease remains an important challenge for clinical investigation. The value of PSA screening has been questioned because of its low sensitivity and specificity. Better screening assays are being sought to help identify only those men in whom the diagnosis of prostate cancer warrants further evaluation and therapy. Urinary biomarkers such as PCA3 levels appear to complement serum PSA as a screening tool and they appear to correlate with tumor volume and aggressiveness.[1037] Once the diagnosis of prostate cancer is established, genetic screens[1038] for cancer aggressiveness will help identify patients for whom aggressive local or systemic therapy is warranted. Treatment decisions in the future will be driven less by conventional anatomic-based stage grouping but by a broad spectrum of clinical and biological markers that select patients for more individualized therapy.

Radiation oncologists will select treatment volumes, radiation doses and adjuvant therapies that target disease specific sensitivity or host factors to maximize tumor control and minimize side effects that contribute to a decline in quality of life.[1039] Adaptive radiation therapy strategies are currently focusing on tailoring technical aspects of treatment delivery to escalate radiation dose in patients that are best able to tolerate the therapy.[1040] Eventually, assays of normal tissue radiation sensitivity should allow biology based dose and fractionation prescriptions.[1041] The choice between conventionally fractionated as opposed to short-course, hypofractionated RT will be made based upon patient and tumor biology.

Continued investigation on systemic therapies and the interplay between the androgen receptor and hormone sensitivity will allow discovery of more effective AD and chemotherapeutic regimens. The complementary role of local therapies such as RT or surgery, along with new systemic agents in locally advanced and high risk disease is currently undergoing evaluation in clinical trials. Traditional ADT used in conjunction with RT may be augmented by new antiandrogen therapies or cytotoxic drugs such as docetaxel.



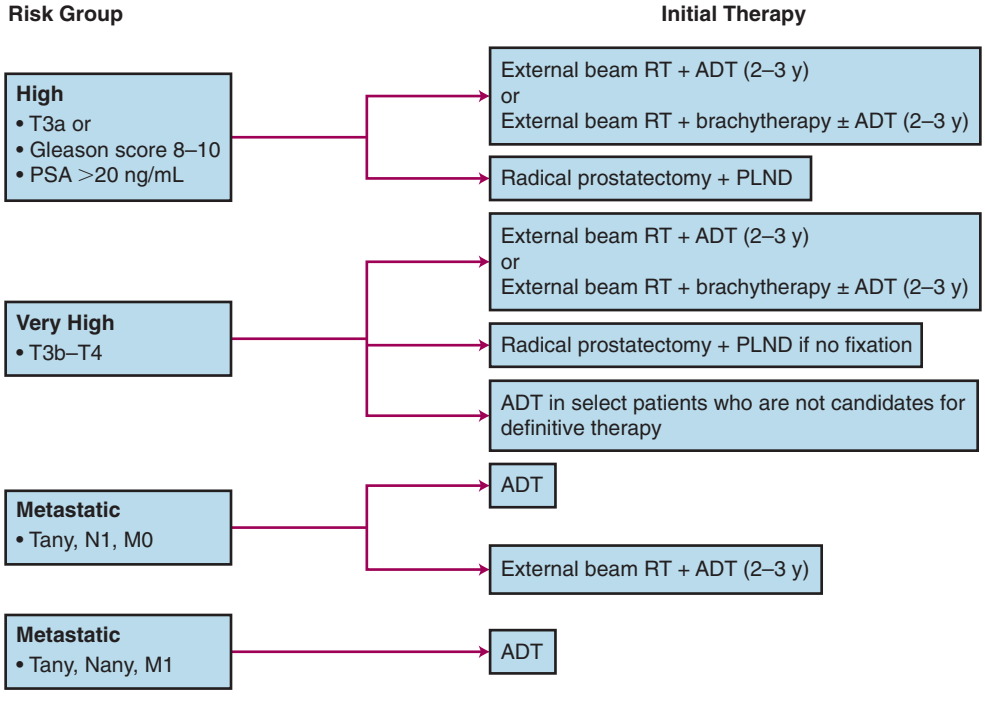


Figure 53-22 A, B, Prostate cancer treatment algorithms: Clinical practice guidelines by the National Comprehensive Cancer Network: prostate cancer version 2:2014. *3D-CRT,* Three-dimensional conformal radiation therapy; *PSA,* prostate-specific antigen; *RT,* radiation therapy.
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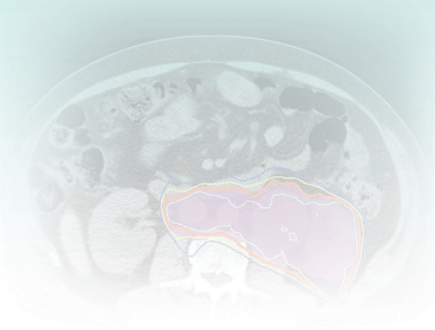
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CHAPTER

54 Bladder Cancer



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INCIDENCE

Carcinoma of the urinary bladder is diagnosed in approximately 74,000 people each year in the United States, making it the fourth-most common cancer in men (56,000) and eleventh in women (18,000). Approximately one third will have muscle-invasive disease. About 16,000 (1,100 men, 4,500 women) will die from bladder cancer in 2015. Urothelial (transitional cell) carcinoma has strong etiologic connections with smoking. The less common squamous cancer is more closely associated with chronic inflammation such as *Schistosoma* infection or indwelling catheter.

BIOLOGIC CHARACTERISTICS

The most important predictors of progression from nonmuscle-invading stage to the muscle-invasive stage are high grade, penetration of the lamina propria, and the presence of carcinoma in situ. Once muscle invasion has occurred, the strongest predictors of metastasis and death are bulk of tumor and depth of invasion.

Expression studies and now large-scale sequencing efforts are providing new insights into the landscape of recurrent molecular alterations in bladder cancer and potentially targetable mutations and personalized treatment selection for patients undergoing selective bladder preservation. These include biomarkers prognostic and predictive of response and outcome involved in cell-cycle regulation, apoptosis, proliferation, DNA repair, chromatin regulation, kinase signaling pathways, and hypoxia. These biomarkers continue to be investigated and need further validation.

STAGING EVALUATION AND WORKUP

Painless hematuria is the classic and most common presentation, though irritative voiding symptoms may occur as well. Urine cytology commonly indicates cancer but cystoscopy and transurethral resection is necessary for definitive assessment of the primary tumor.

Magnetic resonance imaging (MRI) may define penetration of the bladder wall and either MRI or computed tomography (CT) scan can evaluate abdominopelvic lymph nodes. The upper tracts must also be evaluated with CT, intravenous pyelogram (IVP), or retrograde ureteroscopy because synchronous tumors are common. Chest x-ray (or CT of the chest) and bone scan are usually obtained to rule out metastatic disease when cancer invades the muscle.

PRIMARY THERAPY

Nonmuscle-invading tumors are managed by transurethral resection of the bladder tumor (TURBT) alone in the case of low-grade lesions and together with intravesical bacillus Calmette-Guérin (BCG) for high-grade, lamina propria invasion, or carcinoma in situ. Over 10 years as many as 50% of the latter group will progress to muscle invasion.

Radical cystectomy with urinary diversion is the United States standard for the management of muscle-invading cancers. There is 90% control within the pelvis, but up to 50% ultimately die of distant metastasis. Radical radiation alone provides only 30% to 40% local control though the use of salvage cystectomy keeps cure rates close to that of primary cystectomy. When limited surgery (TURBT) is combined with radiation and concurrent (often cisplatin-based) chemotherapy, more than 70% of patients keep their native bladders and cure rates are comparable to published cystectomy series. Quality-of-life studies show high levels of satisfaction with the retained bladder.

ADJUVANT THERAPY

Neoadjuvant chemotherapy downstages the primary tumor more than 50% of the time but only adds 5% to 10% to the chance for cure. Adjuvant chemotherapy is commonly used but has proven utility only in the case of node-positive disease.

Adjuvant radiation may be given after cystectomy for locally advanced disease but the benefits need to be better defined.

LOCALLY ADVANCED DISEASE AND PALLIATION

When there is hydronephrosis, extension into adjacent organs or nodal spread, the likelihood of cure is small. Cystectomy or radiation may be used for palliation of voiding symptoms or bleeding, but the mainstay of care for metastatic disease is combination chemotherapy.

Bladder cancer is a chemoresponsive disease. Cisplatin-based regimens give responses in more than 60% of patients and are often quite durable. Other active agents include Taxotere, gemcitabine, and 5-fluorouracil (5-FU)/mitomycin C.

Radiation therapy is effective in palliating painful bone metastases and in alleviating symptoms from brain metastases.

Approximately 70% of all new cases of bladder cancer are early stage and have not yet invaded the detrusor smooth muscle. In the absence of muscle invasion, endoscopic transurethral resection (TUR) with or without intravesical therapy is the therapy of choice, and the radiation oncologist plays only a limited and occasional role. For muscle-invading disease, the most appropriate treatment algorithm remains controversial. Although radical cystectomy has long been the standard treatment in the United States, organ-preserving regimens using radiation with concurrent chemotherapy are comparably effective alternatives in selected patients.

In this chapter, we separately discuss the treatment of nonmuscle-invading and muscle-invading disease. Special emphasis is placed on the development of combined-modality therapy in muscle-invading bladder cancer with and without bladder preservation.

ETIOLOGY AND EPIDEMIOLOGY

Bladder cancer is the most common malignancy involving the urinary system and the second-most common genitourinary cancer. It is the sixth-most common cancer overall; fourth-most common cancer among men and the eleventh-most common cancer among women. It is estimated that there will be approximately 74,000 new cases and 16,000 bladder cancer deaths in 2015.[1] The rates of new cancers and deaths have been fairly stable in men and have been dropping slightly in women in recent years. The reasons for the disparity between the sexes are not well understood. More than 500,000 people in the United States are bladder cancer survivors.

Internationally, incidence rates of bladder cancer vary almost 10-fold. Highest rates occur in western Europe and North America; relatively low rates are found in eastern Europe and several areas of Asia (China, India, Philippines).[2,3]

Cancer of the bladder occurs primarily in older men. Median age at diagnosis of is 73 years. More than two thirds of cases occur among persons age 65 and older. The incidence rate among African American and Hispanic men is about 50% of that among whites. The male-to-female ratio is at least 3:1, approaching 4:1 in whites.[4] Five-year survival rate for all patients is 77% (96% for in situ disease, 69% localized, 34% regional, and 5% distant). Overall incidence and death rates have been relatively stable over the past 10 years.

Risk Factors

Cigarette smoking and various environmental and occupational exposures are the major risk factors for bladder cancer. These substances concentrate in the urine, where the urothelial lining is exposed to their carcinogenic effects. Cigarette smoking is associated with up to 50% to 60% of bladder cancer diagnosed in men and 30% among women in the United States. Occupational exposure among white men accounts for 25% of bladder cancer diagnoses in men and 11% in women. Specific chemicals linked to bladder carcinogenesis include beta-naphthylamine, 4-aminobiphenyl, and benzidine. Evidence also suggests that chlorinated organic compounds formed as a by-product of drinking water chlorination may account for 10% to 15% of cases. Infection with *Schistosoma haematobium* is a well-documented risk factor and an important cause of bladder cancer in developing countries.

Cigarette smoking increases the risk of bladder cancer two- to fourfold. Risk estimates for moderate to heavy smokers range from 2 to 10 compared with nonsmokers.[5-9] Smokers with less functional polymorphisms of N-acetyltransferase-2 (known as slow acetylators) have a higher risk of bladder cancer than other smokers, presumably because of their reduced ability to detoxify carcinogens.

Some studies indicate a reduction in risk by more than 30% within the first year to 4 years after cessation of smoking, and more than 60% 25 years after cessation, but even after 25 years the risk still does not reach the background level of never smokers.[7,9] Smoking cessation may decrease recurrence rates for patients with nonmuscle-invasive disease.[10] Exposure to secondhand smoke in women may be a risk factor for the development of bladder cancer.[11]

In the 1950s, occupational exposures to aromatic amines in the British dyestuff and rubber industries were found to be associated with bladder cancer.[12,13] The mean time from start to exposure to death was 25 years, with the greatest risk for workers who started before age 25. Workers in the leather industry are at increased risk for bladder cancer.[14,15] The increased risk for painters seems to be the result of many known carcinogens in paint such as benzidine, polychlorinated biphenyls, formaldehyde, asbestos, and solvents such as benzene, dioxane, and methylene chloride.[16] Drivers of trucks, buses, or taxicabs are suspected to have an increased exposure to exhaust emissions containing polycyclic aromatic hydrocarbons (PAHs) and nitro-PAHs.[17]

It was first recognized in the 1970s that chlorination of drinking water generates a wide array of halogenated organic compounds. A number of epidemiologic studies investigated the possible association between exposure to these compounds and cancer. A 1992 meta-analysis of these studies found a significant association between exposure to chlorination by-products and bladder cancer.[18] Several studies published subsequently supported this conclusion.[19,20] High levels of arsenic in drinking water have also been linked to the subsequent development of bladder cancer.[21]

Aromatic amines are detoxified by *N*-acetylation. The *N*-acetyltransferase enzyme in the liver is polymorphic, displaying a slow and a rapid acetylator phenotype. The allele that confers a slow acetylator phenotype is assumed to be associated with an increased risk of bladder cancer (relative risk, 1.1 to 1.9).[22]

There are several other well-documents risk factors. Exposure to *S. haematobium* infection is associated with a predominantly increased risk of squamous cell carcinoma of the bladder.[23] Heavy consumption of phenacetin-containing analgesics was linked to cancer of the renal pelvis, ureter, and bladder.[24] Cyclophosphamide, an alkylating agent, and pelvic radiation have also been linked to the risk of bladder cancer.[25-27] Other risk factors include low total daily fluid intake, chronic cystitis, indwelling catheters, recurrent urinary tract infections, and consumption of Chinese herbs containing aristolochic acid.[28,29]

PREVENTION AND EARLY DETECTION

Primary prevention involves identification and avoidance of cancer-causing factors.[30] In public health terms, avoidance and cessation of cigarette smoking is the most effective means available for the prevention of bladder cancer. Decreasing exposure to workplace carcinogens and increasing fluid intake are other useful approaches.

Secondary prevention involves screening individuals at high risk for a particular cancer with the goal of early detection and treatment. Urine cytology as a screening test is low cost and low risk and has excellent specificity > 98% but relatively poor sensitivity, particularly for low-grade tumors (overall sensitivity 34%, with sensitivities for grades 1, 2 and 3 tumors of 12%, 26%, and 64%, respectively).[31] Furthermore, the prevalence of preclinical bladder cancer is probably too low in the general population for large-scale screening programs to be rewarding. Testing for asymptomatic hematuria does not appear to be a useful method for screening. A single test has a low sensitivity. Repeat testing at short intervals, such as weeks, has been advocated but yields unacceptably high rates of false-positive results.[32,33] Overall, screening has not been particularly useful in the detection of bladder cancer and the most recent statement from the U.S. Preventive Services Task Force concludes that the current data are insufficient to make a definitive recommendation on screening for bladder cancer in asymptomatic adults.[34] When urothelial cancer is suspected, noninvasive screening may be performed using cytology, nuclear matrix protein, telomerase, or fluorescence in situ hybridization (FISH) analysis, but the definitive diagnosis is made only by cystoscopy and biopsy.

Chemoprevention involves the administration of a natural or synthetic agent to healthy people (primary) or patients with precancerous conditions who are at high risk for bladder cancer (secondary) to prevent or retard the development or progression of cancer. Retinoids (vitamin A derivatives) as

well as high-dose multivitamins, pyridoxine (vitamin B6), alpha tocopherol (vitamin E), ascorbic acid, polyamine synthesis inhibitors, polyphenols (green tea extract), COX-2 inhibitors (celecoxib), EGFR tyrosine kinase inhibitors (erlotinib), and oltipraz have been or are under investigation as potential chemopreventive agents,[35-45] but nothing definitive has been established at present. Additional studies are under way.

PATHOLOGY AND PATHWAYS OF SPREAD

In the United States, more than 90% of cancers arising in the bladder are urothelial carcinoma (UC), also known as transitional cell carcinoma (TCC). Less common pathologies are squamous cell carcinoma (SCC), adenocarcinoma, and small cell carcinoma, comprising approximately < 10% of bladder tumors, respectively. In Egypt, SCC comprises 70% of all bladder cancers.

Macroscopically, papillary growth is more frequent than solid tumors (approximately 80% versus 20%). Solid tumors are more likely than papillary tumors to be high grade and invasive into the muscularis propria layer.

Although the collective term *superficial cancer* is still commonly used, it is a category that comprises several classes of transitional cell cancers with different rates of recurrence, different rates of progression to muscle invasion, and quite different treatments. The tumors that arise in the epithelium and develop in an exophytic (papillary) pattern are known as Ta tumors. They are usually low grade (I or II), and although they tend to recur, they are considered to be relatively benign lesions that closely resemble the normal urothelium. Although they have more than the normal seven layers of urothelium, they show normal nuclear polarity in more than 95% of tumors and no or only slight pleomorphism. When progression deeper into the submucosa or lamina propria occurs the tumor is described as T1 and carries a higher risk of progression and even of metastasis.

Grade is an important predictor of recurrence and progression for all categories of superficial disease. Pathologic grades I to III (low, intermediate, or high) are based on the number of mitoses, presence of nuclear abnormalities, and cellular atypia. High-grade tumors show loss of polarization of the nuclei and moderate to prominent pleomorphism. Muscle-invasive disease, however, is usually high grade, and depth of invasion is the more important prognostic factor for outcome.

Carcinoma in situ (Tcis) is defined as noninvasive, high-grade, flat cancer confined to the epithelium, which can be localized or diffuse, and it may occur in association with either superficial or muscle-invasive TCC. Tcis can also occur without a concurrent exophytic tumor. Endoscopically, Tcis presents as a friable red area indistinguishable from inflammation and spreads laterally, displacing normal epithelium. Urine cytology is positive in 90% of patients with Tcis because of a loss in the cohesiveness of cells.

In T2 lesions, muscle invasion is present and the probability of nodal and distant spread is increased. T2 disease is divided into superficial (T2a) or deep (T2b) invasion.[46]

SCCs are associated with chronic inflammation or infection with *Schistosoma* and tend to grow as large masses with a high degree of necrosis. In North America they are more commonly associated with chronic bladder irritation or stasis such as a lifelong indwelling catheter. The North American variant has the distinction of higher metastatic propensity.

TCC is often multifocal both in place and in time (polychronotropism). This is a striking characteristic of this disease but the etiology is uncertain. Two of the most commonly held explanatory theories are a genetic field defect with multiple new tumors spontaneously arising or, alternatively, the local reimplantation of tumor cells ("local metastasis). Evidence strongly suggests that tumor reimplantation or submucosal migration is the predominant mechanism. Multifocal tumors as well as upper tract and lower tract lesions arising in one individual demonstrate clonality.[47] Therefore, the entire urothelium needs to be evaluated if a tumor is found.

External and internal iliac chains as well as perivesical lymph nodes are first-echelon lymph nodes. Common iliac, paraaortic, and paracaval lymph nodes are considered second-echelon lymph nodes. Lymph node sampling in patients undergoing cystectomy should include excision of 12 or more lymph nodes.[47]

Bladder cancer can also spread by direct extension or hematogenous metastases. Direct extension can be to the prostate, pelvic side wall, anterior pelvic structures, symphysis pubis, rectum, or sigmoid colon. Hematogenous metastatic spread is most frequently seen to the lung, liver, and bone. Peritoneal metastases are another route of spread.

MOLECULAR BIOLOGY

Newly discovered cellular mechanisms and their associated proteins have become the subject of intense interest. This is partly for what they tell us about the biology of a tumor but also because of their potential role as prognostic markers or therapeutic targets. It has long been recognized that invasive bladder tumors are extremely heterogeneous in nature despite almost always being of high-grade transitional cell morphology because of complex genetic and epigenetic interactions that play a direct role in the initiation and progression of TCC. When the range of genetic alterations is considered, deletions (e.g., loss of tumor suppressor genes) generally arise in early stage disease, whereas gains and amplifications (e.g., activation of oncogenes) may be more frequent in advanced stages of disease. Genetic factors may also modify the risk associated with exogenous agents through activation or detoxification of potential carcinogens. The search to understand the heterogeneity and use it to therapeutic advantage is only just beginning. At the moment the best prognostic indicators we have in bladder cancer are clinical: stage, grade, tumor size, uni- or multifocality, and the presence or absence of either hydronephrosis or lymph node involvement (see later). No molecular biomarker has yet come close to improving on these clinical markers, but it is anticipated that they will in the near future.[48,49] Likely this will involve a combination of multiple independent markers and an individual tumor's gene expression pattern.

Apoptosis and Cell Cycle Receptors

These receptors provide malignant cells with an evolutionary selective advantage. These include cellular immortalization, escape from G1 checkpoint control, loss of DNA damage checkpoints (G2/M), loss of normal DNA repair mechanisms, loss of apoptotic response, and the development of invasive capabilities.[50-52] The *pRb* and *p53* pathways, which involve several common molecules, provide G1 checkpoint control and regulate the response to DNA damage. Though the *Rb* gene itself is only mutated in a few specific cancers it is thought that abnormalities of its function are far more common and transitional cell bladder cancer is one of these.[51,53-55] Disruption of its function is required to overcome the restraint it imposes on cell-cycle progression. The pro-apoptotic tumor suppressor gene eliminates cells with abnormalities in their *Rb* pathways. Thus, tumors commonly have abnormalities in p16 and p14ARF and abnormalities at these loci may also be required to overcome the checkpoints that protect the cell from aberrant stimuli. *p53* mutations, which may be detected by nuclear immunohistochemistry, are present in more than one half of bladder tumors and appear to be related to the progression of

bladder cancer and to outcome following treatment.[53,56-59] A meta-analysis of 168 studies assessing *p53* overexpression showed a weak, although significant, association with overall risk of relapse and mortality.[60] Cooperative group trials of either methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) chemotherapy or chemoradiation have not shown any clear association between *p53*, *pRb*, or *p16* or status and outcome.[61,62] Other genes that have been studied include *Bax*, *Bcl-2*, *p21*, survivin, and matrix metalloproteinases.[63-70]

Researchers from Germany have suggested that one does not have to analyze the molecular pathways relating to apoptosis to predict response; a measure of the baseline spontaneous apoptotic rate of the tumor may be easier and quite sufficient. High-apoptotic index and high Ki-67 index correlated with improved complete response, local control, and cause-specific survival with a preserved bladder following chemoradiation. The inability to undergo spontaneous apoptosis whether the result of overexpression of *Bcl-2* or survivin appears to predict local failure after irradiation and chemotherapy.[71]

The RAS family of transforming genes is often overexpressed in bladder cancer. Their presence may be related to the original development of the tumor. In a mouse model, farnesyltransferase inhibitors, which inhibit the posttranslational modifications of H-ras, worked synergistically with radiation in reducing tumor relapse.[72]

Growth Factor Receptors

The epidermal growth factor (EGFR) family of receptor tyrosine kinases is known to initiate a complex program of signal transduction events that modulate cell survival, invasion, migration, proliferation, and differentiation. This family has a number of members of which *erb-1* (EGFR) and *erb-2* (Her-2) are characterized the best. The role of these receptors has been studied extensively in recent years in a variety of malignancies and there is evidence that increased activity through this pathway is common.

Both EGFR and Her-2 are commonly overexpressed in urothelial tumors. Numerous studies have investigated expression of Her-2 in bladder cancer using immunohistochemistry and have found overexpression in 30% to 80% of tumors.[60,73-76] There are, however, conflicting data on the relationship between the expression of these receptors with response to treatment and clinical outcome.

An RTOG study evaluated the clinical relevance of EGFR and Her-2 expression as measured by immunohistochemical staining on slides from 73 patients treated on four of the RTOG bladder preservation trials and pointed to a more favorable prognosis in those who overexpress EGFR but a lower complete response rate in patients with TCC who overexpress Her-2.[62] EGFR positivity (EGFR-1 expression identified in 19% of patients) correlated with improved overall survival (OS, $p = 0.044$), disease-specific survival (DSS, $p = 0.042$), and survival with an intact bladder ($p = 0.021$). A trend toward decreased incidence of distant metastases was also associated with EGFR expression. On multivariate analysis, adding tumor stage, tumor grade, whether or not a visibly complete TURBT was done, and patient age to the model, EGFR positivity remained significantly associated with improved DSS. Her-2 overexpression correlated with reduced complete response rates to chemoradiation (50% versus 81%, $p = 0.026$), which remained significant on multivariate analysis. *p53* and *p16* had no prognostic significance. These patients had all been treated with chemotherapy and radiation, and it may be that EGFR has a more direct involvement in improving the response of TCC to these agents than it does other tumors. It will be crucial to elucidate this relationship clearly as a growth factor receptor may be either a favorable or an unfavorable marker depending on the proposed therapy. The RTOG data suggested that targeting the Her-2 pathway may be more profitable than EGFR in the initial therapy of muscle-invasive bladder cancer. There is certainly experimental evidence that Her-2 has an antiapoptotic effect and that tumor radiosensitization can result from targeting this mechanism.[77] RTOG trial 05-24 evaluated the addition of trastuzumab (Herceptin) to paclitaxel and daily radiation following TURBT in the treatment of noncystectomy candidates with muscle-invasive bladder cancer. The protocol was completed with 70 patients accrued in 2013. Thirty-one percent of patients overexpressed Her-2. Among patients with evaluable data, overall complete response rate was 62% (trastuzumab group) versus 58%.[78] This response rate was higher than expected from historical controls.

Another RTOG study evaluated VEGF pathway biomarkers and outcomes following chemoradiation for patients managed with selective bladder preservation.[79] No correlations of ligands VEGF A-D or receptors VEGF R1-2 were found with response to induction chemoradiation or with local tumor recurrence. However, VEGF-B overexpression did predict for distant failure and worse OS. Therefore, VEGF-B might prove useful in identifying patients more likely to benefit from early cytotoxic therapy or anti-VEGF–targeted therapies.

Alterations in fibroblast growth factor receptor (FGFR) expression and signaling have emerged as recurring and potentially important events in bladder urothelial carcinoma. In bladder cancer, these alterations primarily occur in one of the following ways: (1) activating mutations in the extracellular ligand-binding domain of FGFR3 that lead to ligand-independent signaling, (2) overexpression of the receptor, or (3) fusions primarily with TACC3 or BAIAP2L1. In addition, FGFR3 gene copy number alterations occur but are rare.[79a-79e] Data suggests that the presence of mutations in fibroblast growth factor receptor 3 (FGFR3) identifies a subgroup of patients with nonmuscle-invasive disease who may have a favorable prognosis.[80] Further investigation into the potential diagnostic and therapeutic implications of such findings is warranted and may lead to the rational development of targeted therapies.

DNA Repair

Biomarkers involved in DNA repair may also be prognostic and even predictive following radiation-based therapy.

Excision repair cross-complementing 1 (ERCC1) is vital for nucleotide excision repair (NER) and may predict efficacy of chemoradiation. Cisplatin-DNA adducts can by removed by NER, thus high levels of ERCC1 expression have been correlated with cisplatin resistance. ERCC1 also may participate in double-stranded break (DSB) repair and cells deficient in ERCC1 are highly sensitive to ionizing RT. ERCC1 down-regulation in high-expressing cells results in sensitization to RT but not cisplatin. Expression levels of ERCC1 in human tumors correlate with treatment response and survival to platinum-based chemotherapy and chemoradiation. Clinical complete response (CR) rate for patients with negative ERCC1 was 86% (12 of 14), compared to 25% (2 of 8) for patients with positive ERCC1.[81] Five-year OS was 31.2% for those with positive ERCC1 and 69.2% for those with negative ERCC1. Therefore, ERCC1 expression levels may predict for patients unlikely to respond to a chemoradiotherapy-based approach. Another recent effort found that tumors with ERCC2 mutations were enriched among muscle invasive bladder tumors that responded well to cisplatin-based combination cytotoxic chemotherapy.[80a]

X-ray repair cross-complement group 1 (XRCC1) and human AP endonuclease 1 (APE1) are both proteins vital for base excision repair (BER) in DNA repair. Increased expression

A cooperative group trial tested the role of three cycles of combination MVAC chemotherapy in patients with negative nodes but mutated *p53* given that *p53* alteration was thought to be prognostic for relapse in patients with urothelial bladder cancer and predictive for benefit from combination MVAC adjuvant chemotherapy.[61] Accrual was halted on the basis of a futility analysis. Overall 5-year probability of relapse was 0.20 (95% CI, 0.16 to 0.24) with no difference on the basis of *p53* status. Although the study was underpowered, neither the prognostic value of *p53* nor the benefit of MVAC chemotherapy in patients with *p53*-positive tumors was confirmed. These data emphasize the importance of careful validation of any biomarker before proceeding on with Phase III analysis. Work from the Radiation Therapy Oncology Group (RTOG) on patients who were treated with chemotherapy and radiation have also not shown any clear association between either *pRb*, *p16*, or *p53* status and outcome.[62]

Other genes regulating apoptotic function or involved in the initiation of bladder carcinogenesis and its progression have been studied, such as *Bax*, *Bcl*-2, *p21*, survivin, and matrix metalloproteinases.[63-70] In examining a large database containing bladder cancer of different stage all treated by a variety of methods it did seem that those who had Bax or CD40L tumors lived longer. Bcl-2 positivity appeared to predict worse survival. The caveat, however, is that most of these were not prospective studies balanced for other prognostic variables.

The FDA has approved the use of ZD1839, an inhibitor of EGFR1, for patients with lung cancer and of trastuzumab, a monoclonal antibody against EGFR2 or Her-2, for appropriate patients with breast cancer. In breast cancer, overexpression of Her-2 is associated with poor prognosis, and the activity of trastuzumab unequivocally correlates with overexpression of Her-2.

of XRCC1 and APE1 were both associated with improved DSS, but only when both were present ($p = 0.0003$).[82]

Ionizing radiation creates DNA damage sensed by the MRE11/NBS1/RAD50 (MRN) complex, which initiates cell cycle checkpoints, activates apoptosis, and is involved in MRN-mediated DSB repair. MRE11 (meiotic recombination homolog) is a vital member of the MRN complex responsible for detecting DNA DSB. Along with Rad50 and NBS1/XRS2, MRE11 is responsible for activation of checkpoint kinases and induction of cell cycle arrest in response to DNA damage. It is vital for recruiting ATM and other mediators of DSB repair. A group in the United Kingdom has shown that reduced tumor MRE11 protein expression by immunohistochemistry is associated with and appears to be predictive of poorer cause-specific survival (CSS) following radical RT for bladder cancer.[83] High-MRE11 expression was associated with superior CSS in patients treated with radical RT with a 57% improvement in CSS at 3 years ($p = 0.012$). The effect of MRE11 expression on clinical outcomes was only evident in patients treated with RT and not those treated with cystectomy. When compared, similar patients with high-MRE11 expression had improved CSS when treated with RT compared to cystectomy, whereas the opposite was true for those with low-MRE11 expression. MRE11 expression levels may therefore identify a cohort of patients with improved survival when treated with RT compared to cystectomy.

Mechanistically, it was postulated that failure of cell cycle arrest/apoptosis responses may result in radioresistance and reduced local tumor control.

The MRE11 findings were validated by a Danish group, who showed that TIP60 (histone acetyltransferase involved in chromatin remodeling and DNA repair) was a predictive marker for DSS in a cystectomy cohort, and MRE11 in an RT cohort.[84] In that study, *p16* also correlated with DSS, but was not predictive. *Ki67*, *p53*, and *pATM* were not correlated with DSS in any of the cohorts.

Hypoxia

Hypoxia is well recognized to be strongly associated with both radiation and chemotherapy resistance. Indeed, the addition of carbogen and nicotinamide (CON) to RT improves OS in invasive bladder cancer. Hypoxia results in the upregulation of genes that facilitate anaerobic metabolism and promote tumor vascularization. One such hypoxia–inducible factor is carbonic anhydrase IX (CA IX). It appears to be useful as a surrogate marker of hypoxia within bladder tumors. Several studies have shown that the majority of bladder tumors express this marker though it appears, strangely, to be more strongly expressed in superficial than invasive tumors. Evidence on its role as a prognostic marker has been conflicting.[85,86] Necrosis seems to predict benefit from hypoxia modification in patients with high-risk bladder cancer.[87] The hypoxia marker hypoxia-inducible factor-1α (HIF-1α) may be used to predict benefit from CON in patients with bladder cancer but does not improve on use of necrosis.[88]

Future of Molecularly Targeted Therapy

To date, no molecularly targeted agents have been approved for treatment of bladder cancer. Large scale sequencing efforts are likely to change this and provide new insights into the molecular alterations in bladder cancer and targetable mutations.

The addition of rational molecular targeted therapy and personalized treatment selection based on biomarkers (e.g., DNA repair, apoptosis, proliferation, hypoxia, such as high MRE11, normal Her2, low ERCC1, high XRCC1/APE1) of response and outcome, continues to be investigated and needs further validation. Future focused correlative analyses using findings discussed in this section are likely to refine clinically useful biomarkers for patients undergoing selective bladder preservation.

CLINICAL PRESENTATION, PATIENT EVALUATION, AND STAGING

Clinical Presentation

Painless, gross, and episodic hematuria is the most frequent presenting manifestation of bladder cancer (80%), typically present through urination. It also may be associated with irritative symptoms (dysuria, frequency, urgency), which can occur in up to one third of patients and is suggestive of bladder carcinoma in situ (CIS). Ten percent to 20% of patients presenting with gross hematuria are diagnosed with bladder cancer.[89,90] Some asymptomatic patients proven to have bladder cancer are found to have microscopic hematuria or less frequently pyuria. Bladder tumors can cause strangury (pain on straining to urinate), urinary retention, ureteral obstruction, sepsis, and rarely life-threatening hematuria. Regional pelvic disease may cause flank pain because of nerve invasion, edema, and ureteral obstruction. The signs and symptoms of bone, liver, pulmonary, and central nervous system metastases may be present if disease has disseminated.

Workup of Hematuria or Suspected Bladder Tumor

Patient workup should include physical examination (including digital rectal and bimanual), voided urine analysis, urinary cytology, intravenous pyelogram or CT urogram (for upper tract evaluation), and cystoscopy with biopsy of suspicious lesions. If the disease is classified as T1 or greater, the work-up must include abdominopelvic CT scan or MRI and chest radiograph (or chest CT). For those with muscle-invading disease a bone scan is also necessary.

Endoscopy

The endoscopic evaluation forms the mainstay of diagnosis and staging. Initially, an outpatient cystoscopy with biopsy is performed, and urine is obtained for cytology. Cystoscopy provides direct visualization of the bladder and facilitates biopsy of the bladder. Number, size, shape, and location of tumors as well as appearance of the surrounding mucosa, urethra, and urethral orifice are documented. Size (<2 cm, >5 cm), shape (papillary or flat), and associated Tcis lesions are of predictive importance. Using an illustrative bladder map, the location, number, size, and characteristics (papillary versus sessile) of the bladder tumor as well as presence or absence of CIS should be noted. Fluorescence cystoscopy after intravesical instillation of a photoactive substance (a porphyrin such as 5-aminolevulinic acid [5-ALA]) that preferentially accumulates in neoplastic tissue may be more effective than white light cystoscopy. Randomized trials have shown that fluorescence endoscopy detects more tumors (particularly CIS) and this improved tumor identification may result in better patient management and reduced disease recurrence,[91-93] though not all clinical trials have shown a benefit.

If the findings are positive for bladder cancer, a subsequent cystoscopic TURBT, which is generally performed under epidural or general anesthesia, is scheduled.

TURBT and Bladder Biopsy

Cold cup biopsies of all suspicious areas, the mucosa surrounding the area, any exophytic lesions, and the prostatic

The Cancer Genome Atlas project recently reported an integrated analysis of 131 urothelial carcinomas to provide a comprehensive landscape of molecular alterations.[49] There were statistically significant recurrent high frequency mutations/alterations in 32 genes, including multiple genes involved in cell-cycle regulation, chromatin regulation, and kinase signaling pathways, as well as 9 genes not previously reported as significantly mutated in any cancer. RNA sequencing revealed four expression subtypes, two of which (papillary-like and basal/squamous-like) were also evident in microRNA sequencing and protein data. Whole-genome and RNA sequencing identified recurrent in-frame activating FGFR3-TACC3 fusions and expression or integration of several viruses (including HPV16) that are associated with gene inactivation. These analyses identified potential therapeutic targets in 69% of the tumors, including 42% with targets in the phosphatidylinositol-3-OH kinase/AKT/mTOR pathway and 45% with targets (including ERBB2) in the RTK/MAPK pathway. Chromatin regulatory genes were more frequently mutated in TCC than in any other common cancer studied so far, indicating the future possibility of targeted therapy for chromatin abnormalities.

urethra as well as random biopsies of all four quadrants are obtained. All material is collected. When diffuse CIS is present, the prostatic urethra contains neoplastic cells in up to 25% of cases. For evaluation of muscle invasion, sufficient resection to provide adequate staging has to be done. An attempt is usually made to resect the bladder tumor as completely as is safely possible (i.e., a maximal safe resection).

Bimanual Examination

Bimanual examination is performed before and after complete TUR, and the size and mobility of any palpable mass are evaluated. A residual palpable mass suggests muscle invasion. Most invasive bladder cancers are located near the trigone or posterior bladder wall and cannot be reliably palpated. This procedure alone leads to understaging in up to 50% of patients.

Urinary Cytology

Urine cytology should be used to complement the findings of cystoscopy. It is extremely valuable for the diagnosis of high-grade TCC, especially CIS that might be difficult for the endoscopist to visualize, and upper tract malignancies. The presence of high-grade TCC in the cytology specimen in patients with low-grade papillary TCC suggests either unrecognized CIS or less commonly high-grade disease in the upper urinary tracts.[94,95] For the diagnosis of low-grade papillary tumors, cytology is not sensitive because grade 1 TCC appears to be identical to normal urethral cells.[31]

Cytology has been regarded as the gold standard for noninvasive screening of urine for bladder cancer. It has a sensitivity of around 40% to 60% with specificity in excess of 98%.[31] Cytology is illustrative of the problems of noninvasive screening. Poorly differentiated tumors have a 20% false-negative detection rate whereas well-differentiated tumors have up to an 80% false-negative detection rate.

Multiple urine-based biomarkers have been developed because of the low sensitivity of cytology and perhaps benefit from the lack of subjectivity by the person reading the test.[96-101] These tests identify proteins in urine, detect cellular antigens by immunohisto- or cytochemistry, or use FISH microsatellite analysis of free DNA, and telomerase reverse transcriptase determination to identify genetic alterations associated with bladder cancer.

Imaging

Although fewer than 60% of bladder cancers are seen on intravenous urography, this imaging modality provides valuable information about the status of the upper urinary tract.[102] Ureteral obstruction or a nonfunctioning kidney predicts muscle-invasive disease in 90% of cases.[103] Concomitant or subsequent upper urinary tract tumors are found in 2% to 5% of patients. CT urography has replaced IVP as the procedure of choice, though IVP remains an appropriate alternative when CT is not available.

Evaluation of a patient with potential muscle-invading bladder cancer should include CT scan of the abdomen and pelvis (with and without contrast and with delayed images). Although it is not sensitive in reliably describing the depth of invasion or lymph node involvement, it can be helpful in determining extravesical extension and the planning for subsequent treatment. Notably, the detection of lymph node metastases with CT imaging is poor (high false-negative rate). About 20% to 30% of patients with node-negative disease by CT have positive nodes at time of cystectomy with lymphadenectomy.[104,105]

Gadolinium-enhanced MRI imaging may prove useful in distinguishing superficial from invasive disease and in distinguishing intra- from extravesical tumor.[106-110] Lymphangiography using iron nanoparticles and MRI might be particularly useful in detecting early nodal metastases.[110] Positron emission tomography (PET) has limited value. All bladder-specific imaging should be performed before TURBT, because of postsurgical edema.

Patients with Ta or low-grade T1 tumors do not require extensive metastatic workup. However, those with muscle-invading tumors have up to a 50% risk of occult metastatic disease and should have chest imaging and a bone scan.

Staging

Stage is the most important independent prognostic variable for progression-free survival and OS for invasive bladder cancer. The basis for the major staging systems is the classic clinicopathologic study by Jewett and Strong,[111] which correlates the probability of regional lymph node and distant metastases with the depth of invasion of the primary bladder tumor. The tumor, node, and metastasis (TNM) system of 2010 is shown in Table 54-1 and Figure 54-1.[46] Of note, CT and MRI are not used for staging of the primary in the TNM system. If lymphadenectomy is performed, sampling should include excision of an average of 12 or more lymph nodes.

In clinical practice, the correlation between depth of invasion, based on cystoscopic evaluation, and the final cystectomy specimen is only 50% to 60%. Significant rates of clinic-pathologic stage discrepancy and clinical (TURBT) understaging have been described. That is to say that 40% to 50% of patients undergo pathologic upstaging.[113,114] The accuracy of the determination of degree of muscle infiltration is, therefore, modest at best. The clinical staging system as

TABLE 54-1 AJCC 2010 TNM Bladder Cancer Staging

PRIMARY TUMOR(T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Ta	Noninvasive papillary tumor
Tis	Carcinoma in situ
T1	Tumor invades the lamina propria (subepithelial connective tissue), but not beyond
T2	Tumor invades the muscularis propria
pT2a	Tumor invades superficial muscle (inner half)
pT2b	Tumor invades deep muscle (outer half)
T3	Tumor invades perivesical tissue
pT3a	Microscopically
pT3b	Macroscopically (extravesical mass)
T4	Tumor invades any of the following: prostate, seminal vesicles, uterus, vagina, pelvic or abdominal wall
T4a	Tumors invade prostatic stroma, uterus, vagina
T4b	Tumor invades pelvic or abdominal wall
REGIONAL LYMPH NODES (N)	
NX	Regional lymph nodes cannot be assessed
NO	No regional lymph nodes metastasis
N1	Single regional lymph node metastasis in the true pelvis (hypogastric, obturator, external iliac, or presacral)
N2	Multiple regional lymph node metastases in the true pelvis (hypogastric, obturator, external iliac, or presacral)
N3	Lymph node metastasis to the common iliac region
DISTANT METASTASIS (M)	
MX	Distant metastasis cannot be assessed
MO	No distant metastasis
M1	Distant metastasis

Markers include nuclear matrix proteins (e.g., NMP22), fibrin/fibrinogen degradation products (FDP), cytokeratins,[6,16-18] hyaluronic acid, urinary bladder cancer antigen (BTA), basic fetoprotein, survivin, telomerase, microsatellite DNA, UroVysion, and chromosomal abnormalities (3, 7, 17, 9p21). These approaches have demonstrated a higher sensitivity than urine cytology, but lower specificity. However, none of these markers have sufficient sensitivity (especially for low-grade small tumors) and diagnostic reliability to replace cystoscopy and their clinical use has not been recommended by consensus panels. Additional trials are needed to evaluate these newer techniques and their clinical and cost-effectiveness as they are integrated into patient management.

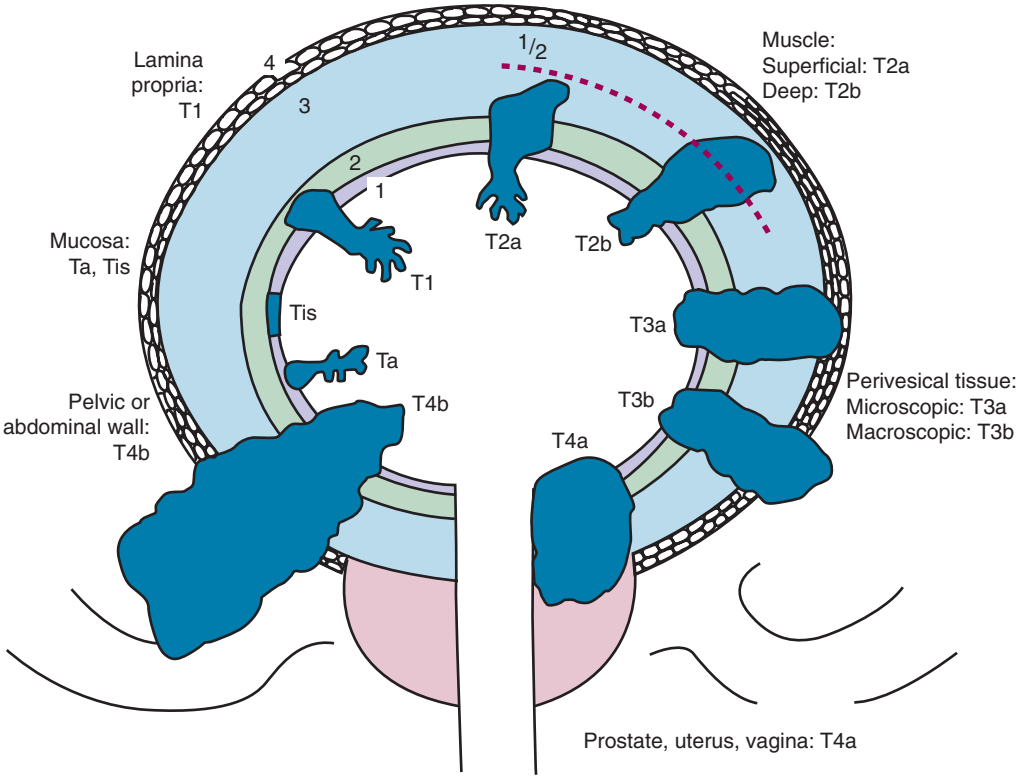


Figure 54-1 Staging of bladder tumors.

proposed by Union Internationale Contre Cancer was often more practical. Cancer without residual induration after TURBT was staged as T2 and cancer with palpable residual induration, T3. The most important determination of treatment outcome seems to be whether the tumor is organ confined (≤T2) or not organ confined (≥T3). When comparing outcome for different treatment modalities, it is important to consider whether the disease was staged clinically or whether a cystectomy specimen was available for a thorough pathologic staging.

PRIMARY THERAPY

The presence or absence of muscle invasion is the key factor in determining the appropriate treatment option for bladder cancer. In the absence of muscle invasion, endoscopic TUR with or without intravesical therapy is the therapy of choice.

The most appropriate treatment algorithm for muscle-invading disease remains controversial. Although radical cystectomy has long been the standard treatment in the United States, organ-preserving regimens using radiation with concurrent chemotherapy have emerged as viable alternatives in select patients (Figure 54-2).[115,116] These two approaches appear to have similar survival rates in uncontrolled comparisons, but strong physician and patient preferences have so far prevented completing a randomized, controlled trial comparing these treatment options.[117]

Noninvasive Bladder Cancer (Ta, T1, Tcis)

Transurethral Resection (TURBT)

Patients with superficial nonmuscle-invasive TCC (including Ta, T1, and Tis) account for approximately 70% of all newly diagnosed bladder cancer cases and are initially treated by TURBT. The appropriate treatment regimen may also include adjuvant intravesical therapy for a selected patient population. Decisions concerning the use of adjuvant therapy are based primarily on the probability of disease progression, not the probability of recurrence.

The majority (40% to 80%) of patients with superficial TCC will eventually experience recurrent disease after TURBT.[118] Progression to invasive disease after TURBT alone occurs in 10% to 25% of patients and is closely associated with tumor type, stage, and grade.[119,120] Other factors include multicentric disease, frequency of recurrence, tumor size, and presence or absence of concomitant CIS.

Although Ta, G1 tumors have recurrence rates higher than 50% at 5 years, they rarely (5% or less) invade or cause death. Consequently, TUR alone may be sufficient treatment for these tumors.

The risk of progression is substantially higher for tumors of higher grade or stage. Ta, G2-3 disease will progress to invasive TCC in 20% of cases at 5 years after treatment with TURBT alone. Nearly all patients (>70%) with T1 disease have high-grade tumors, and approximately 50% experience invasive disease at 5 years. In patients with T1 disease with CIS in the pathologic specimen, the rate of progression rises to 80% at 5 years.[121,122]

Intravesical Therapy

Bacillus Calmette-Guérin

Intravesical therapy involves the instillation of high local concentrations of a therapeutic agent into the bladder, potentially destroying viable tumors cells and preventing implantation. BCG, a live attenuated form of *Mycobacterium bovis*, is currently the most effective and most commonly used intravesical agent for treatment of nonmuscle-invasive TCC of the bladder. BCG is typically instilled into the bladder weekly for 6 weeks. The role of maintenance BCG for longer than 6 weeks remains

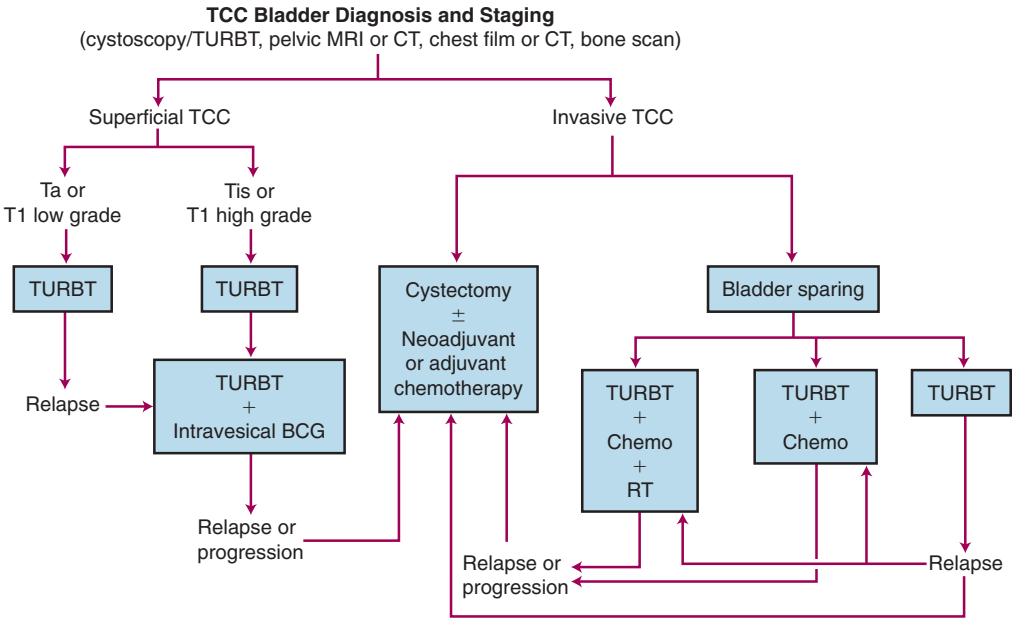


Figure 54-2 Diagnosis and treatment algorithm. *BCG*, Bacillus Calmette-Guérin; *Chemo*, chemotherapy; *CT*, computed tomography; *MRI*, magnetic resonance imaging; *RT*, radiation therapy; *TCC*, transitional cell carcinoma; *TURBT*, transurethral resection of the bladder tumor.

controversial. For a number of patients who respond to induction, maintenance BCG therapy may be used for up to 3 years, although patients frequently discontinue therapy early because of bladder toxicity.

Several randomized, controlled trials compared TURBT alone with TURBT plus BCG.[123-127] Those treated with BCG had significantly fewer recurrences at 12 months. For patients with Ta, G2-3, and T1 disease, adjuvant therapy with BCG reduces the rate of progression to 5% to 15% at 5 years. Nonetheless, 50% of patients with T1/CIS will experience muscle-invading cancer at 10 years. Progression rates to muscle invasion among patients who respond to BCG are 1% at 1 year, 5% at 3 years, and 15% at 5 years.

The positive impact on progression translates into a survival advantage.[128,129] With long-term follow-up, adjuvant intravesical BCG improved survival rates to 88%, compared to 63% with TURBT alone, and reduced the cystectomy rates from 42% to 20%.[128]

Besides reducing progression and improving survival, BCG treatment also delays tumor recurrence in approximately 50% of patients. In the published randomized, controlled trials in which TURBT plus BCG was compared with TURBT alone, recurrence rates ranged from 20% to 42% with intravesical therapy versus 42% to 100% without.

Intravesical therapy is the first-line treatment for diffuse CIS. The average complete response rate of CIS to BCG is greater than 70% for more than 1 year.[130] It prevents subsequent disease in 60% of cases for up to 5 years and in 40% of cases for up to 10 years. Particularly in CIS of the prostatic urethra, BCG has spared many patients cystectomy. TURBT is recommended to stage the disease and to open the bladder neck to allow BCG to bathe the prostatic urethra.

One consequence of controlling the bladder component of disease in a patient with a TCC of the bladder is an increase in the frequency of extravesical relapses,[131] hence careful follow-up is required. Relapses can develop anywhere transitional epithelium is found: renal pelvis, ureters, and urethra. The risk for upper tract tumor is 20% at 5 years, 25% at 10 years, and 33% at 15 years. Prostatic urethra and duct involvement at 5 years is 10% to 15% and at 10 years, 20%. If a complete resection of tumors of the urethra cannot be obtained, patients are managed with cystectomy. Patients with a positive cytology and no obvious bladder tumor need careful monitoring of the upper tracts. Urethroscopic resection and instillation of BCG through the renal pelvis is possible.

Careful follow-up surveillance is required after intravesical therapy. This includes repeat cystoscopy and urine cytology 3 months after therapy, at 3- to 6-month intervals for the first few years and then annually. Surveillance should include imaging of the upper tracts every 1 to 2 years, unless very low risk. For residual or recurrent disease, a repeat TURBT and course of intravesical therapy may be indicated. Cystectomy should be considered for persistent or recurrent tumor after one to two cycles of intravesical therapy.

Role of Irradiation in High-Risk Superficial Bladder Cancer

It is well recognized that TURBT may clinically understage tumors as noninvasive when they have already invaded into the muscle wall (approximately 20% to 30%). Radiation therefore has an advantage in that it can reach tumor deposits too deep for instillation therapy. There have been no randomized trials comparing RT to current intravesical treatment options. The Dutch South Eastern Bladder Cancer Group has presented data in 121 patients with T1G3 cancers.[135] External RT with 50 Gy was one treatment option and 17 patients received this. Though the numbers are limited it appeared to be as effective as intravesical BCG or mitomycin. Good results have also been achieved at the University of Rotterdam with interstitial implants.[136] In this selective but prospective series, patients with single T1-tumors of less than 5 cm in diameter underwent TURBT and subsequent local irradiation of the tumor area in the bladder wall by an interstitial radium implant. The definitive local control rate was 82% and the 10-year survival rate 76%. Another group in the Netherlands has published their results using a combination of transurethral resection, external beam radiotherapy (EBRT; 3.5 Gy × 3 to 4), and interstitial radiotherapy (mean implant dose of 55 Gy) in patients with solitary T1G3 and T2-tumors.[137] The local control rate was 70% in the whole patient population.

BCG triggers a variety of local immune responses and has been shown effective in reducing rates of disease progression, decreasing recurrence and the need for subsequent cystectomy, and improving survival. Toxicities of intravesical therapy include symptoms of bladder irritation (dysuria and frequency).[122a] To minimize risk of systemic infection, intravesical therapy should not be given to patients with traumatic catheterization, active cystitis, or persistent gross hematuria.

Several conditions other than those just outlined call for the use of intravesical therapy with BCG. These include CIS and frequent recurrence of low-grade disease. Urothelial dysplasia or severe atypia can be treated prophylactically with BCG. Persistent positive urine cytology without associated upper tract lesions, and disease involving more than 40% of the bladder surface are also indications for intravesical therapy.

Other Agents

Although BCG is the treatment of choice for intravesical therapy, a variety of other agents have been investigated, such as mitomycin C, doxorubicin, epirubicin, valrubicin, thiotepa, gemcitabine, interferon, and docetaxel. None has proved consistently superior to BCG,[130,132-134] especially in cases of high-risk disease features (high grade, T1, Tis), though they may have a role in BCG failures and as an immediate single postoperative dose for patients at low risk of recurrence following TURBT. Novel approaches to decrease recurrence following initial treatment for nonmuscle-invasive bladder cancer include photodynamic therapy.

The 5-year DSS was 80% for T1 tumors and 60% for T2a. One randomized trial of EBRT alone (60 Gy in 30 fractions) in the management of high-grade T1 TCC of the bladder did not seem to indicate a benefit over observation for patient with unifocal disease or over BCG for those with multifocal disease or CIS.[138]

A large series of 141 patients with high-risk T1 cancers treated with either TURBT plus EBRT with or without platinum-based chemotherapy comes from the University of Erlangen.[139,140] In this series, 88% of patients achieved a CR, about 15% progressed to muscle-invasive disease after 5 years and 30% at 10 years, which compares favorably to most studies of TURBT and instillation therapy. DSS at 5 years and 10 years was 82% and 73%, respectively. More than 80% of survivors preserved their bladder, and 70% were "delighted" or "pleased" with their urinary function. These results suggest that irradiation may have a role to play in patients with high-grade or recurrent T1 lesions and may be attempted ahead of cystectomy on protocol or in place of cystectomy in those who are medically inoperable.

Currently there is an open Phase II protocol in RTOG (protocol 0926) for patients with recurrent BCG refractory T1 bladder cancer evaluating selective organ preserving treatment by irradiation plus concurrent chemotherapy (either cisplatin or 5-fluorouracil [5-FU]/mitomycin C) following a thorough TURBT.

Muscle-Invading Bladder Cancer (T2-4)

Muscle-invading tumors comprise 20% to 25% of all newly diagnosed bladder cancers. The most appropriate treatment algorithm for muscle-invading disease remains controversial. Although radical cystectomy and urinary diversion has been the mainstay for treatment for decades, organ-preserving regimens using predominantly multiple-modality therapy, consisting of TURBT followed by irradiation with concurrent chemotherapy, have emerged as viable proven alternatives in select patients. Refining the treatment choice by maximizing quality of life without compromising survival is the ultimate goal.

Radical Cystectomy

Surgical Methods

Radical cystectomy entails the surgical removal of the bladder, adjacent organs, and regional lymph nodes. Although traditionally performed as an open procedure, laparoscopic and robotic radical cystectomy have been investigated as less-invasive alternatives. In male patients, the bladder, prostate, seminal vesicles, proximal vas deferens, and proximal urethra, with a margin of adipose tissue and peritoneum, are resected en bloc. In females, the procedure involves an anterior pelvic exenteration to remove the bladder, urethra, uterus, fallopian tubes, ovaries, anterior vaginal wall, and surrounding fascia en bloc. The extent of bilateral pelvic lymph node dissection is an important predictor of outcome and many centers have adopted an extended template dissection to include presacral and common iliac lymph nodes to the aortic bifurcation and often more proximal to the origin of the inferior mesenteric artery, in addition to pelvic lymph nodes distal to the common iliac bifurcation.[141] Before cystectomy, grossly abnormal lymph nodes are sampled. In case of metastases, cystectomy is aborted unless urinary diversion is required to relieve symptoms. Urinary diversion is usually accomplished through an ileal conduit opening onto the anterior abdominal wall through a urostoma though continent diversions including a neobladder reconstruction are growing in popularity.

Incontinent Urinary Tract Reconstruction. In the early 1950s, Bricker et al developed what was to become the most common type of diversion after cystectomy, the ileal conduit diversion. Urine drains directly from the ureters through a segment of ileum to the skin surface, where it is collected by an external collection appliance.

Continent Urinary Tract Reconstruction. Techniques for performing continent urinary diversions have been developed over the past 20 years. The two most important approaches are formation of a continent urinary reservoir made of bowel (small bowel alone or plus colon), which drains to a stoma that can be catheterized, and creation of an orthotopic neobladder, in which a newly formed urinary reservoir made out of bowel (ileum, ileo-colon, sigmoid colon) is anastomosed to the urethra.

Morbidity of Cystectomy

Operative mortality from cystectomy in modern series ranges from 1% to 3%, with postoperative complication rates ranging from 15% to 64% and a 26% readmission rate.[147-150] Complications include hemorrhage, rectal injury, deep venous thrombosis, pulmonary embolus, pelvic abscess, sepsis from urine or bowel leak, wound infection/dehiscence, and small-bowel obstruction. The frequency of complications appears to be related to surgeon experience, hospital volume, age, and presence of comorbidities.

The need for urinary diversion and loss of sexual function in patients undergoing radical cystectomy are the most serious side effects and may impair quality of life dramatically. In women, loss of sexual function occurs secondary to subtotal vaginectomy and in men secondary to prostatectomy with loss of vascular supply or nerves serving penile erection. Newer nerve-sparing techniques for men may allow for up to approximately 50% of selected patients to regain their erectile potency.[151]

When feasible, continent urinary diversions achieve 82% continence rates with early complication rates of 15% to 20% and mild hypochloremic acidosis in 50% of the patients. Intestinal obstruction, acute pyelonephritis, ureteral obstruction, hydronephrosis, stomal stenosis, intestinal fistula, and ureteroileal urinary leakage are also reported. Ten percent of patients experience ureteral-intestinal strictures, reservoir dysfunction requiring augmentation of the pouch, and dysfunction of the stoma. Overall, 10% to 15% of patients require reoperation. Decreased renal function is noted in most patients during long-term followup after radical cystectomy.[152] Choice of urinary diversion does not appear to be independently associated with decreased renal function.

Cancer Outcome after Cystectomy

Contemporary large series provide the best data on outcome after radical cystectomy.[153-157] The University of Southern California reported on 633 patients undergoing radical cystectomy with pathologic stages pT2-T4a with an actuarial OS rate at 5 years of 48% and at 10 years of 32%.[153] The series from the Memorial Sloan Kettering Cancer Center (MSKCC) showed that in 184 patients with tumors of pT2-4, the 5-year OS was 36%. The 5-year OS for all 269 patients with pathologic stages ranging from pT0 to pT4 was 45%.[154] Pathologic stage or T category is a significant independent predictor of survival and local control. By clinical stage, 5-year OS was 56% for T1, 50% for T2, and 23% for T3a-b. Five-year local relapse rates by pathologic stage ranged from 6% for pT2 disease to 51% for pT3b.

The presence or absence and extent of lymph node disease, and the lymph node density (ratio of number of positive lymph nodes to the number of lymph nodes removed) are also significant determinants of survival.[158] The estimated

a. Cutaneous Urinary Reservoir. The two main options are reservoirs made from colon and small bowel (Indiana pouch) or entirely from small bowel (Kock pouch).[142,143] The Indiana pouch consists of approximately 25 cm of right colon often including some distal ileum, which is brought to the abdominal wall. It relies on the ileocecal valve for continence. Patients catheterize the pouch on average four to six times per day.

The Kock pouch is a cutaneous continent urinary reservoir constructed from 60 cm of ileum, with an afferent antireflux nipple valve for the ureteral intestinal anastomosis and an efferent nipple valve for the catheterizable stoma. Major complication rates of around 20% are reported. Incontinence, difficulty with catheterization, loss of antireflux features of the nipple valve, and urinary leaks are the major problems with these diversions.

b. Orthotopic Diversion. A neobladder is constructed from ileum, ileo colon, or sigmoid colon and anastomosed to the native urethra as opposed to the abdominal wall. This permits the patient to void in a relatively normal fashion per urethra. The Mainz pouch (neobladder) consists of an ileocecal segment, which is detubularized and anastomosed to the urethra.[144] The Hautmann pouch consists of a W-shaped ileo-neobladder, in which 60 cm ileum is configured into a sphere.[145]

The choice of urinary diversion is based on patient and surgeon preferences and may be influenced by the extent of cancer. Orthotopic bladders are contraindicated when the tumor involves the urethra. Orthotopic neobladders are becoming increasingly common in patients undergoing cystectomy but have been predominantly used in men. They are less common in women because of the technical difficulties in maintaining continence and the risk of urethral recurrence given the shorter length of the female urethra.[146]

It remains true, however, that many patients still do not receive a continent reservoir because of intercurrent disease, impaired renal function, surgery time, dilated ureters, and bowel disease.

probability of 5-year OS of patients with nodal metastases is 29%; with one to five nodes positive 35%, and with six or more nodes positive 17%.[159] The incidence of positive lymph nodes varies according to pathologic tumor stage. In cystectomy series, it ranged from 0% to 6% for superficial disease, 18% to 22% for muscle-invasive disease (pT2, 6% to 20%; pT3a, 30% to 31%), 30% to 64% for disease invading the perivesical fat (pT3b), and 45% to 59% for disease invading adjacent organs (pT4).[160-162]

Other factors that may influence outcome include the quality of surgery, margin status, presence of lymphovascular invasion and marker status (*p53, p21, pRb, p16*). Nomograms that consider multiple prognostic factors such as stage, nodal status, tumor grade and histology, lymphovascular invasion, and age have been developed.[163]

Although the disease is locally controlled, many patients will ultimately develop distant metastases (5-year distant disease rate for T3-4, 40% to 50%; T2, 30%). Median time to diagnosis of distant metastases is approximately 18 months. The most common sites for distant metastases are bone, lung, and liver.

Radiation as an Adjunct to Cystectomy

Preoperative Radiation Therapy

The recognition that moderate-dose radiation (20 Gy to 50 Gy) may reduce the volume of gross disease and eradicate microscopic TCC led to its frequent use before cystectomy in the 1970s.[164,165] In nonrandomized studies, these doses were found to reduce the frequency of metastases in the lymphadenectomy specimens by approximately 50%.[166] By the 1980s, improvements in the technique of radical cystectomy, together with the introduction of more extensive therapeutic lymphadenectomies, made many question the need for radiation.[167] It has been argued that radiation delays the time to definitive surgery, increases its morbidity, and may compromise the surgeon's ability to perform continent urinary diversions. The question was addressed by an intergroup trial reported in 1997[168] in which 140 patients with invasive or recurrent superficial bladder cancers were randomized to receive cystectomy alone or plus preoperative radiation (20 Gy in five fractions). There was no significant survival advantage to either group at 5 years. The trial was small, the doses low, and the predominant pattern of failure distant, all factors that would make it practically impossible to detect any advantage to radiation. Parsons and Million[169] did, however, demonstrate an apparent survival advantage for patients with clinical T3 tumors who received preoperative radiation.

Cole et al reported on 133 patients with T3b disease treated at the M. D. Anderson Cancer Center (MDACC).[170] This retrospective review documented that when pelvic wall recurrence occurs following modern radical cystectomy, it is usually only in patients who had clinical stage T3b or T4 tumors. They report a 28% incidence of pelvic recurrence in patients with stage T3b disease treated by radical cystectomy, with or without multidrug chemotherapy. However, when patients with stage T3b disease were treated with preoperative EBRT (which this institution used extensively before 1980), the pelvic recurrence rate was only 10%. Before 1983, all patients underwent 50-Gy preoperative EBRT (25 to 28 fractions over 5 to 5.5 weeks), followed 4 weeks later by cystectomy. Actuarial 5-year pelvic control was 91%. After 1983, radiation was discontinued, and subsequent pelvic control rates fell to 73% despite improvements in surgical technique, staging, and the addition of systemic chemotherapy. A survival decrement (52% to 42%) was also seen. The extent to which patient-selection factors contributed to this observed difference is unknown. Others have reported lower rates of pelvic recurrence using cystectomy alone for this subset of patients, and it therefore remains uncertain whether these findings are widely applicable.[167]

The morbidity of preoperative RT is small. Whitmore reported comparable rates of wound healing and perioperative mortality for patients who received and those who did not receive irradiation before cystectomy.[166] There is limited experience in the creation of continent urinary diversions after preoperative RT, although Housset et al report that it is possible after the delivery of 44 Gy (24 Gy delivered in 8 fractions over 17 days according to a modified bifractionated split-course schedule [3 Gy fractions twice daily on days 1, 3, 15, 17] followed by a 20 Gy boost [2.5 Gy fractions twice daily on days 64, 66, 78, 80]).[171] TCC of the bladder have a high propensity to autotransplantation. Iatrogenic wound seeding after cystotomy was commonly reported by those who performed partial cystectomies or bladder brachytherapy. Low-dose preoperative radiation (8.5 Gy to 20 Gy) profoundly reduced the incidence of this problem.[172] Low-dose radiation is still occasionally given in the United States before a partial cystectomy. The partial cystectomy is, however, not commonly performed because it is limited to small, unifocal tumors of the dome, an unusual location.

Postoperative Radiation Therapy

When the cystectomy specimen shows extensive extravesical disease or positive surgical margins, the risk for pelvic recurrence is high. Postoperative RT has been evaluated in only one randomized study. The National Cancer Institute of Egypt reported on 236 patients with T3-4 tumors (68% squamous cell) who received either no adjuvant therapy or postoperative radiation (using three daily fractions of 1.25 Gy each, with 3 hours between fractions, up to a total dose of 37.5 Gy in 12 days [75 patients] or conventional fractionation for a total dose of 50 Gy over 5 weeks [78 patients]).[173] The 5-year rates of disease-free survival ([DFS] 44% to 49% versus 25%) and local control (87% to 93% versus 50%) were improved while the incidence of pelvic recurrence was significantly reduced in the groups receiving postoperative radiation. Whether this finding is as applicable to transitional as to squamous cell tumors remains an unanswered question. Today, patients with such extensive disease commonly receive adjuvant chemotherapy, although the ability of this modality to prevent local recurrence has been called into question by Cole et al.[170] RT rarely cures patients with pelvic wall recurrences following radical cystectomy.[174] Perhaps some could be cured if given adjuvant RT.

The morbidity of postoperative irradiation is high because of the large volumes of small bowel that occupy the pelvis after cystectomy if the urologist does not use pelvic reconstruction techniques to displace small bowel loops from the tumor bed (omental pedicle flap, mesh, other). Two series reported a greater than 30% incidence of small-bowel obstruction when 50 Gy was delivered using conventional fractionation.[175] So although adjuvant radiation therapy could reduce local failure it currently has no defined role because of a concern for morbidity. Modern techniques with improved normal tissue sparing have however rekindled interest in RT. Models of risk stratification based on pathologic stage of disease, margin status, and number of nodes removed have been developed that stratify patients into groups with significantly different local-regional failure risks.[176] Patterns of failure studies within the pelvis suggest that RT should target the iliac and obturator nodes and possibly the presacral nodes and cystectomy bed.[177] A cooperative group randomized trial GU001 recently opened in NRG Oncology to further evaluate the role of adjuvant RT in patients at higher risk for pelvic failure after cystectomy.

Salvage Radiation Therapy

Attempts to salvage patients with TCC of the bladder at the time of symptomatic or gross pelvic recurrence after radical cystectomy with RT or with combined chemotherapy and RT are usually unsuccessful. Some palliation can be achieved.[174] In some centers consideration is given to preoperative chemoradiation followed by attempted resection of the pelvic mass and intraoperative radiation. There is no large published experience looking at this approach.

Bladder Preservation

Conservative Surgery

Partial Cystectomy

Surgical resection by partial cystectomy requires careful patient selection, that is, the lesion should be solitary and located in a region of the bladder that allows for complete excision with a 2-cm tumor-free margin (e.g., the bladder dome). The portion of the bladder to be resected should be small enough to allow adequate bladder capacity. Contraindications include association with CIS in other sites of the bladder, prostatic urethral involvement, prior recurrent bladder or upper tract tumors, and bladder neck or trigone tumors in which ureteral reimplantation would be required to achieve an adequate margin. Given these constraints, only 6% to 19% of patients with primary, muscle-invading bladder cancer are potential candidates.[178] Even for this select group of patients, local recurrence rates range from 38% to 78%; one half of the recurrences appear in the first year and two thirds by 2 years.

Transurethral Resection of Bladder Tumor

Clinical complete response rates after TURBT alone (assessed cytoscopically with repeat biopsy 3 weeks after initial TURBT) for T2 and T3 cancers overall are in the 10% to 20% range.[179,180] Five-year OS in 85 patients with grades 1 and 2 T2 cancers was an unacceptable 27%.[181] Some studies have reported 10-year DSS as high as 76%,[182] but these results included only those patients who had no residual disease or no invasive disease on repeat biopsy and urine cytology. Although potentially effective in a small proportion of favorable T2 tumors, TURBT is usually not sufficient as monotherapy in muscle-invading bladder cancer.

Radical External Beam Irradiation

In the past, EBRT was widely used as a single modality for T2-4 bladder cancers, particularly in Europe. In the United States, however, the use of RT was frequently limited to patients whose tumor characteristics or medical comorbidities made them poor candidates for surgical monotherapy.

The total radiation dose used in these series (Table 54-2) varied from 55 Gy to 65 Gy, with 1.8 Gy to 2 Gy per fraction in North America, and from 50 Gy to 55 Gy at 2.5 Gy to 2.75 Gy per fraction in the United Kingdom.[183-196] Most patients were treated with one fraction per day five times a week. Patient response was evaluated by cystoscopic examination and biopsy 3 to 6 months after completion of RT. Patients with residual tumor and no known metastatic disease underwent salvage surgery (range of salvage cystectomy rate, 13% to 24%) if they were suitable surgical candidates. Those unfit received palliative measures.

The 5-year local control ranged from 31% to 50% for the entire patient population and from 49% to 79% for the subgroup of patients with complete response. Factors reported as having a significant favorable effect on local control[196] with RT included:

- Early clinical stage (T2 and T3a)
- Absence of ureteral obstruction

TABLE 54-2 External Beam Radiotherapy Alone for Muscle-Invasive Bladder Cancer

Study	*n*	5-Year Survival By T Category (%)			
		T2	T3 (T3a/T3b)	T4	Overall
Duncan, 1986[183]	963	40	26	12	30
Blandy, 1988[184]	614	27	38	9	—
Jenkins, 1988*[185]	182	46	35	—	40
Gospodarowicz, 1991*[188]	355	50	(38/28)	—	46
Jansson, 1991*[189]	319	31	16	6	28
Davidson, 1990*[194]	709	49	28	2	25
Greven, 1990[186]	116	59	10	0	—
Smaaland, 1991[187]	146	26	10†	—	—
Fossa, 1993[190]	308	38‡	14§	—	24
Pollack, 1994[191]	135	42	20	0	26
Moonen, 1998[192]	379	25	17	—	22
Borgaonkar, 2002*[195]	163	48	26	—	45

**Cause-specific survival.*
†T3/T4.
‡T2/T3a.
§T3b/T4.

- Complete response
- Visibly complete TURBT
- Absence of coexisting CIS
- Small tumor size (<5 cm maximum diameter)
- Solitary tumors
- Tumor configuration (papillary versus sessile)
- Hemoglobin level (>10 mg/dL)

Tumor eradication ranged from as high as 66% for those with solitary T2 tumors to as low as 9% for those with multiple tumors and hydronephrosis. The 5-year OS in these reports ranged from 25% to 46%. Stage-specific 5-year OS ranged from 49% to 71% for T2 to 37% for T3b.

The success of any bladder conserving strategy rests on the ability to rapidly recognize local recurrence and treat promptly with salvage surgery. Salvage cystectomy can be undertaken safely without significantly increased morbidity after a complete course of RT or chemoradiation regimens.[197,198] After radiation, an ileal conduit, rather than a neobladder is the more likely method of urinary diversion. A Kock pouch urinary diversion may also be performed safely in patients who received prior RT to the pelvis.[199]

Interstitial Brachytherapy

This was developed as a technique in the early part of the 20th century but has progressively declined in popularity and is mainly performed in specialist centers in France, Belgium, and the Netherlands. The early technique involved the implantation of permanent radon seeds or temporary radium or cobalt needles.[200,201] Although effective there were substantial problems with radiation safety and significant morbidity from urinary leakage. Hospital stays were protracted. As alternative techniques employing EBRT became available and as the morbidity and mortality of the cystectomy declined, these became preferred approaches. Over the last three decades, however, afterloading techniques and computer planning mean that some centers are again looking at this as an option for selected patients. Brachytherapy has been combined with EBRT to

TABLE 54-3 Treatment Outcome for Brachytherapy in Combination with External Beam Irradiation

Series	Local Control (5 yr)	OS (5 yr)	DSS (5 yr)	Survival with Preserved Bladder (5 yr)
Moonen[202]	84%	86%	—	90%
Wijnmaalen I[203]	88%	48%	69%	—
Van der Steen[137]	70%	—	T1 80% T2 60%	— —
Mazeron[205]	77%	72%	73%	95%
Rozan[206]	—	67%	83%	96.1%
Pernot[207]	73%	71%	77%	—
Pos[208]	73%	62%	73%	90%
Aluwini[209]	80% (5 yrs) 73% (10 yrs)	65% (5 yrs) 46% (10 yrs)	75% (5 yrs) 67% (10 yrs)	93% (5 yrs) 85% (10 yrs)

DFS, *Disease-free survival;* EBRT, *external beam radiation therapy;* OS, *overall survival;* yr, *year.*
All series employed combinations of EBRT and brachytherapy, usually preoperative EBRT does of <15 Gy to reduce the risk of tumor seeding. The series of Moonen and Pos gave 30 Gy in 15 fractions and those of Van der Steen and Wijnmaalen gave 40 Gy in 20 fractions to tumors of stage T2b or higher.

provide a radiation boost to the primary tumor as well. External-beam doses of 30 Gy are used in combination with an implant tumor dose of 40 Gy. Appropriate candidates for brachytherapy are those with a solitary TCC with a diameter of <5 cm, stage T1 (with high grade) to T3a (muscle invasion but no extension through wall).

Early experience made clear that TCC is a tumor that may be surgically seeded either into the wound or to the peritoneal cavity. Van der Werf-Messing demonstrated the value of small doses of preoperative radiation to prevent iatrogenic scar implantation.[172] In those centers using brachytherapy, low doses of EBRT are given preoperatively with fractionation schemes that fit the convenience and ideology of the center. These range from 1×8.5 Gy or 3×3.5 Gy to 15×2 Gy. Historically wound implants occurred in 10% to 20% and are now rarely seen.

Five-year local control rates for selected patients treated with brachytherapy in combination with EBRT do appear excellent varying between 70% and 90% with DSS of approximately 75% and correspondingly high rates of bladder preservation[202-209] (Table 54-3). In selected patients, survival appears similar to cystectomy.[210]

The most serious acute morbidity is fistula with wound leakage. This is most strongly predicted by tumor size, active length of radioactive sources, and use of a partial cystectomy. Serious late toxicity is rarely reported because the treated bladder volumes are relatively small. A study reported by Pos does however raise the possibility that there is more late morbidity using fractionated high-dose rate than continuous low-dose rate.[211]

Combined-Modality Therapy

Chemotherapy as monotherapy achieves a clinical complete response in only 25% to 37% of patients.[212-219] This is more frequently reported in lower stage disease, small tumors (<5 cm), and papillary tumors. Two-year OS with chemotherapy alone is approximately 30% (cT3-4). Even in responders, chemotherapy alone spares the bladder in only 15% to 20% of patients. Chemotherapy is therefore rarely used alone for localized disease and almost invariably in combination with other therapies.

Chemotherapy and Conservative Surgery

Chemotherapy has been used with TURBT in an attempt to spare the bladder. In a highly selected patient population, 5-year local control rates of up to 48% have been reported. CR rates after chemotherapy and TURBT range from 45% to 54%.[219-225] These findings suggest that the addition of TURBT to MVAC confers a considerable local control advantage over either alone. In a highly selected patient population, chemotherapy followed by partial cystectomy in conjunction with pelvic lymphadenectomy has been used in an attempt to spare the bladder.[226] Patients should meet the following criteria to be considered for such treatment:

- complete or major response to chemotherapy,
- solitary lesion in the dome or the anterior wall of the bladder,
- no history of prior invasive bladder cancer,
- no CIS, and
- a good bladder capacity.

Though 5-year survival is high at close to 50%, less than half of these patients preserve their bladders.

Chemotherapy and Radical Local Therapy

In attempts to eradicate micrometastatic disease and improve survival for patients with muscle-invasive bladder cancer, systemic chemotherapy, given either neoadjuvantly or adjuvantly, has been evaluated.

Neoadjuvant Chemotherapy before Definitive Local Therapy

Neoadjuvant chemotherapy offers the potential to assess the response of the primary lesion and for tumor downstaging, though it may lead to a discordance between clinical and pathologic staging and delayed definitive local therapy. Chemotherapy before definitive local therapy has been well tested in invasive bladder cancer. The results of the major randomized controlled trials are shown in Table 54-4.[227-238]

Many of the earlier trials comparing neoadjuvant chemotherapy and definitive local therapy alone used single-drug (cisplatin) chemotherapy regimens. None of these studies detected a survival difference. The survival rates among both treatment arms were almost identical. The Spanish trial using neoadjuvant cisplatin reported a significant prolongation of disease-free interval with chemotherapy (mean time to progression, 13 months versus 30 months, $p = 0.03$).[229] It is important to note that in these trials the definitive treatment of the primary bladder cancer was delayed for 3 months during the administration of chemotherapy, but ultimate survival was not reduced.

A number of more recent trials[228,231-236,238,239] used cisplatin-based multidrug chemotherapy regimens. These studies, unfortunately, do not provide a clear and consistent indication of the efficacy of neoadjuvant cisplatin-based chemotherapy. The Nordic 1 Cooperative Bladder Cancer Study Group

TABLE 54-4 Randomized Phase III Trials of Neoadjuvant Chemotherapy

Study Group	Neoadjuvant Arm	Standard Arm	Patients	Survival
CISPLATIN TRIALS				
Aust/UK[227]	DDP/RT	RT	255	No difference
Canada/NCI[237]	DDP/RT or preop RT+Cyst	RT or preop RT+Cyst	99	No difference
Spain (CUETO)[229]	DDP/Cyst	Cyst	122	No difference
COMBINATION CHEMOTHERAPY				
EORTC/MRC[232]	MCV/RT or Cyst	RT or Cyst	976	5.5% difference in favor of MCV
RTOG[231]	MCV/RT+C	RT+C	126	No benefit
SWOG Intergroup[238]	M-VAC/Cyst	Cyst	317	Benefit with M-VAC
Italy (GUONE)[236]	M-VAC/Cyst	Cyst	206	No difference
Italy (GISTV)[230]	M-VEC/Cyst	Cyst	171	No difference
Genoa	DDP/5FU/RT/Cyst	Cyst	104	No difference
Nordic 1[228]	ADM/DDP/RT/Cyst	RT/Cyst	325	No difference, 15% benefit with ADM+DDP in T3-T4a
Nordic 2[234]	MTX/DDP/Cyst	Cyst	317	No difference
Abol-Enein[235]	CarboMV/Cyst	Cyst	194	Benefit with CarboMV

ADM, *Doxorubicin;* Carbo, *carboplatin;* Cyst, *cystectomy;* DDP or C, *Cisplatin;* E, *epirubicin;* MTX, *methotrexate;* preop, *preoperative;* RT, *radiation therapy;* V, *vinblastine.*

randomized patients with T1G3-T4a bladder cancer to two cycles of neoadjuvant cisplatin and doxorubicin or to no chemotherapy. Patients in both arms received preoperative irradiation (20 Gy in five fractions) and cystectomy as definitive local treatment. A significant survival advantage was seen in the chemotherapy arm for the subgroup of patients with cT3-4a disease (5-year OS 52% versus 37%, $p = 0.03$), but not for the entire patient population.[228] The subsequent Nordic 2 trial evaluated cisplatin plus methotrexate followed by cystectomy versus cystectomy alone in patients with T3 or T4a disease and did not show a statistically significant survival difference.[234]

The RTOG 89-03 trial evaluated two cycles of neoadjuvant MCV (methotrexate, cisplatin, and vinblastine) chemotherapy before concurrent cisplatin and definitive radiation. Neoadjuvant chemotherapy did not confer any detectable survival advantage. Rates of distant metastases, local metastases, and CR rates were similar in the two arms.[231]

The MRC-EORTC trial randomized 976 patients to three cycles of neoadjuvant MCV versus no chemotherapy.[232,239] Definitive local treatment was cystectomy, radical RT, or preoperative RT followed by immediate cystectomy as determined by physician or patient preference. With a median follow-up of 7.4 years, the trial reported a small but significant survival gain for neoadjuvant chemotherapy with the difference in 5-year survival between those who received chemotherapy (49%) and those who did not (43%) just reaching clinical significance ($p = 0.048$). At 8 years the survival for the chemotherapy patients was 43% compared with 37% in the control arm and the risk of bladder cancer death was reduced by 17%.

MVAC, the most aggressive regimen and most extensively evaluated, has been tested in several studies including an intergroup trial led by SWOG.[238] The SWOG trial, after slow accrual and long follow-up, achieved a trend toward significance with a 25% reduction in the risk of death through the addition of MVAC for three cycles (57% versus 43% at 5 years; $p = 0.06$) given before radical cystectomy, but the side effects were appreciable. One third of patients receiving neoadjuvant chemotherapy had a grade 3 or higher hematologic or gastrointestinal adverse effect, though there were no drug-related deaths nor did the chemotherapy adversely affect the performance of surgery. An almost identical study by the Italian GUONE group showed no significant difference.[236]

A meta-analysis that included data from 3005 patients enrolled in 11 randomized trials demonstrated a 5% absolute 5-year OS advantage (50% versus 45%; hazard ration [HR] = 0.86, 95% CI 0.77 to 0.95, $p = 0.003$) for neoadjuvant cisplatin-based combination chemotherapy compared to local therapy alone.[240,241] There was also a significant DSS benefit of 9% absolute improvement at 5 years (HR = 0.78, 95% CI 0.71 to 0.86, $p < 0.0001$).

Debate continues as to the relevance of all these conflicting findings especially when set against the morbidity of chemotherapy. Newer chemotherapeutic combinations that have activity in patients with metastatic disease, such as dose-dense or accelerated MVAC, and more favorable toxicity profiles, such as gemcitabine and cisplatin, are being investigated.

Although neoadjuvant chemotherapy seems to improve survival only marginally, it certainly has a significant impact in terms of tumor down-staging. Major responses (defined as transition from invasive disease to T0, CIS, Ta, or T1) occurs in approximately 40% of patients. Complete clinical response, as evaluated by repeat cystoscopy and biopsy after chemotherapy, ranges from 25% to 57%.

Response to neoadjuvant therapy certainly seems to predict survival. Survival rates at 5 years range from 62% to 75% among responders versus 20% to 26% among nonresponders in several of the trials.

In the 2015 National Comprehensive Cancer Network *Clinical Practice Guidelines in Oncology: Bladder Cancer*, neoadjuvant chemotherapy is a category 1 recommendation for localized stage T2-T4a disease. However, only a minority of patients in the United States undergo any perioperative chemotherapy with most still being given in the adjuvant setting. Gene profiling may in the future identify those most likely to respond to chemotherapy.[80a]

Adjuvant Chemotherapy after Definitive Local Therapy

Adjuvant chemotherapy allows for pathologic staging and avoids delay in potentially curative local therapy. No randomized trials have compared neoadjuvant to adjuvant chemotherapy in patients undergoing definitive local therapy. Although some trials have suggested a survival advantage

for neoadjuvant chemotherapy, there have been no contemporary studies supporting such a benefit with adjuvant chemotherapy.

A study from MDACC attempted to address the optimal timing of perioperative chemotherapy by comparing neoadjuvant plus adjuvant chemotherapy to postoperative chemotherapy alone and did not show any difference.[242] Several randomized, controlled trials provide information on the value of adjuvant chemotherapy after radical primary therapy (Table 54-5).[243-250] All of these studies used three to four cycles of platinum-based multiagent chemotherapy. As with neoadjuvant therapy the results have been conflicting and most of these studies suffered from underpowering and poor accrual.

In three studies, a significant progression-free survival (PFS) benefit at 3 years and 5 years was observed when patients were randomized to adjuvant chemotherapy compared with observation. However, OS was not significantly different. Patients in the observation group were treated with chemotherapy at relapse except in the study reported by Stöckle et al.[244-246] The failure to provide salvage chemotherapy in this study may explain the low survival rates in the observation arm (5-year crude survival, 17%). The PFS benefit does not translate into an OS benefit if patients receive salvage chemotherapy. In other words, observation with salvage chemotherapy might be just as effective as adjuvant chemotherapy in terms of survival. A meta-analysis including 491 patients from six trials suggested a 25% relative reduction in the risk of death (HR 0.75, 95% CI 0.60 to 0.96, $p = 0.019$) for patients receiving cisplatin-based combination adjuvant chemotherapy; however, the power of this meta-analysis was clearly limited and the authors concluded that there was insufficient evidence on which to base reliable treatment decisions.[252]

More recent studies have used different adjuvant chemotherapy regimens or molecular stratification.[61] A randomized Phase III trial from the Spanish Oncology Genitourinary Group (SOGUG 99/01) comparing four cycles of adjuvant paclitaxel/gemcitabine/cisplatin to observation in patients with resected high-risk (pT3-4 or pN+) bladder cancer was prematurely closed because of poor accrual; however, preliminary results suggest improved 5-year OS (60 versus 31%, $p = 0.0009$).[249]

Bladder Preservation with Limited Resection, Chemotherapy, and Irradiation

The rationale for combining chemotherapy with RT is twofold:

1. Certain cytotoxic agents, in particular cisplatin and 5-FU, are capable of sensitizing tumor tissue to radiation, thus increasing cell kill in a synergistic fashion.
2. Patients with muscle-invading TCC harbor occult metastases in approximately 50% of cases, which makes a case for the addition of systemic chemotherapy in an attempt to control occult distant disease.

Trimodality therapy consisting of TURBT with concurrent chemoradiation may, therefore, increase the efficacy of bladder-sparing protocols. The evolution of this approach over the last three decades is shown in Figure 54-3.

Many Phase II trials have combined chemotherapy and RT in different sequences in patients with invasive bladder cancer. Although a variety of different drugs and radiation doses have been used, it is apparent that the highest clinical CR rate (T0) was achieved in patients who received concurrent chemotherapy and RT compared with sequential regimens.[139,171,237,253-256] Table 54-6 shows results from several modern series of multimodality bladder preservation therapy.[139,171,231,256-265]

The recently reported Phase III randomized Bladder Cancer 2001 (BC2001) trial of 360 patients from the United Kingdom demonstrated that concurrent chemoradiation using 5-FU and mitomycin C is well tolerated and significantly improved locoregional DSS compared to radiation alone (67% versus 54% at 2 years; HR 0.68, $p = 0.03$ with median follow-up of 70 months). Survival at 5 years was higher with chemoradiation (48% versus 35%) but did not reach statistical significance (HR 0.82; $p = 0.16$). Bladder function was good, and no increase in late toxicity was found.[256]

Single-Institutional Experiences

One of the clearest indications of the potential of multimodality therapy for bladder preservation can be found in a study from the University of Paris.[171] In this study, TURBT followed by concomitant cisplatin, 5-FU, and accelerated RT was initially used as a precystectomy regimen. The first 18 patients who had no residual tumor on cystoscopy and repeat biopsy (clinical CR) underwent radical cystectomy as planned. None of these patients had any evidence of malignancy in the cystectomy specimens—a 100% pathologic CR rate. Previous studies using TURBT and chemotherapy found residual tumor in as many as 50% of the cystectomy specimens in clinical complete responders.

After this striking evidence of tumor eradication, the University of Paris investigators changed their protocol to one of selective bladder preservation. In 1988, they converted to induction chemoradiation, restaging with cystoscopy, and repeat biopsy of the tumor site 4 to 6 weeks after completion of the chemoradiation. Subsequent consolidation chemoradiation was only selectively given to patients who did not have any evidence of disease at restaging (CR). In cases of persistent

TABLE 54-5 Randomized Controlled Trials of Adjuvant Chemotherapy

Series	Stage	Treatment	5-yr DFS	5-yr OS	Significance
Skinner[243]	pT3-4	Cyst + 4 × CAP	52	49	Sig. for N+
	Nx	Cyst	38	43	
Stöckle[244-246]	pT3b-4	Cyst + 3 × MVAC	63	—	Sig.
	N+	Cyst	13	—	
Studer[247]	pTa-4	Cyst + 3 × Cis	—	57	Neg
	N+	Cyst	—	54	
Freiha[248]	pT3b-4	Cyst + 4 × CMF	50	40	Neg
	Nx	Cyst	22	38	
Paz-Ares[249]	pT3-4	Cyst + 4 × PGC	—	60	Sig.
	N+	Cyst	—	31	
Cognetti[251]	pT2G3-4	Cyst + 4 × AGC	37	43	Neg
	N0-2	Cyst	42	53	

DFS, *Disease-free survival;* Neg, *negative;* OS, *overall survival;* Sig, *significant;* yr, *year.*

A randomized trial performed in Italy randomized patients after cystectomy either to four courses of gemcitabine plus cisplatin or to the same treatment at time of relapse. There was no difference in the 5-year OS across treatment arms. However, because of poor accrual the study was insufficiently powered to detect a survival difference.[251] Ongoing clinical trials will hopefully provide additional insight into the role of adjuvant chemotherapy.

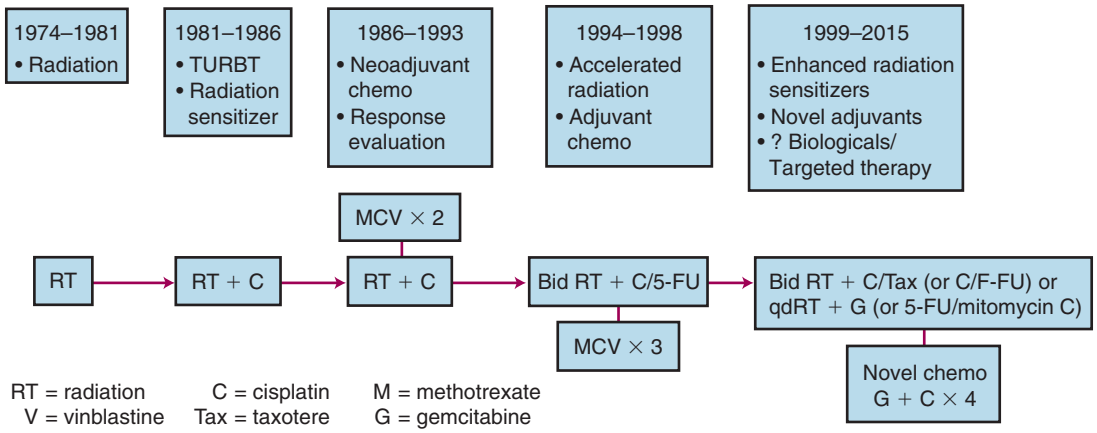


Figure 54-3 Bladder conservation: evolution of multimodality approach. *Bid,* Twice daily; *C,* cisplatin; *chemo,* chemotherapy; *G,* gemcitabine; *M,* methotrexate; *RT,* radiation therapy; *Tax,* Taxotere; *TURBT,* transurethral resection of the bladder tumor; *V,* vinblastine.

TABLE 54-6 Results of Multimodality Treatment for Muscle-Invading Bladder Cancer

Series	Treatment Method	No. Pt.	5-yr OS	5-yr BIS
RTOG 8512 1993[262]	TURBT, external beam radiation + cisplatin	42	52%	42%
RTOG 8802 1996[263]	TURBT, MCV, external beam radiation + cisplatin	91	51%	(4 years)
RTOG 8903 1998[231]	TURBT, ± MCV, external beam radiation + cisplatin	123	49%	38%
RTOG 9906 2009[266]	TURBT, bid external beam radiation + paclitaxel	80	56%	47%
BC 2001 2012[256]	TURBT, QD external beam radiation + 5FU/MMC	182	48%	—
U. Paris 1997[171]	TURBT, 5-FU, external beam radiation + cisplatin	120	63%	NA
Erlangen 2002[259]	TURBT, external beam radiation, cisplatin, carboplatin, or cisplatin and 5-FU	415	51%	42%
MGH 2012[257,258]	TURBT, ± MCV, external beam radiation + cisplatin	348	52%	46%

5-FU, *5-Flourouracil;* BIS, *bladder intact survival;* MCV, *methotrexate, cisplatin, vinblastine;* MGH, *Massachusetts General Hospital;* OS, *overall survival;* TURBT, *transurethral resection of bladder tumor;* U. Paris, *University of Paris.*

disease, patients underwent immediate cystectomy. The 5-year OS for all patients who entered the protocol was 63%.

At the University of Erlangen in Germany, a prospective bladder preservation study was started in 1982. The first 106 consecutive patients, however, were treated only with TURBT followed by EBRT to 50 Gy to 56 Gy at 2 Gy daily. A multimodality approach was initiated in 1985 when chemotherapy (cisplatin or carboplatin) was added concurrently with the radiation regimen in subsequent patients.[139,259] This protocol differed in two aspects from the University of Paris study. All recruited patients underwent the entire course of chemoradiation. Restaging TURBT was performed at 6 to 8 weeks, only after completion of the entire protocol. In addition, only patients with invasive persistent disease or poorly differentiated residual superficial tumors underwent cystectomy. Patients with well-differentiated superficial disease (Ta, CIS) were treated further conservatively with TURBT and intravesical chemo- or immunotherapy. CR was achieved in 72%. Ten-year DSS was 42%, and more than 80% of survivors preserved their bladder. Thirty-five percent developed distant metastases at 10 years. Concomitant chemotherapy was more effective than EBRT alone in terms of CR and survival. The subgroup of patients who either had persistent invasive tumor (nonresponders) at first restaging or needed a cystectomy for early invasive recurrences within 9 months after completion of the treatment had dismal survival rates (5-year OS, 16%) because of early systemic spread. Patients who needed salvage cystectomy later than 9 months after completion of the treatment achieved a 5-year OS comparable to that of the entire group.

In June 1986, investigators from the Massachusetts General Hospital (MGH) implemented a selective bladder preservation protocol for operable patients with muscle-invading bladder cancer. Initially to improve on previous results in terms of both local and distant control, two cycles of neoadjuvant MCV chemotherapy were added before the chemoradiation regimen.[260] MCV was chosen because three- or four-drug (e.g., MVAC) chemotherapy had been shown to be more effective than single-agent cisplatin in metastatic bladder cancer. Five-year OS was 48% (68% for those with T2 disease).

Long-term follow-up of 348 patients with T2-4aNXM0 bladder cancer treated successively at the MGH with combined-modality therapy using concurrent cisplatin-based chemotherapy and RT after maximal TURBT with or without neoadjuvant/adjuvant chemotherapy is available.[258] With a median follow-up for all surviving patients of 7.7 years, the results demonstrate that a visibly complete TURBT was achieved in approximately two thirds of patients and a CR rate to induction chemoradiation (~40 Gy in 1.8-Gy 2-Gy fractions) in 72% (78% in patients with stage T2 disease). Patients with a CR rate and those medically unfit for cystectomy received boost chemoradiation to 64 Gy to 65 Gy. Five- and 10-year OS were 52% and 35%, respectively (61% and 43% for T2 tumors), and 5- and 10-year DSS were 64% and 59% (74% and 67% for T2 tumors). Clinical stage and achieving a CR were significantly associated with both OS and DSS. A nomogram predicting response has been

developed from this data.[261] Ultimately 102 patients (29%) underwent radical cystectomy, 17% for less than a CR and 12% for recurrent invasive tumors. The 10-year DSS for the patients undergoing cystectomy was 44%, illustrating the important contribution of prompt salvage cystectomy. No patient required cystectomy because of treatment-related toxicity. Therefore, combined-modality therapy achieved a CR and preserved the native bladder in ~70% of patients, while offering long-term survival rates comparable to contemporary radical cystectomy series. Use of neoadjuvant chemotherapy did not improve survival or incidence of metastases, though this may warrant further investigation in the modern era.

Cooperative Group Experience: The RTOG

In North America, most cooperative group combined-modality therapy for bladder cancer has occurred within the RTOG. RTOG 85-12 treated 42 patients who were candidates for cystectomy with induction once-daily radiation therapy (40 Gy in 2-Gy daily fractions) and concurrent cisplatin, with prompt cystectomy reserved for patients who responded incompletely.[262] Complete responders received consolidation therapy, with an additional 24 Gy (in 2-Gy daily fractions) delivered with concurrent cisplatin. The approach was feasible and well-tolerated, and yielded a complete response rate of 66%, a 5-year OS of 52%, and a 5-year survival with an intact bladder of 42%.

The subsequent protocol, RTOG 88-02, looked at the role of neoadjuvant MCV given immediately following TURBT. It entered 91 patients and reported a 75% response rate and 51% 5-year OS.[263] This was followed between 1989 through 1994 by RTOG 89-03, which was a Phase III trial that directly tested the contribution of two cycles of neoadjuvant MCV chemotherapy before concurrent cisplatin and once-daily radiation.[231] This study fell short of its accrual goal and was prematurely closed because of an unexpectedly high rate of severe leukopenia in the MCV arm, which resulted in a 67% protocol completion rate (compared to 81% in the non-MCV arm) and three treatment-related deaths. Analysis of 123 patients showed no significant differences between the MCV arm and the non-MCV arm in CR after induction (61% and 55%, respectively), 5-year OS (48% and 49%), 5-year survival with an intact functioning bladder (36% and 40%), or distant metastasis (33% and 39%). Treatment-related morbidity and mortality, however, were significantly higher in the neoadjuvant chemotherapy arm. In summary, this trial suggested that two cycles of neoadjuvant MCV were not a necessary component of a bladder-preservation strategy. Therefore, future studies abandoned neoadjuvant chemotherapy, though they continued to evaluate patient tolerance for newer chemotherapeutic agents and started to explore adjuvant regimens.

In 1995, the RTOG began Phase I-II protocols to evaluate accelerated radiation fractionation schemes in combination with concurrent chemotherapy. RTOG 95-06 evaluated the regimen piloted by the University of Paris, using 5-FU plus cisplatin concurrent with accelerated but hypofractionated radiation therapy delivered over 17 days.[264] Patients with tumor-associated hydronephrosis were excluded, based on findings that these patients had a significantly lower CR rate and a higher cystectomy rate. Among 34 evaluable patients, 67% had a CR on induction and an encouraging 3-year OS of 83%. However, 7 patients (21%) had grade-3 to grade-4 hematologic toxicity on this regimen, though no deaths resulted and no patients required cystectomy for radiation toxicity.

In 1997, the RTOG began to study the role of adjuvant chemotherapy after treatment with either bladder preservation or cystectomy and turned to twice-daily hyperfractionation. In RTOG 97-06, induction and consolidation chemoradiation included twice-daily radiation and outpatient cisplatin (30 mg/m^2) as a radiation sensitizer given on the first 3 days of each week.[265] Radiation doses of 1.8 Gy to the pelvis and 1.6 Gy to the bladder tumor were given daily for 12 days with a 4- to 6-hour interval between fractions during induction treatment. In the consolidation phase, 1.5-Gy fractions were given to both, twice-daily for 8 days (total dose 45.6 Gy to pelvis and bladder, 64.8 Gy to bladder tumor). After consolidation chemoradiation or cystectomy (depending on response), patients received three cycles of adjuvant MCV chemotherapy. The rationale for this protocol was to reduce the duration of the induction treatment to 12 days, thereby decreasing the delay between onset of consolidation chemoradiation or cystectomy for those patients in whom induction therapy failed. The CR rate was 74% and only 11% of patients experienced grade-3 to grade-4 toxicity during induction and consolidation phases. However, only 45% of patients went on to receive a full three cycles of MCV, and of those who did 41% developed grade-3 toxicity. The potential benefit of adjuvant chemotherapy in delaying or preventing metastasis exists because the 2-year actuarial incidence of developing metastasis in this trial was only 18% (compared to about 30% in trials without adjuvant systemic therapy).

RTOG 99-06 added paclitaxel as a radiation-sensitizing agent during the induction and consolidation schedules along with twice-daily radiation.[266] The protocol also used the adjuvant chemotherapy regimen of cisplatin (70 mg/m^2 on day 1) and gemcitabine (1000 mg/m^2 on days 1, 8, and 15). There was a 70% protocol completion rate and an impressive 81% CR rate. Five-year OS and DSS were 56% and 71%, respectively.

More recent RTOG trials have continued to address the question of the optimal concurrent chemotherapy regimen by evaluating different induction regimens in an effort to further enhance the radiation response and improve local control. RTOG 02-33 was a Phase II study that finished accrual of 97 patients in 2008.[267] In this trial, patients were randomized to twice-daily radiation with either concurrent paclitaxel and cisplatin or concurrent 5-FU and cisplatin during the induction and consolidation phases. Adjuvantly, patients received a triplet regimen of gemcitabine (1000 mg/m^2 on days 1 and 8), paclitaxel (50 mg/m^2 on days 1 and 8), and cisplatin (35 mg/m^2 on days 1 and 8). This is similar to the triplet regimen piloted by Bellmunt et al[268] and as tested in a Phase III trial led by the European Organization for Research and Treatment of Cancer (EORTC) and the Southwest Oncology Group (SWOG). RTOG 07-12 is a recently closed Phase II trial randomizing patients to twice-daily irradiation plus concurrent 5-FU and cisplatin or to daily irradiation plus gemcitabine (based on a regimen from the University of Michigan and the United Kingdom) followed by selective bladder preservation and gemcitabine/cisplatin adjuvant chemotherapy. A long-term pooled analysis of a number of RTOG protocols (8802, 8903, 9506, 9706, 9906, 0233) demonstrate an overall CR rate of 69%; 5- and 10-year OS rates of 57% and 36%, respectively; and 5- and 10-year DSS rates of 71% and 65%, respectively. The 5- and 10-year estimates of muscle-invasive LF, nonmuscle-invasive LF, and DM were 13% and 14%, 31% and 36%, and 31% and 35%, respectively.[268a]

Other Experiences

Another original way to combine chemotherapy and radiation has been employed by Eapen et al. This group has combined conventionally fractionated EBRT plus intraarterial cisplatin. Their durable CR rates (83%) are as high as any in the literature. The principal problem they have faced is a high level of sacral neuropathy which, in recent years, they have reduced through reducing the dose of infused cisplatin.[269]

Another novel combination of therapy in locally advanced bladder cancer was undertaken by Hoskin et al who reported a Phase III trial randomizing 333 patients to radiation alone versus radiation plus radiosensitizing carbogen and nicotinamide.[270] A schedule of either 55 Gy in 20 fractions in 4 weeks or 64 Gy in 32 fractions in 6.5 weeks was used. Three-year estimates of OS were 59% and 46% (p = 0.04) and 3-year estimates of relapse-free survival were 54% and 43% (p = .06) for RT + CON compared with RT alone. In multivariate comparison, RT + CON significantly reduced the risk of relapse (p = 0.05) and death (p = 0.03). Risk of death was 14% lower with RT + CON (p = 0.04). There was no indication of an increase in radiation-induced late urinary or gastrointestinal morbidity.

Survival Outcomes Compared to Cystectomy

The primary goal of bladder-preserving therapy, as with any therapy for muscle-invading TCC of the bladder, is optimizing patient survival. Bladder preservation in the interest of quality of life can only be considered a secondary objective. The long-term outcome data presented previously from single-institution and cooperative group experiences suggest that modern combined-modality therapy results in CR rates of 60% to 80%, 5-year OS of 45% to 60%, and 5-year survival rates with an intact bladder of 40% to 45%. Although no completed randomized comparisons of cystectomy with combined-modality therapy exist, these long-term OS rates are encouraging and comparable to those reported in contemporary radical cystectomy series (Table 54-7). Similarly, a retrospective review of a nonrandomized cohort of 458 patients undergoing radical RT or cystectomy in Yorkshire, United Kingdom, showed no significant difference in 10-year OS.[271]

Selection bias makes a nonrandomized comparison difficult. Surgical patients are generally younger with a better performance status. Surgery allows for a more accurate pathologic staging and identification of only surgically identifiable metastatic disease, which leads to a discontinuation of approximately 15% of cystectomies (if node-positive, tumor-unresectable, distant disease), and thus these series do not necessarily report by intention to treat. Furthermore, most cystectomy studies do not provide data on the initial clinical staging and only report outcomes by pathologic stage and rates of clinicopathologic stage discrepancy and clinical understaging are high.[114] The optimum way to compare outcomes of selective bladder-conserving strategies is to compare the outcomes of prospective protocols in which eligibility is based on clinical staging, all patients are cystectomy candidates, and all entered patients are reported for outcome whether or not they completed treatment. Comparison of survival outcomes from contemporary cystectomy and bladder-sparing therapy protocols in patients with muscle-invasive cancer of similar clinical stage, all of whom were potential candidates for cystectomy, are similar, with OS ranging from 45% to 54%.[231,238,256,258,272,273] Martinez-Pineiro et al also reported their cystectomy series by clinical stage.[229] The 5-year OS was 41% (48% for clinical T2); this is similar to that of the bladder-preservation strategy (5-year OS from 45% to 60%), in which all patients who initiated their therapy are reported, not only those whose tumor response was satisfactory to complete the organ-preservation program. It is important to remember that the appropriate strategy for bladder-preservation therapy includes prompt salvage cystectomy for nonresponders. Any comparison of cystectomy protocols with bladder-preservation protocols must include these nonresponders to avoid being biased by patient selection.

Prognostic Factors in Chemoradiation

Complete Response. Clinical CR (or T0 response), evaluated by cystoscopy with tumor site biopsy with or without cytology 2 weeks to 8 weeks after completion of the induction chemoradiation, ranged from 70% to 80%. The CR rate was significantly higher in patients in whom a macroscopically visibly complete TURBT could be achieved compared with patients with residual macroscopic disease after TURBT (80% to 90% versus 60%, $p < 0.001$).[171,257,258] Patients with clinical stage T2-3a achieved significantly more frequent CRs than those with T3b-4 disease (University of Paris, 83% versus 58%, $p < .001$; MGH, T2 vs. T3-4, 81 vs 64%). Patients who presented with *hydronephrosis* achieved a 66% complete response versus 83% in patients who had no hydronephrosis at presentation (University of Paris, $p < 0.05$; MGH, 52% versus 77%). The Erlangen group have shown that those with Tcis disease in the bladder in addition to the invasive tumor are less likely to have a durable response and more likely to require cystectomy.

Chemoradiation added significant improvement to the clinical CR rates compared with the "early" CR after induction chemotherapy alone. After two cycles of MCV, the CR rate for patients with T2 disease was 62% and with T3 or T4 disease, 41%. After adding a course of concurrent chemoradiation, the CR rate increased to 81% and 64%, respectively.[257] Factors predicting for a CR also predict local control and ultimately bladder preservation. For example, among patients who underwent a visibly complete TURBT, only 22% required cystectomy (versus 42% of patients who underwent an incomplete TURBT, $p < 0.001$).[258]

TABLE 54-7 Muscle-Invasive Bladder Cancer: Survival Outcomes Following Curative Therapy in Contemporary Series

		Overall Survival		
Series	**Stages**	**Number**	**5-Year**	**10-Year**
CYSTECTOMY				
USC 2001[153]	pT2-pT4a	633	48%	32%
MSKCC 2001[154]	pT2-pT4a	181	36%	27%
SWOG/ECOG/CALGB*† 2002[238]	cT2-cT4a	317	49%	34%
SELECTIVE BLADDER PRESERVATION				
U. Erlangen* 2002[139,259]	cT2-cT4a	326	45%	29%
MGH* 2012[258]	cT2-cT4a	348	52%	35%
RTOG* 1998[231]	cT2-cT4a	123	49%	—
RTOG 2014 ([268a])	cT2-cT4a	468	57%	36%
BC2001* 2012[256]	cT2-cT4a	*182*	*48%*	—

**These series included all patients by their intention to treat.*

†50% of patients were randomly assigned to receive three cycles of neoadjuvant M-VAC.

Survival. Clinical complete responders generally have significantly higher survival rates than nonresponders. The amount of residual tumor after TURBT is also a prognostic factor for survival as for local control. The same is true for those with T2 clinical category compared with T3-4 and those presenting without hydronephrosis. In multivariate analyses, clinical T category and CR to induction therapy remained significantly associated with improved DSS and OS.[257,258]

The 5-year distant metastasis rate for all patients entered in the protocols ranged from 34% to 40%. In the MGH series, the 5-year distant metastasis rate in the T0 responder group was only 20%.[257,258] Patients who did not respond rapidly (T > 0) and underwent immediate cystectomy had a 50% distant metastasis rate at 5 years. However, it was similar to the 5-year rate of initial T0 responders who subsequently underwent salvage cystectomy for local failure (5-year distant metastasis rate, 54%). Delayed cystectomy for recurrent invasive disease did not confer worse outcomes when compared to immediate cystectomy for a noncomplete response.

Follow-Up after Chemoradiation. All patients with bladder cancer (either superficial or invasive) treated with bladder-preserving therapies must be willing to return for regular, thorough clinical examinations, cystoscopy, biopsy of the tumor site, and urine cytology follow-up so that transurethral surgery, intravesical therapy, or salvage cystectomy can be implemented at the earliest opportunity if necessary. The optimal timing of cystoscopy after RT is unclear but is usually first done at 3 months.[187] At the MGH our protocol mandates cystoscopy and urine cytology every 3 months for the first 2 years, then every 6 months until 5 years and annually thereafter. In patients with a series of negative followup evaluations, the biopsy and examination under anesthesia may be omitted in favor of office cystoscopic evaluation if no worrisome office endoscopic findings are present.

Managing Recurrent Disease in the Bladder. Of patients who have complete response, 84% of patients remained free from invasive recurrence in the bladder at 10 years, and approximately 60% remained free from any noninvasive or invasive occurrence.[257,258] Of patients whose invasive recurrence was cured, 17% to 30% may subsequently experience superficial noninvasive (≤T1) TCC[258,274,275] Eighty-four percent of patients who experienced superficial recurrences (Ta or CIS) at MGH have been maintained in remission by TURBT and intravesical drug therapy.[274] For these individuals the OS and DSS was comparable to those who had no failure. However, significantly fewer patients with a superficial relapse survive with their native bladder and up to one quarter of these patients may ultimately require a salvage cystectomy.

Although superficial tumors may be managed by TURBT and intravesical therapy,[274-276] invasive recurrences are generally managed with salvage cystectomy. In selected series, salvage cystectomy results in a 40% to 50% survival rate at 5 years and good locoregional control rates.[198,258]

Conclusions Regarding Combined Chemoradiation and TURBT. The *ideal* candidate for bladder preservation meets the following criteria:

1. Primary T2-3a tumors that are unifocal
2. TCC (urothelial) histology
3. Tumor size less than 5 cm in maximum diameter
4. Tumor not associated with extensive CIS
5. No presence of ureteral obstruction or tumor-associated hydronephrosis
6. Good capacity of the bladder and good bladder function (i.e., a bladder worth sparing)
7. Visibly complete TURBT
8. Adequate renal function to allow cisplatin concurrent with radiation (though good alternative chemotherapy regimens such as 5-FU/MMC can be considered in patients with lower glomerular filtration rate [GFR][256]).

Notably age is not a contraindication to successful bladder sparing therapy, and indeed results are favorable in patients age 75 or older.[258] This is an important consideration given that the elderly generally appear to be undertreated for invasive bladder cancer in the United States.[277] Bladder-sparing chemoradiation remains a good option for those patients who are not cystectomy candidates and often such patients would be treated with daily radiation and appropriate concurrent chemotherapy without a break.

Quality-of-Life Studies

Radical cystectomy causes changes in many areas of quality of life, including urinary, sexual, and social function; daily living activities; and satisfaction with body image.[278-282] Sexual function has been particularly emphasized because of the high prevalence of erectile dysfunction. Researchers have, over the last decade, concentrated on the relative merits of continent and noncontinent diversions. Available data have been mixed with some groups, surprisingly, reporting few differences between the quality of life of those with an ileal conduit and those with continent diversions.[283] Until recently, little comparative data have been available on those who have neobladders. Hart et al have compared outcome in cystectomy patients who have ileal conduits, cutaneous Koch pouches, or urethral Koch pouches.[282] Of 1074 patients undergoing cystectomy for bladder cancer at the University of Southern California, 368 were eligible for study because they were alive, spoke English, and had no major health issues that would affect global quality of life. Of these, 61% completed self-reporting questionnaires. Regardless of the type of urinary diversion, the majority of patients reported good overall quality of life, little emotional distress, and few problems with social, physical, or functional activities. Problems with their diversions (in approximately 60% of patients) and with sexual function were the most commonly reported. After controlling for age, no significant differences were seen among urinary diversion subgroups in any quality-of-life area. It might be anticipated that those receiving the urethral Koch diversions would be the most satisfied and the explanation why this is not so is unclear. It may be that the subgroups were too small to detect differences, but perhaps it is more likely that each group adapts in time to the specific difficulties presented by that type of diversion.

Zietman et al have performed a study on patients receiving TURBT, chemotherapy, and RT in the treatment of their bladder cancer at the MGH.[284] Of 221 patients with clinical T2-4a cancer of the bladder treated at the MGH from 1986 to 2000, 71 were alive with their native bladders and disease free in 2001. These patients were asked to undergo a urodynamic study (UDS) and to complete a quality-of-life questionnaire. Sixty-nine percent participated in some component of this study with a median time from trimodality therapy of 6.3 years. This long follow-up is sufficient to capture the majority of late radiation effects. Seventy-five percent of patients had normally functioning bladders by UDS. Reduced bladder compliance, a recognized complication of radiation, was seen in 22%, but in only one third of these was it reflected in distressing symptoms. Two of 12 women showed bladder hypersensitivity, involuntary detrusor contractions, and incontinence. The questionnaire showed that bladder symptoms were uncommon, especially among men, with the exception of control problems. These were reported by 19% with 11% wearing pads (all women). Distress from urinary symptoms was half as common as their prevalence. Bowel symptoms (e.g., rectal urgency) occurred in 22% with 14% recording any level of distress. The majority of men retained sexual function.

Global health–related quality of life was high. The great majority of patients treated by trimodality therapy therefore retained good bladder function. It was concluded that there is a small but detectable level of lasting bowel dysfunction and distress and that this might be judged the additional price that these patients have had to pay to retain their bladders.

A prospective Phase II multicenter study from France has recently been reported.[285] It tracked voiding symptoms and quality of life in 53 patients from before their trimodality treatment. Sixty-seven percent retained their bladders and these were interviewed 6, 12, and 24 months later. Levels of urinary symptoms were high but only 5% reported any EORTC grade-3 symptoms. It was also notable that most patients experienced improvement of symptoms over the 2 years after treatment presumably because of the eradication of a symptomatic primary tumor.

Two cross-sectional questionnaire studies, one from Sweden and one from Italy, have compared the outcome following radiation with the outcome following cystectomy.[286,287] The questionnaire results for urinary function following radiation were similar to those recorded in the MGH study. More than 74% of patients reported good urinary function. Both studies compared bowel function in irradiated patients with that seen in patients undergoing cystectomy. In both, the bowel symptoms were greater for those receiving radiation than for those receiving cystectomy (10% versus 3% and 32% versus 24%, respectively) but in neither was this statistically significant.

In the assessment of sexual function, most women in the MGH study preferred not to answer the questions and no data were therefore available for them. Almost all men, however, did. In contrast to patients who have been irradiated for prostate cancer, the majority of male bladder-sparing patients reported adequate erectile function (full or sufficient for intercourse), and only 8% reported dissatisfaction with their sex lives.[284] These are in line with those obtained in the Swedish and Italian series in which 38% and 25% of men retained useful erections as compared with 13% and 8% of cystectomized controls. The MGH series allowed the use of sildenafil probably contributing to the better outcome. Another study reported that 71% of women who underwent bladder-preservation therapy showed no decline in their subsequent satisfaction with sexual intercourse.[288]

An analysis of four prospective RTOG bladder-sparing protocols (89-03, 95-06, 97-06, 99-06) suggested that rates of significant late pelvic toxicity for patients completing combined-modality therapy for invasive bladder cancer and retaining their native bladder is low.[289] Only 7% of patients experienced a late grade-3 pelvic toxicity (5.7% genitourinary and 1.9% gastrointestinal) and in only one patient did the toxicity persist. Notably, there were no late grade-4 toxicities reported and no treatment-related deaths.

LOCALLY ADVANCED DISEASE AND PALLIATION

When bladder cancer has invaded adjacent organs or spread to the pelvic lymph nodes cure is rare, as the primary tumors are typically bulky and distant metastases usually present, even if subclinical. In this situation if the voiding symptoms are not too severe and the renal function allows, it is common to give combination chemotherapy and reassess after several cycles. If the patient has had a good response they may receive consolidation chemoradiation delivered with "curative" intent. If renal function is poor, patients may be given nonplatinum–based regimens such as 5-FU/MMC or taxol either before or with the radiation. If voiding symptoms are severe or there is bilateral hydronephrosis, they may be better served by percutaneous urinary drainage and then cystectomy with urinary diversion. For patients with locally advanced T4 primary tumors or locally recurrent cancer, there is a rationale for combining resection with intraoperative radiation therapy (IORT) but experience is limited. Resection and IORT would preferably be preceded by several cycles of multiagent chemotherapy, then pelvic radiation (45 Gy to 50.4 Gy in 1.8-Gy fractions) plus concurrent weekly cisplatin (see previous section). Trials have been published from our colleagues in Lyon, France, and Pamplona, Spain, demonstrating the potential value of pursuing such approaches in other centers with IORT capabilities.[290-292]

If the patient is unfit for cystectomy then radiation may be given to the bladder for palliation. Duchesne et al reported an MRC trial in the United Kingdom in which 500 patients were randomized to two palliative fractionation schedules: 35 Gy in 10 fractions and 21 Gy in 3 fractions (given weekly). When assessed at 3 months 68% had had some symptomatic improvement but there was no difference between the arms.[293] There was no evidence for a difference in toxicity justifying the use of this ultrahypofractionated regimen for the palliation of patients at the end of their lives.

Metastatic bladder cancer is responsive to platinum-based chemotherapy. MVAC or MCV (often given in dose-dense fashion) have been the usual choices as first-line drugs but gemcitabine and cisplatin (and the addition of taxol) are emerging as reasonable alternatives and may be better tolerated.[294] It is remarkable that, unlike most other solid tumors, CRs are not unusual and durable responses do occur. Recently, immunotherapy with checkpoint inhibitors has shown promise in clinical trials for metastatic bladder cancer.[294a]

Radiation is often used in the palliation of bone and brain metastases. Palliative radiation may also relieve the inferior vena cava or lymphatic obstruction that can occur when there is heavy involvement of the paraaortic nodes.

IRRADIATION TECHNIQUES AND TOLERANCE

External Beam Irradiation

Historically all work on bladder cancer that has been published used RT that was delivered by conventional two-dimensional RT. More recently, three-dimensional (3D) techniques became standard in RTOG protocols employing appropriate margins for an organ as mobile as the bladder. Now, IMRT has emerged as an option given the availability of advanced daily image guidance such as cone-beam CT and even real time tracking of the bladder and the possibility of more conformal treatment to spare central lying low hanging bowel.

At the MGH the following 3D technique has been used on and off-protocol regularly, though IMRT planning has been adopted more consistently in recent years. The standard protocol for radical EBRT as well as combined-modality therapy uses a four-field isocentric technique, which consists of shaped anterior, posterior, right, and left lateral fields for the initial or induction treatment field (Figure 54-4). This is followed by a boost or consolidation field (Figure 54-5).

Simulation

All simulations begin after the patient has voided (i.e., empty bladder). Treatments are also given with the bladder empty as this makes bladder position and tumor localization more reproducible and predictable. The patient is then immobilized in a supine position and a CT simulation is performed.

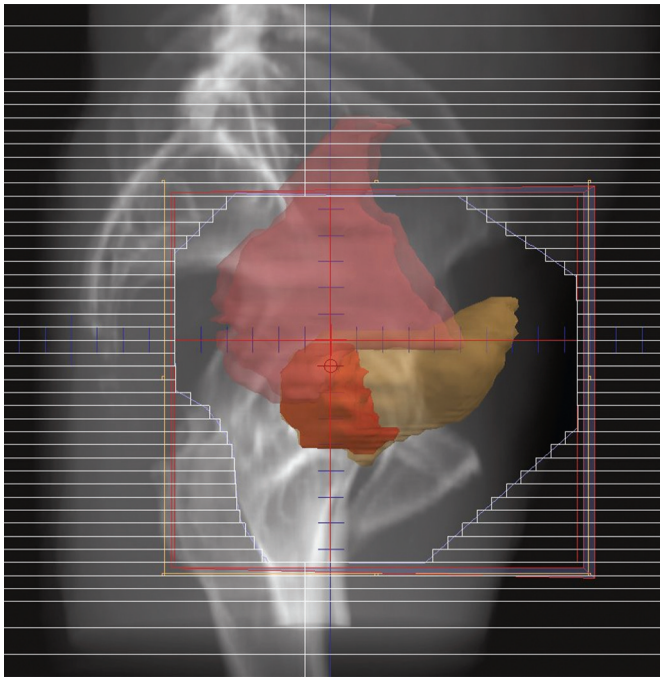


Figure 54-4 Sagittal digitally reconstructed radiograph (DRR) image showing a lateral view of a small pelvis field.

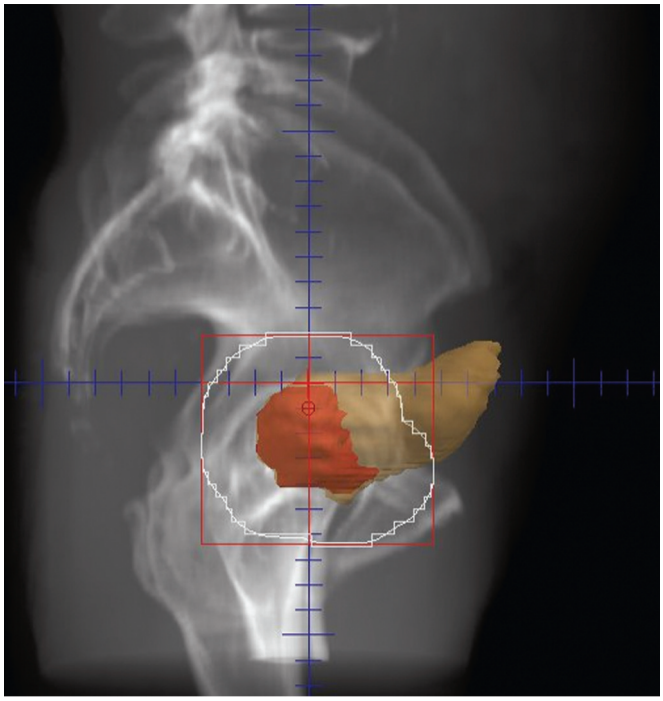


Figure 54-5 Sagittal digitally reconstructed radiograph (DRR) image showing how a lateral boost may be given to a tumor to spare the anterior bladder.

Target Volumes

During the first phase of treatment the bladder is treated along with a margin of 2 cm. In men, the entire prostate is also covered in this first phase because there may be occult stromal invasion or extension into the prostatic urethra. In women, the proximal 2 cm of urethra are also considered target. Care must be taken to avoid the inferior border of the field glancing the vulva because this may limit tolerance. The internal and external iliac lymph nodes of the pelvis are also covered for this phase of therapy. The top border of the field usually lies around the midsacroiliac joint and only at the level of the bifurcation of the common iliac vessels and does not include the entire pelvis. This is because a significant number of irradiated patients may subsequently require salvage cystectomy with urinary diversion. It is therefore prudent to limit the amount of radiation to bowel that may subsequently be needed for this purpose. Another good reason to limit the bowel volume is that quality-of-life studies have shown that the most troublesome consequences of irradiation for bladder cancer relate to the small bowel irradiation rather than the bladder irradiation.[284,287]

During the boost phase of treatment, MGH investigators boost the entire bladder excluding nodes and then further boost the tumor alone with a 2 cm margin (an alternative is to just boost the tumor alone). Defining the tumor may be difficult, but we employ a combination of an operative report and bladder map drawn by the urologist at the time of cystoscopy/TURBT, and CT and MR information from the initial (pre-TURBT) staging work-up. CT scan after TURBT may overestimate the tumor residuum because of edema in the bladder wall. Using these sources of information it is usually possible to exclude at least one third of the bladder from the boost volume (Figures 54-5 and 54-6). Although this may not seem like much, it does mean that less than the entire volume is treated to full dose, a factor that may contribute to the good functional results seen after use of this technique. Fiducial markers may be inserted either cytoscopically or through the anterior abdominal wall into the edges of the resection bed to aid boost visualization (Figure 54-7). Such fiducial markers around the tumor site placed at time of TURBT can help tailor field design and can be used with daily imaging (such as cone-beam CT) for localization to further guide treatment during the tumor boost phase. It is possible that treating with a full bladder during the tumor boost phase could further limit bladder and bowel dose.

Fields

The first phase treats the pelvic lymph nodes, prostate, and bladder (if using a four-field arrangement, roughly mid-SI joint superiorly, bottom of the obturator foramen inferiorly, and 1.5-cm margin on the pelvic brim laterally). The second phase boosts the bladder alone and the third phase the tumor alone. As most tumors are on the bladder trigone or on the postero-lateral walls, it is easiest to boost with opposed lateral fields when not using IMRT. If this is anticipated the 4-field box used in the first phase has to be weighted more heavily toward the antero-posterior (AP) and posterior-anterior (PA) to save femoral head tolerance and allow the lateral boost.

Patients are encouraged to empty their bladders before treatment to achieve a more reproducible target and to minimize volume irradiated. Many patients with bladder cancer have significant postvoid residual volume so artificial emptying of the bladder by catheterization may give a false impression of the shape and size of the target volume at simulation.

IMRT planning has been adopted at the MGH more recently (Figure 54-6). Planning target volume (PTV) expansions of 2 cm around bladder and bladder tumor have been employed, with 0.8-cm margins for prostate (0.5-cm posterior) and pelvic nodes. PTV margins may be decreased a little when targets abut large amounts of low hanging small bowel. A seven-field beam arrangement is typically used for small pelvis, and either a five- or seven-field beam arrangement for bladder only and tumor boost. We start with beams equally spaced and modify the angles as anatomy requires.

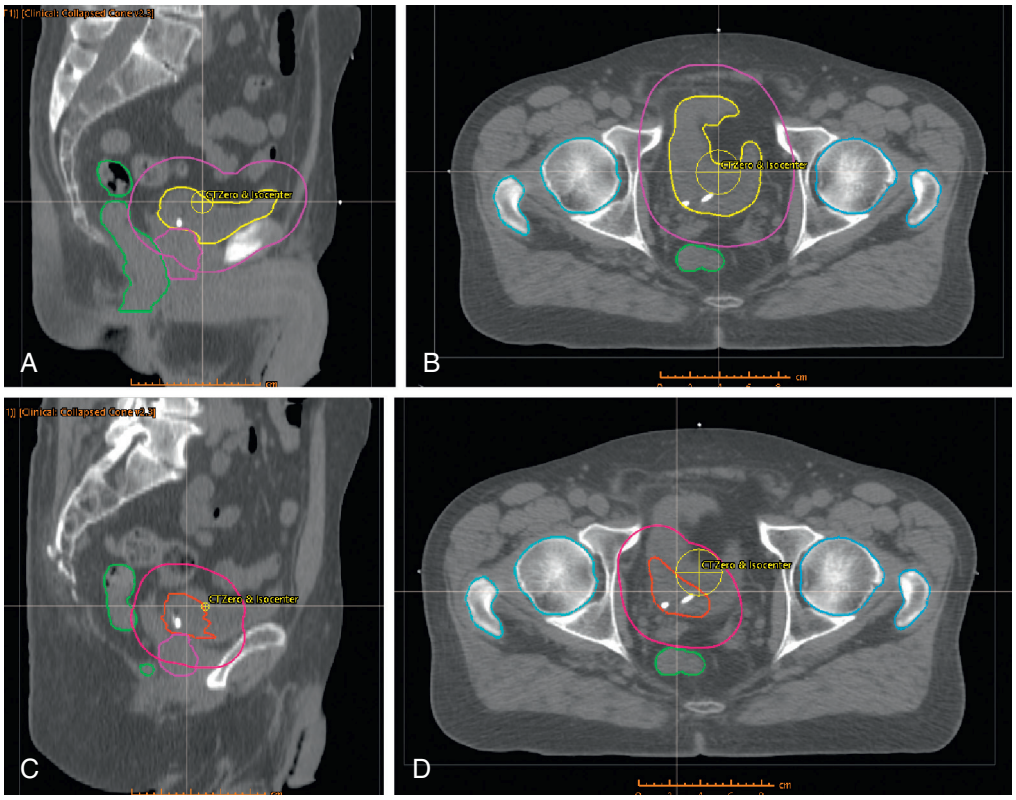


Figure 54-6 **A** and **B,** Planning target volume (PTV) expansions around bladder, tumor, prostate in sagittal and axial CT cuts for small pelvic fields; Panels **C** and **D,** PTV expansions for bladder tumor boost fields.

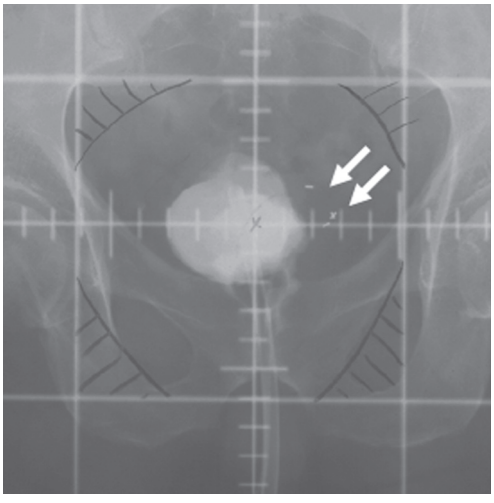


Figure 54-7 Fiducial markers placed adjacent to a bladder tumor at the time of transurethral resection.

Total Dose

At the MGH, investigators have traditionally given total doses on the order of 65 Gy delivered in once daily (1.8-Gy to 2-Gy fractions, 5 days per week) or twice daily (please refer to RTOG 0712) fashion, together with concurrent chemotherapy (cisplatin alone, cis/5-FU or 5-FU/MMC when not on protocol) and a maximal TURBT. Typically, 40 Gy to 45 Gy is delivered in the first phase to the larger small pelvic field covering the entire bladder, prostate, and the low pelvic lymph nodes. The whole bladder receives an additional 10 Gy 14 Gy, and the tumor is boosted to full dose with an additional 10 Gy. If not employing a bladder-alone boost, then the tumor is boosted to the full dose after the small pelvic phase. An invasive local recurrence is limited to only 15% to 18% of all complete responders, implying that this is an adequate dose for durable local control in the vast majority of those who respond to radiation. Investigations into adaptive planning and dose escalation are ongoing.

Treatment Break to Evaluate Response

At the MGH, investigators have routinely built in a 3-week break as an early treatment assessment response following the delivery of 39 Gy to 42 Gy. This is quickly followed by repeat cystoscopy/biopsy of the tumor site (Figure 54-8). Patients are selected to continue and complete radiation (the consolidation phase) on the basis of their response at this point. Those who have had a CR (anticipated to be 80% of patients) or in whom the tumor residuum is less than T1 by stage (Ta or Tis) continue. The others are recommended to undergo an immediate cystectomy. This can thus be performed before the patient has had full-dose radiation, an easier proposition for the surgeon (both in time to cystectomy and in dose to the pelvis). It also means that a patient responding poorly can be identified early and recommended surgery promptly rather than waiting for an entire course of radiation to be completed by which time progression may have occurred that could threaten the efficacy of salvage therapy. Concerns have been expressed on radiobiological grounds that split-course treatment compromises efficacy.[295,296] There is also the worry that those who have not been complete responders after 40 Gy might yet become complete responders after 65 Gy, and thus, some may be recommended an unnecessary

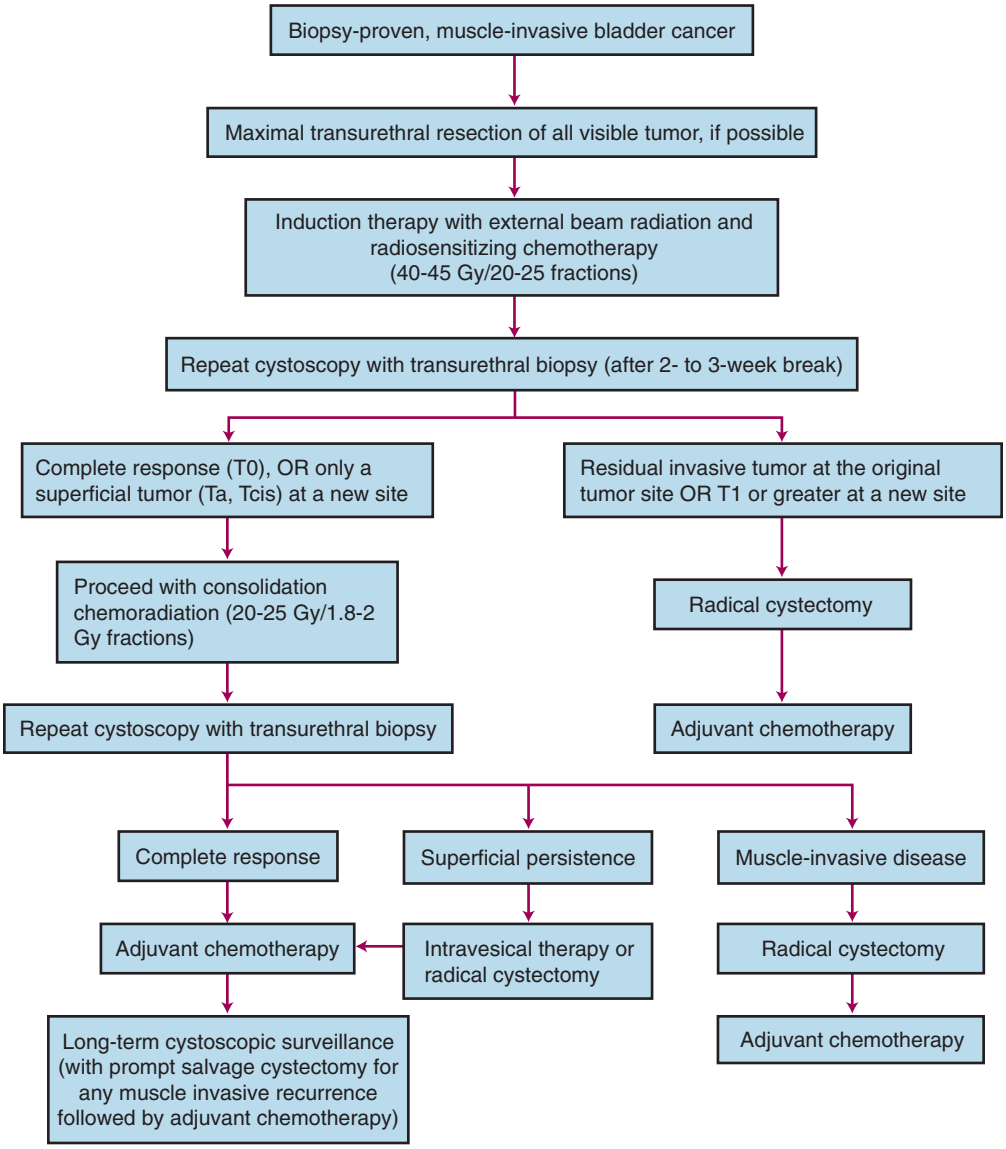


Figure 54-8 **Current algorithm for the trimodality management of invasive bladder cancer.**

cystectomy. This concern, however, probably affects only a minority of patients.

Controversial Issues in EBRT Technique

Nodal Treatment

Lymph node involvement is common in this disease and is seen in approximately 25% of patients coming to a radical cystectomy.[153] The number of lymph nodes involved is well established as a prognostic indicator that surgeons use to determine the extent of their lymph node dissection and the need for adjuvant chemotherapy.[158] This information is, however, unavailable to radiation oncologists. More interesting for them is the knowledge that some patients with positive lymph nodes may be cured by a lymphadenectomy, a situation akin to breast or head and neck cancers. The thoroughness of a lymph node dissection (>10 nodes removed) also correlates with outcome independent of nodal status.[297] Thus, radiation to the pelvis might confer a survival advantage though it comes at the price of additional morbidity. Centers that do irradiate the bladder alone (typical in UK practice) do not report either an increased pelvic failure rate or reduced survival although direct comparisons are difficult and randomized data is not available.[298] It may be that either chemotherapy does the job of the nodal irradiation or that nodal disease extends beyond the confines of the current pelvic template. Surgeons have started to perform extended lymphadenectomies to the level of the inferior mesenteric artery.[141,299]

Partial Bladder Treatment

Estimates of bladder tolerance have been made which suggest that up to 80 Gy could be given if one third of the bladder is spared, whereas 65 Gy is the limit for whole-bladder treatment.[300-302] In addition, the low rate of development of new invasive tumors elsewhere in the bladder after brachytherapy (5% to 7%) suggests that localized partial bladder radiation is a reasonable strategy.[202] Careful selection is, however, necessary with such approaches being limited to smaller tumors (<5 cm), unifocal tumors, and those without extensive Tis tumor elsewhere in the bladder. A randomized trial in the United Kingdom has shown that partial bladder irradiation does allow for the delivery of a higher dose to the

tumor than whole-bladder radiation without an increase in morbidity.[303] It did not, however, show either improvement in local control or survival. One hundred forty-nine patients were randomized to receive whole-bladder conformal RT to 52.5 Gy in 20 fractions or partial bladder conformal radiation to either 57.5 Gy in 20 fractions or 55 Gy in 16 fractions. The 5-year local control rates for these three regimens were 58%, 59%, and 34%, respectively, without any significant differences between arms ($p = 0.18$). The recently reported BC2001 Phase III trial also randomized patients to standard whole-bladder EBRT or reduced high-dose volume EBRT that aimed to deliver full radiation dose to the tumor and 80% of maximum dose to the uninvolved bladder.[304] There were no statistically significant differences between groups in terms of late toxicity and noninferiority of locoregional control could not be concluded formally. Overall low rates of clinically significant toxicity combined with low rates of invasive bladder cancer relapse help to confirm that chemoradiation therapy is a valid option for the treatment of muscle-invasive bladder cancer.

Treatment Margins

At the MGH in expanding the clinical target volume (CTV) to the PTV we have adopted isotropic 2-cm margins around either the bladder (first phase of treatment) or tumor (boost) in all three dimensions. This is to account for set-up errors and organ motion. Several studies employing serial CT scans have shown that margins less than this may be inadequate. Turner et al demonstrated that bladder wall movement of >1.5 cm occurs at least once during a course of treatment in more than 60% of patients.[305] Several others have reported that the gross target volume (GTV) moves outside the PTV on at least one occasion in at least 20%.[306,307] Our own analysis showed that these variations are highly patient dependent and occurred even when strict instructions were given regarding bladder and rectal filling.[308] The greatest degree of bladder wall positional change occurred in the cranial direction with the least variation in the antero-inferior direction, limited by the pubic symphysis. In light of this information it is clear that organ motion is the dominant source of error and that the magnitude of the error depends on the region of the bladder. The solutions are clear though difficult to achieve. Graham et al have recommended anisotropic margin widths of 1.6 cm anterior and posterior, 1.4 cm laterally, 3 cm superior, and 1.4 cm inferior.[309] The problem is that these margins incorporate much normal tissue. Daily image-guided therapy is the only way to reduce these margins significantly. Daily cone-beam CT that can delineate the bladder is one option. There is also interest in the use of fiducial markers that could be placed by the urologist at the time of TURBT in the bladder wall around the tumor crater (Figure 54-6 and Figure 54-7). Roof et al have shown that if the daily treatment is centered on the bladder centroid, rather than referenced to bony anatomy, margins of <1.5 cm could be feasible.[308] None of these studies account for the fact that the bladder not only changes in size but also in shape, it is deformable. This will likely set a limit on our ability to shrink margins significantly anytime soon.

Radiation Dose

There is evidence for a dose-response curve in bladder cancer with most studies showing that doses of <62 Gy (at 1.8 Gy to 2 Gy per fraction) predict poor outcome.[310-312] Most of these studies have, however, employed radiation alone and the curve is likely to be greatly modified by effective debulking of the tumor or by radiation sensitization with concurrent chemotherapy. Increasing dose may result in increased CR rates but may add to the morbidity and may also be limited by the rapid proliferative index and short doubling time of these tumors.[313] Interest recently has therefore concentrated on dose intensification using accelerated regimes rather than an increase in total dose. Acceleration may be achieved through hypofractionation, but this may be better limited to the palliative setting or through the use of conventional 2-Gy fractionation given twice a day.[314] The Royal Marsden Hospital has reported on 85 patients with twice-daily fractions of 1.8 Gy to 2.0 Gy 5 days a week to doses between 57.6 Gy and 64 Gy in 32 fractions over 26 days. Of 70 patients who had cystoscopic reevaluation 3 months to 6 months after RT, 80% were found to be complete responders (i.e., cystoscopy and biopsy negative for tumor 3 months to 6 months later).[315] Plataniotis et al reported a total response rate of 67% when a twice-daily fractionation was used during the last week (fifth week) of RT.[316]

Unfortunately, acceleration with fraction sizes of 2 Gy seems to increase acute toxicity. The RTOG has therefore explored acceleration with hyperfractionation and recent protocols have employed fraction sizes of 1.2 Gy to 1.8 Gy with a concomitant boost technique. No comparative studies have yet been performed but morbidity appears low.[265] The recently closed RTOG protocol 0712 did compare a twice daily to once daily regimen, though results are pending.

Hyperfractionation has also been used to increase the total tumor dose. A randomized trial of 168 patients with T2-4 tumors, unsuited for cystectomy, compared hyperfractionated EBRT (1 Gy three times a day to a total dose of 84 Gy) with conventional fractionation (2.0 Gy every day to 64 Gy).[317,318] Hyperfractionation achieved superior results with respect to 5-year OS (27% versus 18%), local control (12% versus 7%), and clinical CR rates (59% versus 36%) with an increase in late toxicity. Both study arms were treated by a split-course of RT with a 2-week gap after the first 3 weeks, the effect of which is unknown. The benefit of the hyperfractionated schedule persisted over a 10-year follow-up period, both for local control and survival. It should be noted, however, that patients in the conventional fractionation arm did poorly compared with those receiving similar treatment in other studies largely because patients unfit for cystectomy were entered in this study.

Future improvements in the CR rate may also come without any need to escalate radiation dose: better selection of patients, better radiation sensitization (including novel targeted therapy and immunotherapy), and more aggressive TURBT. Others have argued that doses of 65 Gy at 1.8 Gy to 2 Gy per fraction may actually be more than is needed especially for those who have had visibly complete transurethral resections. The Erlangen group has delivered doses tailored to the estimated residuum following resection. These doses are in the range of 50 Gy to 59 Gy (1.8 Gy to 2 Gy per fraction) depending on whether disease to be treated is microscopic or gross in volume.[319]

Brachytherapy

Shortly after completion of the preoperative radiation (<2 weeks), a suprapubic cystotomy is performed to ascertain the true dimensions of the tumor and to confirm that it is indeed unifocal. There are regional differences in the type of surgery performed on the primary tumor. In France, a partial cystectomy is preferred. In the Netherlands, citing concerns about the risk of fistula, this is only performed for lesions on the dome or in a diverticulum. The target area is determined by the surgery and is either the bladder scar after partial cystectomy or the macroscopic tumor plus a 1.5-cm to 2.0-cm margin. It may be marked by fiducials at this point. Narrow afterloading tubes are then inserted into the target area parallel and halfway through the bladder wall. In the case of a partial cystectomy, two tubes one on either side of the scar are sufficient. If a partial cystectomy is not performed, then three to

five tubes in a single plane will encompass most lesions. The tubes are then brought out to the anterior abdominal wall and a suprapubic catheter inserted for drainage. The tubes are removed without anesthesia after the completion of radiation; the urinary catheter is removed 2 weeks later.

Radiation planning may be performed using stereo-shifted radiographs, but it is now preferable to use CT. Doses given vary greatly in the literature according to the additional external beam given and whether or not high- or low-dose rate brachytherapy is planned. If less than 10 Gy to 15 Gy is given preoperatively, then 30 Gy to 60 Gy are given using low-dose rate. The lower doses are given to those who have had partial cystectomies or complete resections. In the Netherlands 30-Gy EBRT is either supplemented with 40 Gy low-dose rate or 10 × 3.2 Gy high-dose rate (two fractions per day with a 6-hour interval).

TREATMENT ALGORITHM, CHALLENGES, AND FUTURE POSSIBILITIES

Selective bladder preservation is based on the response of the tumor to induction combined-modality therapy, which includes a TUR of as much of the primary bladder tumor as is judged safely possible combined with concurrent chemotherapy and EBRT; early salvage cystectomy is recommended for patients whose tumors are not responding to combined-modality therapy or for an invasive recurrence to maximize the possibility of cure (Figure 54-8). In appropriately selected muscle-invasive patients, bladder-preserving treatment with chemo-radiation offers a chance for long-term cure and survival comparable to radical cystectomy, while affording a 70% to 80% chance of maintaining their native bladder (Tables 54-6 and 54-7). Quality-of-life studies have demonstrated that the retained native bladder functions well and long-term toxicity of chemoradiation to pelvic organs is low. These results support the acceptance of modern bladder-sparing trimodality therapy for selected patients as a proven alternative to cystectomy (and for patients who are not good surgical candidates). This approach is not suitable for patients with tumors obstructing a ureter. Twenty percent to 30% of patients cured of muscle-invading bladder cancer will subsequently acquire a new superficial tumor, but these superficial tumors have generally responded well to the usual TURBT and intravesical drug therapy. These patients require close urologic surveillance, as do any patients with superficial bladder cancer treated conservatively. Bladder-preserving treatment usually results in a normally functioning bladder for patients with T2 and T3a disease; however, patients with T3b-4 disease experience local control less frequently using these techniques. No data exist, however, to suggest that patients with more advanced disease are in any way disadvantaged by preoperative chemoradiation as an attempt at bladder conservation. Radiation-based strategies are also being explored in the recurrent T1 BCG refractory and locally advanced postcystectomy settings. Further clinical practice guidelines are available through the updated National Comprehensive Cancer Network[320] and other guidelines.[115]

Although many urologists have found merit in a selective bladder-sparing approach to muscle-invading transitional cell bladder cancer, many more will need to become convinced if there is to be a significant change in treatment practices for bladder cancer across the country. As studies addressing the possibility of organ preservation continue to demonstrate positive results, it is hoped that more patients will become informed about and be offered selective bladder-sparing approaches as an alternative to radical cystectomy. The contribution of selective bladder-sparing therapy to the quality-of-life of patients so treated represents a unique opportunity for urologic surgeons, radiation oncologists, and medical oncologists to work hand in hand in a truly multidisciplinary effort.

The immediate therapeutic challenges for radiation oncologists include:

- More effective radiographic tumor definition and tracking during radiation therapy. This may allow tighter margins, more accurate and higher dose delivery, and higher rates of bladder preservation.
- More effective radiation sensitization. The optimal regimen of combined chemoradiation continues to be investigated. Current standards are cisplatin-based (such as cis/5-FU) or 5-FU/MMC. Gemcitabine has been under evaluation at several centers and by the RTOG.
- More effective evaluation of pelvic lymph nodes using, perhaps, iron nano-particle MR lymphangiography, and more effective treatment of pelvic lymph nodes with either extended lymphadenectomy or radiation delivered using intensity-modulated irradiation (IMRT).
- Further defining a role for radiation-based strategies in the recurrent T1 BCG refractory and locally advanced postcystectomy settings.
- Integrating rational molecularly targeted biologic and immune-based strategies into primary therapy.
- Further defining clinical factors and molecular biomarkers predictive of response and outcome to therapy.

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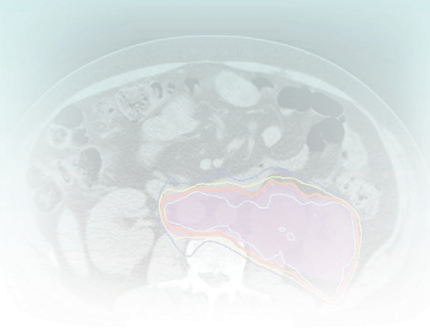
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CHAPTER

55 Testicular Cancer



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INCIDENCE

In men 15 to 35 years of age, testicular cancer represents the most frequently diagnosed malignancy but overall only 1% of all malignant tumors. In 2008, 52,000 new cases and 9000 deaths were estimated worldwide from this disease

BIOLOGIC CHARACTERISTICS

Isochromosome 12p is present in more than 80% of cases.

STAGING EVALUATION

After a history and physical examination is undertaken, serum tumor markers, including alpha-fetoprotein (AFP), β-human chorionic gonadotropin (β-HCG), and lactate dehydrogenase (LDH) is important for further assessment.

Imaging should include chest radiography and computed tomography (CT) scan of the abdomen and pelvis. CT scan of the thorax may be omitted in patients with seminoma with normal abdominopelvic CT but is otherwise usually included. Other imaging modalities such as magnetic resonance (MR) and positron emission tomography (PET) scans are not routinely included for staging patients.

PRIMARY AND ADJUVANT THERAPY

Radical inguinal orchiectomy allows pathological subtyping, enables appropriate management, and is also the initial treatment for testicular cancer.

Seminoma

Stage I seminoma has overall survival (OS) rate of almost 100%. There are three main management options with resultant differing relapse rates. Surveillance is the preferred option, with a 15% relapse rate, whereas adjuvant therapy, with either retroperitoneal irradiation or carboplatin chemotherapy, has a 5% relapse rate. Similarly, stage II seminoma has a 5-year OS of 97%. Radiation therapy (RT) for stage IIA or IIB disease, with a 10% relapse rate, and cisplatin-based chemotherapy for stage IIC disease, with a <5% relapse rate are commonly employed as treatment options. For stage III seminoma, the 5-year OS is approximately 85% and cisplatin-based chemotherapy is the preferred treatment option.

Non-Seminoma

Stage I non-seminoma has a 99% 5-year OS. The main treatment options include surveillance with a 30% relapse rate, retroperitoneal lymph node dissection (RPLND) with a 10% relapse rate, and adjuvant chemotherapy (most often given only for high-risk patients) with a 1% relapse rate.

For stage II non-seminoma, the 5-year OS is ~98%. Stage IIA disease is managed with cisplatin-based chemotherapy alone or RPLND plus chemotherapy (both <5% relapse rate), and stage IIB or IIC disease is managed with cisplatin-based chemotherapy, with a 5% relapse rate. Stage III disease is managed with chemotherapy.

Patients with metastatic germ-cell tumors have been divided into good-prognosis, intermediate-prognosis, and poor-prognosis groups based on anatomic spread and elevated level of serum tumor markers. The *good-prognosis group* (60% of cases) has an approximately 86% OS. These patients have a primary tumor of the testis or retroperitoneum, no visceral metastases (except for pulmonary metastases), and low tumor marker levels (AFP, <1000; β-HCG, <5000; and LDH, <1.5 ULN). The *intermediate-prognosis group* (26% of cases) has an approximately 80% OS. These patients have a primary tumor of the testis or retroperitoneum, no visceral metastases (except pulmonary metastases), and AFP levels of 1000 to 10,000, or β-HCG levels of 5000 to 50,000, or LDH levels of 1.5 to 10 ULN. In the *poor-prognosis group* (14% of cases), the OS is around 50%. A primary tumor of the mediastinum is present, or nonpulmonary visceral metastases are found, or tumor marker levels are high (AFP >10,000; β-HCG >50,000; LDH >10 ULN).

Testicular cancers are uncommon in the general population but are one of the most common and important malignant tumors in young men. Worldwide, 52,000 new cases and 9000 deaths were estimated for this disease in 2008.[1] More than 95% of testicular cancers are primary germ cell tumors (GCTs); the others include lymphomas and sarcomas. The incidence of GCTs has doubled in the past 30 years. Although the majority (70% to 80%) present with early-stage and at the same time highly curable disease, the continued rise in incidence of these tumors presents a challenge in these relatively young men most of whom are in the prime of their lives. As with most cancers, specific management is based in part on histologic subtype but more importantly on disease extent. Advances in chemotherapy, imaging, and adoption of multidisciplinary care have led to continued improvements from a potentially deadly disease to the paradigm of the curable cancer over the past three decades. In this chapter, we will discuss the management principles for patients with primary GCTs of the testis, malignant extragonadal GCTs, and other rare testicular tumors.

ETIOLOGY AND EPIDEMIOLOGY

Testicular cancer accounts for only 1% to 2 % of all cancers in men in most populations across the world.[2] Germ cell testicular tumors are the most common solid malignant tumors in men between 20 and 35 years of age, projections for the United States for 2015 were that 8430 new cases would occur with 380 deaths.[3] The cumulative lifetime risk of developing a GCT for a white man in the United States is 0.2%.[4] Although the disease

is rare, the observed rising incidence is a concern. Between 1973 and 2003 the incidence of GCTs rose by 61% in the United States, with the major rise occurring in seminomas rather than non-seminomas.[5]

The age distribution of testicular cancer is similar in all populations of European origin. There is a small peak in early childhood at around 2 years of age, with rates then remaining low until 15 years of age. There is a second peak in young adults at around 25 to 40 years of age, and the rate then declines, with a small peak again between 65 and 75 years of age. Testicular cancers occurring in childhood and in the young adult years are usually GCTs, whereas those occurring after age 65 years are principally nongerm cell malignant tumors, mainly lymphomas. Nonseminomatous tumors are more common in childhood and in young men between 15 and 30 years of age, whereas seminomas present on average 1 decade later (at 25 to 40 years of age).

Risk factors for testicular germ cell cancer (TGCC) include a family history of cancer, the presence of an undescended testis or gonadal dysgenesis, subfertility, and testicular microlithiasis. Men with a history of cryptorchidism have an approximately sixfold increased chance of developing testicular cancer.[6] Orchiopexy before puberty appears to lower the risk of developing a subsequent tumor and may help preserve Leydig cell function and enhance fertility.[7,8] Although most testicular cancers in men with a history of maldescent occur on the ipsilateral side, approximately 5% to 20% develop in the contralateral testicle.[6] The mechanism by which cryptorchidism increases the risk of developing GCTs is unknown, but the effects of maldescent on the testis (e.g., increased temperature or increased risk of trauma if the testis is in the inguinal region) have been suggested as possible factors. The increase in the incidence of tumors in the contralateral testicle, however, suggests that maldescent and testicular cancer may result from the same prenatal etiologic process. Other genitourinary abnormalities associated with testicular cancers include hydrocele and hypospadias.[9]

There is considerable geographic and ethnic variation in the incidence of testicular tumors, with the highest incidence being reported from Denmark (8.4 per 100,000 men per year) and Switzerland (6.2 to 8.8 per 100,000 men per year).[2] The incidence of testicular cancer is lower in non-Europeans as compared with Europeans. In the United States, white men (6.36 per 100,000 per year) are five to six times more likely to develop testicular cancers than black men (1.30 per 100,000 per year); low incidence rates are seen in other ethnic groups, such as Americans of Chinese and Japanese descent.[5] A high incidence of testicular cancer is seen in some nonwhite populations such as the Maoris in New Zealand and Native Americans.[10]

Prior testicular cancer is a major risk factor for the development of a contralateral malignant tumor. In a large population-based follow-up study of 29,515 patients with unilateral testicular cancer, the cumulative risk (at 15 years after diagnosis of the primary tumor) of developing a contralateral malignant tumor was 1.9%.[11]

Heritability of Testicular Germ Cell Cancer

The racial disparities in persons who develop GCTs and the association with other urogenital abnormalities strongly suggest a genetic susceptibility to this disease. In support of this hypothesis, GCTs are among the most heritable of all cancers. Several studies estimate the risk to brothers and fathers of patients with TGCC to be 4 to 6 times increased and 8 to 10 times increased, respectively. This is far greater than the twofold elevated risk of first-degree relatives in other cancers, such as cancers of the breast or colon or melanoma. The relative risk is much greater in monozygotic and dizygotic twins. In addition, brothers and fathers of patients with bilateral tumors have a risk 3.9 and 4.7 times greater, respectively, than relatives of patients with monozygotic tumors.

Given the strong familial association of TGCC, extended pedigrees with this disease are curiously rare. Most families with TGCC have two affected members, most commonly sibling pairs. The International Testicular Germ Cell Linkage Consortium has carried out two large-scale genome scans, neither of which provided convincing or replicable evidence for susceptibility gene(s).[12] Candidate association studies have demonstrated that rare gr/gr deletions of the Y chromosome predispose to TGCC, but such deletions cannot explain more than a fraction of heritable cases of this disease.

More recently, two groups carried out association studies, based on genome-wide, single-nucleotide polymorphisms (SNPs), of patients with TGCC and controls.[13,14] Both research groups identified strong evidence for two susceptibility loci for seminoma and non-seminoma; one locus is on chromosome 12p22, within the *KITLG* gene, encoding the ligand for the receptor tyrosine kinase KIT, and the second locus is on chromosome 5q31.3 near the *SPRY4* gene, encoding sprouty 4, an inhibitor of the MAP kinase pathway. A third locus on chromosome 6 was identified by only one of the research groups and is not associated with a known gene. The relative risk was approximately 3 for the *KITLG* locus and about 1.4 for the other two loci. Both the *KITLG* gene and the *SPTY4* gene are biologically feasible candidates because their products lie in the same signal transduction pathway. Moreover, activating mutations of the *KIT* gene have been identified in a subset of seminomas, while paradoxically, deletions of the *KIT* gene predispose to germ cell cancer in the SV/129 mouse strain. Of note, cases in the association studies included patients with and patients without a family history of TGCC, but none of these loci were enriched in the familial cases and neither were they associated with other abnormalities such as an undescended testis.

As mentioned previously, the SV/129 mouse strain is particularly susceptible to the development of germ cell cancer, and this system has been exploited by Nadeau et al[15] to map several genes predisposing to the disease. Curiously, none of the corresponding loci in humans appear to have any role in TGCC development.

In summary, TGCC is a highly heritable disease, and at least two loci may contribute to its risk in the general population. Despite almost two decades of studies, however, no gene has yet been identified in families with this disease, suggesting that the genetic underpinnings of TGCC may be highly heterogeneous or novel, or both.

Environmental Factors and Testicular Germ Cell Cancer

Other factors linked to the development of TGCCs include a history of testicular trauma, an increased body mass index, immunosuppression following organ transplantation, and human immunodeficiency virus (HIV) infection.[2,16-18] There is no evidence to suggest a causal relationship between testicular trauma and the development of a tumor, and the likely explanation is that testicular trauma leads to examination of the testes. Because of the age distribution of testicular cancer, exposure must occur early in life if there is an environmental contribution to the etiology of these tumors. Prenatal factors linked to the later development of testicular cancers include threatened miscarriage, excessive maternal nausea, and birth by caesarean delivery.[2] To explain these associations it has been suggested that exposure of the germinal epithelium in utero to an elevated level of free unbound maternal estrogen

could give rise to subsequent cryptorchidism and an elevated risk of developing a testicular tumor; the prenatal estrogen theory remains unproven, however.[2]

PREVENTION AND EARLY DETECTION

The identification of carcinoma in situ (CIS) or testicular intraepithelial neoplasia (TIN) as a precursor of testicular GCTs has raised the possibility that the development of invasive testicular cancer could be prevented by treating CIS. In adults, CIS is found adjacent to GCTs in virtually 100% of cases, and it is thought that, with the exception of spermatocytic seminoma, CIS precedes the development of all invasive tumors.[19] The natural history of testicular CIS is unknown, but the Danish experience suggests that all cases of adult CIS will ultimately progress to invasive cancer.[19]

The diagnosis of testicular CIS can only be made by testicular biopsy. Because the incidence of CIS in the general population is low (at most, 0.7%), screening biopsies are currently not recommended. They should be considered in high-risk patients, however, including those with presumed extragonadal germ cell cancer, intersex individuals, and select patients with contralateral GCT (age <40 years and testicular volumes of <12 mL).[20]

The management of patients with testicular CIS is controversial. Orchiectomy has been suggested for unilateral disease, and in cases diagnosed after orchiectomy for GCT, three options can be considered and discussed with the patient: orchiectomy, low-dose RT, or surveillance.[20] Although both orchiectomy and RT offer definitive treatment for testicular CIS, they both destroy any residual fertility. Surveillance, with careful follow-up of the affected testis, is a reasonable option, especially given the excellent prognosis for metachronous testicular cancers.[21]

Testicular self-examination has been advocated for the early detection of invasive tumors, but its usefulness is unproven. There is no evidence to indicate that a population-based screening program would be of benefit; however, there is a need for education about the early signs and symptoms of testicular cancer to reduce delay at diagnosis. The optimal follow-up schedule for patients with unilateral testicular GCTs and those with cryptorchidism, both of whom have a risk of approximately 2% to 5% of developing a future testicular cancer, is unclear, but a yearly testicular ultrasound examination from age 15 years would seem reasonable.

BIOLOGIC CHARACTERISTICS AND MOLECULAR BIOLOGY

GCTs have a distinctive capacity for totipotential differentiation as demonstrated by the frequent finding of combinations of choriocarcinoma, embryonal carcinoma, and seminoma in a single tumor. They also can retain their ability to differentiate as displayed by the not infrequent identification of mature teratoma in residual posttreatment retroperitoneal masses. Cytogenetic analysis of GCTs has shown that chromosome numbers are more homogenous in seminomas than in non-seminomas.[22-24] Triploid and tetraploid chromosomal patterns are common in seminomas, and hyperdiploid to hypertriploid counts are common in non-seminomas. A characteristic chromosome anomaly in GCTs of all histologic types is the presence of an isochromosome of the short arm of chromosome 12.[25] This isochromosome, first reported by Atkin and Baker in 1982,[22] consists essentially of two chromosome 12 short arms. It is present in more than 80% of cases, and GCTs without a 12p isochromosome have extra copies of 12p segments incorporated into other chromosomes. The 12p isochromosome is also found in testicular CIS.[25] Isochromosome copies tend to be more numerous in non-seminomas than in seminomas.

The study of the genetics and molecular biology of GCTs has enhanced our understanding of these tumors.[23,26,27] To date, however, cytogenetics has had little impact in the clinic, with the possible exception of the use of various markers for the identification of non-TGCCs located elsewhere in the body.[28-30]

PATHOLOGY AND PATHWAYS OF SPREAD

Pathology

Testicular cancers can arise from intratesticular and paratesticular cells (Box 55-1). The vast majority is of germ cell origin, and three major classification schemes have been in use worldwide[31-33] (Table 55-1). The Dixon and Moore classification as modified by Mostofi has been adopted by the World Health Organization (WHO) and is the classification scheme most widely used in North America.[34]

For clinical purposes, GCTs are classified into two major groups: seminomas and non-seminomas (NSGCTs). It should be noted that patients with pure seminoma may have relapse with pure NSGCT, and vice versa. Approximately 60% of GCTs are pure seminomas, 30% are NSGCTs, and 10% are mixed tumors (both seminomatous and NSGCT elements are present).[35] Patients with mixed tumors are clinically considered to have NSGCT, the only exception being tumors with syncytiotrophoblastic cells in cases of seminoma.

Carcinoma in Situ

Intratubular germ cell neoplasia, or CIS, is felt to precede the development of all cases of seminoma and NSGCT in adults (with the exception of spermatocytic seminoma).[36] On light microscopy, CIS cells closely resemble seminoma cells and in most cases are found within the seminiferous tubules. Cytologically, there is no difference between the CIS cells that develop into seminomas and those that develop into NSGCTs. In the general population, the incidence of CIS is low (0.2%),

BOX 55-1 Histologic Classification of Testicular Neoplasms

Germ cell tumors (demonstrating one or more of the following components)
- Seminoma
- Embryonal carcinoma
- Teratoma
- Choriocarcinoma
- Yolk sac tumor (endodermal sinus tumor: embryonal adenocarcinoma of the prepubertal testis)

Sex cord stromal tumors (gonadal stromal tumors)
- Leydig cell tumor
- Sertoli cell tumor
- Granulosa cell tumor (adult and juvenile types)

Tumor with both germ cell and gonadal stromal elements
- Gonadoblastoma

Adnexal and paratesticular tumors
- Mesothelioma
- Tumors of soft tissue origin (e.g., sarcomas)
- Adnexal tumor (e.g., adenocarcinoma) of the rete testis

Miscellaneous neoplasms
- Carcinoid
- Lymphoma
- Cyst

Metastatic neoplasms

It is not known how these chromosomal changes contribute to the development of the neoplastic phenotype. The frequent finding of the 12p isochromosome in both CIS and invasive tumors, however, indicates that this chromosome plays an important role in the biology of these tumors. The possibility of amplification of normal or modified genes, such as the *DDX1* gene on the 12p isochromosome, is currently being investigated.[26] Proto-oncogenes present on the short arm of chromosome 12 could be activated by point mutations, deletions, or translocations to become oncogenes, which could then act in a dominant manner.[27] The *KRAS* gene is located on the short arm of chromosome 12, and amplification or enhanced expression of this gene has been reported to occur in testicular tumors and derived cell lines. Other candidate genes being studied include the *c*-KIT oncogene and its ligand KITGL or SCF, the *c*-MOS oncogene, and the *CCND2* gene. In addition to chromosome 12, 17q is overrepresented in 50% of cases of GCT; this area contains a number of genes of interest, including the *GRB7* gene and the plakoglobin gene.[23]

TABLE 55-1 Three Classifications of Germ Cell Tumors

Dixon and Moore, 1953[30]	WHO Classification[33]	Pugh, 1976[32]
Group I	Seminoma	Seminoma
Seminoma	Spermatocytic seminoma	Spermatocytic seminoma
Spermatocytic seminoma	Embryonal carcinoma, adult-type	Malignant teratoma, undifferentiated
Group II	Teratoma	Teratoma, differentiated
Embryonal carcinoma	Mature	Malignant teratoma, intermediate
Group III	Immature	Yolk sac tumor; orchioblastoma
Teratoma, pure	Teratoma with malignant areas other than seminoma, embryonal carcinoma, or choriocarcinoma	
Group IV	Embryonal carcinoma and teratoma (teratocarcinoma)	
Teratoma with carcinoma or sarcoma	Infantile embryonal carcinoma	
Group V	Polyembryoma	
Teratoma with embryonal carcinoma or choriocarcinoma		

but it is somewhat higher in men with impaired fertility (0.5%) and in those with cryptorchid testes (2% to 4%).[19]

Seminomas

Seminoma, the most common type of testicular GCT, is most often seen in the fourth decade of life. On gross examination, the tumors are usually well demarcated from the residual testicular tissue and rarely have foci of necrosis or hemorrhage. On microscopic examination, the classical or typical seminoma type is made up of large cells with abundant cytoplasm divided by connective tissue septae into sheets or cords.[37] These cells typically have round, hyperchromatic or vesicular nuclei with prominent nucleoli. Frequently, there is a lymphocytic infiltrate, and macrophages, plasma cells, and multinucleated giant cells are often present. Syncytiotrophoblasts are present in 15% to 20% of cases, and their presence does not appear to alter the prognosis.

On immunohistochemical testing, virtually all seminomas express placental leukocyte alkaline phosphatase (PLAP) and do not express low-molecular-weight keratins, blood group antigens, or vimentin. Several histologic variants of seminoma have been identified, including anaplastic seminoma and spermatocytic seminoma. Anaplastic seminoma is diagnosed when there are three or more mitoses seen per high-power field.[37] Spermatocytic seminoma is a rare subtype mainly seen in older men and is not associated with CIS or bilateral disease.[36] Also, these tumors do not stain for PLAP on immunohistochemical testing and rarely, if ever, metastasize. An atypical variant of seminoma with some features similar to those of NSGCT on immunohistochemical examination has been reported, although its morphologic appearance is similar to that of classical seminoma.[38] Usually, there is little or no lymphocytic infiltrate and the tumor cells have less cytoplasm than classical seminoma cells. In terms of prognosis, this atypical variant appears to have the same prognosis as classical seminoma.

Nonseminomatous Germ Cell Tumors

Nonseminomatous tumors make up 40% of TGCCs and occur most commonly in the third decade of life. In the WHO classification system, NSGCTs include embryonal carcinoma, teratoma (mature, immature, or with malignant differentiation), choriocarcinoma, yolk sac tumor, and mixed GCTs. Most tumors are mixed, with two or more cell types present. Although some tumors have a component of seminoma, the association of seminoma within a histologically confirmed NSGCT has no major impact on the clinical outcome.[39]

Patients with combined tumors present at an age (median, 33 years) intermediate between those with seminoma (median, 36 years) and those with non-seminoma (median, 27 years).[39]

On gross examination, there is usually a soft irregular mass poorly demarcated from the surrounding testicular tissue, and a considerable amount of necrosis and hemorrhage is often present. Immunohistochemical studies usually demonstrate cytoplasmic expression of low-molecular-weight keratins in embryonal carcinomas, and yolk sac elements, low-molecular-weight keratin, or vimentin expression in mature teratomas.

Pathways of Spread

Direct extension of tumor into the epididymis, through the tunica vaginalis, into the spermatic cord (T3), and rarely into the scrotum (T4) may occur. Locally extensive tumors are rare, however.

Lymphatic spread is the most common route of metastatic spread. The lymphatic drainage of the testis is directly to the paraaortic lymph nodes. There are differences in the distribution of metastases from left or right testicular tumors. The left testicular vein drains to the left renal vein, and the lymphatic drainage is primarily to the lymph nodes in the paraaortic area, directly below the left renal hilum. On the right side, the testicular vein drains directly to the inferior vena cava below the level of the renal vein, and, therefore, paracaval and interaortocaval nodes are the first ones to be involved in right-sided tumors. Figure 55-1, *A* and *B*, shows the distribution of retroperitoneal lymph node metastases in NSGCT and seminoma.[40,41] Contralateral nodal involvement occurs in approximately 15% of cases and is rarely found in the absence of ipsilateral involvement. Supradiaphragmatic spread can occur through the thoracic duct, and although left supraclavicular nodal disease is infrequent at presentation, it is often seen at the time of relapse.

Pelvic and inguinal lymph node involvement is rare (<3%). Factors predisposing to inguinal lymph node involvement include prior scrotal or inguinal surgery, scrotal orchiectomy with incision of the tunica albuginea, tumor invasion of the tunica vaginalis or lower third of the epididymis, and cryptorchid testis.[42,43] Disruption of lymphatic vessels in the spermatic cord during inguinal surgery has been shown to induce anastomoses between the testicular lymphatic vessels and the regional lymphatics destined for inguinal or pelvic lymph nodes. In an occasional patient, a connection with the contralateral inguinal lymph nodes may be established, but this is uncommon. In a small proportion of patients with inguinal relapse, no predisposing factors may be apparent.[42]

In patients with NSGCTs, hematogenous spread occurs early in the course of the disease. The lung parenchyma is the commonest site of hematogenous spread, but liver, bone, brain, kidney, and gastrointestinal metastases are also seen. In a review of over 5000 patients with metastatic GCT,

Teratomas are tumors composed of cells derived from two or more of the germ cell layers (ectoderm, mesoderm, or endoderm). When one of the component tissues in any of the types of teratoma exhibits the histologic appearance of another malignant tumor, such as sarcoma or carcinoma, the term *teratoma with malignant transformation* is used.

Choriocarcinomas are tumors composed of both multinucleated syncytiotrophoblasts and mononuclear cytotrophoblast cells. Pure choriocarcinoma is rare and is usually associated with widespread metastases, high levels of β-HCG, and a poor prognosis. Elements of choriocarcinoma are found in up to 10% of NSGCTs and do not appear to affect the prognosis.

Yolk sac tumor, also known as endodermal sinus tumor, is composed of cells that usually produce AFP and resemble those seen in the yolk sac in an embryo. Pure yolk sac tumors are rare but are the most common variant of childhood GCT. Elements of yolk sac tumor are found in up to 50% of NSGCTs.

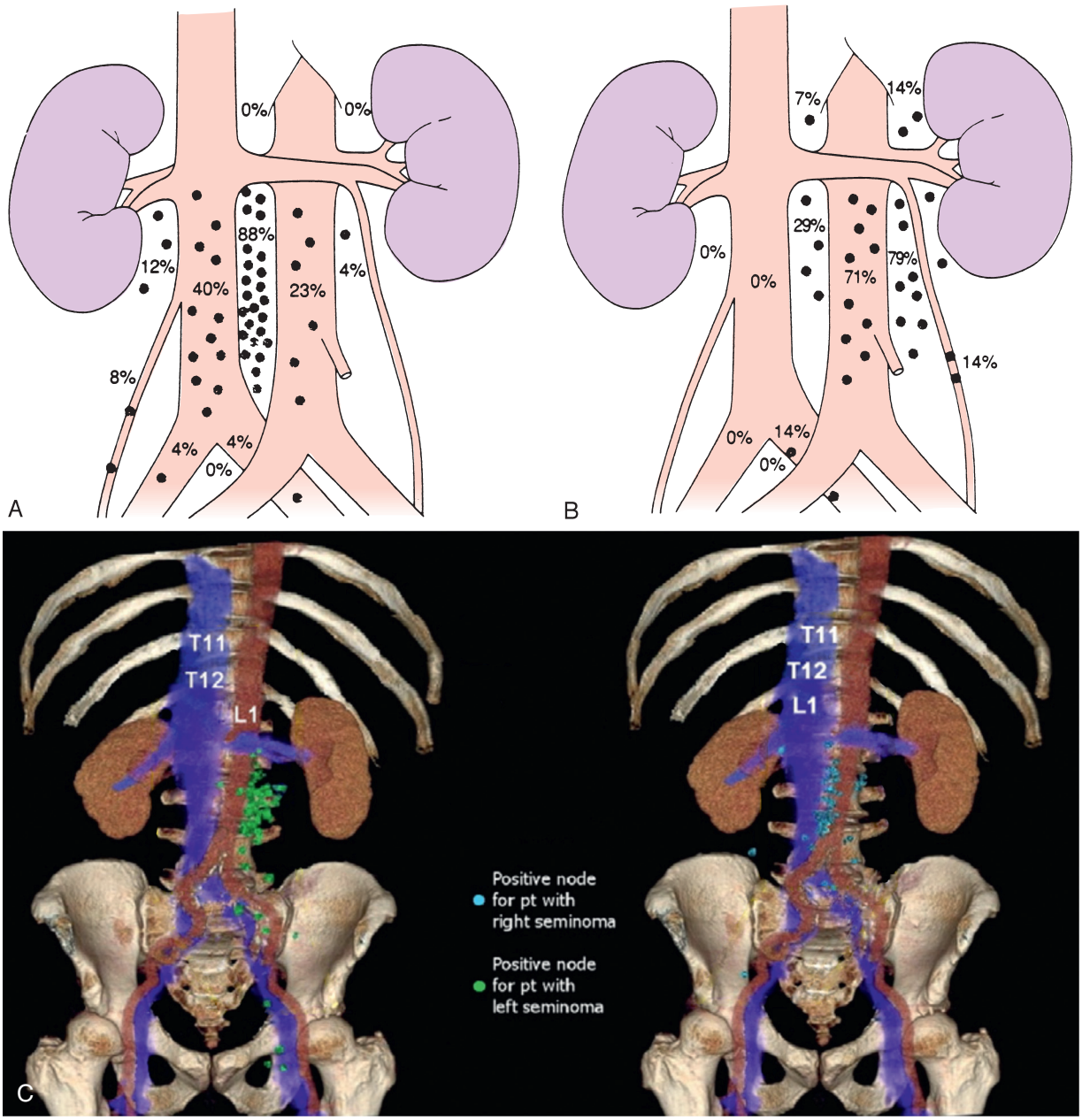


Figure 55-1 Distribution of retroperitoneal lymph node metastases in early-stage testicular non-seminoma germ cell tumor. **A,** Right testis primary tumor. **B,** Left testis primary tumor. **C,** Distribution of retroperitoneal lymph node metastases in early-stage testicular seminoma germ cell tumor. *From Paly J, Efstathoiu J, Hedgire S, et al: Mapping patterns of nodal metastases in seminoma: Rethinking radiotherapy fields. Radiother Oncol 106:64–68, 2013. Copyright © Elsevier.*

pulmonary metastases were present in 44% of cases and liver metastases in 6% of cases, with all other areas of hematogenous spread present in 1% or less of cases.[44] Mediastinal and neck node involvement was present in 11% to 12% of cases.

CLINICAL PRESENTATION, PATIENT EVALUATION, AND STAGING

Clinical Presentation

Testicular cancer most commonly present with a painless mass but up to 45% of patients may have testicular pain, where up to 25% have signs and symptoms suggestive of acute epididymitis. Symptoms and signs suggestive of metastatic disease such as back pain, dyspnea, and gynecomastia (from malignant tumors that produce HCG) is a much less common presentation. Patients with high HCG levels (up to 3.5% of patients) may have hyperthyroidism as a result of stimulation of the thyroid by the alpha subunit of HCG, which behaves identically to thyroid-stimulating hormone (TSH).[45] Various benign conditions including torsion, hydrocele, varicocele, spermatocele, and epididymitis should be considered in the differential diagnosis of a testicular mass (in addition to tumor). Transillumination of the testis on examination does not rule out a diagnosis of malignancy as a small percentage of tumors are associated with a hydrocele.

Patient Evaluation

A solid mass is detected on physical examination or by ultrasonography should prompt a diagnostic and therapeutic radical orchiectomy when there is no obvious evidence of metastasis. Preoperative measurement of serum tumor markers, including AFP, β-HCG, and LDH should be done to allow monitoring of decay with treatment. Staging investigations are usually performed after the histologic diagnosis is confirmed, except for some patients who present with life-threatening advanced metastatic disease where systemic therapy may be instituted based on a clinical diagnosis and unequivocal abnormality of AFP and β-HCG levels. In such cases, pathology may be obtained via needle biopsy or held until orchiectomy, after chemotherapy has been completed.

Staging investigations include chest x-ray, CT scans of the chest, abdomen, and pelvis, and tumor markers. For patients with seminoma and absence of retroperitoneal lymph node involvement, thoracic CT scans add little value. Bipedal lymphography for staging is of historical interest only; however, magnetic resonance imaging (MRI) with lymphotrophic nanoparticles has shown some promise but further data is required to be able to evaluate its role in routine clinical practice.[46] In stage II and III seminomas, especially in patients with bulky retroperitoneal disease, a bone scan may be performed. Abnormal serum marker levels should be monitored to document postorchiectomy decay according to their respective half-lives. Patients with extensive metastatic disease, nonpulmonary visceral metastases (NPVMs), or high tumor marker levels (especially HCG) are at risk for brain metastases, and CT or MRI (preferably) of the brain should be performed.[47] Baseline pulmonary and renal functions are assessed in patients who require chemotherapy.

Tumor Markers

Measurements of AFP, β-HCG, and LDH are essential in the diagnosis and management of patients with GCTs.[48] HCG is a glycoprotein with a molecular weight of 45,000 daltons, composed of two subunits, of which the α-subunit is identical to that of luteinizing hormone (LH), follicle-stimulating hormone (FSH), and thyroid-stimulating hormone (TSH), and a distinct β-subunit. HCG is normally produced by the placenta. About 15% of patients with seminoma have elevated β-HCG levels. Low levels of β-HCG may be found in other neoplasms, including prostate, bladder, and renal tumors. The use of marijuana derivatives also may lead to elevated levels. Because of the possible cross-reactivity with LH, and in cases where an elevated HCG level is thought to be the result of this cross-reactivity, consideration should be given to having levels remeasured after treatment with testosterone.[49] The half-life of β-HCG in blood is approximately 22 hours. In the subset of patients with GCT with elevated HCG, the level of HCG reaches a plateau after the fourth cycle of chemotherapy and is considerably greater than normal. Such persistent HCG levels may not be an indication for salvage therapy because of the possibility of tissue binding of HCG, which slows the decay of serum levels.[47]

AFP is the major serum protein of fetal life. It is a glycoprotein of molecular weight 70,000 daltons. In addition to being elevated in nonseminomatous GCTs, it is elevated in hepatocellular carcinoma, cirrhosis, and hepatitis and during pregnancy. The half-life of AFP is approximately 5 days. AFP is not found in pure seminoma; its elevation in this setting implies the presence of nonseminomatous tumor elements and in those patients is considered to have non-seminoma regardless of the pathologic subtyping seen in the tissue. Liver disease should be considered in the differential diagnosis in patients whose disease appears to be responding and in whom the AFP level fails to fall appropriately or is found to be increasing.

One or both of these markers are elevated in 85% of patients with nonseminomatous GCTs. However, normal markers do not exclude the presence of clinically occult disease.[50]

LDH is another important marker in patients with GCTs. It is elevated in up to 60% of patients with non-seminomas and also in a high proportion of patients with advanced seminomas, but it is the least specific of the three recognized tumor markers in GCTs.[44,51]

Both AFP and β-HCG levels are useful in the diagnosis of malignancy when measured before orchiectomy with the rate of decline (after orchiectomy) indicating the likelihood of residual tumor. Tumor marker levels may be used to assess response to treatment, to predict the likelihood of achieving complete remission, and in regular follow-up to indicate relapse, this is often in the absence of symptoms, physical findings, or abnormal imaging studies.

PLAP is an isoenzyme of alkaline phosphatase and is normally expressed by placental syncytiotrophoblasts. It is also expressed by testicular tissue and has been investigated as a tumor marker in seminoma. Although PLAP levels are often elevated in patients with seminoma, this factor has proven to be of little practical value.[52]

Staging

The 2009 American Joint Committee on Cancer/International Union Against Cancer (AJCC/UICC) TNM classification (Table 55-2) is the recommended staging system. In stage I disease, one of the most important determinants of outcome is the presence of vascular invasion in the primary tumor (particularly in non-seminoma), and this differentiates a pT1 tumor from a pT2 tumor.[53] Tumors with invasion of the spermatic cord are staged as pT3 cancers, and the rare tumors with scrotal invasion are classified as pT4 lesions.

In stage II disease, the extent of retroperitoneal adenopathy and serum tumor marker level determines treatment and outcome. Patients with retroperitoneal lymph nodes less than 5 cm in diameter (N1/N2 disease) are often successfully treated with regional therapy, either RPLND in NSGCTs or external beam radiation therapy (EBRT) in seminomas; however, those with nodal disease greater than 5 cm in diameter have a high risk of distant failure following regional therapy and are usually treated with systemic chemotherapy.

With the current use of cisplatin-based chemotherapy, the survival rate of patients with metastatic testicular tumors is excellent, although a minority of patients still die of testicular cancer despite treatment.

The International Germ Cell Cancer Collaborative Group (IGCCCG) analyzed data from 5168 patients with advanced disease.[44] Independent prognostic variables identified by the IGCCCG were included: histologic type (non-seminoma versus seminoma), site of the primary tumor (testis, retroperitoneal site, or other), presence or absence of nonpulmonary visceral metastases (NPVMs), for example, brain, bone, or liver, and degree of marker elevation (AFP, β-HCG, and LDH). Based on the results of multivariate analysis, the IGCCCG recommended prognostic groupings for patients with metastatic disease. For nonseminomatous cancers, the 5-year OS for the good-prognosis group was 92%, for the intermediate-prognosis group, 80%, and for the poor-prognosis group, 48%. For seminoma, a good-prognosis group without NPVMs had a 5-year OS of 86% and an intermediate-prognosis group with NPVMs with a 5-year OS of 72%. This classification system has been validated by van Dijk et al[51] using Cox regression analysis and recursive partitioning in a cohort of 3048 patients with NSGCT.

TABLE 55-2 Staging of Testis Tumors by the American Joint Committee on Cancer (AJCC)

Primary Tumor	
(The extent of primary tumor is classified after radical orchiectomy)	
pTX	Primary tumor cannot be assessed. (If no radical orchiectomy has been performed, TX is used.)
pT0	No evidence of primary tumor (e.g., histologic scar in testis)
pTis	Intratubular germ cell neoplasia (carcinoma in situ)
pT1	Tumor limited to the testis and epididymis without vascular/lymphatic invasion. Tumor may invade into the tunica albuginea but not the tunica vaginalis
pT2	Tumor limited to the testis and epididymis with vascular/lymphatic invasion, or tumor extending through the tunica albuginea with involvement of the tunica vaginalis
pT3	Tumor invades the spermatic cord with or without vascular/lymphatic invasion
pT4	Tumor invades the scrotum with or without vascular/lymphatic invasion
Regional Lymph Nodes (N) Clinical	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis with a lymph node mass 2 cm or less in greatest dimension; or multiple lymph nodes, none more than 2 cm in greatest dimension
N2	Metastasis with a lymph node mass, more than 2 cm but not more than 5 cm in greatest dimension; or multiple lymph nodes, any one mass greater than 2 cm but not more than 5 cm in greatest dimension
N3	Metastasis with a lymph node mass more than 5 cm in greatest dimension
Pathologic Lymph Nodes (pN)	
pNX	Regional lymph nodes cannot be assessed
pN0	No regional lymph node metastasis
pN1	Metastasis with a lymph node mass 2 cm or less in greatest dimension and five or fewer nodes positive, none more than 2 cm in greatest dimension
pN2	Metastasis with a lymph node mass more than 2 cm but not more than 5 cm in greatest dimension; or more than five nodes positive, none more than 5 cm; or evidence of extranodal extension of tumor
pN3	Metastasis with a lymph node mass more than 5 cm in greatest dimension

Distant Metastasis (M)	
MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis
M1a	Nonregional nodal or pulmonary metastasis
M1b	Nonpulmonary visceral metastasis
Serum Tumor Markers (S)	
SX	Marker studies not available or not performed
S0	Marker study levels within normal limits
S1	LDH <1.5 × N *and* HCG (mIU/mL) <5000 *and* AFP (ng/mL) <1000
S2	LDH 1.5-10 × N *or* HCG (mIU/mL) 5000-50,000 *or* AFP (ng/mL) 1000-10,000
S3	LDH >10 × N *or* HCG (mIU/mL) >50,000 *or* AFP (ng/mL) >10,000
	N indicates the upper limit of normal for the LDH assay

Stage Grouping				
Stage 0	pTis	N0	M0	S0
Stage I	pT1-4	N0	M0	SX
Stage IA	pT1	N0	M0	S0
Stage IB	pT2	N0	M0	S0
	pT3	N0	M0	S0
	pT4	N0	M0	S0
Stage IS	Any T	N0	M0	S1-3
Stage II	Any T	N1-3	M0	SX
Stage IIA	Any T	N1	M0	S0-1
Stage IIB	Any T	N2	M0	S0-1
Stage IIC	Any T	N3	M0	S1
	Any T	Any N	M1	SX
Stage III	Any T	Any N	M1a	S0
Stage IIIA	Any T	Any N	M1a	S1
	Any T	N1	M0	S2
Stage IIIB	Any T	Any N	M1a	S2
	Any T	N1-3	M0	S3
Stage IIIC	Any T	Any N	M1a	S3
	Any T	Any N	M1B	Any S

From Edge SB, Byrd DR, Compton CC, et al, editors: AJCC Cancer Staging Handbook, ed 7, New York, 2010, Springer.
AFP, *α-fetoprotein;* HCG, *human chorionic gonadotropin;* LDH, *lactate dehydrogenase;* mIU, *milli-international unit;* mL, *milliliter;* ng, *nanogram.*

PRIMARY THERAPY

The initial management involves a radical inguinal orchiectomy in almost all cases except for the uncommon life-threatening presentation in which systemic treatment is urgently needed. Postorchiectomy management is based on the histologic type and extent of disease. The management policies for both seminomatous and nonseminomatous tumors have evolved separately but mirror each other quite closely, with the exception of the use of EBRT in early-stage seminoma and RPLND in non-seminoma. Sperm testing and banking should be considered before treatment with chemotherapy, RPLND, and EBRT because of potential effects on fertility.

Surgery

Surgery involves a radical inguinal orchiectomy to allow high division of the spermatic cord. Orchiectomy offers cure in a high proportion (60% to 90%) of patients with stage I disease.[20,54] Although not recommended, a transscrotal approach does not appear to compromise the outcome, provided that the scrotal cavity has not been grossly contaminated by tumor during surgery. In patients with life-threatening metastatic disease and a clear-cut diagnosis of germ cell malignancy, initial management is with chemotherapy and surgery is postponed until completion of systemic treatment.[20,54] The role of partial orchiectomy in patients with metachronous or synchronous bilateral tumors will be discussed later.

Seminoma

Most patients present with stage I disease (70% to 80%); stage II disease is found in 15% to 20%; and stage III disease in 5% of cases. Of the predicted 4700 cases of seminoma in the United States in 2013, 3700 were expected to present as stage I disease.

In stage I seminoma, historically, adjuvant retroperitoneal RT was the most widely applied treatment in postorchiectomy management. RT provided excellent long-term results, with local control in the abdomen and pelvis in virtually all patients. However, it is now known that more than 85% of patients are cured with orchiectomy alone and RT has been associated with an increased risk of late gonadal toxicity, development of secondary malignant tumors, and perhaps an increased risk of cardiovascular disease.[55-60] With this knowledge and also the excellent salvage rates with cisplatin-based chemotherapy, the use of adjuvant RT became questionable. Attempts at minimizing RT-associated morbidity included a reduction in radiation dose and treatment volume, surveillance (avoidance of adjuvant therapy and treating only on evidence of relapse), and adjuvant chemotherapy.[61-65] Of these options, surveillance is now the standard approach, minimizing the burden of treatment while maintaining the cure rate at 100%.[66-68]

For stage II disease, retroperitoneal irradiation is effective and is recommended for patients with nonbulky tumor (stage IIA to IIB), whereas chemotherapy is the treatment of choice for patients with more advanced disease. RPLND is usually reserved for rare situations where neither of the other treatments is possible.

In stage III disease, chemotherapy is the treatment of choice.[20,54]

Management of Stage I Seminoma

Surveillance

Mature series of patients managed with surveillance have reported relapse rates of 15% to 24% (Table 55-3) (also see references 62, 67, 68, 71-73). A large experience of surveillance spanning a period of 24 years (1984 to 2007) was from Denmark using cancer registry linked data with median follow up of 15.4 years, the crude relapse rate was 19.5% (355 of 1822 patients).[69] Similarly, in the Princess Margaret Hospital (PMH), Toronto, series of 484 patients, median follow-up was 6.6 years, crude relapse rate was 15%.[68] The other studies with adequate follow-up (>36 months) have reported similar relapse rates. The predominant site of relapse in all studies was the paraaortic lymph nodes (82% in the Danish Testicular Cancer Study Group [DATECA] study and 89% in the PMH series.[67,68] The median time to relapse ranged from 12 to 18 months, but late relapses (>2 years, 4% and >5 years, 1.4%) have been reported.[69,70]

A number of single institution studies reported prognostic factors for relapse, such as age, primary tumor size, and small vessel invasion were predictive of relapse for surveillance patients. Based on these studies an attempt to further refine a prognostic model based on these factors was undertaken by a pooled analysis of four large surveillance data sets.[74] Tumor size and rete testis invasion predicted for relapse on multivariable analysis in 638 patients managed by surveillance. The effect of tumor size on the relapse rate is shown in Figure 55-2, and the hazard ratio for relapse with a tumor size of more than 4 cm was 2 (95% CI, 1.3 to 3.2) relative to baseline (tumor size <4 cm and no rete testis invasion). The high-risk group had up to 35% risk of relapse. The model was not fully validated in an independent dataset analysis of 685 patients, but similar to

TABLE 55-3 Results of Surveillance in Stage I Seminoma

Series	No. Pts	Median FU (mo)	Relapse: No. Pts (%)	CSS (%)
Daugaard[62]	394	60	69 (17.5)	100.0
Germa Lluch[71]	233	33	38 (16)	100.0
Horwich[66]	103	62	17 (16.5)	100.0
Oliver[72]	67	61	16 (24)	97.0
Von der Maase[67]	261	48	49 (18.8)	98.9
Tyldesley[73]	93	33	16 (17.2)	97.8
Leung[68]	484	79	72 (15)	99.8

CSS, *Cause-specific survival* FU, *follow-up;* mo, *months;* No. Pts, *number of patients.*

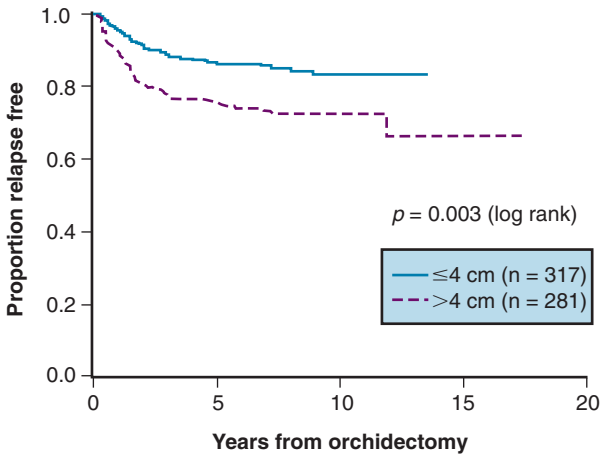


Figure 55-2 Relapse-free rate based on primary tumor size. *From Warde P, Specht L, Horwich A, et al: Prognostic factors for relapse in stage I seminoma managed by surveillance. A pooled analysis. J Clin Oncol 20:4448–4452, 2002. Copyright © American Society of Clinical Oncology.*

TABLE 55-4 Follow-up Protocol for Stage I Seminoma

Years	Month 6	Month 12
1-3	Clinical examination CT of abdomen and pelvis*	Clinical examination Chest radiograph CT of abdomen and pelvis*
4-5		Clinical examination CT of abdomen*
7		Clinical examination CT of abdomen*
9		Clinical examination Chest radiograph CT of abdomen*

CT, *Computed tomography.*
**CT of abdomen and pelvis done only if surveillance or adjuvant carboplatin; may be discontinued after 3 years for carboplatin patients.*

TABLE 55-5 Results of Retroperitoneal Radiation Therapy in Stage I Seminoma

Author	Study Years	No. Pts	Relapse (%)	CSS (%)
Bayens[84]	1975-1985	132	4.5	99.0
Coleman[85]	1980-1995	144	4.2	100.0
Fossa[61,63]	1989-1993	242	3.7	100.0
Hallemeier[91]	1972-2009	199	2	99.0
Hultenschmidt[86]	1978-1992	188	1.0	100.0
Santoni[87]	1970-1999	487	4.3	99.4
Warde[88]	1981-1989	282	5.0	100.0

CSS, *Cause-specific survival;* No. Pts, *number of patients.*

the previous study; larger primary tumors were associated with an increased risk of relapse, whereas median tumor size (>3 cm) was associated with a hazard ratio of 1.87.[75] The more recent analysis of national data from Denmark also confirmed the prognostic value of tumor size but small vessel invasion and HCG elevation >200 IU were also found to be predictive for relapse.[69]

Management options at relapse include irradiation and cisplatin-based chemotherapy. Most patients who relapse while on surveillance are initially treated with retroperitoneal RT and have an associated 10% incidence of second relapse after RT.[76] The likelihood of detecting early progression in the retroperitoneal lymph nodes (nodes <5 cm) and, therefore, suitability of the patient for RT depends on the frequency of follow-up CT scans of the abdomen and pelvis.

The current PMH follow-up policy is shown in Table 55-4. Reducing the frequency of imaging such as chest radiographs and eliminating routine measurement of serum tumor markers has simplified the protocol. There appears to be limited value to routinely including these tests in surveillance protocols because chest radiographs most often were negative in the absence of retroperitoneal nodal relapse and serum tumor markers heralded few relapses in advance of detectable macroscopic disease.[77,78]

One of the concerns regarding the routine use of surveillance was the potential for an increased burden of treatment because of the need for more patients requiring subsequent chemotherapy particularly if first treated with RT in the relapse setting. There seems little to base these fears on as a similar proportion of patients managed with surveillance (4.3%) and adjuvant RT (3.6%) required subsequent chemotherapy as part of their management.[68]

Surveillance does lead to an increased number of imaging studies (most commonly CT scans) during follow up and there are concerns that this might increase the rate of radiation-associated cancers. There is no concrete data available that quantitates the risk of radiation-induced cancer from CT scanning. Estimation of these risks has been derived from long-term follow-up data from survivors of the atomic bombings of Hiroshima and Nagasaki who received low-dose radiation akin to that for medical imaging.[79] The methodologic issues related to these estimations mean that there is doubt as to the accuracy of the data. However, in the pediatric setting there does appear to be some epidemiologic evidence supporting a small increase in the risk of leukemia and brain tumors related to diagnostic radiation.[80] Another epidemiologic study that attempted to estimate radiation-induced cancers in patients with stage I testicular cancer surveillance found no excess cancers in the time period studied but the relatively short follow up in the adult setting may have lead to an underestimation of the risk.[81] The seminoma surveillance population may conceivably be at some risk of radiation-induced cancer, given the young age of many patients and the use of repeated CT scans of the abdomen. Thus, attempts to decrease the frequency of imaging, the use of low-dose CT in surveillance protocols and nonionizing imaging such as MRI to decrease overall exposure is currently under way.[82,83] Currently MRI is not routinely recommended until results of studies become available, although it should be noted that some centers, mainly in Scandinavia, have already adopted this as their standard approach.

Radiation Therapy

OS ranges between 92% and 99% at 5 to 10 years, with the cause-specific survival (CSS) approaching 100%. Although most deaths are the result of intercurrent illness, some premature deaths may be as a result of radiation-induced cancers or possibly cardiac disease.[55,59] Relapse rate after RT has varied from 0.5% to 5%[84-88] (Table 55-5). Wherever local recurrence in-field in suspected, because of its rarity, a biopsy to rule out a nonseminomatous tumor or another malignant tumor is generally recommended. The commonest sites of relapse following adjuvant RT are the mediastinum, lungs, and left supraclavicular fossa. A small proportion of patients, many with predisposing factors, develop relapse in the inguinal nodes. Uncommon sites of isolated metastases such as the brain and tonsils have been noted but are unpredictable.[89,90] For supradiaphragmatic relapse, chemotherapy results in virtually 100% cure rate. Isolated inguinal relapse may be treated successfully with RT alone.[88]

Relapse after adjuvant RT most frequently occurs within the first 2 to 3 years with the occasional relapse beyond this time frame. In the PMH series of 282 patients treated between 1981 and 1999, the median time to relapse was 18 months, with the latest relapse occurring at 6 years. Thus, follow-up policy is concentrated in this early time period and frequency of clinic visits is similar to efforts for patients during surveillance, with the exception that CT of the abdomen and pelvis does not need to be performed because of the exceedingly low risk of local recurrence in the retroperitoneum after adjuvant RT.

Prognostic features that may predict relapse in this group are difficult to ascertain primarily because of the low event rate. The presence of anaplastic seminoma was thought be one possible factor associated with an increased relapse risk,[88] but the WHO criteria for this diagnosis (three or more mitoses per high-power field) are not uniformly used, and contradictory data exist that suggests no difference in relapse between anaplastic and classical histologies.[92] Other features associated with a higher risk of relapse may include tumor invasion of

The more frequent follow up within the first 3 years allows earlier detection of disease relapse in about 90% of those who are destined to relapse. Thereafter only a small proportion of patients will relapse and the frequency of follow up is reduced accordingly. CT thorax is not routinely recommended given the rare instance of chest only relapse but is done to determine extent of disease whenever abdominal relapse occurs.

the tunica albuginea, lymphovascular invasion, invasion of the epididymis, raised preoperative HCG levels, and spermatic cord involvement.[84,88]

Adjuvant Chemotherapy

Seminoma is highly chemosensitive and cures are routinely achieved even in advanced disease settings, thus adjuvant carboplatin has been investigated as an alternative strategy to RT or surveillance in stage I disease. The use of single agent carboplatin after orchiectomy was initially pioneered by Oliver et al[93] in 78 patients, of whom 53 patients had two courses and 25 had one course. Only one patient relapsed with median follow up of 44 months. Relapse rates of 0% to 8.6% have been reported in other Phase II studies with some of the variability in results explained by the method of calculation of the dose of chemotherapy delivered.[94]

In a Phase III noninferiority study design, the United Kingdom Medical Research Council (MRC UK) compared adjuvant RT and a single course of carboplatin (dose calculated with area-under-the-curve [AUC] method) in 1477 patients.[95] The relapse free rates at 5 years were similar, 96% for RT and 94.7% for carboplatin.[96] Relapses in the carboplatin arm occurred largely in the retroperitoneal lymph nodes and similar to adjuvant RT, relapses beyond 3 years was uncommon.[97] A possible benefit of adjuvant carboplatin that was noted was the lower incidence of second primary testicular germ cell tumors, although it is not clear whether the occurrence is eliminated or just delayed.[65] Overall relapse risk may be reduced by higher doses of carboplatin (using the AUC formula) as such patients had lower relapse rates.[98]

Data from other single-institution series indicate that if adjuvant carboplatin is given in this setting, then two courses of treatment may lower the relapse risk further and is consistent with the previous dose-related data.[61,99] Unfortunately, despite the increased dose, small but significant percentage of patients develop relapse in the retroperitoneum, and the usefulness of this approach is uncertain.[61,99] The concept of giving single course, minimally toxic chemotherapy leading to a virtually zero relapse rate allowing patients to be discharged from follow-up with no risk of relapse has not materialized. In addition, the relapse pattern dictates continued surveillance of the retroperitoneal lymph nodes (similar to a surveillance policy albeit with reduced frequency), and although a relative reduction in relapse rates of two thirds is impressive, the absolute reduction of 10% (15% with surveillance and 5% with adjuvant chemotherapy) and small numbers of patients that this affects is less so. Regardless in an adjuvant setting, 85% of patients receive treatment that has no direct benefit, and any long-term toxicity is as yet not fully characterized.[65]

Retroperitoneal Lymph Node Dissection

There is minimal literature about the routine use of RPLND in seminoma. It is a seldom used approach but may be appropriate for patients unwilling to comply with surveillance or unable or unwilling to be treated with RT or carboplatin (e.g., inflammatory bowel disease). RPLND may also be appropriate in patients with a concurrent or previous malignant tumor for whom histologic examination of the lymph nodes is essential to plan treatment.

Overview of Management of Stage I Seminoma

Stage I seminoma is almost universally curable regardless of the approach after orchiectomy. The main advantage of surveillance is the ability to limit further treatment to those who will require it without compromise in survival. The disadvantage is that surveillance requires a commitment to more intense and potentially prolonged follow-up from both patients and clinicians compared to an adjuvant treatment approach. Studies into long-term effects of RT have now documented that patients with seminoma treated with irradiation have an increased risk of second malignant tumors and also the possible risk of developing cardiac disease, and such factors should be considered in management decision making.[55,57,58,100,101]

Patients' role in directing their particular management should likely take precedence and surveillance should be offered as a first choice.[102,103] These preferences may be based on many socioeconomic factors as well as the toxicity associated with adjuvant therapy. Also, the identification of prognostic and molecular factors for occult disease may allow patients and clinicians to adopt a more individualized approach based on a more accurate assessment of risk of relapse.[103,104]

Management of Stage II Seminoma

Stage II disease is usually classified as involvement of paraaortic (and much less frequently pelvic) nodes. These abnormalities are most frequently detected radiologically, and stage II patients are approximately 15% to 20% of patients presenting with seminoma. Patients historically have most often been divided into three groups depending on the transverse diameter of the largest retroperitoneal lymph node mass (≤2 cm, stage IIA; 2.1 cm to 5 cm, stage IIB; and >5 cm, stage IIC), but currently the categories are based on the largest measurement regardless of dimension. Thus, it is possible that over time some of the differences in reported outcomes (i.e., relapse rates), particularly for patients treated with primary RT may have occurred. Approximately 70% of stage II patients have small-bulk retroperitoneal disease at presentation with lymph nodes that are 5 cm or less. Because of the relatively small number of patients in this group, randomized controlled trials have been extremely difficult to accomplish and management has been largely directed by data published from single institutions.

The most important prognostic factor in stage II seminoma (treated with RT) is the bulk of retroperitoneal disease, this as previously mentioned in historic series was often defined by the transverse diameter of the largest lymph node mass visible on CT scanning. It was the only prognostic factor for relapse in a consecutive series of 95 patients with stage II seminoma treated with RT at the PMH between 1981 and 1999.[105] The 5-year relapse-free rate in 79 patients with stage IIA or IIB disease was 91%, compared with 44% in 16 patients with stage IIC disease. Relapse occurred most commonly in mediastinal or supraclavicular lymph nodes, lung, or bone. These results are similar to other series in the literature (Table 55-6) of primary RT in patients with stage IIA or IIB. In a more recent cohort of patients treated at PMH (1995 to 2010), relapse rates have remained at about 10% for patients treated with primary RT.[76] Of 106 patients treated, 49 had stage IIA/B and 57 had retroperitoneal nodal relapse under 5 cm size and the majority (n = 87) were treated with RT with a resultant 5-year relapse rate of 9%. These data support the continued use of RT in this setting.

In stage IIC disease, chemotherapy is recommended. In more recent years, there has been a tendency for larger number of patients even with lower bulk retroperitoneal disease to be treated with chemotherapy.[100,109]

Management decisions, however, should not be based solely on substage of disease; overall tumor bulk, location of disease relative to normal tissue, and anatomic variants must also be considered. Patients with cranial caudal extent of disease in multiple single nodes each smaller than 5 cm may be classified as stage IIB disease, but such a patient should be treated with chemotherapy because of the overall bulk of disease and the possibly higher risk of distant relapse if RT was used. The necessity of irradiating a large volume of

TABLE 55-6 Results of Retroperitoneal Radiation Therapy in Stage IIA or IIB Seminoma

Author	Year	No. Pts	Study Years	Relapse: No. Pts (%)	CSS (%)
Bayens[84]	1992	29	1975-1985	7 (24.0)	93.0
Chung[105]	2004	79	1981-1999	7 (8.8)	97.5
Classen[106]	2003	87	1991-1994	4 (4.6)	100.0
Vallis[107]	1995	48	1974-1989	3 (6.0)	98.0
Zagars[108]	2001	37	1984-1999	5 (13.5)	100.0

CSS, *Cause-specific survival;* No. Pts, *number of patients.*

adjacent renal or hepatic tissue when nodal disease is lateralized or has extensive transverse diameter and other anatomic situations such as a horseshoe, or pelvic kidney usually lead to unacceptable risk of irreversible long-term toxicity. Such circumstances are where chemotherapy would better serve these patients. It should be noted that cisplatin-based chemotherapy may also be associated with toxicity and, in some rare instances, mortality because of unforeseen toxicities such as cardiovascular deaths and not necessarily directly related to the usual expected toxicities of chemotherapy.[110-112] In the unusual situation where the patient has contraindication to both RT and chemotherapy, RPLND may be considered.

The commonest sites of relapse following RT in patients with stage II disease are mediastinal or supraclavicular nodes, lung, and bone. Most relapsing patients are cured with chemotherapy, which emphasizes the importance of regular follow-up with clinical examination and chest x-ray after RT. CT imaging of the abdomen and pelvis is not necessary after complete resolution of abdominal disease.

Carboplatin with RT in stage IIA or IIB seminoma has been used at the Royal Marsden Hospital in 51 patients (of whom 8 had stage I seminoma relapse on surveillance) treated with one course of carboplatin 3 to 6 weeks before RT.[113] The median follow up was 55 months and there had been no relapses, the 95% confidence interval for relapse free survival was 93% to 100%. This approach is interesting and currently under investigation in a Swiss Phase II multiinstitutional study with a smaller volume of RT compared to the Marsden experience.[114]

The technique of irradiation in stage II seminoma is similar to that used in stage I disease and is discussed later in this chapter.

Residual Retroperitoneal Mass

Following treatment, imaging of the abdomen in done until complete resolution of disease is observed. Persistent masses that are stable usually contain fibrotic or necrotic tissue, but occasionally even with pure seminoma primary tumors, a non-seminomatous component within the metastatic disease needs to be considered. However, surgical resection in this setting, often routinely undertaken for non-seminoma, is fraught with technical challenges and also associated morbidity.[115]

Observation of residual masses is an option, particularly if regressing; if disease is suspected, surgical resection may be undertaken or RT may be used to control active disease. PET imaging to help with decision making is controversial in this setting because of false-positive results that may occur, and the decision to treat the residual mass should not be based on a positive PET image alone.[116-118]

There is limited experience of surgical excision in this setting as it occurs with less frequency than residual mass in non-seminoma. Even large experiences may be gathered over a number of years such as that published by the Memorial Sloan Kettering Cancer Center (MSKCC) group where 55 of 104 patients had residual mass following chemotherapy.[119] A substantial minority, 23 (42%), had only intraoperative biopsy because their disease was not resectable; the remaining 32 (58%) did undergo RPLND. Of 27 patients with mass more than 3 cm, 8 (30%) had viable disease (of whom 2 actually had teratoma pathology), whereas no patients with mass smaller than 3 cm had viable tumor. Six of the 8 patients with viable disease remained relapse-free at 47 months of follow-up, the other 2 patients had poorly defined masses on CT scans, died of disease. MSKCC investigators concluded that resection or at least biopsy of masses of 3 cm or larger should be performed. Culine and Droz from the Centre Léon-Bérard in France[120] have recommended an alternative strategy of continued observation as long as the retroperitoneal mass continues to decrease in size after treatment.

Consolidation of treatment with RT localized to the mass was historically used in the postchemotherapy setting. This notion was challenged by Horwich et al[121] who found that the relapse rate was similar whether RT or observation was performed. In addition, the MRC Testicular Tumor Working Party published a retrospective pooled analysis that examined the role of RT for postchemotherapy residual masses among men with seminoma.[122] Of 123 patients with a residual abdominal mass, 56% received consolidative RT. The outcomes reported from this study showed no significant difference regardless of the use of RT, which suggests that routinely applying RT for a postchemotherapy mass should be avoided. Clearly RT in this setting would not be useful for a mass that contains no active tumor or in the setting of distant microscopic disease.

Generally, patients with a residual mass of 3 cm or less may be observed. For those with larger masses, surgery should be a consideration in addition to observation, but should be tailored to the individual situation.

Management of Stage III Seminoma

This uncommon presentation seen in less than 5% of patients with seminoma is usually managed with cisplatin-based regimens (see the section on non-seminoma) and results in high cure rates. Patients with stage III seminoma should be classified according to the IGCCCG system into either the good prognostic group or intermediate prognostic group based on the presence or absence of NPVMs.[44] For patients in the good-prognosis group, three courses of 5-day bleomycin, etoposide, cisplatin (BEP) chemotherapy is considered the standard of care.[100,123] In patients at risk for bleomycin toxicity, four courses of etoposide-cisplatin (EP) is given. For patients with intermediate-prognosis disease, four courses of 5-day BEP is standard.

Non-Seminoma

Since the 1970s, when cisplatin, bleomycin, etoposide, and vinblastine were introduced, non-seminoma has become one of the most curable adult cancers. Before these drugs were available, nonseminomatous tumors were treated with a wide

range of chemotherapeutic agents and there were occasional reports of long-term remissions with the use of single-agent mithramycin and actinomycin D.[124] The modern era in treating advanced disease began at the M. D. Anderson Cancer Center (MDACC) with the use of continuous infusions of bleomycin and vinblastine; at MSKCC with the vincristine plus actinomycin D plus bleomycin (VAB) regimens; and, later, at Indiana University, with the cisplatin plus vinblastine plus bleomycin (PVB) regimen.[125-127] With these regimens, complete responses to treatment became frequent and cures were seen in patients with metastatic disease. The current BEP protocol emerged in the 1990s and is now the standard for first-line chemotherapeutic treatment of metastatic seminoma and non-seminoma.

Management of Stage I Non-Seminoma

The risk of relapse following orchidectomy for Stage I non-seminoma is 25% to 30%. Current treatment options include surveillance with a 30% relapse rate, RPLND with a 10% relapse rate, and adjuvant chemotherapy (most often given only for high-risk patients) with a 1% relapse rate.

The optimal follow-up protocol for nonseminoma surveillance has not been defined. The current National Comprehensive Cancer Network (NCCN) guidelines recommend history and physical examination, tumor marker measurements, and chest x-ray every 2 months, with abdominal and pelvis CT scan every 4 months during year 1 and 4 to 6 months during year 2 for stage IB patients, with less frequent assessments thereafter (see references 53, 62, 125, 126, 129, 131-136).[140] Patients with stage IA disease are also followed on a less intense schedule. It has been suggested that the number of CT scans could be reduced to two, at 3 and 12 months after diagnosis, but this approach has not been widely accepted.[141] There is growing consensus that the optimal CT evaluation schedule may include three to five assessments within the first 2 years of orchiectomy. Given the concern that CT scanning may increase the risk of second malignant tumors, this approach should be explored further. Low-dose CT scanning[83,142] and MRI of the abdomen and pelvis at high-volume imaging centers may be alternatives to reduce cumulative radiation exposure with surveillance imaging.

The OS rate in stage I non-seminoma approaches 100% in most series irrespective of the treatment strategy used.[112] A risk-adapted approach with surveillance for low-risk disease and treatment (either adjuvant chemotherapy or RPLND for patients at a moderate to high risk of occult metastatic disease) has been advocated by some.[147] A surveillance policy, however, is associated with excellent outcomes, and overall, 75% of patients avoid any treatment after orchidectomy.[112,126,148,149] International consensus statements have concluded that all three approaches should be discussed with the patient,[20,54,123] although there is growing support for a universal policy of active surveillance as the preferred approach to reduce the burden of overtreatment.[146] Patients with persistently elevated or rising tumor markers with no radiographic evidence of metastatic disease (Stage IS) are considered IGCCCG good risk and receive treatment with primary chemotherapy with excellent long-term survival.

Management of Clinical Stage II Non-Seminoma

The cure rate for stage II non-seminoma is approximately 98%. Stage IIA disease is managed with cisplatin-based chemotherapy alone or RPLND plus chemotherapy (both <5% relapse rate), and stage IIB or IIC disease is managed with cisplatin-based chemotherapy, with a 5% relapse rate.

For patients with pathologic stage IIA or IIB disease, the risk of relapse with no adjuvant treatment after surgery is 30% to 50%.[123,150] Relapses occur almost exclusively outside the retroperitoneum. Adjuvant chemotherapy with two cycles of BEP in all patients with pathologic stage IIA or IIB disease after RPLND reduces this risk of relapse to 0% to 7%.[151] However, adjuvant chemotherapy represents overtreatment in 50% to 70% of patients with pathologic stage IIA or IIB disease, with resulting treatment-related toxicity and possible late sequelae.

Management of Stage III Disease

Patients with advanced GCTs should always be considered potentially curable. Survival outcomes appear to be better in specialized centers, and this may be related to experience, case selection, volume, or organization of multidisciplinary care. Referral of all patients with advanced GCTs for consultation to a specialized center is strongly recommended

Chemotherapy with or without Retroperitoneal Node Dissection

The standard first-line chemotherapy for all patients is three to four cycles of BEP using a 5-day schedule.[54,123] Modifications in BEP, such as substitution of cisplatin with carboplatin to reduce toxicity or improve convenience, should be avoided because they may reduce efficacy; however, if there is a contraindication to bleomycin, four cycles of EP can be given.

Postchemotherapy radiologic restaging should be performed in all patients 4 to 6 weeks following the final cycle of chemotherapy. If tumor marker decline is seen, as expected, all residual masses should be managed appropriately (see the following section). Only in the case of unequivocal tumor marker rise should salvage chemotherapy be initiated.

Residual Retroperitoneal Mass

In many patients who complete chemotherapy and have normalized tumor markers, residual masses (>1 cm) are seen on imaging. If technically feasible, these masses should be resected 4 to 6 weeks after chemotherapy. On histologic testing, approximately 50% will show necrosis, 35% mature teratoma, and 15% malignant disease.[54] In some centers, RPLND is performed in all cases, even in patients with no residual retroperitoneal disease on imaging. However, there is increasing evidence that observation in patients with complete response after chemotherapy, reserving surgery for those who relapse, gives excellent results and spares many patients unnecessary surgery.[159,160]

Treatment-Related Side Effects

Radiation Therapy Toxicity

RT is generally well tolerated in patients with seminoma partly because of the low doses used in this disease.[111] Nausea and vomiting may occur, but only some patients require regular antiemetics and have fatigue that interferes with activities of daily living. Diarrhea may also occur but usually this is a minority of patients. Severe late radiation complications are unusual but may occur in the patient with underlying medical issues.

Gonadal Toxicity

As the testicular germinal tissue is extremely sensitive to ionizing radiation, it is not surprising that even a small amount of scatter radiation may cause, at minimum, temporary arrest of spermatogenesis. In a series of 451 consecutive patients treated for testicular cancer, RT had a significantly greater deleterious effect on fertility than chemotherapy.[161] Doses between 20 cGy and 50 cGy may produce temporary aspermia, and doses greater than 50 cGy may preclude recovery of spermatogenesis.[162] Scrotal shielding may not eliminate all scatter radiation and thus protection of spermatogenesis is not

The presence of vascular invasion or pure embryonal carcinoma in the primary tumor are associated with a high risk of occult nodal disease. [105,109-111,127-131] Vascular invasion is the most important factor predicting relapse, and the presence or absence of this factor has been used to divide patients into those with high-risk disease (a third of cases), who have an approximately 50% risk of relapse, and those with low-risk disease, who have an approximately 15% to 20% risk of relapse.[53]

In a recent pooled analysis of 1168 patients with clinical stage I non-seminoma managed with active surveillance from six institutions with a median follow-up of 63 months, the overall relapse rate was 22% (256 relapses) with 5-year CSS >99% (six deaths from testicular cancer or treatment).[132] The median time to relapse was 6 months and relapses beyond 2 years from orchidectomy were rarely observed (<5%). Of all relapses, 90% were IGCCCG good risk. At the time of progression, the vast majority of patients were treated with chemotherapy, although RPLND was successfully used in selected cases with small retroperitoneal nodes and negative or low level serum tumor marker elevations. Relapses were more frequently observed in patients who are LVI positive (48% or 117 of 244) compared with patients who are LVI negative (14% or 129 of 903). Relapses occurred earlier (median 5 months versus 8 months) and were more often detected with serum tumor marker elevation ($p < 0.05$) in patients who were LVI positive versus those who were LVI negative. A summary of institutional series of active surveillance for Stage I non-seminoma is provided in eTable 55-1.

RPLND is a recognized alternative to surveillance in clinical stage I disease. A modified unilateral infrahilar RPLND is performed, with nerve-sparing techniques to preserve ejaculation. For right-sided tumors, the interaortocaval nodes and paracaval nodes are removed, with preservation of the left sympathetic chain, and for left-sided tumors, the paraaortic and interaortocaval nodes are removed and the right autonomic chain is preserved. If significant lymphadenopathy is revealed at surgery, a more extensive surgical resection is performed. The relapse rate following surgery is approximately 10% for patients with pathologic stage I disease.[143] Most patients who relapse after RPLND are cured with subsequent chemotherapy.[144]

In some centers, patients with clinical stage I NSGCT at high risk of relapse on surveillance are offered adjuvant chemotherapy with two cycles of BEP or EP chemotherapy.[124] In a recent meta-analysis of one randomized and seven nonrandomized studies of adjuvant chemotherapy, with a total of 873 evaluable patients, 23 relapses (2.6%) were observed.[112] To reduce treatment-related toxicity, a number of studies have tested a single cycle of adjuvant BEP.[145] A recent randomized trial of one versus two cycles of adjuvant BEP chemotherapy for stage I non-seminoma was closed prematurely because of poor accrual.[146] It should be noted that adjuvant chemotherapy does not completely eliminate the need for ongoing clinical and radiological follow-up, although it does reduce the frequency of assessments.

Patients with stage IIA disease with marker elevations (AFP, β-HCG, or LDH) or stage IIB or stage IIC disease regardless of marker status should be treated with chemotherapy according to the algorithms for patients with advanced disease.[54,123] Patients with stage IIA disease with normal or minimally elevated markers have several options. The enlarged nodes may be benign or they may contain teratoma, pure embryonal carcinoma, or mixed tumor elements. In the event of uncertainty about the clinical significant of minimally enlarged nodes, short-term follow-up imaging and tumor marker evaluation to see if the nodes regress without accompanying tumor marker elevation is reasonable. Patients with enlarging nodes or rising markers should receive chemotherapy based on the IGCCG risk classification described in this chapter. Primary RPLND may be considered if there are pathologically enlarged small volume lymph nodes and normal or minimally elevated tumor markers. After RPLND, surveillance or adjuvant chemotherapy may be employed if there are viable germ cell elements.

eTABLE 55-1 Prospective Trials of Surveillance in Stage I Non-Seminoma

Author	No. Pts	Progression Rate (%)	Dead of Disease	Retroperitoneal Progression (%)
Daugaard et al (Copenhagen)[62]	301	29	0	—
Freedman et al (MRC)[129]	259	32	3	55
Freiha et al (Stanford)[133]	23	13	—	67
Jacobsen et al (Denmark)[130]	83	28	—	65
Peckham et al (RMH)[129]	132	27	1	60
Pizzocaro et al (Milan)[134]	85	29	3	66
Raghavan et al (Australia)[135]	49	28	2	38
Read et al (MRC)[53]	396	25	5	61
Sogani et al (MSKCC)[136]	102	25	3	72
Sharir et al (PMH)[137]	170	75	1	65
Thompson et al (New Zealand)[138]	36	33	1 (? + 1)	33
Wishnow et al (MDACC)[139]	82	29	—	—

MDACC, *M.D. Anderson Cancer Center;* MRC, *Medical Research Council;* MSKCC, *Memorial Sloan-Kettering Cancer Center;* No. Pts, *number of patients;* PMH, *Princess Margaret Hospital;* RMH, *Royal Marsden Hospital.*

In patients with IGCCCG good-prognosis disease, three cycles of BEP should be given. If there is a contraindication to bleomycin, four cycles of EP can be given; however, four cycles of EP, however, has been associated with a nonstatistically significant but higher death rate in one randomized clinical trial.[152] Three cycles of BEP with a higher total dose of bleomycin (270 units) and greater dose intensity of etoposide (500 mg/m^2 per cycle) was shown to be superior and less toxic that four cycles of BEP with a lower total dose of bleomycin (120 units) and reduced dose intensity of etoposide (360 mg/m^2 per cycle).[153]

In patients with IGCCCG intermediate- or poor-prognosis disease, four cycles of BEP should be considered the standard therapy.[54,123] The VIP regimen (etoposide, ifosfamide, and cisplatin) has been compared with BEP in this patient population and shows similar outcomes but with more acute toxicity. The VIP regimen represents an alternative to BEP for patients with a contraindication to bleomycin or who develop pulmonary compromise while receiving BEP.[154] The addition of paclitaxel to BEP chemotherapy failed to improved progression-free survival in a randomized clinical trial involving patients with intermediate-risk disease.[155] For patients with intermediate- or poor-prognosis, there is no evidence to date that the use of high-dose chemotherapy with autologous stem cell transplantation is superior to the standard four cycles of BEP.[156,157] A prospective randomized clinical trial has demonstrated that poor-risk patients with unfavorable serum tumor marker decline after 1 cycle of BEP treatment benefitted from dose-intensification of subsequent cycles of treatment compared with standard BEP. However, there was no difference in OS and dose intensification for poor-risk disease is not widely accepted as a standard of care.[158]

Chemotherapy should be given, preferably without dose reductions, even in the setting of a critically ill patient, at 21-day intervals with no delays between cycles. In patients with life-threatening disease, orchiectomy should not delay the initiation of curative therapy and can be performed at the end of therapy. If possible, these patients should be treated in centers with expertise in the management of germ cell tumors. During chemotherapy, assessment of tumor markers before each treatment cycle is essential. As long as tumor markers are declining, a full course of chemotherapy should be completed. If metastases can be seen growing on radiologic examination as tumor marker levels are declining, a diagnosis of growing teratoma syndrome should be considered. In most cases, the full course of chemotherapy should be completed and resection of the residual masses should be done following chemotherapy.

Reduction in fertility appears to have a strong association with testicular cancer as many men who develop testicular cancer may already have a history of subfertility or infertility. However, even with men who have "normal fertility," it is advisable to undertake sperm banking before treatment because there may be a deleterious effect due to therapy and recovery from this may be slow and incomplete. However despite these risks, the majority of men who desired to father children after treatment did so.

universal when using this technique. There has been no evidence to suggest that the incidence of genetic abnormalities in offspring of men previously treated with RT is increased.[163] Although increasing the distance of the testis from the treated volume is expected to reduce scatter dose, this also does not eliminate all dose. However it does appear to have an effect on the length of time to recover normal sperm counts as demonstrated in the MRC randomized trial of paraaortic RT alone versus paraaortic and pelvic RT, where the median time to a normal posttreatment sperm count was 13 months in patients treated to the paraaortic lymph nodes compared to 20 months for patients treated to the paraaortic and pelvic lymph nodes.[63] However, at 3 years, there was no significant difference in sperm counts between the two groups. Testicular shielding is recommended for all patients who wish to retain fertility after treatment.[164]

Cardiovascular Toxicity

Since mediastinal RT has been abandoned, the risk of cardiovascular disease in long-term survivors has decreased. Institutional data from the MDACC and the Royal Marsden Hospital, and population-based data from Norway, however, suggest that long-term survivors of testicular seminoma treated with infradiaphragmatic RT following orchiectomy are at significant excess risk of death as a result of cardiac disease.[55,59,165] Although more recently this notion has been challenged by SEER data that demonstrated no obvious increase in rates in patients treated with RT, the bulk of the published data supports the notion that infradiaphragmatic RT is associated with an increased risk of cardiac mortality.[60] The etiology of the cardiovascular toxicity is currently unclear, but it seems reasonable for patients to be made aware of the data when deciding on whether to undergo adjuvant RT.[166]

Second Malignant Tumor

Second malignant tumors may be induced by RT and a number of studies have been published on this topic. The increased risk is usually expressed more than 10 to 15 years following RT, is often not apparent in series with shorter follow-up times.[167] The largest study of second cancers in long-term survivors of testicular cancer was conducted by Travis et al.[57] This report combined 14 population-based registries including 10,534 patients with seminoma treated with RT. The overall relative risk of a second nontesticular malignant tumor was 2 (95% CI, 1.8 to 2.2). For a 35-year-old man with seminoma, the cumulative 40-year risk of a second malignant tumor was 36%, compared with 23% in the normal population. The increased risk of second malignant tumors after treatment with RT was also shown in a Dutch population-based study of more than 2700 long-term survivors where the risk of a second malignant tumor with subdiaphragmatic RT was 2.6-fold increased as compared with surgery alone.[58] The increased risk associated with irradiation was similar to the increased cancer risk seen with smoking. A recent study from the United Kingdom has confirmed these findings.[101] Limitation of the RT field likely results in a lower risk of second malignant tumors than more extensive fields.

Psychological Toxicity

The issue of psychological morbidity associated with the diagnosis of cancer in young men may result in survivors with a higher level of anxiety and a higher prevalence of anxiety disorders than the normal population, and screening using a simple tool such as the Hospital Anxiety and Depression Scale (HADS) should be part of routine follow-up care.[111,168] Appropriate social support should be offered to patients with testicular tumors. Although highly curable, testicular cancer is still a life-threatening condition in young patients with a concomitant threat of infertility and impaired sexual function as a result of the disease or its treatment.[169]

Chemotherapy Complications

The complications of chemotherapy in testicular GCTs are related to the drugs employed.[111] Nausea and vomiting occur with all the drugs used but are controlled effectively in most patients with 5-hydroxytryptamine receptor-3 (5-HT3) antagonists, steroids, and neurokinin receptor 1 (NK1) antagonists. Myelosuppression is frequent. Febrile neutropenia is seen in about 10% to 15% of patients receiving BEP, and prophylactic hematopoietic growth factors may be considered in some patients at increased risk. Nephrotoxicity, primarily a reduction in the glomerular filtration rate, occurs with the use of cisplatin and ifosfamide. Renal tubule function is normal in most patients, but hypomagnesemia is seen in patients after repeated use of cisplatin. Raynaud phenomenon has been reported in 23% to 49% of patients, although resolution of symptoms is common.[170] Chronic peripheral neuropathy (often asymptomatic) is well recognized after treatment with cisplatin, vinblastine, and etoposide. This symptom may require up to 12 months to 18 months to resolve or may be permanent. Cisplatin-induced hearing loss, particularly at higher frequencies, may occur particular with >400 mg/m^2 of cumulative cisplatin doses. Pulmonary toxicity is seen with the use of bleomycin and can be fatal in a small number of cases.[171] Impaired fertility, which may precede the use of chemotherapy, may also continue after its use. Although chemotherapy also produces infertility, recovery of sperm counts at least to levels compatible with fertility has been observed in the majority of patients.[172] Approximately 75% of patients who attempt paternity after chemotherapy are successful with a strong association with treatment intensity.[173] Hypogonadism is observed is 11% to 35% of long-term survivors (often subclinical), related to the duration of follow-up and the cumulative dose of cisplatin.[109] There is an increased risk of late onset atherosclerotic cardiovascular disease, possibly related to early development of metabolic syndrome (obesity, hyperlipidemia, and hypertension) following cisplatin-based chemotherapy.[174]

Nongerm Cell Testicular Tumors

Leydig Cell Tumors

Leydig cell, or interstitial cell tumors account for less than 2% of testicular tumors.[175] Twenty-five percent occur in children and can present with signs of prepubertal virilization. Seventy-five percent are in patients presenting between the age of 20 and 50 years, usually with a painless testicular mass. Most Leydig cell tumors are benign, and there are no definite histologic criteria for malignancy.[175] The regional lymph nodes are the commonest site of metastatic disease, but lung, bone, and liver metastases have also been reported. The initial management is similar to that for GCTs, with a radical inguinal orchiectomy followed by staging assessment with a chest radiograph and CT scanning of the abdomen and pelvis.[176] Testis-sparing surgery can be considered in experienced hands. Urinary and serum steroids should also be assessed. RPLND can be considered in selected cases.[177] There is no role for adjunctive or definitive irradiation or chemotherapy.

Sertoli Cell Tumors

Sertoli cell tumors account for less than 1% of all testicular tumors.[175] They have been classified into three subtypes: classic, large cell calcifying, and sclerosing.[178] Most present with a painless testicular mass, and initial management is with a radical inguinal orchiectomy. Both precocious puberty and feminization have been reported to be associated with Sertoli

cell tumors in children. Most Sertoli cell tumors are benign, and orchiectomy is nearly always curative.

Extragonadal Germ Cell Tumors

Extragonadal germ cell tumors (EGCTs) have histologic findings similar to those of testicular GCTs but are found in other parts of the body, in the absence of a testicular mass. They account for 1% to 5% of all GCTs and like testicular GCTs tend to occur in young men, although the median age of presentation is 5 to 10 years older than with testicular GCTs.[179] In infants, EGCTs are more common than testicular primary tumors (usually, sacrococcygeal teratomas).[179]

Overall, patients with EGCTs (especially NSGCTs) have a worse prognosis than patients with testicular primary tumors.[180] An increased incidence of EGCTs is seen in Klinefelter syndrome. A number of patients present with poorly differentiated carcinomas (predominantly in midline locations), with a cytogenetic pattern similar to those with typical EGCTs, and do respond to cisplatin-based chemotherapy regimens.[29]

EGCTs most commonly arise in three midline sites in the mediastinum, the pineal and suprasellar regions, and the sacrococcyx (usually in infants). There have been rare case reports of tumors arising in the orbit, prostate, vagina, and liver. Tumors arising in the retroperitoneum are usually thought to be associated with an occult testicular primary lesion. Mediastinal GCTs usually occur in the anterior superior region of the mediastinum adjacent to the thymus. Patients may present with cough, dyspnea, and chest pain, and tumor marker levels are frequently abnormal. Local invasion or metastatic disease to the lungs, liver, or bone is common. Biopsy should always be performed because treatment is dependent on the histologic subtype. For mature teratomatous tumors surgery is advised, whereas for NSGCTs or seminomas the preferred approach is cisplatin-based chemotherapy, omitting bleomycin as many patients require extensive thoracic resection after primary chemotherapy.[181] Surgical resection is recommended for residual mass after chemotherapy. However, the precise role of locoregional therapy after primary chemotherapy is unclear.

The results of an international analysis of 635 consecutive patients with EGCT treated in 11 European and U.S. centers have shown that patients with pure seminomatous histologic typing had a long-term cure rate of 89%, irrespective of the primary site (retroperitoneum or mediastinum).[180] In patients with nonseminomatous tumors, however, a mediastinal primary site was an adverse feature, with only 45% of these patients alive at 5 years as compared with 63% of patients with retroperitoneal presentations. Prognostic variables for response and outcome have been identified, and four prognostic risk groups have been identified based on histologic findings, the presence of liver, lung, or central nervous system (CNS) metastases, elevation of β-HCG levels, and number of metastatic sites involved with disease.[182] The best prognostic group has an 89% 5-year OS and encompasses all patients with seminoma. The other groups all have nonseminomatous histologic findings and 5-year OS of 69%, 55%, and 17%, respectively.

The excellent treatment results with chemotherapy alone of mediastinal seminomatous tumors would suggest that there is no routine role for RT in their management. Platinum-based chemotherapy regimens are recommended. Although a 5-year OS of 73% has been reported with the use of cisplatin, vincristine, methotrexate, bleomycin, actinomycin D, cyclophosphamide, and etoposide (POMB/ACE), there is no evidence that this regimen is superior to BEP.[183] POMB/ACE is considerably more toxic, and its routine use cannot be recommended.

Special Treatment Situations

Germ Cell Tumors in Patients with Horseshoe Kidney

Horseshoe kidney (pelvic kidney) occurs in approximately 1 in 400 persons in the general population.[184] There are two main problems in the management of GCTs associated with horseshoe kidney. The first is related to the technical problem of delivery of RT in patients with seminoma. In a number of cases of horseshoe kidney, a large part of the renal parenchyma directly overlies the regional lymph nodes and lies within the standard radiation volume. The delivery of a standard radiation dose would be associated with an unacceptable risk of radiation nephritis. The second problem is related to the possible abnormalities in lymphatic drainage of the testis, and therefore, the possibility of relapse when the standard radiation fields are used. Unusual patterns of relapse have been observed in patients managed by surveillance, confirming concerns regarding abnormal lymphatic pathways.[185] For these reasons, in patients with seminoma and NSGCTs, postorchiectomy surveillance in stage I and chemotherapy in stage II have usually been recommended. RPLND is another option for patients unwilling to follow the surveillance program, but it has to be assumed that the issue of abnormal lymphatic drainage may also result in technical challenges for the surgeon. However, reports in the literature suggest that RPLND was both safe and effective in the selected cases where it was performed.[185]

Testicular Tumors Developing in Patients Who Are Immunosuppressed

It is well established that the risks of developing Kaposi's sarcoma and non-Hodgkin lymphoma are markedly increased in patients with human immunodeficiency virus (HIV) infection.[186] Initial data suggested that men who are infected with HIV have an increased incidence of testicular cancer, but more recent studies have indicated that this may not be true.[18,186] Organ transplant patients may also have an increased incidence of testicular tumors.[187] The clinical course of patients who are immunosuppressed with testicular tumors is similar to that of patients who are immunocompetent, and these patients should be offered standard oncologic therapy. Both chemotherapy and RT reduce the CD4 count even when antiretroviral therapy is used; therefore, wherever possible, surveillance should be used in patients with stage I disease.[18] Caution must be exercised because benign retroperitoneal adenopathy related to acquired immunodeficiency syndrome (AIDS) may be mistaken for metastasis from a testicular primary tumor. For those receiving chemotherapy, consideration should be given to concomitant prophylaxis for opportunistic infection. Most patients can be cured of their tumors, and the outcome of patients with HIV-related GCTs is similar to that of patients who do not have HIV.

Bilateral Testicular Germ Cell Tumors or Tumors Arising in a Single Testicle

Men who have had cancer in one testicle are at increased risk of developing contralateral disease with reported rates of metachronous or synchronous development of 1% to 5%.[187] Bilateral orchiectomy is recommended as standard management, with resulting infertility, lifelong dependence on androgen replacement, and psychological morbidity because of castration at a young age.[188]

To preserve endogenous hormonal function, organ-sparing surgery followed by low-dose RT (16 Gy to 20 Gy in 2-Gy daily fractions using a direct field with electrons) to the remnant testis to eradicate residual CIS and prevent future invasive disease is an option with a high likelihood of cure in selected patients.[20,189] Close observation after surgery may be

undertaken and adjuvant radiation may be postponed if there is a fertility concern for the patient and he is willing to risk the onset of invasive disease during that period.[189] Patients with large tumors (>30% of the testis volume) or clinical evidence of metastatic disease are not suitable for this approach. Because this is an area that requires expertise, organ-sparing approaches should be concentrated in centers with such experience.[20]

Central Nervous System Metastases

Up to 40% of patients who die of progressive disease have brain metastases at autopsy. Thankfully, presentation with brain metastases is uncommon with approximately 2% to 3 % of patients overall. Such patients are potentially curable, with approximately 50% 5-year CSS, but this requires aggressive treatment.[54] The optimal sequence of chemotherapy, RT, and surgery is unknown, although systemic chemotherapy is required in all cases, only in one study did the addition of cranial RT improve overall survival.[190] Whether the addition of RT when a complete response is obtained with chemotherapy is needed is uncertain, as is the need for RT if surgery removes gross disease. When RT is given, a dose of 40 Gy to 45 Gy should be considered for gross disease if using conventional fractionation. It is unclear if the entire brain should be irradiated but when this is done, the intended dose should not exceed 40 Gy because of the risk of neurotoxicity. A stereotactic approach is now being used more frequently and has the advantage of tumoricidal doses and relatively low risk of toxicity to the surrounding brain. Patients presenting with late relapse with CNS metastases should be treated aggressively because long-term disease-free survival times are possible.[191] Patients who develop brain metastases during chemotherapy have a poor prognosis.[191]

Spermatocytic Seminoma

Spermatocytic seminoma is a rare testicular tumor accounting for only 1% to 2% of all seminomas.[192] It usually occurs at age 50 to 60 years but is seen in younger patients.[192] It is distinct in its histologic characteristics, usually having three different cell sizes, spherical nuclei, a lack of cytoplasmic glycogen, and sparse or absent lymphocytic infiltrate when compared with classical seminoma.[193] Unlike classical seminoma, it does not appear to arise from CIS, occurs solely in the testis and has no ovarian equivalent. All patients present with stage I disease, and subsequent metastatic disease is extremely rare. In the past, the treatment approach was similar to seminoma with adjuvant RT. Current recommendations call for surveillance in all patients and the frequency of investigations may also be reduced given the seemingly minimal metastatic risk this histology poses.[194]

IRRADIATION TECHNIQUES AND DOSE

With the advent of successful salvage chemotherapy in metastatic disease, various strategies have been investigated to reduce the long-term complications of RT and in particular adjuvant RT (the standard of care after orchiectomy in stage I disease). This has included the reduction of the volume of tissue irradiated together with a dose reduction strategy. Alternative to RT including adjuvant chemotherapy and surveillance also have become popular, as has the increasing use of cisplatin-based chemotherapy in stage II disease. All of these strategies have been designed to lessen the potential adverse impact of RT.

Radiation Target Volume

The intended clinical target volume for both stage I and stage II seminoma has included the paraaortic lymph nodes and ipsilateral pelvic lymph nodes. In the case of left-sided tumors, the left renal hilum is included to allow for nodes that cluster around the left gonadal vessels. The most frequently used field arrangement is parallel opposed anteroposterior fields, and patients are treated with 10-MV to 18-MV linear accelerator photons. Although almost identical on both sides of the Atlantic, this classical plan was called the "hockey-stick" field in North America and the "dogleg" field in the United Kingdom and Europe. The superior extent is usually at the T10/T11 interspace and the inferior at the inguinal ligament. The penis is moved out of the field and the contralateral testis is placed in a scrotal shield to protect fertility and to a lesser extent future hormone production. In general, scrotal irradiation is avoided except in patients with extensive local disease, incomplete surgery, and gross scrotal contamination before surgery. Of note is that in the case of transscrotal orchiectomy, scrotal irradiation is still not recommended. Mediastinal irradiation is now of historical interest only.

More conformal radiation techniques such as intensity-modulated radiation therapy (IMRT) have not been pursued in part because the necessity of exposing more normal tissue to the low-dose radiation that is typical for the multiangle beam arrangements used in IMRT, resulting in an increase in the integral dose.[195] Another concern is the possibility that this integral dose may risk an increase in second malignancy rates in this younger population. With the increase in the availability of proton facilities, there has been some interest in exploring the possibility of using proton beams to improve dose conformality as well as minimize the risk of second malignancy.[196]

Reduction in Radiation Treatment Volume

Stage I Seminoma

Recognition of the low risk of pelvic nodal involvement in stage I disease led to the investigation of eliminating pelvic nodal irradiation. Advantages of such an approach would include lower scatter dose to the testes and reduced irradiated volume of normal tissue which in theory might reduce risk of second malignancy. The literature shows excellent results with few pelvic failures.[92,197] This was confirmed in the MRC Testicular Study Group randomized study of 478 patients comparing paraaortic plus pelvic RT and paraaortic RT alone, relapse rates were similar, 4% with paraaortic irradiation and 3.4% relapse rate with paraaortic and pelvic irradiation.[63] The sites of relapse were different, whereas all patients who received paraaortic and pelvic RT relapsed in supradiaphragmatic sites, four patients (1.6%) treated to the para-aortic lymph nodes alone had pelvic relapse. This highlighted the potential need for regular imaging with CT to detect pelvic relapse in these patients. When no imaging of the pelvis is carried out, patients fail with bulky disease (median, 5 cm).[92] It may be reasonable to confine such imaging to the first 3 years after RT as supported by data from the German Testicular Cancer Study Group.[198] Although there are advantages to paraaortic RT alone, its true value in stage I disease remains unclear especially when surveillance is an attractive alternative.

A compromise between traditional irradiation fields and paraaortic irradiation alone is to treat the paraaortic and ipsilateral common iliac lymph nodes by positioning the inferior border of the radiation fields at midpelvis[199] (Figure 55-3). This encompasses the lymph nodes that are typically removed at lymphadenectomy in patients with nonseminomatous tumors and also covers the vast majority of pelvic nodal relapses in patients treated with paraaortic irradiation alone.[197] This treatment volume is also partly supported by the data for stage II disease discussed in this chapter. Similarly a multiinstitutional study that examined nodal relapse sites in 90 patients with

stage I seminoma relapsed surveillance and de novo stage IIA/B found no sites of disease cranial to the L1 vertebral body.[41] This data may therefore support a reduction of the cranial aspect of the traditional RT field to the superior aspect of T12 vertebral body and may allow lower amount of radiation exposure to the heart and upper abdominal structures with the ultimate goal of the minimizing radiation toxicity without sacrificing rates of disease control.[200]

Stage II Seminoma

The RT technique in stage II seminoma is similar to that used in stage I disease. The treatment volume includes the gross tumor as well as the paraaortic and ipsilateral common and external iliac lymph nodes (Figure 55-4, *A*). Previously the dog-leg field was used but data from the German Testicular Cancer Group, although not a randomized study, provide some support for the placement of the inferior extent of the field at the acetabulum.[106] In this study of 87 assessable patients at median follow up of 70 months, only 4 patients relapsed with none distal to the inferior extent of the volume; although this study was small and not designed to test the question of volume reduction it is somewhat reassuring with the low rate of relapse seen. The contralateral iliac lymph nodes may also be treated in cases where lymphadenopathy in the low paraaortic area is deemed to increase the risk of these nodes being involved by tumor. However, such patients often have bulky retroperitoneal lymphadenopathy and are better treated with primary chemotherapy. Adjuvant RT of the supraclavicular lymph nodes in patients with stage II disease has been suggested by some, although it is not justified on a routine basis in view of the low risk of isolated supraclavicular relapse (2 of 79 patients with stage IIA or IIB disease in the PMH series).[108,201]

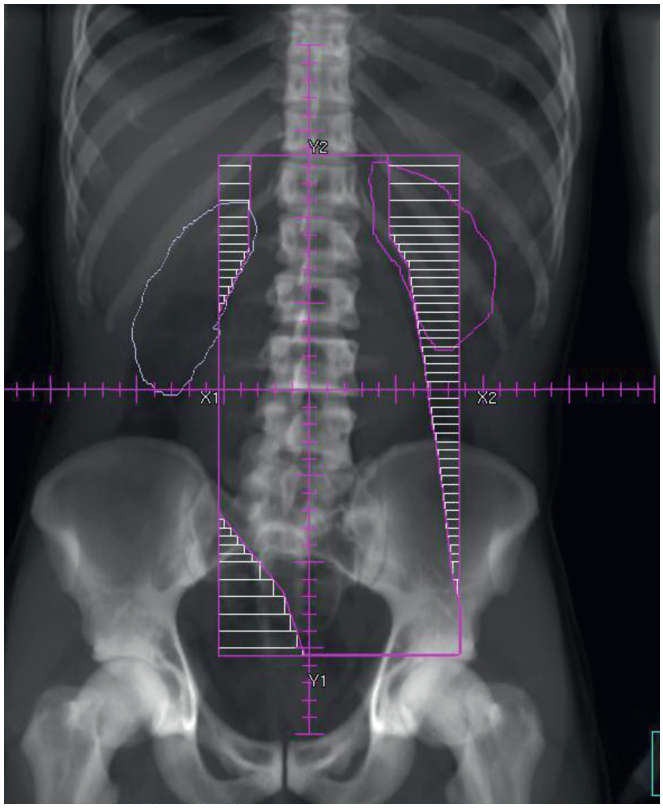


Figure 55-3 Radiation fields, stage I.

Radiation Dose

Stage I Seminoma

Doses of 20 Gy and 25 Gy are more than adequate to eradicate microscopic seminoma. No in-field recurrences have been observed in the series from PMH (Toronto) where 25 Gy is delivered over 20 daily fractions with total duration of 4 weeks.[68] A Phase III study of dose reduction comparing 30 Gy in 15 fractions over 3 weeks and 20 Gy in 10 fractions over 2 weeks in 625 patients was undertaken in the MRC TE18 trial.[64] A total of 10 and 11 relapses, occurred in the 30-Gy and 20-Gy groups (hazard ratio [HR], 1.11; 90% CI, 0.54 to 2.28), respectively, at median follow up of 61 months. The resulting 5-year relapse rates were 3% and 3.6% for the 30-Gy and 20-Gy groups, respectively. Longer follow up data published subsequently have confirmed these findings.[97]

Stage II Seminoma

The radiation dose is typically 25 Gy in 20 daily fractions plus a boost of a further 10 Gy to the gross lymphadenopathy (see Figure 55-4, *B*). At PMH, this boost is given concurrently with the large-field treatment. Some authorities suggest that 30 Gy for small bulk (IIA) gross disease is adequate but no trials have

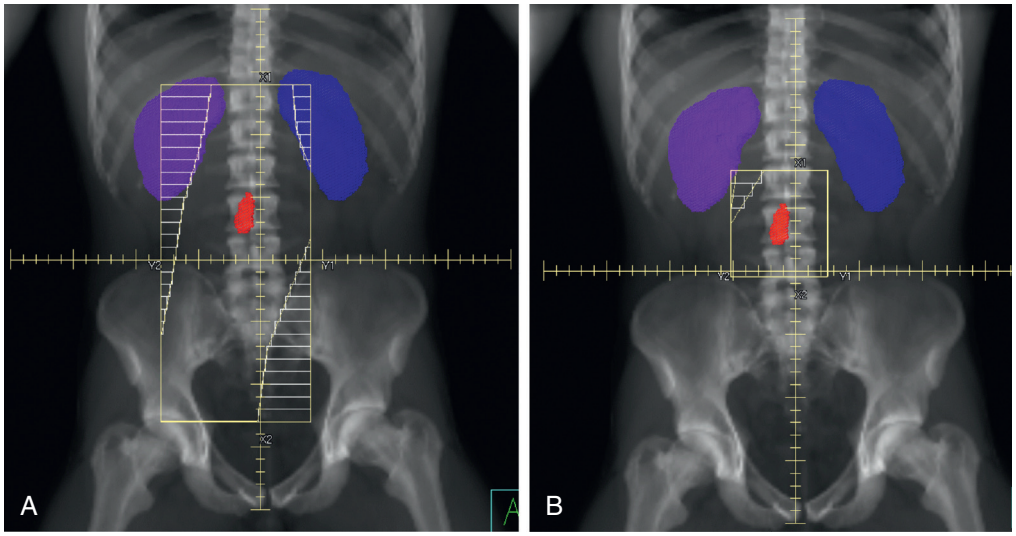


Figure 55-4 Radiation fields, stage II. **A,** Extended field. **B,** Boost field.

been done in this area.[106] One possible mechanism to reduce dose in this setting is the addition of carboplatin in a sequential fashion perhaps allowing even bulky disease to be safely eradicated with lower doses.

TREATMENT ALGORITHMS, CONCLUSIONS, AND FUTURE POSSIBILITIES

The recommended treatment algorithms for seminomas and non-seminomas based on disease extent are outlined in Figures 55-5 and 55-6. Although the overall results are excellent, there are ongoing controversies regarding the optimal management of GCTs.

In seminoma, the major area of controversy involves the management of stage I disease. The mature data from surveillance and adjuvant therapy series suggest that almost 100% of patients with stage I testicular seminoma are cured no matter which approach is chosen as postorchiectomy management. Surveillance should be considered the management option of choice, although the patient should be fully involved in the decision making.[146] Change is adopted slowly and a considerable proportion of urologists and oncologists do not discuss all the options with their patients.[202]

The optimal RT target volume for patients with stage I seminoma is under investigation, and limiting treatment to the paraaortic lymph nodes is now popular. However, if pelvic irradiation is omitted, it does not eliminate the need for ongoing follow up and surveillance of the pelvic lymph nodes; patients thus managed will experience both the morbidity of RT and the ongoing inconvenience of surveillance. Thus, a modified treatment volume to include the common iliac nodes may reduce the need for ongoing surveillance of the pelvis.

The management for patients with NSGCT needs to be further refined and improvements in outcome still remain elusive particularly for patients with the highest risk of death related to disease. In stage I disease, individualized management perhaps based on prognostic factors and patient participation in the decision making should now be routine. For good and intermediate-risk metastatic disease, identification of subgroups that may be adequately treated with reduced toxicity may be a priority area for further research, which may come in the form of less chemotherapy, omission of bleomycin, or even new agents with similar efficacy and less toxicity. In advanced or poor-risk disease, clinical trials are needed to further evaluate high-dose regimens with stem cell support, identify subgroups of patients most likely to benefit from this

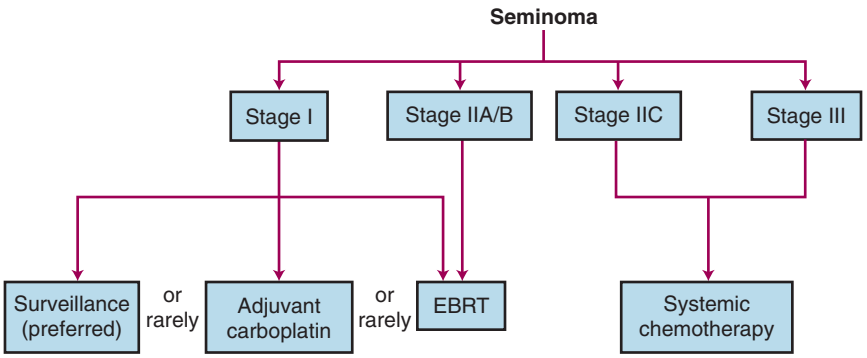


Figure 55-5 Treatment algorithm for testicular seminoma based on TNM groupings.

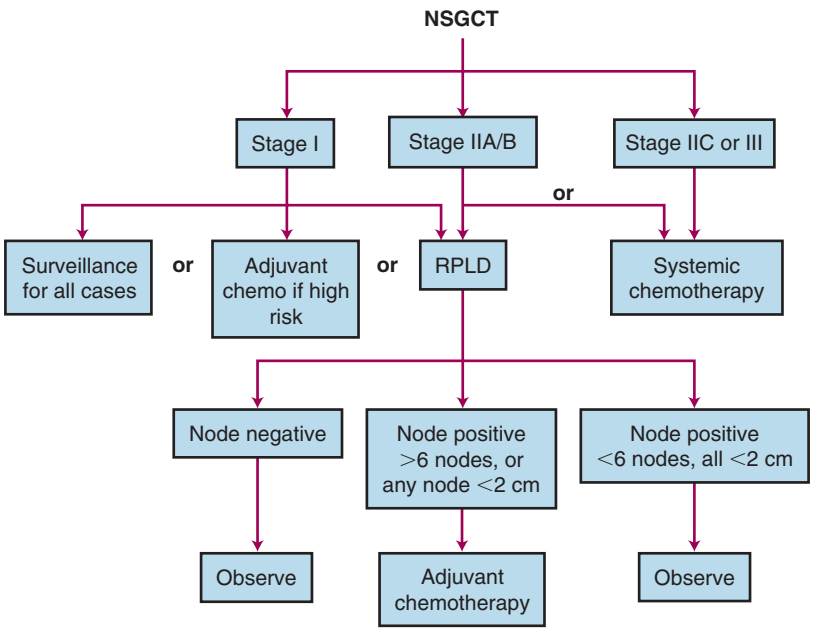


Figure 55-6 Treatment algorithm for testicular nonseminomatous germ cell tumors (NSGCTs) based on clinical TNM groupings.

aggressive approach and identify alternative regimens that reduce toxicity. Finally, new drugs with similar clinical efficacy but less toxicity would be a welcome addition in the treatment of these neoplasms.

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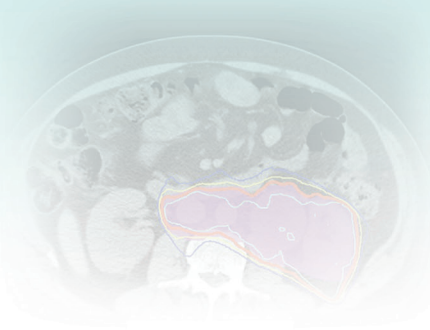
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CHAPTER

56 Kidney and Ureteral Carcinoma

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INCIDENCE

In 2015, an estimated 61,560 new cases of cancers arising from the renal pelvis and kidney proper were expected in the United States and approximately 14,080 deaths. It represents the sixth most common cancer in men and the eighth most common cancer in women. The vast majority (>90%) of these cancers of the kidney are classified as renal cell carcinoma (RCC). By comparison, the projection for ureteral and other upper urinary tract cancers is 2710 new cases and 900 deaths in 2013.

BIOLOGIC CHARACTERISTICS

Factors known to be associated with risk of relapse and death from RCC following surgery include tumor stage, nuclear and Fuhrman grade, tumor size, extension through the renal capsule, nodal involvement, renal vein involvement, histologic pattern, and presence of necrosis. Presence of a sarcomatoid component is also associated with a poor prognosis. The presence of lymphovascular invasion (LVI) is an independent predictor of RCC relapse. To date, there are no molecular markers (either tumor based or otherwise) that are routinely used in the clinic to predict outcome following surgery for localized RCC.

For upper urinary tract cancer (UUTCA) the most important prognostic factors for survival are stage and histologic grade of tumor. The presence of LVI also is predictive of worse outcome.

STAGING EVALUATION

Evaluation of a patient with RCC includes a history and physical examination, complete blood cell count, serum chemistries, urinalysis, chest radiography (CXR), and computed tomography (CT) or magnetic resonance imaging (MRI) of the abdomen and pelvis. Magnetic resonance angiography may be used in some cases for preoperative mapping of vasculature.

Evaluation of patients with renal pelvis and ureteral cancers includes a history and physical examination, complete blood cell count, blood chemistries, urinalysis, urine cytology, CXR, and CT of the abdomen and pelvis. Selective urine cytology of the upper urinary tract (UUT) is more sensitive than routine urine cytology. CT or MR urography is performed to evaluate the UUT bilaterally. Cystoscopy and ureteroscopy are performed to obtain tissue diagnosis and rule out synchronous lesions in the remainder of the urothelial tract.

PRIMARY THERAPY

Surgical resection (partial or radical nephrectomy) is the primary treatment of RCC. The 5-year survival is about 90% for those patients whose tumor is confined to the kidney, about 60% if it has extended to nearby tissues, and about 9% if it has spread to distant sites.

Nephroureterectomy, via either an open or minimally invasive approach, with resection of a bladder cuff at the ureterovesical junction is the standard therapy for resectable UUTCA. When preoperative evaluation or clinical suspicion is high for nodal involvement, lymphadenectomy is also recommended. Five-year survival is 80% or more for minimally invasive disease not having invaded through the wall of the collecting system (T1 and T2 lesions), 30% to 50% for deeply invasive disease without nodal involvement, and 10% to 15% for cases involving lymph nodes or distant metastases. Conservative nephron-sparing surgery is an option for selected patients with distal ureteral tumors and marginal renal function. Endoscopic resection is an option for low-grade and low-stage tumors in patients with marginal renal function.

ADJUVANT THERAPY

Adjuvant therapy for RCC is indicated in selected patients on the basis of failure patterns and survival results with surgery alone. Patients who undergo a gross total resection of tumor have a low risk of local failure and a moderate risk of distant metastases. There is no proven role for routine use of adjuvant radiation, chemotherapy, immunotherapy, or molecularly targeted therapy as part of the primary management for patients with localized RCC. Postoperative radiation therapy can be considered in patients with positive margins or positive lymph nodes.

Patients with UUTCA that are high grade or locally advanced, or with lymph node involvement, are at significant risk for developing both distant and locoregional relapses. Adjuvant radiation decreases local failure rates and may be combined with concomitant chemotherapy. Some studies suggest that adjuvant chemotherapy may benefit patients with high-risk disease.

LOCALLY ADVANCED DISEASE

For RCC, a combined treatment approach consisting of preoperative external beam radiation external beam irradiation (EBRT) and cytoreductive surgical resection with or without intraoperative irradiation has the greatest potential for local control of disease.

For UUTCA, irradiation with or without chemotherapy may occasionally achieve long-term disease control in patients with gross residual or locally recurrent disease after surgery. For patients with unresectable disease, combined EBRT and chemotherapy or EBRT alone may achieve downstaging of disease to allow surgical resection.

PALLIATION

Nephrectomy may alleviate local symptoms of RCC or enhance the effects of systemic therapy. Radiation therapy is effective in palliating painful bone metastases and in alleviating symptoms from brain metastases. Several molecularly targeted and immunotherapeutic drugs have been approved for metastatic RCC.

For metastatic UUTCA, cisplatin-based chemotherapy regimens can achieve a response rate of 50% to 70% and should be considered in patients with good performance status. Radiation therapy provides palliation of local symptoms such as pain or hematuria and improves the quality of life in some patients.

RCC, historically referred to as hypernephroma or Grawitz's tumor, was first reported by Konig in 1826. In 1894, Birch-Hirschfel used the term *hypernephroid* to describe these tumors.

In addition to the classic triad of symptoms (hematuria, abdominal pain, and a flank mass), RCC often presents with numerous other clinical manifestations. Complete surgical resection is the primary treatment of localized tumors. Nephron-sparing surgery is now commonly performed in lieu of radical nephrectomy for patients with small to medium-size tumors. RCC appears to be more resistant to radiation therapy and chemotherapy than most epithelial tumors. Immunomodulation and molecularly targeted treatment have a role in the systemic treatment of patients with metastatic disease.

Primary cancers of the renal pelvis and ureter are uncommon. About 5% of urothelial carcinomas occur in the kidneys and ureters.[1] Radical nephroureterectomy (RNU), with removal of the bladder cuff, is the main means of treatment. In recent years, laparoscopic and robot-assisted surgeries have become available as alternatives to an open approach. The use of more conservative surgery should be limited to well-selected patients who have low-grade and low-stage disease, small unifocal lesions, solitary kidney, or significant medical comorbidity. Patients with high-grade tumors or advanced-stage disease are at significant risk of local as well as distant relapse. Adjuvant chemotherapy or radiation therapy may improve the treatment outcome in patients with locally advanced disease.

ETIOLOGY AND EPIDEMIOLOGY

Kidney

Epidemiology

In the United States, kidney and renal pelvis cancer comprises approximately 4% of new cancer cases and 3% of cancer deaths each year.[2] In 2015, an estimated 61,560 new cases of kidney and renal pelvis cancer diagnosed in the United States and approximately 14,080 deaths. More than 90% of kidney cancers are classified as RCC, and of these the vast majority (>80%) are clear cell RCC.[3]

RCC is most commonly diagnosed in the seventh decade of life, with a median age at diagnosis of 65 years; however, it has been observed in children as young as 6 months old. According to data from the Surveillance, Epidemiology and End Results (SEER) program, the overall incidence of RCC in the United States has increased at a rate of 2% to 3% per year since the early 1970s.[4,5] The greatest increase in RCC incidence has been among localized tumors, many of which are detected incidentally during abdominal imaging performed for unrelated reasons.[4] However, early detection of subclinical tumors cannot fully explain the rising incidence of RCC.

There is a strong gender preponderance, with incidence rates in men approximately twice that of women.[2] The incidence of RCC also varies among racial and ethnic groups. The highest rates occur in whites and African Americans, whereas the lowest rates are reported for Asian Americans. Between 1999 and 2008, incidence rates among African Americans males increased by 3.1% compared with only 2.3% in white males and 2.0% in Hispanic and Latino males. Globally, the incidence rate of RCC is the highest in North America and Scandinavia and the lowest in Asia and South America.[6]

Etiology

Cigarette smoking and obesity are two well-established risk factors for RCC. Large meta-analyses of studies suggest that each of these exposures increases the risk of RCC roughly twofold.[7-9] Hypertension has emerged as a third consistent risk factor for RCC, with several studies suggesting an 80% increase in risk of RCC for individuals with a history of hypertension.[10,11] These three factors (smoking, obesity, and hypertension) may account for approximately 50% of all RCCs diagnosed in the United States.[12]

A number of studies, including a pooled analysis of several large population-based cohort studies support an inverse association between alcohol consumption and risk of RCC.[13-15] Some data also support an inverse association with physical activity, as well as a positive association with a history of urinary tract infections.[16-20]

There are few consistent associations of RCC and dietary factors.[21-23] Consumption of vegetables may be associated with reduced risk, whereas red meat consumption may slightly increase the risk of RCC. However, a recent meta-analysis did not support an independent association of red meat consumption and RCC.[24] Finally, occupational exposures to asbestos, gasoline, lead, and cadmium; use of Thorotrast; and treatment with phenacetin, as well as a history of end-stage renal disease or acquired cystic kidney disease, have been associated with increased risk of RCC.[25-30]

A positive family history increases the risk of RCC as much as twofold.[31] Although genes that are associated with inherited forms of RCC have been identified (e.g., VHL, Met1), it is less clear whether individuals carrying single nucleotide polymorphisms in specific genes may be at increased risk of sporadic (i.e., non-familial) RCC.[32-38]

Renal Pelvis and Ureter

Epidemiology

Although urothelial carcinoma is a common malignancy, most of the cases occur in the urinary bladder. Only about 5% of all urothelial neoplasms occur in the UUT.[1] The age-adjusted annual incidence of renal pelvic and ureteral cancers is 0.73 per 100,000 person-years.[39] There is a strong male predominance, with a male-to-female ratio of 3:1. The peak age at diagnosis is in the sixth and seventh decades of life. The incidence of UUTCA has been increasing.[39,40] Disease-specific annual mortality is greater in black than in white individuals and in women than in men. Primary tumors of the ureter occur only half as frequently as those of the renal pelvis. Patients with UUTCA have a 36% to 50% risk of developing a second bladder cancer.[41,42] The risk of developing UUTCA after treatment of bladder cancer is 0.75% to 6.4%.[43] The median time to the development of secondary UUTCA after bladder cancer diagnosis is 48 months.[44] Contralateral metachronous UUTCA is relatively uncommon, occurring in 3% to 6% of patients.[45,46]

Etiology

Risk factors and environmental agents that cause bladder cancer are considered to play similar roles in the development of UUTCA.[39,40,45,47] However, more recent data suggest that there are genetic and environmental factors that are specific for the promotion of UUTCA and not bladder cancer.

Cigarette smokers have a 2.6- to 7.2-fold increased risk of UUTCA.[48-50] The relative risk of developing UUTCA is 4.8 for smoking more than 40 cigarettes daily. Occupational exposure to organic chemicals is associated with a higher risk of UUTCA for workers in the chemical, petrochemical, or plastic industries.[48] Chronic use of phenacetin as an analgesic causes papillary necrosis, which promotes carcinogenesis and increases the risk of UUTCA.[50-52]

Balkan endemic nephropathy (BEN) in some Balkan countries is associated with a 57- to 100-fold increase in risk of UUTCA.[53,54] The disease is characterized by an interstitial nephritis. These patients often present with higher-grade disease and more solid growth pattern compared with those from nonendemic regions.[55] Recent studies demonstrate that consumption of bread made from grain contaminated by aristolochic acid (AA) is a significant risk factor for BEN and the

development of UUTCA. DNA adducts derived from AA are present in patients with BEN and are also detected in their UUTCA, These tumors have a distinct p53 mutation spectrum involving A:T→T:A transversion.[56-58] The incidence of UUTCA in Taiwan is among the highest in the world and is associated with the widespread use of Aristolochia herbal remedies.[59] These patients develop a nephropathy characterized by progressive renal fibrosis and increased risk of urothelial cancer.[60,61] The p53 mutation in UUTCA of these patients is dominated by A:T→T:A transversion, identical to that seen in UUTCA associated with BEN.[59]

Patients with a history of kidney or ureteral stones have a 2.5-fold increase in risk of renal and ureteral cancers, suggesting that chronic irritation and infection may play a role.[62]

There are reports of kindred with familial UUTCA.[63-65] UUTCA ranks as the third-most common malignancy (5%) in patients with hereditary nonpolyposis colorectal cancer (HPNCC) syndrome (Lynch syndrome), after colon (63%) and endometrial cancers (9%).[66] The risk is 22-fold compared with the general population and the median age of onset is 56 years, which is 10 years to 15 years earlier than usual.[67] There is an inherited mutation in mismatched pair genes, resulting in microsatellite instability and DNA replication fidelity.[68]

PREVENTION AND EARLY DETECTION

Kidney

Cessation of cigarette smoking is the most effective method of preventing RCC. A large case-control study in Iowa reported that the risk of RCC development decreases steadily from the time of smoking cessation.[69] After 15 years of cessation the risk of developing RCC returns to that of nonsmokers. It is unclear whether reduction in weight would decrease the risk for RCC. Some data suggest that daily moderate alcohol consumption and physical activity reduce the risk of RCC; however, more investigations are needed to confirm their benefits.[14,17]

Early diagnosis of RCC is challenging. Twenty-five percent to 40% of patients are asymptomatic at the time of diagnosis.[70] The increased use of imaging modalities including CT, MRI, and ultrasonography for other medical conditions often detect RCC at earlier stages as an incidental finding.[71] Over the past 3 decades, less than 10% of patients present with the classic triad of flank pain, hematuria, and a palpable mass at diagnosis.

Renal Pelvis and Ureter

The risk of UUTCA in smokers is reduced by 60% to 70% after 10 years of smoking cessation.[49] Diet with frequent intake of both green and yellow vegetables may also reduce the risk of urothelial cancers.[72] The value of urine cytology as a screening test for urothelial cancer is not defined and has not been used routinely, even in populations at increased risk of developing these diseases (e.g., occupational exposure to organic chemicals or diagnosis of BEN). For patients with a prior history of bladder cancer under surveillance after treatment, the use of pyelography in any form (i.e., computed tomography [CT], magnetic resonance imaging [MRI], intravenous pyelography [IVP]) as a routine follow-up examination remains controversial.[73]

PATHOLOGY AND PATHWAYS OF SPREAD

Kidney

Pathology

In 1997, an international consensus conference on RCC sponsored by the Union Internationale Contre le Cancer (UICC) and the American Joint Committee on Cancer (AJCC) outlined recommendations for the classification of RCC.[74] The classification system originally proposed at the Heidelberg conference in 1996 was adopted.[75] RCC is categorized as clear cell, papillary, chromophobe, or collecting duct subtypes. RCC that does not fall into one of these four groups is classified as "renal cell carcinoma, not otherwise specified." Granular cell RCC was excluded from the classification because it encompassed oncocytoma (benign kidney tumor) as well as chromophobe and clear cell RCC and was not specific to a single subtype. This classification system recognizes that RCC consists of several histologic subtypes with distinct morphologic and genetic characteristics. Previous reports have demonstrated significant differences in patient outcome based on histologic subtypes.[76-78] Patients with clear cell RCC have a worse prognosis compared with patients with papillary and chromophobe RCC. There is no statistically significant difference in outcome between patients with papillary RCC and those with chromophobe RCC.[79]

Furthermore, features predictive of a poorer prognosis, including histologic tumor necrosis and sarcomatoid differentiation, have been shown to differ by subtype.[77-80] Histologic tumor necrosis is noted in 20% to 45% of patients with RCC, whereas sarcomatoid differentiation occurs in 5% to 15% of patients.

Fuhrman et al developed a nuclear grading system based on the size and appearance of nuclei and nucleoli.[81] The Fuhrman nuclear grade is predictive of outcome in patients with RCC. A large cohort study in Germany reported that presence of LVI is an independent marker of RCC recurrence more than 5 years following nephrectomy.[82]

Algorithms have been developed to predict outcomes for patients with RCC. Using retrospective data from 1801 patients with clear cell RCC, investigators from the Mayo Clinic developed a predictive model using a SSIGN scoring system that incorporated stage, tumor size, nuclear grade, and histologic tumor necrosis.[83] Ten-year cancer-specific survival can be estimated based on a patient's SSIGN score. Kattan et al developed a nomogram to predict 5-year probability of treatment failure using presenting symptoms, histology, tumor size, and stage.[84] Zisman et al developed a clinical outcome algorithm based on 814 patients, using stage, Fuhrman grade, and Eastern Cooperative Oncology Group (ECOG) performance status.[85] This algorithm has been validated by two international multicenter studies.[86,87] Similar algorithms have also been developed and validated for predicting time to death for patients with metastatic RCC.[88,89] Overall, these robust prognostic tools based on multivariate models have become widely accepted in the clinic given the high degree of accuracy for forecasting RCC patient outcome.

Pathways of Spread

RCC may spread by local extension through the renal capsule into the perinephric fat or the adrenal gland, or by direct extension through the renal vein to the inferior vena cava (occasionally reaching the right atrium). Regional lymphatic drainage includes renal hilar, paracaval, aortic, and retroperitoneal lymph nodes. RCC may also spread by blood-borne metastases to the lung, soft tissue, bone, and brain, or by retrograde venous drainage to the ovary or testis.[90]

Renal Pelvis and Ureter

Pathology

Transitional cell carcinoma (TCC) accounts for the majority of renal pelvis and ureter neoplasms.[91] High-grade UUTCA of the renal pelvis may present with a broad spectrum of morphologic variants, including micropapillary, clear cell,

sarcomatoid, lymphoepithelial, and plasmacytoid features.[92] Nonurothelial histology is uncommon in UUTCA. Squamous cell carcinoma (SCC) accounts for about 4% of all cases.[93] Although patients with SCC tend to present with more advanced-stage diseases and worse prognosis, stage for stage, there is no significant difference in prognosis between TCC and SCC. Other rare cell types include adenocarcinoma, neuroendocrine carcinoma, and sarcoma.

Both stage and tumor grade are important prognostic factors for survival.[94-99] Lymph node metastasis and lymphovascular space invasion are associated with stage and grade and predict for worse outcome.[100,101]

Gross tumor architecture (sessile versus papillary growth pattern) is an independent predictor of tumor relapse and cancer-specific mortality.[102] Sessile growth pattern is associated with higher tumor grade, more advanced stage, and nodal metastasis. A history of prior bladder cancer has also been associated with worse disease-specific survival (DSS).[103]

Pathway of Spread

Involvement of multiple areas of the urothelial epithelium by TCC, either synchronously or metachronously, is common in patients with renal pelvis and ureteral cancers. As the tumor progresses, it invades the surrounding tissues with direct extension through the ureteral wall into periureteral tissues or to adjacent renal parenchyma as well as extrarenal tissues. Lymph node metastasis is the most common site of metastasis in UUTCA. In a multiinstitutional series of 1363 patients, lymph node metastasis was shown to increase with advancing pathologic stage: less than 1% for T0/Ta/Tis, 2% for T1, 8% for T2, 17% for T3, and 46% for T4.[104] High-grade tumors were more likely to have nodal involvement (15% for high grade, 2% for low grade).

Kondo et al outline the distribution of nodal metastatic sites.[105] For tumors of the right renal pelvis, the primary metastatic sites are the right renal hilar, paracaval, and retrocaval nodes. Tumors of the upper two thirds of the right ureter primarily metastasize to the retrocaval and interaortocaval nodes. Tumors of the left renal pelvis metastasize to the left renal hilar and paraaortic nodes. Tumors of the upper two thirds of the left ureter primarily metastasize to the paraaortic nodes. Tumors of the lower ureter primarily metastasize inferiorly to the aortic bifurcation. The finding of lymph vessel invasion in the tumor is predictive of regional lymph node metastasis.[106] Nodal metastasis is a predictor for distant metastasis and is associated with worse survival.[101,104]

Patients with high-grade or advanced-stage disease are at significant risk of developing distant metastasis.[94,107] Common sites of distant failure include lung, liver, and bone.[97]

BIOLOGIC CHARACTERISTICS AND MOLECULAR BIOLOGY

Kidney

RCC occurs in both familial as well as sporadic forms. There are several hereditary syndromes associated with the development of RCC, including the von Hippel-Lindau syndrome, tuberous sclerosis, hereditary papillary renal carcinoma, Birt-Hogg-Dubé (BHD) syndrome, and hereditary renal carcinoma.[108] The von Hippel-Lindau syndrome, an autosomal dominant disorder affecting 1 in 40,000 individuals, is caused by a mutation of the *VHL* tumor suppressor gene located on chromosome 3p. Silencing of the *VHL* gene by either somatic mutation or hypermethylation is believed to play a role in 50% to 60% of sporadic cases of clear cell RCC.[109] Tuberous sclerosis is an autosomal dominant disorder affecting 1 in 10,000 individuals and results from mutations of either the *TSC1* gene on chromosome 9q or the *TSC2* gene on chromosome 6p.[110] Hereditary papillary renal carcinoma is also an autosomal dominant disorder in which patients develop bilateral, multifocal lesions with associated germline mutations of the *MET* proto-oncogene located on chromosome 7q.[111] BHD syndrome is a dominantly inherited predisposition to benign fibrofolliculomas and other skin and soft-tissue tumors, including RCC. The gene for BHD syndrome has been mapped to chromosome 17p12-q11.2.[112]

There are currently no molecular markers (either tumor based or otherwise) that are routinely used to predict outcome following surgery for localized RCC. Historically, the focus in this field has been on analyzing single candidate biomarkers within RCC tumor tissue for their association with risk of death from RCC following nephrectomy. From these studies, candidate biomarkers such as B7H1, survivin, ki-67, CAIX, IMP, BAP1, PBRM1, SETD2, and IMP3 have emerged as examples of molecular alterations that are independently associated with RCC aggressiveness and risk of cancer-specific death.[113-121] Unfortunately, the associations reported in these studies are not sensitive or specific enough for them to be used routinely in guiding the postoperative surveillance of patients with RCC for recurrence. Some investigators have combined individual biomarkers into multimarker panels that provide more robust forecasting for patients with RCC; however, the accuracy of these panels is still not at the level to warrant routine clinical use.[122,123] More recently, investigators have harnessed next-generation sequencing technology to broaden the scope of our understanding of the genomic landscape of kidney cancer, primarily RCC.[124,125] These genome wide studies will hopefully provide the benchmark for the next iteration of biomarker discovery in RCC and enhance the future development of prognostic tools for the postoperative management of patients with RCC.

Renal Pelvis and Ureter

The karyotypic profile of UUTCA has been shown to be similar to that of bladder cancers.[126] Loss of the entire chromosome or partial loss of the short arm of chromosome 9 is a common finding, suggesting that it may be an early important event in tumorigenesis. Gains of DNA sequences are frequently observed in chromosome regions 1q21, 2p23, and 8q21.[127] Overexpression of *TP53,* cyclin A, and cyclin E is seen in 24% to 30% of UUTCA and is associated with advanced stage and grade, as well as worse prognosis.[128-130] E-cadherin is a transmembranous cell-cell adhesion receptor responsible for the maintenance of tissue architecture. Loss of E-cadherin expression promotes invasion and metastases, and is associated with an increased risk of recurrence.[131] In a study using immunohistochemical staining of tumor tissues, expression of p21, p27, p53, cyclin E, and ki-67 were altered in 19%, 49%, 45%, 11% and 89% of the specimens, respectively.[132] There was a significant association between the number of altered markers and clinicopathologic findings that predicted worse outcome (e.g., nonorgan-confined disease, sessile architecture). Patients with two or fewer marker alterations had much better survival.

The expression of survivin, an inhibitor of apoptosis, and the apoptotic index are associated with shorter disease-specific survival. Ki-67 is a protein that is involved in cell proliferation. It is overexpressed in 24% of cases and is an independent predictor of progression and cancer-specific survival.[133] Nuclear factor-kB, a transcription factor involved in antiapoptosis, invasion, and angiogenesis, plays a role in the carcinogenesis of UUTCA and is a predictor of disease-specific survival.[134] In UUTCA associated with HNPCC, as well as 25% of sporadic UUTCA, mismatch pair gene mutations and microsatellite instability are present.[68]

CLINICAL MANIFESTATIONS, PATIENT EVALUATION, AND STAGING

Kidney

Clinical Manifestations

RCC may present as an incidental finding on imaging studies. It may also present with multiple signs and symptoms if there is local extension or metastatic disease. Because of these multiple symptoms, RCC has been called the "internist's tumor." Symptoms resulting from local tumor extension include hematuria, abdominal pain, and a flank mass. However, this "classic triad" of symptoms occurs in only about 10% of cases.[90] Symptoms caused by metastatic disease include fever, weight loss, and night sweats. Two percent of male patients present with a varicocele, usually left sided, as a result of impaired drainage of the testicular vein.[135]

Paraneoplastic syndromes occur in about 30% of patients with RCC. Symptoms include hypertension, hypercalcemia, pyrexia, and hepatic dysfunction.[136,137]

Patient Evaluation

The widespread use of CT, MRI, and ultrasonography to evaluate the upper abdomen has significantly increased the detection of asymptomatic renal masses, accounting for 25% to 40% of diagnoses of RCC.[138,139] These tumors are usually smaller, and therefore, are more likely to be surgically resectable.[140,141]

The diagnosis of RCC is usually based on clinical and radiologic findings and pathologically confirmed at the time of nephrectomy. The staging evaluation includes a history and physical examination, complete blood cell count, serum chemistries, lactate dehydrogenase level, urinalysis, CXR or chest CT, and CT or MRI of the abdomen and pelvis (Box 56-1). If clinically indicated, bone scan and brain MRI may be considered. CT can predict tumor extent preoperatively in 90% of cases.[142] MRI is superior to CT in determining inferior vena cava tumor extent.[143] MR angiography can be used to evaluate vasculature preoperatively, especially when nephron-sparing surgery is being considered for patients with bilateral cancers.

Staging

Two staging systems are used to define disease extent in RCC. Historically, Robson's modification of the Flocks and Kadesky system was used.[144] More recently, the AJCC Staging and End Results Reporting Classification has been used (Table 56-1).[145] This system appears to be superior to the Robson system because it delineates more clearly local tumor extent and quantifies lymph node involvement.[71]

BOX 56-1 Diagnostic Evaluation/Algorithm for Kidney Carcinoma

Complete history and physical examination
Laboratory tests
- Complete blood cell count
- Serum chemistries
- Lactate dehydrogenase
- Urinalysis

Radiologic studies
- Chest radiography or chest computed tomography
- Computed tomography of the abdomen and pelvis or magnetic resonance imaging with intravenous gadolinium of the abdomen
- Bone scintigraphy, if clinically indicated
- Brain magnetic resonance imaging, if clinically indicated

Selected additional studies
- Ultrasonography
- Magnetic resonance angiography

Renal Pelvis and Ureter

Clinical Manifestations

The most common presenting symptom is gross or microscopic hematuria (75% to 80%). Flank pain is present in 27% to 35%.[95,146] Urinary symptoms such as frequency and dysuria are reported in 25% to 50% of patients. A palpable mass may be found in up to 10% of patients and is usually a hydronephrotic kidney. Constitutional symptoms such as malaise and weight loss are frequently seen in patients with extensive disease or metastases.

Patient Evaluation

Patients are evaluated with urine cytology, CT urography (CTU), and ureteroscopy. Radiologic findings of UUTCA include a radiolucent filling defect or obstructive hydronephrosis. The sensitivity and specificity of CTU in detecting lesions of 5 mm to 10 mm is 96% and 99%, respectively, but the sensitivity decreases to 40% for lesions <3 mm.[147] Gadolinium-enhanced MR urography has a sensitivity, specificity and accuracy of 74%, 97%, and 94%, respectively, in the detection of UUTCA.[148] Cytology of voided urine detects 35% to 59% of UUTCA and is more useful in higher-grade cancers.[95] Urine specimens obtained by ureteral catheterization, or by washings of the upper tract, improve the positive yield of the study. Upper tract urine cytology is positive in up to 70% of patients.[149] Fluorescence in situ hybridization (FISH) assay to detect specific abnormalities in chromosomes 3, 7, 17, and specific 9p21 deletions has been used as an adjunct to urine cytology.[150] FISH has a lower sensitivity for detecting low-grade than high-grade disease. Ureteroscopy or percutaneous nephroscopy is performed if exfoliative cytology or radiologic studies show suspicious findings. Ureteroscopic biopsy provides the tissue diagnosis in up to 89% of cases.[151]

Additional studies include complete blood cell count and chemistries. CXR or chest CT is performed routinely. Although CT of the abdomen and pelvis is useful to assess the local extent of disease and intraabdominal metastasis, it is not a sensitive or specific test for nodal staging.[152] If there is any concern about the function of the contralateral kidney, a renal scan should be performed before nephroureterectomy.

Staging

The current TNM staging system is listed in Table 56-1. Tumor grade and nodal status are strongly associated with disease stage, and they are important prognostic factors for survival. Table 56-2 illustrates the impact of stage, grade, and nodal status on long-term outcome.[99,104,133,153-155]

PRIMARY THERAPY

Kidney

Surgery

The only possible curative treatment for RCC is complete surgical resection. A radical nephrectomy typically includes removal of the ipsilateral kidney with perinephric tissues including Gerota's fascia and the ipsilateral adrenal gland. Survival results for treatment with standard open radical nephrectomy are delineated in Table 56-3.[144,156-161] In a report of 643 patients, the 5-year disease-specific survival (DSS) was 91% for those with stage I disease, 74% for stage II disease, 67% for stage III disease, and 32% for stage IV disease based on the 1997 TMN staging criteria.[161] In a Mayo Clinic series of 1547 patients, the 10-year cause-specific survival (CSS) was

TABLE 56-1 American Joint Committee on Cancer Staging Classification System for Kidney and Ureteral Carcinoma, 7th Edition (2010)

PRIMARY TUMOR (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Kidney	
T1	Tumor 7 cm or less in greatest dimension, limited to the kidney
T1a	Tumor 4 cm or less in greatest dimension, limited to the kidney
T1b	Tumor more than 4 cm but not more than 7 cm in greatest dimension, limited to the kidney
T2	Tumor more than 7 cm in greatest dimension, limited to the kidney
T2a	Tumor more than 7 cm but less than or equal to 10 cm in greatest dimension, limited to the kidney
T2b	Tumor more than 10 cm, limited to the kidney
T3	Tumor extends into major veins or perinephric tissues but not into the ipsilateral adrenal gland and not beyond Gerota's fascia
T3a	Tumor grossly extends into the renal vein or its segmental (muscle containing) branches, or tumor invades perirenal and/or renal sinus fat but not beyond Gerota's fascia
T3b	Tumor grossly extends into the vena cava below the diaphragm
T3c	Tumor grossly extends into the vena cava above the diaphragm or invades the wall of the vena cava
T4	Tumor invades beyond Gerota's fascia (including contiguous extension into the ipsilateral adrenal gland)
Ureteral/Renal Pelvis	
Ta	Papillary noninvasive carcinoma
Tis	Carcinoma in situ
T1	Tumor invades subepithelial connective tissue
T2	Tumor invades muscularis
T3	(Renal pelvis only) Tumor invades beyond muscularis into peripelvic fat or renal parenchyma
T3	(Ureter only) Tumor invades beyond muscularis into periureteric fat
T4	Tumor invades adjacent organs or through kidney into perinephric fat

REGIONAL LYMPH NODE (N)*	
Kidney	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in regional lymph node(s)
Ureteral/Renal Pelvis	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single regional lymph node, 2 cm or less in greatest dimension
N2	Metastasis in a single lymph node, more than 2 cm but not more than 5 cm in greatest dimension; or multiple lymph nodes, none more than 5 cm in greatest dimension
N3	Metastasis in a lymph node more than 5 cm in greatest dimension
DISTANT METASTASIS (M)	
MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis
STAGE GROUPINGS	
Kidney	
I	T1N0M0
II	T2N0M0
III	T1-2N1M0 T3N0-1M0
IV	T4, Any N0, M0 Any T, any N, M1
Renal Pelvis and Ureteral Carcinoma	
0a	TaN0M0
0is	TisN0M0
I	T1N0M0
II	T2N0M0
III	T3N0M0
IV	T4N0M0 Any T, N1-3, M0 Any T, any N, M1

From Edge S, Byrd D, Compton C: AJCC cancer staging manual. New York, 2010, Springer-Verlag.
**Laterality does not affect the N classification.*

TABLE 56-2 Renal Pelvic and Ureteral Carcinoma: Five-Year Cause-Specific Survival (CSS) Rates Categorized by T-Category, Grade and Nodal Status

		CSS by T Category (%)				CSS by Grade (%)			CSS by Nodal Status (%)	
Study	**No.**	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**N–**	**N+**
Novara[99]	269	92	78	56	0	100	91	63	82	12
Margulis[104]	1363	91	75	54	12	89 (low grade)		63 (high grade)	77	35
Li[153]	145	95	82	47	0	68 (low grade)		36 (high grade)	—	—
Bolenz[154]	136	95	70	54	14	94 (low grade)		63 (high grade)	—	—
Yates[133]	667	86	69	49 (T3/4)		93	91	61	80	37
Berger[155]	100	85	81	61	0	85 (low grade)		71 (high grade)	—	—

TABLE 56-3 Survival Rates after Radical Nephrectomy for Renal Cell Carcinoma

Study	Year	No. Patients	Length of Survival (year)	Survival by Stage (%)			
				I	II	III	IV
Robson et al[144]	1969	88	5	66	64	42	11
			10	60	67	38	0
Skinner et al[156]	1971	309	5	65	47	51	8
			10	56	20	37	7
McNichols et al[157]	1981	506	5	67	51	34	14
			10	56	28	20	3
Selli et al[158]	1983	115	5	93	63	80	13
Golimbu et al[159]	1986	326	5	88	67	40	2
			10	66	35	15	—
Dinney et al[160]	1992	314	5	73	68	51	20
Tsui et al[161]	2000	643	5	83	57	42	28

91% for T1, 70% for T2, 53% for T3a, 42% for T3b, and 43% for T3c tumors.[162]

Removal of the adrenal gland is not required for RCC involving the middle or lower poles. Upper pole cancers may necessitate adrenal gland removal with nephrectomy depending on the size, pathologic type, and extent of invasion of the renal tumor. Preoperative CT has demonstrated 99.6% specificity and a 94.4% negative predictive value in predicting adrenal gland involvement.[163,164] In a review of 511 radical nephrectomies with adrenal gland removal, the incidence of renal cancer involvement with the adrenal gland was 5.7% and T1-2 tumors had an incidence of adrenal involvement of 0.6%.[163]

A radical nephrectomy can include resection of hilar lymph nodes and occasionally includes regional lymph node dissection. Although regional lymph node dissection (LND) provides additional prognostic information, it has not been proven to prolong survival.[71] The European Organization for Research and Treatment of Cancer (EORTC) conducted a Phase III trial evaluating the role of LND.[165] Seven hundred seventy-two patients were randomized to a radical nephrectomy with or without a complete lymphadenectomy. All patients were clinically node negative based on preoperative CT. The incidence of positive lymph nodes was 4%. After a median follow-up of 12.6 years, there were no differences in OS, progression-free survival (PFS), or complications. One criticism of this trial is that 70% of patients were T1 or T2 category, suggesting a low risk of lymph node involvement. For patients with locally advanced tumors, the benefit of LND is not clearly defined. In a study from Mayo Clinic, LND was performed as part of a radical nephrectomy in 955 patients.[166] High-grade tumor, presence of sarcomatoid features, tumor size ≥10 cm, T3 category, and histologic tissue necrosis were significant predictors of lymph node-positive disease. The presence of these high-risk factors can help to determine which patients may benefit from an extensive LND. Pantuck et al retrospectively analyzed 900 patients with RCC and concluded that a LND offered no survival advantage in patients who were clinically node-negative but was associated with improved survival and improved response to immunotherapy in patients who were node-positive.[167]

Nephron-sparing surgery or partial nephrectomy is an option for selected patients. The initial indications for this surgery were presence of bilateral tumors or a cancer involving an anatomic or functional solitary kidney. Local recurrence was low (<6%). The procedure has subsequently been performed in patients with small tumors (<4 cm), achieving a local relapse rate of ≤3%.[168] Recent data suggest larger tumors (>7 cm) can also be considered for nephron-sparing surgery.[169] Patients undergoing nephron-sparing surgery have a decreased cumulative incidence of chronic renal insufficiency compared with patients who undergo radical nephrectomy.[170,171]

Laparoscopic radical nephrectomy and laparoscopic partial nephrectomy have become a commonly used surgical option for patients with RCC. Both pure and hand-assisted laparoscopic techniques for radical nephrectomy and nephron-sparing surgery achieve oncologic outcomes comparable to the standard open approach.[172-175] Laparoscopic approaches have demonstrated advantages regarding blood loss, length of hospital stay, pain medication usage, cosmetics, and patient recovery compared with the standard open approach.[172,173]

Ablation through radiofrequency heating and cryosurgical freezing are two frequently used techniques to obliterate suspicious small renal lesions.[176] These procedures can be performed through an open, laparoscopic, or percutaneous approach.[176-178] In a review, the local relapse rate with laparoscopic approach was 0% to 15% at a follow-up of 5 years.[179] The percutaneous approach demonstrated similar recurrence rates, but follow-up was only 2 years. Major morbidity was infrequent.

In summary, radical nephrectomy continues to be the first line of therapy for localized renal carcinoma. Less invasive techniques, such as laparoscopic radical nephrectomy, are becoming more popular. Nephron-sparing surgery is increasingly performed for patients with normal contralateral kidneys and for small to medium-sized tumors.

Primary Irradiation

Primary irradiation is rarely used for RCC because of its relative radioresistance. The previous experience with improvement in local control for patients treated with stereotactic radiosurgery for renal cell brain metastases have led to growing interests in the treatment of primary RCC with stereotactic body radiotherapy (SBRT) using high-dose per fraction. Beitler et al reported on nine patients with nonmetastatic primary RCC who refused a nephrectomy.[180] The majority of patients received 40 Gy in 5 fractions over 15 days. With a median follow-up of 26.7 months, four of nine patients survived. Only one patient had a local failure, which consisted of a new primary tumor in the unirradiated portion of the kidney. All surviving patients had an initial tumor size <3.4 cm and no clinical evidence of nodal disease, renal vein, or inferior vena caval extension or penetration of Gerota's fascia. Wersall et al treated eight patients with an inoperable primary or local inoperable recurrence. The median follow-up surpassed 58 months and there was only one local failure.[181]

In a Phase II trial by Svedman et al, 30 patients with inoperable primary or metastatic RCC received SBRT to 82 lesions.[182]

TABLE 56-4 Postoperative Irradiation for Renal Cell Carcinoma

Reference	Year	Type of Study	No. Pts	Treatment	Total RT Dose (Gy) Fractions	5-year Survival
Rafla[184]	1970	R	96	N	NS	37
			94	N + RT		56
Finney[185]	1973	P	49	N	55/25	51
			51	N + RT		45
Kjaer et al[186]	1987	P	33	N	50/20	62
			32	N + RT		38
Stein et al[187]	1992	R	63	N	46/23	40
			56	N + RT		50
Kao et al[188]	1994	R	12	N	45/25	62*
			12	N + RT		75*
Ulutin el al[189]	2006	R	14	N	46-50/NS	20
			26	N + RT		70

N, *Nephrectomy;* no. pts, *number of patients;* NS, *not stated;* P, *prospective;* R, *retrospective;* RT, *radiation therapy.*
**Disease-free survival.*

The dose fractionations were 32 Gy to 40 Gy in four or five fractions of 8 Gy, 30 Gy to 40 Gy in three or four fractions of 10 Gy, and 30 Gy to 45 Gy in two or three fractions of 15 Gy. With a median follow-up time of 52 months for living patients and 22 months for deceased patients, local control was 98%. Sixteen of 28 patients experienced side effects, 96% of which were grade I or II.

In a meta-analysis of SBRT for primary RCC, 126 patients from 10 trials were included.[183] Dose and fractionation varied, with 40 Gy in five fractions being the most common. Median and mean follow up ranged from 9 to 57.5 months. The weighted local control rate was 93.1% (range 84% to 100%). Toxicity was acceptable with a weighted rate of grade 3 or higher toxicity of 3.8% (range 0% to 19%).

In summary, early results of SBRT for primary RCC suggest good local control rates in patients unable to undergo a nephrectomy. However, additional studies are needed to confirm the role of SBRT in the management of RCC.

Adjuvant Irradiation

Although the use of postoperative irradiation has been evaluated both retrospectively and prospectively, its role remains controversial (Table 56-4).[184-189] In a nonrandomized comparison of surgery with or without postoperative irradiation, Rafla found a 5-year OS advantage for 94 patients undergoing postoperative irradiation versus 96 patients treated by nephrectomy alone (56% versus 37%).[184] This data was confirmed in an expanded updated analysis.[190] The 5-year OS was 38% (40 of 105) for patients who received postoperative irradiation versus 18% (24 of 135) for those undergoing nephrectomy alone.

In a pseudo-randomized trial of 100 patients (randomization by odd versus even date of birth), Finney found that incidence of distant metastases, local recurrence, and survival were not affected by the addition of postoperative radiation therapy (RT, 55 Gy in 25 fractions in 5 weeks).[185] These results are difficult to interpret because randomization was not blinded or stratified by risk factors. In addition, the mortality of treated patients was high, partly because of liver failure from treatment of patients with right-sided tumors.

A small prospective, randomized study of postoperative RT was conducted by the Copenhagen Renal Cancer Study Group.[186] Patients were randomized to nephrectomy alone (33 patients) versus nephrectomy and postoperative RT (32 patients, 50 Gy in 20 fractions). The 5-year OS was 62% for nephrectomy alone compared with 38% for nephrectomy and postoperative RT. Forty-four percent of the patients treated with RT had significant complications involving the stomach, duodenum, or liver that contributed to the death of 19% of these patients.

The role of postoperative RT using multiple treatment fields and CT-based planning in patients at high risk for local recurrence for RCC was evaluated in several retrospective studies. Stein et al evaluated 147 patients with localized RCC who underwent a nephrectomy.[187] Fifty-six patients received postoperative RT with a median dose of 46 Gy. With a median follow-up of 19 months, there was no difference in OS. However, there were more local recurrences in nonirradiated T3 patients (37% in patients who were nonirradiated versus 11% in patients who were irradiated). In a follow-up descriptive study of patients treated with RT after a nephrectomy, Gez et al reported no benefit of postoperative RT, even for T3 patients.[191]

Kao et al described 12 patients treated with nephrectomy alone and 12 patients treated with nephrectomy and postoperative RT, with a median dose of 45 Gy.[188] After a median follow-up of 5 years, no difference in disease-free survival (DFS) was noted. However, the local failure rate was 30% for the nephrectomy patients and 0% for those who had postoperative RT. In another retrospective study, Ulutin et al found no difference in OS but a significant difference in DFS in favor of radiation therapy for 26 patients treated with postoperative RT compared with 14 patients treated with nephrectomy alone.[189]

Rabinovitch et al performed a patterns-of-failure analysis by CT on patients with localized RCC who underwent a radical or partial nephrectomy alone.[192] The risk of local failure after a gross resection was approximately 5%. Positive surgical margins and positive lymph nodes had an adverse impact on local failure, increasing the rate of local failure to 21%. The risk of distant metastasis after gross resection was 26%. Lymph node involvement and renal vein involvement were significant prognosticators of distant metastases. Approximately half of patients who experienced a local relapse also experienced distant relapse concurrently. Therefore, the risk of micrometastatic disease at the time of surgery must be weighed against the potential benefit of local irradiation.

Tunio et al performed a meta-analysis of seven trials, including 735 patients, to evaluate the effects of postoperative RT.[193] There was a significant reduction in locoregional failure with the use of adjuvant irradiation, with an odds ratio of 0.47. Patient selection for postoperative RT varied among the

studies but included the common high-risk factors of positive margins, lymph node involvement, inferior vena cava or renal vein invasion, and sarcomatoid features. No significant difference in DFS or OS was noted.

In conclusion, the role of routine postoperative irradiation in the management of RCC is not established in patients with localized disease after gross total resection. However, the risk of local failure is higher in patients with positive margins and lymph node involvement, and postoperative irradiation may be considered.

Adjuvant Chemotherapy, Immunotherapy, and Molecularly Targeted Treatment

Adjuvant therapy is given to patients with high risk of systemic disease relapse after curative surgery. Three separate clinical trials evaluating adjuvant interferon-alfa after nephrectomy failed to demonstrate a survival benefit.[194-196] The Cytokine Working Group had conducted a high-dose intravenous bolus interleukin-2 (IL-2) trial versus observation in patients after nephrectomy, and it did not show any survival benefit.[197] A different approach was studied by Jocham et al using autologous tumor cell vaccine.[198] Five hundred and fifty-eight patients with resected pT2-3b, pN0-3, M0 RCC were randomly assigned to vaccine compared with observation. At 4.5 years, PFS was 77% with the vaccine and 68% with observation; however, its effect on OS would require longer follow-up. Phase III studies are being conducted on numerous drugs that have been approved in the metastatic setting for their use in the adjuvant setting, including everolimus, sorafenib, sunitinib, and pazopanib, and the results are pending. At present, there is no indication to support the use of adjuvant systemic therapy for renal cell carcinoma following resection of the kidney for curative intent.

Renal Pelvis and Ureter

Surgery

RNU with removal of the bladder cuff is the standard treatment for patients with UUTCA. The removal of the bladder cuff is recommended because ureteral stump recurrence is seen in 11% to 55% of patients if the stump is left in place.[199,200] Significant factors associated with disease relapse and survival include tumor stage, pathologic grade, nodal metastasis, LVI.[104] Locoregional relapses occur in 9% to 15% of patients with low-grade, low-stage disease and in 30% to 50% of those with high-grade, high-stage disease. The probability of nodal metastasis increases with T category. Although there is controversy about the benefit of lymphadenectomy on the survival of patients, nodal status is a significant prognostic factor and may be used to guide the decision for adjuvant treatment.[101,201,202] Patients with T2-4 disease should have lymphadenectomy. Roscigno et al suggested that at least eight lymph nodes should be removed to achieve a 75% probability of finding ≥1 positive nodes.[203] For selected patients with distal ureteral cancers, distal ureterectomy and lymphadenectomy with reimplantation of ureter may be an option. Jeldes et al developed a nomogram that predicted 5-year CSS based on the age, pT and pN stages, and tumor grade.[204] The nomogram was 75% accurate in predicting 5-year CSS in external validation.

Minimally invasive surgery is now available as an alternative to open nephroureterectomy. The oncologic outcomes of laparoscopic nephroureterectomy (LNU) are similar to open RNU, while achieving a shorter recovery time and hospital stay, as well as fewer blood transfusions.[205-208] In a report of 115 patients, port-site metastasis occurred in one patient (0.9%).[209] In the only prospective randomized trial comparing open RNU with LNU, 80 patients were enrolled.[210] No difference in CSS and metastasis-free survival was found between the two treatment groups except in patients with pT3 and high-grade tumors, for whom open RNU achieved better CSS than LNU. The small number of patients in the study limits the validity of the conclusion. More recently, robot-assisted nephroureterectomy is performed in selected patients.[211-214] It appears to be safe and feasible in some patients, but the long-term oncologic effectiveness of this procedure needs to be confirmed.

More conservative nephron-sparing surgery would be an option for selected patients. These procedures include segmental ureterectomy, or endoscopic surgery with ureteroscopic ablation. The selection criteria usually include low-grade and low-stage disease, superficial disease, small lesion size (<1.0 cm to 1.5 cm), absence of multifocal disease, solitary kidney, bilateral disease, or major medical comorbidities. There are conflicting reports about the efficacy of these nephron-sparing surgery or partial ureterectomy.[212-214] One study reported relapse rate of 68%.[212] Proper patient selection for these procedures is necessary to minimize the risk of local recurrence. These patients would need to be followed closely so that salvage nephroureterectomy can be offered if recurrence is detected.

Primary Irradiation

Primary irradiation is rarely used as initial treatment. The few published reports using primary irradiation are mostly case reports or small series. Some patients with gross residual disease after nephroureterectomy or who have recurrent disease are treated with EBRT. In a series with 19 patients with unresectable disease, the median survival was 11 months for the 11 patients treated with RT versus 4 months for those who did not receive radiation.[199] Two patients were disease free after receiving 45 Gy and 50.4 Gy, respectively, for gross residual disease after surgery. Using doses ranging from 10 Gy to 60 Gy, Batata et al reported one of eight patients had long-term disease control by the use of RT for gross residual disease after surgery.[215]

Combined chemotherapy and radiotherapy has been used successfully as primary treatment for bladder cancer and would seem to be a reasonable treatment for patients with UUTCA who are not surgical candidates. However, there are little data for such an approach. Many patients have medical comorbidities that make them ineligible for surgery as well as poor candidates for cisplatin-based chemotherapy. Prospective studies evaluating the use of combined chemotherapy and radiation are urgently needed.

Adjuvant Irradiation

The risk of local relapse correlates with the stage of disease and tumor grade and can be up to 45% despite radical surgery. In a study by Cozad et al, the 5-year local control rate was 90% for grades 1 and 2 tumors and 41% for grades 3 and 4 tumors, respectively.[199] For stage I and II disease, the 5-year local control rate was 83%, compared with 52% for stage III disease. About half of the local relapses presented initially as isolated site of relapse. Distant metastasis occurred in 19% of patients with stages I and II disease and in 53% with stage III disease. Distant metastasis was the predominant site of initial relapse for stage III disease. The risk of lymph node metastasis also increases with disease stage and tumor grade.[104] The pattern of failure demonstrates that patients with high-stage or high-grade disease have significant risks of both distant and local relapse

Few studies have been published to evaluate the role of adjuvant irradiation in the management of UUTCA. Table 56-5 summarizes several published studies on the outcome of adjuvant irradiation for UUTCA. In a study by Cozad et al, 9 of 26 patients with T3 or T4 N0/+ disease received adjuvant

TABLE 56-5 Adjuvant Irradiation for Renal Pelvic and Ureteral Carcinoma

Study	Stage	Treatment	N	RT Dose	Local Failure	Survival
Cozad[216]	T3/4, N0/+	S S + RT	17 9	Median: 50 Gy	66% (5-yr) 12% (p = 0.07)	24% 44%
Brookland[217]	≥T3 or >grade 2	S S + RT	12 11	Median: 50 Gy	46% 11% (median follow-up: 40 mo)	16.7% 27.3%
Chen[218]	all patients (T1-4, N0/+) T3/4	S S + RT S S + RT	66 67 52 28	Median: 50 Gy	31.7% (LRF) 9.5%	52 mo (Median) 55 mo 11 mo (Median) 30 mo (p = 0.006)
Ozsahin[94]	T1-4, N0/+	S S + RT	81 45	Median: 50 Gy	62% (5-yr LRF)* 67%	33% 21% (p = 0.04)
Maulard-Durdux[107]	T2/3, N0/+	S + RT	26	45 Gy	4% (mean follow-up: 45 mo)	5 year: 49%
Czito[219]	T2-4, N0/+	S S + RT	22 9	Median: 46.9 Gy	45% (5-yr) 22%	27% 67% (p = 0.01)

Positive surgical margins in 22% of patients who had surgery only, compared with 33% of patients who had postoperative radiation.
S, *surgery;* RT, *radiation therapy;* chemo, *chemotherapy.*

irradiation to a median dose of 50 Gy.[216] Local failure occurred in 9 of 17 without and 1 of 9 with adjuvant irradiation. The benefit of adjuvant irradiation was seen only in high-grade tumors. Five-year OS was 44% with, and 24% without, adjuvant irradiation ($p = 0.23$). In a study by Brookland and Richter, adjuvant irradiation was given to 11 of 23 patients who had tumor grade 3 or 4, or pathologic stage ≥T3.[217] The median dose was 50 Gy to the ureteropelvic bed, with or without inclusion of the paraaortic nodes. For the nonirradiated group, the median survival was 26 months and the local relapse rate was 45%, compared with 35 months and 11%, respectively, for those who received adjuvant irradiation. In a study by Chen et al, 67 of 133 patients received 50 Gy of adjuvant irradiation after surgery.[218] The clinical target volume included the ipsilateral ureteropelvic bed, the bladder, and the paracaval/paraaortic lymph nodes. Although there was no difference in the median survival of the radiation and no radiation group, there was a significant improvement in OS for patients with T3 or T4 tumors with adjuvant irradiation (29.9 months versus 11.4 months).

Czito et al reported a series of 31 patients with T3/4 or N+ disease that was treated with adjuvant irradiation to a median dose of 46.9 Gy.[219] Adjuvant MVAC (methotrexate, vinblastine, doxorubicin, cisplatin) chemotherapy and concurrent cisplatin with radiation was given to 9 patients. Five-year OS, DSS, locoregional control, and metastasis-free survival rates were 39%, 52%, 67%, and 48%, respectively. Compared with irradiation alone, the use of concurrent cisplatin improved the OS (67% versus 27%) and DSS (76% versus 41%). This study suggests that the addition of concurrent cisplatin to adjuvant radiotherapy improves the survival of patients with locally advanced disease.

Other studies have questioned the benefits of adjuvant irradiation. In a series of 138 patients, 45 received postoperative RT with a median dose of 50 Gy.[94] The 5-year OS was 21% for those who received postoperative RT, compared with 33% for those who did not. The 5-year locoregional failure rate was 67% for the patients who received postoperative RT, and 62% for those who had surgery only. However, patients who received postoperative RT had significantly higher T category and tumor grade. Moreover, 33% of the patients who had postoperative RT had either microscopic or macroscopic positive surgical margins, compared with 22% of those who had surgery alone. Maulard-Durdux et al treated 26 patients with 45 Gy of adjuvant RT and concluded that local control and OS were similar to those of other surgical series.[107]

Adjuvant Chemotherapy

Urothelial cancers of the bladder are sensitive to chemotherapy. However, there are few studies evaluating the use of adjuvant chemotherapy for UUTCA. Kwak et al reported a series in which 32 patients received more than four cycles of cisplatin-based adjuvant chemotherapy, whereas 11 did not.[220] Most of these patients had T3 cancer. Disease relapses occurred in 38% of those who had adjuvant chemotherapy, compared with 64% for those who did not. The 3-year OS was 81% versus 36%, respectively. In another small series of 46 patients, most of whom had pT3N0 disease, 24 were given adjuvant MVAC chemotherapy while 22 were observed.[221] There was a significant improvement in 5-year intravesical recurrence-free survival in the chemotherapy group compared with the nonchemotherapy group (84% versus 39%). However, there was no difference in OS. In a report that included 93 patients with pT3 disease, Kawashima et al reported an improvement in 5-year CSS from 64% to 81% by the use of adjuvant chemotherapy with MVAC or gemcitabine-cisplatin (GC).[222]

In an international collaborative database that included 542 high-risk patients, among which 121 received adjuvant chemotherapy, there was no difference in median OS and DSS between the chemotherapy and nonchemotherapy group.[223] However, the percentage of patients with high-grade and high-stage disease in the chemotherapy group was significantly more than in the nonchemotherapy group. Another international retrospective collaborative database also failed to demonstrate a survival benefit of adjuvant chemotherapy.[224] In summary, the role of adjuvant chemotherapy for UUTCA remains undefined and prospective studies are needed before its routine use can be recommended.

Neoadjuvant chemotherapy has been shown to improve survival in invasive bladder cancer. It would also be expected to provide benefits for patients with UUTCA because of the similarity in pathology between these two diseases. In a

TABLE 56-6 Preoperative Irradiation for Renal Cell Carcinoma

Study	Year	Type of Study	No. Pts	Treatment	Total RT Dose (Gy) Fractions	5-year Survival
Riches et al[232]	1951	R	685	N	NS	30
			131	RT + N		49
Van der Werf-Messing et al[233]	1973	P	85	N	30/15	50
			89	RT + N		45
Juusela et al[234]	1977	P	44	N	33/15	63
			38	RT + N		47

N, *Nephrectomy;* NS, *not stated;* P, *prospective;* R, *retrospective;* RT, *radiation therapy.*

retrospective study comparing the outcomes of 43 patients with high-risk UUTCA and were given neoadjuvant chemotherapy, using mainly MVAC or GC, to 107 patients treated with surgery only, there was a significant downstaging of disease by neoadjuvant chemotherapy, with a pathologic CR in 14% of patients.[225] Youssef et al reported the result of neoadjuvant chemotherapy with MVAC or GC in 18 patients with node-positive UUTCA and compared the result to 120 patients treated with RNU alone.[226] The 5-year DFS were 49% and 30%, whereas the CSS were 44% and 36%, respectively. After neoadjuvant chemotherapy, 9 patients were pN0, 6 patients were pT0, and 5 patients were pT0N0. Available data suggest that neoadjuvant chemotherapy is likely to be beneficial to patients with node-positive or high-grade, high T category disease. Additional studies are needed to define the efficacy of neoadjuvant chemotherapy for UUTCA.

Adjuvant Topical Therapy

Intravesical therapy with Bacillus Calmette-Guerin (BCG) or other agents like mitomycin C has been studied in both noninvasive and invasive UUTCA. In a prospective randomized trial of 284 patients, a single dose of adjuvant intravesical mitomycin C resulted in an absolute reduction in risk of bladder tumor of 11% within the first year following RNU, compared to no treatment (16% versus 27%).[227] In a Phase II randomized trial by Ito et al, a single intravesical instillation of pirarubicin reduced the 2-year risk of bladder recurrence from 42% to 17%.[228] Topical treatment may have a role in the management of carcinoma-in-situ (CIS) of UUT and spare the patients from RNU. Shapiro et al reported the use of 6 weeks induction course of BCG/interferon α2B via an open-ended ureteral catheter for patients with biopsy proven isolated UUT-CIS. If there was a complete response (CR) (no visualized disease and negative cytology), patients would receive maintenance therapy for 2 years.[229] Eight of 11 patients achieved an initial CR after induction treatment. At a median follow-up of 13.5 months, the kidney preservation rate was 91%. In another study of 55 patients, antegrade perfusion with BCG resulted in recurrence-free survival of 53% after a median follow-up of 42 months.[230]

LOCALLY ADVANCED DISEASE

Kidney

RCCs rarely invade adjacent organs at presentation. Large tumors tend to displace and compress adjacent tissue. However, if tumor directly invades contiguous tissues such as the liver, duodenum, large intestine, and perinephric muscle, surgical resection may not be feasible. Preoperative irradiation can downsize the tumor and cause fibrosis, with thickening of the tumor capsule and sclerosis of small blood vessels, increasing the likelihood of an adequate surgical resection.[231] In a retrospective review, Riches et al reported survival advantages of patients treated with preoperative irradiation versus surgery alone (5-year OS: 49% versus 30%).[232]

Two prospective clinical trials evaluating the role of neoadjuvant irradiation have been conducted (Table 56-6).[233,234] Van der Werf-Messing reported a series of 126 patients from 1965 to 1972 randomized to nephrectomy alone versus low-dose preoperative RT (30 Gy in 15 fractions for 3 weeks) followed by nephrectomy.[233] Complete resection was more frequent for patients with tumors infiltrating intrarenal or extrarenal veins or lymph vessels. Survival was considerably better at 18 months with the use of preoperative irradiation. However, there was no difference in 5-year OS. Juusela et al conducted a prospective, randomized study of preoperative irradiation followed by nephrectomy (38 patients) versus nephrectomy alone (44 patients).[234] Patients treated with preoperative RT received 2.2 Gy per day to a total dose of 33 Gy and had a 47% 5-year OS, compared with 63% for patients treated with nephrectomy alone.

Intraoperative Irradiation Containing Approaches

In addition to neoadjuvant EBRT, an intraoperative irradiation supplement with electrons (IOERT) or high-dose-rate brachytherapy (HDR-IORT) may be used as an additive component of treatment in patients with locally advanced primary or recurrent disease.

IOERT has been used at the Mayo Clinic since 1983 as a component of therapy in selected patients with locally advanced genitourinary malignancies. In a recent update of the Mayo Clinic series, IOERT was used as a supplement to EBRT and resection in 25 patients with locally advanced recurrent (19 patients) or primary (3 patients) renal cell carcinoma.[235] Twenty-one patients (95%) received perioperative EBRT to a median dose of 45 Gy (range, 41.4 Gy to 55 Gy). Surgical resection was R0 in 5 patients (23%) and R1 in the remaining 17 (77%). The median IOERT dose was 12.5 Gy (range, 10 Gy to 20 Gy). With a median follow-up of 9.9 years in surviving patients, 5-year and 10-year survival was observed in 40% and 35%, respectively, and 5-year and 10-year DFS was 31%. Central relapse within the IOERT field was observed in 9%, local relapse in the EBRT field in 27%, and distant relapse in 64% of patients. Five patients (23%) experienced grade-3 or greater toxicity.

The University Gregorio Marañón in Madrid used IOERT as a component of treatment for 25 patients with locally advanced primary (15 patients) or locally recurrent (10 patients) lesions.[236] Patients received IOERT after maximal surgical resection, and 15 of the 25 received perioperative EBRT (median 44 Gy). Six patients had R0 resection and the remaining 19 had microscopic residual disease (R1). The IOERT dose ranged from 9 Gy to 15 Gy (median 14 Gy). Five-year and 10- year OS was 38% and 18%, respectively, and 5-year and 10-year DFS was 19% and 14%, respectively. Local control was achieved in 80% of patients, whereas 5-year distant metastasis

free survival was 22%. Six patients (24%) experienced grade-3 or greater toxicity.

Eble et al reported a University of Heidelberg series of 11 patients with renal cancer in whom IOERT was given as a component of treatment (primary, 3 patients; locally recurrent, 8 patients).[237] Patients had maximal resection, IOERT (15 Gy to 20 Gy), and postoperative EBRT (40 Gy in 2-Gy fractions, 5 days per week). Only 1 patient had R0 resection and the remainder had microscopic or gross residual disease. With mean follow-up of 24 months, no local relapse occurred. Distant metastases, however, occurred in 7 of 11 patients, or 64%. At 4 years, OS and DFS were 47% and 34%, respectively.

At UCSF, 10 of 14 patients who underwent resection of recurrent renal cancer received IOERT.[238] Nine patients died of progressive metastatic disease at a mean of 17 months. Five patients were alive (mean 66 months; range 14 months to 86 months) and OS was 40% at 2 years and 30% at 5 years. Local re-recurrence was observed in 2 patients.

More recently, a multiinstitutional study was published including patients treated at nine centers for locally advanced or recurrent renal cell carcinoma.[239] Of the 98 patients, 28% were treated for locally advanced disease, with a 5-year OS and DFS of 37% and 39%, respectively. In patients with locally recurrent disease, the 5-year OS was 55% and DFS was 52%. Initial nodal involvement, presence of sarcomatoid features, and higher IORT dose were associated with a decrement in OS. For patients with locally recurrent disease, the presence of a positive margin was associated with decrease in OS.

Renal Pelvis and Ureter

The prognosis for patients with locally advanced or unresectable UUTCA is poor. Long-term disease control has been reported in some patients who have gross residual or locally recurrent disease with the use of radiation therapy, with or without chemotherapy.[199,215] In a report by Cozad et al, postoperative irradiation was given to 11 of 19 patients with gross residual disease after surgery.[199] The median survival was 11 months for the irradiated group versus 4 months for those without radiation. Two patients who were treated with 45 Gy and 50.4 Gy of irradiation were disease-free at 21 months and 28 months. One of these 2 also had concurrent MVAC chemotherapy. In selected patients with locally advanced UUTCA, preoperative irradiation with or without chemotherapy may downstage the disease to allow surgical resection.

IOERT is an appealing adjunct in the management of locally advanced UUTCA. After preoperative EBRT with or without chemotherapy to downsize the tumor, patients may proceed to surgery. A boost may be given to areas of close or positive margins with IOERT while sparing the surrounding normal organs. Zhang et al treated 17 patients with locally advanced ureteral cancer with RNU and IOERT, followed by adjuvant EBRT.[240] Five patients had microscopic or grossly positive margins. The median IOERT dose was 14 Gy, and the median EBRT dose was 42 Gy. Adjuvant MVAC was given to 10 patients. The 5-year OS and local control rates were 46% and 51%, respectively. Two patients developed late grade-3 gastrointestinal toxicities. Dose escalation using IOERT appears to be an option for patients with locally advanced UUTCA.

PALLIATION AND METASTATIC DISEASE

Kidney

In patients with demonstrated widespread metastatic disease at initial diagnosis, nephrectomy is not justified if the intent is to induce a spontaneous regression; the incidence of such a regression is less than 1% and the morbidity outweighs the benefit. A palliative nephrectomy can be considered in patients suffering from repeated hemorrhages, tumor pain, or significant paraneoplastic syndromes.[71]

The role of nephrectomy has been evaluated in patients who present with solitary metastatic disease. Among 158 patients who presented to the Mayo Clinic between 1970 and 1980 with metastatic disease and no prior treatment at diagnosis, 56 patients (35%) had a solitary metastasis.[241] Nephrectomy was performed on 67.6% of patients who presented with multiple metastases and 83.9% of patients with solitary metastasis. The OS at 2 and 3 years for patients with solitary metastasis was 29.1% and 19%, compared with 6.8% and 4.3%, respectively, for patients with multiple lesions. Nephrectomy had a significant impact on survival only in patients with solitary metastasis, low-grade primary tumor, and weight loss of less than 10%.

Two clinical trials have shown that debulking nephrectomy may enhance the effect of immunotherapy. The Southwest Oncology Group (SWOG) randomized 241 patients with an ECOG performance status of 0 to 1 to initial nephrectomy followed by interferon versus interferon alone.[242] The median survival of the nephrectomy group was significantly improved by 3 months (11.1 versus 8.1 months). The EORTC also conducted a trial similar to the SWOG trial in 83 patients with metastatic RCC and an ECOG performance status of 0 to 1.[243] Patients undergoing nephrectomy experienced a 10-month median survival benefit (17 versus 7 months) and improved time to progression (5 versus 3 months). These debulking nephrectomy trials show that patients with a good performance status who subsequently receive interferon immunotherapy experience an improved survival. There are no prospective trials evaluating debulking nephrectomy followed by molecularly targeted therapy.

Motzer and associates evaluated prognostic factors for 670 patients with metastatic or recurrent RCC to develop a predictive model for survival.[244] The absence of a nephrectomy was a predictor for lower survival.

Solitary Metastases

Treatment of a solitary metastatic site has been evaluated in patients with both synchronous and metachronous solitary metastasis. Kavolius et al retrospectively evaluated 278 patients who developed recurrent or metastatic RCC after nephrectomy.[245] The 5-year OS for 141 patients treated with a curative metastasectomy for their first relapse was 44% as compared with 14% for patients who underwent noncurative surgery and 11% for patients treated nonsurgically. Factors associated with improved OS included a solitary site of first relapse, curative resection of first metastasis, and a long disease-free interval.

Leibovich et al developed a scoring algorithm to predict CSS based on 727 patients with metastatic RCC.[246] Two hundred eighty-five patients (39%) had metastatic disease at presentation and 87% of patients had a solitary metastasis. One hundred ninety-two patients (26.4%) underwent a complete resection, defined as no evidence of disease after nephrectomy and metastasectomy. Complete resection was associated with an improvement CSS on multivariate analysis. The presence of constitutional symptoms at presentation, bone metastases, liver metastases, tumor thrombus, multiple metastases, less than 2 years from nephrectomy to metastases, high nuclear grade, and coagulative tumor necrosis were associated with an increased risk of death.

Similarly, Naito et al studied 1463 patients with metastatic RCC, of whom 146 patients (20.8%) had undergone a metastasectomy.[247] The median OS in patients undergoing a

metastasectomy was 44.3 months compared with 16.4 months in patients who did not undergo a metastasectomy.

In summary, patients presenting with a synchronous or a metachronous solitary metastasis after a long disease-free interval may experience a prolonged survival compared to patients with extensive metastases and may warrant more aggressive treatment to the initial metastatic site.

Bone and Soft-Tissue Metastases

Metastases to the bone (solitary or multiple) may occur in 25% to 50% of all patients with RCC. Althausen et al evaluated 38 patients with osseous metastases secondary to RCC. Patients were treated with resection with or without allograft implantation, RT alone, or a combination of treatments.[248] The survival for the entire group was 90% at 6 months, 84% at 1 year, 55% at 5 years, and 39% at 10 years. Presentation without metastasis, long disease-free interval between nephrectomy and first metastases, appendicular skeletal location, and solitary metastasis were associated with longer survival. The authors concluded that patients who have an appendicular (preferably solitary) metastasis and who have a long duration from diagnosis of disease to metastasis should be treated with complex orthopedic surgical procedures if necessary. Postoperative irradiation should be considered in selected cases.

Palliative RT is an effective treatment for bone pain. Halperin and Harisiadis evaluated the results of 36 sites irradiated for bone pain.[249] The pain decreased in 77% of the treated sites, and the majority of the sites received a time-dose fractionation (TDF) equivalent dose ranging from 45 to 85. No relation was observed between the TDF equivalent dose and the probability of response. Twenty-four of the 28 sites (86%) were partially or completely free of pain for the remainder of the patients' lives. Wilson et al reported partial and symptomatic response rates to palliative irradiation, with pain reduction of 67% and 73%, respectively.[250] A dose response based on the biologic effective dose could not be established. In a prospective Phase II trial, Lee et al evaluated the effect of radiation therapy on symptoms in 31 patients with bone or soft-tissue RCC metastases.[251] With a median follow-up of 4.3 months, 83% of patients experienced site-specific pain relief with a median duration of response of 3 months.

Stereotactic body radiotherapy (SBRT) has been used for treatment of metastatic RCC to the spine and other extracranial sites. Zelefsky et al treated 105 metastatic lesions, primarily bone, with single fraction SBRT (59 lesions) at a median dose of 24 Gy (range 18 Gy to 24 Gy) or hypofractionated SBRT in three to five fractions to a dose of 24 Gy to 30 Gy (46 lesions).[252] The 3-year local PFS was significantly better for patients receiving 24 Gy in a single fraction (88%) compared to patients receiving lower dose single fraction treatment of <24 Gy (21%) or a hypofractionated course (17%). Gerszten et al treated 60 spinal lesions in 48 patients with a single fraction of radiation at median dose of 20 Gy.[253] Eighty-nine percent of patients experienced improvement in pain. Six patients eventually required surgical intervention because of disease progression. Nguyen et al reviewed 48 patients who underwent SBRT to 55 spinal lesions.[254] Doses included 24 Gy in one fraction, 27 Gy in three fractions, and 30 Gy in five fractions. Fifty-two percent of patients were pain free at 12 months. No grade-3 or grade-4 neurologic toxicity occurred.

Brain Metastases

Brain metastases are diagnosed in approximately 10% of patients with metastatic RCC.[255] In a retrospective study of 119 patients treated at M. D. Anderson Cancer Center, the median radiation dose was 30 Gy (range, 18 Gy to 56 Gy).[255] The median OS from the time of diagnosis of the brain metastases was 4.4 months. The cause of death was neurologic in 90 of the 119 patients (76%), suggesting poor central nervous system (CNS) control with conventional whole-brain irradiation (WBRT) alone. A retrospective comparison of WBRT dose comparing 30 Gy in 10 fractions to higher doses (40 Gy in 20 fractions or 45 Gy in 15 fractions) showed an improvement in both OS and local control with higher doses.[256] The median OS was 4 months versus 12 months and local control at 12 months was 7% versus 35%, respectively.

In view of the poor outcome of patients after WBRT, more aggressive treatments have been evaluated in selected patients with favorable prognostic features. Patients who could undergo surgical resection of brain metastases from RCC had a 12-month median survival.[257] Several retrospective studies, shown in Table 56-7, have reported local tumor control rates of 81% to 100% and median OS of 5 months to 12 months in patients treated with radiosurgery alone, or in combination with WBRT.[258-266] Although the local control rates were impressive, the follow-up interval in most series was short. For patients who have good performance status and systemic disease that is reasonably controlled, radiosurgery is an appealing option for management of brain metastasis.

Chemotherapy, Immunotherapy, and Molecularly Targeted Treatment

There is a plethora of molecularly targeted and immunotherapeutic agents for the therapy of metastatic kidney cancer, specifically clear cell RCC. These include sorafenib, sunitinib, temsirolimus, bevacizumab, interferon alpha (IFN), interleukin-2, pazopanib, and axitinib. The most common criteria used for therapy decisions are the Motzer criteria, which classify patients into different risk categories (favorable,

TABLE 56-7 Results of Stereotactic Radiosurgery for Brain Metastases from Renal Cell Carcinoma

Study	Year	No. Pts.	WBRT	Follow Up (Months)	Dose (Gy)	Local Control	Median OS (Months)
Payne et al[258]	2000	21	None	Min 3	20	100%	8
Amendola et al[259]	2000	22	50% pre	NR	18	91%	8.4
Hernandez et al[260]	2002	29	48% pre 6.8% post	7	16.8	100%	7
Powell et al[261]	2008	23	48.7%	4.9	18	93.6% (12 mo.)	5.1
Samlowski et al[262]	2008	32	38%	Min 12	NR	81%	6.7
Shuto et al[263]	2010	105	1.9%	7	22	84.3%	12
Kano et al[264]	2011	158	36%	NR	18	92%	8.2
Kim et al[265]	2012	46	6.5%	NR	20.8	84.7%	10
Lwu et al[266]	2013	41	56%	6	21	84% (12 mo.)	NR

Min, *Minimum;* mo, *months;* No. Pts, *number of patients;* NR, *not reported;* OS, *overall survival;* WBRT, *whole brain radiation therapy.*

intermediate, and poor risk.).[244] Shorter survival is associated with low Karnofsky performance status (<80%), high corrected serum calcium (>10 mg/dL), low hemoglobin (<12 g/dL), high LDH (>1.5 times the upper limit of normal), and relapse of renal cancer within a year after nephrectomy. Several therapies, including sunitinib, pazopanib, and bevacizumab/interferon, have been approved for favorable and intermediate risk clear cell RCC in the first line setting.

Sunitinib is an oral tyrosine kinase inhibitor (TKI) that inhibits signaling by vascular endothelial growth factor receptor (VEGFR), platelet-derived growth factor receptor (PDGFR), and FLT-3. A Phase III study compared sunitinib and IFN-α in 750 patients who were treatment naive.[267] The median PFS was 11 months for sunitinib and 5 months for IFN ($p < 0.001$). Median OS was 26.4 months versus 21.8 months for sunitinib and IFN, respectively ($p = 0.051$). Common side effects include hypertension, fatigue, hand-foot syndrome, diarrhea, myelosuppression, and thyroid dysfunction.

Pazopanib is an oral multikinase TKI that inhibits signaling for VEGFR, PDGFR, and c-kit. A Phase III study in treatment naïve and cytokine pretreated patients compared pazopanib with placebo.[268] This study showed an improvement in PFS of 9.2 versus 4.2 months ($p < 0.000$). The median duration of response was longer than one year and the response rate was 30% as compared to 3% in the placebo arm. This drug has similar side effect profile as sunitinib. In a Phase III study comparing the tolerability of sunitinib and pazopanib, pazopanib caused fewer side effects and resulted in better quality of life.[269]

Bevacizumab is a monoclonal antibody to VEGFR. Two Phase III studies, including the AVOREN and CALGB 90206, showed improvement of PFS with the combination of bevacizumab and IFN compared to IFN alone. In the AVOREN study, PFS was 10.2 months with bevacizumab and IFN compared to 5.4 months with IFN alone ($p = 0.0001$).[270] In the CALGB study, patients receiving the combination of bevacizumab and IFN had a PFS of 8.5 months as compared to 5.2 months with IFN alone ($p < 0.0001$). Common side effects include hypertension, proteinuria, bleeding, thromboembolism, and poor wound healing.[271]

Temsirolimus is the only drug approved for the treatment of poor risk patients in the first-line setting. Temsirolimus is an intravenous M-TOR inhibitor. A Phase III study comparing interferon alpha, IFN with temsirolimus and temsirolimus alone showed survival benefit of 3 months with single-agent temsirolimus when compared to IFN alone or the combination of drugs in patients who were poor risk based on the Motzer criteria (temsirolimus 10.9 months, IFN 7.3 months, temsirolimus + IFN 8.4 months).[272] Common side effects include myelosuppression, dyslipidemia, hyperglycemia, fatigue, diarrhea, nausea, rash, stomatitis, and pneumonitis.

Sorafenib, pazopanib, everolimus, and axitinib are approved for treatment of metastatic RCC as second-line therapy. Sorafenib is an oral kinase inhibitor that inhibits targets such as VEGFR and PDGFR. A Phase III study by Escudier et al showed a PFS of 5.6 months with sorafenib compared to 5.7 months with IFN.[273] However, patients receiving sorafenib had a better quality of life and more reduction in their tumor burden. Sorafenib was the first targeted drug to be approved for RCC after cytokine therapy tumor progression. Common side effects include hypertension, fatigue, diarrhea, and hand-foot syndrome.

Everolimus is an oral M-TOR inhibitor. It was approved in advanced RCC for use after sunitinib or sorafenib disease progression. A Phase III trial comparing everolimus and placebo showed a median PFS of 4 months with everolimus compared to 1.9 months with placebo.[274] However, OS was 10.8 months with everolimus and 14.4 months with placebo. Cross-over was allowed in the study, which could account for the similar survival. Common side effects include myelosuppression, dyslipidemia, hyperglycemia, fatigue, diarrhea, nausea, rash, stomatitis, and pneumonitis.

Axitinib is another multikinase inhibitor of VEGFR 1, 2, and 3. In a Phase III study comparing axitinib and sorafenib in the second-line setting, axitinib had a longer PFS of 6.7 months versus 4.7 months and an improved response rate of 19% compared to 9.4%.[275] Toxicities are similar to other VEGFR inhibitors.

Renal Pelvis and Ureter

For patients with metastatic disease and good performance status, cisplatin-based chemotherapy can be considered. The response rates range from 54% to 70%.[276-278] At present, no molecularly targeted treatment is available for advanced UUTCA. EBRT can be used palliatively for local symptoms such as pain from bony metastasis.

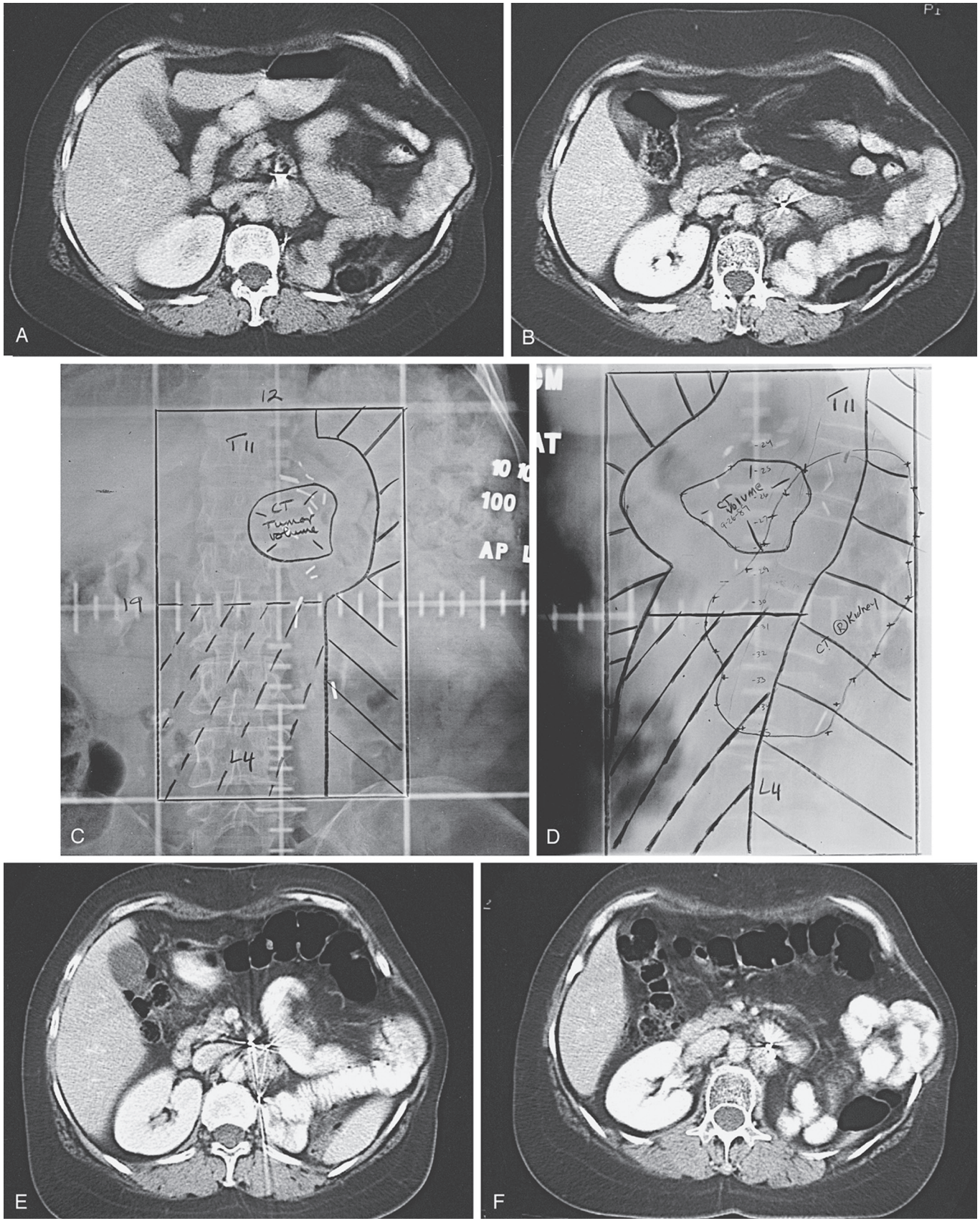
IRRADIATION TECHNIQUES AND TOLERANCE

Kidney

Postoperative radiation should be considered for patients at high risk for local recurrence after surgery. Pathologic features predictive of local recurrence include positive lymph nodes and positive surgical margins. The clinical target volume should include the tumor bed, surgical clips, regional lymph nodes (hilar and paraaortic lymph nodes), and vascular extent of tumor (Figure 56-1). If feasible, the scar should be included in the target volume because scar recurrences have been reported.[187] Total radiation doses of 45 Gy to 50.4 Gy should be delivered with 1.8-Gy to 2-Gy fractions using multiple-field techniques. In addition, small-volume fields can be used to boost areas of residual disease to a total of 55 Gy to 60 Gy. Delivery of the boost can be facilitated by surgical reconstruction to displace small intestine or stomach, placement of surgical clips at the site of residual disease, prone positioning, and false tabletop techniques. Intensity-modulated radiation therapy (IMRT) can be used to treat the target volume and minimize the dose to the normal tissues (liver, small bowel, stomach, opposite kidney, and spinal cord) (Figures 56-2 and 56-3; see also Figure 56-1).

Preoperative irradiation treatment volumes for patients with locally advanced disease should encompass the primary tumor, renal hilar lymph nodes, paraaortic lymph nodes, and vascular extent of tumor. To spare dose-limiting organs, three-dimensional conformal field (3DCRT) combinations of anterior-posterior/posterior-anterior (AP/PA), laterals, or obliques are recommended. IMRT can also be used to minimize the dose to normal tissues (see Figure 56-3). Total doses of 45 Gy to 50.4 Gy in 1.8-Gy to 2.0-Gy fractions should be given preoperatively, followed by surgery in 4 to 6 weeks. If possible, an IORT supplement should be considered if residual disease or narrow margins exist after maximal surgical resection. At the Mayo Clinic, doses of 10 Gy to 20 Gy are usually delivered with IOERT; the dose is dependent on margin status and amount of EBRT delivered preoperatively or planned postoperatively.[235]

Patients in whom a local recurrence has developed in the tumor bed or regional nodes after radical nephrectomy should be considered for aggressive salvage treatment. This treatment includes preoperative RT or chemoradiation with 3DCRT or IMRT to the recurrent tumor volume, postoperative tumor bed, and renal hilar and paraaortic lymph nodes. A traditional field is shown in eFigure 56-1 on the Expert Consult website.



eFigure 56-1 Imaging studies and irradiation fields for a patient with locally recurrent renal cell carcinoma who received preoperative external beam irradiation before resection and intraoperative electron irradiation (IOERT) at the Mayo Clinic. **A** and **B,** Pre-irradiation CT scan demonstrates bulky paraaortic adenopathy and lack of fat plane adjacent to the aorta. **C** and **D,** Irradiation fields encompass the recurrent tumor and paraaortic lymph nodes using a multifield technique of anterior-posterior/posterior-anterior (AP/PA) **(C)** plus paired laterals **(D)** to deliver 45 Gy in 25 fractions to large fields from T-11 through L-4 *(solid lines).* The right kidney was excluded from the AP/PA fields **(C)** except for the upper medial components (>75% excluded). Because approximately 50% of the right kidney was within the lateral fields **(D)**, the lateral dose contribution was limited to less than 18 Gy. Spinal cord was excluded from the lateral fields. After 45 Gy, the field was altered to block from isocenter inferiorly *(interrupted lines).* **E** and **F,** Posttreatment CT scan of abdomen 4 weeks after 50.4 Gy/28 fractions/5 weeks and 2.5 months after pretreatment scan; note shrinkage of mass with the improved fat planes relative to aorta. An IOERT dose of 12.5 Gy was given after a marginal gross total resection.
A, B, E, *and* ***F,*** *From Calvo FA, Zincke H, Gunderson LL, et al: Genitourinary IORT. In Gunderson LL, Willett CG, Harrison JB, et al, editors: Intraoperative irradiation: Techniques and results. Totowa, NJ, 1999, Humana Press, pp 421–436.*

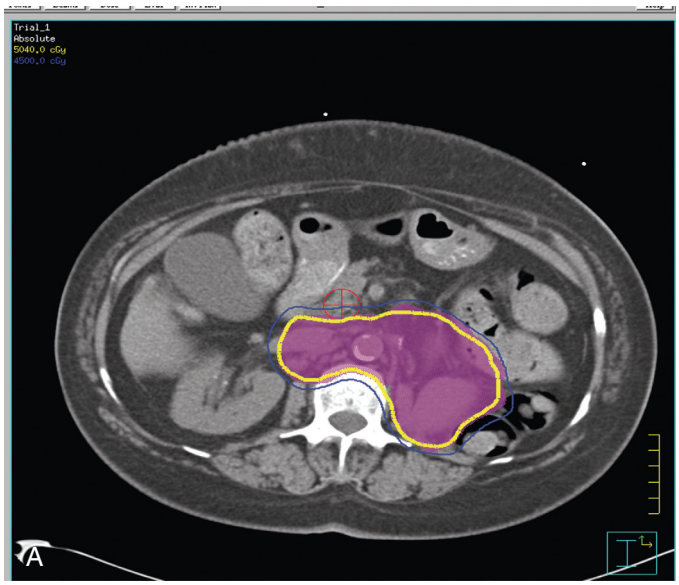


Figure 56-1 Example of a patient with T2N0M0 renal cell carcinoma with positive margins after a radical nephrectomy. **A,** Intensity-modulated radiation therapy (IMRT) was used to deliver 50.4 Gy to the postoperative bed and regional lymphatics while sparing surrounding structures, including the remaining functional kidney. **B,** Dose-volume histogram illustrating coverage of the planning target volume (PTV) and dose to normal critical structures.

Dose Compare **Plan:** Plan_0 **Rev:** R01.P01.D01 Help

Dose Volume Histogram

Norm.Volume

1.0 0.9 0.8 0.7 0.6 0.5 0.4 0.3 0.2 0.1 0.0

0 1000 2000 3000 4000 5000 6000

Dose (cGy)

DVH Calculation
- Cumulative
- Differential

Dose Axis Display
- Normalized Dose
- Absolute Dose
- Auto-Compute Max
- Specify Max Dose

Volume Axis Display
- Normalized Volume
- Absolute Volume

Tabular DVH...

ROI Statistics

Line Type	ROI	Trial	Min.	Max.	Mean	Std. Dev.	% Outside Grid	% > Max
	Bowel	Trial_1	24.4	5362.2	1482.8	1225.7	0.00 %	0.00 %
	LIVER	Trial_1	198.3	5304.9	1905.2	879.0	0.00 %	0.00 %
	PTV	Trial_1	4322.0	5437.7	5169.7	108.3	0.00 %	0.00 %
	right kidney	Trial_1	629.9	4801.7	1724.6	620.2	0.00 %	0.00 %

B

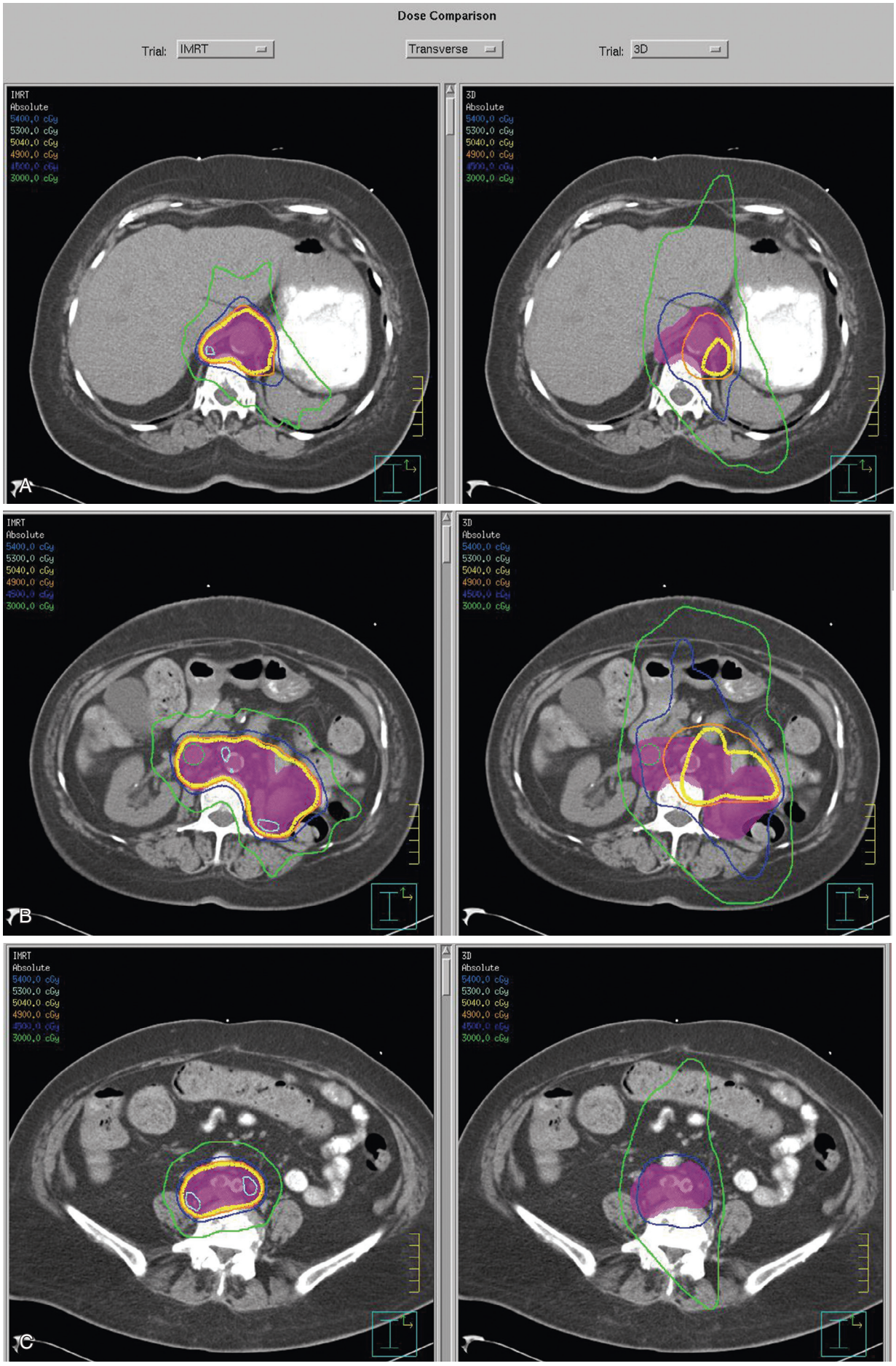


Figure 56-2 Comparison of an IMRT and three-dimensional (3D) conformal plan for a patient undergoing postoperative radiation therapy for a positive margin status after left radical nephrectomy for a T1bN0 renal cell carcinoma. **A** to **C,** Comparison of images taken from an IMRT and 3D conformal plan suggest improved sparing of normal structures, including the liver, right kidney, spinal cord, bowel, and stomach. With IMRT, a dose of 50.4 Gy was prescribed to the tumor bed and regional lymphatics. However, to respect the tolerance of normal tissues, the dose was decreased to 45 Gy with the 3D conformal plan to achieve appropriate sparing of normal structures.

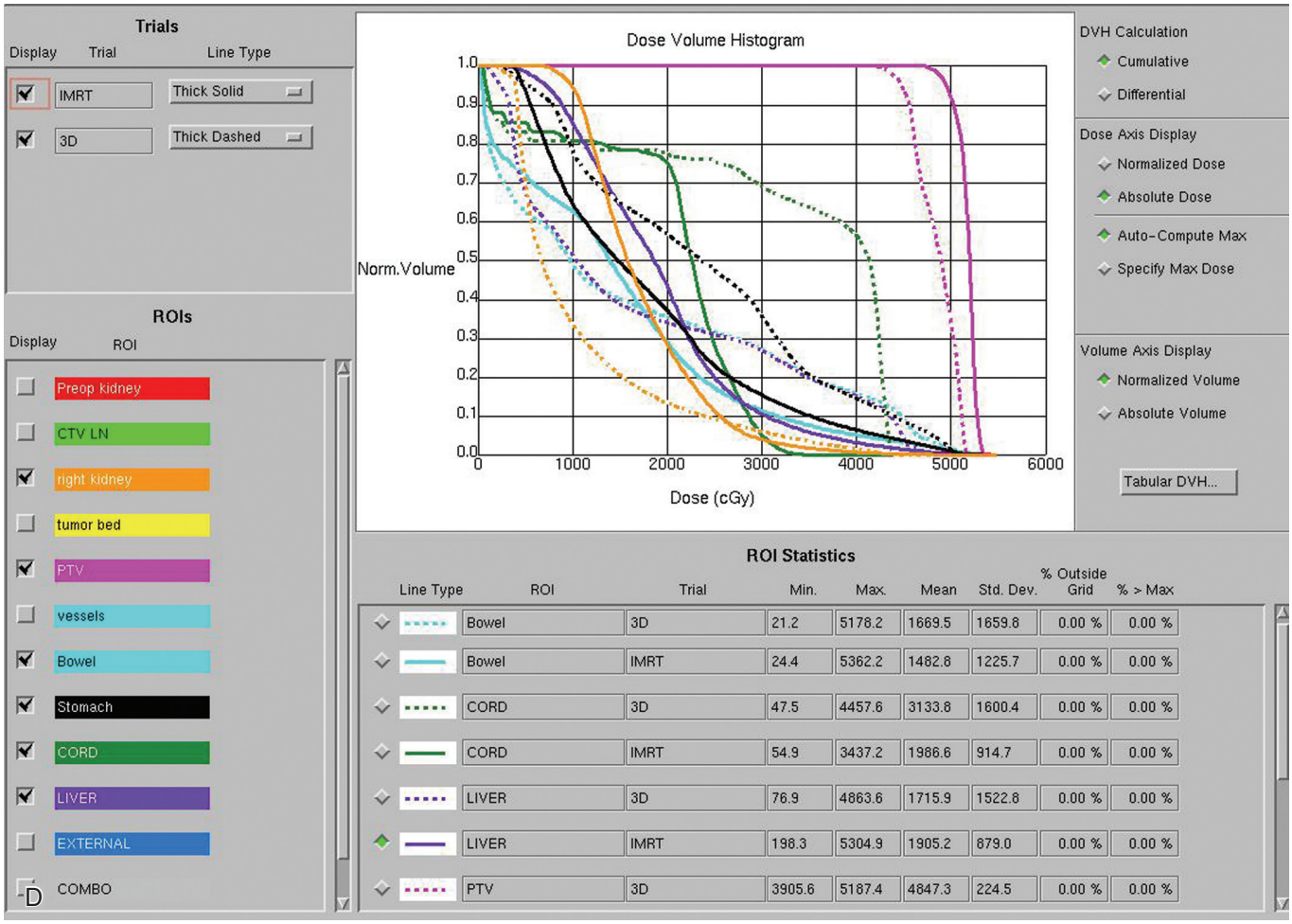


Figure 56-2,cont'd D, The dose-volume histogram demonstrates the ability of the IMRT plan to spare normal structures, most notably the spinal cord, as compared with the 3D plan. Despite lowering of the dose with the 3D plan, only 85% of the PTV is covered by the prescription dose compared with more than 90% for the IMRT plan.

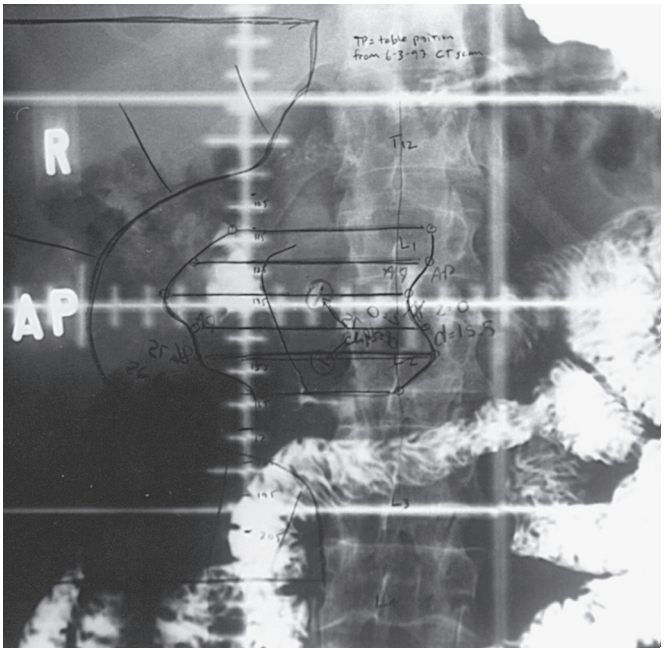
A total dose of 45 Gy to 50.4 Gy in 1.8-Gy to 2.0-Gy fractions should be delivered using multiple treatment fields. Maximal surgical debulking with consideration of IORT should occur within 4 to 6 weeks of completion of EBRT.

Treatment-Related Toxicity

CT-aided radiation therapy treatment planning (3DCRT or IMRT) is essential to reduce the risk of treatment-related toxicity. The Copenhagen Renal Study Group randomized 32 patients to receive postoperative irradiation after surgery.[186] Twenty-seven of the 32 patients randomized completed the course of postoperative RT to a dose of 50 Gy in 20 fractions. Significant complications to the stomach, duodenum, or liver occurred in 12 of the 27 patients and contributed to the death of 5 patients (19%). The increased fraction size of 2.5 Gy may have partially contributed to the high complication rate. In studies using modern CT-based planning, the risk of late complications was less than 5%.[187,188]

Renal Pelvis and Ureter

The radiation treatment field should include the primary tumor bed down to the bladder wall at the ipsilateral trigone with an adequate margin, plus the regional lymph nodes adjacent to the primary tumor bed. The pattern of lymphatic metastasis based on the location of the primary lesion is summarized earlier in the section on pathway of spread.[105] For renal pelvis and upper ureteral lesions, nodal metastasis most commonly occurs near or superior to the primary tumor site, involving the periaortic/pericaval lymph nodes and the renal hilar nodes. The initial treatment field, encompassing the renal pelvis and ureter and the regional nodes, should be treated to 45 Gy to 50.4 Gy with 1.8-Gy per fraction. Areas of gross disease may be boosted to 54 Gy to 60 Gy. CT-based 3DCRT or IMRT is used to reduce the volume of normal organs such as small bowel, liver, and contralateral kidneys in the high-dose region. The dose to the contralateral functioning kidney should not exceed 18 Gy. The volume of irradiated liver (for patients with left-sided lesions) and stomach (for patients with right-sided lesion) can be reduced with AP/PA fields. Lateral fields may be used to deliver part of the treatment to keep the dose to the spinal cord within tolerance. Representative fields for a local recurrence of renal pelvis cancer using 3DCRT are shown in eFigure 56-2 on the Expert Consult website. For lower ureteral lesions, pelvic lymph nodes should be included in the treatment field. The posterior location of the ureter allows the use of a four-field or three-field (PA and opposed laterals) technique. The use of a prone treatment position and small bowel contrast is helpful to minimize the amount of small bowel in the treatment field. A representative radiation treatment field for a lower ureter cancer is shown in Figure 56-4.



eFigure 56-2 Irradiation fields for a locally recurrent renal pelvis transitional cell carcinoma. Original location of the primary tumor is identified by clips. Current size of the gross, unresectable (by virtue of inferior vena cava and other vascular structure invasion) tumor is identified by CT scan–based reconstruction. Periaortic lymph nodes are included within the anterior-posterior/posterior-anterior field.

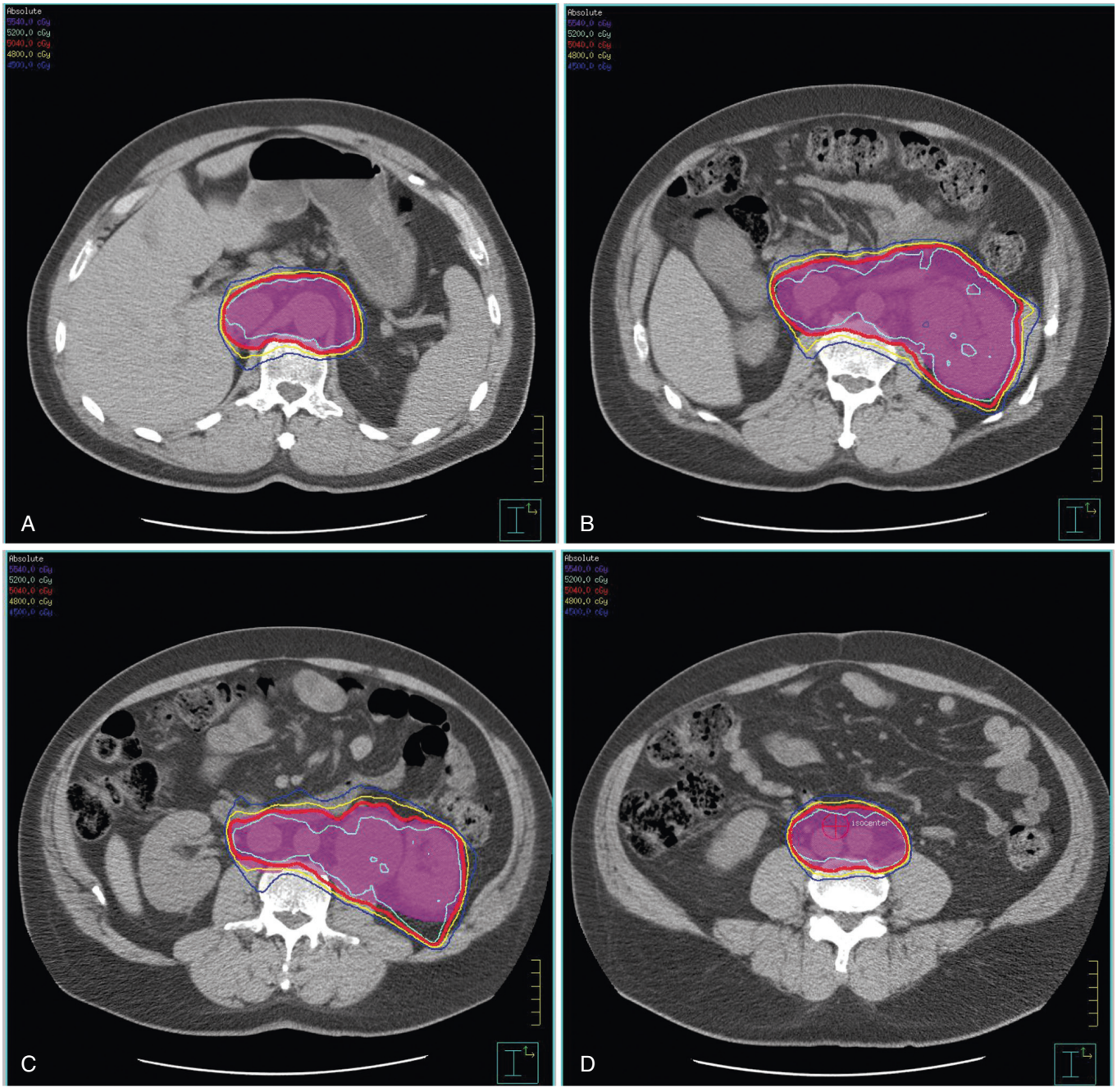


Figure 56-3 **A** to **D,** Illustration of a preoperative treatment plan for a locally advanced renal cell carcinoma with invasion of the psoas muscle. The tumor, involved kidney, and regional lymphatics were treated to 50.4 Gy using an IMRT plan to spare normal structures, primarily the contralateral kidney, liver, and spinal cord (see dose volume histogram in eFigure 56-3).

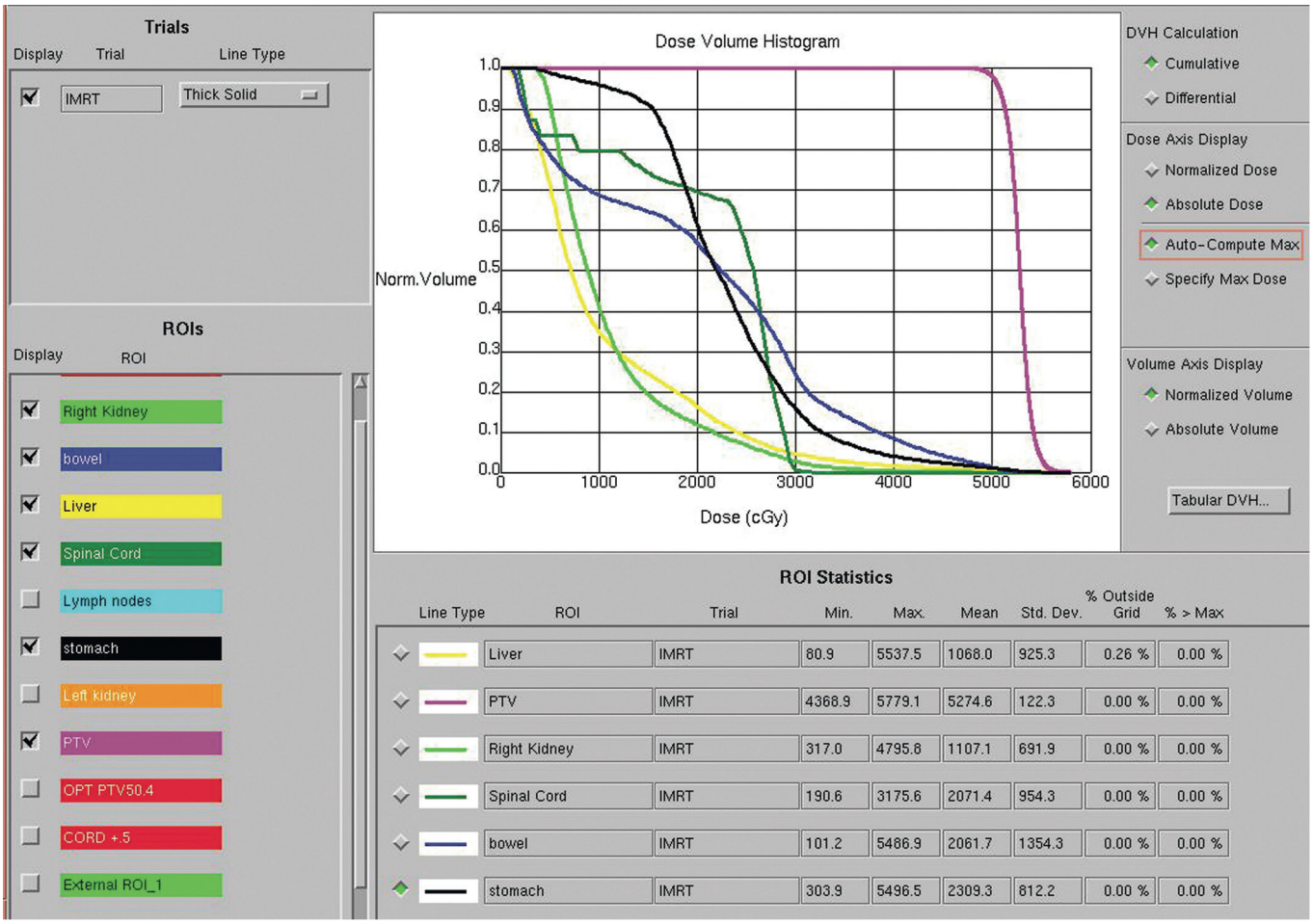
Figure 56-5 shows the dose distribution of an IMRT treatment plan for an 88-year-old patient who had TCC in the midureter and positive cytology from the renal pelvis. He was medically unfit for surgery because of heart disease.

TREATMENT ALGORITHM, CONCLUSIONS, AND FUTURE POSSIBILITIES

Kidney

Some progress has been made in understanding the environmental, occupational, hormonal, cellular, and genetic factors associated with disease development. With better understanding of the molecular pathways of pathogenesis, new systemic molecularly targeted agents have been developed. Future investigations should be directed to prevent local and distant recurrence after surgical resection and to control locally advanced and metastatic disease.

Figure 56-6 presents an algorithm for the current Mayo Clinic philosophy on diagnosis and treatment of RCC. Patients with a tumor 4 cm or smaller, a solitary kidney, bilateral RCCs, or impaired renal function may be candidates for a partial nephrectomy. Patients with tumors larger than 4 cm and a normal-functioning opposite kidney should be treated with radical nephrectomy. If gross total resection with negative margins is accomplished, the patient should be observed. If



eFigure 56-3 Dose-volume histogram for patient with locally advanced left renal carcinoma receiving preoperative treatment (case illustrated in Figure 56-3) using IMRT treatment plan to spare the normal right kidney, liver, spinal cord, and stomach.

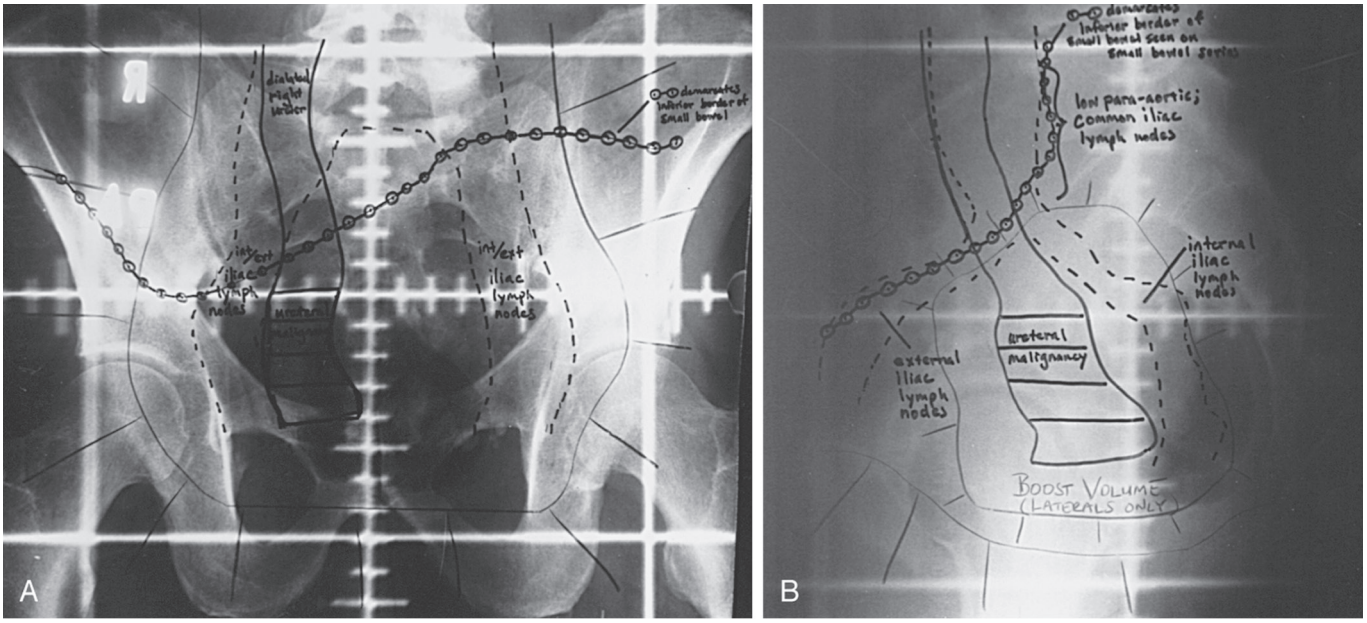


Figure 56-4 **A** and **B,** Radiation therapy fields for a low transitional cell carcinoma being managed by primary radiation therapy because of severe medical comorbidity preventing surgery. Beam's eye-view reconstruction of the lower ureteral tumor, bladder, and draining pelvic lymph nodes is superimposed on the simulation films. Initial blocking for the tumor nodal fields is shown with final boost volumes to the primary lesion plus several centimeters of margin based on location of small bowel identified by small bowel series.

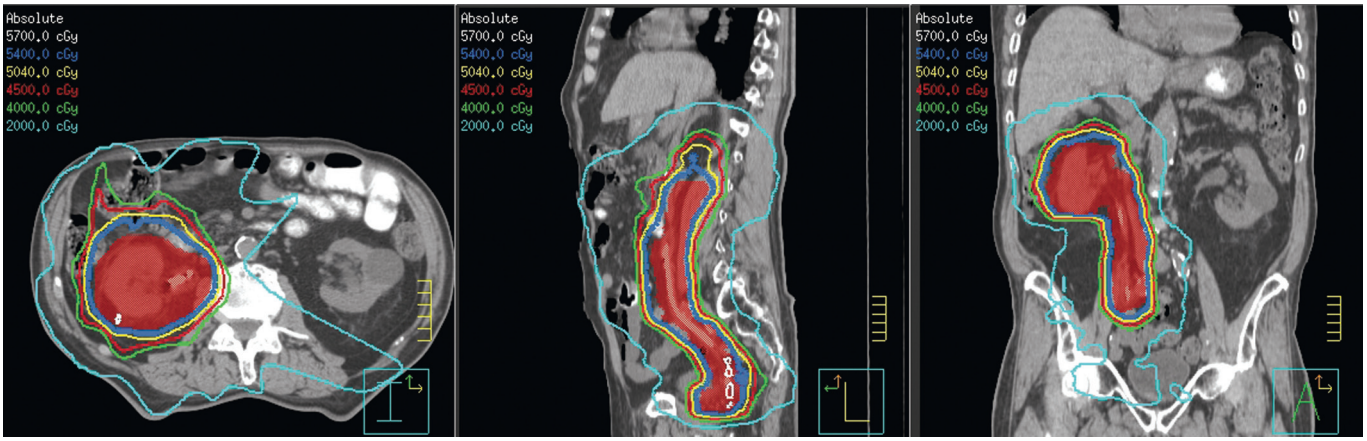


Figure 56-5 Isodose plan for an 88-year-old man with transitional cell carcinoma in the midureter and positive urine cytology from the renal pelvis. The patient had significant heart disease and was deemed medically unfit for nephroureterectomy. He also declined to have surgery. IMRT was used to deliver 54 Gy to the kidney, ureter, and part of the bladder but sparing the bowel and spine. The regional and periaortic lymph nodes were not included as clinical target volume to minimize toxicity. He also was given cisplatin concurrently for two cycles.

positive surgical margins or lymph node involvement is present at radical nephrectomy, consideration should be given to postoperative EBRT.

If locally advanced or locally recurrent disease is present, preoperative EBRT to the tumor, regional lymph nodes, and vascular extent of tumor may downsize the disease to facilitate surgery. Maximal resection, preferably combined with IORT to areas of narrow or positive margins, should be planned at 4 to 6 weeks after completion of EBRT. SBRT can be considered for patients who are medically inoperable or unwilling to undergo nephrectomy, although more studies are needed to evaluate the efficacy of this approach.

Patients who present with metastatic disease are candidates for molecularly targeted treatment. Palliative nephrectomy can be considered to palliate symptoms, to enhance the effects of systemic therapy, or in patients with favorable prognostic factors such as solitary metastasis.

Potential Clinical Trials

Future clinical trials should evaluate both local and systemic treatment modalities. Patients who have positive surgical margins or positive lymph nodes are at increased risk for local failure. A prospective randomized trial comparing observation versus postoperative irradiation (with or without concomitant systemic therapy) would help to define the benefits of postoperative irradiation.

Patients who have positive lymph nodes and renal vein involvement are at increased risk for distant metastases. Future trials should evaluate the use of adjuvant systemic treatment including molecularly targeted therapy for these patients.

Patients with locally advanced disease appear to benefit from aggressive treatment, including preoperative radiation therapy, surgical debulking, and IORT. Future trials can

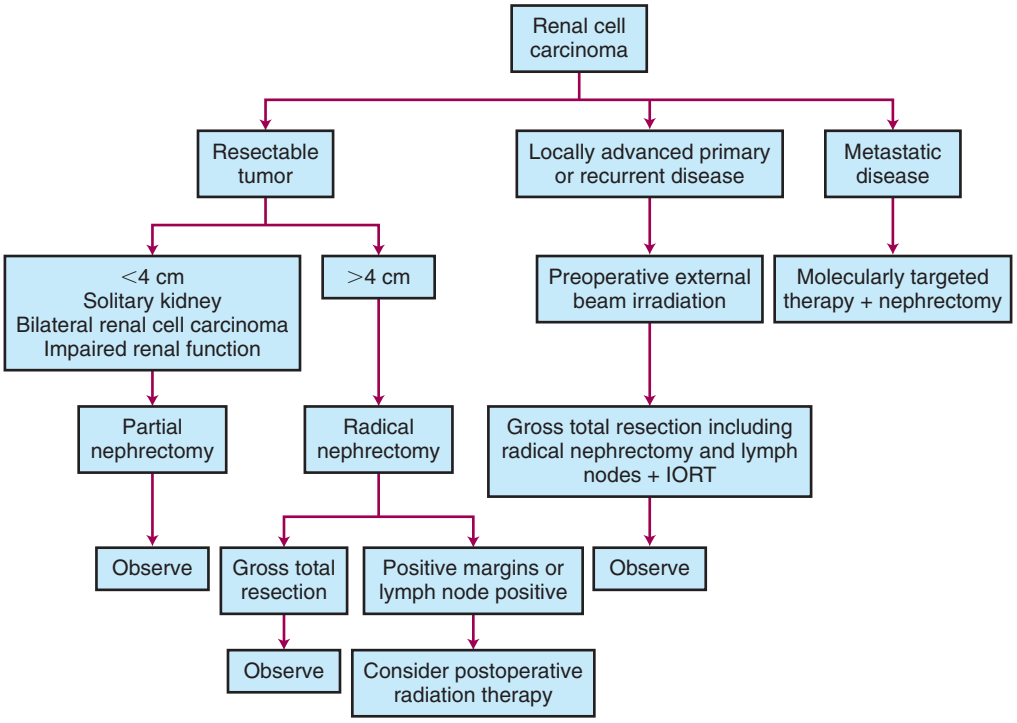


Figure 56-6 Diagnostic and treatment algorithms for renal cell carcinoma. *IORT*, Intraoperative irradiation.

evaluate the combination of systemic agents with local treatment modalities to improve local control and reduce distant spread of disease. For patients with metastatic disease, future clinical investigation should continue to focus on improving survival and quality of life with molecularly targeted therapy while minimizing the toxicity of treatment.

Renal Pelvis and Ureter

The primary management of UUTCA is surgical if the disease is resectable. The standard surgery is radical nephroureterectomy. Laparoscopic nephroureterectomy has been shown to reduce the recovery time from surgery while achieving outcomes comparable to the open approach. More conservative surgery with ureteroscopic nephron-sparing surgery or partial ureterectomy should be limited to patients with solitary kidney or medical comorbidities, as well as selected patients with low-grade, early-stage, and small cancers. Despite radical surgery, patients with locally advanced diseases are at significant risks of locoregional and distant failures. Emerging data suggest that adjuvant chemotherapy and neoadjuvant chemotherapy may improve treatment outcome in patients with high-risk disease and should be studied prospectively. The role of combined chemoradiation, either as adjuvant treatment or as primary therapy, needs to be better defined. There is an urgent need to identify molecular targets and pathways so that new therapeutic agents can be developed that are more specific for this disease.

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CHAPTER

57 Penile Cancer

Juanita M. Crook and Jean-Jacques Mazeron

INCIDENCE

Penile cancer occurs in approximately 1 in 100,000 North American and European men (accounting for 0.4% to 0.6% of all male cancers), but it represents as much as 10% of male malignancies in parts of Asia, Africa, and South America.

BIOLOGIC CHARACTERISTICS

Human papillomavirus (HPV) types 16 and 18 are detected in 40% to 45% of penile cancers. Moderate or poor differentiation, invasion of the corpora, and the presence of tumor emboli in lymphovascular channels predict regional spread.

STAGING EVALUATION

Circumcision is recommended for full evaluation of the primary tumor. Magnetic resonance imaging (MRI) may supplement palpation in the determination of invasion of the corpora. Computed tomography (CT) for staging lacks sufficient sensitivity for evaluation of lymph nodes. For adverse pathology (grade, invasion of corpora, or lymphovascular spaces), surgical staging of lymph nodes is recommended and can be done by either bilateral superficial inguinal lymph node dissection or sentinel lymph node biopsy.

PRIMARY THERAPY

Penile conservation is recommended for Tis, Ta to T1, and G1 to G2 lesions and can be considered for those with G3 T1 or T2 category lesions (tumor < 4 cm) and for selected T3 tumors. Laser surgery for Tis and T1 tumors yields satisfactory local control and cosmesis.

Interstitial brachytherapy for T1 to T2 category tumors allows penile preservation in 70% to 85% of patients. The most common sequelae of treatment are meatal stenosis (12% to 45%) and soft-tissue ulceration (8% to 25%).

For external beam radiation therapy (EBRT), penile preservation rates are 50% to 65%.

ADJUVANT THERAPY

Adjuvant EBRT is recommended after lymph node dissection for patients with multiple positive groin nodes or extracapsular disease.

LOCALLY ADVANCED DISEASE

Locally advanced penile cancer is a highly lethal malignancy that requires a multimodality approach. This may begin with total or partial penectomy and lymph node dissection for cases that are surgically resectable. For unresectable presentations, combined chemoradiotherapy can be used as either a preoperative approach or continued to a definitive dose. Neoadjuvant chemotherapy may render the disease operable (response rate 50%).

PALLIATION

Unresectable nodes are rarely controlled by radiation therapy (RT), but palliation may be possible. A combined approach with systemic chemotherapy is warranted if the patient's general condition permits.

The penis is divided into three portions: the root, the body (or shaft), and the glans. The root is embedded in the superficial perineum. The shaft consists of the erectile bodies composed of the corpora cavernosa, the corpus spongiosum, and the overlying skin. The glans comprises the distal part of the corpus spongiosum and is covered by a skinfold known as the prepuce. The coronal sulcus delimits the glans from the shaft.

Early-stage, well-differentiated cancers of the penis can be effectively managed with local therapy, and attention should be paid to preservation of penile function and morphology. Traditional primary surgical management is effective but is associated with considerable psychosexual morbidity. Even partial penectomy can have a profound effect on sexual health and self-image.[1] Suicide or attempted suicide after partial penectomy has been reported.[2,3] In recent years, emphasis is increasingly in favor of penile-sparing approaches and surgical options have been developed in this regard, including procedures such as glans-sparing penectomy. EBRT and interstitial RT are also organ-sparing alternatives that preserve penile morphology and function without compromising disease control or survival in selected patients. Referral is encouraged to centers specialized in management of this rare cancer. Quality of life and sexual health after treatment requires more study. Sexuality and expectations should be discussed with the patient and partner when deciding on primary management. Advanced or poorly differentiated tumors require a multimodality approach. A recent study of 12 European Cancer registries and the Surveillance, Epidemiology, and End Results (SEER) program in the United States showed no improvement in 5-year survival for penile cancer patients since 1990.[4]

ETIOLOGY AND EPIDEMIOLOGY

Carcinoma of the penis is rare, with an estimated incidence of 1 case per 100,000 men in North America and Europe, where it accounts for 0.4% to 0.6% of cancers. Higher incidences are seen in parts of Asia, Africa, and South America, where it represents up to 10% of malignancies in male patients.[5] The peak incidence is in the sixth decade in developed countries but earlier where the incidence is higher.

Case-control studies have identified important risk factors (odds ratio [OR] > 10) to be phimosis, chronic inflammatory conditions such as lichen sclerosis, treatment with psoralens and ultraviolet A photochemotherapy (PUVA), tobacco products (dose-dependent association), and a history of genital

condylomata (threefold to fivefold increase in risk). Neonatal circumcision is associated with a threefold decrease in risk of penile carcinoma. However, circumcised men with a history of HPV infection remain at increased risk.[6] Oncogenic HPV, especially type 16, has been identified in about 50% of invasive penile cancers.[7] Penile trauma may be another risk factor for penile cancer. There is a threefold increase in development of carcinoma in the scarred penile shaft after penile tears or injury.[8]

PREVENTION AND EARLY DETECTION

Infant circumcision is highly effective in prevention of this disease, but it is not recommended on these grounds alone. The emphasis is instead on education, promotion of good hygiene for the normally retractile foreskin, and surgical correction of phimosis. Men should be aware of the association between certain HPV subtypes, venereal warts,[6] and cancer, as well as the premalignant nature of conditions such as lichen sclerosis, which may precede the diagnosis of cancer by many years. In a recent report from Scandinavia, patients delay an average of 6 months before seeking medical attention.[9]

Genital condyloma or warts and genital HPV infection refer to a sexually transmitted disease caused by HPV. Although not reportable, the number of new infections is estimated at 500,000 to 1 million annually. The prevalence of HPV in U.S. males is more than 50%, being 60% in uncircumcised and 50% in circumcised men, with higher rates of infection with increasing numbers of sexual partners, lack of condom use, and smoking.[10] Some 60 genotypes of HPV virus have been identified that involve the genital tract.[11] Virus types 6, 11, and 42 to 44 are associated with gross condylomata and low-grade dysplasia. Types 16, 18, 31, 33, 35, and 39 have a higher association with malignant disease. Immunocompromised men with human immunodeficiency virus (HIV) infection are more susceptible to development of penile lesions and squamous carcinoma with high-risk HPV types.[12]

An increased incidence of penile intraepithelial neoplasia has been found in the male partners of women with cervical intraepithelial neoplasia. A recently available quadrivalent vaccine (Gardasil, Food and Drug Administration, June 2006) protects against HPV types 5, 11, 16, and 18 and is recommended in females aged 9 to 26 years. Although approved for use in young males, vaccination rates in Australia and North America are far below those for females. Vaccine use in males still targets high-risk populations such as organ transplant recipients and homosexual men.[13] Successful HPV vaccination programs are necessary to combat the rising incidence of HPV-related neoplasms for which effective screening programs are lacking, including squamous carcinomas of the penis, anus, and oropharynx.[14,15]

BIOLOGIC CHARACTERISTICS AND MOLECULAR BIOLOGY

The overall incidence of HPV in penile carcinoma is 40% to 45%, as detected by polymerase chain reaction (PCR) amplification of DNA. HPVs 16 and 18 are the most frequent subtypes detected.[16,17] The frequency of HPV detection depends on histopathologic subtype; HPV association is seen in 80% to 100% of basaloid and warty penile cancers but in only approximately 35% of verrucous or squamous cell carcinomas. The difference in prevalence of HPV in these two groups suggests different pathogenesis. Penile lesions can be classified into HPV-induced (HPV 16 in 76%, followed by HPVs 33, 31, 45, and 18) and HPV-independent, often in the background of chronic inflammation (lichen sclerosis, bowenoid papulosis). HPV presence in a tumor may confer a better prognosis.

The presence of p53 is found in 41% to 75% of invasive penile cancers.[18,19] Nuclear expression of p53 is seen in tumor cells and basal keratinocytes of p-16(ink4a) negative non-HPV induced lesions.[7] In multivariate analysis, p53 positivity and lymphatic embolization are predictive of lymph node metastases.[18,20]

PATHOLOGY AND PATHWAYS OF SPREAD

Premalignant lesions are associated with invasive cancers in 20% to 30% of cases. Intraepithelial neoplasia such as bowenoid papulosis, Bowen disease, and erythroplasia of Queryat[21] are precursor lesions of warty and basaloid penile cancers. Lichen sclerosis (balanitis xerotica obliterans) is associated with non-HPV variants of penile carcinoma.[22,23] Condylomata, Buschke-Löwenstein disease, Kaposi's sarcoma, and leukoplakia are also associated with penile cancer.

The primary tumor most frequently occurs on the glans (48%) or prepuce (25%), with the glans and prepuce involved in 9%, the coronal sulcus in 6%, and the shaft in only 2%. Squamous cell carcinomas represent 95% of invasive cancers of the penis. Other histopathologic primary tumor types are malignant melanoma, transitional cell carcinoma, basal cell carcinoma, and sarcoma.

The lymphatics of the prepuce and the skin of the shaft drain into the superficial inguinal nodes located above the fascia lata. The glans and the deep penile structure drain into the superficial or deep inguinal nodes from which they spread along the femoral vessels to the external iliac, common iliac, and paraaortic regions. The sentinel nodes are located above and medial to the junction of the inferior epigastric and saphenous veins.

CLINICAL MANIFESTATIONS, PATIENT EVALUATION, AND STAGING

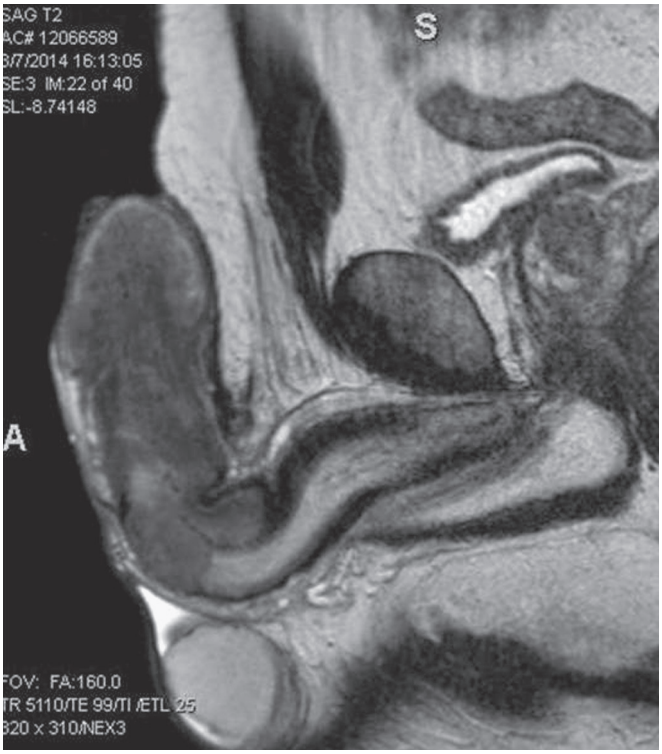
General Approach

Because of the rarity of carcinoma of the penis, reported series often span several decades. Four different staging systems are encountered in a review of the literature of the past three decades[24-27] (Table 57-1).

As clinical staging of carcinoma of the penis is subjective, it may be difficult to distinguish T1 (i.e., invasion of subepithelial connective tissue) from T2 (i.e., invasion of corpus spongiosum or cavernosum). For this reason, techniques that treat less than the full thickness of the penis must be restricted to carefully selected cases. High-resolution MRI is the gold standard for evaluating the primary tumor and local extension.[28,29] Although small-volume lesions on the glans can be adequately staged by palpation in most cases, MRI especially with artificial erection by intracorporal injection of prostaglandin E1 improves staging of the primary tumor where invasion of the corpus cavernosum is suspected (eFigure 57-1).[30,31] Any patient who presents with phimosis and chronic discharge, bleeding, balanitis, or swelling in the region of the coronal sulcus or glans under an unretractable foreskin should have a dorsal slit of the foreskin to allow inspection of the glans, followed preferably by a full circumcision. Any suspicious lesions should be sampled. Figure 57-1 shows the diagnostic algorithm for a patient with clinically node-negative disease.

Lymph Node Assessment: The N0 Patient

Management of the patient with clinically negative groins has been considerably clarified in the past decade. Although many RT series have advocated a "wait-and-see" policy, with no systematic staging investigations such as CT or fine-needle



eFigure 57-1 MRI of the penis. The erectile bodies are normally bright white on MRI. This image shows dark tumor invasion of the shaft.
MRI, Magnetic resonance imaging.

TABLE 57-1 Staging Systems for Carcinoma of the Penis

Stage	Description
JACKSON STAGING SYSTEM*	
1	Tumor limited to the glans or prepuce
2	Tumor extending into the shaft or corpora but without node involvement
3	Tumor confined to the shaft but with malignant but operable lymph nodes
4	Invasion beyond the shaft with inoperable lymph nodes or distant metastases
TNM (UICC, 1978)†	
Tis	Carcinoma in situ
T1	Tumor ≤ 2 cm
T2	Tumor > 2 cm and ≤ 5 cm
T3	Tumor > 5 cm or deep invasion including urethra
T4	Tumor invades adjacent structures
N1	Metastases in unilateral inguinal lymph nodes
N2	Metastases in bilateral inguinal lymph nodes
N3	Fixed inguinal lymph nodes
TNM (UICC, 1987-2002)‡	
T1	Tumor in subepithelial connective tissue
T2	Tumor in corpus spongiosum or cavernosum
T3	Tumor in urethra or prostate
T4	Tumor in other adjacent structures
N1	Tumor in one superficial inguinal lymph node
N2	Tumor in multiple or bilateral superficial inguinal lymph nodes
N3	Tumor in deep inguinal or pelvic lymph nodes
TNM UICC 7TH EDITION 2009§	
Tis	Carcinoma in situ
Ta	Non invasive verrucous carcinoma
T1	Tumor invades subepithelial connective tissue T1a: without lymphovascular invasion; not poorly differentiated or undifferentiated T1b: with lymphovascular invasion or poor differentiation
T2	Tumor invades corpus spongiosum or cavernosum
T3	Tumor invades urethra
T4	Tumor invades other adjacent structures
N1	Palpable mobile unilateral inguinal lymph node
N2	Palpable mobile multiple or bilateral inguinal lymph nodes
N3	Fixed inguinal nodal mass or pelvic lymphadenopathy unilateral or bilateral

UICC, *Union Internationale Contre le Cancer (International Union Against Cancer).*
**From Jackson S: The treatment of carcinoma of the penis. Br J Surg 53:33-35, 1966.*
†From Harmer M: Penis (ICD-0187). In TNM classification of malignant tumours, ed 3, Berlin, 1978, Springer-Verlag, pp 126-128.
‡From Hermanek PS, Sobin LH: Penis (ICD-0187). In Hermanek PS, Sobin LH, editors: TNM classification of malignant tumours, ed 4, Berlin, 1987, Springer-Verlag, pp 130-132.
§From Sobin L, Gospodarowicz M, Wittekind C: Penis (ICD-O C60). In Sobin L, Gospodarowicz M, Wittekind C, editors: TNM classification of malignant tumours, ed 7, Oxford, 2010, Blackwell Publishing, pp 239-242.

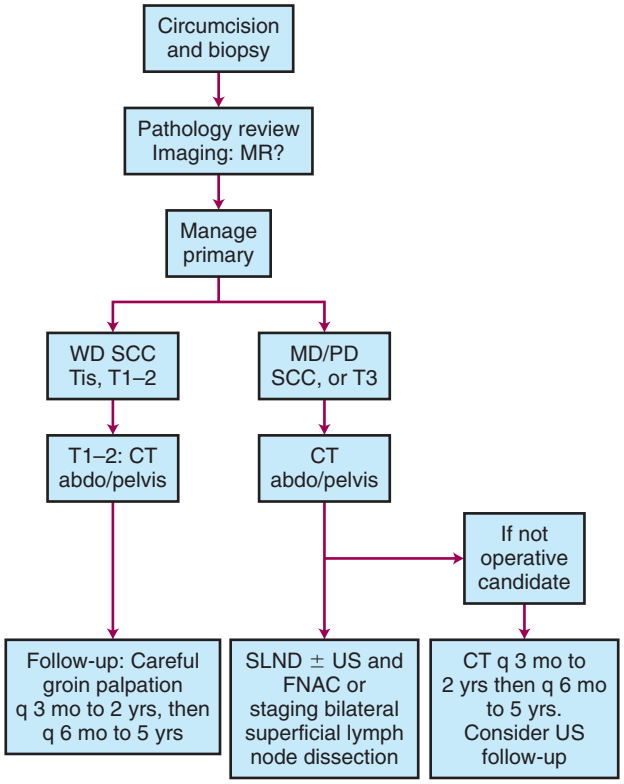


Figure 57-1 Diagnostic algorithm for penile cancer: A patient with clinically node-negative cancer. *CT,* Computed tomography; *FNAC,* fine-needle aspiration cytology; *MR,* magnetic resonance; *MD,* moderately differentiated; *mo,* month; *q,* every; *SCC,* squamous cell carcinoma; *SLND,* sentinel lymph node dissection; *US,* ultrasound; *WD,* well differentiated; *yrs,* year.

aspiration cytology (FNAC),[3,32-35] the predictive factors for lymph node involvement have been established and allow the practitioner to selectively offer surgical staging. Overall, only about 20% of clinically negative nodes have micrometastases, so staging lymph node dissection is not warranted for all patients; traditional inguinal node dissection may be complicated in one third of cases by infection, skin flap necrosis, deep vein thrombosis, or severe leg edema.[36-38] Nodal status is, however, the strongest predictive factor for overall survival (OS) and lymph node dissection may be curative for men with microscopic regional spread. Several surgical series have identified that *therapeutic* node dissection confers an inferior survival compared with *prophylactic* node dissection.[39] McDougal[40] found a 5-year OS after inguinal node dissection of 92% for patients with clinically N0 disease, compared with 33% for those with clinically involved nodes. Modified inguinal lymphadenectomy, sparing the saphenous vein, and limiting the dissection laterally, distally, and proximally, may reduce morbidity.[36]

The reliability of physical examination is diminished markedly in the patient who is obese, so imaging is paramount. Both CT and MRI will demonstrate gross lymph node enlargement but will not detect a small metastasis in a normal-sized node. Nonetheless, CT is the imaging modality recommended to examine the inguinal regions and pelvis as well as to rule out more distant metastases, with a sensitivity and specificity of 36% and 100%, respectively. The combination of positron emission tomography (PET)/CT using the radiopharmaceutical fluorodeoxyglucose (^{18}F-FDG) has been shown[41] to increase sensitivity to 80%. The combination of ultrasound and FNAC has been shown to detect 80% of metastatic disease in

nonpalpable nodes (12 out of 15) with an overall sensitivity and specificity of 87% (48 out of 55) and 99%, respectively.[42]

Stage and histopathologic factors should be used to identify patients at high risk for microscopic regional spread to selectively offer surgical staging of lymph nodes. Chaux and Cubilla[43] have published a stratification system to estimate the likelihood of lymph node metastases based on grade, extent and depth of invasion, and the presence of perineural invasion. T category and lymphovascular invasion are also reported to be predictive for nodal relapse.[44,45] The risk of nodal involvement in patients at high-risk is 64% to 83%, 20% to 33% in intermediate risk, and 0% to 8% in low risk.

The difficulty with applying histopathologic information to decision making in RT is that the primary tumor is not available for complete examination. Invasion of the corpora may be underappreciated clinically. Diagnostic biopsies are often superficial and unreliable in determining the depth of invasion, the presence of lymphovascular invasion, or the ultimate tumor grade.[46] However, if the biopsy shows high-risk features, surgical assessment of regional lymph nodes is recommended. Ultrasound-guided FNAC is a valuable tool to evaluate suspicious inguinal nodes,[47] with reported sensitivity and specificity more than 90%.[48] A 4- to 6-week trial of antibiotics is no longer recommended.

The current European Association of Urology (EAU) guideline recommends observation of the lymph nodes for carcinoma in situ (Tis), verrucous (Ta), and T1-grade 1 tumors because these are associated with less than a 10% incidence of lymph node positivity.[49] T1 grade 2 tumors are classified as intermediate risk and observation is recommended only for those with a superficial growth pattern and no vascular invasion. Category T2 or higher or grade-3 tumors and those with vascular invasion have a higher than 50% risk of lymph node involvement and should have surgical staging. Patients with T1 grade 2 tumors with high-risk features such as tumor thickness or vertical growth should also be considered for surgical staging. Close follow-up of patients at high risk is important.[50]

Dynamic sentinel lymph node mapping uses a gamma probe after intradermal peritumoral injection of technetium-99m and is becoming more widely available for detection of early lymph node involvement (eFigure 57-2). False-negative rates, although initially in the 18% to 25% range, have fallen to 5% to 7% in the recent literature from high-volume centers with experienced surgeons.[51,52] Complication rates of 5% are reported.[53] Lam et al[54] described long-term follow up of 500 inguinal basins in 264 patients with T1G2 or higher disease and nonpalpable nodes managed with ultrasound or FNAC and DSNB. Sensitivity of DSNB alone per inguinal basin was 92% and with ultrasound with or without FNAC 95%. Routine serial sectioning along with cytokeratin immunohistochemistry, exploration of groins with low or no signal, and ultrasound with FNAC to detect positive lymph nodes that may have altered lymphatic flow[55] have helped to decrease false-negatives. The use of PET/CT may further decrease the risk of false-negatives from tumor blockage and rerouting of lymphatics.[56] Superficial inguinal lymph node dissection is still considered the gold standard in centers lacking the expertise for Dynamic Sentinel Node Biopsy (DSLB) because the consequences of a false-negative may be an increased risk of death from disease.

PRIMARY THERAPY

Surgery

Circumcision is generally the first step. Small tumors that are limited to the prepuce can be treated by circumcision alone. Penis-conserving surgical techniques, such as laser or Moh's surgery, may be suitable for selected tumors. Moh's surgery[57] for carcinoma in situ or superficial tumors involves excision of tissue in successive layers until margins are histologically clear. Complete microscopic scanning of each horizontally cut layer identifies any tumor outgrowths that may extend beyond the visible or palpable lesion.

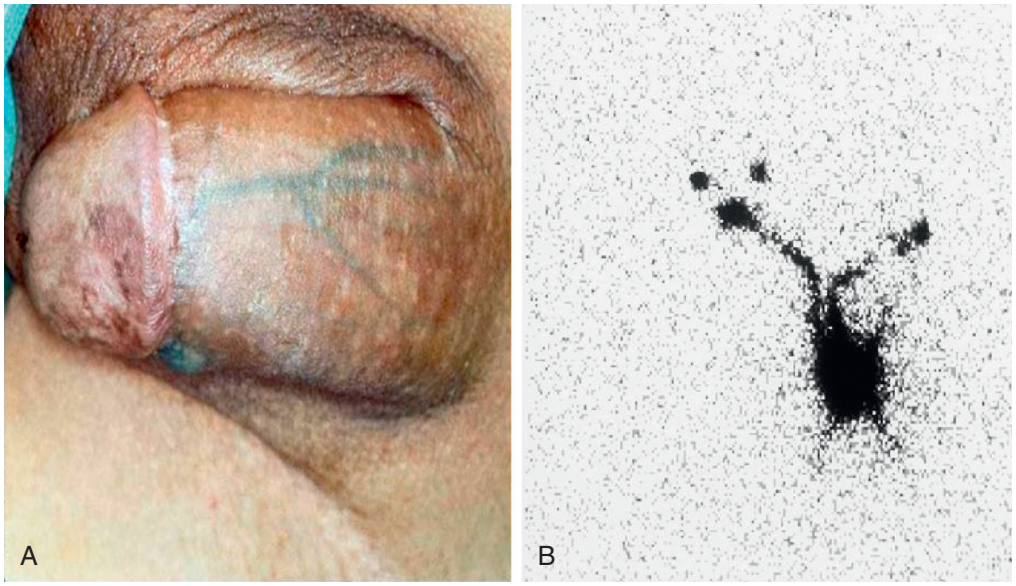
Laser surgery using carbon dioxide or neodymium:yttrium-aluminum-garnet (Nd:YAG) lasers has been reported to provide a superior functional and cosmetic result compared with standard surgical techniques for selected premalignant and malignant lesions (Tis/T1).[58-61] Both carbon dioxide laser (depth of penetration 0.1 mm) and Nd:YAG laser (penetration 6 mm) are used. Tumor-base biopsies to ensure negative surgical margins will reduce failures.[61] High rates of resumption of sexual activity and overall satisfaction are reported. Although local recurrence rates are 17% to 19% at 10 years, many can be retreated with laser, reducing the ultimate amputation rate to about 5%.[59,62] Extended, careful follow-up is required because only 57% of local recurrences occur within the first 2 years, 30% between 6 and 10 years, and 15% after 10 years. Whether these late failures represent true local recurrences or new primary tumors is unknown.

Selected cases, especially those involving only skin, can be treated by wide excision, but local wedge excision is associated with a high recurrence rate. Limited excision of the glans, and glansectomy with reconstruction by a split-thickness skin graft to spare the penile shaft represent surgical strategies to maintain function and penile length.[63] Although Veeratterapillay 2012[64] has reported a 6% local recurrence rate at 40 months in 65 patients, many with T2 disease and intermediate to poor differentiation, local failures increase with longer follow up; 25% occur after 5 years.[65] Traditionally, an adequate resection margin is considered to be 2 cm, but closer margins of 10 mm or less may be acceptable if tumor-free on frozen section. Agrawal et al[66] reported that tumor grade correlated with microscopic spread, with the maximum extent being 5 mm for grade-1 to grade-2 tumors and 10 mm for grade 3. Limited excision is not appropriate for deeply invasive and high-grade tumors. All patients managed with penile-sparing surgical techniques remain at a higher risk for local recurrence. Total or partial penectomy is indicated for tumors greater than 4 cm in diameter, grade 3, or deeply invading. Partial penectomy is possible when the tumor involves the glans or the distal shaft, and the penile remnant will allow the patient to direct the urinary stream. Total amputation and perineal urethrostomy is indicated for larger or proximal tumors.

Radiation Therapy

Radical RT in the form of brachytherapy or EBRT is effective in achieving local control in a high percentage of patients (Table 57-2). Often, series span several decades, during which time treatment techniques and dose prescriptions have evolved. Staging systems have also undergone significant modifications (see Table 57-1).

Interstitial brachytherapy yields a 5-year local control rate of 77% to 87%, with penile preservation rates at 5 years ranging from 72% to 88%. For EBRT, local control rates are less favorable, 41% to 70% at 5 years, and the consequent increase in surgical salvage decreases penile preservation rates to 36% to 66%. Careful extended follow-up is recommended because local failures can occur several years after treatment. Crook et al[75] found that although five of eight local failures in a series of 67 men occurred in the first 2 years, the remaining three occurred at 4.5, 7, and 8 years. Similarly, Mazeron et al[33] reported that 18% of local failures occurred between years 5 and 8, and de Crevoisier et al[68] reported 20% after 8 years. This late recurrence pattern is strikingly similar to that seen after



eFigure 57-2 Sentinel lymph node study: **A,** Blue dye is seen in the lymphatic vessels of the shaft; **B,** radiotracer is seen in the primary tumor and then branching right and left to bilateral inguinal nodes.

TABLE 57-2 Summary of Literature Results for Brachytherapy and External Beam Radiation Therapy

Study	Year	No. Pts	Dose (Gy)	Follow-Up (range, mo)	5-year Local Control	5-year CSS	Complications	Penile Preservation
BRACHYTHERAPY								
Crook et al[67]	2009	67	60	48 (6-194)	87% 72% (10-year)	83.6%	12% necrosis 9% stenosis	88% (5-year) 67% (10-year)
DeCrevoisier et al[68]	2009	144	65	68 (6-348)	80% (10-year)	92% (10-year)	26% necrosis 29% stenosis	72% (10-year)
Delannes et al[35]	1992	51	50-65	65 (12-144)	86% (crude)	85%	23% necrosis 45% stenosis	75%
Delaunay et al[69]	2013	47	60 (42-70)	80 (13-190)	60%	87.6%	Not stated	66%
Kiltie et al[34]	2000	31	64	61.5	81%	85.4%	8% necrosis 44% stenosis	75%
Mazeron et al[33]	1984	50	60-70	36-96	78% (crude)	—	6% necrosis 19% stenosis	74%
Rozan et al[32]	1995	184	59	139	86%	88%	21% necrosis 45% stenosis	78%
Soria et al[3]	1996	102	61-70	111	77%	72%	Not stated	72% (6-yr)
EXTERNAL BEAM IRRADIATION								
Gotsadze et al[70]	2000	155	40-60 at 2 Gy/Fx	Four decades' experience	65%	86%	1% necrosis 7% stenosis	65%
McLean et al[71]	1993	26	35/10 Fx to 60/25 Fx	116 (84-168)	61.5%	69%	28% unspecified	66% (crude)
Neave et al[72]	1993	24	56/84 hr (12 hr/day) (mold)	36-mo minimum	69.7%	67%	13% stenosis	55%
		20	50-55/20-22 Fx (external)	36-mo minimum	69.7%	58%	10% stenosis	60%
Ozsahin et al[73]	2006	33	52	62 (6-450)	44%	—	10% stenosis	52%
Sarin et al[2]	1997	59	60/30 Fx	62 (2-264)	55%	66%	3% necrosis 14% stenosis	50% (crude)
Zouhair et al[74]	2001	23	45-74/25-37 Fx	12 (5-139)	41%	—	10% stenosis	36%

CSS, *Cause-specific survival;* Fx, *fractions;* Pts, *patients;* mo., *months.*

penile-conserving laser treatment[59] and necessitates careful long-term follow-up because the majority can be successfully salvaged.

Surgery for Salvage

Surgery for salvage is successful in more than 80% of failures.[32,74] Local excision is rarely appropriate. The choice between total and partial penectomy[32,34,35,74] depends on penile length and the proportion of shaft irradiated by the primary treatment. The localized nature of brachytherapy should result in less radical salvage operations.

Patient Selection for Radiation Therapy

Several prognostic factors have been identified for penile preservation. For EBRT, a total dose of less than 60 Gy, a protracted treatment time of more than 45 days, and a daily fraction size of less than 2 Gy are all associated with an increased risk of local failure.[2,74]

For brachytherapy, the volume of tumor and depth of invasion are predictive of local control. The ideal tumor for brachytherapy should be less than 4 cm in its maximum diameter, with less than 1 cm of invasion.[3,33,34,76] Local failure rates of 50% to 60% for tumors larger than 4 cm in diameter have been reported, compared with 14% to 30% for those less than 4 cm. Use of more than six brachytherapy needles and tumor volumes greater than 8 mL are also associated with an increased risk of failure.[3,32,34] Crook et al[67] found that wider needle spacing was associated with a decreased risk of failure ($p = 0.006$). Wider spacing results in a wider lateral margin, ensuring more generous margins around the tumor (Figure 57-2).

Histopathology does not appear to be a factor in local control. Moderate to poor differentiation influences OS and the risk of nodal involvement[77] but does not preclude a penile-conserving approach.

LOCALLY ADVANCED DISEASE AND PALLIATION

Although a penile-sparing approach may be warranted for a T3 tumor in a younger patient, most locally advanced tumors require a primary surgical approach with partial or total penectomy, perineal urostomy, and bilateral groin dissection.

Node-Positive Disease

Involved nodes should be resected if possible. As in squamous cancers of the vulva, patients with pathologic findings of multiple positive nodes or extracapsular spread should be offered postoperative RT.[77-79] If dissection of deep pelvic nodes is negative, treatment can be limited to the involved groin. A direct anterior electron field of suitable energy to deliver a dose of 45 Gy to 50 Gy over 5 weeks to the depth of the nodes is

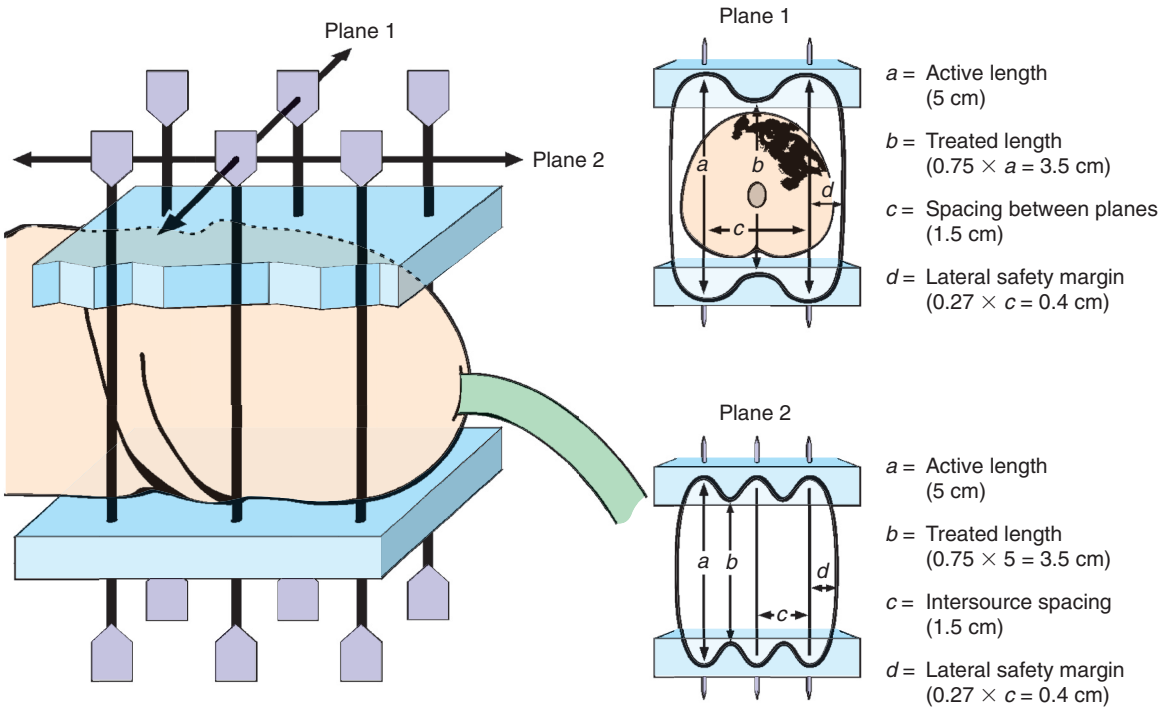


Figure 57-2 Schematic of Paris system of dosimetry for two-plane interstitial implants. Dimensions of treatment isodose can be predicted from length and spacing of radioactive sources.
Reprinted with permission from Crook J, Jezioranski J, Cygler JE: Penile brachytherapy. Technical aspects and postimplant issues, Brachytherapy 9:151-158, 2010.

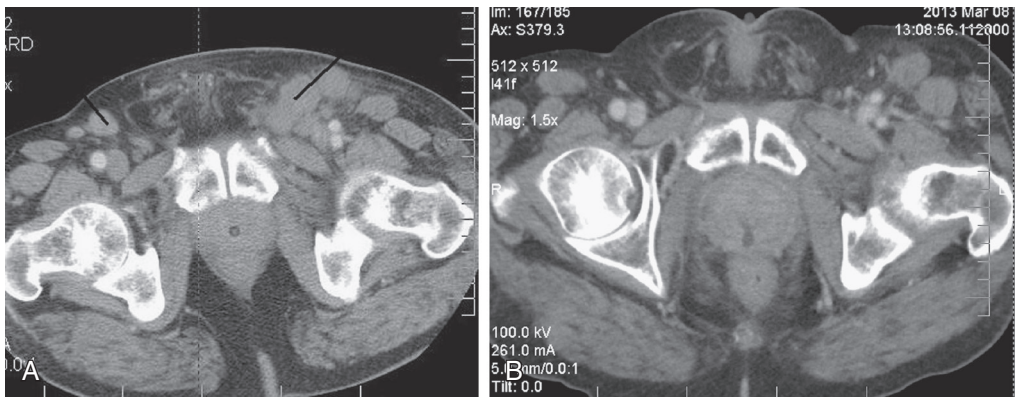


Figure 57-3 Locoregionally advanced penile cancer treated with EBRT and weekly cisplatinum. **A,** diagnostic CT. **B,** Follow-up scan 2.5 years later. *CT,* Computed tomography.

appropriate. If the status of the pelvic nodes is unknown, they should be included in the treatment volume.

Unresectable nodes are rarely controlled by RT alone but can be palliated. A combined approach of concurrent chemotherapy and radiation should be considered (Figure 57-3) in view of the improved local control in other squamous carcinomas when compared with either EBRT alone (cervical cancer) or sequential chemoradiation (CRT; head and neck cancers). One such site is locally advanced squamous cell carcinoma of the vulva,[79] in which the American College of Radiology Appropriateness Criteria[80] recommend the use of neoadjuvant chemotherapy alone only if radiotherapy is not available. The Gynecology Oncology Group (GOG) trial 101 reported that 95% of 41 women with unresectable N2-3 disease who completed CRT subsequently underwent surgical resection with 41% histologically negative. A subsequent Phase II trial (GOG 205) used weekly platinum with daily fractionated RT to a dose of 57.6 Gy in 58 patients. Of 40 who completed the treatment, 37 had a complete clinical response and 29 (50% of the entire series) were histologically negative at subsequent surgery. The role of CRT with or without surgery will be explored in an upcoming international trial for locally advanced penile cancer (InPACT) sponsored by the International Rare Cancers Initiative, using weekly cisplatinum as a radiation sensitizer.

Response rates for neoadjuvant chemotherapy are, at best, 50%. A trial of neoadjuvant paclitaxel, ifosfamide, and cisplatin at the M. D. Anderson Cancer Center has reported a response rate of 50% in 30 patients with N2 or N3 penile cancer. Surgery, CRT, or both, can be used after a response to chemotherapy.[81]

IRRADIATION TECHNIQUES AND TOLERANCE

External Beam Irradiation

EBRT has several advantages in that it is widely available, delivers a homogeneous dose, and does not require the specific expertise of brachytherapy. Well-localized carcinoma in situ (Tis) may be treated effectively using 125-kV orthovoltage beams or 9-MeV electrons with suitable bolus, using fractionation schemes commonly employed for skin cancer such as 35 Gy in 10 fractions over 2 weeks[71]; however, most such lesions would be treated by a penile-conserving surgical technique. Most cases referred for RT require irradiation to the full thickness of the penis with a full dose to the skin surface. Fraction sizes less than 2 Gy are suboptimal[2] and fraction sizes larger than 2 Gy may be associated with increased long-term sequelae.[72] Doses range from 60 Gy in 25 fractions over 5 weeks to 74 Gy in 37 fractions over 7.5 weeks, avoiding interruptions because of acute reactions (e.g., edema, pain, desquamation). A reproducible setup, easily verified by technologists, which is comfortable for the patient despite increasing local reaction, is essential.

Successful application of megavoltage EBRT to treat penile cancer must overcome the technical challenge of positioning the penis in such a way that other tissues will not be exposed to irradiation and counteracting the skin-sparing of megavoltage x-rays. Several techniques have been developed.

A 10- × 10-cm to 10- × 15-cm wax block can be constructed in two halves with a central cylindrical chamber.[71,74] The patient is positioned supine on the treatment couch, and the penis is supported in a vertical position, encased in the wax block. Tissue-equivalent material must be placed in the distal portion of the cylindrical chamber to maintain full dose to the glans. Parallel-opposed beams of cobalt 60 or 4- to 6-MV photons treat the entire length of the penis (Figure 57-4). As treatment progresses, penile swelling may require modification of the wax block. Verification of penile position within the wax is not possible, but a snug fit will prevent the penis from "slumping" inside the wax.

Perspex is a good alternative to wax and provides full buildup to the skin surface while allowing treatment by parallel-opposed beams.[2] Preconstructed blocks in a range of sizes of the central cylindrical chamber can be sterilized for reuse. Penile swelling can be accommodated easily by choosing the next larger size, and penile position within the transparent block can be easily verified visually.

An alternative approach has been described with the patient positioned prone and the penis suspended in a *water* bath. This approach is not appropriate in patients who are obese and day-to-day set up can be challenging because the penis tends to float and position itself too close to adjacent tissues.[82]

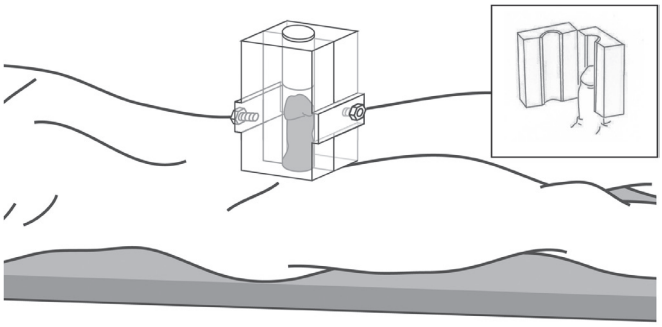


Figure 57-4 Patient positioned with Perspex block in place. Block provides full buildup and is transparent for verification of penile position. The blocks are bivalved and can be made in a range of sizes to accommodate penile swelling as treatment progresses.

Brachytherapy

The penis is well suited to brachytherapy. For centers with appropriate expertise, surface molds or interstitial techniques can be used with good effect. Circumcision should be performed before brachytherapy to ensure complete exposure of the tumor and prevent subsequent phimosis or annular fibrosis of the foreskin.

Molds

Unlike interstitial brachytherapy, a mold is not invasive and does not require anesthesia.[72] The acute reaction develops after the treatment is finished. A surface dose of 55 Gy to 60 Gy is prescribed, with a central axis dose of 46 Gy to 50 Gy over 84 hours (12 hr/day) and may be delivered using a Perspex tube or silicon monomer.[72] Application is limited to superficial tumors of known depth of invasion.

Interstitial Brachytherapy

There is experience with interstitial brachytherapy for T1 or T2 penile carcinoma from many European countries and from Canada. A joint consensus guideline has recently been published by the American Brachytherapy Society and Groupe Europeen de Curiethérapie.[83] Ideally patients should have tumors less than 4 cm in diameter with no or limited invasion of the corpora or involvement beyond the coronal sulcus. Implants can be performed with the patient under general or local anesthesia. The Paris system of dosimetry[84] is applicable to manually afterloaded implants and remote afterloading pulse-dose-rate systems, although for the latter some optimization can be introduced.

Circumcision should always precede penile brachytherapy to allow full visualization of the tumor and to remove any portion involving the foreskin. The foreskin is prone to necrosis and if left in situ during brachytherapy the ensuing painful ulceration can be slow to heal and result in a chronically adherent or phimotic foreskin.

Penile brachytherapy is generally performed as a "volume" or multiplane implant delivering irradiation to the full-thickness of the penis. Only well-selected, superficial tumors may be treated with a single-plane implant. A video of penile brachytherapy is available on the Expert Consult website. For volume implants, two or three parallel planes of sources are inserted, with two or three needles in each plane. Intersource and interplane spacing should be equal, in the range of 12 mm to 18 mm. The distribution, spacing, and total number of needles depend on tumor size. Planes are usually oriented with the needles passing from the dorsal to the ventral surface of the glans, but a left-to-right orientation may work for some tumor locations. Visual verification of coverage can be readily accomplished. Needle placement should be planned such that the prescription isodose will cover 10 mm beyond visible or palpable tumor. Care must be taken to adhere to the rules of the Paris system[66] and to be aware of the relationship of the treated volume to the needles such that placement ensures that the entire tumor and desired margin are within the high-dose volume (Figure 57-5). Specific considerations of needle placement for meatal tumors or unilateral tumors have been described.[53]

Needle placement requires 30 minutes to 45 minutes in the operating room. Catheterization aids in identification of the urethra so as to avoid transfixing it with implant needles. For manually afterloaded iridium-192 wire, 19.5-gauge needles

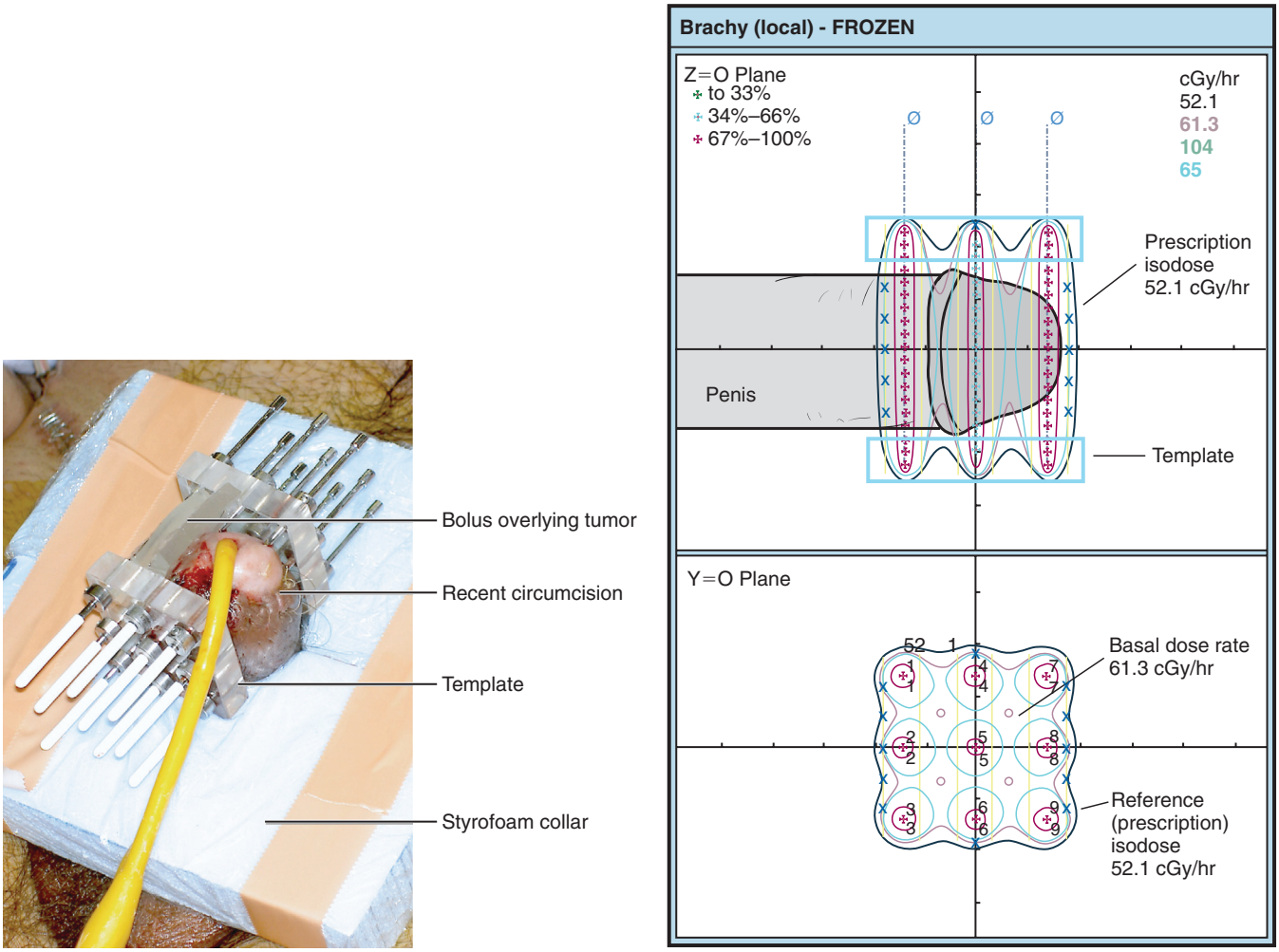


Figure 57-5 Interstitial brachytherapy according to the Paris system of dosimetry.[66] **A,** Six-needle, two-plane implant. **B,** Nine-needle, three-plane implant. **C,** Dose distribution for B. According to the Paris system, dose rate minima in the central plane (61.3 cGy/hr in this case) are the basal dose rate. The prescription isodose is 85% of the basal dose rate (52.1 cGy/hr in this case).

are appropriate, whereas, for a pulse-dose-rate remote afterloader, 17.5-gauge needles are compatible. The needles are stabilized through the duration of treatment with predrilled Plexiglas templates. The prescribed dose is generally 60 Gy at a dose rate of 50 cGy/hr to 60 cGy/hr over 100 to 120 hours (4 days to 5 days). No dose rate correction is required for pulse-dose-rate therapy (hourly fractions) compared with continuous low-dose-rate therapy. A Styrofoam or sponge collar positioned around the base of the penis proximal to the needles supports the penis, distances the implant from the testes, and minimizes unnecessary irradiation of adjacent tissue. A thin sheet of lead can be inserted into the supporting collar to decrease transmitted dose to the testes if subsequent fertility is an issue.

The brachytherapy needles are generally well tolerated. The patient remains catheterized and in bed for the duration of the implant, although with pulse-dose-rate therapy the source cables can be disconnected from the needles to allow the patient to mobilize for brief periods between fractions. Sufficient analgesia is usually provided by acetaminophen, with or without codeine. Leg exercises and embolus prophylaxis are recommended. Removal of the needles occurs at the bedside after premedication with a narcotic analgesic.

Although high-dose-rate (HDR) brachytherapy is becoming widely available, at present there is little evidence on which to base treatment recommendations for penile cancer. One report of 10 patients treated over 8 years used twice-daily fractions of 3 Gy to deliver 54 Gy over 9 days.[85] No necrosis was observed but implants were small volume and the majority was single plane. Limited personal experience with 6 patients, prescribing fractions of 3.2 Gy to 3.75 Gy twice a day for a total prescribed dose of 38.2 Gy to 45 Gy, with needle spacing from 9 mm ($n = 2$) to 14 mm to 17 mm ($n = 4$), resulted in 5 patients being disease free and one local failure. Five of the 6 patients experienced delayed healing and necrosis, including the one with local failure. Of the 5 patients who were NED, one has ongoing ulceration, whereas 3 healed with conservative management including hyperbaric oxygen. CT planning is required with delineation of the gross tumor volume using fine wire. Because of the high rate of troublesome ulceration and necrosis one has to be cautious and preliminary recommendations would be to keep the V_{150} less than 20%, use needle spacing of 9 mm to 12 mm to improve homogeneity, and select cases where the PTV is limited to 30 mL or less. Complications will be worse in patients with diabetes and those who smoke. Further published experience and longer

follow-up is required before any definitive recommendations can be made regarding optimal fractionation for HDR brachytherapy in the management of penile carcinoma.

Tolerance: Acute and Chronic Reactions

Toxicity: Acute Reaction

The acute reaction after brachytherapy is limited to the implant site. Moist desquamation peaks in 2 to 3 weeks but may take 2 to 3 months to heal completely. Local hygiene is important, including frequent soaks in baking soda and water. Sterile distal urethritis is common, but urethral adhesions, causing a divided or deviated urinary stream, should be separated by passing a meatal dilator or an 18-French Foley catheter a few centimeters into the distal urethra. Intercourse can be resumed as soon as the patient is comfortable, but because the healing epithelium is fragile, additional water-based lubricant is recommended.

The acute reaction to EBRT peaks during treatment and may involve edema of the penile shaft and more extensive desquamation. Management is similar to that for patients who had brachytherapy.

Late Reactions

The two most common and significant late complications of RT for penile cancer are soft-tissue ulceration and meatal stenosis. Either can occur with EBRT or brachytherapy (see Table 57-2).

Soft-Tissue Ulceration or Necrosis

Soft-tissue ulceration is reported in 0% to 23% of patients and is more common after brachytherapy than after EBRT. Necrosis (persistent, nonhealing ulceration) is the most common reason for amputation of a tumor-free penis. The risk of necrosis increases with increasing dose more than 60 Gy, stage T3 tumors, larger implant volume (>30 mL; $p = 0.01$), and a greater number of needles ($p = 0.04$) or implant planes (>2; $p = 0.001$).[33,77]

The peak time for soft tissue ulceration is 7 to 18 months after brachytherapy, but it can occur much later. Causative factors include trauma and cold exposure. Areas of ulceration should be treated conservatively, with attention to good hygiene, antibiotics, and topical corticosteroid or vitamin E creams. Biopsy should be avoided unless there is suspicion of concomitant tumor. A deeper or painful area of necrosis may respond well to hyperbaric oxygen treatment[77] (Figure 57-6). If such treatment is available, it should be tried before resorting to amputation.

Urethral Stenosis

Urethral or meatal stenosis is reported in 10% to 45% of patients and tends to occur later in the follow-up period, but usually before 3 years. With EBRT it is more common with higher doses and fraction sizes greater than 2 Gy. For brachytherapy, Rozan et al reported that the only factor predictive of urethral stenosis was the number of needle planes used in the

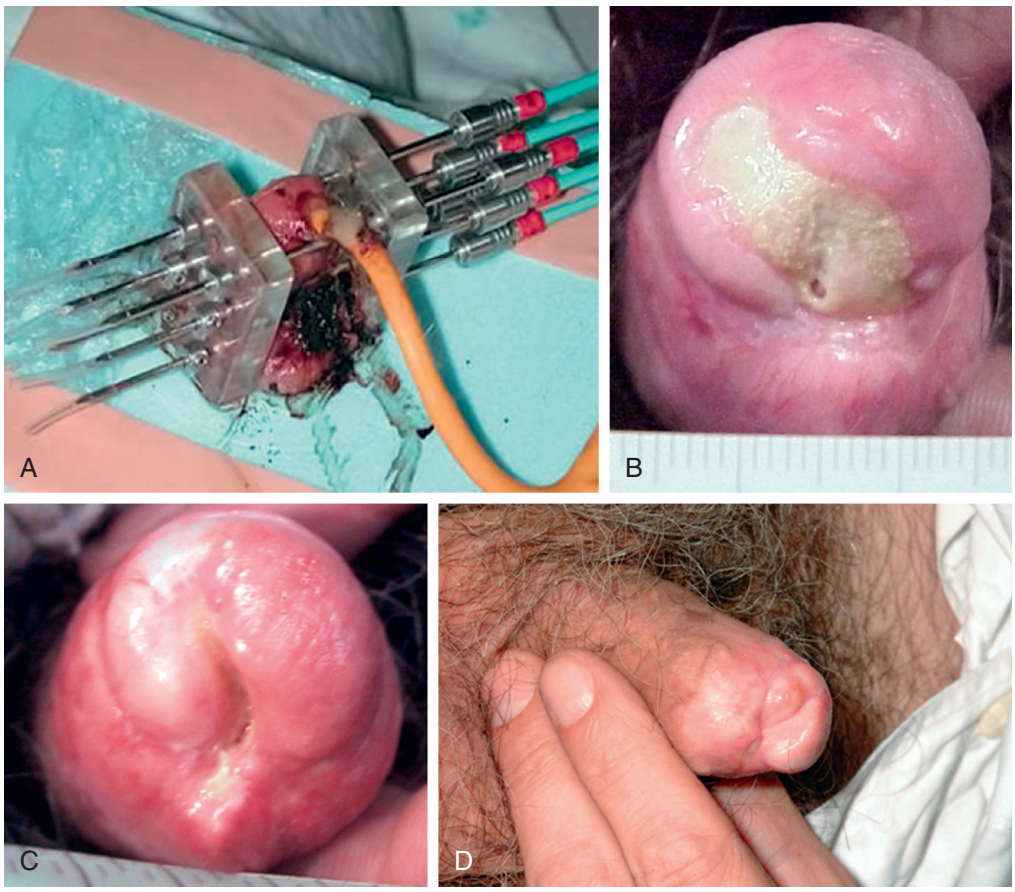


Figure 57-6 **A,** 47 year old man with deeply invasive moderately differentiated SCC, T3pN0 who had staging node dissection but refused penectomy. **B,** The patient suffered a severe necrosis following brachytherapy and tumor response. **C,** Healed with hyperbaric oxygen. **D,** Result shown 5 years later. Patient is potent and disease-free.

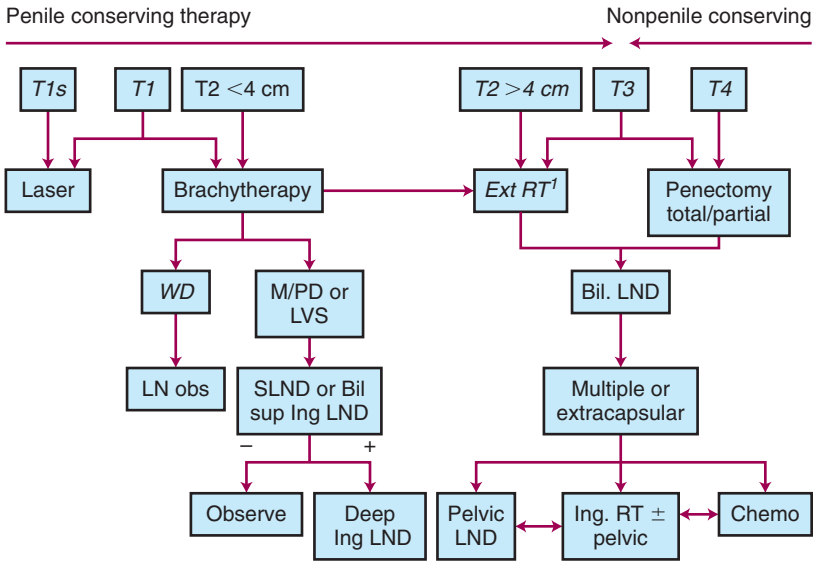


Figure 57-7 Treatment algorithm for penile cancer. External irradiation is a reasonable option for T1 and small T2 tumors if brachytherapy is not available. *Bil sup,* Bilateral superficial; *EXT RT,* external radiation; *Ing,* inguinal; *LN,* lymph node; *LND,* lymph node dissection; *LN Obs,* lymph node observation; *LVS,* lymphovascular space; *M/PD,* moderately/poorly differentiated; *SLND,* sentinel lymph node dissection; *WD,* well differentiated.

implant ($p = 0.001$, if two planes).[32] When a three-plane implant is indicated because of tumor size or morphology, central plane needles will be close to the urethra.[75] A pulse-dose-rate remote afterloader allows optimization of dwell times to limit the urethral dose.

Urethral adhesions in the acute phase should be separated to avoid development of a chronic problem. Patients can be given a meatal dilator at their first follow-up visit with instructions to use it as required. Many late urethral stenoses are low grade and can be managed with repeat dilatations, or even self-dilatations, often at infrequent intervals. Severe cases may require reconstructive surgery, such as urethroplasty or meatoplasty.

Sexual Function

The impact on sexual function often is not assessed. Crook et al[77] found that in a series of 49 men treated with brachytherapy, 22 of 27 who were potent at baseline reported satisfactory potency at last follow-up. Delannes et al[35] observed that apart from one patient who developed painful erections resulting from sclerosis, "sexual function did not appear to be altered by the implant." Sarin et al[2] provided details for only 14 of the 59 patients, commenting that 12 were normal and 2 had minor impairment. Mazeron et al[33] stated that for noninfiltrating or moderately infiltrating tumors less than 4 cm in diameter, "sexual function remained the same as before treatment." A recent systematic survey of 21 French patients (median age 73 years) treated by brachytherapy a median of 80 months previously, 59% remained sexually active, and 79% maintained nocturnal erections. None reported a "loss of manliness," but 53% noted a change in sensitivity of the glans.[69]

Incorporation of a layer of 2 mm of lead into the supporting collar around the penis will limit total dose to the anterior testis to 55 cGy and 26 cGy to the posterior testis during a 60-Gy pulse-dose-rate treatment course[58] as measured by thermoluminescent dosimeter. No data are available on post-brachytherapy sperm counts.

Other Late Sequelae

Mottled hypopigmentation or hyperpigmentation, telangiectasia, and mild to moderate focal fibrosis may occur. Some atrophy of the glans in areas of deep tumor infiltration is common.

TREATMENT ALGORITHM, CONTROVERSIES, AND CHALLENGES

Penile cancer is a rare but psychologically devastating disease. The functional and sexual implications of treatment should be discussed with patients.

Our preferred treatment algorithm is shown in Figure 57-7. For Tis, T1, and T2 tumors less than 4 cm in diameter, a penile-conserving approach as primary management is warranted. Laser surgery can provide satisfactory cosmesis, function, and local tumor control, especially for Tis or small T1 lesions, with the option of retreating local recurrences with further laser surgery. The RT of choice is interstitial brachytherapy, which results in penile preservation in 70% of cases at 10 years. If brachytherapy expertise is not available, EBRT can prevent amputation in 50% to 60% of patients. For more locally advanced lesions (T2 > 4 cm, T3, ? T4), concurrent chemoradiation should be evaluated. With any penis-conserving approach, protracted follow-up is necessary because local failure can occur many years later and surgical salvage can be curative.

Observation of regional nodes is recommended for low-risk T1 and T2 tumors that are well differentiated with no evidence of lymphovascular space invasion. Moderately or poorly differentiated tumors and all T3 tumors should have surgical staging of regional lymph nodes.

Squamous cell carcinoma of the penis remains a clinical challenge. Although it is highly curable in its early stages, the challenge is to minimize the psychosexual morbidity of treatment through less aggressive surgical approaches or alternatives to surgery such as brachytherapy without compromising cure. When diagnosis is delayed and the patient presents with advanced disease, the fatality rate is high.

Rare tumors do not achieve the same level of public awareness as the more common malignancies. Public education and support groups for breast or prostate cancer are well established and successful. For penile cancer there is a need to educate the public and physicians about risk factors, warning signs, and early diagnosis. It is unfortunate that men should ever present with locally advanced disease on such a readily visible and easily examined organ.

Enhanced clinical staging with MRI may prove to be a useful adjunct to physical examination when invasion of the

corpora is suspected but not certain (eFigure 57-2). Dynamic sentinel node mapping spares patients with high-risk disease (G2 to G3 or T3) the morbidity of a staging superficial inguinal node dissection (eFigure 57-2).

Cooperative group efforts such as the upcoming trial from the International Rare Cancers Initiative (InPACT) are required to determine the most effective aggressive multimodality approach for the patient with locally advanced disease.

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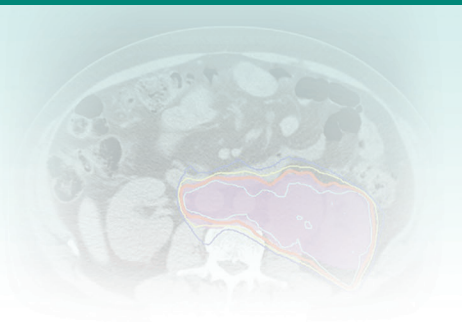
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Overview

Gillian M. Thomas

This overview provides an introduction to the chapters on specific gynecologic tumors that follow, including discussions of cancer of the cervix, uterine corpus, vulva and vagina, and ovary. It highlights important clinical issues and areas of controversy. The etiologic and epidemiologic differences among these tumors are addressed in the relevant chapters. Progress toward improving outcomes is slow but where gains in the therapeutic ratio have resulted they are addressed for each tumor site.

Gynecologic cancers continue to be staged using the FIGO staging system. In 2009 the FIGO staging system was modified from the previous version of 1988. Each sites specific chapter will note the differences. Caution needs to be taken because changes in the FIGO staging system may not allow direct comparisons of outcomes by stage between the new and the old systems.

Conformal radiotherapy techniques including intensity-modulated radiation therapy (IMRT) and image-guided brachytherapy (IGBT) appear in some situations to have improved the therapeutic ratio of radiation principally by decreasing dose received by normal tissues and therefore an expectation for decreasing incidence of acute and late complications. Its implementation for gynecologic cancers has lagged behind that in other tumor sites for a variety of valid reasons. Caution around the possibility of geographic miss of tumor because of imposed dose constraints for normal tissues must be exercised; for cervical cancer close margins in tumor may result in underdosage if internal organ motion and changing tumor configurations are not taken into account.[1] Consistent guidelines for the use of IMRT at least in the postoperative adjuvant setting for endometrial and cervical cancer are published and are undergoing revision. This has facilitated wide uptake.[2] It is critical to deliver acceptable radiation volumes and dose, that strict measures of quality assurance for physics, dosimetry, and tumor volume delineation be practiced.

Promising novel therapies are currently being investigated in Phase I, Phase II, and some Phase III studies in cervical, ovarian, and endometrial cancers. These therapies are based on the identification of specific pathways of tumor progression that can be targeted for interruption (e.g., angiogenesis and the identification of "druggable" molecular targets).

In addition to this direction of development are the multiple progressive steps made in novel imaging techniques. It is anticipated with optimism that techniques such as positron emission tomography–computed tomography (PET-CT) scanning, magnetic resonance diffusion imaging, and spectroscopy will enable a conjunction of anatomic and functional imaging to more accurately define tumor volumes and that these techniques will act as both predictive and response biomarkers as has been observed in cervical cancer.[3,4]

Disseminated metastatic disease remains a problem but the utility of standard chemotherapeutic agents in various combinations, doses, and strategies has leveled out and is far from optimal. Thus, the identification of new biomarkers and targeted molecular therapies to these markers constitutes a rational new research direction for the management of disseminated disease. The ultimate anticipation from these advances is that individual patients or small groups of patients expressing specific biomarkers may be treated with a targeted therapy most suited to those individuals and their respective tumors. It is hoped that cancer research will lead to an era of "personalized" medicine. The splitting of population into smaller groups however, makes the conduct of Phase III trials extremely difficult.

CERVICAL CANCER

In cervical cancer, hypoxia and angiogenesis form part of a common pathway to cancer development and progression. The antiangiogenic agent, bevacizumab, was recently reported in a Phase III trial in recurrent, persistent or metastatic disease to improve overall survival (OS) in a selected population by 3.7 months compared to standard chemotherapy (median OS 17.0 versus 13.3 months, $p = 0.004$).[5]

Although Phase II data have demonstrated the tolerability of combining bevacizumab with definitive pelvic irradiation and concurrent cisplatin, recent discussions with the National Cancer Institute (NCI) and the pharmaceutical producers of bevacizumab suggest that these data will not be used to proceed to a larger randomized Phase II or Phase III trial with this agent.[6] Currently a randomized Phase II trial is proceeding with the agent triapine (ribonucleotide reductase inhibitor that inhibits radiation damage repair) added to chemoradiation.[7] The paucity of patients with cervical cancer in the developed world means that future trials to advance outcomes in locally advanced cervix cancer will of necessity be international in scope. At the present time, the international "outback trial" is proceeding, which examines the role of adjuvant chemotherapy after standard chemoradiation to the pelvis.[8] It is unlikely that further large-scale trials in locally advanced cervical cancer will be conducted until this trial completes accrual.

Although IMRT is being used widely in adjuvant treatment of cervical cancer, its role in the intact cervix is still not widely accepted given the necessity for strict quality assurance measures to ensure tumor coverage of the mobile target of the cervix and uterus.

ENDOMETRIAL CANCER

In endometrial cancer in addition to similar exploration of angiogenesis inhibitors and tyrosine kinase inhibitors is the exploration of MTOR inhibitors including temsirolimus, everolimus, and deforolimus. Forty to 80% of women with type I endometrial carcinoma have a mutation in PTEN, which up regulates MTOR activity making its inhibition a rational target. Significant response rates have been reported in patients who are chemotherapy naïve with advanced or recurrent endometrial cancer although response in this study is not correlated with PTEN status.[9] Various combinations of these MTOR inhibitors with chemotherapy or with other biologic agents are being conducted.

The relative roles of adjuvant chemotherapy and radiation in locally advanced disease remain unclear. The pending results of completed randomized Phase III trials should clarify this considerably.

VULVAR AND VAGINAL CARCINOMA

Vaginal carcinoma treatment continues to be based on extrapolations of information from cervical cancer with its similar herpes papillomavirus (HPV) etiology. Refinements in the delivery of irradiation using conformal methods such as IMRT, at least for boosting locally advanced disease where brachytherapy is inappropriate, may help to decrease potential toxicities of radiation therapy.

The major advance in the treatment of vulvar cancer with definitive or neoadjuvant chemoradiation has been the ability also to use more conformal radiation techniques. Vulvar cancers are often difficult to image on magnetic resonance imaging (MRI) so the importance of merging planning information from scans as well as the clinical appearance of the tumor is vital. It continues to be widely important to encompass the entire tumor rather than compromising tumor volume coverage to further spare some adjacent normal tissues. Unfortunately, no level-1 evidence is available to clearly define tumoricidal doses for definitive chemoradiation. In this highly radiosensitive tumor, application of basic principles with regard to delivering the irradiation component of treatment must apply.

OVARIAN CANCER

In heritable ovarian cancer, those with *BRCAI* or *BRCAII* mutations, poly ADP ribose polymerase (PARP inhibitors), may specifically target tumor cells that are deficient in their ability to repair DNA double-stranded breaks. Several PARP inhibitors are currently under investigation in *BRCA*-deficient cancers. Early results from Phase II trials are encouraging.

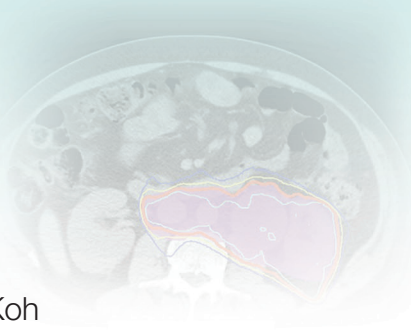
In advanced ovarian cancer results of two Phase III studies were recently reported.[10,11] The combination of bevacizumab and chemotherapy followed by maintenance bevacizumab alone modestly increased the progression-free survival by 3.8 months and 1.7 months compared to the use of chemotherapy alone or with concurrent bevacizumab. This finding has major societal implications not only for patients with ovarian cancer but also for future implementation of widespread use of expensive targeting agents, which may provide some advantage in progression-free survival, not as yet in overall survival but may not be affordable for general use.

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CHAPTER

58 Cervical Cancer



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INCIDENCE

Worldwide, cervical cancer is the third-most common cancer in women, accounting for more than 500,000 new cases and approximately 275,000 deaths. However, in the United States the incidence of cervical cancer is quite low, accounting for less than 13,000 cases annually and approximately 4,000 deaths each year.

BIOLOGY

In 80% to 90% of cases, the histologic type is squamous cell carcinoma; the frequency of adenocarcinoma is increasing. In approximately 90% of patients, there is an association with human papillomavirus (HPV) infection. Recognized tumor-associated prognostic factors are stage, tumor size, lymph node metastasis, and hemoglobin level.

STAGING EVALUATION

International Federation of Gynecology and Obstetrics (FIGO) staging includes physical examination, chest radiography, and intravenous pyelography or alternative imaging to assess for ureteral obstruction; in highly selected cases (based on relevant symptoms), cystoscopy, proctoscopy or barium enema, and bone films are needed. It is often useful, where available (but does not influence the FIGO stage), to include more accurate radiologic tests (e.g., computed tomography [CT], magnetic resonance imaging [MRI], positron emission tomography [PET], and lymph node sampling).

PRIMARY THERAPY

The choice of primary therapy and the resulting overall survival (OS) are related to disease extent at the time of initial diagnosis and staging evaluation:

- For stage IA disease, either simple hysterectomy or brachytherapy result in 5-year OS of >98%. For selected patients, radical trachelectomy represents a fertility-sparing treatment option.
- For stage IA2 or limited IB1 disease, radical hysterectomy with pelvic node dissection is the preferred treatment and results in a 5-year OS of 90% to 95%. However, for patients who are not surgical candidates for whatever reason, primary irradiation with or without concurrent chemotherapy is a reasonable alternative.
- Concurrent chemoradiation (chemoRT) is appropriate primary therapy for stages IB2-IVA disease with 5-year OS dependent on stage (IB2/IIA, 80% to 95%; IIB, 70% to 85%; III, 40% to 65%; IVA, 15% to 25%).

ADJUVANT THERAPY

Radiation therapy (RT), with or without cisplatin-based concurrent chemotherapy after radical or modified radical hysterectomy, is recommended for patients with intermediate- or high-risk features. Adjuvant hysterectomy after RT is not routinely recommended and may be avoided entirely if image-based brachytherapy is feasible but may benefit occasional patients with persistent isolated cervical disease after concurrent chemoRT. Neoadjuvant chemotherapy has no proven benefit before RT or surgery for locally advanced disease. Concurrent RT has resulted in multiple positive Phase III trials for survival compared with RT alone.

PALLIATION

Strategies for symptom relief are most important for residual or recurrent disease. Cisplatin in combination with paclitaxel or topotecan chemotherapy is given but is largely ineffective in prolonging survival times. The addition to bevacizumab was associated with an approximately 4-month improvement in OS at the risk of an increase in grade-2 or higher hypertension, grade-3 or higher thromboembolic events, and grade-3 or higher gastrointestinal fistulas. Irradiation often provides excellent short-term relief of pain and bleeding, particularly in patients with no history of prior RT.

The incidence of and mortality rates from invasive cervical cancer have steadily declined in the United States over the past five decades, in part because of the successful implementation of screening programs that detect many cancers at a preinvasive stage. Unfortunately, cytologic screening programs have failed to comprehensively penetrate the population, with many medically underserved or uneducated communities at risk. Invasive cervical cancer continues to be a major public health problem internationally. In the United States, 60% of women with newly diagnosed invasive cervical cancers have not had a Papanicolaou (Pap) smear for 5 years or longer.

During the past decade, much has been learned about the etiology and biology of cervical cancer. Epidemiologic studies have long demonstrated that patterns of occurrence suggest the disease stems from a sexually transmitted agent. Nearly all cervical cancers contain HPV DNA. There is compelling evidence for a causal relationship between HPV and cervical carcinoma.

Even invasive cervical cancer is highly curable if detected at an early stage. Radiation and surgery yield comparable cure rates of 80% to more than 95% for patients with early-stage disease. RT including brachytherapy plus concurrent chemotherapy, which is the treatment of choice for patients with locally advanced disease, is curative in more than 80% of patients with FIGO stage II disease and in about 50% of patients with FIGO stage III disease.

EPIDEMIOLOGY AND ETIOLOGY

In the United States, cervical cancer is responsible for about 2% of the cancer deaths in women, with less than 13,000 new

cases of invasive disease and 3000 to 4000 deaths each year.[1] Worldwide, invasive cervical cancer is the third-most common malignant tumor in women (after breast and colorectal cancers) and accounts for nearly 500,000 cases and 275,000 deaths per year.[2] Incidence rates range from as low as 3 to 4 per 100,000 in Israel to more than 80 per 100,000 in Recife, Brazil.[3] Presumably, this wide range reflects a variation in epidemiologic risk factors that is compounded by the lack of adequate screening programs in poor communities. The relatively high international mortality rates may also reflect the greater number of women who present with advanced disease when screening programs and patient education are inadequate and access to medical resources is limited or nonexistent. Because of the lack of cancer registries, it is likely that reported incidence and mortality rates grossly underestimate the magnitude of the problem.

Risk factors for the development of carcinoma of the cervix and its intraepithelial precursors follow a pattern typical of sexually transmitted diseases. These include first coitus at a young age, multiple sexual partners, a history of other sexually transmitted diseases, and high parity.[4] Weaker associations have been suggested with cigarette smoking and the use of oral contraceptives. In contrast, the risk of developing cervical cancer is low in women who are nulliparous or virginal. Among women with only one lifetime sexual partner, past and current high-risk sexual behavior by the male partner has a substantial role in the development of cervical carcinogenesis.[5] Conversely, male circumcision is associated with a reduced prevalence of penile HPV infection and a reduced risk of cervical cancer in the current sexual partners.[6]

Until recently, the reasons for these associations were only the subject of speculation. Today, however, the epidemiologic findings, combined with the results of molecular studies (discussed in detail later), are sufficient to identify sexually acquired HPV infection as the primary etiologic agent in the development of most cervical cancers.[7,8]

Although the epidemiology of cervical adenocarcinoma is somewhat less well understood, studies also reveal the presence of HPV DNA in most cases.[9] It is interesting that in the United States, the absolute and relative incidence of adenocarcinoma appears to have increased in contrast to the steady decrease in the rate of invasive squamous carcinoma. This may reflect, in part, differences in the effectiveness of cytologic screening in detecting adenocarcinoma at a preinvasive stage.[10] Some investigators have implicated oral contraceptives as a possible risk factor for adenocarcinoma, with biological differences in gene expression potentially implicated in carcinogenesis.[11,12]

Clear cell carcinoma, a rare form of cervical and vaginal adenocarcinomas, has been clearly linked with prenatal exposure to diethylstilbestrol (DES), a drug that was used to prevent miscarriages in the 1940s and 1950s.[13] Prenatal DES exposure arrests development of the transformation zone in the upper third of the vagina, which accounts for the location of these lesions. The average age at which cancer in patients exposed to DES was diagnosed was 19 years, much younger than the average age of patients with newly diagnosed squamous carcinoma or non-DES–related adenocarcinoma. New diagnoses of DES-related clear cell carcinoma have declined now that the youngest cohort of patients exposed to DES has passed the age of peak incidence.

PREVENTION AND EARLY DETECTION

Although there have been significant changes in the fields of radiation and gynecologic oncology, the dramatic decrease in cervical cancer mortality from the 1940s to the 1980s is primarily the result of the success of mass screening programs.[14,15] The cervix is an ideal target for cancer screening because of its accessibility, the long average time interval from the initial DNA insult to the development of invasive cancer, and the high cure rate with appropriate treatment of preinvasive and early invasive lesions.

Squamous cell carcinomas originate at the squamocolumnar junction (transformation zone) of the cervix. Invasive lesions are frequently associated with adjacent preinvasive or in situ disease (low-grade squamous cell intraepithelial lesion [LGSIL] or high-grade squamous cell intraepithelial lesion [HGSIL]) (Table 58-1).

Longitudinal studies suggest a long average time to progression from HGSIL to invasive disease. Peterson[16] described 127 patients with carcinoma in situ (CIS; HGSIL) who were followed for at least 3 years. At the end of 10 years, invasive carcinoma had developed in about 30%. Koss et al[17] observed spontaneous regression of 25% in 67 patients with untreated CIS (HGSIL) who were observed for 3 years. In a later analysis of this series, the authors reported that invasive lesions had developed in 40% of the original 67 patients.[18] In another longitudinal study of patients with untreated CIS (HGSIL), Kottmeier[19] observed progression to invasive carcinoma in 71% and 80% of patients followed for 12 and 30 years, respectively.

TABLE 58-1 Relationship of the Bethesda System to Previous Classifications

Normal Limits	**Benign Cellular Changes**		**Epithelial Cell Abnormalities**			
	Infection Reactive repair	ASCUS AGUS	LGSIL HPV	HGSIL		Invasive carcinoma
			Mild dysplasia CIN1	Moderate dysplasia CIN2	Severe dysplasia CIS, CIN3	
I	II		III		IV	V
			Papanicolaou Classification			

Bethesda System Terminology
AGUS, atypical glandular cells of unknown significance
ASCUS, atypical squamous cells of unknown significance
HGSIL, high-grade squamous cell intraepithelial lesion
HPV, human papillomavirus
LGSIL, low-grade squamous cell intraepithelial lesion

Adapted from Shingleton HM, Patrick RL, Johnston WW, et al: The current status of the Papanicolaou smear. CA Cancer J Clin 45:305–320, 1995.
CIN, *Cervical intraepithelial neoplasia;* CIS, *carcinoma in situ.*

TABLE 58-2 International Federation of Gynecology and Obstetrics Staging of Carcinoma of the Cervix

Stage I	The carcinoma is strictly confined to the cervix *(extension to the corpus should be disregarded).*
Stage IA	Invasive cancer identified only microscopically. All gross lesions, even with superficial invasion, are stage IB cancers. Invasion is limited to measured stromal invasion with a maximum depth of 5 mm and no wider than 7 mm. *(The depth of invasion should not be more than 5 mm taken from the base of the epithelium, either surface or glandular, from which it originates. Vascular space involvement, either venous or lymphatic, should not alter the staging.)*
Stage IA1	Measured invasion of stroma no greater than 3 mm in depth and no wider than 7 mm.
Stage IA2	Measured invasion of stroma greater than 3 mm and no greater than 5 mm in depth and no wider than 7 mm.
Stage IB	Clinical lesions confined to the cervix or preclinical lesions greater than IA.
Stage IB1	Clinical lesions no greater than 4 cm in size.
Stage IB2	Clinical lesions greater than 4 cm in size.
Stage II	The carcinoma extends beyond the cervix but has not extended onto the pelvic wall; the carcinoma involves the vagina but not as far as the lower third.
Stage IIA	No obvious parametrial involvement.
Stage IIA1	Clinical lesions no greater than 4 cm in size.
Stage IIA2	Clinical lesions greater than 4 cm in size.
Stage IIB	Obvious parametrial involvement.
Stage III	The carcinoma has extended onto the pelvic wall; on rectal examination there is no cancer-free space between the tumor and the pelvic wall; the tumor involves the lower third of the vagina; all cases with a hydronephrosis or nonfunctioning kidney should be included, unless they are known to be due to another cause. No extension onto the pelvic wall but involvement of the lower third of the vagina.
Stage IIIA	Extension onto the lower third of the vagina.
Stage IIIB	Extension onto the pelvic wall or hydronephrosis or nonfunctioning kidney.
Stage IV	The carcinoma has extended beyond the true pelvis or has clinically involved the mucosa of the bladder or rectum.
Stage IVA	Spread of the growth to adjacent organs.
Stage IVB	Spread to distant organs.

From Pecorelli S, Zigliani L, Odicino F: Special communication. Revised FIGO staging for carcinoma of the cervix. Int J Gynecol Obstet 105:107–108, 2009.

In addition, a relatively long interval appears to lapse between the diagnosis of dysplasia and the development of HGSIL. One large prospective study reported mean times for progression to HGSIL development of 58, 38, and 12 months for patients with mild, intermediate, or severe dysplasia, respectively.[20] These results are consistent with the finding that the mean age of women diagnosed with cervical intraepithelial neoplasia (HGSIL) is about 16 years younger than that of women diagnosed with invasive carcinoma.[21]

Although a number of classifications have been used, the Bethesda system is currently the most widely accepted method of categorizing cervical cytologic specimens in the United States.[22] The relationship between this system and previous classification systems is outlined in Table 58-2.

Multiple organizations including the American College of Obstetrics and Gynecology (ACOG),[23] U.S. Preventive Services Task Force (USPSTF),[24] the American Society for Colposcopy and Cervical Pathology (ASCCP), and the American Society for Clinical Pathology (ASCP)[25] have guidelines for screening for cervical cancer, and all are fairly consistent. All endorse that cervical cancer screening begin at age 21 years regardless of age of onset of sexual intercourse and discontinued at 65 years, provided that three prior consecutive tests have been negative. Before the age of 30, cytologic tests should be done every 3 years. For women older than 30 years, HPV DNA cotesting every 5 years is recommended by ASCCP and ASCP (with cytology is recommended by ACOG). However, the USPSTF recommends cytology every 3 years, though accepts cotesting for HPV and cytology every 5 years as an acceptable alternative.

Women with human immunodeficiency virus (HIV) infection, those who are immunosuppressed, those who have been exposed in utero to DES, or those who have been previously treated for cervical intraepithelial neoplasia (CIN) stage II or III or cancer may require more frequent screening. As compared with annual screening, mathematical modeling predicts the excess risk of cervical cancer with less frequent screening intervals to be approximately 3 in 100,000.[26]

Despite the proven efficacy of cytologic screening, many women remain unscreened. In the United States, 50% of women with newly diagnosed invasive cervical cancer have never had a Pap smear and another 10% have not had a Pap smear in 5 years.[8] Women who tend to be underscreened in the United States fall into groups of postmenopausal, uninsured, ethnic minority, and especially, elderly black and poor women in rural areas. In the United States, about 25% of the cervical cancer cases and 41% of the deaths occur in women who are age 65 years or older. In addition, nearly 50% of women older than 60 years have not had a Pap smear in 3 years, even though many have seen a physician for other medical reasons.

In areas of the world in which screening programs are either prohibitively expensive or the infrastructure is not available, alternative and more accessible programs have gained attention. One of these is the use of visual inspection with acetic acid (VIA), which has been evaluated in two large trials in India.[27,28] In one study, more than 150,000 women in rural India were randomly assigned into two cohorts in a planned 16-year study; both had access to cancer education but only one cohort was additionally followed with four rounds of VIA.[27,28] As presented at the 2013 American Society of Clinical Oncology Annual Meeting, VIA resulted in a reduction in the age-adjusted mortality rate compared to just education (14.4 versus 20 per 100,000 women-years of observation),

translating into a 30% reduction in the risk of death. Estimates are that this simple procedure would save almost 22,000 women a year in India alone.

PATHOLOGY AND PATHWAYS OF SPREAD

Eighty percent to 90% of cervical cancers are squamous cell lesions. Squamous cell neoplasms are frequently subcategorized as large cell keratinizing, large cell nonkeratinizing, or small cell carcinomas.[29,30] The latter should not be confused with anaplastic small cell carcinomas, which have histologic features that resemble small cell neuroendocrine neoplasms of the lung and tend to have a particularly aggressive clinical course.[31,32]

The frequency of primary cervical adenocarcinoma is about 10% to 20%, but it appears to have been increasing recently, particularly in younger women.[33,34] Cervical adenocarcinomas can originate high in the endocervical canal and can be missed with standard cytologic screening collection methods. The perceived increased frequency of cervical adenocarcinomas may be attributed to a decreased incidence of squamous cell carcinomas in the screened population without a concomitant decreased incidence of cervical adenocarcinomas. Whether conventional screening methods are insensitive to the detection of adenocarcinoma precursor lesions or whether such precursor lesions progress more quickly to invasive disease has not been determined. Nonetheless, women who participate in a cytologic screening program and develop cervical adenocarcinoma are more likely to have early-stage disease than an unscreened cohort. Most cervical adenocarcinomas are mucinous with features suggestive of endocervical glandular epithelium; about 20% demonstrate other müllerian neoplastic patterns. Others may be adenosquamous in type.

The cervix is richly supplied with lymphatics organized into three anastomosing plexuses that drain the mucosal, muscularis, and serosal layers.[35] The most important lymphatic collecting trunks exit laterally from the uterine isthmus in three groups[35,36]: the upper branches originate in the anterior and lateral cervix and follow the uterine artery, the middle branches drain to the deeper hypogastric (obturator) nodes, and the lowest branches drain posteriorly to the inferior and superior gluteal, common iliac, presacral, and subaortic lymph nodes.

The incidences of pelvic lymph node involvement for patients with FIGO stages IB, IIB, and IIIB cervical cancer are approximately 15%, 30%, and 50%, respectively.[37-40] The incidence of paraaortic lymph node metastasis also increases with tumor stage; about 5%, 20%, and 30% of patients with FIGO stages IB, IIB, and IIIB disease, respectively, have paraaortic lymph node metastasis at diagnosis.[37] For each stage, the risk of lymph node involvement is further correlated with tumor size.[41,42]

Hematogenous metastases are rarely detectable at diagnosis, and recurrent pelvic disease is seen in about two thirds of patients who relapse after treatment. Distant metastases are also a common feature of disease relapse. In a study of disease relapse patterns from the Mallinckrodt Institute of Radiology, Fagundes et al[43] reported 10-year actuarial rates for distant metastasis of 16%, 31%, 26%, and 39% for patients treated with radiation for FIGO stages IB, IIA, IIB, and III disease, respectively. These may well be underestimated if pelvic disease is detected as the first site of relapse because systematic radiologic evaluation may not be performed. The most common site of extrapelvic metastasis was the lungs, followed by the paraaortic lymph nodes. Although the lumbar spine has been reported to be a relatively frequent site of skeletal metastasis, studies that include CT scanning suggest that patients who appear to have had metastases isolated to the lumbar spine may actually have had direct tumor extension from paraaortic disease.[44]

Prognostic Factors

With the exception of distant hematogenous metastases, the presence of retroperitoneal nodal involvement represents the most significant negative prognostic factor in patients with cervical cancer.[38,45] The evaluation of other prognostic factors, however, is to a great degree predicated on whether patients have early-stage tumors that are often managed surgically or more locally advanced cancers that have received definitive chemoRT. The availability of a hysterectomy specimen for full pathologic review allows finer assessment of primary associated and extrauterine risk factors, although these factors may be superseded in larger tumors with obvious extracervical extension.

In a prospective surgicopathologic evaluation of 645 patients with clinical stage IB disease who underwent radical hysterectomy and pelvic lymphadenectomy, independent prognostic factors for disease-free survival included pelvic nodal metastases, clinical tumor size (within stage IB classification), capillary-lymphatic space invasion, and depth of tumor infiltration into the cervical stroma.[38]

In more advanced lesions, a multivariate analysis of 642 patients entered into three Gynecologic Oncology Group (GOG) prospective clinical trials of definitive RT demonstrated that the presence of positive paraaortic nodes was the single most important independent predictor for relapse and survival, overwhelming all other risk factors. The next two most important prognostic factors (pelvic nodal involvement and tumor size) retained significance only in the absence of paraaortic metastases. Other weaker prognostic variables included clinical stage, patient age, and performance status. In this analysis of more advanced tumors, cell type, histologic grade, and pretreatment hematocrit and peritoneal cytologic findings were not significant prognostic factors when the preceding variables were taken into account.[45]

MOLECULAR BIOLOGY

HPV is a small, double-stranded DNA virus that belongs to the papovavirus group. To date, more than 80 different strains of HPV have been isolated using polymerase chain reaction analysis.[42] HPV infection occurs in the basal cell layer of the epithelium, which becomes a continuous reservoir of HPV DNA as the viral genome replicates itself in the dividing cells. As the epithelial cells mature, viral DNA replication continues in the absence of basal cell division, increasing the HPV DNA copy number per cell.[46] Microscopically, this process is associated with koilocytosis, a finding considered pathognomonic of HPV infection.[47]

Of the many strains that have been characterized, HPV-16 and HPV-18 have been most commonly associated with squamous cell carcinoma and adenocarcinoma, respectively.[48,49] HPV 18 has been associated with a worse prognosis than HPV 16.[50] HPV-31, HPV-33, and HPV-35 have also been associated with malignancy, whereas HPV-6 and HPV-11 are usually associated with benign viral condyloma or mild dysplastic epithelial changes such as CIN1.[48,51-56]

HPV carcinogenesis is mediated through oncogenes *E6* and *E7*. Transgenic mouse experiments provide some of the strongest in vivo evidence linking *E6* and *E7* expression to the development of cervical cancer.[57,58] The mechanisms by which HPV influences oncogenic activity are shown in Figure 58-1. The E6 protein of HPV oncogenes binds with the E6-associated

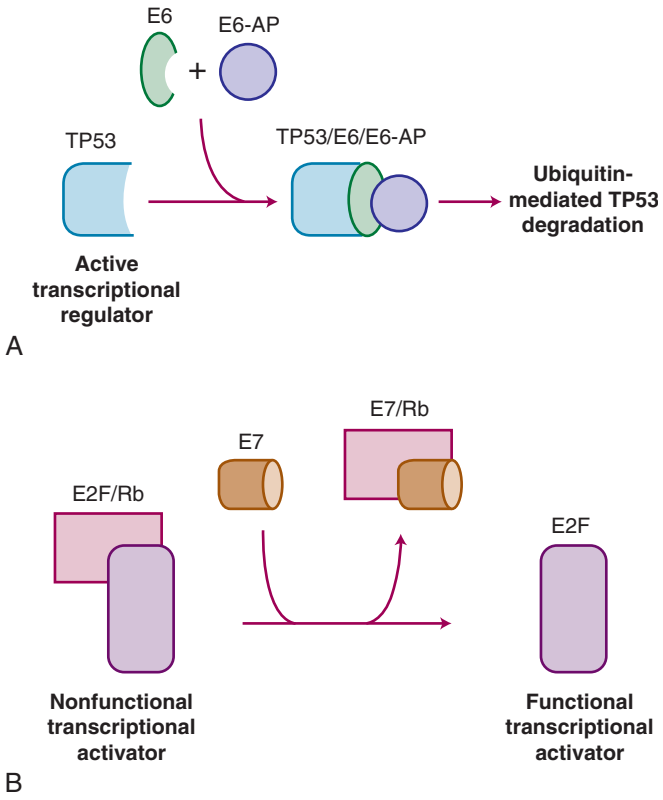


Figure 58-1 Biologic consequences of viral oncoprotein interactions with cellular tumor suppressors. **A,** Schematic representation of mechanism by which the *E6* gene is hypothesized to inactivate the TP53 protein through ubiquitin-mediated degradation of TP53. **B,** Role of *E7* gene in altering activity of the cellular transcription factor E2F via its capacity to bind the RB protein.

protein (E6-AP) to the TP53 protein, which results in the degradation of TP53, an important negative regulator of cell growth. Thus, by binding and degrading the TP53 protein, E6 proteins contribute to the pathogenesis of cancer by removing the critical and protective function of TP53.[59] The E6 proteins of oncogenes from a carcinogenic HPV strain, such as HPV-16 and HPV-18, bind TP53 more efficiently than oncogenes from HPV strains not involved in carcinogenesis, which possibly explains the differences in oncogenicity of these strains.[60] By itself, E6 is not capable of inducing transformation, but it induces immortalization of primary human keratinocytes in conjunction with E7, the protein of which binds to and functionally inactivates the gene product of the retinoblastoma *(RB)* tumor suppressor gene. This binding results in the uncontrolled release of active transcription factors (E2F) and unregulated progression through the cell cycle. Biologic differences between low-risk and high-risk HPV viruses include observations that the latter are capable of inducing chromosome abnormalities in normal keratinocytes and are more likely to interfere with cell cycle regulatory proteins and checkpoints.[61] More recently, several recurrent genomic alterations in cervical carcinomas were identified. Gene expression levels at HPV integration sites were statistically significantly higher in tumors with HPV integration compared with expression of the same genes in tumors without viral integration at the same site.[62]

The evidence implicating HPV in the pathogenesis of cervical cancer is conclusive. It includes (1) multiple epidemiologic studies demonstrating HPV infection as the most important risk factor for the development of squamous cell intraepithelial lesions and cervical carcinomas, (2) detection of HPV DNA in more than 90% of cervical cancers and their precursor lesions, (3) evidence of HPV transcriptional activity in neoplastic tissues, and (4) evidence that HPV oncogenes can mediate malignant transformation in transgenic mice.[57,58] The precise rate of development for both low- and high-grade squamous intraepithelial lesions in women infected with HPV is unknown. Longitudinal studies have demonstrated that the incidence of HPV infections among cytologically normal sexually active young women is high.[63] Most women infected with oncogenic HPV eliminate the infection and are at low or no risk for developing cervical neoplasia. The median duration of most new HPV infections is less than 1 year.[63] More than one third of women remain consistently or intermittently positive for HPV DNA, and many of these women will subsequently test positive for an HPV type that is different from the original HPV type.[64] The transient nature of HPV infections in younger women substantiates the common observation that low-grade cervical neoplasia frequently regresses to normal.[65]

Theoretically, other cofactors may interact with HPV to attenuate the body's immune response, promote persistent HPV infection, up-regulate E6/E7 expression, or enhance the genetic damage caused by HPV oncogene expression. Possible factors include smoking, oral contraceptive use, and infection with HIV.[66] Several case-control studies have linked smoking behavior to an increased risk of cervical neoplasia.[67,68] Carcinogens found in cigarette smoke are concentrated in cervical mucus,[69] and women who smoke have decreased numbers of antigen-presenting cells in cervical epithelium.[70] Thus, smoking may increase the risk for cervical cancer via changes in local immunity. Immunosuppression has long been recognized as a risk factor for the development of cervical carcinoma.[71] A positive link between oral contraceptive use and cervical cancer, however, is still uncertain.[72] Although other cofactors may be involved, the acquisition and persistence of HPV infection are critical to the development of cervical neoplasia.

With this knowledge, specific vaccines have been developed. A quadrivalent HPV (types 6, 11, 16, 18), bivalent HPV (types 16, 18), and 9-valent HPV (addition of types 31, 33, 45, 52, and 58) vaccine have been evaluated in large Phase III trials.[73-76,76a] The two initial trials, FUTURE II and PATRICIA, were designed to demonstrate efficacy in preventing incident HPV infection and high-grade premalignant lesions such as cervical intraepithelial neoplasia (CIN) grade 2 or 3 (CIN2+), or adenocarcinoma in situ (AIS).[74,75] These trials were relatively large (5500-18,500 vaccinees), blinded, randomized, and included women ages 15 years to 26 years.

All three vaccines demonstrate excellent safety and immunogenicity profiles. For these vaccines, in the cohorts with no evidence of baseline cervical cytology abnormalities, infection by any of the HPV types evaluated, or serologic evidence of past exposure to these HPV types, high efficacy against HPV type-related CIN3 was 100%.[74,75] Efficacy was lower (45%) in the analysis of cohorts that included women with prevalent infection at entry. These vaccines demonstrate partial cross-protection against infection caused by some other nonvaccine HPV types. However, the vaccines do not alter the course of established HPV infections.

Although the experience with HPV vaccination is still relatively nascent, ultimate prospects for the primary prevention of cervical neoplasia, particularly in areas of the world where screening is unavailable, are exciting, notwithstanding the currently associated costs of the required comprehensive population strategy.

Currently, the duration of protection has not been established. However, a study has demonstrated persistent serum antibodies for up to 8.4 years for the bivalent vaccine, which leads to an optimistic projection of its effectiveness.[77] The quadrivalent and bivalent vaccines are both approved by the U.S. Food and Drug Administration (FDA) for female and males 9 years to 26 years of age and are commercially available for intramuscular injection (three-dose sequence at 0, 2, and 6 months).

Using mathematical models, Kim and Goldie[78] predicted that the cost-effectiveness of HPV vaccination programs in the United States will ultimately depend on the duration of vaccine immunity and will be optimized by achieving high coverage in adolescent girls, targeting catch-up efforts for women up to 18 years or 21 years of age, and revising screening practices. Unfortunately, research has shown that targeted approaches to HPV vaccination based on specific risk factors are a poor strategy for implementation, and therefore, comprehensive strategies are recommended.[79]

CLINICAL MANIFESTATIONS, PATIENT EVALUATION, AND STAGING

Preinvasive and minimally invasive cervical cancers are usually detected by routine cytologic screening. Most patients with more advanced disease present with some form of abnormal vaginal bleeding—postcoital, menstrual, intermenstrual, or postmenopausal—that may be associated with a clear or foul-smelling discharge. Extreme pelvic tenderness, particularly if associated with fever, should be fully evaluated to rule out complicating pelvic inflammatory disease. The triad of sciatic pain, leg edema, and hydronephrosis is almost always associated with extension of disease into the pelvic side wall. Bladder and rectal symptoms also suggest locally advanced pelvic disease and the need for specific evaluation of the urinary and gastrointestinal tracts.

Staging and Patient Evaluation

The current clinical staging system for cervical cancer by FIGO was updated in 2009[80,81] and is detailed in Table 58-2. The only changes made from the previous 1994 classification were the elimination of stage 0 (preinvasive disease) and the subdivision of stage IIA into IIA1 (tumor ≤ 4 cm in size) and IIA2 (tumor > 4 cm). The subdivision of stage IIA parallels that of stage IB disease and reflects a partial appreciation of the prognostic impact of tumor size.

According to FIGO, only the results of palpation, inspection, colposcopy, endocervical curettage, hysteroscopy, cystoscopy, proctoscopy, intravenous urography, and plain films of the lungs and skeleton can be used to influence stage assignment. Suspected bladder or rectal involvement should be confirmed by biopsy. Because sophisticated imaging is unavailable for many in developing countries with a high incidence of locally advanced disease, FIGO staging precludes the use of other imaging studies, such as lymphangiography; CT, MRI, or PET scanning; or the findings of operative procedures, including laparoscopy or open lymphadenectomy. These cannot be used to change the stage designation. However, if CT is obtained, the urographic findings may be used to rule out hydronephrosis. The results of these other tests are of prognostic value and often influence treatment decisions, but institutions that publish reports on cervical cancer must adhere strictly to FIGO's rules for staging to enable comparisons using consistent data among studies. Although FIGO continues to depend on a predominantly clinical staging approach, it recognizes other clinicopathologic risk factors, such as lymphovascular space invasion and lymph node status, and advises that these features, although not affecting staging per se, be recorded when available. FIGO also acknowledges the potential benefits of contemporary imaging studies and surgical staging, where available, in helping to guide treatment.[81]

Imaging studies used to assess the extent of lymph node involvement include CT, MRI, lymphangiography, and PET. Historically, lymphangiography has previously been used to assist the design of radiation fields; although it was determined to be a good imaging technique for assessing the status of the paraaortic lymph nodes,[8] it is no longer available in most medical communities.

MRI of the pelvis has been increasingly used to evaluate local tumor extent.[82] MRI provides better definition of the extent of disease within the cervix than CT and may be valuable in detecting extension through the periphery of the cervix; it therefore may be particularly useful in assessing patients with disease confined to the cervix for whom surgery is being considered as primary treatment.[83] MRI may also be useful for detecting extension into the uterine body. Pelvic MRI and CT are both useful for designing radiation portals, particularly in defining the position of the draining lymph nodes and, therefore, the borders of and shielding on conformal radiation fields.[83,84] Sensitivity and specificity show no clear advantage with MRI over CT for detecting involved nodes.

PET scanning has been compared with CT scanning for assessing lymph node status before planned RT. Grigsby et al[85] compared PET with CT in a retrospective study of 101 consecutive patients with newly diagnosed cervical carcinoma. CT demonstrated enlarged pelvic lymph nodes in 20% and aortic lymph nodes in 7% of patients. PET demonstrated abnormal uptake in pelvic lymph nodes in 67% and in aortic lymph nodes in 21% of patients. Surgical staging was not routinely performed to verify the accuracy of imaging findings. A multivariate analysis showed that the detection of positive aortic lymph nodes by PET imaging was the most important prognostic factor for progression-free survival. Yen et al[86] conducted a prospective evaluation of PET versus MRI or CT staging of patients with newly diagnosed (35%) or recurrent (65%) cervical cancer. Verification of lesions identified on imaging was obtained via surgical biopsy or clinical follow-up. Although its diagnostic accuracy was similar for local lesions, PET was superior to both MRI and CT in identifying metastatic lesions. As a follow-up to their previous retrospective study,[87] investigators from the Mallinckrodt Institute of Radiology at Washington University have recently published a large prospective series of 560 patients with cervical cancer who underwent pretreatment imaging with fluorodeoxyglucose (FDG) combined with PET. Overall, 47% of these unselected patients had lymph node involvement on FDG-PET, and the prognosis following therapy was highly correlated with positive lymph nodes as shown on PET, as well as the level of involved nodes.[87] As of January 2005, the Centers for Medicare and Medicaid Services (CMS) has approved the use of PET scanning in the evaluation of newly diagnosed, locally advanced cervical cancer as an adjunct to conventional anatomic imaging. Its utility in staging early disease is limited, particularly because of the relatively low incidence of extrapelvic disease in this setting. A suggested approach in the workup of newly diagnosed cervical cancer is shown in Figure 58-2.

The use of FDG-PET imaging at 3 months after completion of RT for early assessment of treatment efficacy has been correlated with survival and also assists with identification of isolated relapses amenable to aggressive salvage therapy.[88]

Surgical staging of the pelvic and paraaortic lymph nodes has been used to obtain prognostic information, to identify patients who would benefit from extended-field irradiation, and to debulk grossly enlarged lymph nodes. Early reports of high complication rates in patients treated with radiation following transperitoneal lymphadenectomy discouraged the use of this procedure,[89,90] but more recent studies have documented a significantly lower incidence of major complications if the operation is performed using a retroperitoneal approach.[91-93] Laparoscopic biopsy of pelvic and aortic lymph nodes is less invasive, with shorter times to recuperation and less potential for adhesions, thereby decreasing the potential for treatment-related bowel toxicity.[94,95] Using a variety of surgical approaches, Goff et al[96] reported that pretreatment surgical staging resulted in modifications in planned RT in 43% of patients.

In studies that have compared PET or PET-CT imaging to histologic paraaortic nodal status, the false-negative rate ranges from 5% to 17% (overall 12%).[97] Similarly, Gouy et al[98] conducted a prospective multicenter study of 237 patients treated from 2004 to 2011 for locally advanced cervical

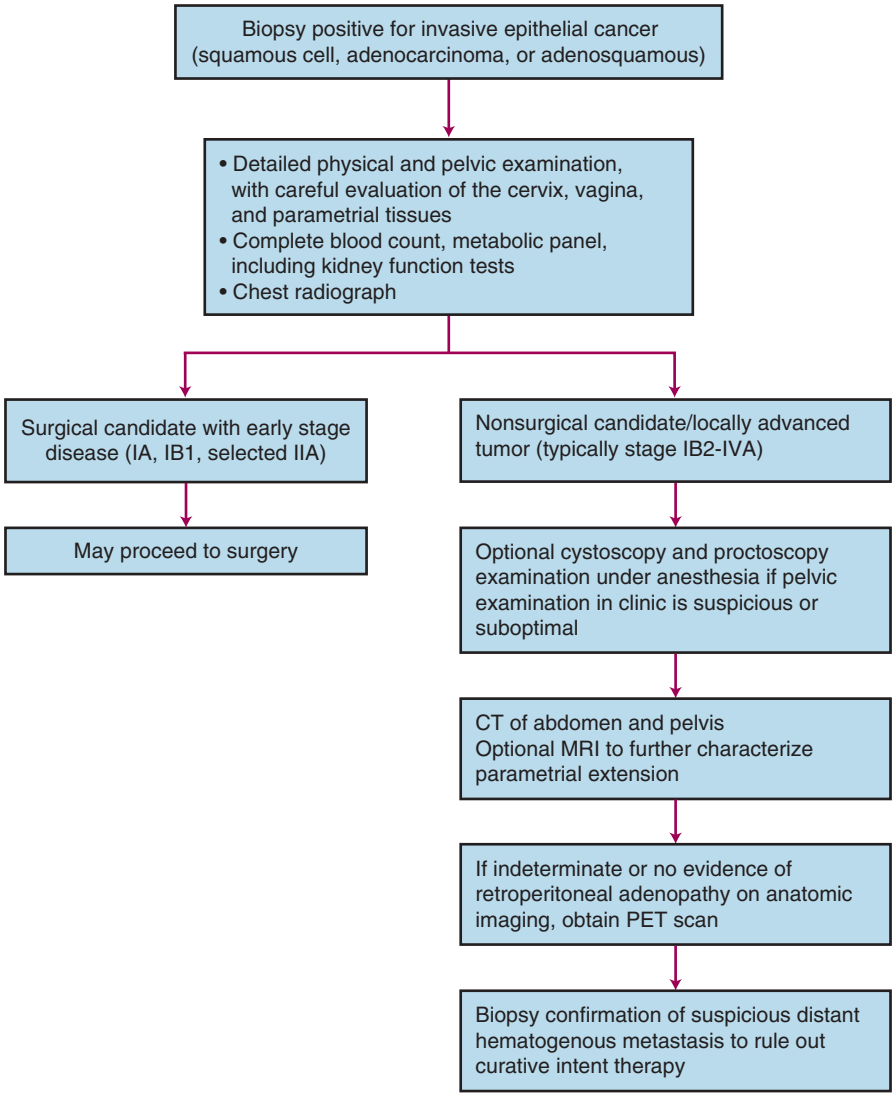


Figure 58-2 Diagnostic algorithm for cervical cancer. *CT,* Computed tomography; *MRI,* magnetic resonance imaging; *PET,* positron emission tomography.

cancer with negative PET imaging of the paraaortic region and undergoing laparoscopic paraaortic lymphadenopathy. Twenty-nine patients (12%) had nodal involvement (false-negative PET-CT result). Thirteen had a nodal metastasis measuring ≤ 5 mm, whereas 16 had a nodal metastasis > 5 mm. Those with paraaortic metastasis ≤ 5 mm and treated with extended-field chemoRT had a similar 3-year event-free survival rate to those without paraaortic lymph node involvement (69% versus 74%), whereas survival of patients with paraaortic nodal involvement > 5 mm remained poor (17%, $p < 0.001$), suggesting a possible impact of surgical staging in a subset of patients.

Overall, the value of pretreatment surgical debulking of tumor-involved lymph nodes is unproven, although the information gained from surgical staging may be valuable in selected patients.[100-102]

PRIMARY THERAPY

Because patients with cervical cancer usually present with disease that is clinically confined to the pelvis, locoregional disease control is the primary treatment challenge. Individualized treatment based on tumor characteristics has produced impressive cure rates in patients with locally confined disease (Table 58-3). Recognizing that most patients with adverse factors, such as pathologic extracervical spread (e.g., positive lymph nodes, parametrial invasion) or multiple adverse primary tumor characteristics identified after surgery, will be offered adjuvant RT or chemoRT, most surgeons now limit radical hysterectomy to premenopausal patients with limited disease, that is, those in whom the expectation is low of finding adverse factors at surgery. In general, patients should be treated with single-modality definitive therapy whether that be surgery, irradiation, or chemoRT, thereby avoiding the potential increased toxicity resulting from the use of multiple modalities.

It should be emphasized that in cervical cancer, progression-free survival (PFS) is closely tracked by OS, reflecting the extremely limited treatment options for women with locally recurrent or metastatic disease. This is unlike the situations with some other malignant tumors, such as prostate and breast cancers or lymphomas, where indolent

Only one randomized trial has been published comparing surgical staging (laparoscopic or extraperitoneal) to clinical staging (CT or MRI) in 61 patients with locally advanced cervical cancer.[99] On interim analysis, patients staged surgically had significantly worse progression-free survival than those without surgical staging, leading to premature trial closure.

TABLE 58-3 Primary Therapy and Survival by Disease Extent*

Stage	Primary Therapy	5-yr Overall Survival
IA1	Cone biopsy; simple hysterectomy; brachytherapy	>98%
IA2	Radical hysterectomy plus pelvic node dissection (PND); irradiation (RT)	≥95%
IB1/limited IIA1	Radical hysterectomy plus PND; RT	~90%
IB2/larger IIA1/IIA2	ChemoRT	80% to 85%
IIB	ChemoRT	70% to 75%
III	ChemoRT	~50%
IVA	ChemoRT; selective exenteration	15% to 25%
IVB, limited†	ChemoRT with dose escalation	5% to 15%
IVB	Chemotherapy; palliative RT	~0%

ChemoRT, *Chemoradiation;* RT, *radiotherapy;* yr, *year.*
**The choice of primary therapy and the overall survival (OS) rates are related to disease extent at the time of initial diagnosis and staging evaluation.*
†*Solitary para-aortic, inguinal or supraclavicular node involvement.*

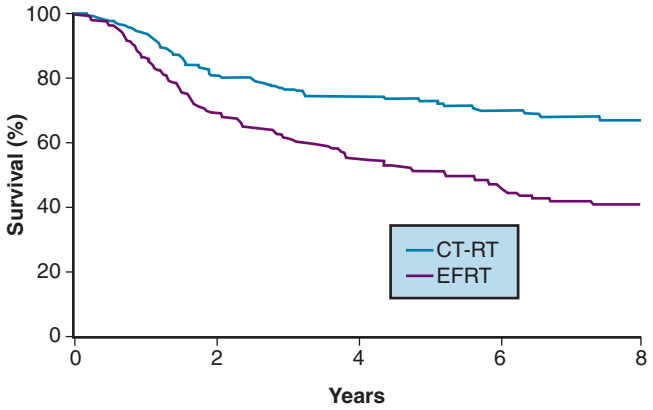


Figure 58-3 Updated overall survival by treatment arm in RTOG 90-01, comparing concurrent chemoradiation (CT-RT) with extended-field radiotherapy alone (EFRT) ($p < 0.0001$).
From Eifel PJ, Winter K, Morris M, et al: Pelvic irradiation with concurrent chemotherapy versus pelvic and para-aortic irradiation for high-risk cervical cancer. An update of Radiation Therapy Oncology Group trial (RTOG) 90-01. J Clin Oncol 22:876, 2004, Figure 1. Reprinted with permission from the American Society of Clinical Oncology.

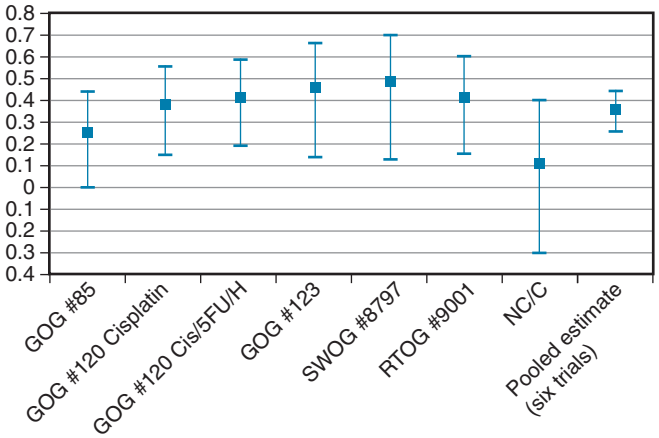


Figure 58-4 Reduction in the risk (1, relative risk) of death from six chemoradiation clinical trials in cervical cancer, with 95% confidence intervals. A value above 0 represents a benefit for cisplatin-containing chemoradiation. *5-FU,* 5-Fluorouracil; *Cis,* cisplatin; *H,* hydroxyurea; *SWOG,* Southwest Oncology Group (Intergroup protocol 0107).
From Rose PG, Bundy BN: Chemoradiation for locally advanced cervical cancer. Does it help? J Clin Oncol 20:891, 2002, Figure 1. Reprinted with permission from the American Society of Clinical Oncology.

tumor biology or the availability of multiple salvage options can lead to wide variances between the preceding two outcome measures. It also highlights the importance of achieving ultimate tumor control with upfront definitive therapy in cervical cancer.

RT is effective for patients with locoregional confined cervical cancer of any stage, especially if they are not candidates for surgery. Treatment must be carefully tailored to the patient and to the extent of disease, but usually consists of a combination of external beam irradiation (EBRT) with concurrent chemotherapy and brachytherapy. Overall, historically reported 5-year OS of patients treated with *RT* alone are 75% to 85% for FIGO stage IB, 65% to 70% for FIGO stage II, 30% to 40% for FIGO stage III, and 10% to 15% for FIGO stage IVA disease.[103-107] Within stage subsets, cure rates are strongly correlated with the size of the primary tumor and the extent of regional involvement.[42,108]

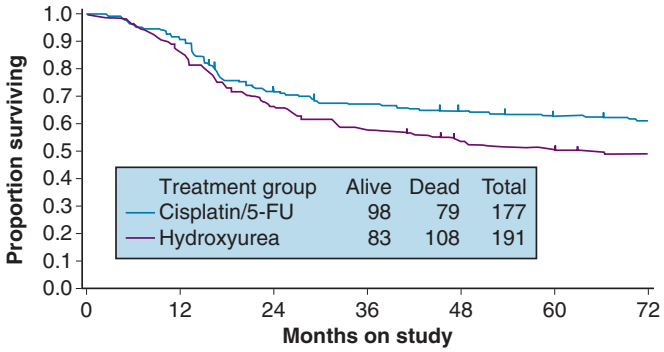
Chemoradiation

For patients with locally advanced disease, chemoRT has been the standard of care since the 1999 publication of a National Cancer Institute (NCI) alert based on the results of five Phase III randomized clinical trials (GOG 85, GOG 120, GOG 123, SWOG 8797/Intergroup 0107 [eFigures 58-1 to 58-4] and RTOG 9001 [Figure 58-3]).[109-113] The five studies had different eligibility criteria, but in total included a broad spectrum of clinical presentations:

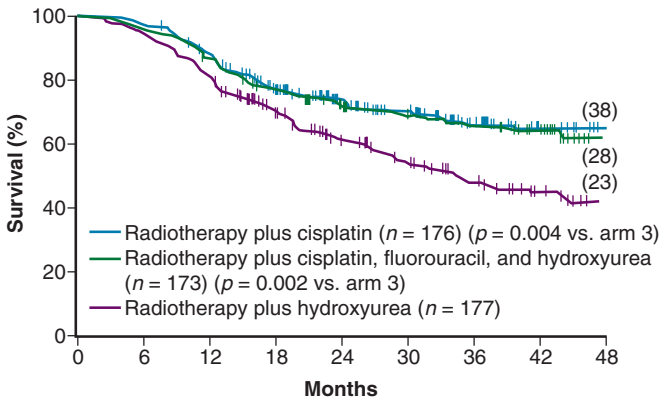
1. Locally advanced tumors for whom chemoRT represented primary therapy
2. Bulky early-stage cancers (tumor size ≥ 4 cm) in which chemoRT was delivered before adjuvant hysterectomy
3. Adjuvant therapy following radical hysterectomy in cases with high-risk pathologic factors (positive lymph nodes, positive parametria, positive margins)

Rose and Bundy[114] summated the collective results of the randomized trials (the preceding five and one from the National Cancer Institute of Canada[115] [eFigure 58-5]) and showed a cumulative and statistically significant 36% reduction in the risk of death favoring combined cisplatin-based concurrent chemoRT over RT alone or combined with hydroxyurea[114] (Figure 58-4).

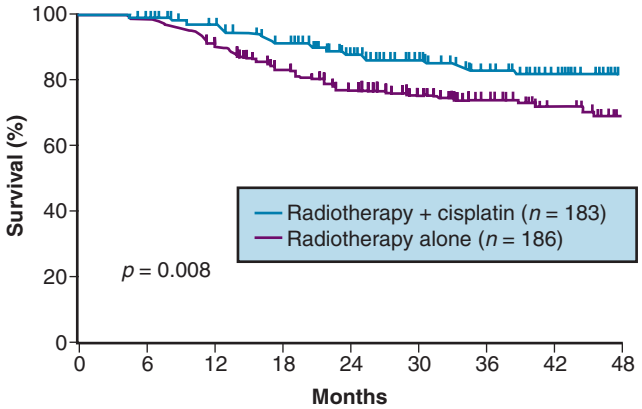
That these clinical trial results can be applied to a general population was confirmed in an analysis in which Pearcey treated patients with cervical cancer between 1992 and 2001[114] and that found a significant improvement in cervical cancer OS, which could not be explained by differences in stage presentation or an imbalance in cases selected for primary surgery. The investigators attribute the survival gains to the generalized and appropriate use of concurrent, predominantly cisplatin-based chemoRT in the majority of patients receiving RT for cervical cancer.[115] Specific details of the seminal



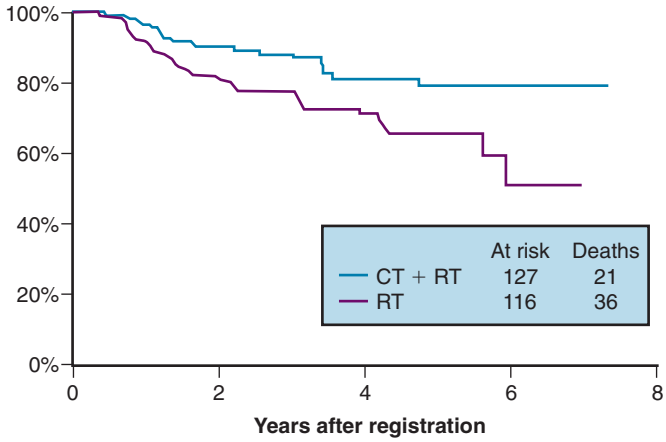
eFigure 58-1 Overall survival by treatment arm in GOG 85 ($p = 0.018$). *5-FU,* 5-Flouruoracil.
From Whitney CS, Sause W, Bundy BN, et al: Randomized comparison of fluorouracil plus cisplatin versus hydroxyurea as an adjunct to radiation therapy in stages IIB-IVA carcinoma of the cervix with negative paraaortic lymph nodes. A Gynecologic Oncology Group and Southwest Oncology Group study. J Clin Oncol 17:1344, 1999, Figure 2. Reprinted with permission from the American Society of Clinical Oncology.



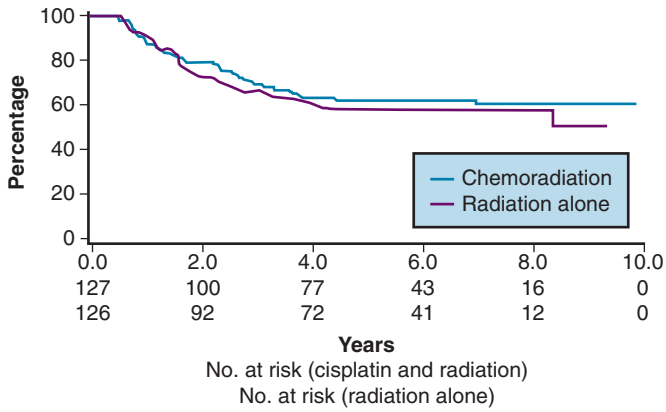
eFigure 58-2 Overall survival by treatment arm in GOG 120 ($p < 0.005$ for both cisplatin-containing arms compared with the hydroxyurea control group).
From Rose PG, Bundy BN, Watkins EB, et al: Concurrent cisplatin-based chemoradiation improves progression-free and overall survival in advanced cervical cancer. Results of a randomized Gynecologic Oncology Group study. N Engl J Med 340:1144–1153, 1999.



eFigure 58-3 Overall survival by treatment arm in GOG 123 ($p = 0.008$).
From Keys HW, Bundy BN, Stehman FB, et al: A comparison of weekly cisplatin during radiation therapy versus irradiation alone, each followed by adjuvant hysterectomy in bulky stage IB cervical carcinoma. A randomized trial of the Gynecologic Oncology Group. N Engl J Med 340:1154–1161, 1999. Copyright © Massachusetts Medical Society. All rights reserved.



eFigure 58-4 Overall survival, by treatment arm, in Intergroup protocol 0107, comparing postoperative chemoradiation (CT + RT) with irradiation alone (RT) ($p = 0.007$).
From Peters WA, Liu PY, Barrett RJ II, et al: Concurrent chemotherapy and pelvic radiation therapy compared with pelvic radiation therapy alone as adjunctive therapy after radical surgery in high-risk, early-stage carcinoma of the cervix. J Clin Oncol 18:1609, 2000, Figure 2. Reprinted with permission from the American Society of Clinical Oncology.



eFigure 58-5 Overall survival by treatment arm (chemoradiation; irradiation alone) in the National Cancer Institute of Canada (NCIC) study ($p = 0.53$).
From Pearcey R, Brundage M, Drouin P, et al: Phase III trial comparing radical radiotherapy with and without cisplatin chemotherapy in patients with advanced squamous cell cancer of the cervix. J Clin Oncol 20:970, 2002, Figure 3. Reprinted with permission from the American Society of Clinical Oncology.

Phase III trials of RT compared with chemoRT are detailed in eTable 58-1.

In North America, where cisplatin-based chemoRT is currently considered the standard of care, there remains ongoing debate as to what specific regimen to use when cisplatin is combined with RT. The Gynecologic Oncology Group (GOG) has selected weekly cisplatin at 40 mg/m^2 (maximum 70-mg weekly dose) for up to six cycles, concurrent with EBRT, as its foundation for chemoRT of cervical cancer. Whether to combine 5-flourouracil (5-FU) with cisplatin remains a topic of discussion as the positive arm of RTOG 90-01 included both concurrent cisplatin and 5-FU, given on a 3-week cycle (cisplatin 75 mg/m^2, 5-FU, 1000 mg/m^2/day for 4 days). However, a subsequent randomized trial of protracted venous infusion fluorouracil with standard weekly cisplatin was closed prematurely because 5-FU/RT had a higher risk of treatment failure (relative risk [RR] 1.29) and a higher mortality rate (RR 1.37), with an increase in distant failure in the 5-FU arm.[116]

The benefit of chemoRT for cervical cancer is one of the single largest contemporary therapeutic gains in the management of patients with cancer. Updates with significantly longer follow-up periods continue to confirm the survival advantage with the administration of cisplatin-based chemoRT.[118-120] They also suggest that for future trials in locally advanced cervical cancer, estimates of PFS and OS with median follow-up intervals of 3 years represent fairly mature results.

Although there is general acknowledgment of the efficacy of cisplatin in combination with RT, various investigators have formally evaluated other non-cisplatin chemoRT regimens, including carboplatin[121] and gemcitabine.[122] A Phase II study demonstrated the feasibility of administering bevacizumab concurrently with cisplatin and pelvic radiation.[123] Current studies are looking at every week versus every 3-week administration of cisplatin.

Role of Systemic Therapy after Definitive Chemoradiation

The risk of distant relapse is as high as, if not higher than, pelvic relapses following chemoRT.[117,118] Adding adjuvant chemotherapy to a "backbone" of concurrent cisplatin and RT may provide a therapeutic benefit, in terms of both distant and locoregional tumor control.[117] In a post hoc subset analysis of Intergroup 0107, Peters et al[112] found that the number of cycles of chemotherapy given with pelvic RT (including up to two cycles following completion of RT) correlated with an improved outcome.

In a prospective randomized trial, Duenas-Gonzalez et al evaluated the administration of chemoRT with cisplatin versus cisplatin plus gemcitabine and additional systemic therapy after chemoRT completed.[124] With a median follow-up of 3 years, women who received cisplatin plus gemcitabine with RT and then as post-RT treatment had a 32% reduction in progression (hazard ratio [HR] 0.68, 95% confidence interval [CI] 0.49 to 0.95) and a higher rate of PFS at 3 years compared to those treated with cisplatin alone (74% versus 65%, respectively). In addition, cisplatin plus gemcitabine resulted in a 32% survival advantage (HR 0.68, 95% CI 0.49 to 0.95). Concerns from other reports indicate that the combination of cisplatin, gemcitabine, and pelvic irradiation may result in high toxicity rates.[125,126] Enthusiasm for added systemic therapy, whether with conventional cytotoxics or new biologic agents, must be tempered by consideration of toxicity and impact on quality of life.

Based on the observations of Intergroup 0107[112] and a meta-analysis[117] that suggested possible therapeutic benefit of extra cycles of chemotherapy given after RT, two international Phase III trials have been activated to evaluate the role of additional chemotherapy (carboplatin and paclitaxel in four cycles) following cisplatin and RT. One trial addresses patients at high risk after hysterectomy who have positive lymph nodes, positive margins, or parametrial extension, whereas the second evaluates outcome in patients with locally advanced intact cervical cancer (stages IB2 to IVA) treated with definitive chemoRT (OUTBACK ANZGOG-led trial).

Radiation Treatment Variables

The delivery of radiation for patients with cervical cancer requires careful consideration and integration of several critical treatment decisions. These include the role of concurrent chemotherapy with RT, the use and timing of brachytherapy in combination with EBRT, the total dose and overall duration of RT, and the volume of elective nodal coverage. These treatment variables should be judiciously balanced against tumor risk factors, overall patient performance status, and the risk of complications.

Brachytherapy Plus External Beam Irradiation

The importance of brachytherapy in the curative treatment of intact cervical cancer is indisputable. Clinicians have sometimes been inclined to deemphasize the use of brachytherapy in patients with FIGO stage III disease, arguing that disease at the pelvic wall is beyond the reach of traditional intracavitary therapy. Reports from the Patterns of Care Study[127] and from the M. D. Anderson Cancer Center (MDACC),[108] however, have demonstrated significantly better survival rates for patients treated with a combination of EBRT and intracavitary irradiation. In the MDACC report of 1007 patients treated with irradiation for FIGO stage IIIB disease, the disease-specific survival (DSS) was 43% for patients who had intracavitary irradiation versus 21% for those treated with EBRT alone. Patients treated during periods when policies emphasized the use of brachytherapy had significantly better survival rates. Patients who received higher doses of EBRT (and concomitantly lower doses of intracavitary irradiation) to the central pelvis had poorer survival rates. The rate of major complications was also correlated with the proportion of central pelvic treatment given with EBRT, and this correlation suggested that the therapeutic ratio narrows when the dose of EBRT given to the whole pelvis exceeds 45 Gy.[108] More recently, a SEER analysis showed a decline in the use of brachytherapy starting in 2003 and continuing over a decade, with a 34% (HR 0.66, 95% CI 0.6 to 0.74) increase in OS in patients that received versus did not receive brachytherapy.[128] A 2005 to 2007 survey through the quality research in radiation oncology (QRRO, formerly Patterns of Care study) showed that although 87.5% of patients had received brachytherapy treatment, the proportion of patients treated without brachytherapy had doubled compared to the 1996 to 1999 survey.[129] A careful balance between EBRT and brachytherapy components of therapy, accounting for tumor volume, anatomic presentation, and disease regression rate, represents the hallmark of appropriate cervical cancer radiotherapy planning.

Radiation Dose and Duration

Historically, a cumulative dose (linear-quadratic dose equivalent [LQED] 2 Gy per fraction or low-dose rate [LDR] equivalent) of 80 Gy to 85 Gy or higher to point A was considered desirable for patients receiving primary RT for locally bulky cervical cancer (stages IB2 to IVA), with a dose of at least 45 Gy via external beam radiation to all volumes at risk for microscopic tumor spread. Over the past decade an increasing number of institutions have transitioned from specifying dose to point A to instead contouring a tumor volume on either CT or MRI.[130] Although these dose guidelines are widely quoted

eTABLE 58-1 Radiation versus Chemoradiation Phase III Trials for Squamous Cell Carcinoma of the Cervix

Study	N	FIGO stage	Local Rx	Concurrent Chemo	F/U (yr)	OS, %	PFS, %	RR death	*p*-value (OS)
GOG 85 Whitney et al.	368	IIB-IVA	WPRT + LDR	Hydroxyurea vs cis/5-FU (q4w)	8.7	43 (5-yr) 65*	47 57*	0.72	0.018
GOG 120 Rose et al.	526	IIB-IVA	WPRT + LDR	Hydroxyurea (HU) vs HU + cis/5-FU (q4w) vs. weekly cisplatin	8.0	35 (5-y) 53* 53*	26 46* 43*	0.58 0.61	0.002 0.004
GOG 123 Keys et al.	369	IB2	WPRT + LDR + Adj hyst	None vs. weekly cisplatin	3.0	74 (3-yr) 83*	63 79*	0.54	0.008
RTOG 90-01 Morris et al.	386	IB2-IVA	EFRT vs WPRT + LDR	EFRT alone vs WPRT + cis/5FU q3w	6.6	41 (8-y) 67*	36 61*	0.52	<0.0001
SWOG 8797/INT 0107 Peters et al.	268	IB or IIA (high-risk post-op)	s/p hyst WPRT	None vs. cis/5-FU q4w	4.0	71 (4-yr) 81*	63 80*	0.50	0.007
NCIC Pearcey et al.	253	IB2-IVA	WPRT + LDR/ MDR/HDR	None vs. weekly cisplatin	5.0	58 62	62 64	0.90	0.53

3-y, *3-Year;* Adj, *adjuvant;* Chemo, *chemotherapy;* cis, *cisplatin;* EFRT, *extended field irradiation;* GOG, *Gynecologic Oncology Group;* HDR, *high-dose-rate brachytherapy;* hyst, *hysterectomy;* LDR, *low-dose-rate brachytherapy;* NCIC, *National Cancer Institute of Canada;* OS, *overall survival;* PFS, *progression-free survival;* post-op, *postoperative;* RR, *relative risk;* RTOG; *Radiation Therapy Oncology Group;* SWOG, *Southwest Oncology Group;*- WPRT, *whole pelvic irradiation.*

In another study 234 women were randomly assigned to standard EBRT (50 Gy in 25 fractions) or hyperfractionated RT (52.80 Gy in 33 fractions) with a second randomization to concomitant 5-FU (1 g/m^2 daily for during the first and last 4 days of RT) or no additional chemotherapy. With a median duration of follow-up of 59 months, there were no differences in survival or pelvic control among these arms.[117] Of note, patients in this trial did not receive concomitant cisplatin, and hence, it specifically evaluated 5-FU as a single-agent chemosensitizer for women with cervical cancer.

and used by cooperative groups, the dose prescription should clearly be carefully tailored to tumor- and patient-specific factors. Smaller and earlier tumors (stages IA to IB1) may be treated to somewhat lower overall doses of 75 Gy to 80 Gy. Many centers favor initiating whole-pelvis EBRT to a dose of 40 Gy to 45 Gy before proceeding with brachytherapy. Gross parametrial or pelvic nodal disease can then be boosted with limited and conformal EBRT fields, blocking critical central pelvic structures, to a cumulative dose of 55 Gy to 65 Gy, or even higher (combining EBRT and brachytherapy components), depending on disease volume and the ability to avoid adjacent normal tissues. Other institutions prefer to emphasize and initiate brachytherapy earlier, at whole-pelvis EBRT doses of 20 Gy to 30 Gy, especially for patients with earlier-stage and smaller-volume disease. EBRT is then continued to the pelvis, with or without midline blocking. Although recommendations have been made to try to limit the rectal and sigmoid dose to 2 cc (D2cc) to 70 Gy and 75 Gy, respectively, and to the bladder D2cc to 80 Gy to 100 Gy,[131] it is recognized that the most important consideration is to deliver adequate tumoricidal doses, even if the normal tissue dose recommendations are somewhat exceeded. Use of the International Commission on Radiation Units and Measurements (ICRU) rectal and bladder points for determining maximal doses is a practice continued in institutions that lack access to CT or MR imaging. On the other hand, a total D90 clinical target volume (CTV)[132] or point A dose of 85 Gy to 90 Gy for intact bulky cervical cancer represents a reasonable limit, based on integral doses to surrounding normal pelvic structures. For adjuvant RT following primary surgery, where there is no gross tumor residual, an EBRT dose of 45 Gy to 50 Gy to the pelvis is considered tolerable.

These preceding dose discussions are based on a conventional EBRT fractionation of 1.8-Gy to 2-Gy daily and LDR brachytherapy. The use of altered fractionation or, in particular, high-dose-rate (HDR) brachytherapy necessitates a different system of reference doses and is discussed in greater detail later.

The adverse impact of treatment duration protraction in cervical cancer has been evaluated by several investigators. There is general consensus that prolonging a course of radical RT beyond approximately 7 weeks is associated with a 0.5% to 1% decrease in pelvic control per extra day.[133-138] Although debate remains about whether an increase in treatment duration adversely affects outcome or is simply a reflection of unfavorable tumor or patient characteristics or whether this pertains to patients treated with chemoradiation, there is compelling radiobiologic demonstration of accelerated tumor repopulation that mitigates the efficacy of RT.[139] In contrast, there is no evidence that prolongation of treatment duration results in a reduction of late normal tissue sequelae.[138] Therefore, it is now considered prudent to complete a course of definitive RT for cervical cancer within 7 weeks to 8 weeks by eliminating all elective treatment breaks, delivering EBRT parametrial boosts between, or interdigitated with, brachytherapy insertions, and actively supporting patients through acute toxicities so as to avoid RT interruptions.

Role of Extended-Field Irradiation

The prognosis of patients with cervical carcinoma is inversely related to the extent of regional and nodal involvement. Because hematogenous metastasis is usually a late event in the course of this disease, however, patients with lymph node metastases often can be cured with regional EBRT if pelvic disease can be controlled. Even patients with documented paraaortic lymph node metastases have 5-year OS of 20% to 50%, depending on the extent of pelvic disease.[131-136]

Two groups have explored the use of prophylactic extended-field EBRT in patients who do not have overt paraaortic metastases. A trial from the European Oncology and Radiation Therapy Consortium (EORTC)[140] was conducted before the use of concurrent chemotherapy. Randomized patients had more locally advanced pelvic disease (bulky FIGO stage IIB, FIGO stage III, or biopsy-proved pelvic lymph node metastases). Disease-free survival (DFS) of patients in the two treatment arms was not significantly different at 4 years, although the rate of relapse in the paraaortic lymph nodes was higher in patients who had not received RT to this site. OS was not reported.

The results of RTOG 90-01 clearly indicate that concurrent chemotherapy with pelvic RT leads to significant improvements in OS and DFS over extended-field EBRT without chemotherapy in patients with FIGO stages IIB to IVA disease (plus stages IB-IIA tumors 5 cm or larger or biopsy-proven pelvic nodal metastases).[118] Underlying the question of benefits of prophylactic paraaortic RT is the assumption that the paraaortic nodes may represent isolated occult extrapelvic disease in some patients for whom sterilization by RT would translate to cure (assuming achievable pelvic control and no distant metastases). The results of RTOG 90-01, which showed significant reductions in both pelvic and distant relapse with chemoRT (Table 58-4), suggest that the use of concurrent chemotherapy to some degree addresses subclinical metastases beyond the volume of RT. Unanswered is the question of whether prophylactic extended-field RT in addition to systemic chemotherapy would provide additional therapeutic gain.

Practice patterns vary for patients with negative paraaortic nodes but who are deemed to be at elevated risk for occult disease in this nodal chain. At the University of Washington, prophylactic paraaortic nodal EBRT to 45 Gy in 25 fractions over 5 weeks, concurrent with chemotherapy (to the level of the renal vessels, or at the L1 to L2 vertebral interspace), is often considered for patients with the highest potential risk of subclinical paraaortic disease (i.e., those with common iliac adenopathy on surgical staging or those who have negative paraaortic nodes but extensive pelvic lymphadenopathy by radiologic imaging [recognizing the limitations of even the best imaging modalities to detect microscopic tumor]).

TABLE 58-4 Patterns of Relapse in RTOG 90-01, Comparing Pelvic Irradiation with Concurrent Chemotherapy (CT/RT) versus Extended-Field Radiotherapy without Chemotherapy (EFRT)

Pattern of Relapse	CT/RT	EFRT	Relative Risk*	*p* Value
Locoregional (pelvic)			0.42	<0.0001
5 yr	18%	34%		
8 yr	18%	35%		
Paraaortic			1.65	0.15
5 year	7%	4%		
8 year	9%	4%		
Distant metastases (excluding paraaortics)			0.48	.0013
5 year	18%	31%		
8 year	20%	35%		

From Falfetano J, Keys H, Kredentser D, et al: Weekly cisplatin and radical radiation therapy for advanced, recurrent and poor prognosis cervical carcinoma. Cancer 71:1703–1706, 1993.

**A value less than 1 indicates an advantage in favor of CT/RT.*

Whereas the efficacy of such an extended-field prophylaxis approach has not been proven, especially in the era of chemoRT, the use of concurrent cisplatin-based chemotherapy with extended-field RT has been shown to be tolerable in several Phase II trials.[141,142]

Impact of Anemia and Tumor Hypoxia on Radiation Therapy Outcome

The adverse association of anemia on outcome following primary RT for cervical cancer has been well documented in many previous clinical reviews.[140,143,144] Whether this association reflects cause and effect or whether anemia is simply a surrogate for worse prognostic and predictive variables, such as larger and more radiation-refractory tumors, is still being debated. Potential mechanisms for a negative impact of anemia on cervical cancer RT outcomes may be linked to tumor hypoxia and consequent radioresistance, as well as induction of angiogenesis, increased tumor aggressiveness, and enhanced metastatic potential.

Some retrospective reports have suggested that anemia is an independent negative prognostic factor, with the average hemoglobin level during RT being more predictive than the level before therapy.[145,146] Only one small prospective randomized trial directly addressing the value of transfusion has been completed, and that was in the 1970s. This study indicated improved pelvic control for irradiated patients whose hemoglobin level was corrected by transfusion, but the analysis was hampered by limited patient numbers and lack of stratification.[147]

In an attempt to provide definitive answers, the GOG conducted a prospective Phase III trial (GOG protocol 191) in which patients with locally advanced cervical cancer undergoing primary chemoRT (concurrent weekly cisplatin at a dose of 40 mg/m^2) were randomized to hemoglobin maintenance at a level of 10 g/dL versus aggressive intervention to raise hemoglobin levels to 12 g/dL to 13 g/dL (by transfusion and erythropoietin). However, concerns about an increased incidence of thromboembolic events and a possible negative impact on survival associated with erythropoietin in several other disease sites, although not statistically significant in this trial, led to its early closure, leaving the impact of maintaining optimal hemoglobin levels on outcome following chemoRT still undetermined.[117] Although erythropoiesis-stimulating agents have been previously used to correct anemia and may be considered in highly selected cases, their generalized use is currently discouraged because of concerns of thromboembolism and possible tumor progression.[148]

As standard of practice, radiation oncologists attempt to maintain patient hemoglobin levels at generally 10 g/dL during treatment for cervical cancer. Although the impact of maintaining this hemoglobin level on tumor control is unclear (recognizing that the studies discussed previously had noted optimal outcome at hemoglobin levels of 12 g/dL), it is recognized that lower hemoglobin levels adversely affect patient quality of life and may affect the ability to tolerate aggressive chemoRT. Besides the use of transfusion, every effort should be made to minimize cervical trauma and blood loss during a patient's evaluation and treatment. Local hemostatic agents (Monsel's solution) and vaginal packing should minimize blood loss after necessary biopsies and examinations. When local hemostatic measures fail to control bleeding, radiotherapeutic hemostasis may be achieved with prompt initiation of EBRT, possibly using 2 or 3 days of hyperfractionated pelvic RT. In patients with curable cancers, use of a hyperfractionated EBRT approach (e.g., 1.5 Gy to 1.8 Gy per fraction twice daily for 2 to 3 days) achieves the same likelihood of hemostasis as larger daily fractions while preserving normal tissue tolerance and ultimate treatment planning flexibility. Although some authors have recommended emergency intracavitary therapy to control bleeding, this approach may likely compromise subsequent curative treatment or be infeasible.

Tumor hypoxia, as measured by oxygen electrodes, has been identified in many cervical cancers and is a predictor of poor outcome.[149] Although there may be a link, the relationship between host status (anemia and hemoglobin level) and tumor milieu (hypoxia) remains ambiguous. To exploit hypoxia as a potential therapeutic target, the GOG opened a randomized Phase III trial (GOG 219) that investigated the efficacy of a new-generation bioreductive drug, tirapazamine, added to the present standard of concurrent cisplatin and RT for locally advanced cervical cancer. In addition to its radiosensitizing effects, tirapazamine had generated significant interest because it is itself a potent and selective hypoxic cell cytotoxin and is also potentially synergistic with cisplatin.[150,151] However, the lack of expected benefit for the combination of tirapazamine, cisplatin, and RT in a large Phase III trial of head and neck cancers,[152] and subsequent loss of sponsorship support, led to premature closure of GOG 219.

The issue of anemia and hypoxia as prognostic factors, and therapeutic targets, in cervical cancer remains unresolved. Future trials in this arena will require safer and more tolerable pharmacologic agents and should be limited only to patients in whom radiobiologically significant anemia or hypoxia can be accurately and reliably measured.

Recent studies have identified significant modulations of gene expression in hypoxic tumors that may be associated with tumor aggressiveness and progression, including hypoxia-inducible factor 1, TP53, vascular endothelial growth factor (VEGF), platelet-derived endothelial cell growth factor, nitric oxide synthase, and matrix metalloproteinases.[153] These biomolecular markers provide potential new targets for future therapeutic investigations.

Smoking and Cigarette Cessation during Radiotherapy

Smoking is a known risk factor for the development of cervical cancer. Several retrospective series have shown conflicting correlations between smoking and cervical cancer prognosis. A recent prospective, multicenter analysis, however, strongly suggested that smoking during chemoRT was associated with poorer outcomes compared with those in patients who had never smoked or who had quit smoking before treatment. An added strength of this study was the use of urine cotinine levels to confirm patient-reported smoking status.[154] In another large retrospective review, smoking has also been associated with an increased risk of late complications following pelvic RT for cervical cancer.[155] Although the mechanisms underlying smoking and treatment outcome and toxicity remain to be elucidated, and even though it is not a specific cancer treatment variable, it seems intuitive that concerted efforts to assist patients in smoking cessation during cervical cancer therapy would be reasonable and may contribute to better outcomes.

The Role of Neoadjuvant Chemotherapy

Although concurrent cisplatin-based chemoRT has become the widely accepted standard of care, caution is raised regarding the use of strategies employing neoadjuvant chemotherapy before RT or surgery.[156] Multiple randomized trials, most with small patient numbers, have not identified an optimal strategy of neoadjuvant chemotherapy followed by definitive RT or surgery. A systematic review and individual patient data meta-analysis showed no benefit and, indeed, an overall trend to detriment, for patients receiving neoadjuvant chemotherapy (predominantly cisplatin-based) before definitive local treatment.[157] In two of the randomized trials, it was reported that the neoadjuvant chemotherapy approach, although

associated with a reasonable initial response, ultimately resulted in statistically significant inferior pelvic control and OS compared with definitive RT alone.[158,159] A plausible explanation for the lack of benefit seen with chemotherapy preceding RT is that although responses can be seen with systemic cytotoxics alone, the remaining clonogens undergo accelerated repopulation, thereby offsetting the efficacy of RT.[139]

At this time, there is no consistent benefit with neoadjuvant chemotherapy, in either survival or reduction of radiotherapy use, to justify its use for these reasons. The use of neoadjuvant chemotherapy strategies should be considered only in the context of carefully designed clinical trials. Unless more effective cytotoxic agents are identified, there is no current reason to consider neoadjuvant chemotherapy followed by definitive surgery, RT, or chemoRT in patients with localized, curable cervical cancer.

Primary Therapy by Disease Stage

Preinvasive Disease

Preinvasive lesions are usually treated with local ablative procedures (cryosurgery or laser ablation) or excisional procedures (loop excision or cervical conization). Hysterectomy is an appropriate treatment option for women with high-grade cervical dysplasia who no longer desire fertility preservation. Ablative treatment is contraindicated if the entire transformation zone has not been well visualized, if there is a marked discrepancy between Pap smear results and colposcopy findings, or if colposcopy evaluation with biopsies leaves unresolved the presence of invasive disease. In these situations, conization should be performed to exclude the presence of invasion. In particular, given the associated challenges in pathologic assessment, patients with AIS on cervical biopsy should always undergo conization to assess the presence of invasive adenocarcinoma.

Microinvasive Disease (FIGO Stage IA Disease)

Early microinvasive (FIGO stage IA1) disease is conventionally treated with nonradical abdominal or vaginal hysterectomy after the depth of invasion has been confirmed by cone biopsy. However, for selected patients who wish to maintain fertility and who agree to close follow-up, therapeutic conization of the cervix may be adequate treatment.

Approximately 10% to 15% of cervical cancers will occur in women during the reproductive years, and some of these patients are hesitant to undergo radical pelvic surgery or RT with resulting permanent loss of fertility. A number of investigators have subsequently reported their experiences with fertility-preserving surgery for early-stage (predominantly IA2 but also including women with IB tumors no larger than 2 cm) cervical cancer using both vaginal and abdominal approaches.[166-170] The rate of cancer relapse following these fertility-sparing procedures appeared to be comparable to that of women undergoing radical hysterectomy. Although the rate of relapse following vaginal trachelectomy has historically been higher for larger tumors (>2 cm), recent advances, including the adoption of abdominal trachelectomy techniques, as well as possible neoadjuvant chemotherapy in larger-sized lesions, may broaden the feasibility of fertility-sparing options for more patients (see subsequent section).[171]

For women with medical contraindications to surgery, brachytherapy can be an effective treatment with 10-year PFS of 98% to 100% reported. Treatment usually consists of one or more intracavitary insertions that deliver a total of 65 Gy to 75 Gy to point A in LDR equivalents, with a maximal vaginal surface dose of 100 Gy to 120 Gy, depending on the extent of microinvasive disease, size of the cervix, and normal tissue anatomy.[172-174]

Although the risk of regional lymph node spread from FIGO stage IA2 carcinomas is less than 5%, early reports of conservative surgery for IA2 cervical cancer yielded suboptimal cancer control results.[175] Most patients with stage IA2 cervical cancer have, therefore, traditionally undergone radical hysterectomy with node dissection.

More recent analyses, with contemporary emphasis on quality of life, have led to a reappraisal of the surgical extent required for these early-stage tumors. Based on a low risk of parametrial involvement in prior radical hysterectomy series for patients with small tumors and good prognostic factors, in the future, such patients may be good candidates for nonradical surgery.[176-179]

As with stage IA1 disease, the use of irradiation for stage IA2 cancer is usually reserved for those who refuse, or have medical contraindications to, primary surgery. Brachytherapy alone may be used, with doses to point A of 70 Gy to 80 Gy (LDR equivalents). For patients with lymphovascular space invasion on the cone specimen, a combination of EBRT and intracavitary irradiation may be used, in which 40 Gy to 45 Gy of pelvic EBRT (often with midline blocking) is combined with intracavitary brachytherapy to deliver a cumulative point A dose of 70 Gy to 80 Gy. The 5-year cancer-specific survival rate with either surgical or radiation treatment is at least 95%.

Recognizing the outstanding cure rates with RT alone in stage IA cervical cancer, combined with the fact that irradiation is typically used in lieu of primary surgery in such patients with early-stage disease who have significant medical comorbidities, the use of concurrent chemoRT for these cases is not routinely justifiable. Furthermore, clinical trials to evaluate the role of chemoRT in this population of patients, who have an excellent cancer control rate, would not be statistically feasible.

Previous reports of "microinvasive" cervical cancer have focused on squamous cell tumors; however, accumulating evidence suggests that early-stage adenocarcinoma of the cervix have similar oncologic outcome to early stage squamous cell carcinoma. Smith et al[180] identified 560 cases of early cervical adenocarcinoma (200 with stage IA1, 286 with stage IA2, and 74 with "localized" disease) in the Surveillance, Epidemiology, and End Results (SEER) registry. Simple hysterectomy was performed in 272 (49%) and radical hysterectomy in 210 (38%). Combining their data with all other published series of early cervical adenocarcinomas, they identified 1170 cases, including 585 stage IA1, 358 stage IA2, and 227 "others" with less defined early disease. Among 531 patients who underwent lymph node biopsy, 15 (1.3%) had one or more positive nodes; of these 15 patients, 11 (73%) later relapsed or died. For IA1 versus IA2 disease, there were no significant differences in the frequency of positive lymph nodes, relapse, or death. However, the cases that were considered "others" based on less well-defined tumor dimensions, as well as those with lesions larger than IA2, were at increased risk of relapse.[180] The authors concluded that well-defined early invasive adenocarcinoma (stages IA1 and IA2) has an excellent prognosis, and conservative surgery may be appropriate.[181] Reynolds et al performed a meta-analysis including 25 published reports and 735 cases of microinvasive adenocarcinoma.[182] There were 367 cases that met criteria for FIGO stage IA (217 stage IA1, 47 stage IA2, and 103 stage IA not further stratified). There were 294 cases with information regarding the type of surgery, and of these, 193 had radical surgery. There were no reported cases of parametrial involvement. Of the 210 patients who underwent lymphadenectomy, 2 demonstrated lymph node metastasis.[182] These retrospective data suggest that the management of patients with stage IA1 and stage IA2 cervical

The efficacy of neoadjuvant chemotherapy prior to surgery has also been investigated. This strategy may reduce the tumor bulk and increase the possibility of negative resection margins. Evidence demonstrates that those who have response to neoadjuvant chemotherapy can have a reduction in tumor size, and reduction of other poor prognostic factors, such as lymphovascular space invasion (LVSI), parametrial invasion, and lymph node metastases.[106-163] Although response rates have been observed with neoadjuvant chemotherapy, recent meta-analyses of the published literature have not demonstrated a survival advantage.[164,165] The major concern with the neoadjuvant approach is that a delay in therapy for those that are not sensitive to chemotherapy, and the impact of chemotherapy in terms of increasing toxicity, may prohibit patients from receiving curative chemoRT. In addition, the likelihood of some patients requiring postoperative chemoRT is high, resulting in unnecessary increased toxicity.

Several retrospective studies have reviewed large cohorts of patients with early cervical cancers who underwent radical hysterectomies to determine the risk of parametrial involvement.[176] Covens et al[177] identified 536 patients who were defined as low risk, including patients with tumor size ≤ 2 cm, negative pelvic nodes, and depth of tumor invasion ≤ 10 mm. The incidence of parametrial involvement in this group of patients was 0.6%.[177] Similar findings have been described by Kodama et al,[178] where among 200 patients with radical hysterectomy for stage IB1 cervical cancer, the patients with a depth of invasion ≤ 10 mm and no LVSI had a 1.1% rate of parametrial involvement, and by Gemer et al,[178] where among 530 patients with radical hysterectomy specimens, those with tumor size ≤ 2 cm, no LVSI, and negative pelvic nodes had a rate of parametrial involvement of 0%. These findings illustrate that patients with these criteria could be candidates for nonradical surgery without removal of the parametria.

Several studies have also reported good oncologic outcomes for patients with early-stage cervical cancer treated with simple hysterectomy. Landoni et al[179] conducted a prospective study where 125 patients with stages IB1 and IIA cervical cancer ≤ 4 cm in size were randomized between simple hysterectomy ($n = 62$) and type III radical hysterectomy ($n = 63$). Adjuvant RT was given to patients with paracervical involvement, positive or close (<3 mm) resection margins, LVSI close to resection margins and positive lymph nodes. Sixty-nine percent of the simple hysterectomy arm received radiotherapy compared to 55% in the radical hysterectomy arm ($p = 0.11$). Pelvic recurrences were equal in both groups. After a minimum follow-up of 280 months (>20 years), 5-year OS was 85% for simple hysterectomy group versus 95% in the radical hysterectomy group ($p = 0.11$). There was no statistically significant difference in survival for patients with tumors measuring ≤ 3 cm (15-year OS 76% versus 80%, $p = 0.88$). This trial suggests that nonradical surgery may be appropriate for patients with small tumors and good prognostic factors.

adenocarcinomas need not differ from their counterparts with squamous cell lesions.

Overall, the management of early-stage cervical cancer continues to evolve. Nonradical surgery may be appropriate for women with small tumors and good prognostic factors and can subsequently reduce the morbidity associated with radical surgery. Ongoing prospective studies may help guide management for early stage cervical cancer in the future.

FIGO Stages IB and IIA Disease

Primary surgical management is probably best suited for physiologically fit patients with small FIGO stage IA or IB1 cervical cancers without clinical evidence of regional metastasis, parametrial or vaginal spread. Depending on the size of the cervical tumor, surgeons may vary somewhat in the extent of resection of the paracervical tissues and uterosacral ligaments (Figure 58-5). The risk of major complications, particularly bladder and rectal dysfunction or ureteral injury, is proportional to the extent of surgical resection and may therefore be greater when radical hysterectomy is used to treat larger tumors. The ovaries of premenopausal women are usually not removed, which provides an advantage for radical surgery over irradiation in young women with relatively small tumors. Massive obesity and other medical problems that increase the risk of a major pelvic surgical procedure are usually considered relative contraindications to a primary surgical approach.

Reported results of treatment with radical hysterectomy versus those of RT for FIGO stage IB cervical carcinomas are comparable, with 80% to 90% of patients surviving after 5 years; however, complications are much higher in patients treated with a radical hysterectomy that require postoperative radiation because of intermediate- or high-risk prognostic features.[183] Surgeons tend to select young patients who have relatively small tumors for surgical treatment and to refer patients who have large tumors or evidence of regional spread for RT.

For patients with FIGO stages IB and IIA disease, treatment results are strongly correlated with tumor size, and this factor thus influences the appropriate selection of primary therapy. Most FIGO stage IB1 tumors can be treated effectively with radical hysterectomy or combined EBRT and intracavitary irradiation; both have cure rates of 85% to 90%.[184]

In a report of the only randomized trial comparing radical surgery (with or without postoperative RT) with RT alone, Landoni et al[183] reported 5-year OS of 87% for patients with FIGO stages IB to IIA tumors of 4 cm or less in diameter treated with primary surgery compared with 90% for patients treated with definitive RT. Morbidity was somewhat greater in patients initially treated with surgery because many also received postoperative pelvic RT per the protocol for parametrial or lymph node involvement, positive tumor margins, or deep invasion into the stroma. In the same study, 5-year OS of patients with bulky FIGO stages IB2 and IIA tumors larger than 4 cm was similar for both treatments (70% for patients treated with surgery and 72% for patients treated with RT). However, 84% of patients with the larger lesions had the aforementioned high-risk features and received postoperative pelvic RT. As a result, morbidity was again greater in patients who had undergone surgery upfront, as compared with those who had received definitive RT alone.[183] The equivalent survival results were obtained even though the combined dose of EBRT and LDR intracavitary irradiation used to treat patients in this study (median cumulative dose to point A was 76 Gy) was lower than that recommended as standard dose levels internationally.[185]

Although some authors recommend radical surgical treatment for patients with FIGO stage IB2 cervical carcinomas

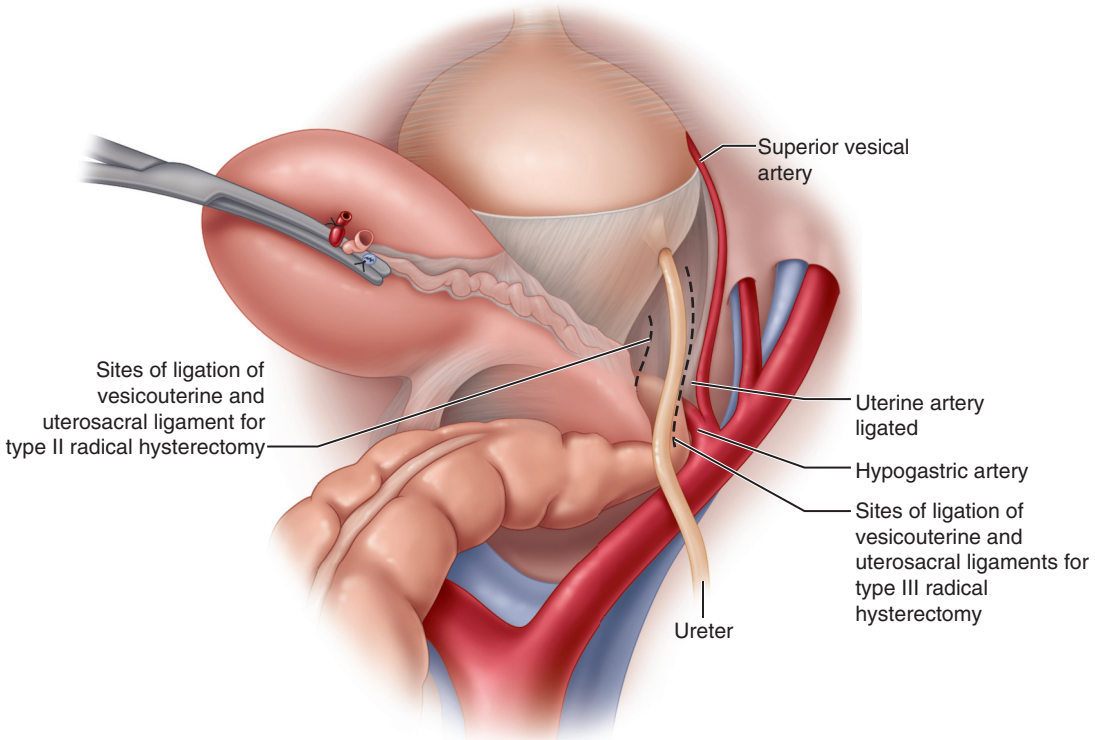


Figure 58-5 Sites of ligation of the vesicouterine and uterosacral ligaments for a type II or type III radical hysterectomy.
From Berek JS, Hacker NF: Practical gynecologic oncology. Baltimore, 1994, Williams & Wilkins, pp 256.

regardless of size, the risk of complications after postoperative pelvic radiation and the risk of pelvic recurrence are high for most of these patients. To avoid exposing these patients to the combined risks of a radical hysterectomy and RT, concurrent chemoRT without surgery is often preferred as the primary treatment. For the same reason, other findings that have been associated with an increased risk of pelvic lymph node metastasis and pelvic recurrence (extensive lymphovascular space invasion, deep stromal penetration) are considered by some clinicians to be contraindications to surgery as primary disease management. Unfortunately, the presence or absence of these factors cannot be reliably determined with conventional clinical staging. A recent cohort analysis suggested that elevated preoperative squamous cell carcinoma antigen levels predicted an increased likelihood of postoperative RT and cancer relapse.[186] Although intriguing, these observations should be validated with further studies.

In patients selected for primary RT for stages IB to IIA tumors, the use of concurrent chemotherapy should be based on tumor size or the presence of pelvic lymphadenopathy. In small-volume disease (IB1) with no clinical evidence of pelvic nodal disease, RT alone provides excellent tumor control and cure rates. Similar to patients with stage IA tumors, many of these cases are referred for irradiation based on medical conditions that render primary surgery less desirable. However, with increased tumor size (i.e., stage IB2 disease) or the presence of pelvic nodal metastases, present evidence indicates the benefit of concurrent cisplatin-based chemoRT.

Minimally Invasive Surgery

Several surgical innovators have applied their laparoscopic or vaginal surgical skills to the treatment of cervical cancer as an alternative to the abdominal operation.[187-192] In a prospective study of various approaches to pelvic lymphadenectomy for surgical staging, consecutive patients scheduled for radical surgery were randomly assigned to transperitoneal, extraperitoneal, or laparoscopic pelvic lymphadenectomy. Extraperitoneal and laparoscopic approaches were feasible and as effective as transperitoneal lymphadenectomy. Although laparoscopic pelvic lymphadenectomy showed a significantly longer operative time, both extraperitoneal and laparoscopic approaches minimized some postoperative complications and reduced the length of stay compared with transperitoneal surgery.[187]

For early cervical cancers, there are numerous retrospective studies describing laparoscopic-assisted radical vaginal hysterectomies (LARVH)[188] and total laparoscopic radical hysterectomies (TLRH).[189] In general, laparoscopic surgery has several advantages over abdominal surgery, including shorter hospitalization time, less blood loss, faster overall recovery time, and better cosmetic results. Despite the benefits of laparoscopic surgery, the uptake of this surgical technique has been slow, likely reflective of the long learning curve, two-dimensional views with reduced depth perception, and rigid instrumentation.

The advent of robotic technology has added another dimension to minimally invasive laparoscopic surgery. Robotic-assisted surgery has rapidly been adopted within a relatively short period of time.[193] Advantages include improved dexterity with increased range of motion, three-dimensional (3D) views, tremor reduction, and more ergonomic positioning for the surgeon. Some surgeons without previous experience in laparoscopy are able to perform robotic-assisted surgery with shorter learning curves.[194] However, the increased cost of this surgical technique can be prohibitive for some institutions. After many case series documenting the feasibility and clinical efficacy of robotic surgery, comparative studies are now emerging, and a Phase III trial has been initiated.[193-201]

Sentinel Lymph Nodes Assessment

In early-stage cervical cancer, the incidence of pelvic lymph node metastasis is approximately 15%.[38] Therefore, more than 80% of patients do not benefit from a full pelvic lymphadenectomy, but may suffer from the associated morbidity of the procedure, such as blood loss, neural injury, lymphocyst formation, and lymphedema. The sentinel lymph node is the first lymph node to receive lymphatic drainage from a particular anatomic location, and the first node where metastatic disease will spread from a primary tumor. Conceptually, if the sentinel node is negative, then the other lymph nodes in the regional basin are also negative, and a full lymphadenectomy can be avoided.

Many single-institution series have been published in the literature, demonstrating their experience and feasibility of the sentinel node procedure in cervical cancer. A systematic review included 23 studies comprising a total of 842 patients.[202]

Prospective multicenter studies are needed to confirm the safety of omitting the full lymphadenectomy in patients with negative sentinel lymph nodes. Over time and with increased experience, it is anticipated that sentinel lymph node mapping will eventually become a standard part of surgical management of early-stage cervical cancer.[206]

Fertility-Preserving Surgery

Dargent et al reported their pioneering experience with laparoscopic pelvic lymph node dissection and radical vaginal trachelectomy for patients with highly selected, nonbulky stages I and IIA disease. The cervix, parametria, and upper vaginal cuff were removed, preserving the uterine corpus and adnexae, and an isthmic cerclage was placed around the lower uterine segment that is sutured to the vaginal cuff.[207]

A number of investigators have subsequently reported their experiences with fertility-preserving surgery for early-stage (predominantly IA2 and IB tumors no larger than 2 cm) cervical cancer using both vaginal and abdominal approaches.[166-168,208-210] In patients with these early-stage tumors, studies suggest that radical trachelectomies have similar oncologic outcomes compared to radical hysterectomies.

Radical abdominal trachelectomy has also been reported in the literature as a fertility-sparing option.[211] The oncologic outcome of radical abdominal trachelectomy is reasonable with a relapse rate of 4.8%.[211] The rate of relapse following radical trachelectomy, however, has historically been higher for larger tumors (>2 cm). In reports that have subdivided tumors into two groups, either smaller than 2 cm or larger than 2 cm, relapse occurred in 1.9% of patients with tumors less than 2 cm versus 20% in those larger than 2 cm.[211] Patients who desire fertility preservation should, therefore, be carefully selected and adequately counseled with regard to the risks.

Adjuvant Postoperative Irradiation

Postoperative irradiation is most commonly recommended in two clinical situations: (1) when pathologic findings in specimens resected during radical hysterectomy suggest a significant risk of pelvic disease recurrence without adjuvant treatment, and (2) when findings in specimens resected during simple hysterectomy show clinically unsuspected invasive cervical cancer.

Most clinicians recommend postoperative pelvic RT when histologic examination of a specimen resected during radical hysterectomy reveals involved positive lymph nodes, parametrial involvement, or positive tumor margins. Historically, the use of adjuvant RT in these patients led to an improvement in pelvic control but without clear evidence of survival benefit.[215,216] However, present evidence, based on a randomized controlled trial, clearly shows an outcome advantage,

Steed et al[191] retrospectively compared 71 patients who underwent LARVH with 205 patients who underwent radical abdominal hysterectomy for stages IA to IB cervical carcinoma. Both groups were similar with respect to age and Quetelet (obesity) index. There were no differences in tumor size, grade, histologic type, depth of invasion, lymph node metastasis, or surgical margins. All laparoscopic procedures were completed successfully, with no conversions to laparotomy. Differences in laparoscopic versus abdominal factors included blood loss (300 mL versus 500 mL; $p < 0.001$), operative time (3.5 hours versus 2.5 hours; $p < 0.001$), and intraoperative complications (13% versus 4%; $p < 0.03$). Intraoperative complications in the LARVH group included cystotomy (7), ureter injury (1), and bowel injury (1). The median time to normal urine residual was 10 days versus 5 days ($p < 0.001$), and the median length of hospital stay was 1 day versus 5 days ($p < 0.001$). Two-year relapse-free survival (RFS) was 94% in both groups. These data showed that LARVH yielded similar efficacy and relapse rates to radical abdominal hysterectomy. The major benefits are less blood loss and a shorter hospital stay. However, laparoscopic-assisted radical vaginal surgery is associated with an increase in intraoperative complications and an increased time to return to normal bladder function.[191]

Similarly, Frumovitz et al[192] retrospectively reviewed 35 patients who underwent total laparoscopic radical hysterectomy compared to 54 patients who underwent abdominal radical hysterectomy between 2004 and 2006. The mean blood loss was significantly lower in the laparoscopic group (319 versus 548 mL; $p = 0.009$), and the median hospital stay was significantly shorter (2.0 versus 5.0 days, $p < 0.001$). However, the mean operative time was significantly longer in the laparoscopic group (344 versus 307 minutes; $p = 0.03$). There was no difference in the amount of parametrial tissue, vaginal cuff, or negative margins obtained. Postoperative infections were much less common after laparoscopic surgery (18% versus 53%; $p = 0.001$).

Boggess et al reported on a cohort of patients treated with robot-assisted radical hysterectomy compared with a historical control group of patients treated with open radical hysterectomy[195]; robotic procedures resulted in less blood loss, a shorter operative time, a higher lymph node yield, and a shorter length of hospital stay.[195] Postoperative complications were lower in the robotic surgery group, but the difference was not statistically significant.

Other similar studies have confirmed these results.[194,196] Although several studies have demonstrated the feasibility of this operative procedure, few have assessed the long-term outcomes. Cantrell et al assessed the survival outcomes for women undergoing robotic radical hysterectomy for cervical cancer compared to a historical cohort of those undergoing open radical hysterectomy.[197] Between 2005 and 2008, there were 63 evaluable patients with robotic radical hysterectomies; 32% of these patients received chemoRT. Median follow-up was 12.2 months. Three-year PFS and OS was 94%, which was not significantly different in the historical cohort of open radical hysterectomies (PFS 89%, $p = 0.27$; OS 93%, $p = 0.47$).[197]

Soliman et al compared the perioperative and pathologic outcomes of 30 open radical abdominal hysterectomies (RAH), 31 laparoscopic radical hysterectomies (LRH), and 34 robotic radical hysterectomies (RRH) performed between 2007 and 2010.[198] There were no differences in age, body mass index, or other baseline characteristics. Pathologic findings were similar among all groups. Operative time was significantly shorter in the RAH group (265 minutes versus 338 minutes for LRH versus 328 minutes for RRH, $p = 0.002$). Estimated blood loss was significantly lower in the LRH group ($p < 0.001$). Median length of stay was shorter in RRH (1 day) compared with LRH or RAH (2 versus 4 days, $p < 0.01$).

In a review by Kruijdenberg et al,[189] 27 studies were included, accounting for 342 RRHs and 914 total LRHs. There was no difference mean operative time, blood loss, and number of lymph nodes retrieved. Both methods resulted in similar adjuvant chemoRT rates and relapse rates. Major postoperative complications were more frequent in robotic surgery patients (9.6%) compared to patients who underwent laparoscopic surgery (5.5%, $p < 0.05$), which could be reflective of the smaller number of robotic cases.

Obermair et al[201] have initiated a Phase III randomized trial comparing LRH or RRH with abdominal radical hysterectomy for the treatment of stage IA1 (with lymphovascular invasion), IA2, and IB1 cervical squamous cell carcinomas and adenocarcinomas. Researchers hope that this study will eliminate the selection bias of retrospective analyses and elucidate the optimal surgical approach for early-stage cervical carcinoma.[201]

For sentinel lymph node assessment, the tumor is injected peripherally with blue dye or technetium-99 (^{99}Tc) radioactive tracer. Intraoperatively, the sentinel node is detected when it is blue, or by high radioactive counts with a gamma probe. The sensitivity of sentinel lymph node mapping in early cervical cancer was 92% (95% CI 84% to 98%) and the detection rate was 97% (95% CI 95% to 98%) when the combined technique of radioactive tracer and blue dye was used. The sensitivity is improved when restricting to tumors measuring ≤ 20 mm, compared to larger tumors.[203] Benefits of sentinel node mapping include minimizing morbidity by avoiding a full lymphadenectomy, identifying aberrant pathways of drainage, which could ultimately alter treatment decisions, and detection of micrometastases by ultrastaging that may not be identified by standard hematoxylin and eosin staining.[204] In up to 80% of cases the sentinel lymph node is the only node harboring metastatic disease.[205]

If lymphatic metastases are not identified and left untreated, this places the patient at increased risk of relapse and possible death. False-negative rates can be minimized if there is adherence to specific criteria and quality assurance of the sentinel node procedure. The procedure should be restricted to patients with early stage disease (FIGO stages IA-IB1) because patients with larger tumors have a higher rate of lymph node replacement by tumor, impairing lymphatic drainage. Any enlarged lymph nodes should be removed, even if they are not the sentinel node. Each hemipelvis should be assessed even if the sentinel node is detected unilaterally. Additionally, a collaborative effort of the gynecologic oncologist, gynecologic pathologist, and nuclear medicine expert is important to gain experience with sentinel lymph node mapping and improve the quality of the procedure.[171]

Beiner et al[170] compared 90 patients who underwent radical vaginal trachelectomy for cervical cancer of 2 cm or less with fertility-sparing intent, to a similar group of patients who were clinicopathologically matched which were treated with radical hysterectomy. Patients were matched for age, tumor size, histology, grade, depth of invasion, LVSI, pelvic node metastases, and adjuvant therapy. There was no statistically significant difference in 5-year RFS or OS between the two groups. Their analysis also indicated that histologically typed adenocarcinoma can be treated safely with radical trachelectomy when patients are appropriately selected (this type was found in 50% of the patients and its frequency is increasing in younger women). Although some have reported an increased relapse rate in patients with lymphovascular space invasion, these authors postulate that lymphovascular space invasion alone (found in 68% of their cases), without other adverse pathologic prognostic factors, did not jeopardize the outcome in patients undergoing fertility-sparing surgery.[170]

A retrospective study by Marchiole et al[208] compared 118 patients with radical vaginal trachelectomy to 139 radical vaginal hysterectomies in the same time period. There was no statistically significant difference between the two groups with respect to 5-year RFS or OS.

With regard to obstetrical outcomes, more than 250 pregnancies have been reported following radical vaginal trachelectomy.[171,209] In reports that include information on the number of women attempting pregnancy, pregnancy rates of 41% to 79% were achieved.[209,210] Overall, approximately 40% of all pregnancies resulted in a term delivery (>37 weeks).[209,210] Preterm birth rates range from 20% to 30%.[209,210]

Neoadjuvant chemotherapy has been used in small limited series to reduce tumor size prior to fertility-sparing surgery. Pelvic lymphadenopathy should be performed.[212] Robova et al[213] reported on 15 women with tumors larger than 2 cm that have not infiltrated more than two thirds of the stroma. Chemotherapy was followed by simple trachelotomy and pelvic lymphadenopathy. Fertility was preserved in 12 patients. There were three relapses, one resulting in death. Seven pregnancies were achieved, six delivered at time of reporting, two of which were premature deliveries.[213] In another study, treatment consisted of laparoscopic pelvic and paraaortic lymphadenectomy, and when no nodal metastasis was detected, neoadjuvant chemotherapy followed by radical vaginal trachelectomy.[214] In a cohort of 18 women eligible for the study, 12 (67%) were diagnosed with metastasis after laparoscopic lymphadenectomy, and therefore underwent primary chemoRT. Six underwent neoadjuvant chemotherapy with cisplatin, paclitaxel, and ifosfamide. Three patients had a complete response, whereas only three had more than 50% size reduction. After a mean follow-up of 30.6 months, there were no relapses. The assessment of lymph nodes, which may include PET imaging before initiating neoadjuvant chemotherapy, may be warranted in this early stage IA or IB1 population to guide management.[214] Further investigation with careful selection and follow-up of a larger number of patients to validate this conservative approach is needed.

including an OS benefit, for combined chemoRT in such patients, who may be collectively defined as having pathologic evidence of extracervical disease following radical hysterectomy for clinical early-stage disease.[112] In the absence of any gross tumor residual, a dose of 50 Gy to the whole pelvis is typically prescribed as adjuvant treatment. Although some clinicians also add a vaginal brachytherapy boost, the added therapeutic benefit of this is unclear, and it should be remembered that the results from the aforementioned trial were achieved without the use of intravaginal brachytherapy. Tumor features associated with a high risk of local recurrence, especially nodal metastases, also tend to be predictors of distant metastasis, decreasing the benefit of improved local control on survival rates. In addition, a number of factors may reduce the efficacy of postoperative RT.[217] Higher doses of irradiation may be required to sterilize microscopic disease in a disturbed operative site. Furthermore, clinicians' fears of causing major complications in patients who have had an extensive transperitoneal pelvic surgical procedure often limit the irradiation dose that can be administered safely.[218-221]

More controversial indications for adjuvant postoperative RT may include findings of a single microscopically positive node, bulky primary disease, deep stromal penetration, invasion into the lymphovascular space, or high-grade adenocarcinoma. The GOG conducted a trial (GOG 92) of postoperative RT versus observation alone following radical hysterectomy in stage IB cervical cancer with risk factors limited to the primary tumor (without extracervical spread or nodal metastases).[222] Eligible patients were those modeled to have an approximately 3-year risk of relapse of 30% following surgery alone, based on varying combinations of tumor size, lymphovascular space involvement, and depth of cervical stromal invasion. They are sometimes referred to as "intermediate-risk" patients. A total of 277 eligible patients were entered into the study between 1988 and 1995. Patients randomized to postoperative RT (no concurrent chemotherapy) received 50.4 Gy of whole-pelvis RT, without a vaginal brachytherapy boost. There was a statistically significant improvement in RFS at 2 years (88% versus 79%) favoring the RT arm over the observation-only controls. There was also a higher incidence of severe toxicity in the radiation therapy cohort (6%) compared with the surgery only cohort (2.1%). An updated analysis with approximately 10 years of at-risk follow-up confirmed that adjuvant pelvic RT significantly reduced the risk of relapse and prolonged the PFS time in patients with intermediate-risk early-stage cervical cancer. Although there was a trend toward improved OS for adjuvant RT, this did not reach conventional statistical significance ($p = 0.074$), which may have reflected an underpowered trial.[223] An interesting observation from GOG 92 was that postoperative RT seemed particularly beneficial for patients with nonsquamous cell histologic findings (adenocarcinoma, adenosquamous cancer). Although not a primary analysis endpoint of the trial, and not adjusted for by multivariate analysis, the magnitude of the reduction in relapse for nonsquamous cell versus squamous cell histologic types was statistically significant ($p = 0.019$).[223] At present, the use of adjuvant RT following radical hysterectomy for node-negative patients with multiple risk factors confined to the cervix is generally recommended, but its use should be based on careful consideration of patient physiology, surgicopathologic findings, and multidisciplinary consultation between the patient, surgeon, and radiation oncologist.

An NCI consensus conference concluded that "primary therapy should avoid the routine use of both radical surgery and RT."[8] If clinical evaluation reveals risk factors that would require pelvic RT after radical hysterectomy, RT should be considered the primary treatment of choice. Although improvements in imaging technology allow better determination of nodal disease and may eventually permit evaluation of more subtle intratumoral risk features, such as depth of stromal invasion and lymphovascular space involvement, the only tumor parameter that can be routinely evaluated before hysterectomy is tumor size. It is clear that the larger the cervical lesion, the more likely the indications for postoperative RT following radical hysterectomy. For this reason, many clinicians avoid primary surgery in patients with tumor diameters greater than 4 cm (stage IB2) because 50% to 80% of such cases undergo recommended postoperative RT.[183,224,225]

Although it is standard practice to screen women for cervical cancer before a hysterectomy is performed for any reason, unsuspected invasive cancer is occasionally discovered in the resected specimen from a simple hysterectomy performed for benign disease or CIN. If cancer invasion is more than 3 mm or if there is extensive invasion into the lymphovascular space, then there is a significant risk of paracervical or pelvic lymph node involvement, and postoperative pelvic RT or chemoRT for risk factors is indicated. With this treatment, the prognosis is still good, with 5-year OS of approximately 80% if the tumor appears to have been confined to the cervix and if surgical margins are negative.[226]

Patients who have gross residual disease after hysterectomy may still be curable but have 5-year OS of only approximately 30%. Given the presence of gross residual disease after "cut-through" hysterectomy, concurrent chemoRT is indicated.

The use of brachytherapy in addition to EBRT should be individualized. It is reasonable to consider a brachytherapy boost for patients with positive vaginal mucosal margins. For patients with radial or parametrial positive margins, the rapid dose fall-off from intravaginal brachytherapy may not provide sufficient coverage, and a highly conformal EBRT boost of additional 10 Gy to 15 Gy may be considered following whole-pelvis RT to 45 Gy to 50 Gy. This conformal EBRT boost will include the vaginal cuff and parametria and must extend to the pelvic sidewalls to adequately cover the margin given the retraction of the parametrial tissue to the sidewall after a hysterectomy. For patients with gross residual tumor, a boost with interstitial brachytherapy or intraoperative electrons may be needed.

Adjunctive Surgery

In a retrospective study of cases from the University of Texas MDACC, Durrance et al[227] suggested that the rate of central disease recurrence after radiation therapy of bulky (≥6 cm) endocervical cancers may be reduced when irradiation is combined with an extrafascial hysterectomy. Authors of a subsequent report emphasized that acceptable complication rates could be achieved only if the dose of irradiation was reduced and if surgery was limited to a simple (type I) extrafascial hysterectomy performed with careful, sharp dissection.[228] After these reports, the use of combined treatment increased, and some clinicians began arbitrarily extending the use of adjunctive hysterectomy to treat patients with smaller endocervical tumors (<6 cm in diameter) and tumors with an exophytic morphology.

In 1992, Thoms et al[229] reexamined the experience of the MDACC and concluded that biases that led to the selection of patients with more favorable disease for combined treatment made it impossible to compare meaningfully the relative efficacy of the two approaches. Mendenhall et al[230] compared the outcome of patients treated before or after treatment policy changed at the University of Florida to include planned adjuvant hysterectomy. No difference in outcome was seen between patients treated before or after the change in policy.

The GOG conducted a Phase III trial (GOG 71) in patients with stage IB2 cervical cancer randomized to receive RT alone versus RT followed by extrafascial hysterectomy (this trial did not use concurrent chemotherapy). Although adjuvant hysterectomy following primary RT appeared to modestly reduce the rate of local recurrence, there was no improvement in OS.[231]

More recently, in the era of image-planned brachytherapy, equivalent outcomes with less toxicity (3% versus 15%) were seen after brachytherapy rather than adjuvant hysterectomy.[232] There are no clear data to support the routine role of adjuvant hysterectomy after primary RT for bulky tumors confined to the cervix, particularly after optimal doses of irradiation have been delivered. In a large retrospective analysis of almost 3000 patients with stages I to II squamous cell cervical cancer treated with definitive RT, Eifel et al[233] reported low central disease (cervix, upper vaginal, proximal paracervical tissues) recurrence rates of 6.8%, 7.8%, and 9.6% at 5, 10, and 20 years, respectively. This indicated that few patients might benefit from adjuvant hysterectomy following adequate RT.[233] However, surgery may be selectively applied in patients with a poor tumor response to RT, in those whose tumor and pelvic anatomy precluded good brachytherapy geometry, or as salvage treatment for isolated cervical cancer recurrence.

LOCALLY ADVANCED DISEASE AND PALLIATION

The treatment of choice for most patients with locoregionally advanced disease (IB2 to IVA) is definitive RT with concurrent chemotherapy, usually cisplatin-based. RT consists of a combination of EBRT and brachytherapy. Most authorities today consider optimal RT as a cumulative CTV or point A dose of 80 Gy to 90 Gy (in conventional equivalents), with all treatment completed within 8 weeks. Five-year OS of patients treated with chemoRT now approach 70% to 90% for stage IIB disease, 50% to 70% for stage IIIB disease, and perhaps 15% to 25% for stage IVA disease[109-113,118,119] (see Table 58-4). With aggressive treatment, even patients with massive, locoregionally advanced tumors have a realistic chance of being cured.

Treatment of Recurrent Disease

Isolated Locoregional Relapse

Following primary management for cervical cancer, a small percentage of patients will present with isolated locoregional relapse for whom radical therapy may be contemplated, including the options of pelvic exenteration, chemoRT, and intraoperative irradiation (IORT) with electrons or HDR brachytherapy. Patient selection, careful "restaging," and individualization of therapy are essential.[236] The most important determinant of therapy options is the type of prior treatment the patient has received.

Patients who experience local recurrence after initial surgery alone may be candidates for radical RT plus concurrent chemotherapy (as extrapolated from the primary management of locally advanced disease). Customized combinations of EBRT, often using highly conformal techniques including IMRT and intracavitary or interstitial brachytherapy, ideally with imaging to help guide insertion and treatment planning,[237] are used. Salvage RT is particularly effective for small central relapses limited to the vagina or paravaginal tissues, with 5-year OS of 69% reported in one series.[238,239] Novel techniques of placing a hydrogel spacer between the rectum and the cervix or vaginal hold promise to further reduce normal tissue doses.[240]

There are limited reports of radical reirradiation for patients who relapse following prior pelvic RT.[241,242] However, radical surgery forms the primary cornerstone of salvage treatment for isolated pelvic recurrences without pelvic side wall disease in previously irradiated patients. In most cases, the only potentially curative option is pelvic exenteration. For highly selected patients with central recurrence, in whom pelvic exenteration is successfully completed, 5-year OS of approximately 50% may be achieved.[241,243,244]

Proximity or fixation of locally recurrent tumor to the pelvic sidewall is an adverse prognostic finding, leading most investigators to suggest that attempted surgical salvage be abandoned with intraoperatively detected side-wall involvement. However, some patients previously considered incurable with exenteration have survived with the incorporation of preoperative chemoRT (EBRT dose is dependent on the amount of prior RT) followed by maximal resection plus IORT (electrons or HDR brachytherapy) directed to the initially involved pelvic side wall (i.e., to narrow or involved margins of resection).[245,246] (See Chapter 17, Intraoperative Irradiation, for information on techniques for multiple disease sites, including the cervix, and their results.)

Advanced Disease and Palliation

The prognosis is extremely poor and survival times are short for patients with recurrent or metastatic cervical cancer that is not amenable to surgery or irradiation with curative intent. Systemic chemotherapy is a therapeutic option often used, although no trials to date have compared chemotherapy with the best supportive care for palliation.

Chemotherapy

For women who relapse, combination cisplatin-based chemotherapy is the national standard (eTable 58-2). Compared with cisplatin alone, Omura et al[247] showed a higher objective response rate and PFS with cisplatin plus ifosfamide; however, there was no improvement in OS, and toxicity rates with combination chemotherapy were significantly increased. Another GOG Phase III trial demonstrated no advantage with the addition of bleomycin to the cisplatin plus ifosfamide combination.[248] The GOG has compared single-agent cisplatin with a combination of cisplatin plus paclitaxel with quality-of-life assessments included among outcome measures. The combination of cisplatin plus paclitaxel resulted in a higher objective response rate, longer PFS, and higher toxicity rate, with no apparent decrement in patient-reported quality of life.[249]

GOG 204 was a four-arm study comparing four cisplatin doublets with paclitaxel, topotecan, gemcitabine, and vinorelbine. After 513 patients were enrolled, a planned interim analysis recommended early closure of the trial based on the fact that none of the other arms would ever statistically show benefit over the control arm of cisplatin plus paclitaxel, demonstrating the challenge in achieving major progress for this patient population.[250] PFS was as short as 4 months to 6 months. Although multiagent systemic therapy remains an active area of investigation, the benefits of salvage chemotherapy remain modest at best (see eTable 58-2).

It is now recognized that a majority of patients who recur after initial therapy are not platinum-naïve, having received platinum-based chemoRT as definitive or adjuvant therapy. Previous exposure to platinum clearly influences the potential response when platinum is used in a palliative setting. In an analysis of prognostic factors for response to cisplatin-based systemic chemotherapy for recurrent or metastatic disease, Moore et al[100] identified five factors as independent predictors of a poor response: African American patient, Eastern

For patients with gross paraaortic nodal disease, doses to the entire paraaortic chain of 45 Gy in 25 fractions over 5 weeks followed by dose escalation to the paraaortic nodes has been shown to be feasible at the University of Washington. Sequential treatment doses of 20 Gy in 2 Gy fractions for a total up to 65 Gy have been administered with good effect; careful maintenance of normal tissue dose constraints, including kidney, spinal cord, and small bowel are critical. Daily prophylactic proton-pump inhibitor therapy as well as antiemetic medication should be considered. An intensity-modulated radiation therapy (IMRT) planning constraint for the small bowel (contouring contrast-enhanced loops) of 5 mL less than 55 Gy has resulted in few small bowel toxicities.[234] For patients with large nodal disease adjacent to the duodenum, duodenal planning dose constraints of a volume receive 55 Gy (v55) less than 15 mL and a dose to 2 mL of less than 60 Gy are also recommended to prevent possible fatal duodenal perforations.[235] An alternative to the EBRT boost dose following 45 Gy over 5 weeks would be restaging 2 weeks to 4 weeks later followed by an exploratory laparotomy with removal of gross nodal disease plus intraoperative electron irradiation (IOERT).

eTABLE 58-2 Phase III Trials of Cisplatin and Cisplatin-Containing Regimens in Advanced, Recurrent, or Metastatic Cervical Carcinoma

Author	Year	Regimen	No. Patients	OR (%)	CR (%)	PFS (mo)	OS (mo)
Omura[205]	1997	P	140	19	6	3.2	8.0
		P + IFX	151	31	13	4.6	8.3
Bloss[206]	2002	P + IFX	146	32	NS	4.6	8.5
		P + IFX + B	141	32	NS	5.1	8.4
Moore[208]	2004	P	134	19	6	3.0	8.9
		P + T	130	36	15	4.9	9.9
Long[208] (old)	2005	P	145	13	NS	2.9	7.0
		P + Topo	148	26	NS	4.6	9.2
Monk[209]	2009	P + T	103	29	3	5.8	12.9
		P + Topo	111	23	2	4.6	10.3
		P + Gem	112	22	1	4.7	10.3
		P + Vin	108	26	7	4.0	10.0

B, *Bleomycin;* CR, *complete response;* DFS, *disease-free survival;* Gem, *gemcitabine;* IFX, *ifosfamide/MESNA;* NS, *not stated;* OR, *objective response;* OS, *overall survival;* P, *cisplatin;* PFS, *progression-free survival;* T, *paclitaxel;* Topo, *topotecan;* Vin, *vinorelbine.*

Cooperative Oncology Group (ECOG) performance status score greater than 0, pelvic disease, prior radiosensitizer, and time interval from diagnosis to first recurrence of less than 1 year. They suggest that with a simple prognostic index, which combines the risk factors, a subgroup of patients can be identified who are unlikely to benefit from cisplatin-containing regimens and who should be evaluated for other novel investigational agents or best supportive care.[100]

Recently, incorporation of bevacizumab into the first-line setting was evaluated in GOG 240, which enrolled more than 450 patients between 2009 and 2012 randomly assigned patients to platinum-based chemotherapy with or without bevacizumab.[251] These patients were in their 40s and predominantly had squamous histologies (approximately 70%). The majority had recurrent disease and has previously received cisplatin. Approximately half of these patients had pelvic disease. The addition of bevacizumab to chemotherapy increased OS (17 versus 13 months; HR for death, 0.71; 98% CI, 0.54 to 0.95; $p = 0.004$ in a one-sided test) and resulted in higher response rates (48% versus 36%, $p = 0.008$). Bevacizumab, as compared with chemotherapy alone, was associated with an increased incidence of hypertension of grade 2 or higher (25% versus 2%), thromboembolic events of grade 3 or higher (8% versus 1%), and gastrointestinal fistulas of grade 3 or higher (3% versus 0%). Despite this outcome, the median survival is still less than 2 years.

Irradiation

Radiation therapy can also play an important role in the palliation of patients with incurable advanced disease. Hypofractionated pelvic irradiation usually controls bleeding and frequently provides some relief of pelvic pain. There is a paucity of data and no randomized trials on optimal palliative irradiation regimens. A variety of fractionation schemes have been used. No standardized instruments for measuring symptom relief have been used.[252] The choice of dose and fractionation schedule will be influenced by expected survival times, patient performance status, symptoms, site(s) and bulk of tumor involvement, adjacent normal tissue considerations, medical comorbidities, and logistic considerations.

The RTOG reported the results of a Phase I/II study in which patients with advanced pelvic malignant disease were given up to three fractions of 10 Gy at 1-month intervals with misonidazole.[253] The overall objective response rate was 57%, but the rate of grade-3 and grad-4 toxicities was high (45%), although it is unclear if some of the complications may have been the result of tumor progression. Studies of the MDACC experience with this method have demonstrated a symptomatic response rate of approximately 75% with two fractions of 10 Gy but have also revealed an unacceptable rate of major complications when a third fraction of 10 Gy was given.[254,255]

In a second RTOG study, accelerated split-course EBRT was used as palliative treatment for patients with advanced pelvic malignant disease. Patients received up to three courses of 14.8 Gy given in 3.7-Gy fractions twice daily over 2 days. A 3-week to 6-week rest interval was given between courses. Patients who completed three courses of EBRT had an overall response rate of around 60%, with complete relief of pain achieved in 50% of patients.[256]

Other typically used fractionation schemes, such as 30 Gy in 10 fractions or 20 Gy in 5 fractions, have been used with some success. Prolonged fractionation is rarely indicated for palliation of patients with extraregional metastases from cervical cancer because the median life expectancy for these patients is short. Above all, these patients benefit from close monitoring of their symptoms; prompt, aggressive treatment with analgesic drugs; and sensitive, supportive care. Anesthetic or neuroablative treatments may be helpful in selected cases, and prompt referral to a multidisciplinary pain service is warranted for patients with intractable pain.

IRRADIATION TECHNIQUES AND TOLERANCE

External Beam Irradiation (EBRT)

In the radical radiation treatment of carcinoma of the cervix, EBRT is used to treat central disease and to sterilize known or suspected regional metastases. For patients with bulky central disease, a course of EBRT to the pelvis usually causes significant tumor regression, potentially improving the dose distribution of subsequent intracavitary irradiation by shrinking endocervical disease or by reducing exophytic tumor that would have caused undesirable caudad displacement of intracavitary vaginal applicators. For these reasons, patients who have locally advanced disease usually begin treatment with EBRT.

The proportion of treatment given with EBRT or intracavitary irradiation must be balanced carefully, however. Because of the relatively large volume of bladder, rectum, and small bowel included in EBRT pelvic fields, the dose of intracavitary therapy that can be safely given is relatively compromised when a high dose (>45 Gy to 50 Gy) of whole-pelvis EBRT is delivered.

Some radiation oncologists prefer to begin intracavitary irradiation as early as possible, even in patients with initial bulky disease, shielding central normal structures with a midline block on anteroposterior/posteroanterior (AP/PA) fields after 20 Gy to 30 Gy. In the past, use of a midline block of 3 cm to 4 cm in diameter was considered standard.[257] A review of urinary tract complications in patients treated with RT for FIGO stage I cervical cancers at the MDACC demonstrated a significantly higher rate of ureteral stenosis when parametrial EBRT was combined with relatively high doses of intracavitary therapy, presumably because the relatively narrow standard central blocks failed to protect the ureters from irradiation.[258] For this reason, customized blocks are preferred when higher doses of parametrial irradiation are given.

To optimize the match between EBRT and intracavitary irradiation, Perez et al[259] developed an elaborate central gradient step-wedge block designed to compensate for the lateral dose gradient from intracavitary treatment. For this method, one of several standard gradient blocks is matched to the patient's intracavitary distribution and used to shield central structures on AP/PA fields. They were able to deliver high paracentral RT doses by using intracavitary therapy to give most of the central treatment. However, the gradient blocks can only be matched to the dose distribution calculated in a single plane (usually, in the center midcoronal plane of the implant). Theoretically, anterior and posterior structures (such as the uterosacral ligaments) may be underdosed with this method, although the survival rates reported by Perez et al[259] have generally been excellent.

Alternatively, a somewhat higher dose of EBRT (35 Gy to 45 Gy) may be given to the whole pelvis before intracavitary RT. Although this approach somewhat reduces the total paracentral dose that can be delivered via brachytherapy, it may be advantageous to deliver a more homogeneous dose sufficient to eradicate microscopic disease to the entire pelvis, particularly for locally advanced tumors. Additional tailored EBRT can be delivered to disease involving the pelvic wall or lymph nodes after the first intracavitary treatment. The medial edge of such boost fields is usually placed at about the 50-cGy/hour isodose margin of the intracavitary dose distribution

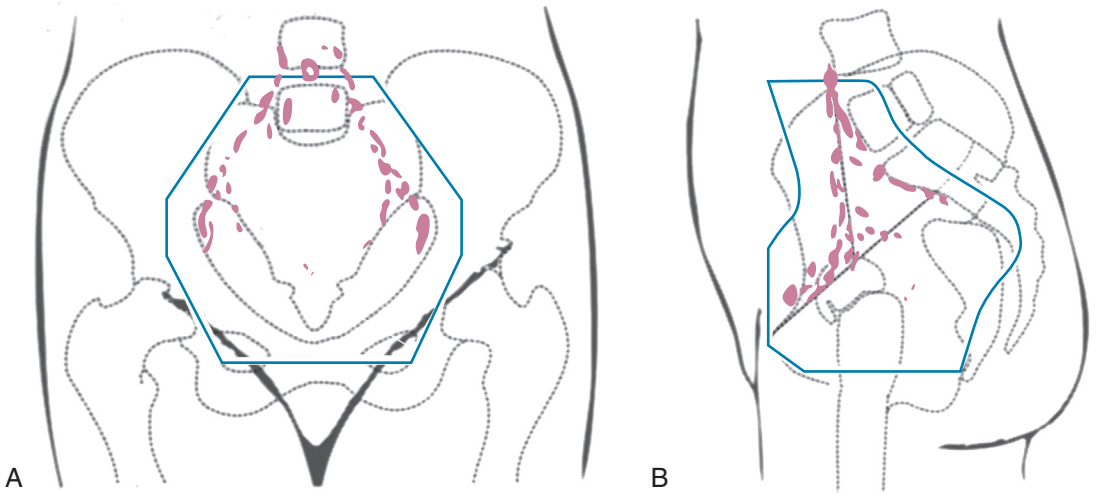


Figure 58-6 Typical anteroposterior-posteroanterior **(A)** and lateral **(B)** fields for treatment of carcinoma of the cervix. On the lateral view, external iliac nodes are typically centered about a plane between S1 to S2 and the tip of the pubis and common iliac nodes along a plane from the anterior aspect of L4 to the bisector of the external iliac plane. Care must be taken to design fields that cover regional lymph nodes and the primary tumor with margin.

or about 0.5 cm from the lateral surface of the vaginal applicator.

EBRT tends to cause some contraction of the vaginal apex. Because the vaginal capacity may limit the size of vaginal applicators, small tumors in women who have a narrow (usually postmenopausal) vagina may be more effectively treated by administering intracavitary irradiation before or early in the course of EBRT.

In all cases, care must be taken to include all areas at risk for disease in the pelvis. Conventional field arrangements for treating the pelvis typically include the use of four fields (anterior, posterior, and two lateral fields). Occasionally, especially in thinner patients, anterior and posterior opposed fields are used, and this is generally tolerable as long as EBRT doses do not exceed 40 Gy to 45 Gy. Historically, field borders that define the volume of the EBRT have been based on empirically derived bony anatomic landmarks. These bony landmarks, which are still widely promulgated in textbooks and RT protocol guidelines, represent the careful attempts of past clinical investigators to match skeletal anatomy, which can be readily appreciated radiographically, with potential soft-tissue tumor extent, nodal drainage, and pathways of regional spread. These "standardized fields" for "field-based planning" are illustrated in Figure 58-6 for a four-field "box" technique. The anterior and posterior fields usually incorporated an inferior border placed at the mid or lower obturator foramina or at least 3 cm to 4 cm below the lowest extent of clinically appreciated cervical or vaginal disease, and lateral borders were placed approximately 1.5 cm to 2 cm beyond the bony margins of the true pelvis. Lateral fields generally were placed with an anterior border anterior to the symphysis pubis; the posterior border previously was historically described as passing through the S2 to S3 junction, but clinical examination and contemporary pelvic imaging have suggested that such a conventional posterior border would frequently shield gross tumor in patients with disease extending posteriorly, particularly in the uterosacral ligaments. Without the benefit of modern imaging techniques to approximate tumor extent, shielding of the anterior-superior border of the lateral fields must be done with care or possibly omitted because of the possibility of shielding disease in the upper external iliac nodes. Although broadly useful, the routine use of "standardized fields" based on bony anatomy has been questioned as lacking in precise individual case coverage based on intraoperative measurements and imaging studies.[84,260-262]

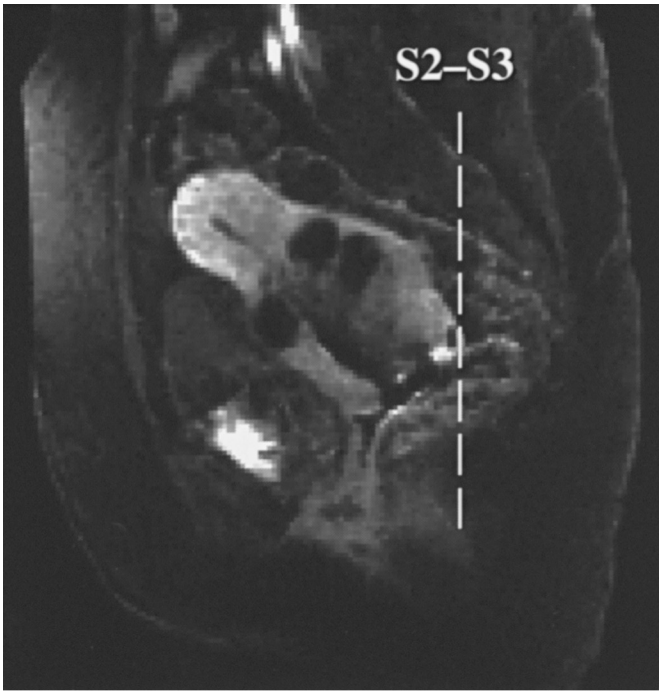


Figure 58-7 Sagittal magnetic resonance imaging (MRI) of a patient with a bulky stage IB2 adenocarcinoma. MRI demonstrated a normal uterine fundus and a bulky endocervical tumor, clarifying the site of origin of this lesion. The study also illustrates the risk of using a "standard" posterior margin for lateral fields because the posterior extent of gross disease extends posterior to the S2 to S3 interspace.

Most centers use image-guided CT or MRI planning to design radiation volumes[84] (Figure 58-7). Although even these imaging techniques are inaccurate and may underestimate the extent of microscopic spread within the pelvis, they do at least

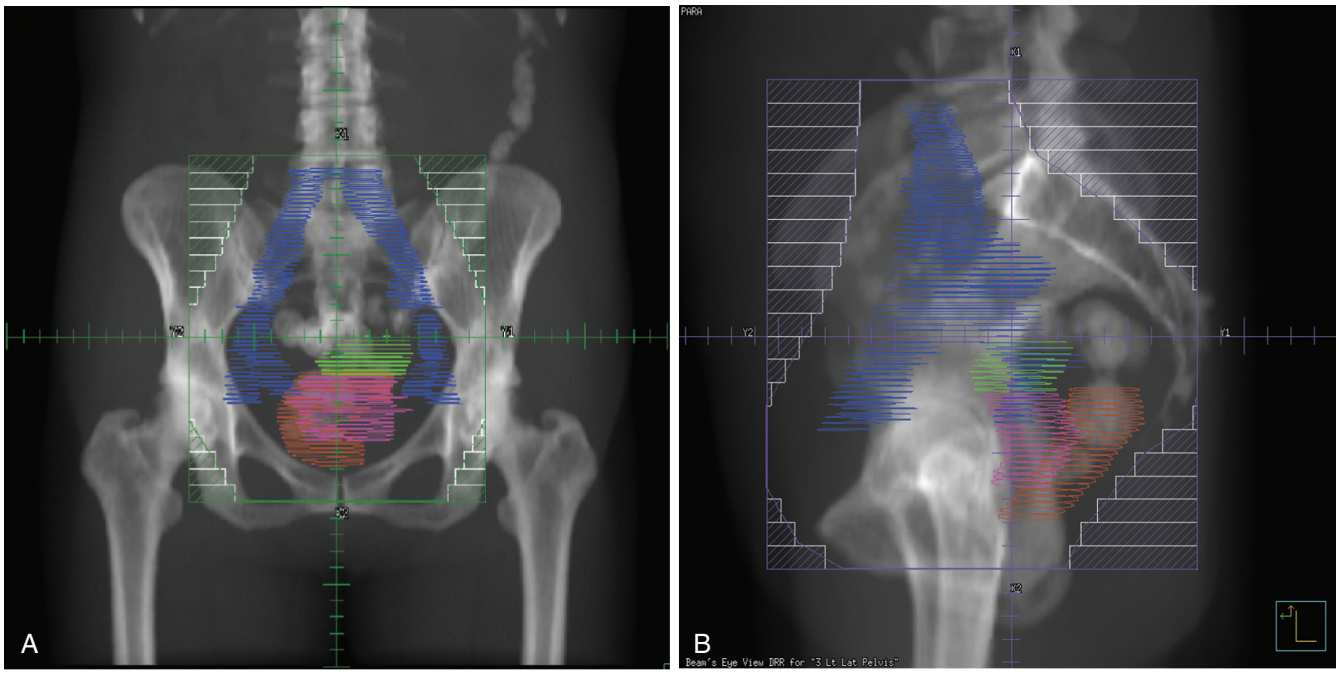


Figure 58-8 Anterior **(A)** and left lateral **(B)** digitally reconstructed radiographs (DRRs) of external beam pelvic fields for a patient with stage IIIB cervical cancer with bilateral parametrial extension and left pelvic side wall involvement but without nodal metastases on radiologic imaging. (Areas selectively illustrated: *pink*, cervical tumor gross volume; *green*, fundus; *brown*, rectum; *blue*, pelvic vessels as surrogates for nodal basins, including internal iliacs, external iliacs, and common iliacs. Other organs such as the bladder and small bowel can be alternately turned on or off on the computer screen to facilitate visualization.)

allow a somewhat better approximation of the location of the nodes and gross disease. These imaging technologies clearly improve the ability to define gross tumor extent, but they also underscore several critical issues that need to be addressed. To take full advantage of these imaging modalities, radiation oncologists must have adequate training and formalized experience in interpreting radiologic studies. Findings from a detailed pelvic examination must be carefully incorporated into the treatment plan because there are areas of potential tumor extension, such as in the vagina and parametria, which are imprecisely defined by imaging alone. Planners must have a clear awareness of the potential pathways of regional and nodal spread from cervical cancer because it is not possible to obtain images of microscopic disease, and lack of such recognition may lead to inadequate coverage of the volume at risk. There are no data examining the necessity for inclusion of the whole uterine body, but most recommend its inclusion in the treated volume given the potential for myometrial extension of disease from the cervix.

Examples of EBRT ports for patients with cervical cancer based on contemporary CT simulation are shown in Figures 58-8 and 58-9. An example of a composite EBRT dosimetry plan is illustrated in Figure 58-10. Although CT-based treatment planning and field design allow customization based on individual patient findings, it should be noted that the general similarity of these fields to the traditional "standardized" bony anatomy–based fields serve as a testament to the clinical acumen and observational skills of previous clinicians who did not have access to the imaging modalities of today.

Intensity-Modulated Irradiation

Modern technologies in radiotherapy delivery such as IMRT allow the delivery of highly conformal dose distributions

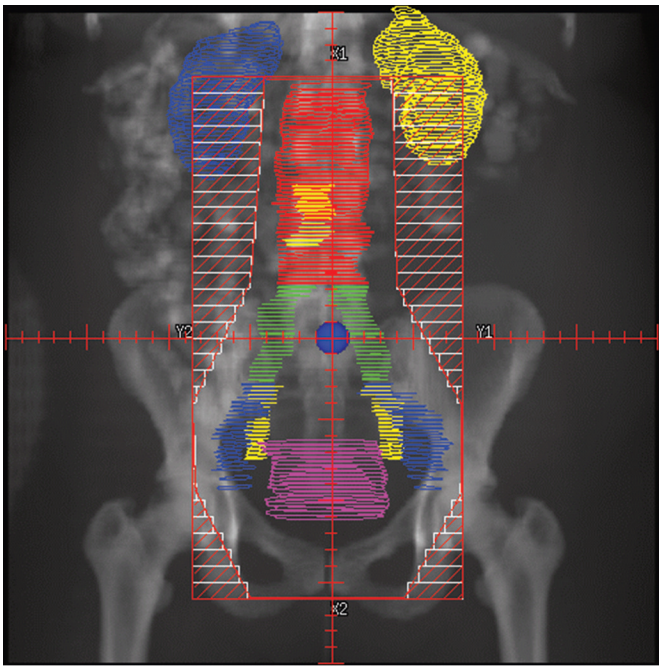


Figure 58-9 Anterior digital reconstructed radiograph of an extended pelvic and paraaortic external beam field in a different patient with stage IIIB cervical cancer and multiple pelvic and low paraaortic lymph node metastases. Areas selected on this image included the cervical tumor gross volume *(pink),* the areas of gross nodal involvement as determined by computed tomography/positron emission tomography (CT/PET) imaging *(yellow),* the associated pelvic and paraaortic nodal basins, and the bilateral kidneys.

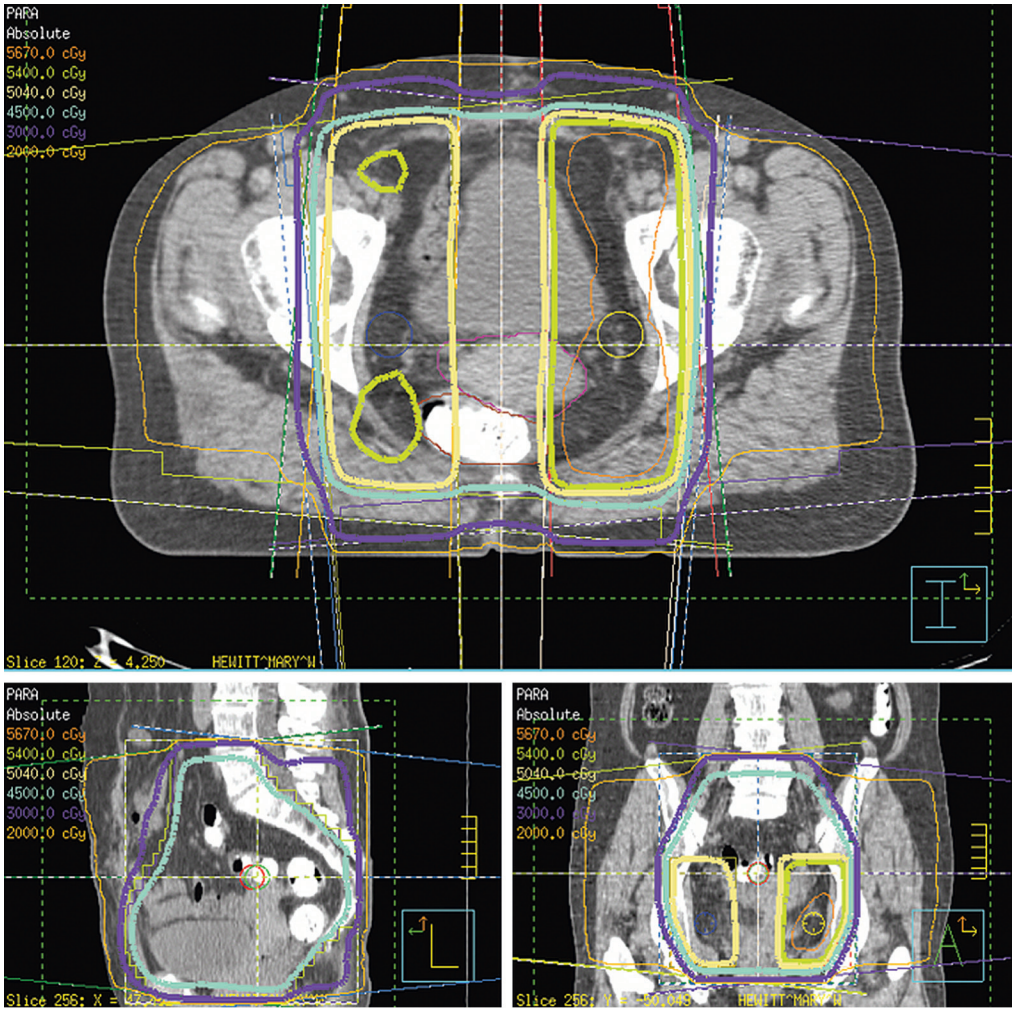


Figure 58-10 External beam dosimetry planning (for patient shown in Figure 58-8). The prescribed dose was 45 Gy to the whole pelvis, with parametrial boosts to 50.4 Gy to the right and 54 Gy to the left (patient had bulkier disease on the left, with extension to the pelvic side wall). The central dose in this patient was supplemented by intracavitary brachytherapy.

unachievable using conventional approaches. They combine high-resolution imaging, advances in computer treatment software and linear accelerator collimation capabilities, inverse planning, and radiation beam flux modulation. IMRT has been most widely used in head and neck and prostate cancers, simultaneously allowing sparing of surrounding normal structures and dose intensification to the tumor target volume. The success of highly conformal RT such as IMRT in various tumor sites is heavily dependent on the accuracy of tumor delineation through imaging. Dosimetric evaluation of its use in gynecologic cancers suggests IMRT may significantly reduce unwanted radiation exposure to adjacent bowel and bladder while preserving tumor coverage.[263] Early clinical experience at the University of Chicago has demonstrated a reduction in acute gastrointestinal toxicity for patients with gynecologic cancer undergoing pelvic IMRT compared with contemporaneous historical controls treated with traditional standard techniques.[264] Recent analysis has also indicated a decrease in acute hematologic suppression, favoring patients treated with IMRT, especially in those who also received chemotherapy.[265] Although there is excitement about the potential eventual application of IMRT to definitive cervical cancer RT, questions remain about accurate target definitions, treatment standardization, intrapatient and interpatient reproducibility, and time-intensive requirements for treatment planning and delivery.

Currently, there is an emerging consensus that IMRT may be a useful technique in posthysterectomy irradiation. It may allow greater sparing of normal tissues, especially the small bowel, displaced into the pelvis, provided that meticulous attention is paid to anatomic detail and contouring of targets. However, issues regarding dose heterogeneity within the target volume and broad "low-dose scatter" remain to be resolved.[266] The RTOG atlas "Consensus Guidelines for the Delineation of the CTV in the Postoperative Pelvic Radiotherapy of Endometrial and Cervical Cancer" for posthysterectomy contouring is available at www.rtog.org/CoreLab/ContouringAtlases/GYN.aspx. A normal tissue contouring atlas is also available at www.rtog.org/CoreLab/ContouringAtlases/FemaleRTOGNormalPelvisAtlas.aspx RTOG-0418, a Phase II trial evaluating the use of pelvic IMRT in the posthysterectomy setting for patients with endometrial or cervical carcinoma showed general feasibility for the use of posthysterectomy IMRT in multiinstitutional trials when stringent guidelines are specified and quality assurance measures are employed.[267] However, a high proportion

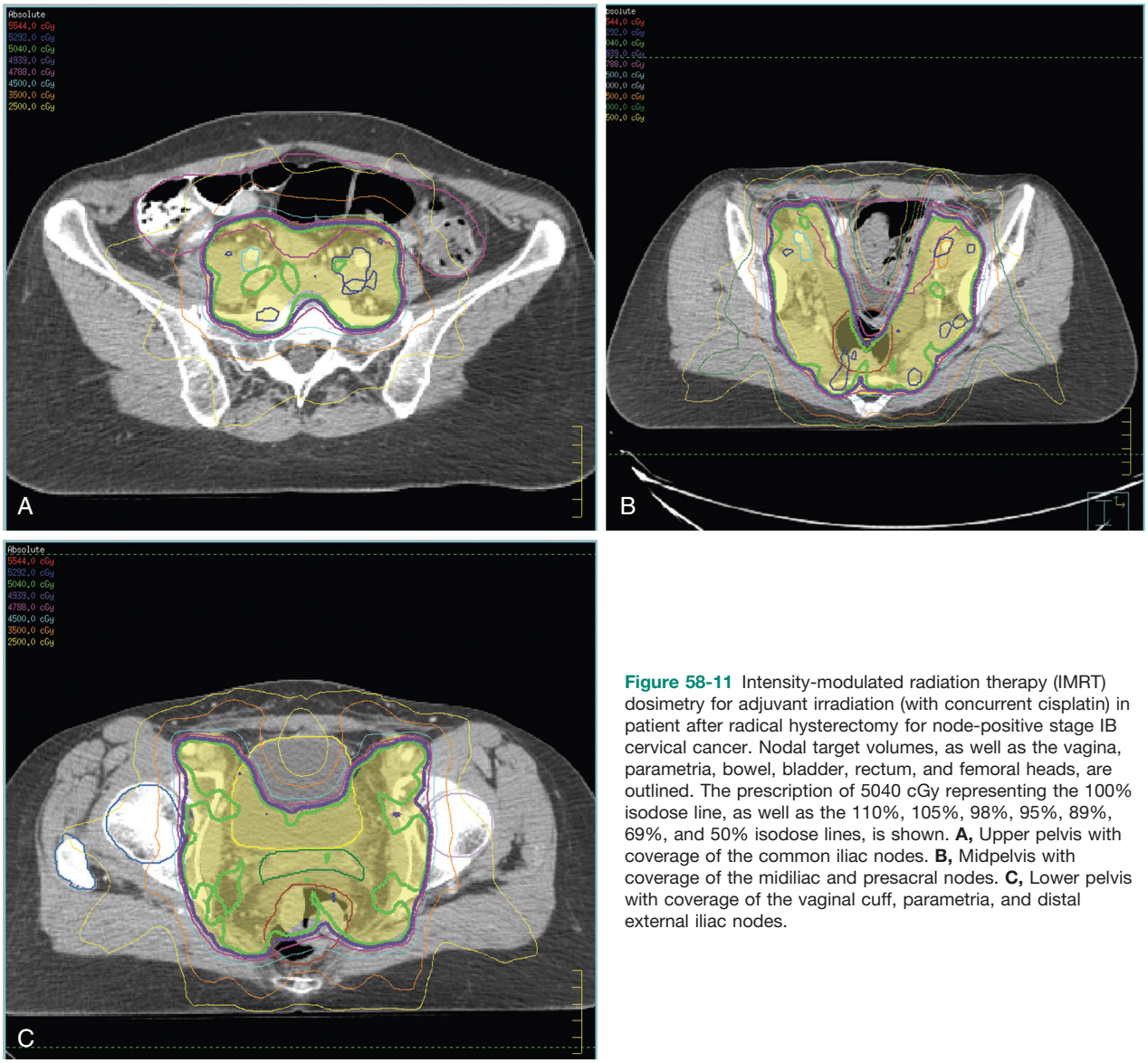


Figure 58-11 Intensity-modulated radiation therapy (IMRT) dosimetry for adjuvant irradiation (with concurrent cisplatin) in patient after radical hysterectomy for node-positive stage IB cervical cancer. Nodal target volumes, as well as the vagina, parametria, bowel, bladder, rectum, and femoral heads, are outlined. The prescription of 5040 cGy representing the 100% isodose line, as well as the 110%, 105%, 98%, 95%, 89%, 69%, and 50% isodose lines, is shown. **A,** Upper pelvis with coverage of the common iliac nodes. **B,** Midpelvis with coverage of the midiliac and presacral nodes. **C,** Lower pelvis with coverage of the vaginal cuff, parametria, and distal external iliac nodes.

of patients did not meet the IMRT planning constraints, and therefore less stringent constraints were written for subsequent trials. Current Phase III trials in postoperative irradiation following radical hysterectomy for cervical cancer (RTOG 0724, GOG 263) permit the use of IMRT but require detailed institutional and individual investigator credentialing, as well as "real-time" central review of the first IMRT protocol case treated. An example of IMRT dosimetry in a patient undergoing adjuvant chemoRT following radical hysterectomy for node-positive stage IB cervical cancer is shown in Figure 58-11; it shows highly conformal shaping of the higher isodoses, with relative sparing of small bowel, bladder, and some rectum compared with a more traditional four-field pelvic technique, despite the use of generous target volumes for the IMRT plan.

The role of IMRT for intact cervical cancer remains more nascent and must be considered investigational at present despite considerable current implementation. Target mobility, as well as tumor deformation/regression during a course of RT, is of greater concern in intact cancer cases than in the posthysterectomy setting.[268-270] A preliminary attempt at target volume consensus in intact cervical cancer (based on a single case study) was recently published and showed appreciable variability in target volumes even when assessed by experienced gynecologic radiation oncologists.[271] Prospective multicenter trials of IMRT in intact cervical cancer have been proposed but have not yet been activated.

Brachytherapy

Encapsulated radium sources were first used to treat cervical cancers shortly after Marie Curie's discovery more than a century ago. The origin of cervical cancers at the mouth of a hollow, relatively radioresistant organ made the disease ideal for intracavitary treatment. With careful placement of sources in the uterus and vagina, clinicians are able to capitalize on the inverse-square law, delivering a high dose of radiation to the central cervical tumor while relatively sparing radiation exposure to critical surrounding normal tissues such as the bladder, rectum, and small bowel.

Empirical evidence, in vitro studies of the effect of dose rate on tumor cell kill and late normal tissue effects, available technology, and radiation protection considerations led to the initial use of sources that delivered ionizing radiation at relatively low dose rates over time. Although LDR intracavitary brachytherapy had traditionally been used for most patients with cervical cancer treated in the United States, HDR brachytherapy use has increased dramatically in the past decade.[272]

Over the past two decades, manufacturers have withdrawn support for LDR systems. Comparison data from several randomized trials,[273-276] reviews,[277] and large single-institutional retrospective experiences[278,279] have led to an increasing acceptance of the efficacy and tolerability of HDR brachytherapy for cervical cancer. Large clinical cooperative trial groups such as the GOG and RTOG accept that when performed appropriately and within clearly specified guidelines of dosing and fractionation, HDR and LDR intracavitary cervical brachytherapy regimens are therapeutically similar. Faced with issues related to LDR-associated personnel exposure, source regulation and storage, source replacement, and withdrawal of technical support from suppliers, most centers now use outpatient-based HDR brachytherapy for cervical cancer. In a patterns-of-care survey of cervical cancer cases treated between 1996 and 1999, 16.4% of patients who underwent brachytherapy had at least part of their therapy delivered using an HDR regimen.[280] By 2005 to 2007, a new survey indicated that 68.5% of patients undergoing intracavitary brachytherapy for cervical cancer were treated with HDR techniques.[129] Primarily in Europe, pulsed-dose-rate (PDR) brachytherapy is utilized, arguing that it is more radiobiologically similar to LDR therapy and may cause fewer late complications.

Low-Dose-Rate Intracavitary Therapy

Historically, until the early 1980s, most intracavitary therapy was delivered using radioactive radium (radium-226 [^{226}Ra]). Cesium-137 (^{137}Cs), an artificially produced isotope of similar average energy, gradually began to replace ^{226}Ra in most practices. Because the half-life of ^{137}Cs is only about 30 years, the sources had to be replaced periodically. Commercially available cesium sources are usually slightly shorter (≤17 mm to 20 mm) than ^{226}Ra sources. Therefore, standard loadings designed for radium produce higher dose rates to critical structures if short cesium sources are used without spacers.

Many intracavitary applicator systems have been used to position sources in the uterus and vagina. All include a central uterine tandem; the major differences are in the design of the vaginal source holders. In the United States, most radiation oncologists use some variation of the Fletcher-Suit-Delclos applicator system that was first developed at MDACC. The most characteristic feature of this system is the pair of cylindrical vaginal colpostats that are placed against the cervix on either side of the tandem. Ideally, these holders position the axis of the vaginal sources approximately perpendicular to the uterine tandem (Figure 58-12). This positioning is designed to take advantage of the anisotropy of the sources, and combined with the anterior and posterior tungsten shields incorporated in the design, to reduce the volume of bladder and rectum exposed to high doses of radiation while spreading the dose laterally to the parametria. For patients with a narrow vagina, unshielded miniovoids and Lucite cylinders of various sizes can be used to position the intravaginal sources. Another applicator system used successfully by a number of groups, including the Memorial Sloan Kettering Cancer Center, is the Henschke applicator. With this system, the vaginal sources are positioned parallel to the axis of the intrauterine tandem.

Today, all these systems are afterloading, to minimize personnel exposure to the radiation. Radiation exposure from LDR implants can be further reduced to negligible levels with computerized remote afterloading equipment that removes the cesium sources automatically when persons enter the room.

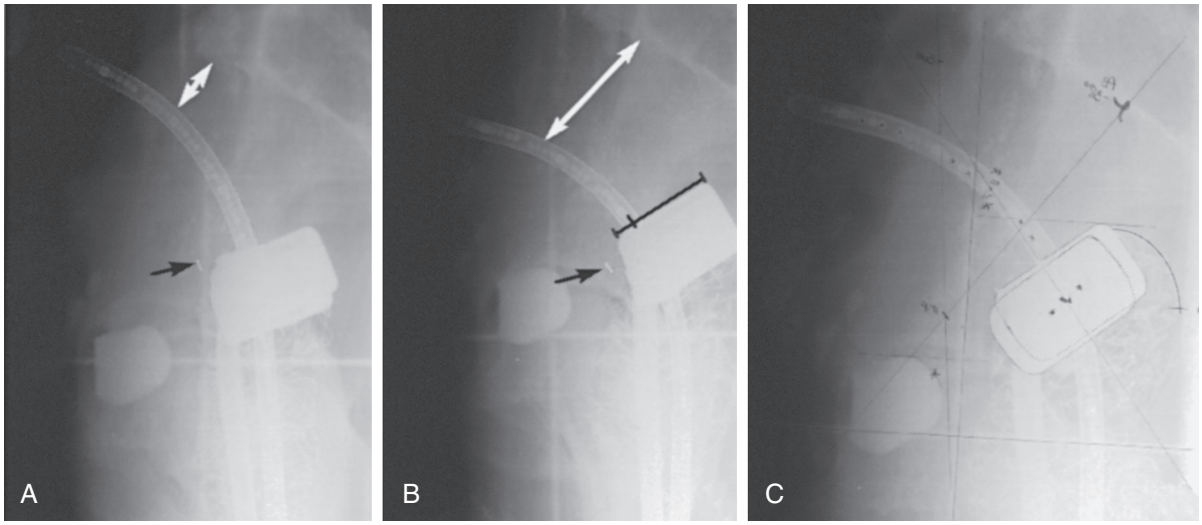


Figure 58-12 Lateral views of Fletcher-Suit-Delclos intracavitary placements in a young woman with a FIGO IB2 endocervical tumor. **A,** The patient had a pliable vagina, and aggressive packing pushed the uterus and the system high in the pelvis against the sacrum, potentially trapping bowel between the intracavitary system and the sacrum. **B,** The system was repacked using a suture slipped through the cervix to provide countertraction during packing. This kept the system lower in the pelvis, but the ovoids were allowed to fall posteriorly. This position can lead to overdosage of the rectum, particularly cephalad to the ovoids. **C,** A second repacking resulted in a good placement with acceptable positioning of the system midway between the sacrum and bladder. Ovoids are bisected by the tandem and are close to the cervical marker seeds; posterior packing protects the rectum. It is rare to need two adjustments of an intracavitary system, but the significant improvement achieved with this effort should improve the therapeutic ratio for this patient and underscores the importance of intraoperative radiographs in cervical cancer brachytherapy.

Successful intracavitary therapy requires experience, skill, some pragmatism, and a willingness to persist until an "optimal placement" has been achieved.[281] Proper positioning of the applicator and packing is essential to maximize local control.[282] Radiation sources must be positioned in the uterus and vagina in a way that avoids underdosing areas in the cervix and paracervical tissues with a sensitivity to the limits of mucosal tolerance. Every tumor presents a somewhat different challenge because of the wide variations in tumors and patient anatomy encountered clinically. A thorough discussion of the methods that can be used to address these variations is beyond the scope of this chapter, but some basic principles apply to most common clinical situations.

Although there has been considerable debate regarding the "optimal" intracavitary brachytherapy system, and there is no doubt that brachytherapy requires technical skill and attention to detail, it is also apparent that whether intracavitary brachytherapy is used is more important than the details of how it is placed. In the United States, most radiation oncologists are familiar with some variation of the Fletcher-Suit-Delclos applicator system, but other systems are also used. What is clear is that the introduction of radioactive sources into the endocervical and endometrial canal permits a central tumor dose intensification that is unachievable by any EBRT technique, regardless of the nuances of source placement (Figure 58-13). It is this high radiation dose, placed in direct juxtaposition to the tumor, within a radiotolerant organ, that allows for control of even large cervical cancers.

Placement of the system can be performed under intravenous sedation with monitored anesthesia care; general or regional anesthesia may be preferred, unless the patient is at increased risk for anesthetic complications, because it permits a good examination of the pelvis and provides maximal relaxation of the perineal musculature during placement and packing of the intracavitary applicator. The system should be packed in place with lubricated gauze, preferably a type that contains a radiopaque thread, while the vagina is retracted by an assistant. Packing should be carefully placed anteriorly and posteriorly, displacing the rectum and bladder away from the system. Care should be taken not to force the cervix away from the colpostats during the packing. Gradual withdrawal of the retractors during the procedure permits placement of additional packing in the space occupied by the retractors. With firm packing, the risk of displacement during a 48-hour to 72-hour placement is minimal. However, when vaginal cylinders are used instead of packing or when a remote afterloading device is used, a stitch should be placed in the labia and secured to the system to prevent displacement. The accuracy of the applicator position should be confirmed while the patient is still under sedation by anteroposterior and lateral radiographs. If the placement is unsatisfactory, the system should be repositioned and repacked. For patients undergoing LDR brachytherapy with prolonged immobilization, thromboprophylaxis with subcutaneous heparin and sequential compression devices should be initiated as early as during anesthesia for insertion, given the elevated risk for deep venous thrombosis in this setting.

Dose Specification

Several conventional standardized methods have been used to specify the radiation dose delivered by an intracavitary system. In the Manchester system, the dose and dose rate are specified to a paracentral point (point A) and to a point near the pelvic wall (point B) (Figure 58-14). Point A is placed 2 cm lateral and superior to the applicator along the axis of the intrauterine tandem, although a number of methods have

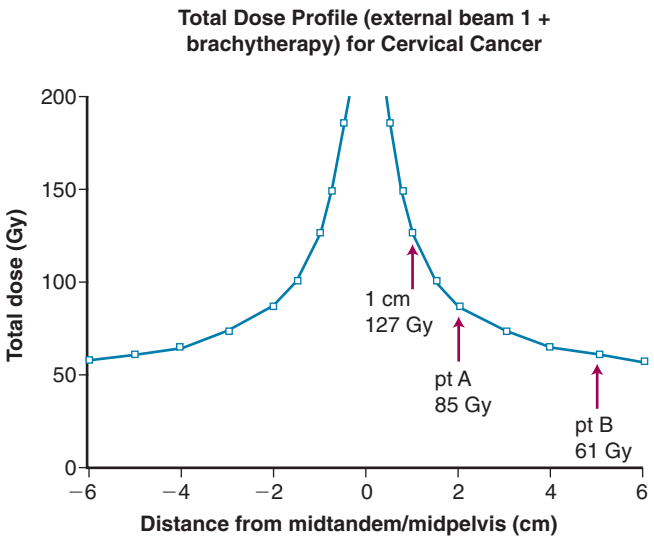


Figure 58-13 Illustration of the central dose escalation achieved when combining intracavitary brachytherapy with external beam radiation therapy. Although the diagram is idealized, it is based on current GOG guidelines for radiation dosing in locally advanced cervical cancer: 45 Gy to the whole pelvis, intracavitary brachytherapy to an LDR equivalent dose of 85 Gy to point (pt) A, and an additional external beam parametrial boost of 4.5 Gy to 9 Gy with central structures shielded. The *x* axis represents the distance from the centrally placed tandem toward each pelvic side wall, along the transaxial plane encompassing bilateral point As.

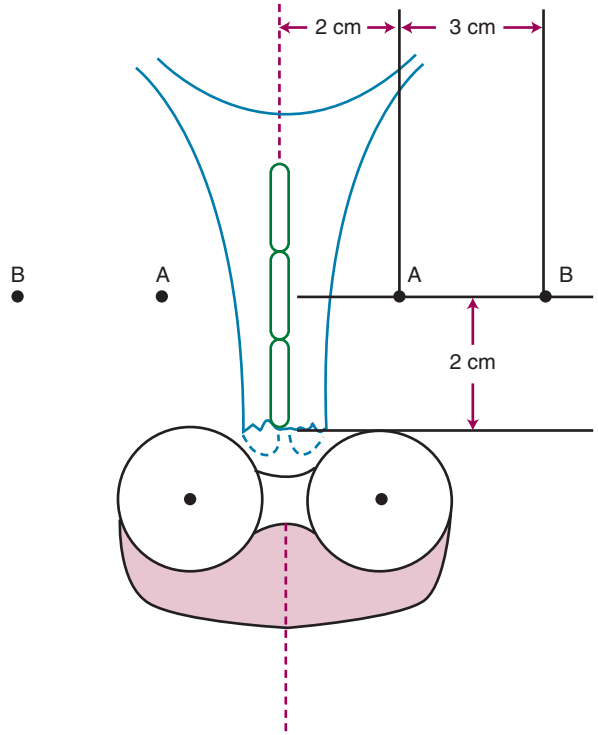


Figure 58-14 Location of point A and point B using the method recommended in ICRU 38.
From International Commission on Radiation Units and Measurements: Dose and volume specifications for reporting intracavitary therapy in gynecology, vol 38, Bethesda, MD, 1985, ICRU, pp 1–23.

Conventionally for most cases, the highest sources in the tandem should extend superiorly at least 6 cm above the external os or, if the uterus is small, as high as possible in the uterine cavity. A relatively long line of sources will provide better lateral dose penetration and coverage of high endocervical tumor, as well as providing some incremental dose to pelvic side wall nodes. A tandem of 6.5 cm to 8 cm will accommodate 35 mgRaEq to 40 mgRaEq of cesium distributed in three linear sources spaced with their centers 22 mm to 25 mm apart. Typical loadings (cephalad to caudad) of LDR linear cesium sources would be 15-15-10 mgRaEq for relatively large tumors that still expand the endocervix at the time of intracavitary placement or 15-10-10 mgRaEq for smaller tumors. The caudad source in the tandem should not protrude more than a couple of millimeters below the superior surface of the colpostats to avoid a hot spot in the adjacent bladder and rectum. Similar distributions can be achieved with remote afterloading units by distributing 5-mgRaEq point sources along the length of the tandem.

The choice of vaginal applicator is determined by the vaginal capacity and by the distribution of any vaginal disease. Vaginal cylinders are usually reserved for patients who have a narrow vagina or significant vaginal mucosal disease where the dose needs to be delivered inferiorly in the vagina. In general, when colpostats are used, their medial surfaces should be separated by 1 cm or less to avoid a central cold spot. Instead, to maximize the dose deliverable from intravaginal sources and optimize the relative depth dose, the vagina should be fitted with the largest ovoids that can be placed snugly against the cervix. The anterior and posterior lips of the cervix should always be marked with radiopaque seeds (see Figure 58-12) so the relationship between the cervix and vaginal applicators can be verified on intraoperative films. Significant caudad displacement of the colpostats will dramatically reduce the dose to the cervical tumor and lead to increased vaginal stenosis and probable fistula risk. The colpostats should be centered over the cervical portion; unless the anterior or posterior lip is disproportionately involved, the colpostats should be bisected by the tandem on the lateral view. Very posterior displacement of the colpostats usually results in an underdosage to anterior disease and an unacceptable overdosage to the rectum, particularly to the portion of the rectum that is superior to the colpostat. The standard loadings for Fletcher-Suit-Delclos ovoids are 10 mgRaEq or 15 mgRaEq for 2 cm (small); 15 mgRaEq or 20 mgRaEq for 2.5 cm (medium); 20 mgRaEq or, rarely, 25 mgRaEq for 3 cm (large); and 5 mgRaEq to 10 mgRaEq for miniovoids. These loadings will result in a dose rate at the lateral vaginal surface of 75 cGy/hr to 110 cGy/hr. The higher-activity sources are used when the placement is excellent or when the patient has bulky central disease. The lower activities tend to be used for patients with small tumors, for suboptimal (but acceptable) positioning, and to keep the total vaginal surface dose beneath the cumulative maximum of 120 Gy to 140 Gy.

been used to identify the position of this reference point. Of note, point A was redefined for an upcoming ICRU document and published by the American Brachytherapy Society.[283] Because point A lies in a region of steep dose gradient, relatively small variations in its position can result in substantial differences in the calculated dose rate. For this reason, the use of point A or similar reference points was criticized by the ICRU in its 1985 report on intracavitary dose and volume specification.[284] The commission recommended a system, used in some parts of Europe, in which the volume of tissue treated to a certain dose (usually, 60 Gy) and the reference air kerma (in micrograys [μGy] at 1 m) are specified. Some physicians place an additional emphasis on the vaginal surface dose, substituting mgRaEq hours for reference air kerma as a means of limiting pelvic integral dose and relying on a set of empirically derived rules concerning the position and activity of the radiation sources. When point A is used as a reference point for dosing and reporting, attention must also be given to the 3D isodose distributions surrounding the entire implant. Unexpected results can occur when a standard dose is delivered to point A from a system that is poorly positioned or has unusual source arrangements. For this reason, the use of point A to specify the dose from interstitial implants is not recommended; rather 3D conformal dosimetry after CT or MR contouring of a tumor volume are recommended for interstitial brachytherapy.[285]

High-Dose-Rate Brachytherapy

Computerized remote afterloading technology has now made it possible to deliver intracavitary irradiation at high doses in minutes instead of hours or days. Worldwide use of HDR brachytherapy as an alternative to LDR brachytherapy has increased rapidly in recent years. Because HDR treatment is always delivered with remote afterloading equipment, radiation exposure to personnel is eliminated. Patients do not have to be hospitalized for treatment, providing a possible economic advantage, and the delivery of treatment in several short fractions may permit greater control over the position of sources during treatment. The most important concern has been that treatment with large HDR fractions reduces the opportunity for recovery of sublethal normal tissue injury and therefore may narrow the therapeutic ratio between tumor control and complications. Other possible disadvantages include the labor intensity of the process and the opportunity for an irreversible error that is not discovered during a short duration of exposure.

Investigators have been reporting their experiences with HDR brachytherapy for more than 20 years, describing thousands of patients with cervical cancer who were treated with this approach. The authors of numerous retrospective studies have demonstrated that HDR treatment is feasible, effective, and safe.[277] In addition, there have been four randomized trials of HDR versus LDR brachytherapy[273-275] (Table 58-5). Although each study had flaws, the data would suggest, in total, that HDR brachytherapy, within carefully applied dosing and fractionation guidelines, provides therapeutic equivalency to traditional LDR approaches.

The biologic effect (particularly to normal tissues) of a nominal dose of radiation will be significantly greater when it is given with HDR as compared with LDR brachytherapy, and this depends on the fraction size. This factor leads to the need for increasing fraction numbers when using HDR versus LDR therapy. To select an HDR schedule that may be comparable with LDR treatment, it is helpful to consider the fractionation and dose-rate effects and, specifically, applications of the linear quadratic (LQ) model used to describe these effects.

The LQ model has been used to describe a biologically effective dose (BED), given as

$$\text{BED} = \text{Total dose}\,[1 + \text{dose per fraction}/(\alpha/\beta)]$$

where α/β describes the varying influence of fraction size on radiation effects in different tumors and normal tissues. This is then converted to the EQD2 (equivalent dose in 2 Gy fractions) using BED/1.2 for the $\alpha/\beta = 10$ for tumor.

TABLE 58-5 Randomized Trials of High-Dose-Rate (HDR) Versus Low-Dose-Rate (LDR) Brachytherapy in Cervical Cancer

Author	No. Patients	Survival	Severe Late Toxicity	Comments
Patel[244]	Group I: early stage			Equivalent outcomes for HDR and LDR in local control, survival, and late toxicity
	LDR: *n* = 36	72% (5-yr OS)	GI 3%	
	HDR: *n* = 34	82% (5-yr OS)	GI 0%	
	Group II: bulky/advanced tumor			No severe late GU toxicity noted
	LDR: *n* = 210	55% (5-yr OS)	GI 2%	
	HDR: *n* = 202	54% (5-yr OS)	GI 1%	
Teshima[245]	LDR: *n* = 171	Stage I/II/III (5-yr CSS) 93%/78%/47%	4%	Unbalanced randomization; includes older patients specifically referred for HDR
	HDR: *n* = 259	Stage I/II/III (5-yr CSS) 85%/73%/53%	10%	Equivalent local control and CSS Higher late toxicity with HDR, but still considered within acceptable levels
Hareyama[246]	Stage II			No significant differences in DSS and complication rates
	LDR: *n* = 26	87% (5-yr DSS)	13%	
	HDR: *n* = 22	69% (5-yr DSS)	10%	
	Stage III			
	LDR: *n* = 45	60% (5-yr DSS)	—	
	HDR: *n* = 39	51% (5-yr DSS)	—	
Lertsanguansinchai[247]	LDR: *n* = 109	70% (3-yr RFS)	3%	Comparable local control, RFS, and complication rates
	HDR: *n* = 112	70% (3-yr RFS)	7%	

CSS, *Cause-specific survival; DSS, disease-specific survival;* GI, *gastrointestinal;* GU, *genitourinary;* n, *number;* OS, *overall survival;* RFS, *relapse-free survival;* yr, *year.*

A well-placed LDR system loaded according to the preceding recommendations will produce a dose rate at point A of approximately 45 cGy/hr to 55 cGy/hr. Somewhat higher activity loadings have been recommended and used successfully. However, higher activity sources will result in higher dose rates and may have a somewhat greater biologic effect with the number of brachytherapy insertions limited to one or two; dose rates of more than 65 cGy/hr to point A should be used with caution. In a prospective randomized study, Haie-Meder et al[286] reported an increased rate of major complications when the dose rate to point A was increased from 40 cGy/hr to 80 cGy/hr.

Patients who have bulky central disease and favorable anatomy can usually be treated to a combined dose of "85 [Gy] to 90 Gy" to point A (40 Gy to 45 Gy with EBRT and 40 Gy to 50 Gy with brachytherapy), with an acceptable risk of late complications. Higher doses of central EBRT tend to compromise the total paracentral dose that can be delivered. Somewhat lower doses (75 Gy to 85 Gy) are usually recommended for smaller (IA to IB1) tumors. Adjustments to these doses and to the distribution of sources in the intracavitary applicators may be needed, however, taking into account the position of the system in relation to other pelvic structures and the distribution of tumor as determined by physical examination and imaging studies.

LDR brachytherapy has been used successfully in combination with EBRT since the 1950s to treat thousands of patients and to achieve high local control and cure rates with a low risk of complications. The radiobiologic advantages of delivering brachytherapy at LDR have been emphasized by many, and a number of clinicians continue to express skepticism about the comparability of HDR therapy, particularly in the treatment of patients with unfavorable anatomy, for whom the dose to critical normal tissues may be similar to the paracentral dose.[287] On the other hand, increased acceptance of, experience with, and training in HDR brachytherapy techniques have led many to adopt outpatient-based HDR brachytherapy. Whether using LDR or HDR therapy, the importance of attention to anatomic detail, an understanding of normal tissue tolerance, an appreciation of radiobiologic principles, and an adherence to guidelines for loading and fractionation cannot be overemphasized.

The use of the LQ equation allows one to calculate and approximate the biologic equivalency of HDR-based to traditional LDR-based dosing. Typically, an α/β ratio of 10 is used for tumor and acutely responding tissues and a ratio of 3 is used for late-responding normal tissues. Using the LQ equation, tumor doses of 80 Gy to 85 Gy to point A in LDR equivalent would result in BEDs of 96 Gy_{10} to 102 Gy_{10}. Conservatively accounting for late-responding normal tissue tolerances, LDR equivalent doses of 70 Gy to the rectum and 75 Gy to the bladder correspond to 120 Gy_3 and 125 Gy_3, respectively.

There is emerging evidence that small volumes of the rectum and bladder can tolerate a total of 130 Gy_3 to 140 Gy_3. Ogino et al[288] did not observe any severe grade-4 rectal complications with a dose equivalent of less than 147 Gy_3 to the rectum. Lower grade-2 to grade-3 rectal toxicity was reported in less than 5% of patients with a BED of less than 119 Gy_3 and in less than 10% with a BED of less than 146 Gy_3. Their current fractionation schedules are designed to keep the BED for late-responding tissues to less than 119 Gy_3 for early-stage disease and to less than 147 Gy_3 for locally advanced cancers, allowing a tailoring of dose to disease extent.[288] In the era of CT or MR imaging after brachytherapy applicator insertion, contouring and calculation of the dose-volume histogram (DVH) values for the normal tissues has been standardized. A D2cc dose of 70 Gy to 75 Gy for the rectum and sigmoid, and 80 Gy to 100 Gy to the bladder is recommended.[131] A dose limit for the bowel is not clear, though a recommendation of 5cc < 55Gy[234] or D2cc < 65 Gy may be considered. Contoured bowel (small and large bowel may be indistinguishable) at the time of brachytherapy 5.

Although point A remains the most commonly reported tumor specification point, in the past 10 years, an increase in the use of imaging has permitted contouring of tumor volumes. The GEC-ESTRO guidelines describe, for MR-imaging after brachytherapy applicator insertion, a high-risk CTV encompassing the entire cervix and tumor extension into the parametria, vagina or uterus at the time of brachytherapy, and the intermediate-risk CTV, which is the disease extension at diagnosis. In practice in the United States, the high-risk CTV D90 is used for dose calculations (goal 80 Gy to 90 Gy), and therefore the high-risk CTV is the most commonly contoured volume, and also correlates the most with the CT-contoured CTV.[130] CT does not permit imaging of the superior border of the cervix, and therefore an estimate of the superior border is made where the shape of the cervix changes and the broad ligament ends. CT contours are wider than MR-based contours, though it is not clear whether this difference has any meaningful dosimetric impact.[289]

HDR fractionation schedules reported in the literature vary markedly, with insertion numbers and point A dose fraction sizes ranging from 2 Gy to 7 Gy and 3 Gy to 14 Gy, respectively.[277] Assuming an α/β ratio of 3 for late damage to normal tissues, Stitt et al[290] used the LQ model to predict how a dose of HDR brachytherapy would have to be divided so its effect on normal tissue was comparable to that of 70 Gy of LDR brachytherapy. According to their model, five or six fractions are sufficient if the dose to critical normal tissues is 80% or less of the dose to the paracentral reference point. If the anatomy is somewhat less favorable and the normal tissue dose is 90% of the tumor dose, however, more fractions may be considered.

A detailed analysis of 24 reported series studying HDR brachytherapy in locally advanced cervical cancer failed to identify a dose-response relationship for either tumor control or late tissue complications.[291] Although this does not refute the importance of radiobiologic considerations and calculations in the implementation of HDR brachytherapy, it does underscore the complexity of patient- and treatment-related variables involved in the radiotherapeutic management of cervical cancer and the difficulty in reducing HDR dosing issues to a simple mathematical formula.

Viswanathan et al[185] reported on a recent survey of international HDR brachytherapy practice among members of the Gynecologic Cancer Intergroup (GCIG). The average EBRT dose to the pelvis approximated 45 Gy. For stages IB to IIA tumors, the three most common regimens were 6 Gy for five fractions, 6 Gy for four fractions, and 7 Gy for three fractions, with brachytherapy doses predominantly prescribed to point A. For stages IIB to IVA tumors, the three most common regimens were 6 Gy for five fractions, 7 Gy for four fractions, and 7 Gy for three fractions. For its most recent protocols in locally advanced cervical cancer (where HDR therapy was permitted), the GOG had prescribed a whole-pelvic dose of 45 Gy, supplemented by an HDR boost of 6 Gy to point A for five fractions, as well as a 5.4-Gy to 9-Gy parametrial boost to the involved side(s). This regimen, when converted using the LQ model, corresponded to a calculated LDR/conventional equivalent dose of 85 Gy to point A. However, it has recently been recognized that absolute adherence to inflexible guidelines does not take into consideration the uncertainties in assumptions and applications of the LQ model, nor the specific tumor geometry and patient factors associated with each case, leading to potential increased toxicity. Although the LQ model is a useful tool for comparing fractionation schemes, no mathematical formula can take the place of clinical judgment and observation. Going forward, the GOG has proposed modifications of its dosing parameters in locally advanced cervical cancer as follows: a whole-pelvis dose of 41.4 Gy to 45 Gy, followed by HDR brachytherapy of 5.4 Gy to 6 Gy for five fractions, with optional parametrial boosting based on tumor regression during EBRT. This new "scheme," although seeking to maintain a minimal LDR equivalent dose of 80 Gy to point A, provides for flexibility in HDR application and allows for dose escalation to 85 Gy as clinically appropriate. To preserve biologic equivalency dosing to late-reacting normal tissues, the GOG has recommended that the ICRU rectal dose point receive no more than 4.1 Gy (68% of the point A dose) and the bladder dose point no more than 4.6 Gy (77% of the point A dose) per insertion, though using DVH values and D2cc limits is recommended with 3D-image based brachytherapy.. The increased flexibility in dose shaping with HDR brachytherapy may be useful in optimizing tumor-to-normal-tissue dose ratios.

Planning for brachytherapy begins at the time of initial diagnosis. Patients must be made aware and prepared for the procedure, and the physician should carefully document the clinical examination, and initial imaging such as MRI and PET findings. Careful examination while the patient receives external beam allows assessment of tumor regression; the physician should determine which applicator is most appropriate based on the tumor extension at diagnosis and remaining disease at the time of brachytherapy. Commonly used applicators include the tandem and ovoid or tandem with interstitial template, and in HDR systems, the tandem and ring, or tandem and ring/ovoid with additional interstitial needles extending through the ring/ovoid.

As with LDR brachytherapy, the timing of HDR insertions depends on the stage and volume of disease and its response to EBRT. For small cervical cancers, brachytherapy may be initiated during the first 2 weeks of RT; for more locally advanced lesions, brachytherapy is performed near or at the end of EBRT. If most or all of the EBRT is to be given before brachytherapy, two, or even three, HDR fractions may be delivered per week to avoid unnecessarily protracting the



Figure 58-15 Magnetic resonance (**A** and **B**) versus computed tomography (**C** and **D**) axial and sagittal views of an intracavitary tandem and ring insertion for HDR afterloading brachytherapy. The source dwell positions selected for "loading" include those in the intrauterine tandem, as well as the lateral positions in the ring corresponding to the lateral vaginal fornices, thereby mimicking the dosimetry distribution of tandem and ovoids. Computerized brachytherapy or magnetic resonance imaging dosimetry allows visualization of dose in the traditional planes of calculation (coronal, sagittal, and transverse) but also permits three-dimensional representation of dose distribution that may be exploited to conform better to unusual tumor geometries.

overall treatment time (which should generally not exceed 8 weeks).[292] EBRT can be interdigitated with HDR brachytherapy; however, on days in which HDR brachytherapy is performed, EBRT to an overlapping treatment volume must not be given.

The literature describes a wide range of sedation methods used during the administration of HDR brachytherapy, including general, spinal, oral, or intravenous conscious sedation, which involves administration of intravenous midazolam and fentanyl by a trained nurse. To accommodate conscious sedation in the radiation oncology clinic, the patient must at least be continuously monitored by pulse oximetry and blood pressure measurements. The physician and nurse must be certified in conscious sedation procedures, be up to date on cardiopulmonary resuscitation measures, and have ready access to a resuscitation cart.[293] After review of an MRI if available, the first HDR insertion in each patient may be facilitated with transabdominal ultrasound guidance for placement of the intrauterine tandem. If the endocervical card is difficult to negotiate for insertion of the tandem, an intrauterine Smit sleeve may be placed at the first implant to facilitate subsequent applications. When available, an MRI or CT performed after insertion can allow assessment of applicator position in 3D, contouring of the normal tissues and tumor, and dose optimization off these critical tissues. A contouring atlas is available at www.nrgoncology.org/Resources/Contouring-Atlases/GYN-Cervical-Brachytherapy.[293a]

At present, most standard HDR loading schemes attempt to recapitulate the familiar and symmetric "pear-shaped" dose distribution typically used in LDR brachytherapy. This isodose distribution can be obtained by designating a series of dose points surrounding the tandem and colpostat and using the dosimetry program to calculate source dwell times in each source location to create the desired dose distribution (inverse planning). After creating a standard plan, this plan should be "optimized" to allow sculpting of the dose away from normal tissues and to optimize coverage of the CTV as seen on CT or MR. The physician may specify the relative weight of each selected dwell position in the brachytherapy apparatus, somewhat analogous to the loading of individual sources in an LDR system. Most HDR practitioners use tandem and ovoids that are based on the LDR Fletcher-Suit-Delclos applicator. Others, however, favor a tandem and ring system that has the advantage of having fixed geometry and may be faster to insert (Figure 58-15).

As with LDR, practitioners of HDR must be well trained and sufficiently experienced in the system of brachytherapy they ultimately choose to use. Extensive international efforts in 3D image-guided and adaptive brachytherapy recommend exerting caution to maintain the central symmetry of a classical pear-shaped distribution inherent in the point A system but with a gentle shift to a more conformal and often asymmetric dose distribution biased toward residual tumor volume and away from normal tissues. A prospective trial of 705 patients with cervical cancer, of whom a subset received chemoRT followed by either plain film or 3D (mainly CT) image-based PDR brachytherapy. Patients treated chemoRT with CT image-based brachytherapy had a 20% reduction in toxicity, 5% improvement in local control, and 9% increase in OS.[294] CT imaging can help in delineating adjacent organs at risk and suffices to treat tumor target volumes in patients that do not have or have minimal parametrial extension.[130] MRI-based brachytherapy is preferable for defining large tumor target volumes, particularly

in patients with large residual disease after chemoRT, those with adjacent organ invasion, or those with parametrial extension, where the discrepancy between CT and MRI may be greatest.[130,289,295] It has been suggested that MRI image-guided brachytherapy allows customization that decreases the dose to adjacent organs at risk when treating small tumors, while permitting dose escalation in larger tumors to improve local control.[131,132,296] To further tailor the brachytherapy dose, investigators have developed an applicator that combines a tandem and ring or ovoids with templated parametrial interstitial needles and have reported enhanced and effective brachytherapy coverage with dose escalation of asymmetric, bulky tumors.[297]

Although it is intriguing, the use of image-guided brachytherapy remains to be standardized and validated on a wide scale; this forms the basis for the ongoing Int**E**rnational study on **M**RI-guided **BR**achytherapy in locally **A**dvanced **CE**rvical cancer (EMBRACE) trial.[296] Interobserver reproducibility of target definitions and normal tissues[298] to published principles (such as the GEC-ESTRO guidelines)[295] and multiinstitutional assessment of tumor control and complication rates will be evaluated. A clear danger would be underestimation of residual tumor volume for brachytherapy planning. Also of concern is that strict adherence to proposed dose volume constraints for organs at risk may result in tumor underdosage compared with that achieved with conventional dosing. Furthermore, there remain unanswered the issues of resource utilization and whether multiple MRI scans and complex planning are feasible for the majority of patients with cervical cancer. A survey of practice patterns by members of the American Brachytherapy Society showed that the numbers of centers in the United States using MRI-based brachytherapy is increasing (from 2% to 23%). Although the majority of physicians used CT postimplantation imaging rather than plain films for visualizing the gynecologic brachytherapy apparatus, most (76%) still prescribe to point A alone, indicating the need for further development and experience with 3D image-guided brachytherapy dosimetry.[299]

Interstitial Brachytherapy

Interstitial brachytherapy has long been used to treat patients with massive volume residual disease, extensive vaginal involvement, adjacent organ invasion, or vaginal disease recurrence after hysterectomy, to encompass all areas of involvement. Several groups have advocated a broader role for interstitial irradiation by reporting on the use of large interstitial implants, usually guided by a perineal template, for patients with a variety of clinical presentations, including poor anatomy, bulky disease, or extensive involvement in the parametrium or pelvic wall.[285] Reports of this technique report high local control rates[300-302] (see Chapter 15, Brachytherapy). It is critical to place a tandem with the interstitial implant, rather than just needles alone, in cases with an intact uterus.[303] However, a review of 1992 to 1994 practice patterns from the Patterns of Care Study indicates that less than 6% of patients in the United States are treated with interstitial brachytherapy. Comparisons across series are rendered difficult by patient selection and the inherent case individualization in technique and dosimetry.

To visualize the tumor, image guidance should be considered, using either iterative CT or MR in a CT or MR simulator or procedure room with the patient under general or epidural anesthesia.[237] An alternative is laparoscopic guidance in the operating room. This decreases the risk of needles entering the bowel. Excellent results have been obtained with the image-guided approach.[237] Either LDR iridium-192 (^{192}Ir) may be used, or HDR ^{192}Ir; in some centers the patient treated twice a day until completion, while kept in the hospital under patient-controlled anelgeesia when feasible, whereas at Washington University this procedure may be performed as an outpatient.[292,303a]

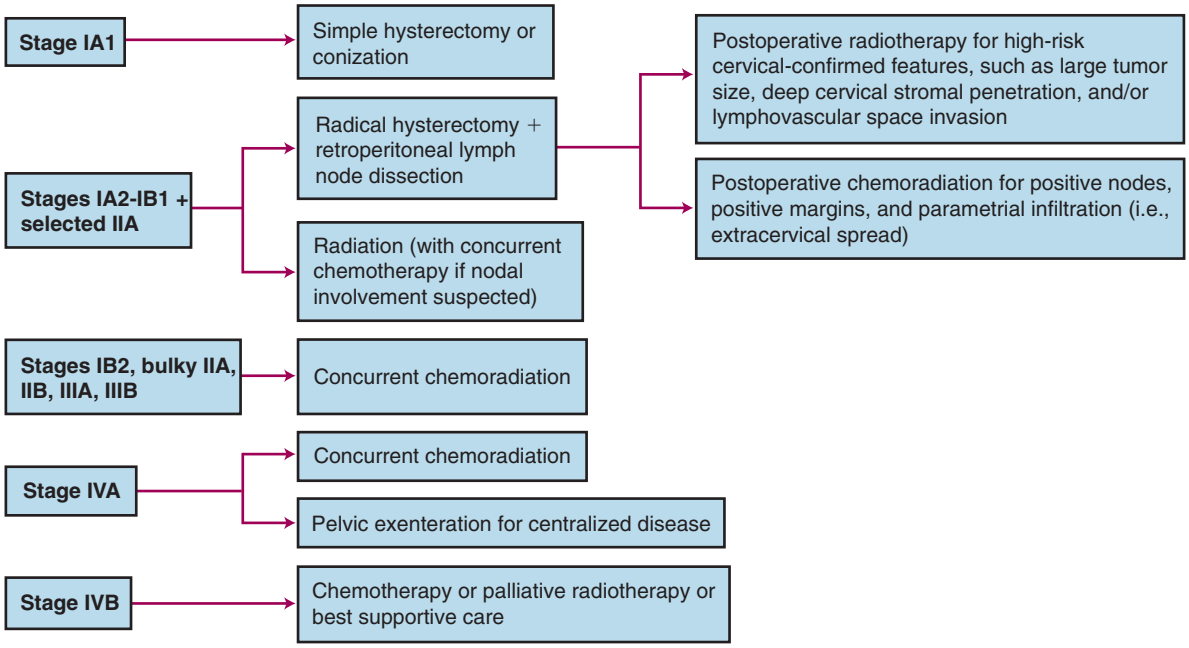
Normal Tissue Effects of Irradiation

An appreciation of the tolerance of normal tissues to irradiation is needed to determine optimal treatment doses. Experience suggests that the upper third of the vaginal mucosa can tolerate radiation doses as high as 120 Gy to 140 Gy, whereas the lower two thirds usually should not receive more than 80 Gy to 85 Gy. Most institutions do not exceed 75 Gy to 80 Gy (combined EBRT and LDR intracavitary dose) to the ICRU bladder reference point and 70 Gy to 75 Gy to the ICRU rectal point, based on orthogonal plain film dosimetry.[304] These reference doses should be used only as general guidelines, however. It has long been recognized, using CT-based dosimetry, that small volumes of rectum and bladder routinely receive much higher doses than those calculated from orthogonal films.[305] Also, concern about reference dose limits should always be balanced against the need to deliver a tumoricidal dose to the cancer.

Historical reports of severe late normal complications, usually defined as injury to the bladder, rectum, or small bowel requiring hospitalization or surgical intervention, typically range from 5% to 10% using crude estimates, but they may be higher using actuarial calculations.[105,306] Complications are related to the presenting stage and volume of disease, as well as to the dose delivered to the individual normal tissues. The severe complications occur in the first 3 years to 5 years after completion of RT, but there remains a small but continuous added risk thereafter.[306] Smoking during RT has been associated with a significantly higher risk of late complications.[155] Most reports of late morbidity have focused on severe gastrointestinal and genitourinary toxicities; only recently have rigorous efforts been made to monitor for less severe sequelae that, although not requiring surgery or extensive medical care, still have an impact on patients' quality of life. Other late effects, such as pelvic insufficiency fracture, vaginal stenosis, lymphedema, and neuropathy, are now recognized as important consequences.[307]

The recent use of concurrent chemoRT has been clearly shown to increase acute toxicities, especially with respect to hematologic and gastrointestinal function, compared with RT alone, but although there does not appear to be a coincident increase in late morbidity, accurate long-term follow up data are scant.[308] Unfortunately, most prospective clinical trials have based much of their toxicity assessment on the NCI common toxicity criteria scales, which favor acute effects reporting. Newer trials that emphasize late effects and employ validated quality-of-life assessment tools will give us much needed and useful information.

Radiobiology principles may predict an unacceptable complication rate for patients treated with curative HDR brachytherapy if the rectum and bladder receive the same dose as point A. With careful retraction and packing, however, the doses to these normal tissues can usually be substantially reduced, and studies generally have not demonstrated an increased complication rate when the dose of HDR therapy is adequately fractioned.[273,277] As with LDR brachytherapy, careful technique and the expertise of the brachytherapist may be as important as any other factor. These parameters are difficult to evaluate. Studies have suggested that the complication rates from HDR treatment



Notes:
1. Concurrent chemotherapy may be weekly cisplatin, or cisplatin combined with 5-FU every 3 to 4 weeks
2. Brachytherapy is a critical component of radiotherapy for intact cervix cancer

Figure 58-16 Treatment algorithm for cervical cancer.

of cervical cancer tend to decrease with increasing institutional experience.[309-311]

TREATMENT ALGORITHM, CONCLUSIONS, AND FUTURE POSSIBILITIES

Although cytologic screening programs have made it possible to prevent most invasive cervical cancers, and the promising development of HPV vaccines may lead to primary prevention, cervical cancer remains a major public health problem worldwide.

Both radical hysterectomy and RT achieve high cure rates for patients with stage IB1 disease (Treatment Algorithm, Figure 58-16). The rates of major toxicity from the two treatments are similar, but the types of side effects differ. Surgery tends to be the preferred treatment for young women with small squamous cell carcinomas or adenocarcinomas to avoid radiation-related ovarian relapse and to minimize the risk of sexual dysfunction.

Aggressive radiation therapy, including a combination of EBRT and brachytherapy, given concurrently with cisplatin-based chemotherapy, is now the primary treatment of choice in the management of bulky and locoregionally advanced disease. Irradiation remains the most active single modality for the treatment of cervical cancer not amenable to surgical resection or sterilization. Improvements in RT targeting and delivery are being realized by advances in imaging modalities, including PET scanning, careful conformal radiation treatment planning, and appropriate incorporation of brachytherapy. Current efforts in image-guided RT, including brachytherapy, may eventually provide confirmation that such techniques reduce toxicity or allow for appropriate tumor-directed dose escalation that can improve tumor control and cure.

Adjuvant hysterectomy has not been shown to improve the outcome of patients treated with radiation therapy for stage IB2 disease if adequate doses of RT are delivered. Radical RT or chemoRT is also preferred over a combination of radical hysterectomy and postoperative RT because the increased cost and complications of combined treatment are not justified by any significant improvement in local control or survival rates. Although treatment is successful in most primary cervical cancer cases, pelvic disease recurrence continues to be an important problem, particularly for patients who present with extensive locoregional disease. Recent studies have emphasized the influence of radiation dose, volume, fractionation, and treatment time on locoregional control and survival rates for patients with locally advanced disease.

The present focus on improving outcomes in bulky and locoregionally advanced cervical cancer is related to attempts to identify promising systemic agents such as antiangiogenic and antiepidermal growth factor receptor agents to add to the current standard of concurrent cisplatin and radiotherapy and to use for patients with locally advanced, locoregionally recurrent, or metastatic disease not amenable to definitive surgery, irradiation, or chemoRT.

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A full list of cited references is published online at www.expertconsult.com.

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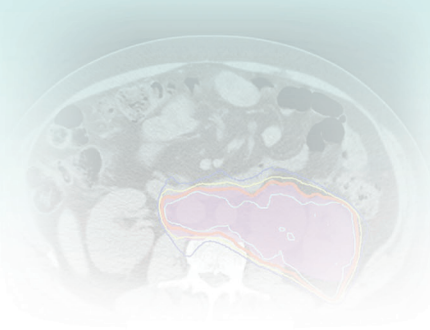
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CHAPTER

59 Endometrial Cancer



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INCIDENCE

Endometrial cancer is the most common gynecologic malignancy, and according to the Surveillance, Epidemiology and End Results (SEER) statistics for 2006 to 2010 it is the fourth-most common cancer in women, with an age-adjusted incidence rate in the United States of 24.3 cases per 100,000 women per year.

The estimated incidence for U.S. women in 2015 was 54,870 cases. The age-adjusted mortality rate is 4.3 deaths per 100,000 women per year, with an estimated 10,170 deaths in 2015.

BIOLOGIC CHARACTERISTICS

Two prototypes of endometrial carcinoma have been distinguished: type I, which is associated with estrogen and has a favorable prognosis, and type 2, which is unrelated to estrogen, is more often nonendometrioid, and has an inferior outcome.

More than 75% of endometrial cancers are endometrioid carcinomas, whereas 5% to 10% are serous, 1% to 5% clear cell, and 1% to 3% mucinous carcinomas. Up to 5% are other histologies, including uterine sarcomas (i.e., carcinosarcoma, leiomyosarcoma, and endometrial stromal sarcoma).

Risk factors for worse outcomes include tumor stage, histologic cell type, tumor grade, depth of myometrial invasion, lymphovascular space invasion, lymph node metastases, and the patient age.

STAGING EVALUATION

Evaluation should include the patient's history and physical examination, including vaginal inspection and bimanual pelvic examination, endometrial biopsy or D and C, chest radiography, complete blood cell count, and chemistries. The International Federation of Gynecology and Obstetrics (FIGO) staging is based on the surgical and pathology findings.

Computed tomography (CT) or magnetic resonance imaging (MRI) of the abdomen and pelvis is indicated for locally advanced disease and patients with medically inoperable disease. Positron emission tomography/computed tomography (PET/CT) labeled with 18F-fluorodeoxyglucose (^{18}FDG) may be a promising method for the presurgical evaluation of pelvic node metastases and for evaluation of relapse during follow-up.

PRIMARY THERAPY AND RESULTS

Primary therapy is surgical including abdominal hysterectomy and bilateral salpingo-oophorectomy. The surgery may be accomplished by laparotomy, laparoscopy, or robot.

The role of lymphadenectomy remains a subject of controversy. It is used primarily for staging purposes and to tailor adjuvant therapy. It may have therapeutic value for grade-3 cancers, unfavorable histologic types, and advanced disease; however, no survival benefit has been seen in Phase III trials.

The 5-year overall survival (OS) rate for women with endometrial carcinoma is 80% to 90% for patients with stage I endometrial carcinoma, 60% to 80% for stage II, and widely divergent for stage III (30% to 80%), because of the diverse disease extent for tumors classified as FIGO stage III.

Primary radiation therapy for medically inoperable patients provides 5-year OS of 50% to 85% and local control rates of 70% to 90% for stage I disease.

ADJUVANT THERAPY

Radiation therapy can significantly improve local control and disease-free survival (DFS) for patients with stage I disease, but it confers no OS advantage. For "intermediate-risk disease," the indications for radiation therapy are tailored to prognostic factors. Patients with grade-3 tumors with outer 50% myometrial invasion, advanced age, or lymphovascular space invasion should be considered for adjuvant pelvic irradiation. Brachytherapy alone may be considered for grade-1 or grade-2 disease with outer 50% myometrial invasion, and for grade-3 or unfavorable histologies with no or inner 50% myometrial invasion.

Adjuvant therapy is not indicated for treating low-risk disease (i.e., FIGO 2009 stage IA, grades 1 to 2 endometrioid carcinoma).

Pelvic irradiation is indicated for high-risk and locally advanced disease. Adjuvant chemotherapy, concurrent chemoradiation, or sequential irradiation and chemotherapy should be considered, preferably within the scope of clinical trials because the utility of these approaches although widely used, is still unproven.

LOCALLY ADVANCED DISEASE

Optimal treatment for patients with locally advanced pelvic disease has not been defined. Radiation may proceed or follow surgical attempts to complete hysterectomy or "debulk disease." These patients should be considered for clinical trials of chemotherapy or concurrent chemoradiation or innovative biologic agents.

Gross residual disease should be considered for palliative treatment.

PALLIATION

Metastatic disease or nonresectable local disease can be treated with chemotherapy or hormonal therapy. Targeted agents are currently being investigated in clinical trials.

Endometrial cancers are highly responsive to irradiation. Therefore, palliative irradiation should be offered to symptomatic patients because it provides excellent relief of symptoms, such as blood loss, vaginal discharge, pain and edema caused by local disease or lymphadenopathy, and symptoms from distant metastases, such as pain caused by bone involvement or symptomatic brain metastases.

Endometrial carcinoma is the most frequent gynecologic malignancy diagnosed in the United States and European countries, and it is the fifth-most common cancer in women. Because most patients present with early-stage disease, their prognosis is usually favorable. The relative 5-year survival rate is 82.8% for all patients. Patients with disease confined to the uterus have a 5-year relative survival rate of 95.3%, compared with 67.5% for those with regional involvement.[1]

Even after the publication of multiple randomized trials, controversies in the management of stage I endometrial carcinoma remain. The optimal extent of surgery, especially the role of pelvic and paraaortic lymphadenectomy, is one of these issues. The indications for external beam pelvic irradiation and the use of brachytherapy and of chemotherapy and combinations thereof, are also a source of dispute. Trials investigating these issues are being conducted.

Despite the favorable outcome for most patients, there remain patients with advanced disease or unfavorable histologic subtypes who have poor prognoses. The optimal treatment for these patients is the challenge for current research, including studies of full staging surgery, sentinel node biopsy, and appropriate systemic adjuvant therapies, such as concurrent and adjuvant chemotherapy or novel biologic agents with or without pelvic radiation therapy or brachytherapy. Clinical and basic research continues to investigate the biology, especially of nonendometrioid cancers and to search for new molecular markers and targeted therapies, including biologic agents.

EPIDEMIOLOGY AND ETIOLOGY

Epidemiology

The incidence of endometrial cancer in the United States is 24.6 cases per 100,000 women per year, and rates for new endometrial cancer cases have been rising on average 1.1% each year over the last 10 years whereas death rates have increased by 0.4% in the same period. In 2015, there were an estimated 610,804 women living with endometrial cancer.[1] The U.S. incidence rates are among the highest in the world. Incidence rates are especially high in developed countries and have been rising as a result of aging of the population and increased obesity rates. The American Cancer Society estimates that a total of 54,870 new cancers of the uterus diagnosed in 2015.[1a] This is based on all women; because 20% to 30% of women in the United States have had a hysterectomy by age 50, rates are even higher when only women with a uterus are considered.[1a] European countries report age-standardized incidence rates ranging from 12 to 20 cases per 100,000 women.[2,3] The estimated incidence of 54,870 new uterine cancers in 2015 represented 3% of all cancers, and 6.1% of the estimated 805,500 new female malignancies. Endometrial cancer is the most common gynecologic malignancy and the fourth most common cancer in women. The mortality rate for uterine cancer in the United States is 4.3 deaths per 100,000 women per year, and the estimate for 2015 is 10,170 deaths, which is 1.4% of all cancer deaths, 3.0% of cancer deaths among women, and 29% of all deaths from gynecologic malignancies. The mortality rate decreased from 5.3 to 4.1 deaths per 100,000 women between 1973 and 1995 and has remained more or less stable since 1995.

Uterine cancer is typically a cancer of postmenopausal women between 55 and 85 years old. Incidence rates exceed 80 per 100,000 women in those aged 60 to 80 with a peak incidence of 95 per 100,000 in women aged 65 to 69.[1] Less than 5% of the patients are younger than age 40 years. The median age at diagnosis is 62, and at death 71 years. Uterine sarcomas also manifest primarily in the postmenopausal population. Leiomyosarcomas occur at an earlier age than carcinosarcomas.[4]

Etiology

The cause of the common type of endometrial cancer, endometrioid carcinoma, is related to exposure of the endometrium to unopposed increased estrogens both exogenous or endogenous.[5] Early menarche, late menopause, obesity, nulliparity, infertility, and estrogen-producing ovarian tumors are classically associated with the development of endometrial cancer. In obese women, elevated estrogen levels caused by increased peripheral conversion in fat of androstenedione may be the underlying mechanism for the increased risk. Endometrial cancer has also been associated with conditions such as hypertension and diabetes, but it is not clear whether these are true independent risk factors or related to obesity.[6,7] Unopposed exogenous estrogen levels have a strong association with the risk of endometrial cancer.[8] The use of tamoxifen for the prevention or treatment of breast cancer has been documented to statistically increase the risk of subsequent endometrial cancer.[9,10] Despite its antiestrogenic effects on breast tissue, tamoxifen has some weak estrogenic effects on other organs of the body, including the uterus, which accounts for this risk.

Hyperplasia with atypia is considered a premalignant phase of endometrioid carcinoma and has a similar origin[11]; when endometrial biopsies confirming complex hyperplasia with atypia, there is a 30% to 40% risk of subsequent development of endometrial cancer.

An increased risk associated with a family history of endometrial cancer has been observed, especially in women younger than 50 years, but less than 1% of all endometrial cancers were attributable to familial and potentially genetic factors.[12-14] Familial clustering of ovarian and endometrial cancers specific to the endometrioid morphology has been reported.[15] The risk of developing other malignancies, especially of the colon and breast, is increased after the diagnosis of endometrial carcinoma.[16-18] Women with mutations in the *MLH1, MSH2,* or *MSH6* genes, which are responsible for the hereditary nonpolyposis colorectal cancer (HNPCC) syndrome, are at increased risk for developing endometrial cancer.[19] HNPCC, or Lynch syndrome, is classified based on the presence or absence of tumors other than colorectal cancers. Patients with HNPCC syndrome type II have a high risk of endometrial cancer, second only to that of colorectal cancers.[20,21] These women have a 20% risk of developing endometrial cancer before 50 years of age, which increases to 60% by age 60 years.[22] Different screening policies for Lynch syndrome in young patients with endometrial cancer have been evaluated, based on microsatellite instability (MSI) or immunohistochemisty (IHC) of tumor specimens for mismatch repair protein expression, indicated either by age younger than 50 or 60 years, or by age and a first-degree relative having a Lynch-associated cancer, or by the Amsterdam criteria. Of these, IHC triage of women with endometrial cancer having at least one first-degree relative with a Lynch-associated cancer seemed most cost-effective.[23,24] Germline DNA mutation testing should be offered to those patients whose tumor shows loss-of-function of MMR protein(s) when analyzed for MSI or by IHC. MSI and IHC have a sensitivity of 80% to 100% and specificity of 60% to 80% for detecting a mutation in an MMR gene, and false-positive tumor test results because of somatic hypermethylation of the MLH1 gene promoter should be excluded.[25]

PREVENTION AND EARLY DETECTION

No measures that may contribute to prevention of endometrial cancer other than avoiding unopposed estrogen use and

avoiding obesity have been identified. Prophylactic hysterectomy is recommended in patients with known hyperplasia with atypia,[26] and prophylactic hysterectomy and oophorectomy is advised in HNPCC type II gene carriers, for whom the risk of concurrent or subsequent endometrial cancer is substantial.[27]

Screening for endometrial cancer has not been performed in the general population. The early symptoms and favorable prognosis of this disease preclude efficacy of population screening.[28] Vaginal ultrasound studies alone have not been found effective for screening purposes.[29] Prompt analysis of every patient with postmenopausal or abnormal vaginal bleeding with vaginal ultrasound and endometrial biopsy is indicated.

Screening of patients taking tamoxifen has been suggested, but the characteristic endometrial hyperplasia on ultrasound leads to high false-positive rates and subsequent frequent invasive diagnostic procedures in asymptomatic tamoxifen users.[30,31] In a prospective ultrasound screening study of 247 tamoxifen users, it was shown that of 52 asymptomatic patients with a thickened endometrium, most had an atrophic endometrium and only 1 had cancer, whereas in 2 of 20 patients with vaginal bleeding, endometrial cancer was diagnosed.[30] The study authors concluded that routine ultrasound screening is not indicated in asymptomatic women using tamoxifen, but that all women with abnormal bleeding should be evaluated.

Screening programs of gene carriers for the HNPCC syndrome not electing prophylactic surgery have shown increased efficacy when using annual endometrial biopsy plus vaginal ultrasonography.[32] An evaluation of gynecologic surveillance among 175 mutation carriers (503 surveillance visits during 759 person-years at risk) using vaginal ultrasonography and endometrial biopsy at 94% and 74%, respectively, of the visits showed that 11 of 14 endometrial cancer cases were diagnosed by surveillance and 8 by endometrial biopsies. Vaginal ultrasonography indicated only four patients with endometrial cancer and missed 6 other cases. Endometrial biopsy detected 14 additional cases of potentially premalignant hyperplasia. The stage distribution and survival tended to be more favorable, although not statistically so, in the 14 cases of endometrial cancer in the surveillance group (no deaths) than in a group of 83 symptomatic mutation carriers of whom 6 died of endometrial cancer.[33]

PATHOLOGY AND PATHWAYS OF SPREAD

Pathology

Almost all uterine epithelial cancers are adenocarcinomas. The World Health Organization (WHO) has described several subtypes (eBox 59-1). The most common type of endometrial adenocarcinoma is the endometrioid type, which accounts for 75% of cases.[34] Other nonendometrioid histologic types include serous (5% to 10%), mucinous (1% to 3%), and clear cell (1% to 5%) carcinomas. Uterine mesenchymal and mixed tumors, usually called the *uterine sarcomas*, include leiomyosarcoma, endometrial stromal sarcoma, and carcinosarcoma (or malignant mixed müllerian tumor). The WHO classification of mesenchymal and mixed tumors of the uterus is summarized in eBox 59-2. Carcinosarcoma is the most common type of uterine mesenchymal and mixed tumor (45%), followed by leiomyosarcoma (40%) and endometrial stromal sarcoma (10% to 15%). Carcinosarcomas are composed of malignant epithelial and stromal components; because of this biphasic appearance, their origin has long been debated. Based on molecular genetic analysis, the current opinion is that these cancers should be considered metaplastic carcinomas. Clinical data support this view that carcinosarcomas should be considered high-risk carcinomas, particularly because the epithelial component is usually of high grade.[35,36]

Nonendometrioid histologic types have a poorer prognosis. Serous and clear cell carcinomas are uniformly identified in this category. Serous adenocarcinoma has previously been called previously called *uterine papillary serous carcinoma* (UPSC). It is histologically similar to its ovarian counterpart. Uterine UPSC, first described in 1982, was found to have a higher rate of peritoneal failure similar to that of ovarian cancer.[37] This entity can be confused with the papillary villoglandular, a subtype of endometrioid adenocarcinoma with a significantly more favorable prognosis. Serous carcinoma is frequently diagnosed at a higher stage than endometrioid adenocarcinomas. Clear cell carcinoma has also been reported to have a poor prognosis, with more advanced disease at diagnosis.[38] Early-stage serous and clear cell carcinomas have been shown in some analyses to have outcomes similar to grade-3 endometrioid carcinoma, although recurrence rates for serous cancers were highest.[39-41]

Adenosquamous cell carcinoma has been suggested by some investigators to be another poor-prognosis histologic subtype,[38,42] but others think the prognosis of these patients is no different from that for the typical endometrioid adenocarcinoma.[43,44] Zaino et al evaluated a large population of patients who were part of a Gynecologic Oncology Group (GOG) study and found a parallel between the glandular grade and the degree of differentiation in the squamous component. It was subsequently suggested that the name of this histologic subtype should reflect the lack of importance of this feature by calling it adenocarcinoma with squamous differentiation.[43]

Endometrial hyperplasia with atypia frequently precedes endometrioid endometrial carcinoma. Endometrial intraepithelial carcinoma has been associated with the development of nonendometrioid carcinoma. The International Society of Gynecological Pathologists has identified two architectural forms of endometrial hyperplasia, simple and complex. Where marked architectural abnormalities are displayed it is designated as *complex hyperplasia;* lesions with a lesser degree of architectural abnormalities are designated *simple hyperplasia*. Atypical nuclear changes can be associated with the simple or complex types and are regarded separately from hyperplasia that is not displaying atypia. Progression of simple hyperplasia without atypia to endometrioid carcinoma is rare (<2%), whereas progression to carcinoma occurs in 30% to 40% of the patients with simple and complex hyperplasia with atypia.[11,45] The risk of subsequent endometrial cancer warrants hysterectomy in patients with atypical hyperplasia.

Not all endometrial cancers arise in a setting of atypical hyperplasia. Nonendometrioid cancers, especially serous carcinomas, appear to represent malignant transformation of atrophic endometrium, which is found in the adjacent endometrium of up to 90% of serous carcinomas.[46]

Pathways of Spread

Most endometrial cancers remain confined to the uterine body for a long time. The initial spread is by local extension along the endometrial surface. Longitudinal growth may result in involvement of the lower uterine segment and the cervix, initially involving the endocervical glands and later spreading by cervical stromal invasion. The tumor can also extend along the cornua to the fallopian tubes. Radial growth results in myometrial invasion, of varying depth and ultimately penetrating to the subserosa and serosa. Two patterns of myometrial invasion have been described: an expansive growth pattern with pushing borders and an infiltrating growth

eBOX 59-1 World Health Organization Histologic Classification of Epithelial Tumors of the Uterus

Endometrioid adenocarcinoma
Villoglandular
Secretory
Ciliated cell
Variant with squamous differentiation
Mucinous adenocarcinoma
Serous adenocarcinoma
Clear cell adenocarcinoma
Mixed cell adenocarcinoma
Squamous cell carcinoma
Transitional cell carcinoma
Small cell carcinoma
Undifferentiated carcinoma

eBOX 59-2 World Health Organization Histologic Classification of Mesenchymal and Mixed Tumors of the Uterus

MESENCHYMAL TUMORS

Smooth muscle tumors
Leiomyoma, not otherwise specified
Smooth muscle tumor of uncertain malignant potential
Leiomyosarcoma
Epithelioid variant
Myxoid variant
Endometrial stromal and related tumors
Endometrial stromal nodule
Endometrial stromal sarcoma, low grade
Undifferentiated endometrial sarcoma
Miscellaneous mesenchymal tumors
Mixed endometrial stromal and smooth muscle tumor
Adenomatoid tumor
Perivascular epithelioid cell tumor
Other mesenchymal tumors (benign and malignant)

MIXED EPITHELIAL AND MESENCHYMAL TUMORS

Adenofibroma
Adenomyoma
Atypical polypoid adenomyoma
Adenosarcoma
Carcinosarcoma (malignant mixed müllerian tumor)
Carcinofibroma

pattern with cancer cells and nests penetrating the myometrium haphazardly.[47] The infiltrating growth pattern is associated with frequent lymphovascular space invasion (LVSI) and early lymphatic spread. Foci of adenomyosis may be seen deep within the myometrium. The prognostic significance of tumor cells in adenomyosis is unclear. Tumor cells may grow only superficially from these foci located deep in the myometrium. They may not carry the same worse prognosis as those penetrating directly from the endometrium. After the tumor breaches the serosa, transperitoneal dissemination can occur, with a pattern resembling that of ovarian cancer. Occasionally, after extensive penetration of the myometrium or the cervix, direct invasion of the bladder or the rectum may occur, or the tumor may involve the pelvic soft tissues and continue to reach the pelvic sidewall. Peritoneal seeding can result from growth through the serosa or from transtubal spillage of tumor cells into the peritoneal cavity.

As the tumor invades the myometrium more extensively, the risk of lymph node metastasis is higher.[48,49] The endometrium has few lymphatics, but after the tumor penetrates the myometrium and especially when it reaches the lymphatic-rich subserosa, spread by lymphatic invasion is common. LVSI as diagnosed in the hysterectomy specimen is thus an early marker of disease spread.[50] Lymphatics from the uterine fundus can drain directly to the paraaortic lymph nodes. Typically, the internal and external iliac lymph node groups are the first echelon of spread although isolated para-aortic nodal involvement also occurs. Sentinel node detection studies[51-53] have shown the sentinel nodes to be located in the obturator, external iliac, and paraaortic regions. Lymphatic spread is also believed to be responsible for involvement of the vagina and for isolated adnexal involvement.

Overall, about 11% of patients with clinical stage I and occult stage II endometrial carcinoma and 5% to 7% of patients with tumors confined to the uterus have pelvic or paraaortic lymph node involvement.[48,54] The extent of myometrial invasion correlates strongly with the histologic grade of the tumor, and the depth of invasion and tumor grade correlate with the risk of lymphatic involvement for endometrioid tumors. For serous tumors depth of invasion is not well-correlated with risk of lymph node involvement; one older series of 50 serous cancers, of which 66% were pure serous cancers and 72% had extrauterine spread, showed a 36% rate of lymph node involvement for tumors with no myometrial invasion.[55] The risk of intraabdominal dissemination is also higher in patients with clear cell carcinomas. Abdominal involvement of endometrioid carcinoma is associated with other risk factors, such as lymph node involvement, adnexal involvement, and LVSI.

Hematogenous spread is uncommon in endometrial cancer, occurring mainly with high-grade tumors, unfavorable histologies, or advanced stages. The most common metastatic sites include the lungs, liver, and bones. Distant nodal metastases (i.e., supraclavicular or inguinal) result from extensive lymphatic involvement or from hematogenous spread.[56]

BIOLOGIC CHARACTERISTICS AND PROGNOSTIC FACTORS

Biologic Features

Two different types of endometrial carcinoma have been identified and described first by Bokhman in 1983.[57] Type I tumors are estrogen related, are often preceded by hyperplasia, and are typically low-grade endometrioid histology. They usually develop in an estrogen-rich environment (e.g., obesity, premenopausal and perimenopausal phases), and they have a good prognosis. Type II tumors are unrelated to estrogen and develop in atrophic endometrium, presumably preceded by endometrial intraepithelial carcinoma, and they are more often serous and clear cell carcinomas. Patients with type II tumors are older and postmenopausal and have high-grade, deeply invasive tumors with an unfavorable prognosis. A summary of the differences between these two groups is shown in Table 59-1. The genetic abnormalities involved in the carcinogenesis of endometrial cancer are different for type I and II carcinomas.

TABLE 59-1 Predominant Features of Types I and II Endometrial Cancer

Characteristic	Type I	Type II
Clinicopathologic Features		
Estrogen relation	Yes	No
Precursor lesion	Hyperplasia	Intraepithelial carcinoma
Age	Younger	Older
Histologic type	Endometrioid	Nonendometrioid
Grade	1 or 2	3
Stage	1	More advanced
Prognosis	Good	Poor
Genetic Features		
Ploidy	Diploid	Aneuploid
TP53 mutation	10%-20% (late event)	60%-90% (early event)
PTEN inactivation	35%-50%	5%-10%
ERBB2 protein overexpression	10%-15%	20%-25% (serous: 60%)
EGFR overexpression	10%-30%	60%-80%
KRAS mutation	15%-30%	0%-5%
Microsatellite instability	20%-30%	0%-5%

Specific molecular alterations have been found in type I and II endometrial cancers, supporting and refining the clinicopathologic distinction by molecular data, such as loss of *PTEN;* mutations of *TP53, KRAS,* and *PIK3CA;* MSI; and overexpression of ERBB2, epidermal growth factor receptor (EGFR), and P16.[58,59] In type II cancers, *TP53* mutations have been found in up to 90% of cases (invasive and intraepithelial carcinomas), suggesting it to be an early event in carcinogenesis. ERBB2 protein overexpression has been reported in a significant proportion of serous carcinomas, and about 20% to 30% of serous carcinomas are found to have amplification of the *ERBB2* gene. The ERBB2 gene product, similar to EGFR, is a transmembrane receptor protein that plays an important role in the ERBB signaling network that is responsible for regulating cell growth and differentiation. ERBB2 overexpression is associated with aggressive biologic behavior and poor survival. The Cancer Genome Atlas Project (CGA) has provided a comprehensive genetic characterization of endometrial cancer and confirmed previous findings that *PTEN* mutations are uncommon in serous tumors and common in low-grade endometrioid cases; that *TP53* mutations are common in high-grade and serous cancers, whereas *PIK3CA* mutations are distributed across histology and grade. These alternatives and others offer the opportunity for exploration of biologic targeting agents specific to the abnormality.

No specific abnormalities have been associated with type I cancers in general, which suggests that type I is a heterogeneous group of tumors with different combinations of abnormalities. *TP53* mutations have been found in 10% to 20% of

Targeted therapy using trastuzumab, a monoclonal antibody to ERBB2, is theoretically one such treatment strategy.[60] However, the one prospective clinical trial testing single-agent trastuzumab in heavily pretreated endometrial carcinomas with ERBB2 overexpression or amplification reported no major responses.[61] A randomized trial of carboplatin and paclitaxel with or without trastuzumab in women with HER2-positive, platinum-sensitive endometrial cancer is ongoing. EGFR overexpression occurs in 60% to 80% of type II cancers, and it correlates with advanced-stage disease and poor prognosis.[62] Targeted therapy with anti-EGFR agents including tyrosine kinase inhibitors such as gefitinib, lapatinib, and erlotinib as well as monoclonal antibodies such as cetuximab has been investigated in Phase II studies.[63,64] Results thus far have been modest. The National Cancer Institute of Canada (NCI Canada) reported the best results with a 12.5% response rate to single-agent erlotinib for chemotherapy-naïve tumors. There was no correlation found between response and *EGFR* gene mutations or amplification.[63] In a trial of the dual EGFR/HER2 inhibitor lapatinib (which showed a 3% response rate overall), three mutations in EGFR were identified. Two of these were not associated with response or progression-free survival, but, a newly identified mutation in exon 18, E690K, was found in the tumor of the patient with a partial response.[65]

type I cancers. Mutant TP53 protein expression has been associated with advanced stage and other adverse factors, such as grade 3, deep invasion, and poor survival.[66,67] In the recent The Cancer Genome Atlas (TCGA) analysis, 25% of high-grade endometrioid cancers cluster with serous tumors and have extensive copy number alterations, few DNA methylation changes, low estrogen receptor/progesterone receptor (ER/PR), and frequent TP53 mutations.[68] More general markers of genetic damage such as DNA aneuploidy have consistently been associated with an inferior outcome.[69,70]

PTEN is frequently altered in endometrioid endometrial carcinomas (37% to 61%) and is considered an early event in carcinogenesis. The loss of *PTEN*, with consequent activation of the phosphatidylinositol-3-kinase (PI3k)-serine/threonine-specific protein kinase (AKT)-mammalian target of rapamycin (mTOR) signaling pathway, has been found in 32% to 83% of endometrioid-type endometrial carcinomas.[71] Comutations are common; most tumors with loss of *PTEN* have mutations in PIK3CA or PIK3RA as well. TOR is the central component of a complex signaling network that regulates cell growth and proliferation and is interconnected with the PI3K/AKT signaling pathway. *PIK3CA* mutations are frequently found in association with myometrial invasion, advanced stage, and adverse prognostic factors.[72-74] Inhibition of the mTOR pathway is currently regarded as an important "druggable" target for therapy.[75] Phosphorylated mTOR overexpression has been found in both type I and II endometrial carcinomas.[76]

In vitro data have suggested that inhibiting the PI3K/AKT pathway reverses progestin resistance in endometrial cancer,[79] and attempts have been made to improve results of endocrine therapy by combining it with an mTOR inhibitor (analogous to the approved use by the Food and Drug Administration of everolimus with exemestane in patients with breast cancer). Multitargeted growth factor TKIs such as brivanib and pazopanib are also being studied.

Gene expression clusters based on high expression of mitotic genes, hormonal genes, and immunoresponsive genes have been identified. The mitotic cluster was found to contain serous and serous-like tumors; the hormonal cluster contained samples with greater ER/PR expression, and the immunoresponsive cluster contained immune activated genes, identifying endometrial cancers with distinct clinical behavior. Genomic instability increases as tumors become less differentiated, with high frequencies of chromosomal losses and gains in grade-3 and serous tumors.[68]

As listed in Table 59-2, some molecular abnormalities such as *PTEN* and *KRAS* mutations, have been associated with favorable and unfavorable outcomes.[85] Recently, L1CAM expression was identified as a promising molecular prognostic factor.[86] In most multivariate analyses, however, the prognostic significance of these molecular markers is lost in the presence of the traditional major prognostic factors: stage, grade, depth of invasion, and histologic subtype. The major promise of the molecular markers is the identification of specific targets for therapy and development of individual, effective therapeutic strategies for patients with advanced or metastatic disease.

TABLE 59-2 Prognostic Value of Genetic Abnormalities

Genetic Abnormality	Prognostic Value
Aneuploidy	Decreased survival
TP53 mutation	Decreased survival
PTEN inactivation	Conflicting data
ERBB2 overexpression	Decreased survival
EGFR overexpression	Decreased survival
KRAS mutation	Conflicting data
Microsatellite instability	No prognostic significance

Prognostic Factors

Numerous comprehensive retrospective analyses and prospective, randomized studies have identified the major clinically identifiable prognostic factors in endometrial carcinoma. These are stage, patient age, histologic cell type, tumor grade, depth of myometrial invasion, and presence of LVSI.[50,87,88] Randomized trials have confirmed the prognostic value of these factors.[89,90] In stage I endometrial cancer, grade has been found to be a major factor, with grade-3 tumors associated with a threefold to fivefold increased risk of relapse and cancer death.[91,92] In most studies, grade-2 tumors do not have significantly different outcomes compared with grade 1, and a two-tiered grading system, low risk compared with high risk has have been proposed to overcome the limited clinical value and poor reproducibility of the intermediate grade.[47,93] The specific binary grading system proposed by Lax et al is based on the proportion of solid growth, the pattern of myometrial invasion, and the presence of tumor cell necrosis.[47] A simple two-tiered system, dividing tumors into low or high risk based on the proportion of solid growth (<50% versus >50%), was shown to have superior prognostic power and greater reproducibility over the FIGO grading system.[94] Alternatively, the FIGO grading system may be used as a binary system by dividing tumors into grades 1 and 2 versus grade 3. This has been shown to have strong prognostic significance, and it has the additional advantages of being highly reproducible and familiar to practicing pathologists worldwide.[94,95]

In most studies, depth of myometrial invasion had less prognostic value than tumor grade. Deep invasion, particularly into the outer third or half of the myometrial wall is associated with increased risk of relapse and inferior outcome. A diffusely infiltrating pattern of myometrial invasion, as opposed to an expansive growth pattern with pushing borders, has been suggested to be a stronger adverse prognostic factor than the depth of invasion.[92,96] Because the effluent lymphatics and capillaries are mainly located in the subserosa, the tumor-free distance from the serosa may prove to be the strongest prognostic factor. In a multivariate analysis of 153 patients, tumor-free distance, especially when only a few mm, was found to be a highly significant predictor of relapse and death from disease, stronger than depth of invasion, and to have greater reproducibility.[97]

LVSI has been found to be a major prognostic factor that significantly and independently increases the risk of relapse, especially distant relapse.[50,90,98,99] In an analysis of 609 patients with stages I to III endometrial cancer, those with LVSI were found to have a 5-year relapse rate of 39%, in contrast to 19% for patients without LVSI ($p < 0.0001$). Even in otherwise low-risk stage I disease (defined by low grade and depth of invasion), the presence of LVSI significantly increased the risk of relapse (28% with versus 14% without LVSI). In patients with stage I disease with high-risk features, those with LVSI had a 43% relapse rate.[84]

CLINICAL MANIFESTATIONS, PATIENT EVALUATION, AND STAGING

Clinical Manifestations

Abnormal uterine bleeding is the most common presenting sign of patients with endometrial cancer. Because blood loss is an early sign of endometrial proliferation, 75% of patients

Phase II trials using mTOR inhibitors including deforolimus, temsirolimus, and everolimus have been performed. The most promising preliminary results thus far have been reported by the NCI Canada in women with chemotherapy-naïve disease, in whom a 14% response rate to single-agent therapy with temsirolimus was observed.[77] To date, despite extensive exploration of patient samples on studies of mTOR inhibitors, no markers of activation of the PI3K/AKT signaling pathway have proven to be predictive of response to mTOR inhibitors in patients. Newer agents, including pan-PI3K inhibitors, PI3K isoform-specific inhibitors, dual PI3K/mTOR catalytic inhibitors, mTOR-specific catalytic inhibitors, and AKT inhibitors are in development. On the basis of tight interactions between the PI3K and RAS/RAF/MEK pathways,[78] combinations of agents designed to block both pathways seem of interest. The Gynecologic Oncology Group (GOG) has recently opened GOG#2290, a randomized Phase II study of the MEK inhibitor Trametinib alone or in combination with GSK2141795, an AKT inhibitor.

In a Phase II trial of everolimus compared with everolimus/letrozole in 63 patients, the response rate was 31% for everolimus/letrozole compared with 0% for everolimus alone in a similar patient population.[80] However, the GOG found no advantage to the addition of temsirolimus to the combination of megestrol acetate and tamoxifen (response rate 14%) when compared to temsirolimus alone (response rate 22%) in tumors unselected for histologic subtype or ER/PR expression.[81] Other potential targets include Fibroblast Growth Factor Receptor 2 (FGFR2)[82,83] and VEGF: Vascular Endothelial Growth Factor (VEGF).[84]

present with early-stage disease. However, only about 15% to 20% of the patients with postmenopausal bleeding are found to have endometrial cancer. Another, rather nonspecific symptom is profuse, watery discharge. In premenopausal or perimenopausal patients, the presenting symptom may be irregular blood loss or menorrhagia. It is unusual for screening cervical cytology to be the method of diagnosis, but malignant endometrial cells occasionally may be found in routine Papanicolaou (pap) smears. Normal-appearing endometrial cells in a Pap smear in woman who is postmenopausal may also be a sign of malignancy. One recent study of 1183 Pap cytology cases (739 with normal endometrial cells, 423 with atypical endometrial cells, and 21 with endometrial cancer cells in women 40 years or older) noted that significant endometrial lesions were found in 2.7% of cases with normal endometrial cells, 18.4% of cases with atypical endometrial cells, and 100% of cases endometrial cancer cells.[100] Ongoing research is evaluating DNA from Pap smears a screening test for endometrial and ovarian cancers.[101] Pain is usually absent unless there is pyometra. Patients with more advanced stages of endometrial cancer can present with abdominal symptoms, gastrointestinal symptoms, back pain, or lymphedema.

Patient Evaluation

Patient evaluation for confirmed or suspected malignancy includes a medical history and physical examination, including vaginal inspection and bimanual pelvic examination. Medical history should include the presence of risk factors associated with endometrial cancer, such as obesity, hypertension, diabetes mellitus, estrogen or tamoxifen use, nulliparity, a family history, especially of colon, endometrial, breast, or ovarian cancers, and (especially for sarcomas) prior pelvic radiotherapy.

Most patients with endometrial carcinoma have early-stage disease and do not have significant abnormalities on pelvic examination. However, a complete pelvic examination should be performed to exclude gross cervical extension, vaginal metastases, and adnexal pathology.

Outpatient procedures, such as transvaginal ultrasonography and endometrial biopsy or aspiration curettage, establish the diagnosis in more than 90% of patients suspected to have endometrial cancer. Various endometrial biopsy tools are available, such as a small Novak curette, Pipelle instrument, or Vabra aspirator, that permit the endometrial biopsy to be performed as an outpatient procedure without general anesthesia. If these procedures are not conclusive, a formal dilation and fractional curettage (D&C) should be performed, with or without hysteroscopy. Hysteroscopy allows direct visual assessment of the endocervix and the endometrial cavity and can be useful in guiding biopsy of any visible abnormality in symptomatic patients when other procedures have been nondiagnostic. Figure 59-1 presents a diagnostic algorithm for patient workup and evaluation.

Staging

After a diagnosis of malignancy is established, the preoperative evaluation and staging workup are done. Definitive staging according to the FIGO system is based on the surgical and pathology findings. In 2009, a revised FIGO staging system was published, and this has replaced the 1988 FIGO staging system.[102] Table 59-3 lists the 2009 FIGO staging and the differences between the 1988 and 2009 systems. The changes in stages IA, IB, and IC especially should be kept in mind when evaluating literature data because FIGO 1988 stages IA (no myometrial invasion) and IB (less than 50% myometrial invasion) have been grouped together in FIGO 2009 as stage IA and because FIGO 1988 stages IC (greater than 50% myometrial invasion) is IB in FIGO 2009. The previous nonsurgical (clinical) FIGO staging system continues to be used for patients not undergoing surgery.

The patient's general evaluation should include standard blood tests and a chest radiograph. Patients with endometrial

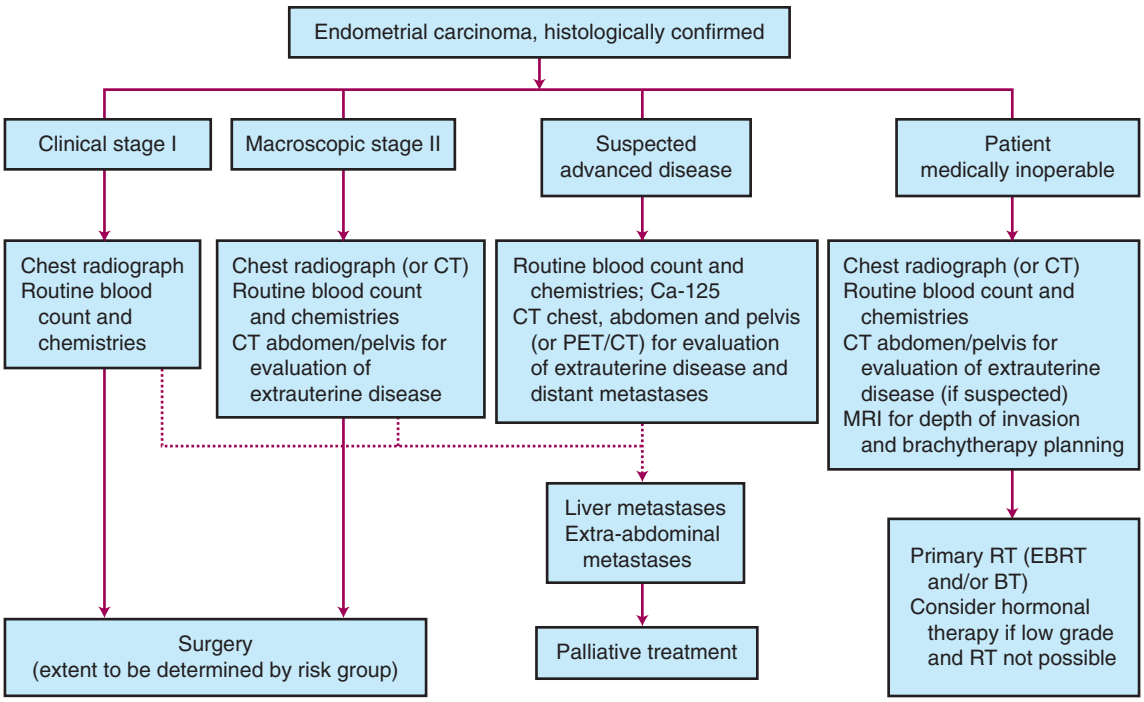


Figure 59-1 Diagnostic algorithm for patients with endometrial carcinoma. *BT,* Brachytherapy; *CT,* computed tomography; *EBRT,* external beam irradiation; *MRI,* magnetic resonance imaging; *PET,* positron emission tomography.

TABLE 59-3 Federation of Gynecology and Obstetrics (FIGO) 2009 Surgical Staging System for Endometrial Carcinoma[102]

Stage and Grade		Description
I		Tumor confined to the corpus uteri (and or cervical mucosa)
IA	(G1, 2, 3)	No or less than half myometrial invasion
IB	(G1, 2, 3)	More than half myometrial invasion
II	(G1, 2, 3)	Tumor invades cervical stroma but does not extend beyond the uterus*
III		Local and/or regional spread of the tumor
IIIA	(G1, 2, 3)	Tumor invades the serosa of the corpus uteri or adnexae
IIIB	(G1, 2, 3)	Vaginal or parametrial involvement
IIIC	(G1, 2, 3)	Metastasis to pelvic or paraaortic lymph nodes†
IIIC1	(G1, 2, 3)	Positive pelvic lymph nodes
IIIC2	(G1, 2, 3)	Positive paraaortic lymph nodes with or without pelvic nodes
IV		Tumor invades bladder or bowel mucosa, or distant metastasis
IVA	(G1, 2, 3)	Tumor invasion of bladder or bowel mucosa
IVB	(G1, 2, 3)	Distant metastasis, including intraabdominal metastases or inguinal lymph nodes
FIGO Histologic Grading		
G1		<5% nonsquamous or nonmorular solid growth pattern
G2		5%-50% of a nonsquamous or nonmorular solid growth pattern
G3		>50% of a nonsquamous or nonmorular solid growth pattern

**Endocervical glandular involvement should be considered stage II.*

carcinoma are often elderly and frail and may have a number of concurrent medical problems, including morbid obesity and diabetes, that influence selection of the appropriate treatment. CT and MRI are not routinely performed for patients with clinical stage I disease who will be undergoing surgery, but imaging should be done if locally advanced disease is suspected. The major limitations of CT are its unreliability in assessing myometrial invasion, especially in atrophic uteri, and the failure to detect minimal parametrial, lymph nodal, or local extrauterine invasion.[103] The greatest value of CT may be for staging in patients with clinical stage III or IV disease and in medically inoperable patients, for whom CT is useful for evaluating the size and extent of the tumor, for excluding gross extrauterine disease, and for planning of appropriate target volumes for radiation therapy. MRI using an intravenously administered contrast agent is superior to CT in determining myometrial invasion and diagnosing stage II disease.[104]

Initial studies of the potential role of FDG-PET/CT suggest a promising role for evaluation of relapse during follow-up and for presurgical evaluation of pelvic node metastases. In an analysis of PET/CT in 25 women with suspected relapse during follow-up, lesion site–based sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV), and accuracy of PET/CT were 94.7%, 99.5%, 94.7%, 99.5%, and 99.0%, respectively.[105] Other follow-up studies confirmed the efficacy of PET or PET/CT in detecting relapse both in asymptomatic and symptomatic patients, with sensitivity of 100% and specificity, PPV, NPV and accuracy of 83% to 100%.[106,107]

Although the FIGO staging system requires a pelvic lymphadenectomy, the role of lymphadenectomy and the optimal extent of lymphadenectomy (e.g., lymph node sampling, selective or complete lymphadenectomy, and pelvic and aortic lymphadenectomy and its proximal extent) are subjects of controversy, as is the question of whether lymphadenectomy is a purely diagnostic and prognostic procedure or whether therapeutic benefit can be obtained. Most commonly, lymphadenectomy is reserved for those with high-grade malignancy or with deep myometrial penetration detected at surgery.

PRIMARY THERAPY

Surgery

Surgery is the mainstay of the initial treatment of endometrial carcinoma. The standard surgical procedure has for decades been a total abdominal hysterectomy with bilateral salpingo-oophorectomy (TAH-BSO). The standard surgical approach has traditionally been laparotomy through a midline incision, which allows full exposure of the abdomen, pelvic areas, and lymphatic sites. Surgical evaluation includes thorough examination and palpation of the pelvic and abdominal organs and lymph node regions, and sampling of any suspicious sites and variably collection of ascites or peritoneal lavage fluid for cytologic evaluation.

More recently, laparoscopic and robotic techniques have been explored for clinical stage I disease and evaluated in randomized trials.[109-111] The advantages of laparoscopy are the shorter hospitalization and recovery time and decrease of surgical morbidity.[109,111,112] Disadvantages are the increased length of the operation and the learning curve involved with laparoscopic techniques.

The first randomized trials comparing laparoscopy to laparotomy were powered for morbidity and showed similar OS and relapse-free survival (RFS) rates with lower postoperative complication rates and better short-term quality of life, most notably better physical and functional well-being and body image.[109,112,116,117] The largest randomized trial, the GOG-LAP2 study, was powered to establish noninferiority of laparoscopy, the primary endpoint being noninferiority of the recurrence-free interval (defined as a maximum hazard ratio [HR] of 1.4 for laparoscopy relative to laparotomy).[110] This trial recruited 2616 patients with clinical stages I to II endometrial cancer, and at a median follow-up duration of 59 months, the estimated HR for laparoscopy relative to laparotomy was 1.14, with a 95% confidence interval (CI) upper level of 1.46. However, the actual recurrence rates were lower than anticipated, with estimated 3-year recurrence rates of 11.4% after laparoscopy compared with 10.2% after laparotomy. The estimated absolute difference in 3-year recurrence rate was only 1.14%. Estimated 5-year OS was 84.8% on both arms, and sites of first recurrence and use of postoperative adjuvant therapy (in 31% of patients) were also similar. It should be noted that 70% of patients had early-stage disease with no or superficial myometrial invasion. Only a minority had risk factors such as deep myometrial invasion, grade-3 or stage II disease.[110] The rate of conversion from laparoscopy to laparotomy was 26%, higher than in the other trials (10.8%[109] and 2.4%[112]), mostly because of the requirement on this protocol for full lymphadenectomy even in patients at low risk. Laparotomy remains preferable to laparoscopy in patients who are morbidly obese, in patients with intraabdominal adhesions, and those with more advanced disease.

In situations with gross cervical involvement (macroscopic stage II disease), a radical or modified hysterectomy can be considered, although preoperative external beam radiation therapy (EBRT) is also used. Retrospective data support the

PET/CT detected relapse in 3 patients with elevated tumor markers but negative CT findings and altered treatment in 22% of patients.[107] Diagnostic accuracy of PET/CT was evaluated among 37 patients with high-risk endometrial cancer, of whom 9 (24%) had pelvic node metastases on histopathologic analysis. Patient-based sensitivity, specificity, PPV, NPV, and accuracy of PET/CT for detection of nodal disease were 77.8%, 100.0%, 100.0%, 93.1%, and 94.4%, respectively. Nodal lesion site–based sensitivity, specificity, PPV, NPV, and accuracy of FDG-PET/CT were 66.7%, 99.4%, 90.9%, 97.2%, and 96.8%, respectively, showing that PET/CT has a high NPV and may be useful in selecting patients for lymphadenectomy.[108]

Completeness of the surgical staging procedure can upstage the disease in patients otherwise considered as having stage I disease, and the problems of stage migration and patient selection preclude definitive conclusions on the value of lymphadenectomy in the absence of randomized data. The approach to these surgical staging issues varies among gynecologists and gynecologic oncologists and among different countries. Although knowledge of nodal involvement may be useful to aid in choosing any adjuvant therapies, the low incidence in low-risk disease precludes utility in the low-risk setting. Significant lymphedema may occur with systematic node dissection. The variability in staging of patients clearly affects the reported distribution of stages in patients with endometrial cancer.

Initially, increased risks of malignant cells in the peritoneal cytology specimen[113] and vaginal cuff recurrence or port-site metastases[114] were reported with laparoscopic techniques. The importance of early occlusion of the fallopian tubes and uterine artery and avoidance of intrauterine manipulators to prevent such peritoneal spread and vaginal cuff recurrence has been stressed.[115]

TABLE 59-4 Risk Factors for Lymph Node Metastases†

Risk Level	Lymph Node Metastasis	
	Pelvic Nodes (%)	Aortic Nodes (%)
ALL CLINICAL STAGE I		
Low Risk		
Grade 1, endometrium only, no intraperitoneal disease	0	0
Moderate Risk		
No intraperitoneal disease		
Inner-middle invasion or grade 2 or 3	3	2
Both factors	6	2
High Risk		
Deep invasion	18	15
Intraperitoneal disease	33	8
NO GROSS EXTRAUTERINE DISEASE		
Low Risk		
No invasion or grade 1 with invasion*	<5	<2
Moderate Risk		
All other	5-10	<5
High Risk		
Grade 3, outer 33% invasion	>10	>10

Excluding serous or clear cell histology.
†*Data from Creasman WT, Morrow CP, Bundy BN, et al: Surgical pathologic spread patterns of endometrial cancer. A Gynecologic Oncology Group study. Cancer 60:2035-2041, 1987.*

use of radical hysterectomy in macroscopic stage II disease to clear potential parametrial disease, although a survival advantage over TAH-BSO and pelvic radiation therapy has not been proven.[118,119]

The role of pelvic and paraaortic lymphadenectomy or lymph node sampling in endometrial cancer has been widely debated. Determination of nodal involvement has prognostic implications, and in patients with nodal involvement it may direct further therapy. The potential therapeutic implications of lymphadenectomy are directly related to the risk of nodal disease in the population studied. Prospective and retrospective studies of lymphadenectomy in patients with clinical stage I or II endometrial carcinoma without extrauterine spread identified at surgery have shown the rates of pelvic and aortic nodal involvement to be 7% to 9% and 2% to 3%, respectively.[48,120] The risk of lymph node involvement varies with the major risk factors, as was demonstrated in the landmark GOG surgical pathologic staging study[48] (Table 59-4).

For the majority of patients with clinical stage I or occult stage II disease, the risk of nodal involvement is extremely low. Therefore, it is difficult to justify staging in all patients.[127]

Two randomized trials investigating the role of lymphadenectomy in clinical stage I endometrial cancer have been published and show no benefit. In the U.K. Medical Research Council ASTEC trial, 1408 patients were randomized: 704 to TAH-BSO with pelvic lymphadenectomy and 704 to TAH-BSO alone.[128] The baseline characteristics were well balanced between the groups: 9% of the lymphadenectomy group had nodal involvement. The 3-year OS rates were 89% (TAH-BSO alone) and 88% (TAH-BSO plus lymphadenectomy), and 3-year RFS was superior in the TAH-BSO alone arm (HR 1.35, $p = 0.017$; HR 1.25 after adjustment, $p = 0.14$). An Italian randomized trial comparing TAH-BSO with pelvic lymphadenectomy (30% had also paraaortic lymphadenectomy, with a median of 23 [pelvic] to 30 [pelvic and paraaortic] nodes removed in the patients in the lymphadenectomy study arm) with TAH-BSO alone for stage I endometrial carcinoma confirmed these results.[129] Although the rate of nodal involvement was 13% in the lymphadenectomy arm as compared with 3% in the standard arm, rates of DFS, OS, and relapses were the same in both arms. Even the pattern and sites were similar, with vaginal recurrences in 2.6% versus 2.4% and lymph node recurrences in 1.5% versus 1.6% of patients in the lymphadenectomy versus standard study arms.[129]

The ongoing controversy regarding the role of lymphadenectomy staging compared with uterine prognostic factors directing adjuvant therapy, especially for high-risk tumors, has prompted design of a randomized trial. This is being developed by groups collaborating in the Gynecological Cancer InterGroup (GCIG).[130]

Sentinel node detection may be an alternative way to identify patients at high risk for relapse while sparing most patients the risks and added toxicities of lymphadenectomy. However, it is not without side effects including lymphocyst formation, infection, bleeding, and lymphedema. For patients with low-risk disease, the potential benefits should be weighed against detecting micrometastatic disease in only 3% to 6%.

Evaluation of sentinel node biopsy is especially promising in patients with high-risk factors. This will be an integral part of the planned GCIG lymphadenectomy trial.

Primary Radiation Therapy: Indications and Results

The approximately 3% of patients who are medically inoperable because of comorbidity can be offered primary curative radiation therapy (RT). Substantial local control and DSS rates have been reported, although these patients have a high mortality rate because of their coexisting medical conditions. Patients at low risk for extrauterine spread potentially may be treated with intrauterine brachytherapy alone, but it may be impossible to encompass an enlarged uterus in the clinical target volume using only an intrauterine tandem. Pelvic EBRT is based on the risk of extrauterine disease or uterine size. It is usually employed in cases with grade-3 disease, larger uterine volume, or cervical involvement. Some patients are not candidates for curative irradiation because of their coexisting illnesses. They should be offered palliative RT to stop bleeding.

Several studies have demonstrated the efficacy of primary RT for clinical stage I disease. With the use of uterine brachytherapy with or without EBRT, 5-year uterine control rates of 70% to 90%, and DFS ranging from 50% to 80% have been reported.[133-137] Inferior survival rates with radiation instead of surgery are related to inferior control of uterine disease. Patients with low-grade tumors and smaller uteri, brachytherapy can be a good alternative to hormonal treatment or observation for morbidly obese patients.[134,135] Grade-3 tumors had significantly lower pelvic control and survival rates than grade-1 or grade-2 disease, and usually a combination of EBRT and brachytherapy is used. Studies that included patients with stage II disease reported 5-year pelvic control rates of 40% to 60% and DSS of 50% to 60%.[134]

Surgical Results: Early-Stage Disease

Many retrospective studies have reported invariably good outcomes for stages IA and IB grade-1 and grade-2 endometrioid carcinoma treated with surgery alone, with a 5-year RFS of 95% and 5-year vaginal relapse rates of 2% to 5%.[138,139]

Some of these features can be identified at the time of hysterectomy and have been used to evaluate the indication for lymph node dissection. As discussed previously, the risk of extrauterine spread for serous tumors is much higher and for serous cancers, full surgical staging including omentectomy and peritoneal biopsies is recommended (see section on unfavorable histologic types). The addition of lymphadenectomy, especially if pelvic and aortic lymphadenectomies are performed, prolongs operation time and has side effects, such as leg edema (5% to 10%), lymphocysts (symptomatic in 5% to 7%), increased rates of deep vein thrombosis (2%) and small bowel obstruction (up to 5%), and increased blood loss and higher transfusion rates (5% to 10%). The studies suggesting a survival advantage of lymphadenectomy have been small, single-center retrospective analyses that were flawed by patient selection and stage migration.[121-123] The larger National Cancer Institute and Duke University analyses reported a survival benefit with full lymphadenectomy for grade-3 cancers, whereas no benefit was found for grade 1 or 2 disease.[120,124] Analysis of data from the SEER program did not show benefit from lymphadenectomy for patients with stage I grade 1 or 2 disease but suggested improved disease-specific survival (DSS) for those with stage I grade 3 or more advanced-stage disease.[125,126] Lymphadenectomy should therefore be considered for patients with grade-3 disease, cervical involvement, and high-risk histologic findings.[126] It has been shown that if pelvic lymphadenectomy is performed, a minimum of 11 nodes should be removed from multiple sites.[123] Retrospective analyses are, however, flawed because of elimination of patients from earlier-stage categories (i.e., stage migration) and exclusion of patients at increased surgical risk as a result of advanced age or concurrent morbidities (i.e., selection bias).

Although many U.S.-based gynecologic oncologists continue to advocate nodal staging in patients with low-risk disease despite level-one evidence, the data do not support the routine use of lymphadenectomy for patients with stage I endometrial carcinoma. Subsequent therapy in the ASTEC trial was not determined by the lymph node status found at time of surgery, and the trial therefore tested the therapeutic value of lymphadenectomy per se, not whether any subsequent treatment based on lymph node status could affect outcomes. In the Italian trial, the use of adjuvant therapy was only slightly and not significantly different between the study arms; the rates of patients receiving radiation therapy, chemotherapy, or both were 17%, 9%, and 6%, respectively, in the lymphadenectomy study arm and 25%, 6%, and 4%, respectively, in those who did not have lymphadenectomy. Ten of 59 patients received extended-field radiation therapy (EFRT) in the lymphadenectomy group versus 5 of 74 who did not have lymph nodes removed. There was, however, no difference in rates of total (12.8% versus 13.2%), intraperitoneal (3% versus 2.8%), or other relapses.

Initial results show the combined use of radiocolloid labeling and patent blue dye results in sentinel node detection rates of 82% to 94%, with identification of two or three sentinel nodes per patient.[51-53,131,132] The sentinel nodes were located in the obturator, external iliac, or paraaortic regions. Ultrastaging techniques are also used to identify micrometastases and isolated tumor cells in the sentinel nodes. The clinical significance of micrometastases and isolated tumor cells is however unknown, although other risk factors such as LVSI may be present, which can be used to direct further treatment.[52] Increasing surgical volume (and experience) has been shown to be associated with increased detection rates (77% versus 94% after at least 30 cases).[132] Additional larger studies are needed to further explore this concept, establish optimal techniques, and develop reliable accuracy data.[53]

Several investigators stressed that lymphadenectomy is not indicated in these patients with low-risk disease.[54,138,140] In some studies, vaginal brachytherapy was used.[140] The addition of brachytherapy to surgery may reduce vaginal relapse rates from between 2% and 5% to between 0% and 2% but without a survival difference and at the considerable procedural cost and the (albeit minimal) morbidity. In a randomized trial of vaginal brachytherapy versus observation among 645 patients with low-risk endometrial carcinoma, the rate of vaginal recurrences was 1.2% in the brachytherapy group versus 3.1% in the control group (difference not statistically significant, $p = 0.114$). The overall relapse rate and survival rate were similar.[141]

Salvage treatment with RT is available for the occasional patient with vaginal relapse alone or plus pelvic relapse. Depending on size and grade, 5-year and 10-year DFS in the range of 70% to 80% and OS of 50% to 70% are obtained (see the section on adjuvant therapy).[142-144] EBRT is not indicated for patients with low-risk endometrial cancer because their outcome will not be improved and EBRT may even contribute to decreased survival as a result of late toxicities and secondary tumors.[145,146]

Adjuvant Therapy: Stages I and II

Four randomized trials have been published that evaluated the role of pelvic EBRT in endometrial carcinoma.[88-90,147] They are summarized in Table 59-5.

The Norwegian trial, published in 1980, included 540 women with clinical stage I endometrial carcinoma. After hysterectomy and postoperative vaginal brachytherapy (60 Gy to the mucosal surface), patients were randomly assigned to additional pelvic irradiation (40 Gy in 2-Gy fractions, with a midline block after 20 Gy) or observation. Although additional pelvic irradiation reduced vaginal and pelvic relapse rates (2% at 5 years versus 7% in the control group), more distant metastases were found in the pelvic irradiation group (10% versus 5%), and survival was not improved (89% versus 91% at 5 years). An exploratory subset analysis identified the subgroup with grade-3 tumors and deep (>50%) myometrial invasion seemed to have improved local control and survival after pelvic irradiation (18% verus 27% cancer-related deaths), although, however, there were too few patients in this category to reach firm conclusions.[88] In a recent update of this series with a median of 20 years follow-up of these patients, treated with old techniques between 1968 and 1974, the absence of any OS benefit of EBRT in early-stage endometrial carcinoma was confirmed. In patients with low-risk disease younger than age 60 years, pelvic radiation even decreased survival and increased the risk of secondary cancer.[146]

In the first Postoperative Radiation Therapy in Endometrial Carcinoma (PORTEC) trial, 714 patients with stage I endometrial carcinoma, grade 1 or 2 with deep (>50%) myometrial invasion or grade 2 or 3 with superficial (≤50%) ("intermediate high-risk") invasion were randomized after TAH-BSO to receive pelvic EBRT (46 Gy in 2-Gy fractions) or no further treatment.[89] The 10-year locoregional relapse rates were 5% in the radiation therapy group and 14% in the control group ($p < 0.0001$). There was no significant survival difference between the treatment arms with 10-year OS of 66% (irradiation) and 73% (controls; $p = 0.09$).[149] Endometrial cancer-related death rates were 10% in the RT group and 8% in the control group ($p = 0.47$). The patients younger than age 60 years (both study arms) had a 5-year locoregional relapse rate of 3%, compared with 9% for patients 60 to 70 years old and 10% for those older than 70 years. Patients with grade-2 tumors with superficial invasion had a 5-year locoregional relapse rate of 5%. Risk criteria for relapse were grade 3, age older than 60 years, and outer 50% invasion. Long-term data confirmed the conclusions that radiotherapy should be avoided in those with low-risk disease and only be considered in patients with risk factors.[150]

An analysis of survival after relapse in the PORTEC trial showed 5-year postrelapse survival of 13% in the RT group and 48% in the control group ($p < 0.001$). High salvage rates after local (vaginal) relapse were found, with 5-year survival of 70% after vaginal relapse in the control group. Most (87%) of the 39 patients with isolated vaginal relapse could be treated

TABLE 59-5 Comparison of the Randomized Trials of Adjuvant Radiation Therapy for Stage I Endometrial Carcinoma

Trial (years)	No. Eligible Patients/Stage‡	Surgery	Randomization	Locoregional Recurrence	Survival	Severe Complications
Norwegian[88] (1968-1974)	540 Stg I	TAH-BSO	BT vs. BT plus pelvic RT	7% vs. 2% (5-yr); $p < 0.01$	89% vs. 91% (5-yr); p = NS	NA
PORTEC[89] (1990-1997)	714 Stg IB, G2-3 Stg IC, G1-2	TAH-BSO	NAT vs. pelvic RT	14% vs. 4% (5-yr); $p < 0.001$	85% vs. 81% (5-yr); $p = 0.31$	3% GI (5-yr, actuarial)
GOG-99[90] (1987-1995)	392 Stg IB, IC Stg IIA (occult)	TAH-BSO and lymphadenectomy	NAT vs. pelvic RT	12% vs. 3% (2-yr); $p < 0.01$	86% vs. 92% (4-yr); $p = 0.56$	8% GI (2-yr, crude)
ASTEC/EN5[147] (1996-2005)	905 Stg IAB, G3 Stg IC Stg I-IIA serous/clear cell	TAH-BSO ± lymphadenectomy	NAT* vs. pelvic RT*	7%† vs. 4% (5-yr); $p = 0.038$	84% vs. 84% (5-yr); $p = 0.98$	3% vs. 7%; G3-4 (crude)
PORTEC-2[148] (2002-2006)	427 Age > 60 and Stg IB grade 3 or IC grade 1-2	TAH-BSO	VBT vs. pelvic RT	2% vs 2% (5-yr); $p = 0.74$ NS	85% vs 80% (5-yr); $p = 0.57$	

BT, *Brachytherapy;* G, *grade;* GI, *gastrointestinal;* NA, *not available;* NAT, *no additional treatment;* RT, *radiation therapy;* Stg, *stage;* TAH-BSO, *total abdominal hysterectomy with bilateral salpingo-oophorectomy;* VBT, *vaginal brachytherapy;* yr, *year.*

**54% of patients in both arms of ASTEC/EN5 received vaginal brachytherapy.*

†53% of patients in the NAT arm had received BT; only isolated recurrence reported.

‡FIGO 1988.

with curative intent, usually with pelvic EBRT and brachytherapy (BT) and with surgery in some. A complete remission was obtained in 89%, and 77% remained in complete remission after further follow-up.[142] (It is unclear whether those with vaginal mucosal relapse benefit from the addition of EBRT, although this is common practice). In contrast, only 4 of 10 patients who were treated for pelvic relapse reached a complete remission, and the outcome after pelvic and distant relapse was poor, with only 6% and 11% of patients, respectively, surviving 5 years.

The GOG-99 trial included 392 evaluable patients with stage IB, IC, or IIA endometrial carcinoma of any histologic grade who were randomized after TAH-BSO and limited lymphadenectomy (confirmed node negative) to receive pelvic irradiation (50.4 Gy in 1.8-Gy fractions) or no additional treatment.[90] A high-intermediate risk group was defined based on similar prognostic factors identified in the PORTEC study: of age, histologic grade, myometrial invasion, and additionally the presence of LVSI. This group (33% of the study population) had a 2-year incidence of relapse of 27% in the no-additional-treatment arm in contrast to 6% for those without these risk factors (i.e., low-intermediate risk group [67% of patients]). RT resulted in similar hazard reductions for the high- and low-intermediate risk subgroups (58% and 54%, respectively), but in absolute terms the differences were greater for the patients with high-intermediate risk disease, with a reduction of 4-year cumulative relapse from 27% (in the group with no additional treatment) to 13% (those with irradiation). There was a small, although nonsignificant survival benefit: 4-year OS was 86% for the no-additional-treatment group and 92% for those who had RT. The 2-year estimated vaginal and pelvic failure rate was 12% in the no-additional-treatment group and 3% in the RT group, for a 58% hazard reduction by irradiation. These results are strikingly similar to those obtained in the PORTEC study without lymphadenectomy. However, the 4-year crude rate of severe complications in GOG-99 was 13% for patients who had received EBRT, compared to a 3% 5-year actuarial rate in the PORTEC trial, which underlines the increased risk of toxicity when combining extended surgery with lymph node dissection and pelvic RT.[90] Most notable was the rate of gastrointestinal (GI) toxicity in the GOG#99 trial; 8% grade-3 and grade-4 GI toxicity, including 6 (RT) compared with 1 (NAT) women with intestinal obstruction.

The multicenter randomized ASTEC/EN5 trial included 905 patients with stages I to IIA endometrial carcinoma with high-risk features (deep invasion or grade 3 with superficial invasion or serous histology), who were randomly allocated to EBRT or observation. Brachytherapy was permitted in both study arms, and 53% of the patients received vaginal brachytherapy (VBT). Again, there was no difference in OS (84% at 5 years in both groups).[147] The HR for isolated vaginal or pelvic RFS was 0.46 ($p = 0.02$), with 5-year cumulative incidence rates of 6.1% (observation only) versus 3.2% (RT). The relatively low rate of isolated vaginal or pelvic recurrence can probably be explained by the fact that 53% of the patients in the observation study arm received VBT. A meta-analysis of pooled data from the ASTEC/EN5, GOG-99, and PORTEC-1 trials reliably excluded an absolute survival benefit of pelvic EBRT of more than 3%.[147] This was confirmed in the updated Cochrane review and meta-analysis.[145]

An inevitable conclusion is drawn from these trials that (1) overall adjuvant pelvic EBRT for patients with stage I endometrial carcinoma provides a highly significant improvement in local control but offers no survival advantage. (2) A large proportion of patients with endometrial cancer have a favorable prognosis. These patients should be observed after TAH-BSO because use of EBRT in patients with low-risk disease could be detrimental for long-term survival and increase the risk of second cancers.[145,146,150] (3) RT is an effective salvage treatment for vaginal relapse in patients not previously irradiated.[142]

The data suggest that the use of postoperative RT should be limited to the group of patients at sufficiently high risk for locoregional relapse to accept the risk of treatment-associated morbidity to maximize initial local control and RFS. These data from randomized trials has resulted in a reduction of the use of pelvic EBRT and use of high-intermediate risk criteria to determine indications for RT. In the PORTEC study, patients with two of the three major risk factors (grade 3, age 60 or older, and outer 50% myometrial invasion) were found to have the highest absolute benefit from pelvic irradiation. The 10-year locoregional relapse rates in this high-intermediate risk category were 5% in the RT group and 20% in the control group.[149] In the GOG-99 trial, similar high-intermediate risk criteria were identified, with reduction of isolated 4-year local relapse in the high-intermediate risk group from 13% to 5%.[90] The risk criteria as defined in the PORTEC and GOG-99 trials and the relapse-risk reduction with radiation therapy in the high-risk groups are listed in Table 59-6.

Because most relapses occur in the vagina especially after extensive surgical staging, the use of VBT alone has been advocated. Vaginal control and complication rates for high-dose-rate (HDR) VBT are comparable to those of low-dose-rate (LDR) therapy.[151] Data from mostly retrospective studies that used VBT alone for stage I endometrial cancer have shown the 5-year risk of vaginal relapse to be 0% to 7%.[151-155] Pelvic and distant failure rates, however, remain similar to those of patients treated with surgery alone, which is the reason that

TABLE 59-6 Comparison of the Risk Groups in the PORTEC and GOG-99 Trials and Risk Reduction with Radiation Therapy

	Risk Groups and Relapse Rates	
Risk Levels	**PORTEC[89]**	**GOG-99[90]**
Risk factors		
Age	≤60 vs. >60	≤50 vs. ≤70 vs. >70
Grade	Grade 1-2 vs. 3	Grade 1 vs. 2-3
Deep invasion	≤50% vs. >50%	≤66% vs. >66%
Lymphovascular space invasion		Absent vs. present
High-intermediate risk group	At least two of the three factors	Any age and three factors Age ≥ 50 and two factors Age ≥ 70 and one factor
Results for the high-intermediate risk group	10-yr locoregional relapse RT: 5% NAT: 23% Rel. risk: 0.22	4-yr relapse (any) RT: 13% NAT: 27% Rel. risk: 0.48
	With GOG high-intermediate risk criteria RT: 8% NAT: 22% Rel. risk: 0.36	4-yr isolated local relapse RT: 5% NAT: 13% Rel. risk: 0.38

GOG, *Gynecologic Oncology Group;* NAT, *no additional treatment;* PORTEC, *Postoperative Radiation Therapy in Endometrial Carcinoma;* Rel. risk, *relapse with RT compared with NAT;* RT, *radiation therapy;* yr, *year.*

most studies included only or mainly patients with low-risk disease (i.e., grade-1 to grade-2 disease with no or superficial invasion). Local control rates of 98% and higher were obtained with modest doses (e.g., 30 Gy to 35 Gy LDR to the surface or 21 Gy HDR to 5-mm depth in three fractions). The use of higher doses did not further increase local control, but complication rates were higher. Several studies of HDR after surgical staging included patients with high-risk stage I or II disease. Vaginal control rates were 98% to 100%. Subsequent pelvic and distant relapses were found mainly in the patients with stage I or II with high-risk features.[153-155]

The results of the randomized trials for intermediate-risk endometrial carcinoma suggested that, in view of the absence of survival benefit with EBRT and of the fact that most recurrences were located in the vagina, VBT alone for patients with high-intermediate risk features might suffice for local control with fewer side effects than EBRT and better quality of life. This was the rationale for the randomized PORTEC-2 trial (2002 to 2006), which compared EBRT and VBT for efficacy and health-related quality of life. In this trial, 427 patients with stage FIGO 1988 stages I to IIA endometrial carcinoma with high-intermediate risk features (i.e., age of at least 60 years, grade-1 or grade-2 tumors with outer 50% invasion or grade 3 with inner 50% invasion) were randomly assigned after surgery (TAH-BSO without lymphadenectomy) to EBRT (n = 214) or VBT (n = 213). Quality of life was significantly better in the patients in the VBT arm. Patients who had brachytherapy reported better social functioning ($p < 0.002$) and lower symptom scores for diarrhea, fecal leakage, the need to stay close to the toilet, and limitation in daily activities because of bowel symptoms ($p < 0.001$). The data for patients in the brachytherapy arm remained at the level of population controls. At baseline, 15% of patients were sexually active; this increased significantly to 39% during the first year ($p < 0.001$). Sexual functioning and symptoms did not differ between the treatment arms but were somewhat lower than for age-matched population controls, probably reflecting the impact of gynecological cancer diagnosis and treatment.[156,157] Final results of the PORTEC-2 trial confirmed the efficacy of VBT. At median follow-up of 45 months, estimated 5-year rates of vaginal recurrence were 1.8% for VBT and 1.6% for EBRT (p = 0.74). Five-year rates of locoregional relapse (vaginal recurrence or pelvic recurrence) were 5.1% and 2.1% (p = 0.17). Only 1.5% versus 0.5% (p = 0.30) presented with isolated pelvic recurrence; other pelvic recurrences were part of widespread disease relapse, whereas rates of distant metastases were similar (8.3 versus 5.7%, p = 0.46). There were no differences in OS (84.8% versus 79.6%, p = 0.57) and DFS (82.7% versus 78.1%, p = 0.74). Rates of grade-1 to grade-2 GI toxicity were significantly lower in the VBT group.[148]

In a Swedish randomized trial VBT alone was compared to combined EBRT and VBT in 527 patients with (high-) intermediate-risk disease. Five-year locoregional relapse rates were 1.5% after EBRT plus VBT and 5% after VBT alone (p = 0.013), whereas 5-year OS was 89% and 90% (p = 0.548). The authors concluded that such combined EBRT with brachytherapy boost should be reserved for high-risk cases.[158]

In view of the efficacy of VBT with few side effects and better quality of life than EBRT, VBT alone has internationally become the standard adjuvant treatment for patients with high-intermediate risk disease, both with and without lymphadenectomy. Controversy remains, however, as to the relative benefits of VBT compared with observation when disease recurrence is rare and salvage of vaginal recurrence is high.

In the absence of a survival benefit for RT, some groups have decided to omit any radiotherapy or brachytherapy in endometrial cancer.[159,160] In a population review from Denmark of treatment outcomes of 1166 patients with endometrial carcinoma the consequences of the decision to omit RT for patients with stage I, low-risk (grade 1 or 2 with <50% invasion) and intermediate-risk (grade 1 or 2 with >50% invasion, or grade 3 with <50% invasion) endometrial cancer were evaluated. After 14 years, 6.3% of patients with low-risk, 22% of those with intermediate-risk, and 32% of patients with high-risk disease had relapsed. High-intermediate risk was, in the absence of information on LVSI, defined as either age older than 50, grade 2 and more than two thirds myometrial invasion, or age older than 70, grade 1, and more than two thirds invasion. Patients with such high-intermediate risk features had 25.8% relapse, of which 11.4% were vaginal relapse and 6.1% were pelvic relapse.[144] This should be compared to 1.8% and 3.8%, respectively, after 5 years in the vaginal brachytherapy arm of the PORTEC-2 trial.[148] The Danish population review confirmed that most recurrences in patients with low- and intermediate-risk disease were locoregional, whereas distant relapses were prominent in high-risk disease. Treatment of vaginal recurrence in patients with low- and intermediate-risk disease was effective. The survival rates had not changed compared to previous Danish population-based data.[144] A Swedish randomized trial of VBT compared with observation in 645 patients with low-risk disease showed low locoregional (2.6%) and distant (1.4%) recurrence rates, with 1% versus 3% locoregional recurrence for brachytherapy and for control. This trial again confirmed that patients with low-risk disease do not benefit and should not have additional treatment after surgery. Adjuvant treatment should be tailored to prognostic factors.[141]

In an attempt to resolve the controversy as to whether adjuvant VBT should be given to all patients with high-intermediate risk features compared with only the 15% patients with local relapse, albeit more intensively with EBRT and VBT, the randomized PORTEC-4 trial has been initiated and is currently ongoing.[161] Omitting adjuvant VBT in patients with stage I, high-intermediate-risk features spares 85% of patients the cost (both in terms of healthcare costs and burden of travel and so on for the patient) and (minor) morbidity of VBT. However, for the 15% of patients who relapse, the toxicity, intensity, and psychological burden of full curative-intent treatment for relapse are much greater than simple adjuvant therapy with VBT alone. First results of a patient preference study showed that patients tend to prefer adjuvant VBT over a watchful waiting policy at low risk of relapse.[162] Several groups have published nomograms to help establish individual patient risks, which can be helpful in shared decision making.[163-165]

FIGO 2009 Stage IB, Grade-3 Disease (High Risk, Early Stage)

Clinical stage I endometrial carcinoma, grade 3 with outer 50% myometrial invasion is usually regarded as a separate group among patients with stage I disease because this subgroup is at increased risk for pelvic relapse and distant metastases and has lower survival rates.[91,166,167] In an analysis of 220 patients with FIGO 1988 stage IC endometrial cancer who had surgical staging including pelvic and paraaortic lymphadenectomy, 99 (45%) patients treated with RT (pelvic EBRT or VBT alone; selection criteria not specified) were compared with 121 (55%) who did not receive RT. The 5-year DFS were significantly lower for the observation group (75% versus 93%), but OS were similar (90% versus 92%). Among the 47 patients with grade 3 and outer 50% myometrial invasion, 5-year DFS were 90% after RT and 59% for the observation group.[166] During the inclusion period of the PORTEC-1 trial, 99 evaluable patients with grade-3 tumors with deep myometrial invasion but without staging were registered and received pelvic EBRT. The 5-year actuarial vaginal and pelvic relapse rate was 13% in this

group, significantly higher than for other patients with stage I disease, who had excellent pelvic control after RT (97% to 99%). The 5-year rates of distant metastases were 20% for grade-3 disease with less than 50% invasion and 31% for grade-3 disease with more than 50% invasion, compared with 3% to 8% for grade-1 and grade-2 diseases. OS at 5 years was 58% for those with grade-3 disease and outer 50% invasion and 74% for those with grade-3 disease and inner 50% invasion compared with 83% to 86% for the patients with grade-1 and grade-2 tumors ($p < 0.001$).[91] In multivariate analyses, grade-3 disease was the most important adverse prognostic factor, with HRs for any relapse and for endometrial carcinoma-related death of 5.4 ($p = 0.0001$) and 5.5 ($p = 0.0004$), respectively.

Whether surgical staging has been performed or not, pelvic irradiation is usually recommended for grade-3 tumors with deep myometrial invasion.[168,169] An increasing number of authors, however, recommend VBT alone for patients with FIGO 2009 stage IB grade-3 disease who underwent surgery with full lymphadenectomy.[155] It is unclear how much reduction in relapse risk or change in relapse sites is present if lymph nodes are negative, but high-risk factors are present in the uterus. In view of the small numbers, with patients with grade-3 disease always being a small minority in clinical trials, firm data are lacking. In view of the increased risk of abdominal and distant relapse and cancer-related death, both adjuvant chemotherapy and combined chemotherapy and radiotherapy are being investigated by several groups (see section on adjuvant chemotherapy).

Stage II Disease

Stage II endometrial carcinoma includes patients with minimal microscopic involvement of the cervical stroma (often called stage II occult) and those with macroscopic gross cervical involvement, even though these two groups have different prognoses. Cervical involvement has been associated with a poorer prognosis because of the increased risk of LVSI and pelvic lymph node metastases.[73] Patients with minimal extension to the endocervix used to be in stage IIA; however, in the FIGO 2009 staging endocervical glandular involvement has been included in stage I because outcomes are identical to those of patients with stage I disease. Their treatment should be the same as for stage I disease. Patients with FIGO 2009 stage II (former stage IIB) disease have a less favorable outcome.[170]

Patients with occult stage II disease have already undergone TAH-BSO or TLH-BSO. Pelvic EBRT often with vaginal cuff brachytherapy boost is usually recommended for stage II disease treated with TAH-BSO because cervical involvement increases the risk of parametrial lymphatic disease.[171] Its contribution, however, to better outcomes is unclear. For stage I disease, the addition of VBT does not significantly add to local control when pelvic EBRT is used, but it does increase toxicity.[172,173] For occult stage II disease, because a vaginal cuff is usually not taken at TAH-BSO, most investigators continue to recommend a cuff boost. Two retrospective analyses, however, did not find any difference in recurrence with or without brachytherapy.[170,174] Reported adverse prognostic factors for stage II disease are grade 3, lymphovascular space invasion, and advanced age.[175,176] VBT alone has been advocated for stage II disease after full surgical staging and in absence of risk factors such as deep invasion, high grade, and LVSI. This analysis is flawed, however, because 30% of patients with FIGO 1988 stage IIA disease would now not be considered stage I.[176]

Patients with macroscopic gross stage II disease should be considered either for initial radical hysterectomy, if surgically suitable, with adjuvant pelvic irradiation depending on the surgical findings (e.g., parametrial or vaginal extension, lymph node involvement, surgical margin involvement) or for primary radiation with "completion hysterectomy." Retrospective studies have shown that radical hysterectomy alone for macroscopic stage II endometrial cancer has local control and survival rates similar to those obtained with TAH-BSO plus risk-based radiotherapy.[119,177-179] Some studies reported improved survival after radical hysterectomy compared with TAH-BSO alone, but the selection criteria for radical hysterectomy and for RT were unclear and might have influenced the results.[177,178,180] Pelvic irradiation improved local control for patients with macroscopic stage II disease treated with TAH-BSO.[175,177] A SEER analysis of 1577 women with stage II endometrioid type endometrial carcinoma included 1198 women who underwent simple hysterectomy (76%) and 379 who underwent radical hysterectomy (24%). Radical hysterectomy had no significant effect on survival ((HR, 0.86; 95% CI, 0.61 to 1.23). Patients who did not receive radiation were 48% (HR, 1.48; 95% CI, 1.14 to 1.93) more likely to die than those who underwent adjuvant RT. The survival benefit from irradiation was most pronounced in women who underwent radical hysterectomy.[181] Recent data from the SEER registry, however, show that selection factors in such analyses may determine outcome.[182] Although the selection criteria are unclear, patients with high-risk stage II tumors seem to benefit from RT, even after radical hysterectomy. An overview of the results for stage II disease is presented in Table 59-7.

Patients with macroscopic stage II tumors with bulky cervical extension, precluding radical hysterectomy with adequate margins, should be treated with preoperative pelvic EBRT, followed by hysterectomy if feasible. In case of insufficient tumor regression after pelvic irradiation, intrauterine brachytherapy should be added although special applicators are to be used as it is difficult to achieve a satisfactory dose distribution including the whole uterine body with a single tandem. Depending on the regression and clinical situation after brachytherapy, completion hysterectomy should again be considered, because the excess of failures when primary radiation is used instead of surgery occurs often in the enlarged uterine body, where the radiation dose may be suboptimal. The risk of distant metastases, however, is increased and determines final outcomes.[183]

Unfavorable Histologic Types

Serous and clear cell cancers, approximately 10% and 5% of endometrial carcinomas, respectively, have been identified as histologic types with an inferior prognosis because of aggressive growth and spread patterns with frequent diffuse intraabdominal and distant dissemination. These histologic types often present with advanced disease (46% stage II to IV, compared with 21% for all endometrial cancers). Different treatment approaches (e.g., extended surgery, surgery with whole-abdomen irradiation, surgery with adjuvant chemotherapy) have been suggested.[184,185] Several studies have shown that serous and clear cell carcinomas have similar relapse and survival rates compared with grade-3 endometrioid carcinomas.[39,40,186,187] In an analysis of 5694 surgically staged endometrial cancers in the 25th annual report of FIGO, 3996 were stage I. Serous and clear cell cancers represented 5.2% of stage I cancers, and grade-3 carcinomas accounted for 8.1%. Five-year survival rates were 72% and 81%, respectively, for serous and clear cell cancers, compared with 76% for grade-3 disease. Postoperative RT was associated with an about 8% improvement in survival for these histologic types (76% versus 68% for grade 3; 74% versus 66% for serous cancers; and 83% versus 77% for clear cell carcinoma), but these differences were not significant.[40] A retrospective analysis of treatment results of 119 patients with grade-3 endometrioid, 211 with serous and 40 with clear cell carcinomas showed that although clinicopathological risk factors varied among the subtypes, survival did not differ significantly. The 5-year CSS rates in stages

TABLE 59-7 Outcome for Patients with Stage II Endometrial Carcinoma

Study	Year	No. Patients	Stage	Treatment	5-Yr Survival Rate	Remarks
Wright[181]	2009	1577 SEER	II	1198 SH 379 RH (24%)	RH no better than SH RT better than no RT	
Cannon[176]	2009	71	IIA: 23 IIB: 48	50 EBRT + VBT 1 EBRT 20 VBT	OS: 82% DFS: 82%	LVSI and depth of invasion risk factors for recurrence
Cozad[174]	2008	86	II	34 EBRT 33 EBRT + VBT 5 VBT, 14 Obs	OS: 77% CSS: 82.8%	No difference EBRT with or without VBT
Jobsen[170]	2008	142	IIA: 59 IIB: 83	69 EBRT 71 EBRT + VBT 2 VBT	DFS: 77% IIA: 81% IIB: 75%	LR 5% (IIA) vs. 11% (IIB) Grade 3 and LVSI prognostic factors
Cohn[180]	2007	162	IIA: 84 IIB: 78	SH: 76% RH: 24% 48% RT	OS: 88% DFS: 81%	RH better than SH: 94% vs. 76% DFS; $p = 0.05$ RT no survival impact
Ayhan[118]	2004	48	II	21 RH alone 22 SH + EBRT 5 SH + VBT	OS: 86% SH: 83% RH: 90%	Recurrence: 17%
Sartori[119]	2001	203	IIA: 111 IIB: 92	135 SH 68 RH IIA: 66 EBRT IIB: 67 EBRT	IIA: 86% IIB: 74% SH: 79% RH: 94%	Recurrence: 14% RT: 11% No RT: 19%
Mariani[177]	2001	82	II, III II: 57	22 SH 35 RH 38 EBRT	DRS:73% SH: 68% RH: 76% Stage III: 47%	RH and RT both produced fewer relapses
Eltabbakh[171]	1999	48	II	11 RH alone 20 SH + EBRT + VBT 13 SH + EBRT 4 SH + VBT	OS: 92% IIA: 93% IIB: 91% No difference between RH vs. SH + RT	6.3%

CSS, *Cause-specific survival;* DFS, *disease-free survival;* DRS, *disease-related survival;* EBRT, *external beam radiation therapy;* LR, *local recurrence;* LVSI, *lymphovascular space invasion;* OS, *overall survival;* RH, *radical hysterectomy;* RT, *radiation therapy;* SH, *simple hysterectomy (i.e., total abdominal hysterectomy with bilateral salpingo-oophorectomy);* surg, *surgery;* VBT, *vaginal brachytherapy;* yr, *year.*

I to II were 85%, 90%, and 84%, respectively, with LVSI being the only independent prognostic factor. For stage III, 5-year OS rates were 49% and 40%, respectively, for grade-3 endometrioid and serous cancers; 18% and 41%, respectively, of these cancers had received adjuvant chemotherapy only, 9% and 6%, respectively, EBRT only, and 7% in each group chemotherapy and EBRT. Age, LVSI, unresectable nodal disease, and regional radiotherapy were prognostic factors, whereas chemotherapy alone had no significant impact on outcome.[186] In a SEER analysis of 4180 women with serous (1473), clear cell (391), and grade-3 endometrioid (2316) cancers, these unfavorable histologic types accounted for 10%, 3%, and 15% of all endometrial cancers, but for 39%, 8%, and 27% of the cancer deaths, respectively. The 5-year DSS were 55, 68, and 77%, respectively ($p < 0.0001$), showing serous cancers to have poorer outcomes.[188] The question is whether lack of pathology review and of a uniform definition of serous cancer (any percentage of serous component, or at least 10% or 25% within otherwise endometrioid cancers) influenced the results.

Generally, full surgical staging (TAH-BSO plus lymph node dissection [LND] and omentectomy and peritoneal biopsies) is recommended for serous and clear cell cancers to confirm stages I to II disease extent, and complete debulking of visible tumor in more advanced disease.[189,190] In case of limited volume surgical stage IA disease, VBT alone has been suggested to be safe and effective adjuvant treatment.[191,192] Single-center analyses of outcomes of patients with early stage serous[193] or clear cell cancers[191] suggested better survival with pelvic radiation therapy for patients with additional risk factors. Some authors have explored the addition of adjuvant chemotherapy to VBT for early stage serous cancers, but the impact on survival remains unclear.[186,194,195] Initial results from the GOG 249 trial, which compared pelvic EBRT to three cycles of adjuvant carboplatin and paclitaxel plus VBRT for early-stage high-intermediate and high-risk disease, were presented in 2014.[196] Similar 2-year RFS and OS rates were found, with no evidence of superiority for adjuvant chemotherapy in this trial population, which included 15% serous and 5% clear cell cancers.

For clear cell cancers, evidence for sensitivity to endometrial or ovarian type chemotherapy is lacking.[190] However, the number of patients with advanced stage clear cell disease is exceedingly small, so firm conclusions cannot be made.

Current conclusions from these analyses are that serous and clear cell cancers should be treated similarly to grade-3 carcinomas, but ideally based on their specific cell type. Adjuvant treatment using radiation therapy should be considered, with concurrent or sequential systemic therapy preferably within clinical trials.

Adjuvant Hormonal Therapy

Adjuvant hormonal therapy for endometrial cancer has been extensively studied in view of the high incidence of progesterone receptor positivity and the 18% to 34% response rates

It has been suggested that clear cell cancers are related more closely to clear cell cancers of other organs than to other endometrial cancers and have gene expression profiles similar to ovarian or renal clear cell cancers. Inaugural studies based on cell type rather than tissue of origin for clear cell cancer are under way.

to progesterone therapy seen in metastatic grade-1 or grade-2 disease. However, a meta-analysis of six randomized trials with a total of 3544 patients did not show a survival benefit for adjuvant progesterone treatment.[197] A randomized trial enrolling 1148 patients showed a higher intercurrent death rate in the progesterone group owing to an increased risk of thromboembolic disease.[198] Among the 461 high-risk patients, a tendency toward fewer cancer-related deaths in the progesterone group was observed, but OS was unchanged. The COSA-NZ-UK trial showed a decrease in the rate of relapse with 3 years of adjuvant progestins, but it did not show a difference in DSS.[199] In general, tumors showing high ER/PR receptor expression rates are usually low-risk, grade-1 tumors and have higher response rates to progesterone therapy when recurrent.[200]

Adjuvant Chemotherapy

Optimal therapy for advanced and high-risk nonendometrioid cancers has not been defined. Three randomized trials have evaluated the efficacy of adjuvant chemotherapy as compared with radiation therapy (Table 59-8).

The results of GOG-122, a randomized trial comparing whole-abdominal irradiation (WAI) to combination doxorubicin-cisplatin chemotherapy in advanced endometrial carcinoma (i.e., stages III to IV; up to 2-cm residual disease after surgery allowed) showed combination chemotherapy to improve PFS and OS, with a predicted difference in DFS of 12% at 5 years (50% versus 38%) and 5-year OS difference of 13% (55% versus 42%).[201] The OS for patients who received chemotherapy was substantially higher than their RFS, suggesting that salvage treatment, often by RT, contributed importantly to their survival.[169] Relapses remained common in both arms (55%) and longer follow-up seemed to suggest delay rather than eradication of metastases. Twenty-five percent of initial recurrences on the WAI study arm and 35% on the chemotherapy arm were limited to the pelvis; 30% and 28%, respectively, of recurrences were intraabdominal.

The chemotherapy used in GOG-122 was the most aggressive of the regimens in adjuvant trials to date, with seven cycles of doxorubicin 60 mg/m^2 plus cisplatin 50 mg/m^2 every 3 weeks followed by an eighth cycle of single-agent cisplatin. Most have abandoned this regimen now in favor of carboplatin and paclitaxel.

The Japanese multicenter randomized JGOG-2033 trial compared whole-pelvic EBRT (at least 40 Gy) with three or more cycles every 4 weeks of cyclophosphamide (333 mg/m^2), doxorubicin (40 mg/m^2), and cisplatin (50 mg/m^2) (CAP) chemotherapy in 385 evaluable patients with FIGO 1988 stages IC to IIIC endometrioid adenocarcinoma (intermediate risk; 60% stage IC, median age 59; 55% grade 1). At a median follow-up of 5 years, no differences in PFS (whole-pelvis RT 83.5% versus CAP 81.8%) and OS (85.3% versus 86.7%) were seen. Relapse rates were similar: 15.5% versus 17.2% of the patients had a relapse, with 6.7% and 7.3% being pelvic and 13.5% and 16.1% extrapelvic, respectively.[202]

An Italian randomized trial used a design similar to that of the JGOG trial but in a somewhat higher-risk group of patients.[203] The Italian study compared whole-pelvis irradiation (45 Gy to 50 Gy) with five cycles every 4 weeks of cyclophosphamide (600 mg/m^2), doxorubicin (45 mg/m^2), and cisplatin (50 mg/m^2) chemotherapy and included 345 evaluable patients with stages IC to IIIC endometrioid adenocarcinoma. In this trial, most patients had stage III disease (64% stage III, 36% stage IC to II, grade 3). After a median follow-up of 95.5 months there were no significant differences in PFS and OS, with 5-year OS of 69 (EBRT) versus 66% (CAP regimen) and 5-year PFS of 63% versus 63%. RT appeared to delay pelvic relapses and chemotherapy appeared to delay distant metastases (both nonsignificant trends).[203]

Where pelvic radiation has been omitted, increased pelvic relapse rates have been reported. A retrospective series used adjuvant chemotherapy alone in patients with high-risk or advanced-stage endometrial carcinoma.[204] Of the 67% who relapsed, 40% had pelvic recurrence and 56% had distant relapse. The 3-year pelvic failure rate was 47%, and in 31% the pelvis was the first or only site of relapse.

Because these data support the use of pelvic RT in patients with high-risk and advanced-stage disease undergoing adjuvant chemotherapy, the use of combined chemoradiation has been explored (Table 59-9). Initial pilot studies had indicated combined therapy to be tolerable.[208] The first early randomized trial, using single-agent doxorubicin after completion of radiotherapy, did not show any benefit.[205] This trial, with only 181 patients, was underpowered, and 25 of the 92 patients assigned to doxorubicin received no chemotherapy. A small Finnish trial randomly assigned 156 patients to pelvic radiation therapy alone (split-course irradiation, 56 Gy in 2-Gy fractions with 3-week interval after 28 Gy) versus pelvic EBRT plus three cycles of cisplatin 50 mg/m^2, epirubicin 60 mg/m^2, and cyclophosphamide 500 mg/m^2.[206] The first cycle of chemotherapy was given 1 to 2 weeks after surgery, the second during the pause in RT, and the last within 2 weeks after completion of the second course of RT. Women with FIGO 1988 stages IA/B grade-3 and IC to IIIA grade-1 to grade-3

TABLE 59-8 Adjuvant Trials which Tested Radiotherapy versus Chemotherapy

Trial	Year	No. Patients/Stage (FIGO 2009)	Randomization	LR	PFS (5-yr)	OS (5-yr)
GOG-122[201]	2006	396 III IV optimal*	WAI vs. AP	13%† vs. 18%	38% vs. 50%‡; $p < 0.01$	42% vs. 55%‡; $p < 0.01$
JGOG[202]	2008	385 I-III with >50% MI	Pelvic RT vs. CAP	7%§ vs. 7%	84% vs. 82%; p = NS	85% vs. 87%; p = NS
Italian[203]	2006	345 IB grade 3 II grade 3 + >50% MI III	Pelvic RT vs. CAP	12%§ vs. 16%	63% vs. 63%; p = NS	69% vs. 66%; p = NS

AP, *Doxorubicin (Adriamycin)/cisplatin;* CAP, *cyclophosphamide/doxorubicin (Adriamycin)/cisplatin;* LR, *locoregional recurrence;* MI, *myometrial invasion;* OS, *overall survival;* PFS, *progression-free survival;* WAI, *whole-abdomen irradiation;* yr, *year.*

**Up to 2 cm residual disease after surgery.*

†*Isolated LR as initial site of recurrence.*

‡*Predicted 5-year PFS and OS rates, adjusted for stage.*

§*Includes LR as component of distant failure.*

Strangely there appeared to be no significant differences in relapse rates in the pelvis or abdomen in GOG-122, although chemotherapy appeared to somewhat reduce distant metastases. Benefit from chemotherapy was observed for both those with stage III and those with stage IV disease, although a significant difference was only obtained after adjusted analyses. Adverse effects were substantial, especially in the doxorubicin/cisplatin study arm, although current antiemetic therapy and use of granulocyte colony-stimulating factors might have mitigated many of the observed toxicities. Because those with residual intraabdominal disease were included, this trial did not study true adjuvant treatment for microscopic disease; it is debated whether the radiation dose used would be appropriate for macroscopic residual disease.

In a post hoc subset analysis of JGOG-2033 the subgroup of high- to intermediate-risk cases (stage IC > 70 year, IC grade 3, stage II or stage IIIA [cytology], $n = 120$) was suggested to have a survival benefit for CAP, whereas no PFS or OS difference was found among 75 high-risk cases (stages IIIA to IIIC). Grade-3 to grade-4 toxicity rates were 1.6% (whole-pelvis irradiation) and 4.7% (CAP), $p = 0.08$. Bowel obstructions were the main toxicity in the group undergoing whole-pelvis irradiation, and myelosuppression was the most common toxicity in the chemotherapy group.[202]

TABLE 59-9 Adjuvant Trials That Tested Radiotherapy versus Combined Modality Therapy

Trial	Year	No. Patients/Stage (FIGO 2009)	Randomization	LR	PFS	OS (5-yr)
GOG-34[205]	1990	181 Clinical I/occult II 31% node+	Pelvic RT vs. RT + doxorubicin*	NA	NA	No difference between study arms
Finland[206]	2008	156 IA grade 3 IB-IIIA grade 1-3	Pelvic RT† vs. RT + CEP × 3	4%‡ vs. 2%	18 mo. vs. 25 mo. DFS; p = NS	85% vs. 82% DSS; p = NS
NSGO/EORTC[207]	2010	382 I, II, IIIA IIIC with high-risk factors	Pelvic RT vs. RT + CT (various regimens)	NA	72% vs. 79%; p = 0.04	76% vs. 83%; p = 0.10
Pooled results with ILIADE-III trial[207]	2010	534	Pelvic RT vs. RT + CT (various regimens)	NA	69% vs. 78%; p = 0.009	75% vs. 82%; p = 0.07

CEP, *Cyclophosphamide/epirubicin/cisplatin;* CT, *chemotherapy;* DFS, *disease-free survival;* DSS, *disease-specific survival;* LR, *local recurrence;* NS, *not statistically significant;* OS, *overall survival;* PFS, *progression-free survival;* RT, *radiotherapy;* yr, *year.*

**25 of 92 patients assigned to doxorubicin received no chemotherapy.*

†*Split-course RT 56 Gy with 3 weeks split after 28 Gy.*

‡*Isolated LR as initial site of relapse.*

cancers were enrolled; the overall prognosis of the group was better than anticipated with 4-year DSS of 84.7% and 82.1%, respectively, in the group with RT alone versus combined chemoradiation groups. There were no differences in the rates of local recurrence.

The Radiation Therapy Oncology Group (RTOG) has reported a nonrandomized Phase II trial (Phase IIR) of concurrent pelvic radiotherapy (45 Gy in 1.8-Gy fractions and a brachytherapy boost) and cisplatin (two cycles of 50 mg/m^2 on days 1 and 28), followed by four cycles of cisplatin (50 mg/m^2) and paclitaxel (175 mg/m^2 as a 24-hour infusion) every 28 days after RT for high-risk or advanced-stage endometrial carcinoma.[209] A total of 46 patients were included: 44 were evaluable, 15 had stages I to II disease with high-risk features and 29 (66%) had stage III disease. Surgery consisted of TAH-BSO with or without additional surgical staging. The 4-year rates of pelvic, regional, and distant relapse were 2%, 2%, and 19%, respectively. There were no relapses among patients with stages IC and II disease, suggesting possible additive effects of chemotherapy and irradiation.

Sequential chemotherapy and radiotherapy (either sequence) were investigated and compared to pelvic EBRT alone in the randomized NSGO-EC-9501/European Organization for Research and Treatment of Cancer (EORTC)-55991 trial, which included 382 patients with stages I to III disease (85% stage I) who had risk factors for relapse (one or more of grade-3 tumor, deep myometrial invasion, nondiploid DNA, or serous/clear cell/anaplastic histology). Chemotherapy regimen and timing of administration was not standardized and could be doxorubicin/cisplatin, paclitaxel/doxorubicin/cisplatin, paclitaxel/platinum, or paclitaxel/cisplatin/epirubicin. First results showed a 7% improvement in PFS in the chemotherapy arm (at 5 years, 79% versus 72%, p = 0.03) and a nonsignificant 8% increase in OS (82% versus 74% p = 0.08).[210] Final results of this trial were published in a pooled data analysis with the Italian MaNGO ILIADE-III trial, which had been closed prematurely and had accrued 157 patients, with stage II (30%) and stage III disease (65%), for a combined total of 534 evaluable patients. Pooled results were similar, with a statistically significant difference in 5-year PFS favoring the combined arm (78% versus 69%, HR 0.63, p = 0.009), but only a trend for improved 5-year OS (82% versus 75%, HR 0.69, p = 0.07).[207] Interestingly, for patients with serous and clear cell tumors, although they were few in number (n = 140), there was no evidence of benefit from adjuvant chemotherapy (HR for PFS 0.83, p = 0.59 and for OS 0.94, p = 88).

Since these first reports of possible efficacy of adjuvant chemotherapy, three trials (two recently closed for completed accrual, and one with preliminary data presented) have followed that further explore the relative contributions of concurrent chemoradiation, radiation, or adjuvant chemotherapy. As noted previously, in GOG 249, similar 2-year RFS and OS rates were found, with no evidence for superiority of adjuvant chemotherapy in this trial population, which included 15% serous and 5% clear cell cancers.[196] All trials are better powered than their predecessors and should help resolve many of the uncertainties regarding which patients may benefit from chemotherapy as well as the role of radiotherapy (eTable 59-1).

Although adjuvant chemotherapy for women with serous carcinomas is widely practiced and systemic therapy is rational in view of the propensity for metastases even with minimal endometrial disease, its benefits remain unproven in the randomized trials.[201,207,213] Despite similar response rates (approximately 40%) to doxorubicin/cisplatin or doxorubicin/cisplatin/paclitaxel (42%) chemotherapy for endometrioid, serous and clear cell cancers, the subset analyses of GOG 122 and NSGO–EORTC adjuvant trials did not show benefit.[201,207]

LOCALLY ADVANCED DISEASE AND PALLIATION

Locally Advanced Disease: Stages III and IV

The FIGO stage III category includes patients with a wide variation in tumor volume and local extension and with a wide range of survival rates. In the FIGO 2009 revised staging system, positive peritoneal cytology as an isolated finding has been removed from stage IIIA because data have shown that positive cytology as a sole adverse factor has a risk profile similar to stage I disease.[214,215] To best assess treatment, stage III disease must be evaluated as several different entities with different disease extents rather than as a single stage.

Most patients with stage III endometrial carcinoma in retrospective analyses have been treated with adjuvant pelvic irradiation.[216,217] In view of the high rate of abdominal relapse, the use of whole abdominal irradiation (WAI) has been investigated, and several studies have demonstrated favorable results with this modality.[218] However, because of the toxicity and limited efficacy of WAI and the risk of distant metastases, adjuvant chemotherapy has been studied. The results of GOG-122,[201] a randomized trial comparing WAI with doxorubicin-cisplatin chemotherapy in advanced (stages III to

The protocol completion rate in the RTOG Phase IIR trial was 98%. During the adjuvant phase, 35 of the 44 patients received all four cycles. Acute toxicities during chemoradiation were grade 3 in 27% and grade 4 in 2%. During adjuvant chemotherapy, 21% grade-3 and 62% grade-4 toxicity was observed, with severe toxicity being primarily hematologic. Late toxicity was grade 3 in 16% and grade 4 in 5%. Four-year DFS and OS were 81% and 85% for the whole group and 72% and 77% for patients with stage III disease.

Women with early-stage serous carcinomas were eligible for both the PORTEC-3 and GOG-249 studies. Hopefully accrual of these subsets will be adequate to show if the benefit of adjuvant chemotherapy is different between endometrioid and serous cancers.

The ongoing ENGOT-EN2-DGCG trial investigates the role of adjuvant chemotherapy vs no adjuvant treatment (vaginal brachytherapy permitted in both arms) for early stage, high-risk, node negative disease. Target accrual is 678 patients.

eTABLE 59-1 Adjuvant Trials Testing Radiotherapy versus Combined Modality

Trial	Planned No.	Stages (FIGO 2009)	Randomization
PORTEC-3[211]	670 Completed accrual	IA grade 3 LVSI+ IB grade 3 II, IIIA, IIIC I-III serous/clear cell	Pelvic RT vs. Cisplatin × 2/pelvic RT→paclitaxel + carboplatin × 4
GOG-249[196]	562 First results presented	I with HIR features* II occult I-II serous/clear cell	Pelvic RT† vs. VBT→paclitaxel + carboplatin × 3
GOG-258[212]	804 Completed accrual	III-IVA	Cisplatin × 2/pelvic RT→paclitaxel + carboplatin × 4 vs. Paclitaxel + carboplatin × 6

Cis, *Cisplatin;* LVSI, *lymphovascular space invasion;* RT, *radiotherapy;* VBT, *vaginal brachytherapy.*

**High-intermediate risk (HIR) features include grade 2 or 3, lymphovascular space invasion, outer half myometrial invasion; eligibility requires age ≥ 70 year with one risk factor, age ≥ 50 years with two risk factors, age ≥ 18 years with risk factors.*

†Optional vaginal cuff boost for stage II disease or stage I clear cell or serous tumors.

IV) endometrial carcinoma were discussed previously (see Adjuvant Chemotherapy section). Current studies are focusing on the relative benefits of chemotherapy and pelvic or involved field (pelvic and paraaortic) irradiation, alone or combined.

Stage IIIA Disease

FIGO stage IIIA disease varies from serosa breakthrough or isolated adnexal metastasis to extensive macroscopic involvement of the pelvic tissues and ovaries. Patients with microscopic stage IIIA disease have a better outcome than those with gross clinical stage III disease.[216] Patients with stage IIIA disease because of the involvement of the serosa have a better DFS (42% versus 20%) than patients with multiple extrauterine disease sites.[219,220] The number of extrauterine disease sites correlates with probability of relapse. Patients with one, two, and three or more extrauterine sites had 5-year DFS of 68%, 56%, and 0%, respectively.[221] In a large series of 126 patients with stage III disease, isolated ovarian or tubal involvement (usually associated with low-grade histology) had a better outcome (60% 5-year survival) than pelvic peritoneal or parametrial involvement (44%). Local control and survival were improved with surgical resection.[216]

Stage IIIA disease should be treated with curative intention whenever possible. Complete debulking surgery plus radiation or chemotherapy based on histologic findings is the preferred treatment approach, preferably within the scope of a randomized trial.[220,222,223] For unresectable disease, depending on the tumor extent and patient condition, irradiation or chemotherapy could be considered followed by surgery if the tumor becomes resectable. Patients with advanced disease or poor general condition should be considered for palliative hormonal therapy or radiation therapy in case of symptoms.[223]

Stage IIIB Disease

Because stage IIIB disease is rare (<1% of all endometrial carcinomas), outcome data are scarce. FIGO 2009 staging has included tumors with parametrial extension in the IIIB category.[102] Treatment of patients with stage IIIB disease should be individualized with respect to sites and volume of disease and the degree of vaginal extension. It may involve radical surgery plus RT and brachytherapy or primary pelvic RT.

Stage IIIC Disease

Stage IIIC disease varies from microscopic involvement of a single pelvic node to extensive macroscopic disease involving the pelvic and paraaortic nodes. Patients with stage IIIC disease with nodal involvement only have a more favorable outcome compared with patients with both nodal and adnexal diseases or extensive pelvic involvement. Women with only pelvic node metastases have a better outcome than those with metastases in pelvic and paraaortic nodes, and DFS up to 80% has been reported.[224-227]

The standard treatment approach to stage IIIC disease is generally agreed to be TAH-BSO with debulking of all macroscopic nodes (or complete pelvic and paraaortic lymphadenectomy) followed by pelvic and paraaortic RT.[227-229] In a retrospective analysis of 71 women treated for stage IIIC endometrial cancer, 50 received definitive pelvic or extended field radiotherapy (EFRT) with or without systemic therapy (regional RT group), whereas 18 received adjuvant platinum-based chemotherapy or hormonal therapy without EBRT.[228] Five-year pelvic-RFS (98% versus 61%, $p = 0.001$), DSS (78% versus 39%, $p = 0.01$), and OS (73% versus 40%, $p = 0.03$) were significantly better for the regional RT group than the systemic therapy group.

DSS in the aforementioned analysis was not significantly correlated with number of nodes removed in the regional RT group but was in patients treated without regional RT ($p = 0.001$).[228] Relapses in patients treated with EBRT primarily occurred in patients with grade-3 cancer who may be most likely to benefit from combined chemoradiation.

In a recent multicenter retrospective analysis of 265 patients with optimally resected stage IIIC disease, 45 had received RT alone, 46 chemotherapy alone, and 161 had both RT and chemotherapy, with 3-year RFS of 73%, 56%, and 73%, respectively. Those patients receiving chemotherapy alone had lowest 3-year OS rates (78%, compared to 95% and 90% for RT and combined RT and CT, $p = 0.005$).[230]

The risk of microscopic paraaortic disease increases with clinical stage. Microscopic paraaortic nodal metastases were diagnosed in 10%, 22%, and 71% of patients with clinical stage I with high-risk factors, stage II, and stage III disease, respectively.[231] EFRT is indicated for documented paraaortic node involvement. Complete removal of macroscopic ($n = 50$) or microscopic ($n = 17$) paraaortic nodal disease followed by EFRT resulted in a 5-year OS of 46% and 53%, respectively; patients with residual macroscopic nodal disease or omission of paraaortic field radiation had significantly decreased survival rates (13% to 18%).[35,232,233] The combination of extended surgery and EFRT has, however, a substantial complication rate, with reported intestinal obstruction rates of 12% to 27%.[231,234] These results are reported from a time period when intensity-modulated radiation therapy (IMRT) was not available to potentially increase the dose delivered to the nodal area while giving better sparing of organs at risk for radiation damage. EFRT therefore should be reserved for patients with suspected or proven paraaortic lymph node involvement.

The randomized GOG-184 trial confirmed that chemotherapy can be given after EFRT if granulocyte colony-stimulating factor is used. Women (mostly with stage III disease) were treated with "involved-field" RT (pelvic RT in women with negative paraaortic nodes and pelvic RT plus EFRT in women with positive paraaortic nodes or no nodal sampling) followed by six cycles of doxorubicin/cisplatin or doxorubicin/cisplatin/paclitaxel chemotherapy.[236] No survival differences were observed with the addition of paclitaxel to doxorubicin/cisplatin chemotherapy in this setting, with 3-year RFS of 64% and 62% with and without paclitaxel.

Stage IV Disease

Patients with stage IV disease have a poor prognosis with reported median survival of 12 months to 15 months. Patients with extensive abdominal disease, particularly those with serous carcinomas, may benefit from initial cytoreductive surgery. Retrospective analyses have shown that maximal cytoreduction is an important prognostic factor, with median survival of 18 months to 30 months for optimal (<2 cm) cytoreduction, in contrast to 3 months to 7 months without debulking.[237] However, if debulking did not result in optimal cytoreduction, survival was severely impaired owing to a 37% rate of major postoperative complications and a 13% mortality rate. In an analysis of 45 patients with stages III to IV treated after surgery (usually TAH-BSO) with chemotherapy (four courses of cisplatin, epirubicin, and cyclophosphamide) and radiation therapy, 9-year PFS and OS of 30% and 53%, respectively, were reported.[238] The randomized GOG 122 trial showed 5-year OS and PFS rates of about 30% and 15%, respectively, after optimal debulking (residual < 2 cm) and eight cycles of doxorubicin and cisplatin in the 28% of patients with stage IV disease.[201]

Patients with bulky disease should be considered for clinical trials. Targeting agents are being investigated in clinical trials. Because many patients are elderly and have concurrent morbidities, such trials should include quality-of-life analysis. Outside the scope of clinical trials, treatment of these patients

After adjustment for stage and grade, patients in the multicenter analysis receiving chemotherapy alone had a HR of 2.2. for relapse and 4.0 for death, whereas there was no difference for the groups treated with RT alone or RT plus chemotherapy suggesting an essential role of RT for stage IIIC disease.[230] Similar results were found in an analysis of 119 uterine grade-3, 211 serous, and 40 clear cell carcinomas, in which regional radiotherapy was found to be an independent prognostic factor for stage III disease, whereas chemotherapy alone did not impact on survival.[186] Nonetheless, these analysis are all subject to the uncertain biases of retrospective reviews, and the contribution of radiation to the treatment of stage IIIC endometrial cancer should be definitively answered by GOG#258, described previously.

Some alternatives have suggested, however, that EFRT should be used prophylactically for patients with positive pelvic nodes in combination with other adverse factors such as grade-3 disease.[224] Mariani et al stressed the importance and complementary role of both complete removal of all involved nodes and pelvic and paraaortic radiotherapy.[235]

The cumulative probability of a late grade-3 or higher treatment-related GI adverse event was 5% in the GOG-184 trial (all RT groups combined). As seen in other reports, grade-1 endometrioid disease even in the advanced disease setting had a relatively good prognosis: compared to grade-3 the RFS HZ was 3.12 for grade 3, similar to the HR of 3.45 for clear cell histology. Serous histology had the largest effect on RFS relative to grade-1 endometrioid adenocarcinoma, with a HR of 4.43.

Recent first results of the GOG-209 randomized noninferiority trial comparing paclitaxel, doxorubicin, and cisplatin with carboplatin and paclitaxel chemotherapy suggest that carboplatin and paclitaxel can be used with similar efficacy and reduced toxicity.[239] Neoadjuvant chemotherapy (carboplatin/paclitaxel) followed by cytoreduction was used in a series of 30 patients with stage IV disease. Partial and complete response rates were 67% and 7%, respectively. Despite achieving optimal debulking in 80%, the median PFS and OS were only 13 months and 23 months.[240] In a small group of 28 patients grade-1 or grade-2 endometrioid subtype and zero and one sites of extraperitoneal metastasis appear to be independent predictors of survival, whereas neither surgery as primary therapy nor optimal cytoreduction was significantly related to OS.[241] The indication for surgery and decision to undertake maximal surgery or use a palliative approach should be carefully made.[223]

is highly individualized, depending on the extent of the disease and the patient's condition.

Radiation Therapy for Recurrent Disease

The management and prognosis of locoregional recurrent disease requires consideration of patient, treatment, and tumor-related factors, including tumor histology and grade, prior surgical and radiation therapy, size, extent and location of the relapse, the presence of distant metastases, the relapse-free interval, and the performance status of the patient.[242-245]

Reported local control rates after radical treatment for isolated vaginal relapse in patients who were previously unirradiated range from 80% to 90% for patients with recurrences confined to the mucosa to 60% to 80% for those with more advanced disease. Five-year OS are 40% to 70%.[142,242,245-248] For patients previously treated with pelvic irradiation, survival rates after vaginal relapse of 10% to 30% have been reported. In the PORTEC trial, the 5-year actuarial survival rate after vaginal relapse was 38% in the RT group and 70% in the control group.[150]

Curative treatment for isolated vaginal recurrence in patients not previously irradiated has consisted of EBRT and VBT although it is not clear that EBRT is necessary for all patients because not all vaginal relapses may be accompanied by other occult pelvic disease. The use of a brachytherapy boost is essential.[248,249] Distal vaginal recurrence in the suburethral region or more extensive vaginal recurrence requires careful individualized BT planning to encompass the target volume with vaginal cylinder or interstitial BT, or both.[250]

Pelvic and distant relapses generally have a poor prognosis. Complete remission rates of treatment for pelvic relapse range from less than 5% for patients who had previous pelvic RT and those with sidewall disease to 5% to 30% for patients not previously irradiated.[142,251] To try to improve prognosis for recurrent vaginal or pelvic disease, the GOG has initiated a randomized trial (GOG-238) of pelvic RT with or without concurrent weekly cisplatin in patients with pelvic-only relapses. This may be preceded by surgical resection.

Selected patients with pelvic relapse may be candidates for a curative approach with extended surgery alone or with preoperative chemoradiation, intraoperative irradiation (IORT), or both. Patients with isolated distant metastasis (i.e., single lung nodule) may have long symptom-free periods after local resection or consideration of stereotactic body radiation.

The frequency of follow-up examinations and their value in detecting asymptomatic relapses have been subject of discussion.[252-254] It has been argued that 50% to 75% of women with disease relapse were symptomatic and that regular follow-up is not cost effective because patients can only occasionally be salvaged after relapse. However, patients with early-stage disease treated with surgery alone (usually low risk) should be cautioned about symptoms of vaginal bleeding, which almost always signals vaginal relapse, because salvage rates are high. Routine surveillance rarely detects asymptomatic recurrence. Follow-up examinations should include a careful history focusing on symptoms of recurrence or of side effects of treatment and visual inspection of the vagina and bimanual rectovaginal examinations. Biopsy should be taken if abnormalities are found. Because distant relapse only occasionally can be treated with a view to a long symptom-free interval, it cannot be recommended to actively screen for distant metastases outside the scope of clinical trials. In general, after the first 2 years less frequent and more patient-directed follow-up visits are preferred, after specific patient education with written information as to which symptoms would necessitate evaluation and with contact numbers they could use for rapid access.[254]

Radiation Therapy for Palliation

Radiation therapy has an important role in palliation of symptoms from locally advanced, recurrent, or metastatic endometrial cancer. Vaginal bleeding, vaginal discharge, or pain from advanced or recurrent disease or lymphedema from enlarged pelvic lymph nodes can be successfully palliated with RT. Optimal doses of palliative radiation have not been established Commonly used schedules include a short course of fractionated EBRT using 3-Gy to 4-Gy fractions to a dose of 20 Gy to 30 Gy over 1 to 2 weeks or, depending on the general condition and symptoms, shorter schedules of 1 to 3 in 8-Gy fractions can be used. Other sites of symptomatic metastases, such as brain metastases or distant lymph node disease, are uncommon but can also be effectively palliated with similar radiation doses. Rapid and effective palliation of pain from bone metastases can be obtained using a single 8-Gy dose.[255-257]

Systemic Therapy for Recurrent or Metastatic Disease

Hormonal Therapy

Progestational agents are often chosen as the first treatment for advanced or metastatic grade-1 or grade-2 disease, especially for PR-positive tumors.[258-260] Reported response rates range from 15% to 34%, with a median response duration of several months. For PR- or ER-positive tumors response rates up to 77% have been observed, in contrast to 9% for receptor-negative tumors.[258,261] For relatively asymptomatic patients with unknown receptor status and grade-1 or grade-2 disease, progestins should be considered before the more toxic chemotherapy.

Chemotherapy

The majority of women with recurrent or metastatic disease will not have low-grade tumors. Symptomatic patients with recurrent or metastatic disease, especially grade-3 or receptor-negative or unknown tumors should be considered for chemotherapy.

Platinum drugs, anthracyclines, and taxanes are the most active agents tested to date for endometrial carcinoma, and multiagent chemotherapy has been shown to produce higher response rates than single-agent therapy.[262-266] Platinum- or taxane-containing multiagent therapy provides response rates of 30% to 75%, respectively, with median remission durations of 6 months to 12 months.[232,235-237] Median OS on most trials of chemotherapy for measurable metastatic or recurrent endometrial carcinoma is only in the range of 12 months to 15 months. The only randomized trial showing a survival benefit for chemotherapy in the setting of advanced or recurrent disease is GOG-177, which compared doxorubicin/cisplatin to paclitaxel/doxorubicin/cisplatin with filgrastim support. The triple-drug regimen showed an improved response rate (57% versus 34%) and somewhat longer survival (58% versus 50% 1-year survival), but at the cost of significant neurotoxicity.[262] Carboplatin/paclitaxel therapy, which is the standard for ovarian cancer and is used commonly in the community, has less toxicity than doxorubicin/cisplatin or paclitaxel/doxorubicin/cisplatin, and may be equally effective.[266,267] Preliminary results of a large randomized GOG noninferiority trial comparing carboplatin/paclitaxel with paclitaxel/doxorubicin/cisplatin (GOG-209) in women with stages III, IV, or recurrent disease showed no difference in PFS (14 months in each arm) or median OS (32 months for carboplatin/paclitaxel, 38 months for paclitaxel/doxorubicin/cisplatin, not statistically significant) between the groups, while toxicity was increased for the TAP regimen.[239]

Current interest has focused on developing and evaluating molecular targeted therapies and integrating them with

Current IHC assays to determine levels of hormone-receptor positivity do not predict response to hormonal therapy. The GOG studied alternating cycles of tamoxifen and progestin therapy in an attempt to use tamoxifen to upregulate the PR, reporting a response rate of 27%.[260] This has not been compared with single-agent progestin therapy in any randomized trials. For patients with disease progression after a response to progestins, tamoxifen and aromatase inhibitors may be considered. Many of the large trials of progestin therapy were completed years ago, and it is not certain that response rates would be as high using more stringent current response criteria. Toxicity reporting was also less complete then, and progestins may cause weight gain and increase thrombosis risk in a population already prone to these complications. Grade-3 disease is unlikely to respond to hormonal therapy (<10%). High-dose therapy (800 mg/day of megestrol acetate or 1000 mg/day of medroxyprogesterone acetate [MPA]) was not found to be more effective than standard doses (160 mg/day of megestrol or 200 mg/day of MPA).[258] Some data suggest that even lower doses of MPA may be as effective. Recent attempts to combine hormone therapy with mTOR inhibition are described previously.

Because most patients with advanced disease are elderly women with comorbidities, their performance status and concurrent diseases may preclude the use of multiagent chemotherapy. Many will have had prior pelvic irradiation, and chemotherapy dose reductions or use of growth factor support will need to be considered.

The Multicentre Italian Trials in Ovarian Cancer and Gynecologic Malignancies Group (MITO) conducted a single arm Phase II trial of pegylated liposomal doxorubicin plus carboplatin in the front-line therapy of advanced endometrial cancer and reported a response rate of 59.5% and a median survival of 80.1 weeks. This might be an attractive alternative regimen for women at risk for neurotoxicity.[268]

cytotoxic chemotherapy. Trials of mTOR inhibitors and other agents affecting the AKT/PI3K/mTOR pathway are discussed previously; single-agent response rates are modest, and combinations are being explored.

TREATMENT OF UTERINE SARCOMAS

Uterine sarcomas are rare, comprising more than three distinct types with different characteristics and different outcomes: carcinosarcomas (or malignant mixed müllerian tumors), 45%; leiomyosarcomas, 40%; and endometrial stromal sarcomas, 15%. Uterine sarcomas, especially leiomyosarcomas, have a higher metastatic rate without preceding lymph node involvement compared with the adenocarcinomas.[4] Most patients present with vaginal bleeding, much like patients with adenocarcinomas, but the tumor is typically larger before this occurs. Uterine sarcoma may also be an unexpected diagnosis in a uterus resected for presumed symptomatic leiomyoma.[273] Other patients can present with local discomfort from uterine enlargement. The lungs are the most common sites of metastatic disease. Because of the high rate of metastases especially to the lung, initial evaluation should include CT of the chest.

Management varies because data from randomized studies is lacking. Because patterns of failure are different for the different sarcoma types, treatment should be tailored to the specific sarcoma type. Initial treatment is primarily focused on the initial surgery. Hysterectomy is the mainstay of treatment.

Endometrial stromal sarcoma, formerly called low-grade endometrial stromal sarcoma, is composed of cells that resemble normal proliferation phase endometrial stroma. These tumors are almost all ER- and PR-positive, are usually diagnosed at stage I (90%), and should be treated with TAH-BSO alone.

Because of the indolent growth pattern of endometrial stromal sarcomas, patients with advanced or recurrent disease usually have a long survival and may have second or third debulking surgery and several lines of hormonal therapies. For the rare hormone receptor-negative recurrence, chemotherapy may be considered.[4]

Undifferentiated uterine sarcoma, formerly called high-grade endometrial stromal sarcoma, should be treated with more extensive surgery. Carcinosarcomas and undifferentiated uterine sarcomas warrant lymph node evaluation, and most current authors favor full surgical staging, including TAH-BSO, peritoneal cytology, full pelvic lymph node dissection, and omentectomy. Several authors have pointed to a more aggressive behavior and genetic differences from high-grade cancers.[274,275]

The weight of clinical molecular and genetic data support the view that carcinosarcomas should be considered high-risk carcinomas and be treated accordingly.[35,36] The risk and patterns of relapse seem to be related to the epithelial component, Based on the data summarized previously, pelvic radiation therapy is usually considered indicated for patients with risk factors similar to those with carcinomas (e.g., high mitotic count, deep myometrial invasion, advanced age, cervical involvement) and for cases with residual microscopic or macroscopic pelvic disease.

Retrospective studies of adjuvant radiation therapy have shown improved pelvic control, especially for carcinosarcomas but no survival benefit.[276-278] In a SEER analysis among 2461 women with carcinosarcomas an OS benefit was reported for the 890 women who had been treated with radiotherapy,[279] but as with any of such population series, selection factors are unknown and may have influenced the results.[182] The EORTC-55874 prospective, randomized trial compared pelvic RT versus no further therapy in 224 patients with uterine sarcomas stage I and II (103 leiomyosarcomas, 91 carcinosarcomas, 28 endometrial stroma sarcomas). RT provided a significant reduction of pelvic recurrence for carcinosarcomas, with 5-year pelvic recurrence rates of 22% with irradiation versus 40% for the control group ($p = 0.0004$). However, survival was not improved (5-year OS of 58% and 56%, $p = 0.92$). This trial showed the need to separate the different sarcoma types. Carcinosarcomas were found to benefit from pelvic irradiation in terms of pelvic control. Leiomyosarcomas had no benefit from RT (20% versus 24% pelvic recurrence) and were most likely to relapse at distant sites. Therefore, pelvic RT should be considered only for microscopic or macroscopic residual disease, preferably within clinical trials evaluating radiation therapy with concurrent or sequential chemotherapy. There were too few endometrial stromal sarcomas in the EORTC study to allow specific analysis.[280]

Chemotherapy for recurrent or metastatic sarcomas has limited efficacy. Agents with activity against carcinosarcoma include ifosfamide, platinum drugs, and taxanes.[281-285] Combination therapy with cisplatin, doxorubicin, and ifosfamide was found to produce an overall response rate of 56%, albeit with considerable toxicity.[282]

In leiomyosarcoma, the risk of lymph node involvement is low, and lymphadenectomy is therefore not indicated. Ifosfamide and doxorubicin have single-agent activity in the treatment of advanced and metastatic uterine leiomyosarcoma, and the combination of the two has produced a response rate of 30%.[286]

Adjuvant chemotherapy has been investigated in uterine sarcomas in view of their increased risk of distant metastases. A small older ($n = 156$ total, 48 leiomyosarcoma, 93 carcinosarcoma, 15 other sarcoma) randomized study evaluating eight cycles adjuvant doxorubicin showed no benefit overall.[290] In the leiomyosarcoma subgroup, a nonsignficant decrease in the risk of relapse (44% versus 61%) was observed.

A retrospective study among 49 patients with stages I to IV carcinosarcoma showed nonsignificantly better survival after chemotherapy (carboplatin and paclitaxel) with or without RT than after RT alone (3-year OS of 66% versus 34%, $p = 0.15$).[291] A number of studies have suggested the combination of RT and chemotherapy (sequential or sandwiched) to be more effective than chemotherapy or RT alone.[292-297] A prospective GOG study using adjuvant ifosfamide and cisplatin (without radiation therapy) among 65 patients with stages I to II carcinosarcoma showed the combination to be tolerable, but impact on PFS (69%) and OS (82% at 2 years) was unclear owing to absence of controls, and the pelvic recurrence rate was high.[298] A randomized GOG trial among 232 patients with stages I to IV (45% stage III) carcinosarcoma compared chemotherapy (three cycles of cisplatinum, ifosfamide, and mesna) with WAI (30 Gy, with pelvic boost to 50 Gy). The recurrence rate was nonsignificantly lower for chemotherapy than for WAI (52 versus 58%, HR = 0.789, $p = 0.24$), and survival was nonsignificantly better (47% versus 34%, $p = 0.08$). After chemotherapy alone, more vaginal recurrences were found.[299]

IRRADIATION TECHNIQUES AND TOLERANCE

External Beam Pelvic Irradiation

Most patients receive pelvic RT in the postoperative setting. The clinical target volume for pelvic RT consists of the parametrial tissues, the proximal half of the vagina, and the pelvic lymph node areas (i.e., internal and external iliac and the lower common iliac lymph node regions; in case of cervical involvement and for node-positive disease the presacral and upper iliac lymph node regions are included). The planning target volume is derived by adding an appropriate margin around the

A GOG Phase II trial of the anti-VEGF monoclonal antibody bevacizumab in women with endometrial carcinoma with one to two prior chemotherapy regimens noted a promising 13.5% major response rate, and 40% of subjects were progression-free at 6 months.[269] Other antiangiogenic agents tested have generally not appeared as active; aflibercept showed only a 7% response rate.[270] A preliminary report suggested that sunitinib produced a 15% response rate.[271] Trials of multiple other multitargeted antiangiogenic agents, including cediranib, brivanib, cabozantanib, nintedanib, lenvatinib, and AMG 386 (trebananib) are ongoing or completed but not yet reported. A frontline randomized Phase II GOG trial testing paclitaxel/carboplatin/bevacizumab versus paclitaxel/carboplatin/temsirolimus versus ixabepilone/carboplatin/bevacizumab has been completed and results should be available soon.

Anti-ERBB2 and anti-EGFR agents (discussed previously) have not yet provided much promise. Metformin is a relatively nontoxic inexpensive oral agent widely used in the treatment of diabetes. Retrospective studies have suggested that patients with diabetes and endometrial cancer who use metformin have superior OS and RFS compared to patients with or without diabetes with endometrial cancer who do not use metformin.[7,75,80,272] In preclinical models metformin inhibited cell proliferation, induced apoptosis, and decreased tumor growth in, with one study showing the greatest response in cells harboring activating mutations in K-Ras. The GOG will shortly activate a randomized trial of carboplatin/paclitaxel/metformin versus carboplatin/paclitaxel/placebo in the frontline setting.

Hormone-replacement therapy should not be prescribed because of the tumor's hormone sensitivity. Chemotherapy and RT should not be used. In the case of pelvic or abdominal recurrent disease, debulking surgery should be employed, followed by hormonal therapy (i.e., progestins such as medroxyprogesterone acetate). Aromatase inhibitors, gonadotropin-releasing hormone agonists, and selective ER-modulators are used as second- and third-line hormonal therapy.

Two randomized trials of first-line treatment for advanced disease have compared single-agent therapy with ifosfamide to ifosfamide plus cisplatin[283] and to ifosfamide plus paclitaxel,[284] respectively. In each case the combination produced higher response rates at the cost of added toxicity. The addition of paclitaxel also improved survival, with response rates of 29% and 45% and median OS of 8.4 and 13.5 months for single-agent and combination therapy, respectively.

A prospective Phase II trial of carboplatin plus paclitaxel in patients who are chemotherapy-naive produced a response rate of 52%. This combination would appear to be better tolerated than ifosfamide-based regimens.[285] An ongoing Phase III trial, GOG 261, is testing the combination of carboplatin/paclitaxel versus the combination of ifosfamide/paclitaxel in women with newly diagnosed stages I to IV persistent or recurrent uterine carcinosarcoma. Results will hopefully justify use of the less toxic combination.

As second-line therapy for advanced and metastatic leiomyosarcoma, single-agent gemcitabine had a 20.5% response rate,[287] and the combination of docetaxel and gemcitabine, which requires growth factor support, produced a 28% response.[288] As first-line chemotherapy for metastatic uterine leiomyosarcoma the response rate to the combination was 35.8%.[289] A recently completed Phase III study, GOG 250, tested the addition of bevacizumab to the gemcitabine/docetaxel combination; results should be available soon. Other agents with some activity include temozolomide and pazopanib.

As discussed previously, carboplatin/paclitaxel is currently being compared with ifosfamide/paclitaxel in this same setting. Optimal treatment of patients with uterine carcinosarcoma has not been determined.

Trials of adjuvant chemotherapy in leiomyosarcomas are few. The French Sarcoma Group recently published results of their randomized clinical trial of adjuvant chemotherapy with doxorubicin, ifosfamide, and cisplatin followed by pelvic radiotherapy versus pelvic radiotherapy alone in patients with localized uterine sarcomas. The study was closed prematurely for poor accrual. Eighty-one patients were included, of whom 53 had leiomyosarcoma and 9 had undifferentiated sarcoma. The DFS for the leiomyosarcoma and undifferentiated sarcomas combined at 3 years was 51% (95% CI 34% to 69%) in patients receiving both chemotherapy and radiotherapy versus 40% (95% CI 25% to 58%) in patients receiving radiotherapy alone (p = NS), and DFS at 5 years was 51% (95% CI 34% to 69%) versus 29% (95% CI 16% to 47%) in arm B, respectively (P = 0.098).[300] A prospective nonrandomized Phase II trial of four cycles of adjuvant gemcitabine plus docetaxel followed by four cycles of doxorubicin for completely resected high-grade uterine leiomyosarcoma was recently reported to show a PFS of 78% at 2 years and 57% at 3 years, which compares favorably with historical controls without adjuvant chemotherapy.[301] An ongoing randomized trial, GOG 277, which is being performed in collaboration with the EORTC and Cancer Research UK (NCRI), is testing this regimen (adjuvant gemcitabine/docetaxel followed by doxorubicin) versus no further treatment after surgery for uterus-limited leiomyosarcoma. This trial prohibits whole pelvic radiotherapy.

clinical target to allow for the beam penumbra, geometric uncertainties, and variability in daily patient setup and movement of internal organs. The main organs at risk for complications are the rectosigmoid, small bowel, and bladder. Most acute and late complications are of the GI tract, and it is essential to reduce the volume of small bowel within the treatment fields as much as possible. A four-field box technique has traditionally been employed, which had a smaller volume of small bowel in the high-dose region compared with anterior and posterior parallel-opposed ports. The prone treatment position has been found to reduce the volume of small bowel within the pelvis, and special belly board devices have been designed that are more effective in pushing the small bowel out of the treatment fields than the prone position alone. Several studies have shown decreased volumes of irradiated small bowel with the use of a belly board in the postoperative setting.[302-304] In thin patients with firm abdominal walls, there may be less benefit. High-energy photons from a linear accelerator are preferred to ensure a homogeneous dose distribution.

Most RT departments are using three-dimensional CT planning, and multileaf collimators are used in all fields to shield organs at risk and reduce the treated volume. The use of CT planning has the clear advantage of delineating the actual nodal sites, instead of using standard field borders, which risk insufficiently or too generously encompassing the lymphatic chains. Determining field borders based on bony landmarks should now be considered obsolete in the developed world. Excellent contouring atlases have been published[305,306] that guide the radiation oncologist to ensure adequate delineation of the areas at risk (Figure 59-2, contouring examples in A to D and conventional CT-planned box technique with anterior-posterior and lateral fields in E and F).

A total dose of 45 Gy to 46 Gy is usually prescribed in the postoperative setting, with daily fractions of 1.8 Gy to 2.0 Gy for five fractions per week. For cases with involved margins or residual macroscopic disease, the target dose is 50.4 Gy with a boost dose to the areas of involvement using CT planning to a cumulative dose of 60 Gy to 70 Gy, depending on

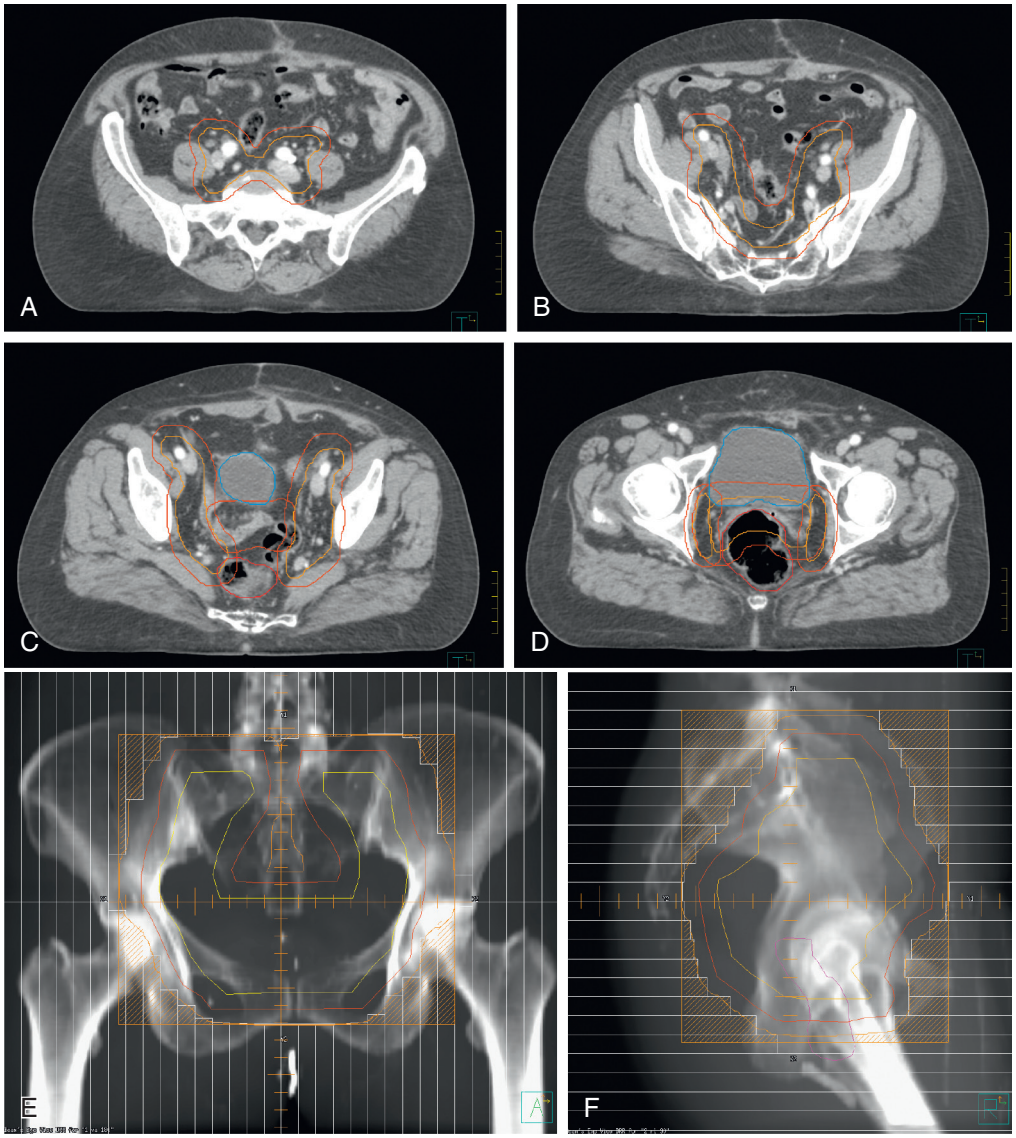


Figure 59-2 **A** to **D,** Computed tomography planning scan slices at four levels through the pelvis. The contours represent the clinical target volume *(nodal and primary CTV, orange)* and planning target volume *(red)*. **E-F,** Digitally reconstructed radiographs of posterior-anterior **(E)** and lateral **(F)** pelvic fields using three-dimensional conformal treatment planning. Highlighted are the clinical target volume *(yellow-orange)* and the planning target volume *(red)*.

the situation. Ideally, these risk areas should be marked with clips during surgery. Rarely an omentoplasty or insertion of a hydrogel spacer may be considered to move the small bowel out of the high-dose area.[307,308]

Intensity-Modulated Radiation Therapy

In view of the additional toxicities when combining surgery, EBRT, and chemotherapy in patients with high-risk endometrial cancer, several groups have investigated the use of IMRT to reduce the dose to critical organs surrounding the target tissues and reduce rates of GI toxicity and of hematologic toxicity when combined chemotherapy and RT are used.

IMRT uses multiple beams of various intensities that conform the high-dose region to the shape of the target tissues in three dimensions, minimizing the dose to the surrounding organs. Adjuvant pelvic IMRT requires careful quality assurance measures and margins for the clinical target volumes to be large enough to account for significant internal motion related to bladder and rectal filling.[306,309] Use of integrated target volume (to account for differences in organ filling) and repeated planning CT scans may be needed to ensure adequate coverage of the clinical target volume (Figures 59-3, 59-4, and 59-5). Treatment planning studies[310-312] have shown that a substantial reduction of the doses to the small bowel, rectum, and the pelvic bone marrow can be realized. The volume of small bowel irradiated to the prescription dose is reduced by a factor of 2, compared with a CT-based, conventional, three-dimensional, four-field box technique.[312] Clinical studies have shown a reduction of acute GI toxicity in patients treated with pelvic IMRT compared to three-dimensional conformal RT,[310,313,314] and of acute hematologic toxicity in patients with gynecologic cancer receiving pelvic IMRT combined with chemotherapy.[315] In an analysis of 36 patients with gynecologic cancer treated with pelvic RT with or without chemotherapy or brachytherapy (or both), IMRT also resulted in a significant reduction of patients experiencing chronic GI toxicity (11% mild symptoms compared with 50% in a historical series of patients receiving pelvic irradiation) and less severe GI complications (0% versus 3%).[316] Other somewhat larger series have confirmed these results.[313,314] Especially for the increasing number of patients with high-risk endometrial carcinoma treated with surgery, RT, and chemotherapy, IMRT may be an essential tool in reducing the chronic toxicities of multimodality treatment. A Phase II study among 58 patients with endometrial cancer conducted by the RTOG showed that pelvic IMRT can be safely delivered in a multicenter setting, provided that clear guidelines for target definition and delineation, dose prescription, quality assurance, and dose-volume constraints for the target volume and organs at risk are provided.[317] Currently a randomized trial of the RTOG (1203) is comparing acute toxicities between a four-field box and IMRT in the adjuvant setting for both endometrial and cervical cancer.[318]

Extended-Field Irradiation

Patients undergoing treatment to the pelvic and paraaortic regions are usually treated in the supine position to ensure a dorsal position of the kidneys. CT-directed planning using three-dimensional conformal radiotherapy or IMRT ensures adequate sparing of the kidneys and bowel. The superior field border is usually placed at the T12-L1 junction, but it may be individualized according to the level of detected or suspected lymph node involvement. Doses used for pelvic and paraaortic treatment are typically 45 Gy to 50.4 Gy with standard 1.8-Gy fractions. For macroscopic involved lymph nodes a boost dose may be used, preferably using IMRT.[319]

Complications of Pelvic Irradiation

Side effects of radiation therapy for gynecologic malignancies have been well documented. Complication rates are dose and volume dependent and are higher for the combination of pelvic EBRT and VBT than for EBRT alone.[172,320-323] Complication rates after EBRT are also increased if a full lymphadenectomy is added to the hysterectomy.[320,324] Other treatment-related factors associated with the risk of complications are treatment volume, daily fractionation, and irradiation technique.[325] Patient-related risk factors are prior abdominal surgery, young age, low weight, concurrent diabetes, hypertension, inflammatory bowel disease, or other pelvic inflammatory conditions, although literature data show conflicting results regarding several of these factors. The most significant complications are obstruction of the small bowel, chronic diarrhea, proctitis, fistula formation, vaginal stenosis, and insufficiency fractures of bone. The use of EBRT is associated with the risk of small bowel complications.[324,326] The addition of VBT to EBRT especially increases the incidence of vaginal and rectal side effects, such as fibrosis, stenosis, ulcers, and fistula.[321,325] Reported rates of severe complications after TAH-BSO plus EBRT range from 2% to 6%; after surgery followed by EBRT

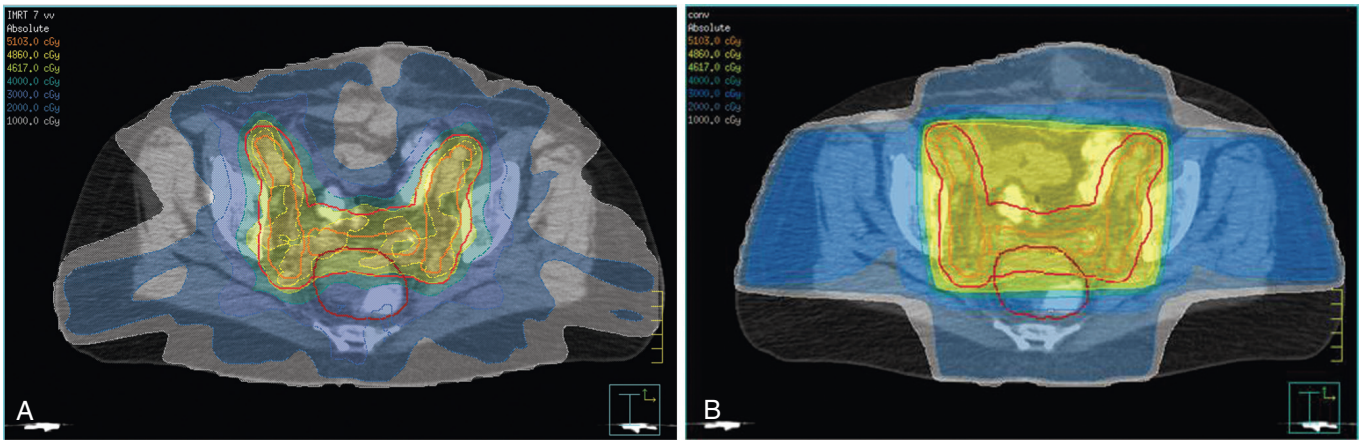


Figure 59-3 Comparison of **(A)** an intensity-modulated treatment plan and **(B)** a three-dimensional conformal four-field treatment plan for a representative patient. Highlighted are the planning target volume *(red)* and the clinical target volume *(orange)* and the areas receiving at least 10 Gy *(white)*, 20 Gy *(gray-blue)*, 30 Gy *(blue)*, 40 Gy *(green)*, 46.2 Gy (=95%, *yellow-green*), and 48.6 Gy (=100%, *yellow*) of the prescription dose.

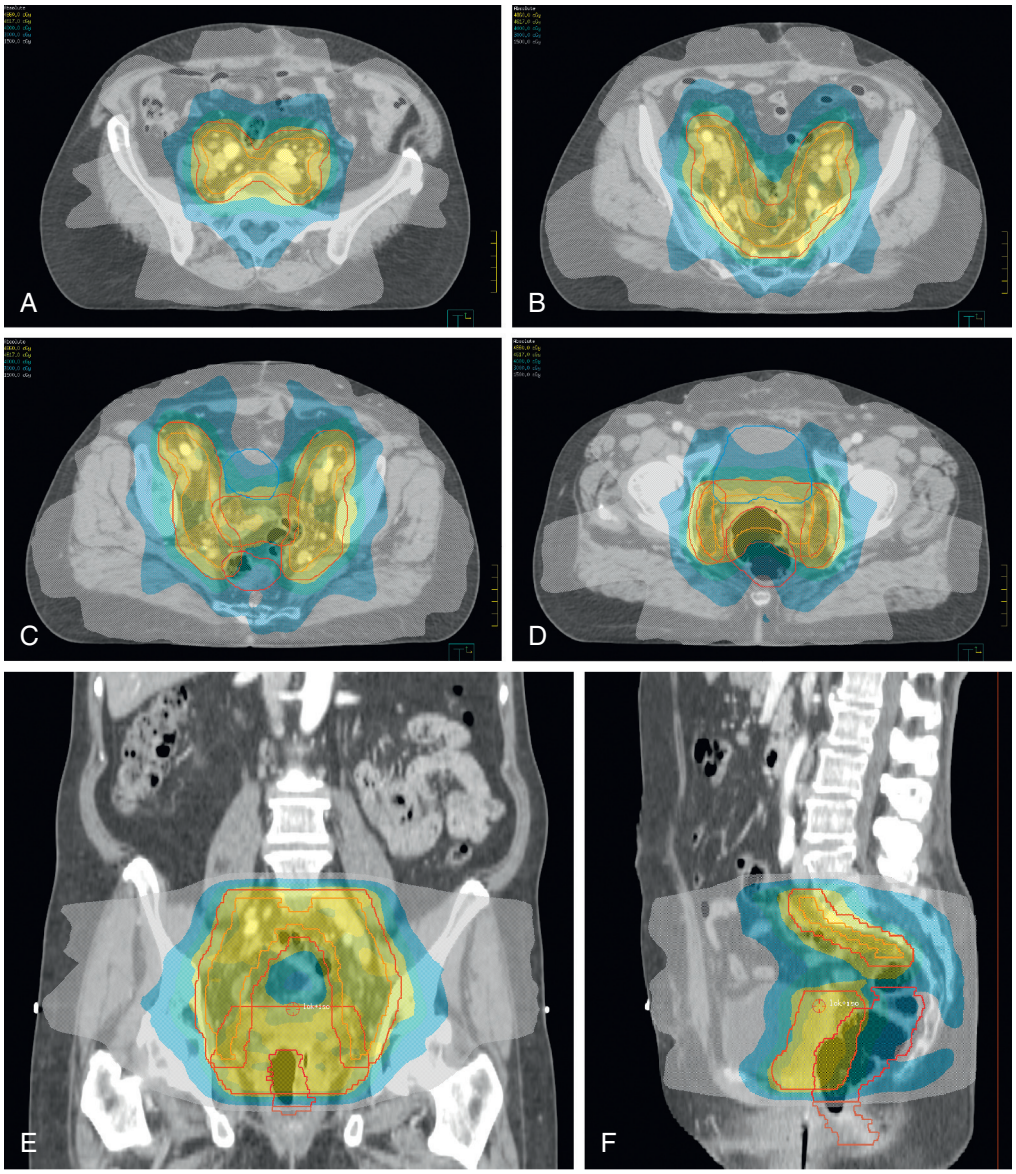


Figure 59-4 Intensity-modulated treatment planning using seven beam directions and multiple segments, depicted for the same four transverse sections through the pelvis as in Figure 59-2, *A-D*, and sagittal and coronal images of the same treatment plan. Highlighted are the areas receiving at least 15 Gy *(white)*, 30 Gy *(blue)*, 40 Gy *(blue-green)*, 46.2 Gy (=95%, *green*), and 48.6 Gy (=100%, *yellow*) of the prescription dose.

and VBT, from 4% to 13%; after VBT alone, from 0% to 7% (dose dependent); and after EBRT and surgery, including lymphadenectomy, from 7% to 18%.

The rates of mild to moderate complications are less well established. Acute side effects of EBRT, such as diarrhea, urgency, abdominal cramps, and urinary frequency are usually not reported if they do not cause an interruption or discontinuation of treatment.[283] Mild late side effects (including increased bowel movements, episodes of diarrhea, abdominal cramps, frequent urination, and minor incontinence) are underreported.[326,327]

In the PORTEC trial, 63% of the patients were treated during standard four-field pelvic EBRT with medication or dietary measures, or both, for mild, acute symptoms. Discontinuation of irradiation because of acute symptoms occurred in 2% of cases.[328] In the ASTEC trial, any acute toxicity was reported in 57% of patients who underwent RT compared with 27% for controls and involved mostly mild (32%) or moderate symptoms. Severe acute toxicity was reported in 3% versus less than 1% of patients.[147] The 5-year actuarial rates of any late complication in the PORTEC trial were 26% in the RT group and 4% in the control group ($p < 0.001$). Most complications (67%) were mild (grade 1), and almost 50% of symptoms resolved in the course of 2 year to 3 years. GI symptoms were the predominant side effects, with a 5-year actuarial rate of (mostly mild) GI complications in the RT group of 20%. The 5-year actuarial rates of severe (grade 3 or 4) late complications were 3% in the RT group and 0% in the control group. No severe late genitourinary or vaginal complications occurred. In the ASTEC trial, slightly higher late toxicity rates were reported: grades 1, 2, 3, and 4 predominantly GI or urogenital late toxicity was reported in 30%, 22%, 7%, and 1%, respectively, of patients with EBRT, compared with 24%, 16%, 35%, and 0% among control subjects. In the GOG 99 trial, the combination of lymphadenectomy and EBRT resulted in higher GI complication rates, including more bowel obstructions.[90]

The presence of acute treatment-related symptoms is one of the most important risk factors for late complications.[328] The

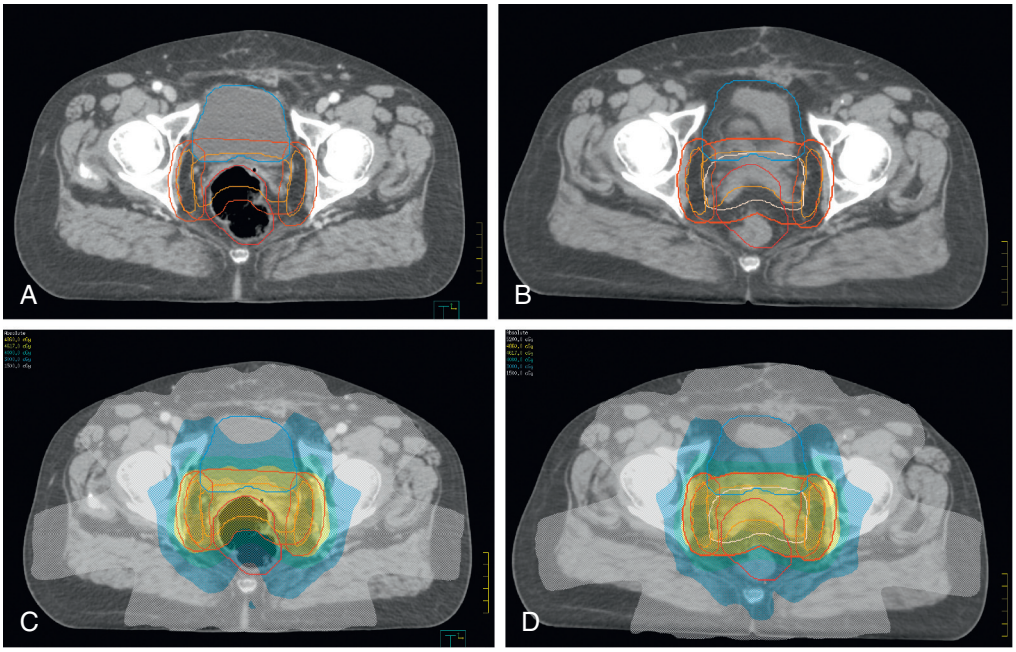


Figure 59-5 Examples of planning computed tomography (CT) scans showing differences in bladder and rectal filling with clear impact on margins and resulting treatment plans. *Left panel:* contouring and planning using the initial CT scan with full bladder; *right panel:* contouring and planning with fusion of a second planning CT scan with empty bladder and bladder and rectum; the resulting integrated target volume *(white contour)* requires a more generous dorsal margin.

association between acute and late treatment complications has become a topic of interest and research.[329,330] The fact that a subset of patients with acute toxicity have no symptom-free interval between acute and late complications supports the theory that late injury occurs as a consequence of persisting acute injury of the intestinal mucosa.[330] Pelvic RT is associated with short-term and long-term effects on GI function, most notably increased frequency of bowel actions, less bile acid absorption, and faster intestinal transit.[326] Most of these changes improve with time, but some long-term effects persist. A long-term quality-of-life analysis from the PORTEC-1 trial showed that even 15 years after treatment, patients treated with EBRT reported significant ($p < 0.01$) and clinically relevant higher rates of urinary incontinence, diarrhea, and fecal leakage leading to more limitations in daily activities. Increased symptoms were reflected by the frequent use of incontinence materials after EBRT (day and night use, 42.9% versus 15.2% for NAT; $p = 0.001$). Patients treated with EBRT even reported lower scores on the SF-36 scales for physical functioning and role-physical functioning.[331] The radiation oncologist has an essential role during follow-up of patients with gynecological cancer who underwent EBRT to evaluate and treat these late, mainly GI symptoms, which significantly impact on daily quality of life especially because specific treatments are available.[332,333] A recent randomized trial of algorithm-based management of GI symptoms among 218 patients showed that patients given targeted intervention following a detailed clinical algorithm had better improvements of their symptoms than did patients given "usual care."[333]

Results from the PORTEC-2 trial showed that rates of complications after VBT alone (700 cGy at 0.5-cm depth times three to proximal 4 cm of vagina) were low. During irradiation there was a significantly increased rate of acute RTOG grade-1 and grade-2 acute GI symptoms among patients with EBRT as compared with patients who had VBT (53% verus 12%, $p = 0.001$). This difference decreased with further follow-up and lost significance after 24 months. Late grade-3 GI toxicity was reported in four (1.9%) patients with EBRT and in one patient (0.5%) who underwent VBT and required surgery for bowel obstruction because of adhesions or fibrosis. Late grade-2 moderate mucosal atrophy (without narrowing or shortening) was significantly more frequent after VBT than after EBRT (17% versus 4% after 2 years). Grade-3 atrophy (marked atrophy with or without shortening or narrowing) was reported in only one patient (0.5%) who underwent EBRT and in four patients (1.9%) who underwent VBT. Patient-reported outcomes showed that patients who underwent VBT reported significantly better social functioning ($p = 0.005$) and lower symptom scores for diarrhea, fecal leakage, need to stay close to a toilet and limitation in daily activities because of bowel symptoms ($p < 0.001$), than those treated with EBRT. The scores of the patients who underwent VBT remained in the range of the normal population. There were no differences in sexual functioning or symptoms between the treatment groups, although both groups had lower functioning scores than an age-matched norm population, probably reflecting the impact of diagnosis and treatment of a gynecological cancer.[156,157]

Brachytherapy Techniques

LDR, pulsed-rate, and HDR brachytherapy techniques are available with a variety of manual and remote afterloading applicators for intracavitary and interstitial brachytherapy. The LDR technique has been replaced in most centers by PDR techniques simulating LDR treatment, but with the convenience of modern HDR machines.[334] Iridium-192 is used for pulsed and HDR brachytherapy. HDR techniques may be preferred to avoid the increased morbidity of prolonged bed rest required for the LDR and PDR treatment and for the convenience of the patient and staff.

In primary treatment of endometrial carcinoma, brachytherapy has traditionally been administered with LDR techniques such as Heyman packing or Simon capsules or with a

single intrauterine tube, depending on the size of the uterus. The technical aspects of intracavitary placement of a single tube are similar to those for cervical carcinoma, but different dose specification points have been used (e.g., point *My* for myometrium, 2 cm laterally and caudally to the tip of the most advanced applicator, or the *A-line*, 2 cm laterally from the tip). A small uterus can be treated with a single tube, using a stepping source and increasing the dwell times at the fundus to obtain a pear-shaped isodose distribution (i.e., inverted pear). However, an individualized approach is preferable with dose specification at the serosa at the site of the tumor. MRI or CT is used, ideally with the intrauterine tubes in place, to determine the depth of tumor invasion and the myometrial width in relation to the tubes. CT or MRI planning ensures adequate coverage of the tumor while avoiding overdosing in the bowel surrounding the uterus. Specific uterine applicators for HDR and PDR intracavitary brachytherapy are currently available. An intermediate-size uterus can be treated with a two-channel applicator (one applicator in each uterine cornu), which results in a pear-shaped isodose distribution at the fundus. For treatment of a large uterus with a tumor deeply infiltrating the myometrium, Heyman packing using Norman-Simon applicators is preferred and although rarely used. The American Brachytherapy Society has published treatment guidelines.[335]

For HDR brachytherapy alone, more commonly used fractionations include five fractions of 7.3-Gy HDR therapy prescribed at 2 cm from the midpoint of the uterine sources, or if used in conjunction with EBRT, two fractions of 8.5 Gy to four fractions of 5.2 Gy are suggested. CT or MRI is recommended to optimize dosing to the thickness of the uterine wall in individual patients.

Vaginal Brachytherapy

In patients with vaginal recurrence the most common site is the upper vagina, and adjuvant vaginal cuff brachytherapy has long been used to decrease the risk of vaginal cuff recurrence after hysterectomy. Since the mid-1990s, HDR fractionated VBT alone has been increasingly used as adjuvant therapy after hysterectomy in selected patients. There are institutional variations in the target volume for VBT, especially the length of the vagina to be treated: the vaginal cuff, proximal half or two thirds of the vagina, or the entire vagina. Vaginal recurrences are mainly located in the vaginal vault and upper vagina.[142] It is recommended that only the upper half or proximal 3 cm or 4 cm of the vagina be treated, because this is associated with lower complication rates (i.e., vaginal stenosis and fistula) than treating the entire length of the vagina. Although most radiation oncologists use vaginal cylinders treating the upper half to two thirds of the vagina, others claim that vaginal colpostats have the advantage of providing a better dose distribution around the vaginal vault with lower doses to the bladder and rectum.[151,336]

Convenient, moderate-dose fractionation schedules of VBT provide high vaginal control rates (>95%) and low morbidity rates.[337] The use of higher doses increases the risk of side effects and does not further increase the vaginal control rates. Based on these data, optimal LDR and HDR schedules seem to be those that give an equivalent of 45 Gy to 50 Gy to the mucosal surface of the upper half of the vagina. Typical examples are LDR 30 Gy, specified at a 5-mm depth at a dose rate of 60 cGy to 65 cGy per hour and given in one session of 2 days to 3 days, or HDR 21 Gy, specified at a 5-mm depth and given in three fractions of 7 Gy each, 1 week apart, as used in the PORTEC-2 trial.[148]

Usually, the dose is specified at 5 mm from the surface and 5 mm from the apex of the vagina. Because of the distention of the vagina after placement of the vaginal cylinder, it has been argued that the wall becomes less than 5 mm thick and that the reference isodose should be chosen at a 3-mm, 4-mm, or 5-mm depth, depending on a clinical estimation of the mucosal thickness. By individualizing the depth and avoiding applicators with small diameters, the rate of vaginal side effects was significantly reduced (17% and 1% for grades 1 and 2, compared with 26% and 8%), without a difference in vaginal control.[338] In individual cases, the target depth can be adjusted according to the clinical situation. For example, in case of a thick scar at the cuff the dose can be specified at 10 mm from the apex and 5 mm along the wall. CT or MRI planning should be used for treatment of such thicker targets and especially for brachytherapy treatment of vaginal recurrence. CT- and MRI-compatible cylinders and colpostats are available for this purpose.

VBT can be performed as an outpatient procedure, especially when a vaginal cylinder is used, for which no sedation or anesthesia is needed. If vaginal colpostats are used with vaginal gauze packing, intravenous sedation or general or regional anesthesia is commonly used. Most U.S. centers use fentanyl and midazolam intravenously for sedation. With the patient in the lithotomy position, an indwelling bladder catheter is inserted in the bladder and the balloon is filled with radiopaque contrast material to visualize the bladder base on applicator placement radiographs. Two radiopaque metal seed markers may be inserted submucosally in the vaginal cuff to assess applicator position on radiographs. The colpostats are positioned in the upper vagina against the cuff. Vaginal packing is used to secure the colpostats in place and to displace the bladder base and anterior rectum away. When a vaginal cylinder is used, the largest diameter that smoothly fits the vagina should be chosen to increase the relative dose at depth compared to the surface. With smaller diameters the volume of the vaginal mucosa receiving more than 150% of the dose is increased. The applicator is held in place by an external immobilization device. Traditionally, orthogonal radiographs are obtained to verify the appropriate placement of the applicator in relation to the vaginal cuff markers and for dosimetric calculations. A small amount of rectal contrast agent may be injected or a marker placed before the lateral radiograph is filmed. Increasingly, CT or MRI planning is used, especially if brachytherapy is given as a boost for treatment of vaginal recurrence. After the appropriate quality assurance checks, the HDR treatment is administered, which takes less than 10 minutes, depending on the dose and source activity. Applicators and catheters are then removed, and the patient is discharged.

For vaginal recurrences a multichannel cylinder applicator may be used to individually tailor the dose distribution to various parts of the vaginal circumference and to varying depth depending on the tumor configuration. Interstitial brachytherapy (e.g., with interstitial needles inserted through ovoids or ring applicator) may also be used when the thickness of vaginal tumor cannot be adequately treated with intravaginal sources in a (multichannel) cylinder.

TREATMENT ALGORITHM, CONCLUSIONS, AND CHALLENGES

Management of each endometrial cancer patient must consider the risk factors for tumor relapse and tolerance of the treatment that is being considered. Ideally, patient evaluation and surgery should be performed by a gynecologic oncologist or by a gynecologist with specific oncology expertise and dedication. Deciding on the indication for and extent of surgery and adjuvant therapy requires a multidisciplinary team of gynecologic oncologists, radiation oncologists, and medical oncologists. The approach to the management of

endometrial cancer patients is summarized in the treatment algorithm (Figure 59-6) and the follow-up algorithm (Figure 59-7).

The main developments in radiation therapy for endometrial carcinoma have been the reduction of indications for pelvic EBRT, shifting the role of RT in low-risk disease toward treatment reserved for patients with vaginal or pelvic relapse, the standard use of VBT alone for patients with high-intermediate-risk disease, and the studies of adjuvant chemotherapy and RT for high-risk and locally advanced disease. IMRT techniques have been developed that reduce the risk of acute and late complications, especially in conjunction with extended surgery or chemotherapy.

The role of pelvic irradiation in treating intermediate-risk endometrial carcinoma has been established with the results of randomized trials. Pelvic RT provides a highly significant improvement of local control, but it does not increase OS and does not reduce the risk of distant metastases. For patients at high-intermediate risk features based on the presence of major risk factors (grade 3, deep myometrial invasion, age older than 60 years, LVSI; PORTEC criteria, or GOG/high-intermediate-risk criteria having similar results), a treatment shift from pelvic EBRT to VBT alone has occurred based on results from the ASTEC and PORTEC-2 trials. Patients with FIGO 2009 stage IA, grades 1 and 2 disease should be observed after TAH-BSO. The inclusion of such low-risk cases in clinical

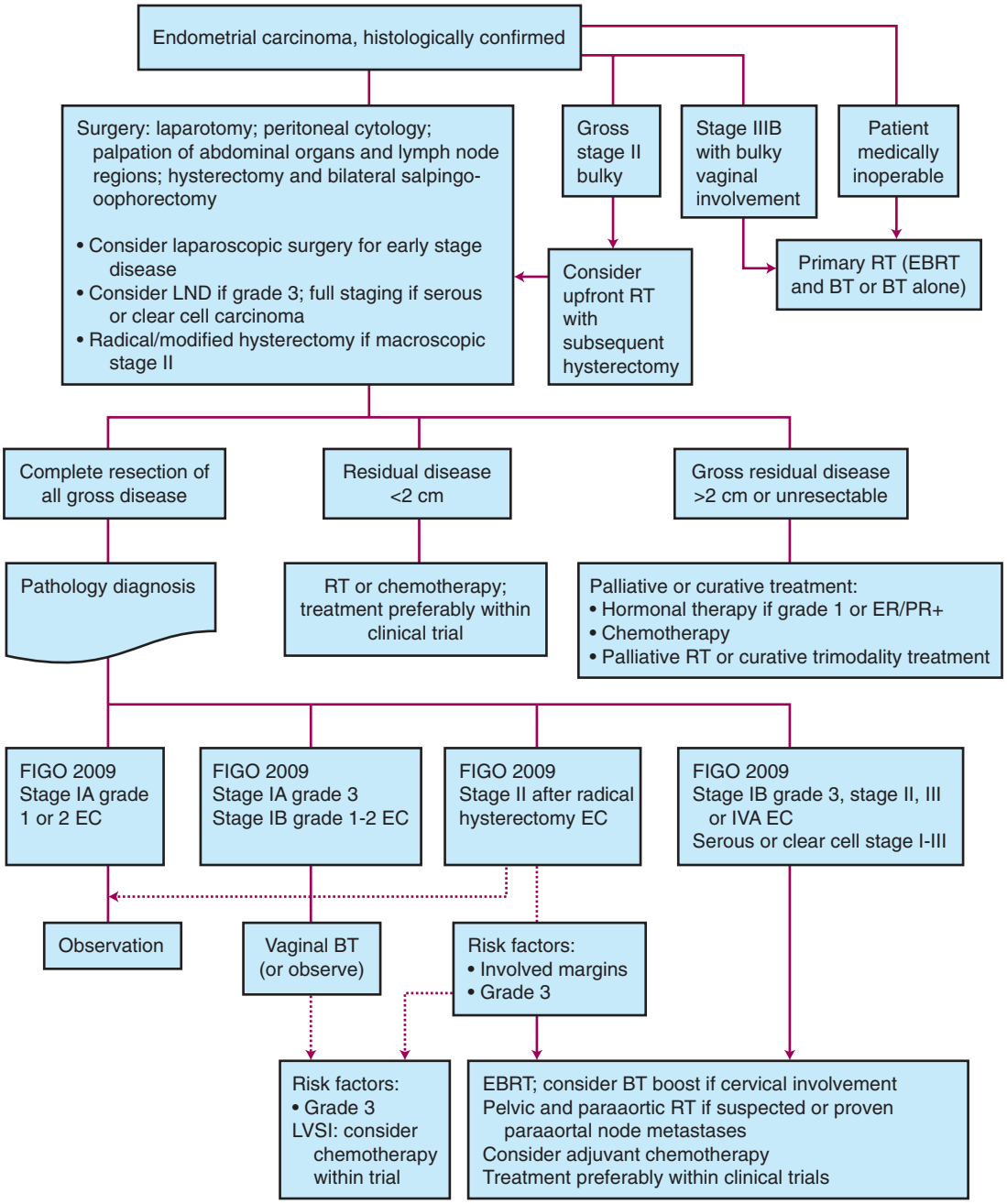


Figure 59-6 Treatment algorithm for patients with endometrial carcinoma. *BT,* Brachytherapy; *EBRT,* external beam irradiation; *ER,* estrogen receptor; *LND,* lymph node dissection; *PR,* progesterone receptor; *RT,* radiation therapy; *EC,* endometrial cancer.

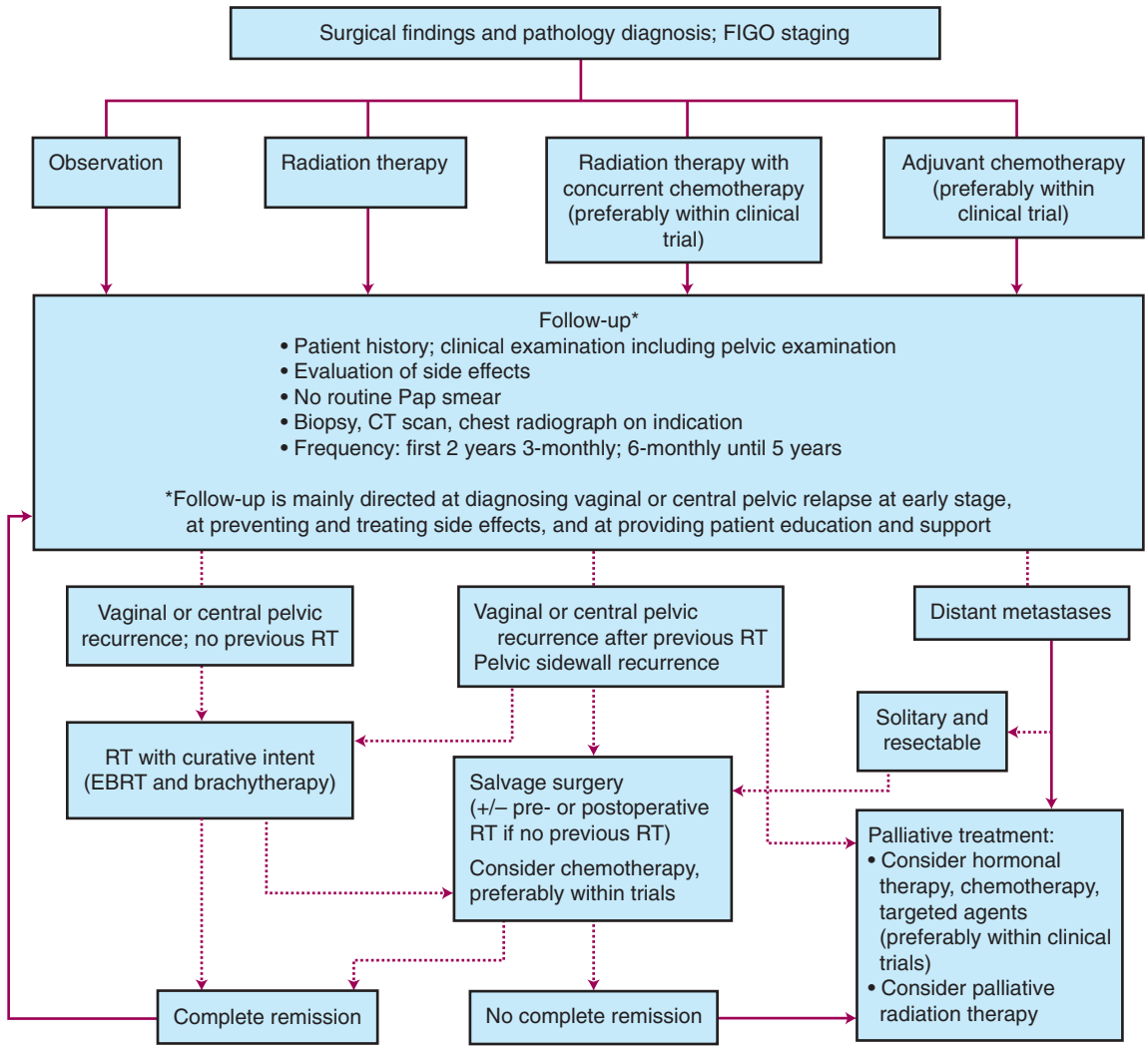


Figure 59-7 Follow-up algorithm for patients with endometrial carcinoma. *CT,* Computed tomography; *EBRT,* external beam irradiation; *RT,* radiation therapy.

studies of the role of RT or of lymphadenectomy reduces the likelihood of observing a benefit for the higher-risk subsets and subjects these patients to increased risks of toxicity. Radiation therapy is an effective salvage treatment for vaginal relapse in patients not previously irradiated, with 80% to 90% local control rates and 5-year OS of 50% to 70%.

High-risk endometrial carcinoma is the challenge for current and future research. Ongoing trials need to evaluate concurrent chemoradiation, adjuvant chemotherapy, and targeted agents.

Recent and current trials for high-risk disease are investigating the roles combinations of adjuvant radiation therapy and chemotherapy (see eTable 59-1). The PORTEC-3 trial (pelvic radiation alone versus RT with two cycles of concurrent cisplatin followed by four cycles of carboplatin/paclitaxel) was recently closed at a total of 686 randomized patients with high risk or locally advanced stage disease. The GOG-249 trial (pelvic radiotherapy alone versus VBT followed by three cycles of carboplatin/paclitaxel) recruited 601 patients with stages I to II tumors with high-intermediate or high risk factors; first results were reported at the 2014 Annual Meeting of the Society of Gynecologic Oncology. With a median follow-up of 24 months, there were no differences in RFS or OS (RFS, 82% versus 84% for pelvic RT versus brachytherapy/chemotherapy; OS, 93% versus 92%).[196]

The ongoing GOG-258 trial aims to include 804 women with stages III to IVA disease (six cycles of carboplatin/paclitaxel with no radiotherapy versus the same regimen of RT and chemotherapy as used in PORTEC-3) (eTable 59-1). The ENGOT-EN2-DGCG trial (adjuvant chemotherapy or observation for patients with early stage high-risk disease who are node-negative after lymphadenectomy) aims to include 678 patients (adjuvant VBT is permitted in either arm). Results of these trials are awaited and may guide future adjuvant strategies.

Targeted therapies may yet prove to be effective, especially in the treatment of serous carcinoma. IMRT techniques that reduce the risk of complications should be further developed, especially in conjunction with multimodality treatment. For patients with locally advanced disease in whom trimodality treatment (i.e., surgery, irradiation, and chemotherapy) is indicated, laparoscopic staging followed by preoperative concurrent chemoradiation, restaging, and surgical resection alone or plus IORT and adjuvant chemotherapy should be evaluated.

Quality-of-life and cost-effectiveness analyses have become essential because patients with high-risk and locally advanced

stage disease are typically elderly and have concurrent medical illnesses. The approach to these patients needs to balance the benefit of more aggressive adjuvant therapies with the cumulative toxicities. The ultimate goal of treatment for endometrial cancer patients remains the maximization of event-free and complication-free survival.

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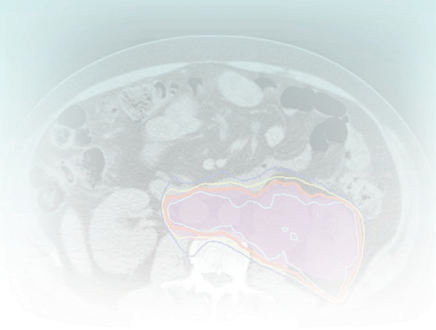
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CHAPTER

60 Cancers of the Vulva and Vagina



Anthony Henryk Russell and Neil S. Horowitz

VULVAR CARCINOMA

INCIDENCE

Vulvar carcinoma accounted for an estimated 5150 cancer cases and 1080 deaths in the United States in 2015, comprising 0.58% of all cancers in women, 5.1% of gynecologic malignancies, 0.36% of cancer deaths in women, and 3.5% of gynecologic cancer deaths.[1]

BIOLOGIC CHARACTERISTICS

Eighty percent to 90% of primary vulvar tumors are squamous cell carcinomas. Carcinomas of the vestibular (Bartholin) gland complex may be adenocarcinomas or adenoid cystic carcinomas, but 30% to 50% will have squamous histology as they arise in ductal epithelium.

Younger vulvar cancer patients more commonly smoke and have a higher incidence of human papillomavirus (HPV) infection, which are factors associated with vulvar intraepithelial neoplasia (VIN). In older patients, HPV infection is less prevalent, and invasive vulvar cancer is often seen arising in a background of lichen sclerosus, although only 4% of patients with lichen sclerosus will develop clinically apparent neoplasia.

STAGING EVALUATION

Primary tumor size and anatomic distribution, depth of invasion, presence of capillary-lymphatic space involvement, and width of surgical margins correlate with risk of recurrence at the primary site. Number, size, location of lymph node metastases, and extracapsular extension in metastatic groin adenopathy all correlate with risk of regional recurrence, distant dissemination, and survival. Many of these factors are included in the hybrid clinical-pathologic International Federation of Obstetrics and Gynecology (FIGO) 2009 staging formalism.[2]

Pretreatment evaluation includes patient history and comprehensive physical examination including inspection and palpation of the primary tumor and clinical assessment of inguinofemoral lymph nodes. Regional imaging assessments may include positron emission tomography/computed tomography (PET/CT), magnetic resonance imaging (MRI), ultrasonography, and the combination of blue dye and lymphoscintigraphic sentinel node localization. Regional imaging may aid in understanding extent of disease, guiding biopsies, and selecting therapeutic modalities, but regional imaging findings alone do not affect assignment of stage.

PRIMARY THERAPY

Except when surgery would compromise functionally important midline structures (clitoris, urethra, vagina, anus), radical local excision is the preferred initial therapy for invasive primary disease. When the location and extent of the primary tumor suggests that surgery will not be able to accomplish secure negative margins (≥8 mm in fixed tissue), initial chemoradiation may precede conservative local excision or definitive chemoradiation may be used.

Management of potential groin metastases will be contingent on clinical and imaging assessment as well as the degree of laterality (distance from midline) and the modality selected for initial therapy of the primary tumor. Positive sentinel node biopsy mandates further treatment to the groin, by comprehensive, therapeutic superficial, and deep groin node dissection or groin radiation or chemoradiation. Fixed or ulcerated groin nodes indicate chemoradiation should be the initial intervention.

For advanced primary lesions invading or encroaching on functionally or cosmetically important midline structures, initial chemoradiation followed by conservative excision is preferred to extirpative surgery. Chemoradiation alone may be curative in some patients with locally advanced disease for whom an exenterative procedure would be the only feasible surgical alternative.

ADJUVANT THERAPY

Adjuvant local vulvar and tumor bed irradiation may be administered for risk factors including involved or close surgical margins (<8 mm), or capillary lymphatic space involvement and deep invasion (>5 mm). For one macroscopic node metastasis, two or more microscopically involved nodes, or extracapsular extension, unilateral or bilateral radiation to the groin and low pelvic lymph nodes is given following surgical resection of inguinofemoral nodes. Controversy exists over whether the clinical target volume (CTV) should include the primary tumor bed. Generally, when adjuvant radiation is administered for nodal contamination, the CTV will include the primary tumor bed. There is no accepted role for adjuvant cytotoxic chemotherapy except when administered concurrently with radiation (chemoradiation).

Corrected 5-year survival for surgical patients with negative nodes is 96% to 70% depending on the extent of the primary (stages I to II). When groin lymph nodes are contaminated (stage III), corrected survival is approximately 50%. However, patients with only one microscopic intracapsular metastasis can expect a 5-year actuarial survival of 68% to 94%,[3,4] whereas patients with two nodes involved will have an expectation of 80%[3] and patients with three or more nodes involved or extracapsular extension will be cured in only 25% of cases.[5]

PALLIATION

Radiation therapy often provides relief of pain or bleeding. Chemotherapy alone has minimal or no impact on disseminated disease.[6]

Melanoma, basal cell carcinoma, Merkel cell tumor, sarcoma, carcinoid, apocrine gland cancer, Paget's disease, and metastatic lesions constitute rare histologic types of vulvar malignancy.

For patients with intact, small primary tumors (≤4 cm) in whom clinical or imaging assessment reveal no obvious spread to nodes, negative sentinel node biopsy with subsequent groin observation has emerged as satisfactory management instead of more morbid comprehensive groin node dissection. When groin nodes are grossly contaminated but resectable, options include debulking node surgery followed by planned adjuvant regional radiation and chemoradiation or initial radiation and chemoradiation followed by planned excision of residual nodal disease.

Late radiation sequelae may be less severe if conservative surgery can be accomplished following a moderate preoperative dose of chemoradiation rather than chemoradiation escalated to radical intensity.

Neoadjuvant chemotherapy alone before surgery for locally advanced disease has been associated with less predictable responses than chemoradiation, and complete pathologic responses are rare. Therapy with biologics is investigational.

Vulvar carcinoma is an uncommon disease, accounting for only 5.1% of all gynecologic cancers and only 0.003% of all malignancies in the United States in 2015.[1] Diversity in the location and clinical extent of disease at presentation, ranging from in situ or small-volume invasive primary disease to neglected extensive tumors that may locally extend to involve the vagina, urethra, anus, or ischial rami suggests the wisdom of individualized treatment. The presence or absence of metastatic spread to inguinal lymph nodes adds to the heterogeneity of the patient population at the time of diagnosis. The range of patient age at diagnosis, the extent of medical comorbidities, and the diversity of patient concerns regarding function and cosmesis further complicate treatment decisions. Appreciation of the broad clinical spectrum of patients afflicted with vulvar cancer and the utility of radiation and chemoradiation has resulted in major changes in disease management in the past 30 years.

Historically, radical vulvectomy and bilateral inguinal node dissection was the standard approach for the majority of patients, regardless of disease extent.[7-10] Consequent to the chronic, often debilitating physical and psychological sequelae of radical vulvectomy in long-term survivors, questions arose regarding the need for radical vulvectomy in patients with limited disease at diagnosis. Unsatisfactory rates of local-regional control in patients with advanced disease as well as the morbidities associated with exenterative surgery stimulated exploration of novel combinations of therapies. Increasing awareness of the sensitivity of squamous vulvar cancer to radiation and chemoradiation further suggested management changes.

Although optimal therapy for many situations remains to be defined, avenues of change include conservative surgery for selected patients with early disease and multimodality therapy (chemoradiation alone, or integrated with less extensive surgery) for the patients with locally advanced disease. Chemoradiation is increasingly accepted as alternative therapy for patients with disease that would require partial or total exenteration if treated by initial surgery. Pre- or postoperative adjuvant radiation or chemoradiation are now commonly used to complement conservative surgery in patients with adverse clinical or histopathologic features.

Mature published results remain sparse for patients treated on the basis of the newer concepts of integrated multimodality management tailored to the site and extent of disease. Valuable information continues to accumulate from Phase II study reports, most of which support the concept of integrated, multimodality therapy. Selecting the order in which therapies are employed, defining the intensity and scope of radiation and the extent of surgery when these complementary modalities are used sequentially, and optimizing the choice and schedule of chemotherapy when combined with radiation represent ongoing challenges in treatment refinement.

ETIOLOGY AND EPIDEMIOLOGY

No universal cause for vulvar cancer has been identified, and it is probable that the pathogenesis is multifactorial.[11] Many patients with vulvar carcinoma have had previous malignant or premalignant lesions of the genital tract.[12-14] Between 2% and 5% of VIN 3 lesions (severe dysplasia or carcinoma in situ) will progress to invasive disease.[15] The risk factors for progression to invasive cancer are poorly understood but do include advanced age. One study observed that that the relative risk for vulvar or vaginal carcinoma after treatment for cervical carcinoma was 2.9% regardless of whether the patient received radiation for treatment of the cervical cancer. Compromised immune status, whether iatrogenic in the setting of organ transplantation, congenital, or acquired based on HIV infection, leads to an increased risk for cancers in the lower genital tract, including the vulva and vagina.[16] Improvement in immune function with highly active anti-retroviral therapy (HAART) may decrease the risk in patients with HIV,[17-21] although longer survival with HAART may permit emergence of papillomavirus associated ano-genital malignancies in long-term survivors of HIV infection.[22,23]

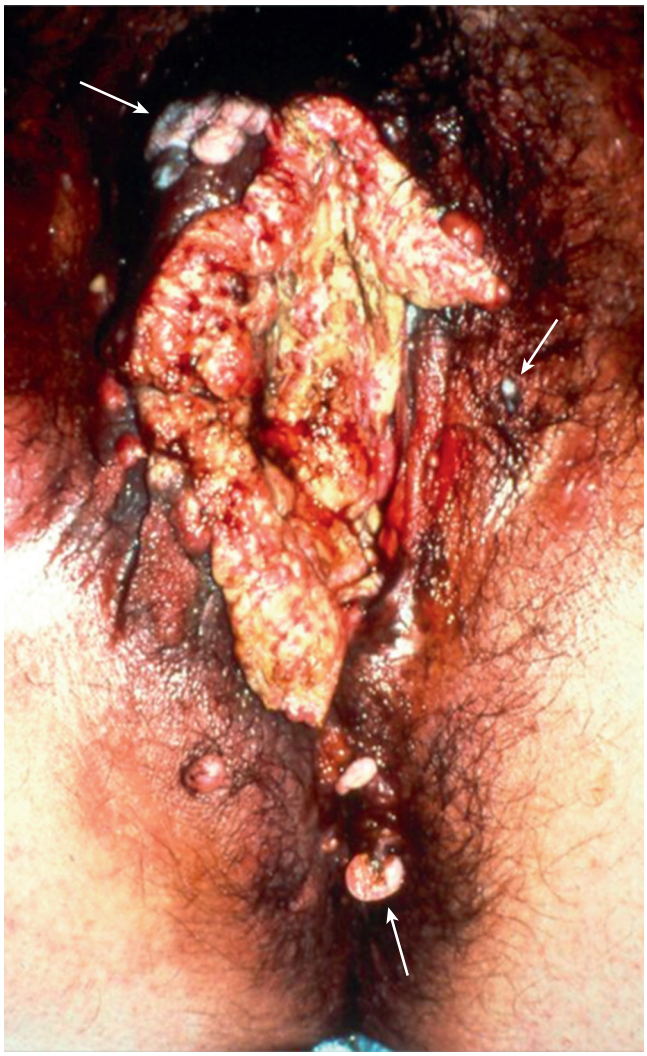
HPV has been implicated as a major cause of vulvar cancer. Brinton et al established a relative risk of vulvar cancer of 15.2 when there is a history of condylomata acuminata.[24] HPV has been detected widely in sexually active women. The type of HPV is related to the risk for benign versus malignant tumors of the vulva. In patients with condylomata acuminata, the detected HPV is usually type 6 or 11, whereas for vulvar in situ neoplasia or vulvar carcinoma, HPV 16 and 18 are more common.[25,26] Invasive vulvar cancer and condyloma may be present synchronously in the same patient (eFigure 60-1), delaying diagnosis of malignancy in some patients. Similarly, delay in diagnosis may be the consequence of failing to examine a patient with known, symptomatic lichen sclerosus (eFigure 60-2). Multiple studies have investigated the presence of HPV in vulvar carcinoma. It may be detected in both primary tumors and nodal metastases.[27,28] Review of published data employing polymerase chain reaction or hybrid capture assays for HPV DNA detection in 2790 patients with invasive vulvar cancer, 1320 patients with VIN 2/3, and 71 patients with VIN 1 reveals HPV prevalence in invasive cancer to be 40.1% in invasive lesions, 80.4% in VIN 2/3, and 77.7% in VIN 1, respectively.[278] HPV 16 serotype was the most common, detected in 29.3% of invasive cancers and 71.2% of VIN 2/3. Globally, HPV 16, 33, and 18 comprise the causative agents in most HPV-related vulvar malignancies with HPV 16 comprising 72%.[29]

Smoking is an additional risk factor for vulvar carcinoma, and the combination of smoking with a history of genital warts results in a strong increase in the relative risk for vulvar cancer.[13,24] It is possible that smoking and HPV infection have a synergistic effect on the genesis of vulvar cancer with smoking functioning as a promoter.[30,31]

It has been observed that there are two broadly different groups of patients with vulvar cancer. The first consists of younger patients who more frequently smoke, are at higher risk for HPV infection, and whose invasive cancers are commonly associated with VIN. The second, and more common group, consists of elderly patients whose disease may be unrelated to smoking or HPV infection but in whom lichen sclerosus and squamous hyperplasia are common associated findings.[36] These two groups of patients may have different prognoses and may carry different risks for development of second malignancies in residual vulvar tissue when conservative surgery, with or without adjuvant radiation, preserves substantial vulvar tissue.[28,37,38] At this time, data regarding the independent prognostic significance of HPV are conflicting.[28,39] This issue may be resolved through larger series of patients suitable for disciplined multivariant analysis controlling for all other known prognostic factors and treatment modalities.

PREVENTION AND EARLY DETECTION

With the exception of cancers arising in the Bartholin's complex, most vulvar malignancies arise from cutaneous surfaces readily accessible to examination both visibly and palpably. Invasive lesions should be diagnosed when small and easily treated. Unfortunately, most advanced vulvar cancers are a result of patient delay or neglect or physician failure to diagnose. Some elderly patients may be mentally impaired. Modesty, anxiety, or frank denial may lead a patient to ignore



eFigure 60-1 Synchronous presence of vulvar and anal condylomata *(white arrows)* and invasive squamous carcinoma that can delay cancer diagnosis. Condylomata antedated cancer in this immunologically intact patient, illustrating the difficulties inherent in developing effective polyvalent human papillomavirus (HPV) vaccines.



eFigure 60-2 Squamous cancer arising in an elderly patient with clinical stigmata of lichen sclerosis including white thickening of vulvar skin, introital narrowing, and fusion of the major and minor labia.

Data are conflicting as to the etiologic role of vulvar dystrophies (lichen sclerosus and squamous cell hyperplasia) in the cause of vulvar cancer. These epithelial alterations may be seen in approximately half of patients with vulvar cancer.[32-34] Patients with vulvar cancer and associated lichen sclerosus are, on average, significantly older than patients with newly diagnosed lichen sclerosus with or without squamous hyperplasia.[35] However, less than 5% of patients with these epithelial alterations will progress to invasive vulvar malignancy.

or minimize symptoms of pruritus, oozing, bleeding, and pain. There is little justification for failure of a physician to perform a thorough visual inspection and pelvic examination when patients have such symptoms.

No known measures to prevent invasive vulvar cancer exist except for the appropriate treatment of high-grade VIN when it is detected. Encouraging results from Phase III trials of HPV vaccines suggest that substantial reductions can be expected in the incidence of VIN 2/3 and invasive vulvar malignancies in addition to corresponding pathologies of the cervix and vagina when prophylactic immunization is widely implemented.[40] At this time, the target population for whom efficacy seems most likely consists of adolescents who are sexually naïve and unexposed to HPV. Whether comprehensive population coverage can be logistically accomplished given multiple economic, cultural, and logistical barriers to implementation in countries where genital HPV infection is a leading cause of subsequent cancer remains to be seen. As VIN-3 may be associated with an occult invasive lesion in as many as 20% of symptomatic patients, care must be taken when employing treatment techniques that do not include full-thickness histologic evaluation.[41] Excisional techniques, provided that there is minimal loss of functionality and cosmesis, are preferable to ablative techniques without histologic material for study. Wedge biopsy or excisional biopsy of smaller lesions is suggested for most vulvar abnormalities, if necessary under colposcopic guidance. Even if vulvar lesions appear to have a warty appearance and are believed to be benign, confluent warts should undergo biopsy to exclude an underlying diagnosis of squamous cell carcinoma.

A history of smoking tobacco is associated both with VIN and invasive vulvar malignancy. Patients who smoke should be encouraged to quit because the statistical risk of anogenital malignancy associated with former smoking is observed to be substantially less than that associated with current smoking and diminishes with increasing time since cessation of smoking.[31] Additionally, women with vulvar or vaginal cancer appear to have a fourfold increased risk of subsequently developing a second primary cancer of the lung.[42]

Because of the risk for multifocal disease throughout the lower genital tract and anus, it is appropriate to perform pap smear and colposcopy of the cervix, vagina, and vulva, and digital rectal exam or anoscopy to evaluate for the presence of synchronous lesions at other sites.

PATHOLOGY AND PATHWAYS OF SPREAD

Pathology

Squamous cancer is the most common malignant lesion of the vulva and constitutes 80% to 90% of vulvar tumors. Variants of squamous cancer include cancers with discontiguous, infiltrative borders permeating lymphatic spaces with a so-called "spray" pattern of local invasion[43-45] and verrucous cancers[46-49] (Figure 60-1, *A* and *B*).[50] Sarcomatoid differentiation is seen in a minority of squamous cancers and can be associated with an aggressive course.

Poorly differentiated cancers with a trabecular growth pattern manifesting fingerlike projections and an infiltrative border with discontiguous islands and nests of malignant cells may spread to regional nodes, even when small, and frequently recur beyond the margins of local excision within dermal lymphatic channels. Recognition of this pattern of growth should prompt consideration of adjuvant radiotherapy.

Verrucous cancers may clinically manifest a warty appearance resembling a cauliflower, with exuberant hyperkeratosis microscopically. Broad, bulbous borders characterize these tumors, which rarely metastasize to regional nodes. Morphologic and biologic studies on 10 cases of verrucous carcinoma of the vulva suggest the theory that verrucous cancers constitute a discrete clinicopathologic subset of vulvar cancer.[51]

Other, much less common tumors found in the vulva include malignant melanoma, basal cell carcinoma, Merkel cell tumors, carcinoid, transitional cell carcinomas, adenoid cystic carcinoma, vulvar Paget's disease, and a variety of sarcomas. Tumors metastasizing from other sites may become manifest in the vulva.[52]

Melanomas constitute less than 10% of primary tumors, but are the second-most common malignancy of the vulva. Even tertiary referral centers will see only one or two such patients annually. Melanomas may arise de novo or from preexisting junctional or compound nevi. Rare, amelanotic vulvar melanomas may occur. Prognosis correlates with depth of invasion using the classifications of Clark, Breslow, and Chung, and with the presence or absence of spread to regional nodes.[53-55]

Primary malignant tumors of the vulva may arise in the Bartholin's complex, and some of these are variants of adenocarcinomas. Adenoid cystic carcinomas uncommonly disseminate to regional nodes and may have an indolent natural history with late local recurrence and hematogenous dissemination. Perineural invasion is a common feature, and these tumors resemble adenoid cystic cancers of the salivary glands.[56] Tumors in the Bartholin's areas may also be squamous and are thought to arise in ductal squamous epithelium. Bartholin's tumors tend to be deeply infiltrative and solid, often with the overlying skin remaining intact. This clinical presentation may be confused with benign cysts or infection, causing delay in diagnosis, and difficulty in accomplishing surgical clearance with wide, negative margins because of proximity to the anorectum and the ischial ramus.[57]

The International Society for the Study of Vulvar Disease (ISSVD) recommended abandoning the term *microinvasion*

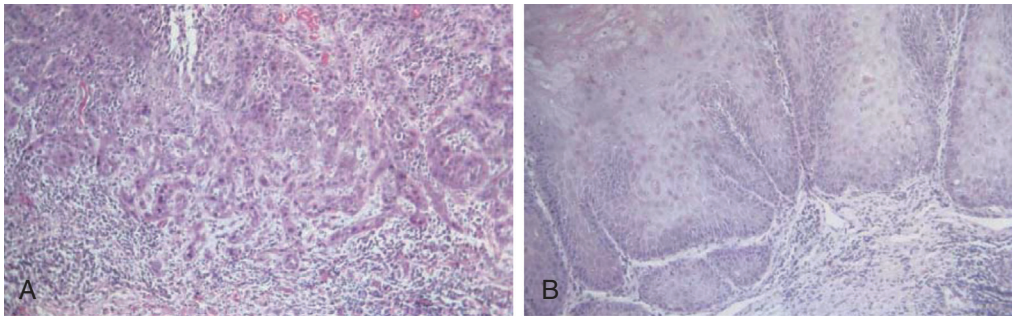


Figure 60-1 Variants of squamous cell cancer of the vulva. **A,** Infiltrative pattern of growth with discontinuous satellites of malignant cells, sometimes called a *spray pattern* of growth. **B,** Verrucous cancer with a bulbous, pushing front of invasion into the surrounding stroma.
Photomicrographs courtesy Dr. Richard Oi, Department of Pathology, University of California at Davis.

when applied to carcinoma of the vulva and proposed the current use of stage IA that incorporates criteria for both tumor size and depth. The depth of invasion is defined as the distance from the epithelial stromal junction of the most superficial adjacent dermal papillae to the deepest point of invasion. Stage IA is defined as a solitary squamous cancer of the vulva measuring less than 2 cm in diameter, with clinically negative nodes where the depth of invasion is 1 mm or less.[58,59] This definition encompasses the previous understanding of microinvasion because the risk of nodal involvement with invasion less than 1 mm is close to 0%. In addition to tumor stage and depth, other pathologic features of the primary should be noted including presence or absence of vascular space invasion, tumor grade, and tumor growth pattern.[60]

Pathways of Spread

Vulvar cancer spreads by direct extension to adjacent structures including the vagina, urethra, perineum, anus, and ischial rami. Tumor may spread by embolization through the lymphatics to the regional nodes. Permeation of local lymphatics is uncommon (eFigure 60-3), but may account for the occasional patient with recurrence in the skin bridge conserved when surgery has employed separate incisions for the primary and the regional node dissection. This is rare in the absence of extensive groin node metastases.[61]

The lymphatics of the vulva (Figure 60-2) consist of a network that covers the entire labia minora, fourchette, prepuce, and distal vagina below the hymenal membrane.[50] Lymphatics coalesce anteriorly, forming larger trunks, which run lateral to the clitoris to the mons veneris, acquiring tributaries from the lymphatics of the labia majora, which run in a parallel fashion anteriorly from the perineal body. At the mons veneris, the vulvar lymphatic trunks diverge laterally to the inguinal nodes. Study of the localization of dye or radiolabeled tracer in regional lymph nodes after focal injection of discrete sites in the vulva and on the perineum reveals that the lymphatic drainage of the perineum, clitoris, and anterior labia minora is often bilateral, whereas the lymph flow from well-lateralized sites (>2 cm from midline structures) in the vulva is predominantly to the ipsilateral groin.[62,63]

The vulvar lymphatics run through the vulva and do not traverse the labiocrural fold. Perineal lymphatics course lateral to the labiocrural fold through the superficial tissues of the upper medial thigh. In the radiation treatment of patients with advanced vulvar cancer that extends to the perineal skin, these lateral channels should be taken into consideration. Advanced vulvar cancer extending up the vagina proximal to the hymenal ring may spread through vaginal lymphatics directly to pelvic nodes.

Primary lymphatic drainage is usually to the superficial inguinal nodes with secondary lymphatic drainage through the cribriform fascia to the femoral nodes, with subsequent tertiary flow under the inguinal ligaments to the external iliac nodes. However, metastases have been reported to the femoral lymph nodes without involvement of the superficial inguinal lymph nodes, especially from carcinomas of the clitoris and Bartholin's gland.[63,64] Sentinel node studies have demonstrated primary lymphatic flow to deep nodes in as many as 15% of cases, and a Gynecologic Oncology Group (GOG) study also found an unexpectedly high incidence of ipsilateral groin recurrences secondary to presumed involvement of lymph nodes deep to the cribriform fascia despite prior negative superficial inguinal lymphadenectomy.[65] The actuarial risk of groin recurrence at 5 years was 16% (19 of 119) among a series of patients with vulvar cancer whose groins were treated with lymphadenectomy alone at M. D. Anderson Cancer Center, of whom 111 of 119 had only superficial inguinal node dissections. Of these 119 patients, 117 had groin node specimens negative for metastases.[66] In contrast, groin recurrence after superficial and deep groin dissection retrieving histologically negative nodes is 2% or less.[67-69]

Clinical assessment of groin node status by palpation is notoriously inaccurate; approximately 20% of groins judged

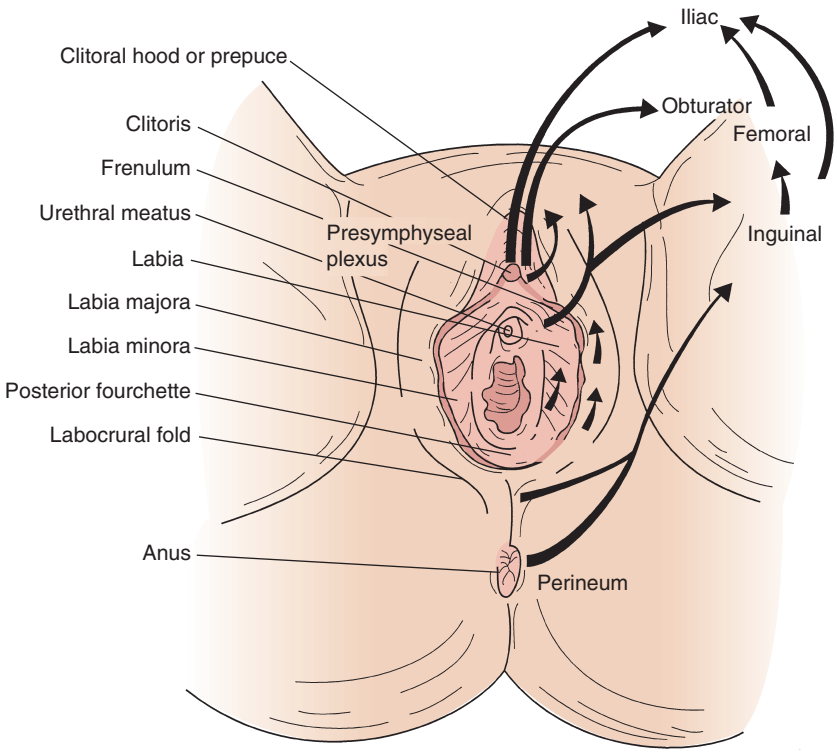


Figure 60-2 Lymphatic drainage of the vulva and perineum. *Arrows* indicate the flow patterns. *Adapted from Russell AH: Cancer of the vulva. In Leibel SA, Phillips TL, editors: Textbook of radiation oncology, ed 2, Philadelphia, 2004, WB Saunders, p 1179.*



eFigure 60-3 Pretreatment photograph of a patient with extensive dermal lymphatic permeation (peau d'orange) from a locally advanced squamous cancer of the vagina with extensive bilateral groin metastases.

TABLE 60-1 Assessment of Inguinofemoral Nodes by Palpation*

Node Status	Histologically (–), n (%)	Histologically (+), n (%)
Clinically (–)		
FIGO N0, N1*	363 (80.5)	88 (19.5)
n = 451		
Clinically (+)		
FIGO N2, N3*	53 (21.8)	190 (78.2)
n = 243		

Pooled data, six institutions.[7,70-74]
**1969 FIGO Node Staging.*
N0 No nodes palpable.
N1 Nodes palpable in either groin, not enlarged, mobile (not clinically suspicious of neoplasm).
N2 Nodes palpable in one or both groins, enlarged, firm, and mobile (clinically suspicious of neoplasm).
N3 Fixed or ulcerated nodes.

TABLE 60-2 Incidence of Groin Node Metastasis Correlated with Depth of Invasion for Primary Tumors 2 cm or Smaller

Depth of Invasion, mm	Patients, *n*	Positive Nodes, *n*	Percent (%)
≤1	120	0	0
1.1-2	121	8	6.6
2.1-3	97	8	8.2
3.1-4	50	11	22
4.1-5	40	10	25
>5	32	12	37.5

Pooled data, six series.[45,75-79]

TABLE 60-3 Primary Vulvar Tumor Size versus Nodal Risk[80]

Primary Tumor (cm)	Clinically Occult Node Metastases (%)
0-1.0	3/43 (7)
1.1-2.0	14/63 (22.2)
2.1-3.0	14/52 (26.9)
3.1-5.0	14/41 (34.1)
>5.0	3/15 (20)
Total	48/214 (22.4)

clinically nonsuspicious harbor occult node metastases, and approximately 20% of groins considered clinically suspicious for metastases containing only reactive or inflammatory nodes (Table 60-1). The frequency of inguinofemoral lymph node metastases is related to the depth of stromal invasion (Table 60-2). The incidence of occult nodal involvement in clinically nonsuspicious groin nodes treated by complete lymphadenectomy is cross-tabulated by primary tumor size in Table 60-3.

Metastases to the contralateral groin in the absence of ipsilateral groin metastases may be seen in up to 15% of patients with advanced primaries.[81] Metastases to contralateral groin nodes in the setting of uninvolved ipsilateral groins have been reported in patients with Bartholin's gland primaries,[82] and tumors of the anterior labia minora.[75] In the absence of spread to ipsilateral nodes, discrete (2-cm diameter or less), well-lateralized primary cancers limited to the vulva and not approaching midline structures manifest spread to contralateral groin nodes in less than 1% of patients undergoing bilateral lymphadenectomy.[75-78,83-85] However, 5 patients (2.6%) of 192 pooled patients with T1 lateralized cancers managed with ipsilateral groin dissection that was negative have manifested contralateral groin recurrence.[65,77,86-90] A theoretic explanation for this discrepancy is the possibility that dissection of negative groin nodes may be therapeutic in a small number of patients in whom routine sectioning of groin nodes (as opposed to pathologic ultrastaging) may fail to detect minute micrometastases consequent to undersampling.

The overall incidence of pelvic lymph node metastases is 5%. Lymphadenectomy will detect metastatic involvement in pelvic nodes in 15% to 28% of patients with metastases to inguinal nodes.[70-73,81,91,92] Pelvic node metastasis is extremely rare in the absence of groin node metastases and uncommon in the context of occult, microscopic involvement of a single groin node.

Hematogenous spread, usually to lung and bone, is unusual in the absence of prior inguinofemoral lymph node involvement and generally occurs late in the course of the disease. Most patients die with uncontrolled local-regional disease. However, in patients with three or more positive lymph nodes, the ultimate risk of hematogenous spread is 66%. In contrast, patients with fewer than three positive lymph nodes have only a 4% risk of hematogenous spread.[93,94]

BIOLOGY AND PROGNOSTIC FACTORS

In multivariate analysis the presence or absence of lymph node involvement remains the single-most important prognostic factor in outcomes of treatment for local-regional vulvar cancer.[95] For those with negative lymph nodes, the average 5-year survival from nine large literature series is 91% (range, 83% to 100%).[70-72,81,91,96-99] For those with involved lymph nodes treated with curative intent, the average 5-year survival is 52% (range, 38% to 61%).[3,70,72,91,96,97,100] Ninety-five percent of relapses after primary surgical treatment occur in the vulva, perineum, or groins.[68,76,101-105] The extent of lymphatic involvement is prognostic and includes type of nodal spread (unilateral or bilateral), volume of tumor in the involved nodes, extracapsular penetration number of positive nodes, and level of metastatic disease in the nodal chain.[3,5,27,97,106]

Because of the dominant negative impact of inguinal node metastasis, some investigators only examine primary tumor–related characteristics in relation to their correlation with nodal involvement rather than their impact on risk of recurrence of disease at the primary site.

A number of primary tumor–related characteristics, identified on multivariate analysis, predict for vulvar relapse regardless of nodal involvement, among them tumor size and depth of invasion.[72] Depth of invasion correlates not only with locoregional recurrence but also with the risk of node metastasis. Because most relapses after primary surgical treatment occur in the vulva or groin, to improve outcomes it is necessary to understand not only factors predictive of overall survival (OS), but those predictive of local recurrence and nodal relapse as well. Although risk probably increases continuously with depth, two data sets suggested that a sharply defined classification into low-risk versus high-risk groups may occur depending on tumor depth (first series—low risk <5 mm and high risk ≥5 mm; second series—low risk <9 mm, high risk ≥9 mm).[84,104] Heaps identified stage, width of surgical margin, depth of invasion, tumor thickness, growth pattern (infiltrative as opposed to pushing), and presence of vascular space

TABLE 60-4 Width of Surgical Margin and Risk of Local Recurrence[60,107,108]

Series/Author	Margin <8 mm	Margin ≥8 mm
Heaps	21/44 (48%)	0/91
Chan	13/61 (21%)	0/29
De Hullu*	9/40 (23%)	0/39
TOTAL	43/145 (30%)	0/159

**Surgical margin ≤8 mm versus >8 mm.*

invasion as factors predictive of local recurrence following primary surgery.[60]

Three publications (Table 60-4) have reported a clear association between risk of vulvar recurrence and width of surgical resection margins.[60,107,108] When microscopic margins are 8 mm or less in formalin-fixed tissue, local recurrence has been observed in 43 of 145 patients (30%). Allowing for estimated fixation shrinkage artifact between 25% and 45%, this correlates with a margin of at least 1.0 cm to 1.45 cm in unfixed tissue. A minimal clinical free space of 1 cm of uninvolved normal tissue provides a practical guideline for identifying patients who are highly likely to be advised to undergo further excision or postoperative local radiation for inadequate margins if treated by initial surgery. Under such circumstances, preoperative chemoradiation may be preferable to secure better margins and to reduce the scope of subsequent conservative surgery.

CLINICAL MANIFESTATIONS, PATIENT EVALUATION, AND STAGING

Clinical Manifestations

The virus-related cause of vulvar cancer in some patients, its association with preinvasive or invasive cancers in other parts of the lower genital tract, and the risk of recurrent or second cancers in conserved vulvar tissues in patients with cancer arising in association with lichen sclerosus suggests that vulvar cancer may be one manifestation of a multifocal disease or "field cancerization" in some patients.[37,109,110] However, at the time of diagnosis only about 5% of vulvar cancers are multifocal (eFigure 60-4).

Patients usually present with a vulvar mass or ulcer often following a variable history of pruritus or vulvar pain. Depending on the location and size of the lesion within the vulva, the patient may also complain of dysuria, difficulty with defecation, bleeding, or discharge. Rarely, patients may present with advanced inguinal node involvement, occasionally with ulcerating masses in the groins or with lower extremity lymphedema resulting from obstruction (eFigure 60-5, *A* and *B*). In rare instances, neglected vulvar cancer may directly extend to, or invade, adjacent bone (eFigure 60-6, *A* and *B*). Progressive organ destruction by untreated stage IV vulvar cancer may progress to incompetence of anal or bladder sphincters or urinary or fecal incontinence from fistula formation (eFigure 60-7).

Patient Evaluation

The diagnosis of vulvar cancer requires biopsy. For lesions smaller than 1 cm, a definitive excisional biopsy, including surrounding skin, underlying dermis, and connective tissue, may be preferable to obtain surgical margins of at least 1 cm grossly in all dimensions around the lesion. For larger lesions, a wedge biopsy should be performed. When vulvar dystrophy is present and the vulva is more difficult to assess visually, use of a colposcope may assist in identifying abnormal areas for appropriately directed biopsies. The remainder of the lower genital tract and anus should be examined, if necessary by colposcopy and anoscopy, to evaluate for the presence of synchronous preinvasive or invasive cancers.

Clinical evaluation of the groin nodes by palpation is inaccurate (see Table 60-1). Assessment of groin nodes is particularly compromised in the patient who is obese, when even superficial inguinal nodes may be several centimeters below the skin. Because of the imprecision of clinical assessment and the importance of the influence of nodal status or management, pathologic verification of nodal status is vital when feasible.

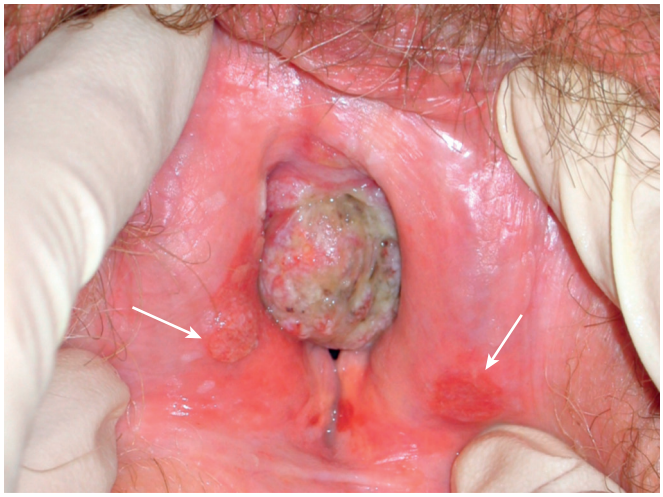
TABLE 60-5 FIGO Staging of Cancer of the Vulva

Stage	Description
Stage I	Tumor Confined to the Vulva
IA	Lesions ≤2 cm in size, confined to the vulva or perineum and with stromal invasion ≤1.0 mm,* no nodal metastasis
IB	Lesions >2 cm in size or with stromal invasion >1.0 mm,* confined to the vulva or perineum, with negative nodes
Stage II	Tumor of any size with extension to adjacent perineal structures (1/3 lower urethra, 1/3 lower vagina, anus) with negative nodes
Stage III	Tumor of any size with or without extension to adjacent perineal structures (1/3 lower urethra, 1/3 lower vagina, anus) with positive inguinofemoral lymph nodes
IIIA	(i) With 1 lymph node metastasis (≥5 mm), or (ii) 1-2 lymph node metastasis(es) (<5 mm)
IIIB	(i) With 2 or more lymph node metastases (≥5 mm), or (ii) 3 or more lymph node metastases (<5 mm)
IIIC	With positive nodes with extracapsular spread
Stage IV	Tumor invades other regional (2/3 upper urethra, 2/3 upper vagina), or distant structures
IVA	Tumor invades any of the following: (i) upper urethral or vaginal mucosa, bladder mucosa, rectal mucosa, or fixed to pelvic bone, or (ii) fixed or ulcerated inguinofemoral lymph nodes
IVB	Any distant metastasis including pelvic lymph nodes

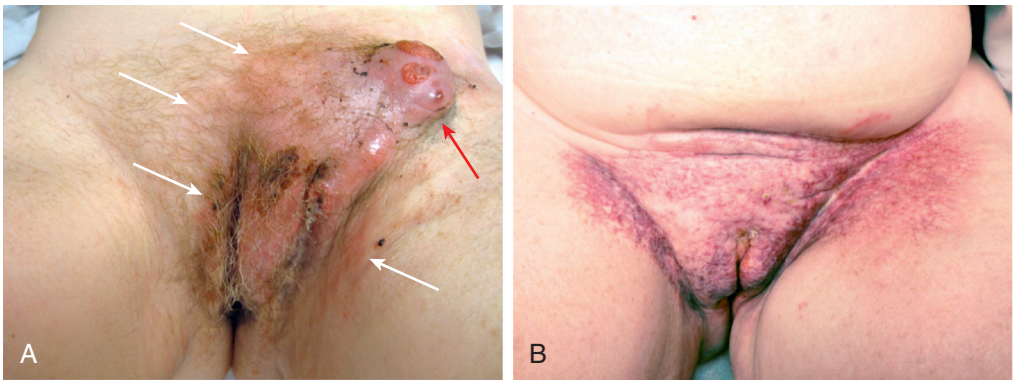
**The depth of invasion is defined as the measurement of the tumor from the epithelial stromal junction of the adjacent most superficial dermal papilla to the deepest point of invasion.*

Staging

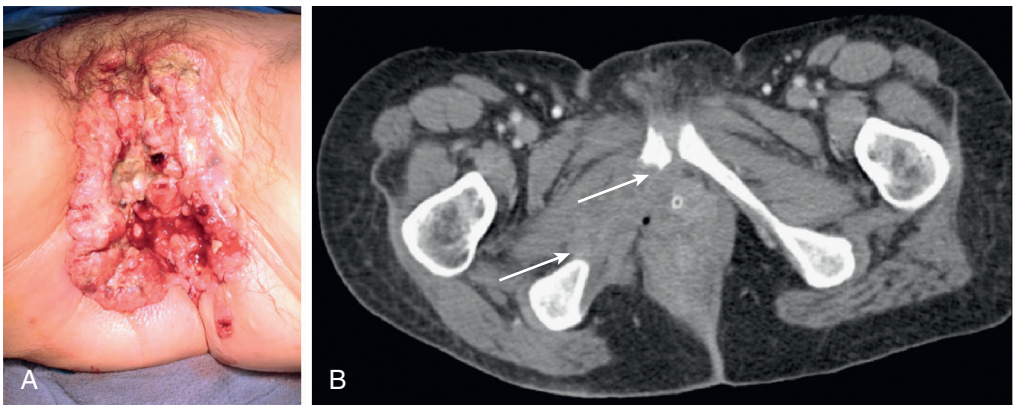
In 1988 FIGO introduced a surgical staging system for vulvar cancer that has since undergone several revisions, most recently in 2009 (Table 60-5).[2] Staging systems are intended to standardize reporting of treatment efficacy allowing comparison of the outcomes of treatment from different institutions and comparison of results employing different treatment strategies. Ideally, stage should not be employed to determine therapy and should be assigned before any major therapeutic intervention such as surgery. Unfortunately, the current clinical-pathologic system defines stage for many patients based, in part, on information derived subsequent to surgical treatment of the groin nodes. Because of the strong association between prognosis and the number and size of groin node



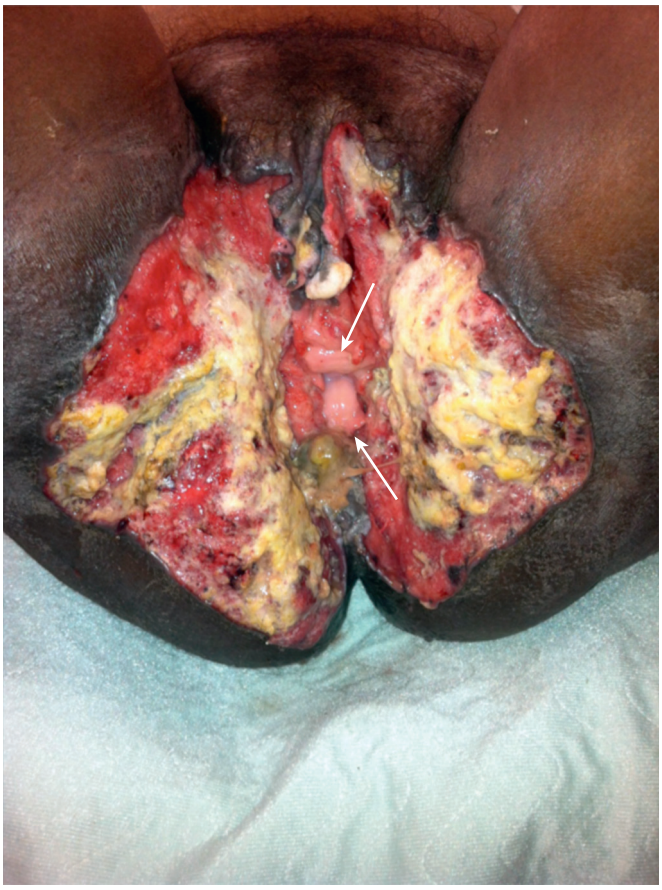
eFigure 60-4 Multifocal squamous cancer of the vulva with dominant mass involving distal urethra and vagina. Bilateral, somewhat symmetric, noncontiguous foci of invasive disease *(white arrows)* may represent autotransplantation of malignant cells onto moist mucosal surfaces, so-called *contact lesions*.



eFigure 60-5 **A,** Pretreatment photograph of a 50-year-old patient with a large vulvar cancer with bilateral groin metastases and extensive dermal lymphatic permeation *(white arrows)*. Bulky left inguinofemoral node metastases encased the femoral artery and vein and eroded through overlying skin *(red arrow)*. **B,** Photograph of patient 2.5 years after completion of high-dose chemoradiation consisting of three cycles of 5-fluorouracil/cisplatin with predominantly twice daily radiation and planned volume reductions. Treatment was initiated urgently with three-dimensional technique because of intermittent arterial bleeding from a branch of the femoral artery. Subsequent reduced volumes were treated with intensity-modulated radiation therapy (IMRT). Cumulative dose to gross disease was 65 Gy. Extensive bolus was employed to assure full dose to areas of dermal lymphatic permeation based on both clinical assessment and imaging findings (positron emission tomography/computed tomography [PET/CT] and magnetic resonance imaging [MRI]). The patient remains clinically cancer-free with late sequelae attributed to radiation including severe skin changes (atrophy, telangiectasis, fibrosis) and left leg edema with multiple episodes of cellulitis mandating chronic prophylactic antibiotic administration.



eFigure 60-6 **A,** Neglected, locally extensive vulvar cancer in a 47-year-old woman with a remote history of vulvar surgery for extensive condylomata. Despite extensive destruction of soft tissues, the patient remained continent of urine and feces. Progressive pain from bone destruction (see Figure 60-8, *B*) ultimately brought the patient to medical attention. **B,** Destruction of the inferior ischial ramus *(white arrows)* by direct extension of locally advance squamous cancer of the vulva.



eFigure 60-7 Locally extensive squamous cancer of the vulva in an African immigrant with inadequately treated HIV. Progressive destruction of the entire vulva and adjacent organs (urethra, anus) resulted in the functional equivalent of a cloaca. Visible at the center of the photograph is grossly normal distal vaginal epithelium covering anterior and posterior walls *(white arrows).*

metastases, the staging system appears to implicitly endorse surgical management of the groin nodes but this may not be prudent or feasible in all clinical circumstances. In a patient with a locally advanced primary requiring preoperative chemoradiation in an effort to avoid compromise of functionally important midline structures, it may be reasonable to electively include the groins in the irradiated volume provided that they appear grossly uninvolved by physical examination and diagnostic imaging. Without subsequent groin dissection and without sampling of groin nodes before treatment, such patients are reported to have a low probability of groin failure if treatment is carried out with appropriate technique.[111,112] They are, however, strictly speaking "unstaged." Comprehensive pretreatment evaluation of disease extent may be less important when institutional treatment policy is to carry out initial surgery in all patients who are medically operable and technically resectable, even in the presence of limited node metastases. If the detection of nodal disease pretreatment will impact the selection, sequencing, or intensity of treatment modalities, the diagnostic cascade illustrated in Figure 60-3 may help to guide therapy. It must be emphasized that there exists no consensus standard for the pretreatment evaluation of disease extent. Experience with sentinel node identification is not universal, and its routine use outside tertiary referral centers remains controversial. Thus the algorithm in Figure 60-3 may not be applicable in all venues.

Confirmation of node status is often accomplished by surgical exploration of the inguinal nodes. The most common surgical practice is to obtain histologic examination of the ipsilateral inguinal lymph nodes for lateralized lesions of the vulva and of bilateral nodes for lesions considered to be midline. Although there is no widely accepted definition of midline, a minimum of 1 cm of clinically involved tissue separating the border of the tumor from a structure which has bilateral lymphatic drainage should be mandatory before considering omission of contralateral node assessment or treatment, and many clinicians recommend 1.5 cm to 2 cm. Because lymphatic drainage from the anterior labia minora may be bilateral,[62,113] bilateral groin assessment should be considered for lesions arising in these areas even if otherwise apparently lateralized as contralateral groin metastases with negative ipsilateral groin nodes have been described with primary tumors in this location.[75] Possibly because precise tumor extent may be more difficult to appreciate on physical examination, contralateral groin node metastases with negative ipsilateral groin nodes have similarly been reported in patients with primary cancers of the Bartholin's gland, suggesting consideration of bilateral histologic groin assessment in such patients as well.[82]

For those with primary cancers <4 cm diameter, sentinel nodes may be identified for selective excisional biopsy by injection of blue dye, fluorescent dye, or radiocolloid at the primary.[114-124] It is increasingly clear that use of a blue dye

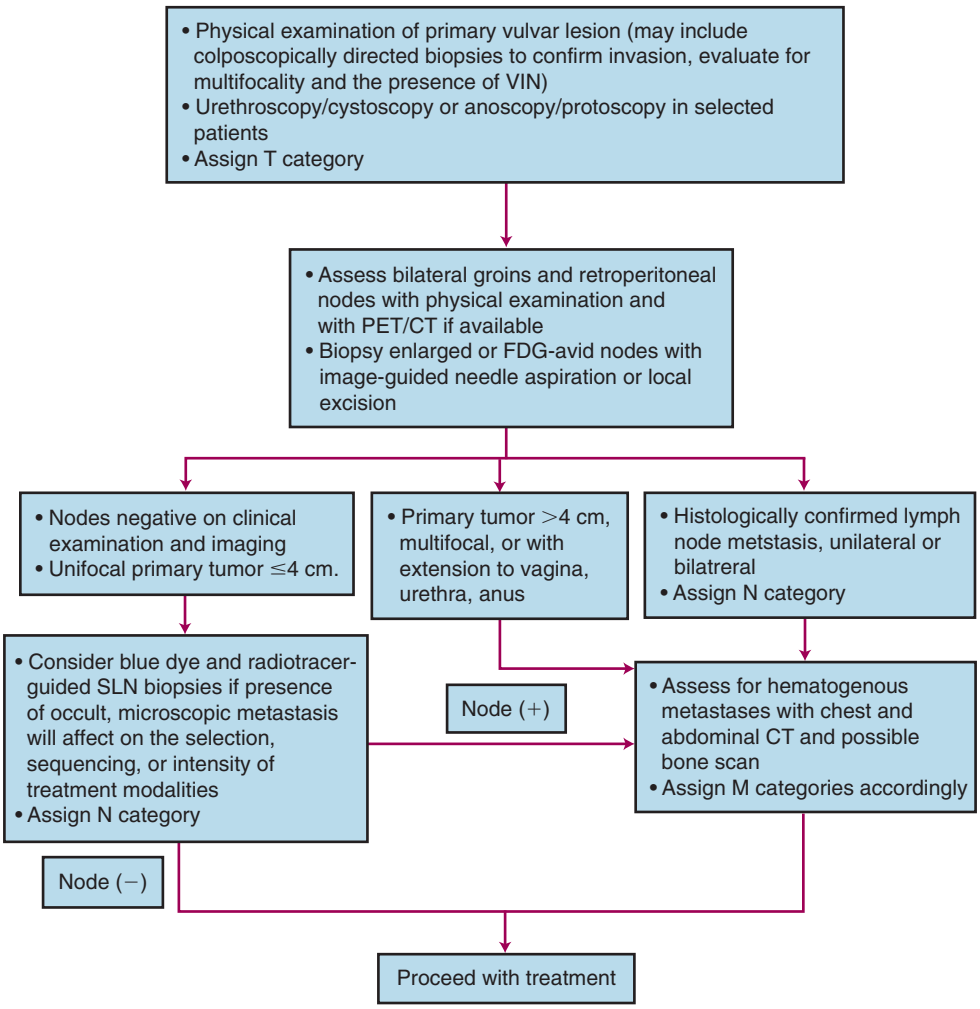


Figure 60-3 Diagnostic algorithm for vulvar cancer. *CT,* Computed tomography; *FDG-PET,* ^{18}F-fluorodeoxyglucose positron emission tomography; *M,* metastasis; *N,* node; *SLN,* sentinel lymph node; *T,* tumor; *VIN,* vulvar intraepithelial neoplasia.

alone is insufficient to identify sentinel nodes. Results are better when a radioactive tracer is used in combination with blue dye. Sentinel nodes should ideally be both "hot and blue" because greatest accuracy although radiotracer alone appears to be as accurate for other anatomic sites where sentinel node evaluation is performed. Use of indocyanine green fluorescent dye intraoperatively in patients who are lean is currently under investigation.[124] Meta-analysis of published vulvar sentinel node work reports a 92% sensitivity (by patient and by groin) with negative predictive values of 97% (by patient) and 98% (by groin).[125] Results will be most accurate when use of the technique is restricted to patients with intact (un-excised) tumors ≤4 cm in diameter in the absence of palpably enlarged groin nodes and nodes enlarged or considered suspicious for metastatic contamination by medical imaging (ultrasound [US], MRI, PET/CT).

Pathologic ultrastaging of groin nodes has been used to increase the sensitivity of sentinel node excisional biopsy in the discovery of occult microscopic groin node metastases not detected by routine processing.[120,126] Ultrastaging may include thin step-sectioning of retrieved nodes with hematoxylin and eosin staining with or without immunohistochemical staining,[127] however immunohistochemical staining will identify some metastatic deposits in nodes otherwise missed by routine hematoxylin and eosin processing.[123] When nodal disease is advanced and initial surgery to the groin area is not planned, histologic confirmation of metastatic contamination may be obtained by fine-needle core biopsy or aspiration cytology.

Noninvasive imaging with PET/CT, US, or MRI (with diffusion-weighted imaging) may assist in assessing lymph node status, particularly in patients who are larger or obese in whom femoral nodes may be many centimeters below the skin, beyond a depth where node palpation is feasible.[128-132] Metabolic imaging may sometimes detect metastases in the absence of gross nodal enlargement. PET/CT may occasionally detect in-transit dermal metastases as well as nodal spread (eFigure 60-8, *A* and *B*). CT using size criteria alone is less accurate because of the frequency with which groin nodes are nonspecifically enlarged as a result of inflammatory or reactive changes or fat replacement. Spatial imaging may identify nodes accessible for image-guided fine-needle biopsy.

PRIMARY THERAPY

The treatment of patients with vulvar cancer has been in a state of evolution for more than three decades. Previously, en bloc radical vulvectomy with bilateral groin dissection with or without bilateral pelvic node dissection was the treatment of choice for all patients with vulvar cancer.[7,10,135] Although extirpative surgery improved cancer outcomes compared with results obtained during previous eras, it was associated with substantial acute and chronic postoperative morbidity as well as major psychological sequelae. Leg lymphedema following radical groin and pelvic node dissection may be temporary or permanent and disabling.[91,136] Pelvic relaxation, organ prolapse, and urinary incontinence can develop in some patients, particularly when removal of the distal urethra or a portion of the lower vagina is required to achieve surgical clearance. Vaginal introital stenosis can occur, and the absence of the vulva and venereal fat can have the functional equivalence of shortening effective vaginal depth and removing a protective cushion from the pubic arch. These changes may contribute to dyspareunia in many patients. Additionally, clitorectomy will profoundly diminish capacity for arousal and climax. The psychosexual consequences of vulvectomy are frequently devastating.[137-139]

The clinical extent of vulvar cancer at the time of diagnosis may be decreasing, possibly consequent to more enlightened attitudes regarding the pathogenesis of the disease and improved access to health care. Among operable patients undergoing radical groin dissection, the frequency of lymph node metastasis fell from approximately 50% in reports from the 1940s and 1950s[7,10,135] to approximately 30% in surgical literature from the 1970s and 1980s.[3,71,97-99] As younger, sexually active patients were being diagnosed with preinvasive disease or unifocal disease of minimal volume and depth of invasion, modifications in the surgical approach to vulvar cancer were provoked by concerns about the chronic morbidities of ablative surgery particularly in patients with disease of limited extent.

Refined understanding of pathologic predictive factors, patterns of failure after standard radical surgery, and efficacy and tolerability of radical radiation in vulvar cancer has led to progressive change from the recommendation for radical surgery in all patients. The focus of vulvar cancer management has moved toward decreasing the morbidity and mortality of radical vulvectomy in patients with early-stage, prognostically favorable tumors, and improving results without increasing morbidity in patients with advanced, poor-prognosis disease by using integrated multimodality therapy that includes radiation, chemotherapy, and functionally conservative surgery.[9] The diversity of the disease and the afflicted patients requires tailoring the nature and extent of treatment to the location and severity of the cancer, cognizant of the activity, efficacy, and toxicity of each available treatment modality used alone or in combination.

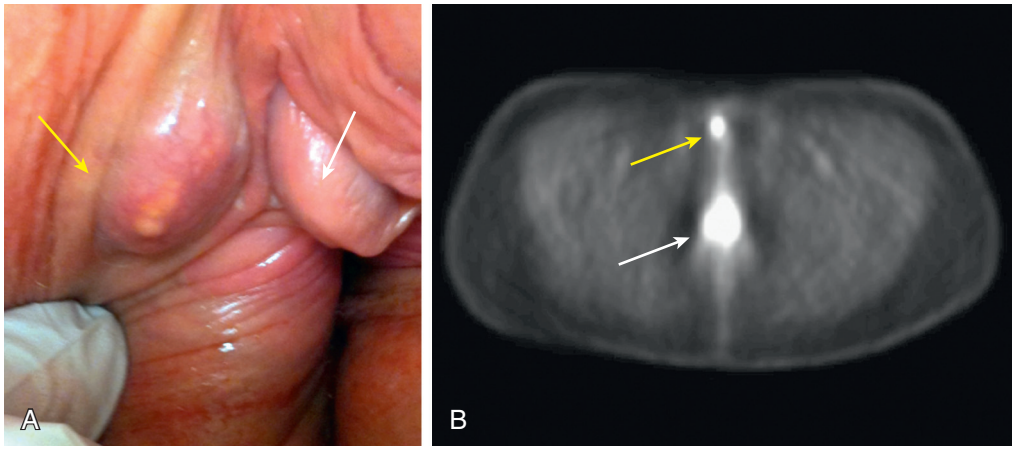
Decisions regarding management of the primary tumor in the vulva are made on the basis of primary tumor volume, location and anatomic extent (direct involvement or impingement on functionally important midline structures) taking into consideration the potential impact of both biopsy and definitive surgery on anatomic function and cosmesis.

Decisions regarding management of the groin nodes are directed by whether or not histologically confirmed node metastases are present, their extent, and the size, location, and depth of invasion of the vulvar primary.

Surgical Trends Including Sentinel Node Studies

Radical surgery for vulvar cancer has moved away from the classic radical vulvectomy with en bloc bilateral inguinal lymph node dissection toward less extensive vulvar and groin surgery, particularly in patients with early-stage lesions. Indicators of this trend include: (1) the use of separate vulvar and groin incisions (so-called "triple incision") with preservation of the intervening skin bridges; (2) use of sentinel lymph node procedures and less comprehensive groin node surgery coupled with adjuvant radiation where indicated; (3) the use of chemoradiation in patients with gross inguinofemoral node metastases, and (4) use of pelvic radiation in lieu of pelvic node dissection in patients with confirmed groin node metastases.[78,84,140] The definition of radical vulvar surgery has changed with the realization that the efficacy of radical surgery is best defined by the closest resection margin rather than by achievement of total organ ablation (vulvectomy).[60,107,141]

In patients with limited disease and clinically negative groin nodes or occult groin node metastases, utilization of separate incisions for the primary and groins is associated with decreased acute and morbidity without compromise of disease-specific survival (DSS) or OS compared to en bloc resection.[142] However, when corrected for other prognostic variables in a multivariate analysis, the type of surgical treatment (triple incision versus en bloc) was an independent predictor for vulvar recurrence but not for inguinal and pelvic relapse.[143] The lack of impact on DSS and OS may be attributed to high salvage rates for isolated vulvar recurrence reported



eFigure 60-8 **A,** Mass in the right labia *(yellow arrow)* in a phenotypically female patient with XXY karyotype (Klinefelter's syndrome) with X-linked androgen insensitivity and ambiguous genitalia. Note the clitoral hypertrophy *(white arrow)*. The primary squamous cancer was in the right Bartholin's complex. The labial mass was initially thought to be a sebaceous cyst. However sebaceous cysts are usually at the hairline along the crests of the labia majora, and the presence of subtle neovascularity over this mass was concerning. **B,** When positron emission tomography/computed tomography revealed both groin node metastases and intense radiotracer uptake in the labial mass, a biopsy confirmed an in-transit labial metastasis. Intense fluorodeoxyglucose (FDG) uptake at the primary site *(white arrow)* involving the posterior fourchette and perineal body, and at the in-transit metastasis in the right labia *(yellow arrow)*.

Although clinically useful in some patients, the results of imaging assessment, unless confirmed histologically, do not alter assignment of FIGO stage. Accurate measurement of the depth of femoral nodes below the anterior skin surface at the level of the femoral artery as it passes under the inguinal ligament is critical in the design and implementation of radiation-based therapy of undissected groins as well as in the context of adjuvant irradiation of the groins after superficial or total inguinal lymph node dissection.[133,134] Axial imaging is probably the most precise means of making this measurement.

in some clinical series.[103,144] However, a 2-year actuarial survival after vulvar recurrence has been reported to be as low as 25% and uncontrolled local recurrence was a contributing cause of death in 15 of 16 patients dying from cancer in one series.[141] Risk of recurrence in preserved skin bridges appears related to trapped dermal lymphatic emboli in patients with extensive groin adenopathy and is rare in the absence of groin adenopathy because lymphatic dissemination in vulvar cancer is characteristically embolic rather than permeative.

Radical excision for invasive tumors extends to the level of the deep perineal fascia usually 1 cm to 2 cm below the skin and should have a minimal margin of 1 cm of clinically uninvolved tissue in all dimensions. For tumors less than 2 cm in diameter with less than 1 mm of invasion (stage IA) treatment of the groins may be omitted. For stage IB tumors, surgical treatment must include the ipsilateral groin unless a successful sentinel node study confirms at least one negative sentinel node. For patients with well-lateralized primaries, preferably approximately 1.5 cm or more from midline structures, exploration and treatment of the contralateral groin may be omitted unless the ipsilateral groin is involved.

Although there is some uncertainty about the optimal extent of surgical margin after wide local excision, data from three clinical series reveal high local control rates for cases in which the surgical margin was greater than 8 mm in the fixed state postoperatively (Table 60-4). This suggests that, in the nonfixed state, tumor margins of at least 1 cm to 1.5 cm in all dimensions are desirable to achieve high local control rates. Many clinicians endorse a clinical margin of 1.5 cm to 2 cm. Implicit is the understanding that radical local excision should include dissection down to the deep perineal fascia. Although radical local excision is widely accepted in the treatment of small lesions, there is a growing trend to extend its use to lesions larger than 2 cm. Unless preservation of the clitoris and sexual function are priority patient concerns, radical vulvectomy is generally the best surgical option for patients with multifocal invasive disease, patients with invasive cancer associated with extensive VIN, and patients with cancer associated with symptomatic vulvar dystrophy unresponsive to topical therapies.

Optimal management of the inguinal nodes is essential because >90% of patients who experience relapse in regional lymph nodes after unsuccessful primary nodal therapy will ultimately die of cancer.[68,103,105,145-148] Patients whose primary lesion in the vulva invades to a depth less than 1 mm and is smaller than 2 cm have a minimal risk of groin node metastasis and do not require treatment of the inguinal region (see Table 60-1). In every patient with a primary tumor larger or more deeply invasive, treatment must include groin node management.

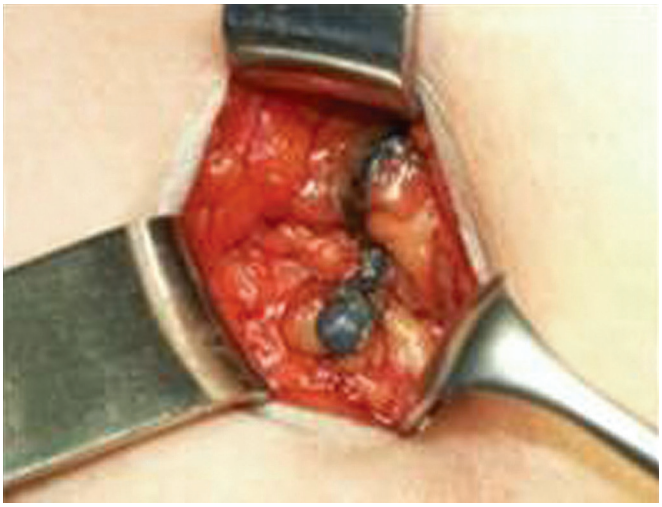
The move toward more conservative, tailored surgical management has led to changes in the extent of groin dissection and the use of unilateral groin dissection for selected patients. The previous standard radical bilateral superficial and deep inguinofemoral lymph node dissection results in as much as a 50% incidence of acute wound breakdown, lymphangitis, or lymphocyst formation, and a 10% to 25% incidence of chronic lower extremity lymphedema.[72,91,136,149] The surgical morbidity associated with limited, superficial groin dissections is less than that with superficial and deep dissections.[140] The rationale for limiting the extent or depth of groin dissection relates to the somewhat orderly sequence of metastatic progression in the groin nodal chain and the observation that involvement of the deep femoral nodes without involvement of the superficial is uncommon.[140] However, the actuarial risk of groin relapse at 5 years was 16% among patients with vulvar cancer treated with superficial groin node dissection alone at MDACC.[66]

Anatomic study of sentinel node location has shown that sentinel nodes will include deep femoral nodes in as many as 16% of patients thus explaining the relapse rate.[122] Surgical results might be improved by extending the superficial groin dissection to remove the medial portion of the cribriform fascia and underlying femoral nodes en bloc with the superficial inguinal fat pad.[150] Routine study of sentinel nodes by combined injection of blue dye and lymphoscintigraphy might further reduce the risk of groin failure by identifying the minority of patients with direct lymphatic pathways to deep nodes.[114-123] A sentinel groin node identified by blue dye is illustrated in eFigure 60-9.

If the sentinel nodes show no evidence of tumor contamination, full-therapeutic groin dissection may be sensibly omitted in patients with discrete, unifocal vulvar tumors less than 4 cm in diameter as subsequent groin relapse will be rare. A large international observational study, GROningen INternational Study on Sentinel nodes in Vulvar cancer (GROINSS-V), on sentinel node detection using radioactive tracer and blue dye was conducted in 15 institutions.[151] Team skill verification in sentinel node biopsy technique was required before patient enrollment. Patients with a unifocal primary tumor confined to the vulva and less than 4 cm in diameter with one or more sentinel nodes identified and histologically negative by ultrastaging were treated by vulvar surgery without groin dissection. A total of 623 groins were studied in 403 assessable patients. Among 259 patients meeting criteria for groin observation, six groin recurrences were subsequently diagnosed (2.3%). The 3-year DSS rate for patients with unifocal disease and negative sentinel nodes was 97%.[151]

A parallel multiinstitutional study was conducted by the Gynecologic Oncology Group in the United States (GOG protocol 173) that enrolled 452 eligible patients commencing in December 1999.[123] Skill verification in sentinel node biopsy technique was not required before study participation, and patients with primary cancers ≤2 cm and ≤6 cm in diameter were included as well as some patients with prior gross total local excision. Initially the node identification was accomplished by blue dye technique with lymphoscintigraphy optional, but in 2001 the protocol was amended to require preoperative lymphoscintigraphy with intraoperative radiolocalization. Following sentinel node retrieval, complete groin dissection was performed. In 34 patients, sentinel nodes could not be identified. Sentinel nodes underwent ultrastaging by processing the nodes into blocks of 3-mm thickness with a minimum of 2 sections 40 microns apart being obtained from each block. Of the 418 patients in whom sentinel nodes were identified, 132 patients were ultimately found to have lymph node metastases. The sensitivity of the sentinel node procedure was 91.7% with a false-negative rate of 8.3%. Because of protocol compliance issues, immunohistochemical analysis was performed on only 200 of 285 patients (71%) with negative sentinel nodes. Twenty-three percent of true-positive cases were identified by immunocytochemistry when routine hematoxylin and eosin staining did not reveal micrometastases.

If one or more sentinel nodes were involved with tumor in the GROINSS-V study and other sentinel node studies, surgery would generally proceed to complete the therapeutic superficial and deep groin node dissection. However, radiation or chemoradiation to undissected nodes after a positive sentinel node biopsy was thought to be a sensible alternative to completion of the groin dissection perhaps carrying a lower risk of chronic lymphedema and erysipelas, particularly if groin radiation might follow full groin dissection because multiple nodes are found to be contaminated. This alternative was the subject of the initial study design of a second observational study (GROINSS-V II) from the Netherlands, which has



eFigure 60-9 Sentinel groin node identified by blue dye technique.

Short-term morbidity was decreased in patients after sentinel node dissection only compared with patients who had a positive sentinel node biopsy who underwent complete inguinofemoral lymphadenectomy.[151] Acutely, groin wound breakdown was seen in 11.7% of sentinel node biopsy only patients compared with 34.0% of patients undergoing complete groin dissection. Cellulitis was observed in 4.5% compared with 21.3% of patients, respectively. Chronic morbidity also was less frequently observed after removal of only the sentinel node compared with sentinel node removal and inguinofemoral lymphadenectomy.[151] Recurrent erysipelas was seen in 0.4% compared with 16.2% of patients respectively, and lymphedema of the legs observed in 1.9% of patients undergoing sentinel node biopsy compared with 25.2% of patients undergoing full groin dissection.

accrued patients since 2006. Eligible patients are limited to those with unifocal squamous cancers confined to the vulva <4 cm. In diameter without encroachment on the urethra, vagina, or anus and with clinically and radiographically negative groin nodes. Patients who have successful identification of negative sentinel node(s) undergo no further therapy directed to the groins. Patients with positive sentinel node(s) initially would undergo groin radiation or chemoradiation (at individual investigator discretion) as an alternative to conventional completion of a therapeutic superficial and deep inguinofemoral lymphadenectomy. The study design was modified when interim safety monitoring revealed an unexpectedly high rate of in-field groin failures in patients with nodal metastases exceeding 2 mm in size who were treated with 50 Gy of radiation alone to the affected groin. The study was reopened in 2011 modified so that patients with nodal micrometastases exceeding 2 mm in size would undergo full groin node dissection followed by radiation (50 Gy to 56 Gy) with concurrent chemotherapy at investigator discretion. Because in-node–positive cervical cancer the addition of concurrent chemotherapy to adjuvant pelvic radiation after radical hysterectomy substantially improved local control compared with radiation alone,[152] the use of concurrent chemotherapy with adjuvant groin radiation is reasonable in patients with groin node metastases from squamous cancer of the vulva.

Rob et al published the most detailed study concerning sentinel node anatomical location in vulvar cancer.[122] They divided groin nodes into four regions: the superficial medial group located above and medial to the femoral vein and medial to the saphenous vein; the superficial intermediate group located in the vicinity of but superior and lateral to the saphenous and femoral veins; the superficial lateral group located in the outer third of the groin; and the profundum nodes located deep and medially along the femoral vein. Of the 118 sentinel lymph nodes found in 82 groins in this study, 84% were in the superficial medial region or in the superficial intermediate region, and 16% were in the profundum group. Importantly, no sentinel lymph nodes were found in the superficial lateral region. These findings are informative for the determination of radiation target volumes and the design of radiation ports for patients with clinically and radiographically negative groins undergoing elective or prophylactic groin radiation. Covering only tissues overlying and medial to the femoral vessels allows substantial reduction in radiation dose to the femoral necks and metaphyseal regions while assuring that first echelon nodes are comprehensively included. As insufficiency fractures of the femur[153] constitute a rare but serious complication of groin node irradiation, tailored treatment volumes based on understanding of the relative risk of different node groups within the groin may be a sensible way to help reduce the risk of this major cause of delayed treatment morbidity.

For patients with lateralized lesions and no involvement of the ipsilateral nodes, the incidence of contralateral groin node involvement is extremely low[62,84] and routine dissection of the contralateral nodes is omitted. Bilateral dissections are recommended for patients whose tumors involve or approach within 1 cm of midline structures or involve the anterior labia minora.

When nodal disease is fixed or ulcerating, the local tumor burden is large and unlikely to be controlled by either surgery or radiation alone. In such patients, combined therapy with initial chemoradiation followed by surgery may offer the best chance of local control if groin nodes become resectable.[154] In rare patients with unresectable groin nodes, local and regional control can sometimes be obtained with high-dose chemoradiation (eFigure 60-5, *A* and *B*).

Radiation Therapy

Radiation therapy for vulvar cancer was pioneered in Europe in the early 20th century in an era when surgical options for advanced vulvar cancer were limited. As radical surgery became more feasible and surgical results improved consequent to improvements in anesthesia, postoperative nutritional support, blood transfusion, antibiotics, and refinements in reconstructive surgery and wound care, primary radiation therapy (RT) with its attendant morbidity was largely abandoned. Because of the acute desquamation accompanying radical irradiation of the vulva and the severe late effects of radiation on the vulva in long-term survivors, the use of RT was largely restricted to palliative use and patients with anatomic extent of disease or medical comorbidities precluding operative intervention.[155-159] With focused hindsight, RT equipment and techniques were primitive in comparison to current technology, and radiation fractionation and total dose were naïve with respect to potential late normal tissue effects. The perception that radiation was a poor second choice as a curative modality stemmed, in part, from the low survival rates reported in early series for patients selected for RT who were unsuitable for primary surgery because of poor general medical condition, locally advanced tumors, or both.

In the past three decades, the use of RT (alone or in concert with concurrent radio-potentiating chemotherapy) in the treatment of vulvar cancer has increased dramatically. Commonly administered as adjuvant therapy before, or following conservative surgery, chemoradiation has also emerged as an alternative treatment for patients whose extent of disease would require exenterative procedures or other extensively deforming surgical interventions. Two important prospective clinical trials of the Gynecologic Oncology Group (GOG 37, GOG 101) helped form the foundation for these changes in management. Additionally, two randomized prospective trials demonstrated the superiority of chemoradiation to RT alone in the treatment of the analogous cancers of the anal canal.[160,161] Extension of chemoradiation to treat patients with vulvar cancer was a natural extrapolation and has led to publication of a number of single-institution series reporting encouraging results in limited numbers of patients.[112,162-177]

Adjuvant Postoperative Radiation

The GOG conducted a randomized trial (GOG 37) to determine whether pelvic radiation could improve survival over the standard pelvic node dissection. Ipsilateral pelvic lymphadenectomy (n = 55) was compared to RT (45 Gy to 50 Gy, n = 59) administered to the bilateral groins and pelvis (excluding the tumor bed and residual vulva) in 114 patients who were surgically treated and were found to have groin node metastasis.[92] Metastases were detected in pelvic nodes in 15 of 53 patients (28%) undergoing pelvic lymphadenectomy, 9 of whom expired within 1 year. With median follow-up in survivors of 74 months, the OS was 51% in irradiated patients at 6 years compared to 41% in patients treated by pelvic node dissection. The cancer-related death rate was 51% in patients undergoing pelvic node dissection, compared to 29% in patients undergoing RT (p = 0.015). The major benefit of RT was in patients with gross node metastasis, extracapsular extension, or metastases to two or more nodes. The major effect of RT was a reduction in groin failures in the patients who were irradiated who had a 5% crude incidence of groin relapse compared to a 24% crude incidence in patients treated surgically. The tumor bed and residual vulvar tissues were not irradiated, and a 12% crude incidence of vulvar recurrence was observed across both treatment arms. Data from two other studies suggest that macroscopic involvement of a single node and extracapsular invasion confer a risk of inguinal

recurrence after surgery that is as high as in those with multiple lymph node involvement, suggesting that such patients may also benefit from postoperative groin and pelvic nodal irradiation.[5,178] After therapeutic groin dissection, patients with microscopic intracapsular metastasis to a single groin node do not appear to benefit from the addition of radiation.

The target volume for adjuvant postoperative RT depends on the indications for adjuvant therapy. For patients with negative groin nodes but adverse histopathologic factors discerned on study of the excised primary, focal RT targeted at the primary tumor site, is appropriate. For patients with unilateral node metastases in whom the contralateral groin has been dissected and is uninvolved, generally most do not treat the contralateral groin and pelvic nodes although they were routinely treated in the GOG 37 study of adjuvant radiation, which showed the survival benefit.[92]

Many patients with node involvement will also have indications to treat the primary tumor bed and residual vulva. However, whether or not to routinely include the tumor bed and residual vulva in all patients undergoing adjuvant postoperative RT because of node metastasis remains an issue of controversy. Dusenbery et al reported 27 patients with squamous carcinoma of the vulva and 1 to 15 (average 4) histologically involved inguinal lymph nodes who were treated after radical vulvectomy and bilateral lymphadenectomy (25 patients), radical vulvectomy and unilateral lymphadenectomy (1 patient), or hemivulvectomy and bilateral lymphadenectomy (1 patient). Postoperative RT was directed at the bilateral groin and pelvic nodes (19 patients), unilateral groin and pelvic nodes (6 patients), or unilateral groin only (1 patient). Twenty-six patients had the midline (primary tumor bed) shielded. Actuarial 5-year OS and DFS estimates were 40% and 35%. Relapses developed in 63% (17 of 27) of the patients at a median of 9 months from surgery (range 3 months to 6 years). Central recurrences (under the midline block) were present in 13 of these 17 patients (representing 50% of the patients treated with the midline blocked), as central only (8 patients), central and regional (4 patients), or central and distant (1 patient), leading the authors to conclude that the target volume for adjuvant postoperative RT for patients with node metastases should include the tumor bed.[179] Unfortunately the presence or absence of recognized risk factors for vulvar recurrence was not presented.

Some late local recurrences may actually represent true second primary cancers in conserved vulvar tissue that is predisposed to malignant transformation. This is more recognizable where second lesions develop in residual contralateral vulva following wide local excision of initially well-lateralized lesions. Whether adjuvant radiation to all of the remaining vulva would reduce or increase the risk of such second primary cancers is unknown. However, morbidity is definitely increased if the entire vulva is included in adjuvant treatment of a localized lesion. Assessment of risk factors associated with the primary tumor may assist in making this determination.

Whether adjuvant local radiation can overcome the negative prognostic impact of close or positive margins, capillary lymphatic space involvement, and depth of invasion is unproven. However, strongly suggestive evidence regarding margins is provided by the outcomes observational study of Faul et al.[141] Sixty-two patients with invasive vulva carcinoma and either positive or close (less 8 mm) margins of excision were retrospectively studied. Thirty-one patients were treated with adjuvant RT to the vulva and 31 patients were observed after surgery. Local recurrence occurred in 58% of observed patients and 16% of patients treated with adjuvant irradiation. Adjuvant RT appeared to significantly reduce local recurrence rates in both the close-margin and positive-margin groups. On multivariate analysis, adjuvant radiation and margins of excision were significant prognostic predictors for local control. The positive margin observed group had a significantly worse 5-year OS than the other groups ($p = 0.0016$) and adjuvant RT appeared to significantly improve survival for this group. The 2-year OS after developing local recurrence was only 25%, lower than is often reported for salvage therapy, and local recurrence was a significant predictor for death from vulva carcinoma (risk ratio 3.54).

The optimal pathological margin for reducing the risk of local recurrence width remains controversial. In one report local recurrence was observed in 8 of 21 patients with pathologic margins between 5 mm and 8 mm.[60] In another report, there were 0 of 18 recurrences in patients with margins between 5 mm and 8 mm.[141] The most commonly used indication for adjuvant vulvar irradiation is close margins; some use <8 mm as the criterion and others <5 mm. Depth of invasion >5 mm or the presence of lymph-vascular space invasion where other risk factors are present such as this may tip the decision in favor of local radiation.

Preoperative Radiation

In the 1960s, Boronow pioneered the use of preoperative RT followed by more conservative surgery in patients with locally advanced or recurrent vulvo-vaginal cancers as an alternative to pelvic exenteration. With a total of 48 treated cases (37 primary cases and 11 cases of recurrent disease) he reported a 72% 5-year survival for all 48 cases treated. One patient required a total pelvic exenteration for local failure, and one had a posterior exenteration for local failure. One bladder and one rectum were lost to permanent diversion because of RT injury. Five of 96 viscera (48 urinary bladders and 48 rectums) were lost and 91 (94.8%) were retained.[180] Three small series totaling 26 patients treated with 30-Gy to 55-Gy preoperative RT reported histologically negative surgical specimens in 13 patients (50%) with only microscopic residual disease in others.[181-183] These series provide further evidence for the radiation sensitivity of vulvar cancer.

Preoperative Chemoradiation

Several single-institution studies reported encouraging results employing preoperative chemoradiation before conservative resection in locally advanced or locally recurrent vulvar cancer.[162,163] These reports, along with reported treatment successes using chemoradiation for patients with anal and esophageal cancer, provided much of the foundation for protocol work commencing in 1989 in the GOG.

GOG Protocol 101 used planned preoperative chemoradiation (chemoRT) consisting of 47.6 Gy in once or twice daily fractions of 1.7 Gy synchronously with two courses of infusional 5-fluorouracil (5-FU) and cisplatin as initial therapy for 71 evaluable patients with extensive squamous cancer of the vulva, 1969 FIGO stages III and IV judged not resectable by radical vulvectomy, followed by surgical excision of residual primary tumor plus bilateral inguinofemoral lymph node dissection.[184] The dose-fractionation schedule for chemoradiation employed in GOG 101 is schematically depicted in Figure 60-4 and the target volumes depicted in Figure 60-5. The planned 1.5- to 2.5-week treatment interruption was intended to mitigate the severity of acute RT dermatitis that can progress to confluent moist desquamation, as well as to permit hematologic recovery. Twice daily RT was employed to optimize the RT and drug synergism. Following chemoRT, 33 of 71 (46.5%) patients had no visible vulvar cancer at the time of planned surgery and 38 of 71 (53.5%) had gross residual cancer at the time of operation. Five of the 38 had positive resection margins and underwent either further RT to the vulva (3 patients), wide local excision and vaginectomy necessitating colostomy (1 patient) or no further therapy (1 patient). Only 2 of 71 (2.8%)

Cycle 1

	MON—FRI							MON—FRI				
Day	1	2	3	4	5	6	7	8	9	10	11	12
Radiation*	R	R	R	R	R	0	0	R	R	R	R	R
	R	R	R	R								
5-FU†	F	F	F	F								
Cisplatin‡	P											

1½–2½ Week planned rest

Cycle 2

	MON—FRI							MON—FRI				
Day	1	2	3	4	5	6	7	8	9	10	11	12
Radiation*	R	R	R	R	R	0	0	R	R	R	R	R
	R	R	R	R								
5-FU†	F	F	F	F								
Cisplatin‡	P											

* 1.7 Gy/fx.
† 1000 mg/m^2/24 hr.
‡ 50 mg/m^2.

Figure 60-4 Gynecologic Oncology Group (GOG) protocol 101 for treating advanced vulvar cancer with preoperative chemoradiation. Patients who are judged to have unresectable disease after completion of 47.6-Gy preoperative chemoradiation receive an addition 20 Gy in fractions (Fx) of 1.7 Gy to 2.0 Gy, with a reduced treatment volume encompassing gross residual disease, or they may receive an additional radiation dose by brachytherapy. A third cycle of chemotherapy is recommended if teletherapy is employed. *0,* A day without radiation treatment; *F,* 5-fluorouracil given by continuous intravenous infusion (1000 mg/m^2/24 hr for 96 hours on days 1 to 4 of each cycle); *P,* short infusion of cisplatin (50 mg/m^2 on day 1 of each cycle); *R,* a fraction of external radiation encompassing the primary site and regional extensions; a 4-hour minimum intertreatment interval is mandatory, but 6 hours or more is suggested when feasible.
Adapted from Moore DH, Thomas GM, Montana GS, et al: Preoperative chemoradiation for advanced vulvar cancer. A phase II study of the Gynecologic Oncology Group. Int J Radiat Oncol Biol Phys 42:79–85, 1998.

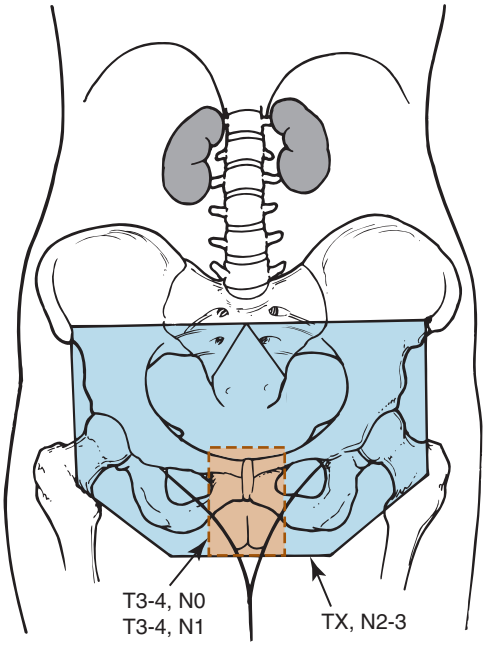


Figure 60-5 Radiation Volumes for Preoperative Chemoradiation GOG Protocol 101. Patients with unresectable primaries and clinically nonsuspicious groin nodes (FIGO 1969 formalism T_3/T_4, N_0/N_1) received radiation therapy to the vulvar primary only *(dotted line)*. For patients with clinically positive, fixed, or matted groin nodes judged unresectable (FIGO 1969 N2/N3) the volume was increased to include the groin and lower pelvic nodes.
Adapted from Moore DH, Thomas GM, Montana GS, et al: Preoperative chemoradiation for advanced vulvar cancer. A phase II study of the Gynecologic Oncology Group. Int J Radiat Oncol Biol Phys 42:79–85, 1998.

had residual unresectable disease. In only three patients was it not possible to preserve urinary or fecal continence. The authors concluded that preoperative chemoRT is feasible and may reduce the need for more radical surgery including primary pelvic exenteration.

In parallel with the study of preoperative chemoRT for patients with locally advanced primary vulvar cancer, the GOG studied patients presenting with advanced disease in the inguinofemoral nodes, 1969 nodal classification N2/N3, including some patients with matted, fixed, or ulcerated groin nodes not judged resectable by initial surgery and any extent of vulvar disease. The identical preoperative chemoRT schedule was employed to treat 46 patients except the treatment volume was increased to encompass the groins and caudal pelvic nodes (see Figure 60-2). Three patients expired during treatment and one refused to complete the therapy. Four patients who completed chemoRT did not undergo planned surgery, 2 patients dying of causes not related to cancer and 2 patients remaining unresectable. Following preoperative chemoRT, the disease in the lymph nodes was judged resectable in 38 of 40 patients. Two patients who completed chemoRT did not undergo surgery because of pulmonary metastasis. One underwent radical vulvectomy and unilateral node dissection and the other radical vulvectomy only. The operative lymph node specimen was histologically negative in 15 of 37 patients. Nineteen patients developed recurrent or metastatic disease. Local control of the disease in the lymph nodes was achieved in 36 of 37 and in the primary area in 29 of 38 of the patients. Two patients died of treatment-related complications. The authors concluded that resectability and local control of advanced nodal disease may be obtained with a high probability following preoperative chemoRT in patients with carcinoma of the vulva with extensive groin adenopathy even with this modest dose of radiation (47.6 Gy).[154]

Acute toxicity in GOG 101 was primarily in the irradiated skin, with moist desquamation reported in many patients. Major hematologic toxicity was rare, presumably because the volume of irradiated bone marrow was small in patients with clinically negative groins who received radiation only to the vulva and immediately adjacent tissues. When initial RT target volume includes the groins and pelvic nodes (Figure 60-5) because of confirmed node metastasis, hematologic and gastrointestinal toxicities can be expected to be significantly more severe.

Because vulvar cancer and level-one evidence to support optimal treatment approaches are both rare, there is a large variation in management strategies. At Massachusetts General Hospital (MGH) the initial RT volume electively encompasses

the groin nodes bilaterally in all patients with locally extensive primary cancers selected for preoperative or definitive chemoRT, regardless of whether groin node metastases have been histologically verified. Evaluation for potential surgical resection of residual disease is carried out 2 weeks to 3 weeks following completion of preoperative chemoRT. If resection can be carried out without compromising functionally important midline structures, this is considered preferred management to avoid the chronic sequelae of high-dose RT on the vulva and perineum. Reduced volume boost treatment is administered to gross residual primary disease that has not become resectable by conservative excision. Often this is accomplished through the use of an en-face shaped perineal port employing electron beam or low-energy photons to minimize the volume of tissue carried to high dose (eFigure 60-10). To assure accurate perineal port placement and reproducible inclusion of residual disease with narrow (approximately 10 mm) margins, each treatment is done under direct supervision of the responsible physician. In patients with initially negative groin nodes (palpably and by diagnostic imaging assessment), electively irradiated groin nodes are not subsequently routinely dissected.

In some patients, a complete clinical response may be seen after moderate dose preoperative radiation. In GOG Protocol 101 preoperative chemoRT resulted in a complete clinical response in 34 of 71 patients evaluable for therapeutic efficacy (48%) and a pathologic complete response in 70% (22 of 31) of the 34 complete responders undergoing surgery.[184] Possible options for further management of patients with a clinical complete response to preoperative chemoRT include generous biopsy to confirm pathologic complete response (eFigure 60-11, *A* and *B*), conservative surgery to remove palpable scar tissue and the tumor bed, or a modest dose of radiation consolidation (8.5 Gy to 9 Gy in 5 fractions over 1 week).

In GOG Protocol 205 (successor study to GOG 101) with similar patient eligibility requirements, 5-FU was dropped and the more commonly used regimen of concurrent weekly cisplatin at 40 mg/m^2 was adopted. RT was administered once daily in 32 fractions of 1.8 Gy to a total dose of 57.6 Gy, escalating the physical dose 21% from the 47.6 Gy administered in fractions of 1.7 Gy in GOG Protocol 101, while dropping the twice daily fractionation schedule employed on 8 of the 20 treatment days in the previous study. Primary endpoints were clinical and pathologic complete response.[186] Because of these substantial differences in total dose, dose per fraction, and drug regimen, it is difficult to discern which of these factors may have contributed to the higher rates of complete clinical and pathologic response than was observed in GOG 101 (Table 60-6).

Additionally, prechemoRT groin dissections were done in 34 patients entered on GOG 205 of whom 19 (56%) had positive nodes, 12 (35%) had negative nodes, and 3 (9%) had unknown nodal status. Pathologic complete response at the primary site was observed in 8 of 19 (42%) patients with node-positive disease but 9 of 12 (75%) patients with node-negative disease, suggesting the possibility that nodal status and the efficacy of chemoRT at the primary site may be interrelated clinical factors. Pretreatment histologic groin status was not reported for patients treated on GOG 101, although 23 patients were reported to have FIGO 1969 N2/N3 clinical groin assessment. The comparability of patients entered on these sequential trials is not clear.

TABLE 60-6 Outcomes with Different Chemoradiation Schedules in GOG Protocols 101 and 205

	GOG 101*	GOG 205†
Evaluable Patients	71	58
Clinical Complete response	34 (48%)	37 (64%)
Pathological Complete response	22 (31%)	29 (50%)

**47.6 Gy in 1.7 Gy fractions (twice daily days 8 to 20) 5 d/wk plus concurrent 5-flourouracil.*
†57.6 Gy in 1.8 Gy fractions (once daily), 5 d/wk plus concurrent 5-weekly cisplatin.

Primary Radiation or Chemoradiation

Treatment of Primary Lesions

Given the complexity of treatment decision making and the many possible ways of integrating surgery, RT and chemotherapy, all patients should be managed by an experienced multidisciplinary team.

Whether high-dose radiation, alone or combined with concurrent chemotherapy, can or should replace radical surgery for all patients with vulvar cancer is unclear. Reports of RT using contemporary techniques and dose-fractionation schedules used as monotherapy after biopsy are uncommon. Consequent to probable selection biases in choosing patients for such treatment, it is impossible to meaningfully compare outcomes to alternative treatment strategies. It can only be concluded that some patients enjoy local-regional control and prolonged DFS when managed employing radiation or chemoradiation alone.[175,191]

Increasingly, the trend is to employ RT and synchronous radiopotentiating chemotherapy as definitive therapy for patients with disease judged too extensive for functionally conservative surgery.[112,162-175,184,186,192-195] Unfortunately, the heterogeneity of the small numbers of patients selected for this approach, using variable selection criteria, diverse drug programs, and a spectrum of RT doses and fractionation schemes conspire to defy identification of an optimal regimen. However, as experience continues to accumulate and observational data become more mature, it seems probable that definitive chemoRT will emerge as a viable treatment plan for patients either with unresectable disease by virtue of disease extent, or medically inoperable because of comorbidities and for midline lesions for which surgery would impair cosmesis or function.

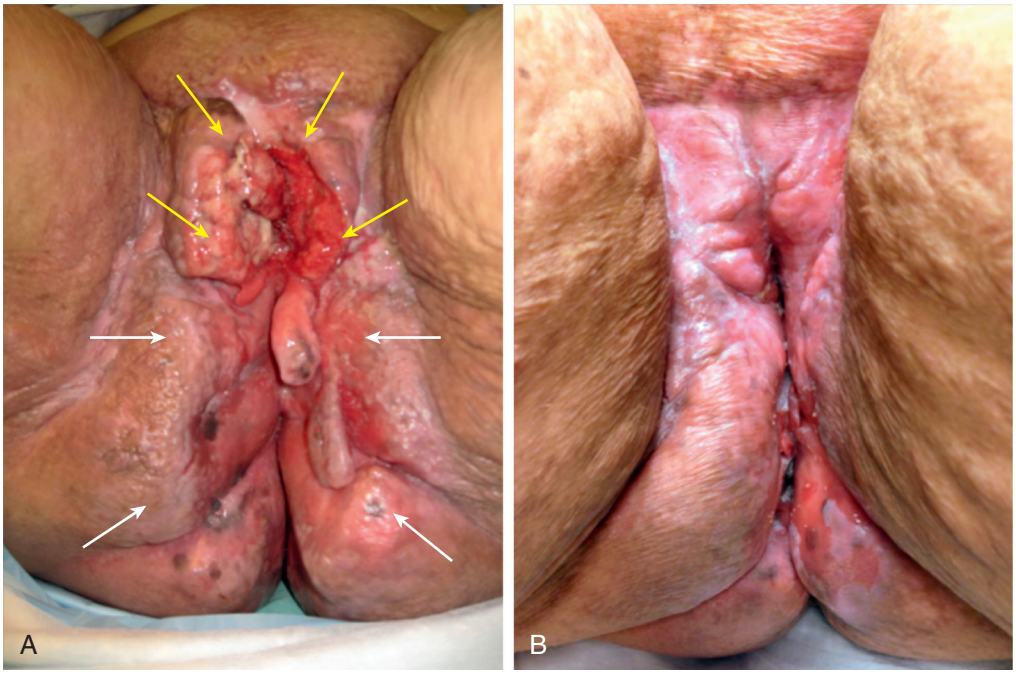
The optimal choice of cytotoxic drugs to administer in conjunction with RT remains unknown. Although Bleomycin is no longer used in this context, whether 5-FU alone or combined with cisplatin or mitomycin-C is more or less effective than weekly cisplatin remains unclear. In a nonrandomized, retrospective outcomes comparison of two different chemoRT approaches used contemporaneously in the treatment of advanced vulvar cancer at two Harvard Medical School affiliated radiation oncology departments in Boston (MGH and Brigham and Women's Hospital/Dana-Farber Cancer Center) there were no clear differences in the apparent efficacy of these two different concurrent chemoRT approaches.[196] In circumstances in which cisplatin is contraindicated it is reasonable to use infusional 5FU.

The currently active study (Figure 60-6) of the GOG (GOG 279) builds on prior efforts by escalating primary RT dose to 64 Gy for patients with locally advanced vulvar cancer unresectable by initial radical vulvectomy and augmenting the radiation potentiating effects of weekly cisplatin 40 mg/m^2 by the addition of weekly gemcitabine 50 mg/m^2, a second drug with known radiosensitization effect. This represents an extrapolation from the proven benefit of the two-drug regimen demonstrated in a prospective randomized trial of



eFigure 60-10 Shaped, en-face perineal port treated with electron beam or low-energy photons. The patient's legs are supported and immobilized by plastic operating room boots or stirrups attached to the treatment couch. To assure reproducible and accurate tumor coverage, it is suggested that each fraction be administered after direct visualization of the light field on the patient by a physician.

In other centers (Sunnybrook Odette Cancer Center) where chemoRT is chosen for the vulvar disease, the groin node status will be confirmed histologically so that patients with negative groins may be spared unnecessary groin irradiation.



eFigure 60-11 **A,** Pretreatment photograph of a young woman with locally extensive T3Nx squamous cancer of the vulva with involvement of the distal urethra and vagina arising in chronic dermatitis of the vulva, anus, and perineum associated with severe inflammatory bowel disease (Crohn's colitis). Yellow arrows delineate gross tumor. White arrows indicate areas of markedly abnormal and inflamed skin without clinical involvement of malignancy. Following diverting colotomy this patient was treated with preoperative chemoradiation delivering 47.6 Gy with two cycles of synchronous 5-flourouracil/cisplatin employing a dose and fractionation schedule modified from GOG Protocol 101 (see Figure 60-4). Target volumes included the primary and both groins using the modified segmental boost technique.[185] Three weeks following completion of chemoradiation an examination under anesthesia suggested complete clinical involution. Seven negative deep circumferential biopsies were obtained from the periphery of the original tumor volume and no further treatment was employed. **B,** Photograph of this patient 4.5 years after completion of treatment. There has been no evidence of recurrence.

Preoperative neoadjuvant chemotherapy (without radiation) has been used in the treatment of locally advanced vulvar cancer.[187-190] Response rates have been quite variable, and although complete clinical or pathologic responses have been recorded, these are rare. This approach has not gained broad acceptance, presumably because response to combined chemoRT is predictable.

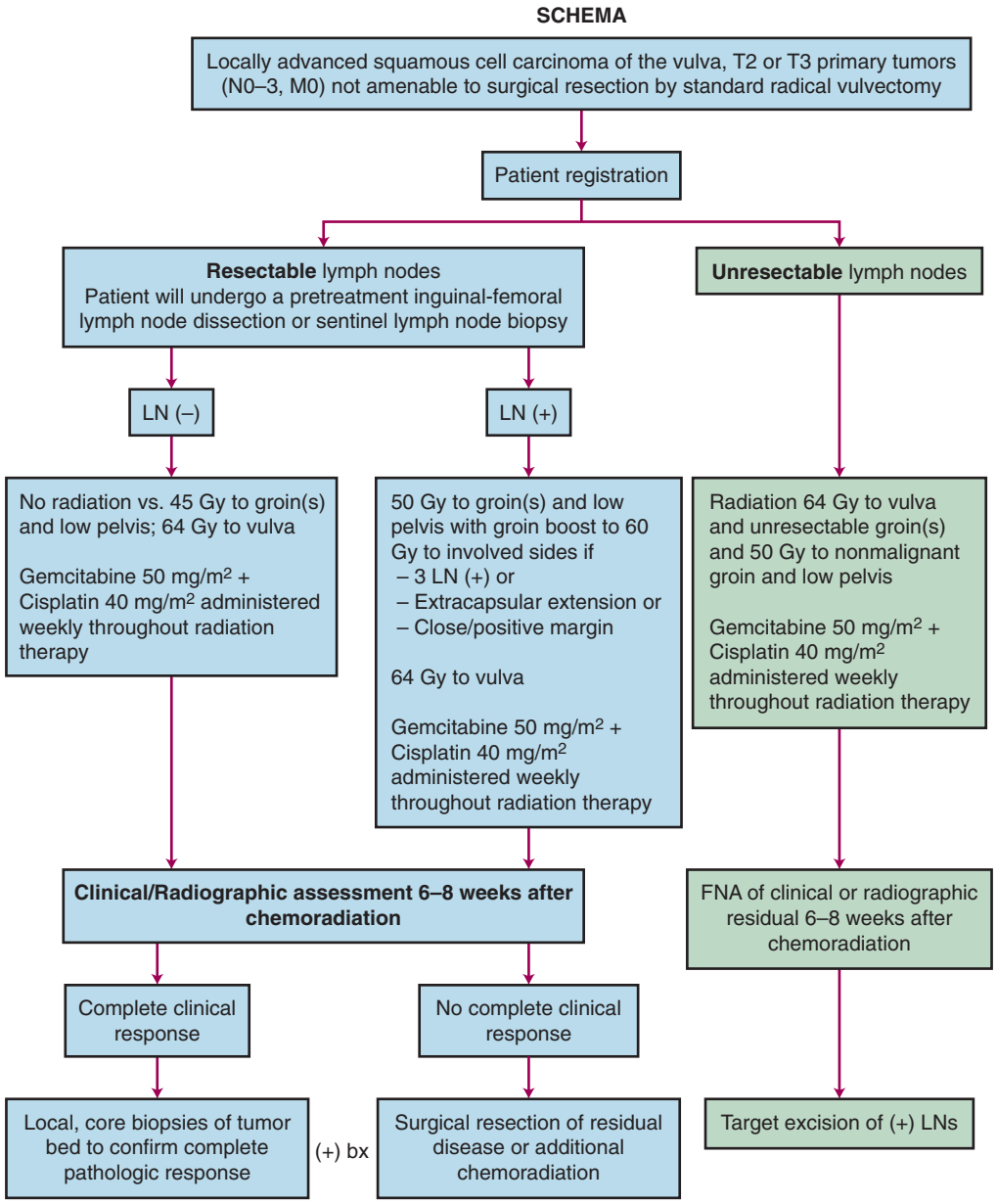


Figure 60-6 Protocol schema for GOG 279.

preoperative treatment of locally advanced cervical cancer conducted in Mexico City.[197] In that study 83 patients with FIGO IB2/IIA/IIB were randomized between 50 Gy in 25 fractions plus weekly cisplatin at 40 mg/m^2 versus 50 Gy in 25 fractions plus weekly cisplatin 40 mg/m^2 and weekly gemcitabine 125 mg/m^2. Although both acute gastrointestinal and hematologic toxicities were greater with the two-drug regimen, 77.5% of subsequent radical hysterectomy specimens were negative for residual cancer in patients treated with both drugs compared to 55% in patients treated with weekly cisplatin alone. Because RT target volumes for patients with vulva cancer treated on GOG Protocol 279 will include less bowel and less bone marrow than conventionally irradiated volumes used in the treatment of cervical cancer, it is hoped that the two-drug regimen will be tolerated in this mainly elderly population. All RT is to be administered by intensity-modulated radiation therapy (IMRT). The primary study endpoint is pathologic complete response at the primary site.

Treatment of Inguinal Nodes

It is unclear whether primary RT or chemoRT can replace primary surgery as definitive therapy for the inguinal regions. A randomized study conducted by the GOG compared primary inguinal dissection with primary groin irradiation to control the inguinal-femoral nodes in conjunction with radical vulvectomy in patients with squamous cancer of the vulva and clinically nonsuspicious groins.[198] This study was terminated before completion of accrual when interim monitoring revealed an excess of nodal relapse and death among patients treated with nodal irradiation. RT consisted of 50 Gy in daily fractions of 2 Gy fractions administered to a depth of 3 cm below the anterior skin surface. On the groin dissection arm, there were 5 of 25 (20.0%) patients with positive groin nodes. Those patients with node-positive disease received postoperative radiation. There were five groin relapses among the 27 (18.5%) patients randomized to receive the groin radiation

regimen, and none among patients treated with initial groin dissection. Patients who underwent an initial groin dissection had significantly better progression-free interval (PFS; $p = 0.03$) and OS ($p = 0.04$). Although resistance of the inguinal node metastases to radiation is one possible reason for the unacceptable groin failures in patients treated without groin dissection, a subsequent analysis of that study indicated that the groin RT technique employed was inadequate.[134] It was based on the assumption that the inguinal lymph nodes lay 3 cm to 4 cm below the surface, and a substantial percentage of treatment was delivered using electrons of energy (12 MeV or 13 MeV) appropriate to that depth. Koh's study illustrated that the median depth of lymph nodes in the groin was 6 cm from the surface but could be as deep as 17 cm in large patients. Kalidas obtained measurements of the inguinal node depths of 31 patients with cervical, vaginal, or vulvar malignancies from their planning CT scans. Twenty-four of 81 superficial inguinal node depth measurements were greater than 3 cm, and all of 84 deep inguinal (femoral) node measurements were beyond the 3 cm range.[133] The RT technique used in the GOG study almost certainly resulted in significant RT underdose of the nodal bed. In planning radiation-based therapy to the groins, there can be no substitute for direct measurement of groin node depth by CT or US. Depth of the deep femoral lymphatics, for radiation prescription purposes, is now usually specified as the depth of the femoral artery because it passes beneath the inguinal ligament.

A review of primarily observational studies[66,180,198-204] indicates that the risk of groin node failure after RT alone in the patient with clinically negative groin nodes is approximately 10% (Table 60-7). These studies did not always report the expected incidence of nodal disease in the patients irradiated, so the efficacy of RT is uncertain. However, approximately 20% of patients with clinically nonsuspicious groin nodes are expected to have subclinical metastases if complete nodal dissection is performed (see Table 60-1). This would suggest that RT alone in the doses applied sterilizes occult groin metastases in only 50% of patients. The results appear somewhat better when synchronous chemotherapy is administered; however, only 36 total patients have been reported treated in this manner[111,112] (Table 60-7).

TABLE 60-7 Results of Elective Groin Radiation or Chemoradiation in Patients with Vulvar Cancer and Clinically Negative Inguinofemoral Lymph Nodes*

Author	No. Pts	Groin Failure	Percent (%)
Radiation Alone			
Frankendal	12	0	0
Simonsen	65	11	16.9
Boronow	13	0	0
Perez	39	2	5.1
Lee	16	3	18.8
Petereit	23	2	8.7
Stehman	27	5	18.5
Manavi	65	3	4.6
Katz	29	3	11
Total	289	29	10
Chemoradiation			
Leiserowitz	19	0	0
Wahlen	17	0	0
Total	36	0	0

Patients with FIGO 1969 $N_{0,1}$ negative groin nodes by clinical evaluation.

Two of the articles provide indirect evidence that RT without surgery can eradicate microscopic disease in clinically negative groin nodes in some patients. Frankendal et al[200] performed radical vulvectomy without inguinal node dissection in 29 patients with clinically negative groin nodes. Twelve patients received elective inguinal nodal irradiation; RT dose ranged from 30 Gy to 60 Gy in 15 days to 55 days. There were no nodal recurrences. Seventeen patients received no RT and 3 experienced inguinal failure. Manavi reported on 135 patients who underwent simple vulvectomy for T1 cancers without groin dissection.[204] Sixty-five patients underwent elective groin irradiation. Those patients had, on average, less favorable primary tumors than the 70 patients who had no treatment to their groins. There were three groin recurrences in the irradiated patients (4.6%) and seven groin recurrences in the unirradiated patients (10%).

Treatment Algorithms and Approaches

The initial management decision for vulvar cancer is based on clinical features including the extent of the primary, presence or absence of detectable node metastases, as well as the age, comorbidities, and preferences of the patient. The need for adjunctive therapies is determined by histopathologic findings. Management of the nodes and the primary tumor is based on the potential contributions of each treatment modality.

Because there are no precise definitions of what constitutes "favorable" or "early" disease compared to locally advanced disease, clinical definitions are provided to outline the principles that guide therapeutic choices.

Early, Favorable, or Low-Risk Disease

A practical definition of early, favorable disease (low risk) is disease that can be reasonably expected to be curatively managed by conservative surgery alone. The extent and location of the primary tumor are amenable to radical excision without sacrificing the function of the urethra, the anorectum, the clitoris, and vagina. Generally this will include patients without palpable or imaging evidence of inguinal node metastasis. For low-risk cancers that are unifocal and well-lateralized, radical wide local excision of the primary lesion in the vulva is recommended for most patients. The reported results from observational studies of radical wide local excision for T1 or T2 tumors suggest an average OS of approximately 90%. The criteria proposed for the initial selection of patients for such conservative surgical resection vary but in general include patients with tumors less than 2 cm in diameter.[65,84,86,140,205] Groin assessment, either by sentinel node biopsy or groin dissection, can be limited to the ipsilateral groin in patients with well-lateralized tumors ≤4 cm in diameter. However, when the depth of invasion increases to >5 mm or the ipsilateral groin is involved, contralateral groin metastases are more likely and the contralateral groin should be assessed.[206]

The role and indications for postoperative adjuvant vulvar irradiation are ill defined. Although data have clearly demonstrated that surgical margins less than 8 mm, increasing depth of invasion, presence of capillary lymphatic space involvement, and increasing size of primary cancer portend increased risk for vulvar recurrence after excision of any extent, it is still unclear to what extent postoperative adjuvant irradiation can overcome these risks.

Although wider reexcision, if feasible, may decrease or eliminate the risk of close or involved margins, it may not be feasible or advisable for medial or deep margins and may not overcome other risk factors. Residual cancer in the reexcision specimen is rare except when cancer is present at the original margin (33%), and reexcision is associated with a 23% rate of

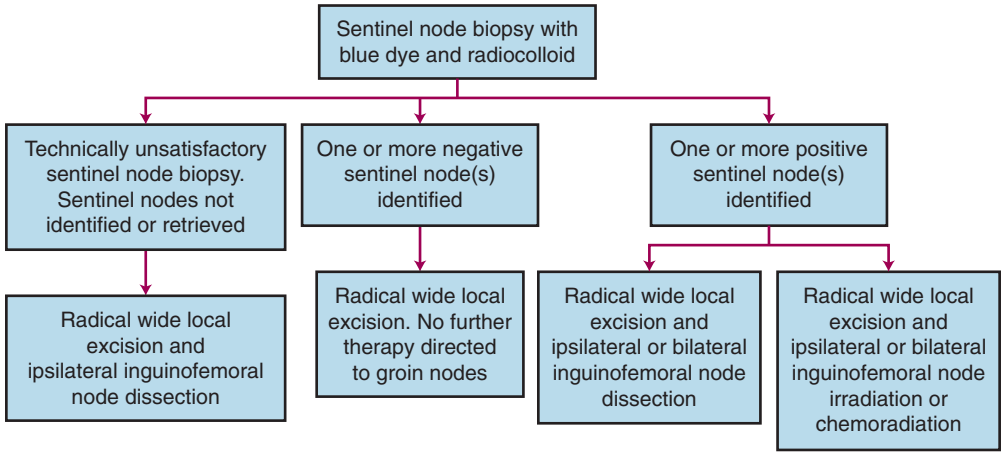


Figure 60-7 Treatment algorithm. Limited, unifocal vulvar cancer <4 cm without encroachment on clitoris, vagina, urethra, or anus. Groins clinically uninvolved. Experienced sentinel node team available.

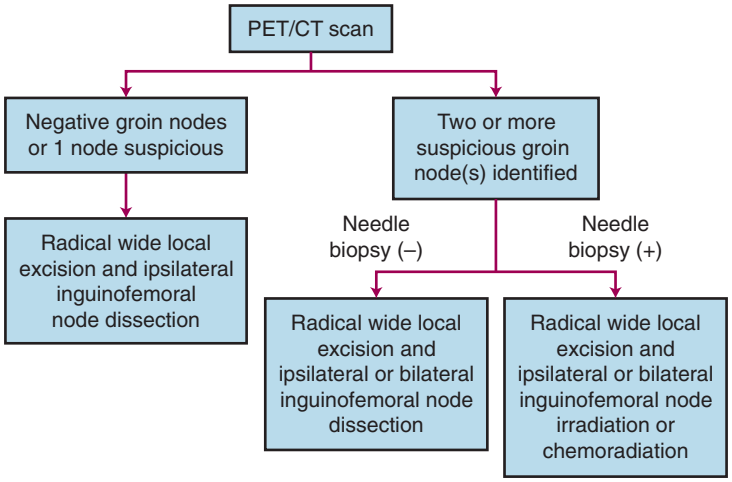
wound breakdown.[207] Reexcision may be easier for the patient if it results in sparing the patient adjuvant local radiation. If primary tumor risk factors (size, depth of invasion, lymphvascular space invasion) suggest adjuvant RT independent of margin width, it is difficult to justify the morbidity and delay incurred by reexcision. One retrospective series of 62 patients with positive or close (<8 mm) margins showed, on multivariate analysis, that adjuvant irradiation significantly reduced local recurrence rates and significantly improved survival rates for the positive-margin group.[141] If adjuvant RT is to be administered for positive or close margins <10 mm, a dose ≥56 Gy is recommended.[208] The role of adjuvant RT after radical wide local excision of vulvar cancer was being explored in a GOG randomized clinical trial, but the trial had to be abandoned as a result of lack of accrual.

Historically, standard management of the inguinal regions for all patients with invasive disease of larger than 2 cm or greater than 1 mm depth of invasion (FIGO stage IA) has been groin dissection. Results from the GROINSS-V study suggest that in selected patients with unifocal primaries <4 cm without encroachment on the urethra, vagina, or anus and successful and retrieval of sentinel node(s) that are negative by pathologic ultrastaging, the acute and chronic morbidities of groin dissection may be avoided with subsequent careful observation. The risk of subsequent groin relapse is low and its consequence may be less ominous than groin recurrence in a previously treated groin because salvage therapy at the time of nodal relapse, in an undissected groin, may be more successful. Postoperative RT to the inguinal and pelvic nodes is recommended for patients with involvement of two or more nodes and for those with a single node with macroscopic metastasis (>5 mm) or extranodal extension. In patients with diagnostic imaging that shows no evidence of pelvic adenopathy, it is unlikely that extending the superior border of the treatment volume more cephalad than the middle of the sacroiliac joints is useful. Limiting the superior extent reduces acute and chronic enteric morbidity. The randomized study (GOG 37) from which these recommendations are largely drawn gave prophylactic adjuvant irradiation to both groins even when involvement was unilateral only.[92,209] The contribution of adjuvant RT to the contralateral negative groin is uncertain and is now largely omitted. Two issues remain controversial. Whether it is beneficial to include the tumor bed or residual vulva routinely in the treatment volume when groins and pelvic nodes require irradiation remains unclear; histopathologic risk features in the primary may suggest that this may be prudent in many, if not all patients. Whether concurrent chemotherapy should be administered with purely adjuvant treatment to further enhance the regional efficacy of RT is also the substance of conjecture and debate. Hypothetically, the increase in acute toxicity could be offset by improved regional control, possibly with a reduced dose of RT that might translate into diminished late RT effects. The therapeutic ratio of this strategy is unlikely to be rigorously defined in studies. Algorithms for management of patients with early, lateralized disease are found in Figure 60-7 and eFigure 60-12 premised on the presence of a team skilled in the performance of sentinel node biopsies or the availability of PET/CT. Absent either capability, radical wide local excision and at least ipsilateral inguinofemoral lymphadenectomy is recommended. Predicated on histopathologic findings, subsequent management is suggested by the algorithm in Figure 60-8.

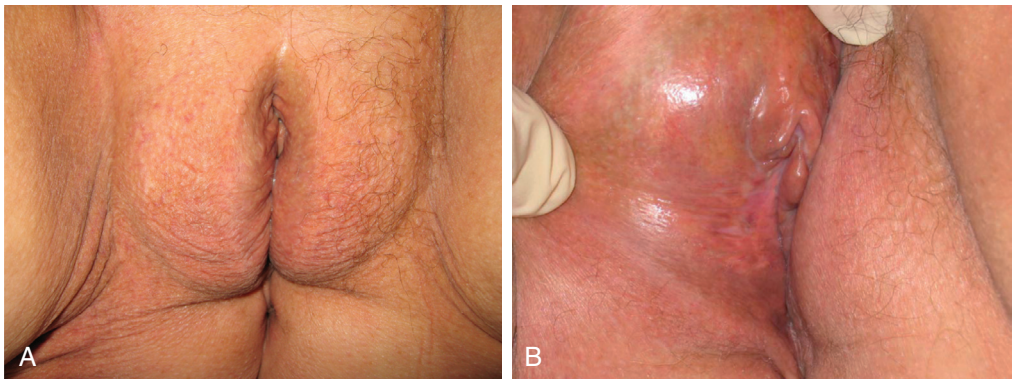
Small Primary Tumors Encroaching on Midline Structures

Although surgical excision remains the historical standard treatment for patients with small, midline primary tumors, it is not unreasonable to consider treating a primary midline lesion, regardless of size, with a localized field of primary RT or chemoRT if surgical excision would result in predictable loss of cosmesis or function. Although such patients can be cured with surgery as monotherapy, the functional and cosmetic impairments can be psychologically devastating. In many patients, clinical shrinkage after a modest dose (45 Gy to 54 Gy) of RT or chemoRT will permit conservative excision of residual tumor with excellent preservation of function and cosmesis (eFigure 60-13, *A* and *B*).

This recommendation remains controversial, not because of a lack of efficacy for RT (which has been proven effective in more locally advanced disease) but rather because no systematic studies of subsequent sexual function and morbidity have been performed. Anecdotally, clitoral function can be preserved in some sexually active patients following 45 Gy combined with 5-FU–based chemotherapy supplemented by clitoris-sparing local excision. Some such patients, sexually active and orgasmic before treatment, are sexually active and orgasmic 12 or more months following completion of treatment, and subjectively report intact sensation and vascular engorgement and erectile clitoral function. Whether functionality is preserved after higher doses of radiation is unknown.



eFigure 60-12 Treatment algorithm. Limited, unifocal vulvar cancer <4 cm without encroachment on clitoris, vagina, urethra, or anus. Groins clinically uninvolved. Experienced positron emission tomography/computed tomography (PET/CT) diagnostic imaging available.



eFigure 60-13 Clinical results after combined modality therapy for a small T2 N0 anterior right labia minora primary invading clitoris. Images obtained at follow-up 18 months following treatment that consisted of 45 Gy in 25 fractions to a volume encompassing the primary and electively including the groin nodes bilaterally with two courses of concurrent infusional 5-fluorouracil and bolus cisplatin. Conservative excision of residual tissue followed that spared the clitoris and most of the vulva. Images obtained with labia apposed **(A)** and with right labia majora retracted revealing excision scar **(B)**.

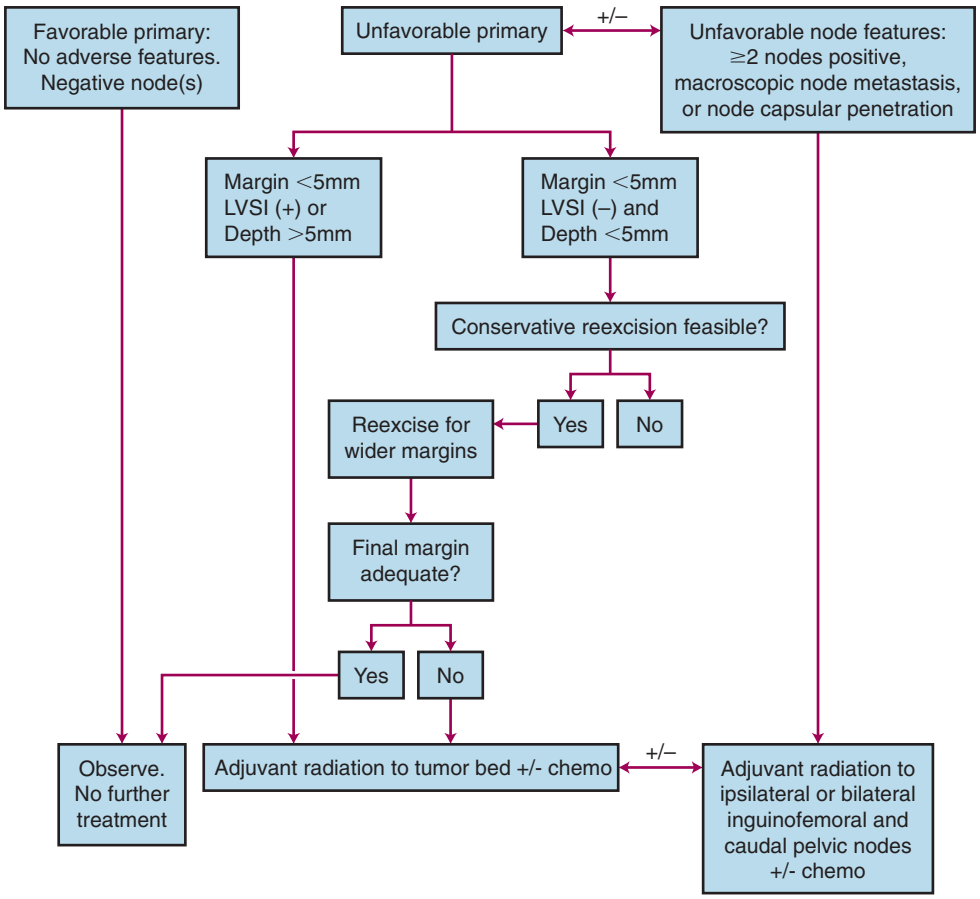


Figure 60-8 Treatment algorithm. Limited, unifocal vulvar cancer <4 cm without encroachment on clitoris, vagina, urethra, or anus. Management algorithm subsequent to initial surgical management according to either Figure 60-7 or eFigure 60-12 and based on histopathologic findings.

LOCALLY ADVANCED DISEASE AND PALLIATION

Patients may be considered to have locally advanced disease if the location and extent of the primary lesion in the vulva is such that radical excision would require functional compromise or sacrifice of functionally important midline structures. Patients with clinically involved groin nodes, particularly matted, ulcerated, or fixed, are also considered to have locally advanced disease. Such patients are predictably inadequately treated by surgery as monotherapy, and combined-modality therapy (chemoRT alone or coordinated with conservative surgery) should be considered by multidisciplinary consultation before initiation of any therapeutic intervention.

Historically, adequate surgical clearance of large primary tumors that involve the anus, rectum, rectovaginal septum, or proximal urethra would usually include radical vulvectomy plus some type of pelvic exenteration. Five-year OS with primary surgery for locally advanced disease range up to 50%.[210] However, physical and psychological morbidity from such surgical procedures is high.

Boronow et al, in a landmark study, explored the use of preoperative RT in locally advanced disease with the intent to reduce the scope of subsequent surgery. Thirty-seven patients with locally advanced vulvar cancer were treated with variable doses of RT (median, 48 Gy) followed by surgery. The 5-year OS was 75.6%, and approximately 40% of patients had no residual disease in the operative specimen.[180]

Subsequently, multiple investigators reported favorable results in observational studies of patients with locally advanced disease treated with chemoRT employed preoperatively if shrinkage permitted nonexenterative surgery. Consequent to these studies as well as the results of GOG 101, there is a growing acceptance by gynecologic oncologists that concurrent chemoRT constitutes the initial treatment of choice for primary management of patients with locally advanced disease.

Randomized trials for vulvar cancer have not been performed to test whether concurrent chemotherapy confers additional benefit to RT alone, but Phase III trials have shown benefit for chemoRT compare with RT alone in both anal and cervix cancer.[160,161] The drugs regimens commonly used with vulvar cancer include 5-FU, alone or in combination with cisplatin or mitomycin-C, or weekly cisplatin alone. Results with Bleomycin have been found unsatisfactory either as a result of gross tumor persistence or a high local relapse rate after initial favorable response.[168,193]

An algorithm for the management of patients with locally advanced primary cancer, with or without locally extensive groin metastases, is depicted in Figure 60-9. The rationale for interval evaluation after a preoperative dose of chemoRT inherent in the management algorithms for both limited and advanced disease depicted in Figures 60-8 and 60-9 is to assess the efficacy of the initial management strategy to determine whether to continue with it or change to a possibly more effective one. Ideally these reassessments should include both the

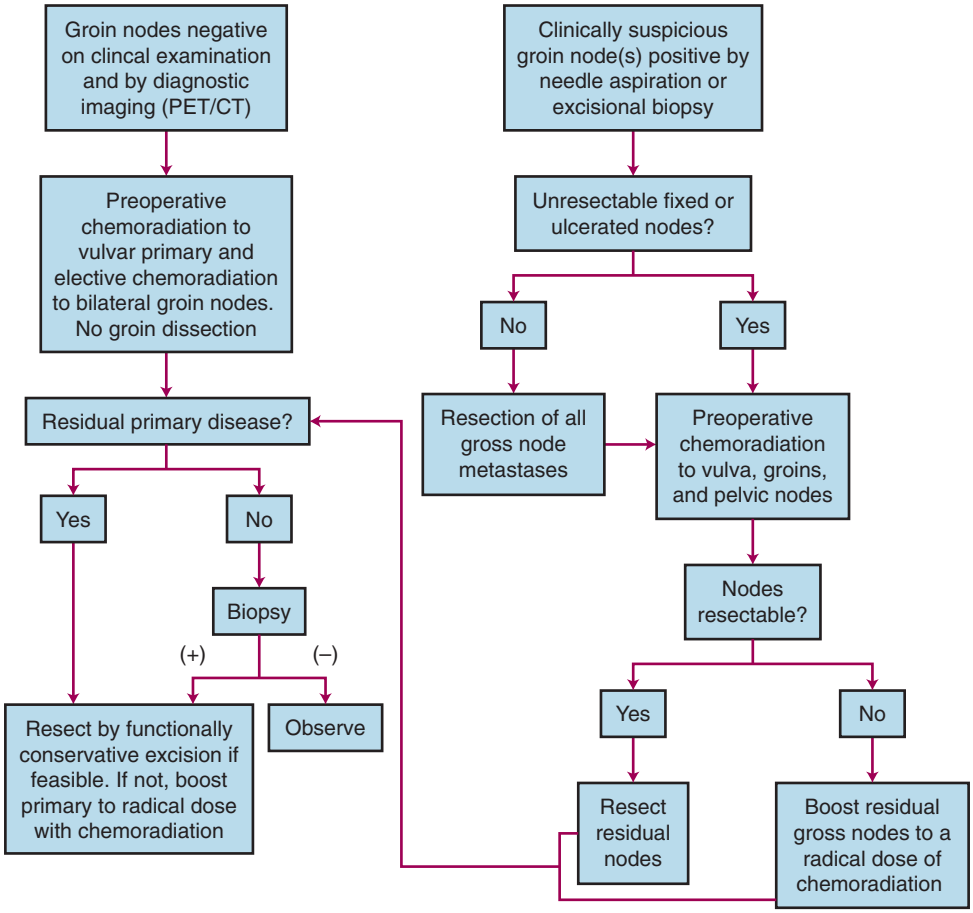


Figure 60-9 Treatment algorithm for extensive primary lesion encroaching on or invading functionally important midline structures (clitoris, urethra, vagina, anorectum) that cannot be surgically resected without potential compromise to the functional integrity of those structures. *PET-CT*, Positron emission tomography/computed tomography.

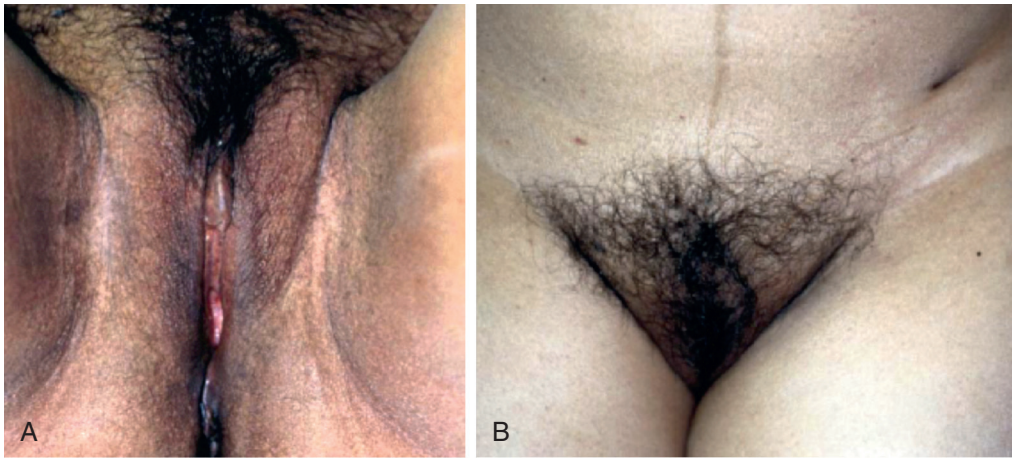
radiation oncologist and the gynecologic oncologist to determine the optimal integration of the modalities.

Locally Advanced Nodal Disease

When groin nodes are ulcerating or fixed, initial treatment of the inguinal regions consists of primary RT or chemoRT. Because it is unclear whether chemoRT in tolerable doses can reliably eradicate bulky nodal disease, if there is substantial regression of nodal disease after modest dose irradiation it is reasonable to subsequently operate to remove residual adenopathy rather than incur the possible attendant morbidity of completing radiation to a radical dose.

Patients with bulky involved nodes that are initially resectable may undergo either initial surgical removal of the bulky nodes followed by postoperative RT or chemoRT, or initial RT or chemoRT followed by operative removal of any residuum. The optimal sequencing of therapies remains controversial because surgery and its possible complications of problems with delayed wound healing or infection will delay initiation of RT, whereas preoperative RT or chemoRT may compromise wound healing. Commonly, patients with bulky inguinal nodes will also have locally advanced primary tumors, in which case initial RT or chemoRT is a logical sequence choice. Conversely, initial gross adenopathy may be difficult to reliably identify and excise after preoperative chemoRT, and a good case can be made for initial surgical removal if negative margins of resection can be achieved by R0 resection. If there is clinical uncertainty whether all gross adenopathy can be removed from the groins, imaging with US, CT, or MRI may aid in elucidating the spatial relationships between blood vessels, nerves, bone, and metastatic adenopathy. These imaging modalities may be particularly useful in defining disease extent in large patients in whom the femoral nodes lie deeper than can be realistically assessed by clinical palpation.

When combined therapy is used, regardless of the sequencing of therapies, to minimize complications, groin surgery should be limited to removal of gross nodes rather than an en bloc removal of all groin lymphatic tissue. It should be accomplished through the smallest feasible incision to accomplish this objective. The intent of such surgery is to reduce groin cancer volume to a microscopic, occult burden that can be controlled by modest doses of fractionated RT, or preferably chemoRT. Conversely, RT dose or chemoRT administered either before or after surgical cytoreduction should generally be restricted to an effective dose for controlling microscopic or occult disease (i.e., 45 Gy to 50 Gy in 1.8-Gy to 2-Gy fractions). By limiting the extent of groin dissection in anticipation of subsequent RT, and by limiting RT dose in anticipation of surgical removal of residual, bulky disease, some acute complications (wound dehiscence, infection) and late sequelae (lymphedema, femoral fracture, arterial occlusion) might be reduced in severity or avoided altogether (eFigure 60-14, *A* and *B*). At MGH, for patients with residual, unresectable node metastases after moderate dose neoadjuvant chemoRT (45 Gy to 50 Gy), limited volume boost radiation (plus concurrent chemo) is used to carry grossly involved nodes to 65 Gy.



eFigure 60-14 Clinical photographs obtained 10 years after completion of all treatment for a primary squamous cancer of the Bartholin's complex presenting with gross left inguinal adenopathy. Appreciating that postoperative radiation would be administered for multiple positive groin nodes as well as inadequate margins on the primary, initial surgery was limited to gross total local excision of the primary and ipsilateral groin dissection limited to removal of all enlarged nodes. Postoperative chemoradiation was administered with to a volume encompassing the residual vulva, the involved groin, next echelon nodes in the left pelvis, as well as contralateral groin nodes over and medial to the right femoral vessels. Radiation dose was limited to 45 Gy in 25 fractions of 1.8 Gy with two cycles of concurrent 5-fluorouracil and mitomycin-C. The patient remains cancer-free, continent of urine and feces, sexually active, and free of lymphedema.

Locally Recurrent or Metastatic Cancer

The outcome for patients who experience relapse of vulvar cancer after primary therapy is markedly dependent on the site of relapse. For the rare situation of distant metastases, chemotherapy with agents active against squamous cancer particularly as concurrent to radiation such as (5-FU, cisplatin, mitomycin-C) is often offered, but response rates and response durations are generally poor.[6,103,211-221] At this time, treatment with targeted agents remains investigational[222] (eFigure 60-15).

Although inguinal recurrences may be amenable to local management with RT or chemoRT, only occasional patients survive long term.[68,103,105,147,148] Several reports have suggested that up to 75% of patients with vulvar recurrence of cancer may be cured, with surgical reexcision.[68,223] Boronow et al reported a 5-year OS of 63% with modest-dose RT.[180] However, Faul et al reported only a 25% 2-year OS after vulvar recurrence.[141] The discrepancy in reported outcomes may relate to the site and extent of recurrence and what prior treatments have been given. RT or chemoRT for local recurrence is an option, particularly when the lesion is not amenable to repeat resection without predictably inadequate surgical margins or compromise of functionally important midline structures.[163,166,224]

IRRADIATION TECHNIQUES AND TOLERANCE

Groin and Nodal Irradiation

GOG 37, which established the usefulness of postoperative adjuvant groin and pelvic irradiation in patients with metastases to inguinofemoral nodes, used external beam radiation therapy (EBRT) bilaterally to the inguinal and femoral dissection beds and pelvic nodes even when node involvement was unilateral.[92] The specific radiation doses in the study—45 Gy to 50 Gy in 1.8-Gy to 2.0-Gy fractions—are commonly those prescribed to control of microscopic disease. The technique used was an anterior and posterior (AP) parallel, opposed pair of fields, a technique rarely appropriate now when more conformal techniques are available. The GOG study used a superior border somewhat arbitrarily placed at the L5-S1 interspace, although the value of extending the field to this level superiorly is uncertain as the observed survival gains appear to be related to improved control of the inguinal regions and not to improved control of the pelvic nodes. Treating this volume with this technique necessarily limits the radiation dose 45 Gy to 50 Gy because of normal tissue dose limitations (bowel, femoral necks, pelvic girdle).

Involved nodes located high in the pelvis or in the common iliac region connote a high probability of extrapelvic failure, and it is unclear that irradiation of the entire pelvic volume contributes to cancer control or survival. In the interest of reducing morbidity, it seems sensible to define nodal target volumes based on the principle of electively irradiating the next echelon of lymph nodes proximal to the lymph node group that is clinically involved. For patients with unilateral node metastases to inguinofemoral nodes without clinical or radiographic evidence of pelvic node metastases, the CTV can sensibly be limited to obturator and external iliac node groups on the affected (ipsilateral) side. Irradiation of hypogastric nodes and the contralateral external and obturator areas will rarely be indicated unless there is significant extension of the primary cancer proximal to the hymenal ring in the vagina or invasion of the urethra or rectum. The patient can be treated in the supine position with the feet apart or in the "frog-leg" position with leg supports to minimize skin reaction in the medial thigh. The central residual vulvar tissue may or may not be included depending on risk factors associated with the primary tumor and institutional philosophy. Each groin should be evaluated where bilateral spread is possible (midline lesions or involved ipsilateral nodes) and radiation directed to each side when there is an indication to do so (any involvement greater than a microscopic focus in a single node). The nodal volume is determined using CT planning. The necessity for specifically encompassing the inguinal lymphadenectomy scar is unclear because the incidence of scar recurrence is unknown. Depending on beam energies and technique employed, the tumor dose may be brought out to the skin. Generally, if a midline block is used because risk factors for local recurrence are minimal, it should be no wider than the distance between the pubic tubercles because it is intended only to reduce dose to midline structures (distal urethra, vagina, and anorectum) and residual vulva.

For patients with clinically and radiographically negative groin nodes in whom elective nodal irradiation or chemoRT is to be used without subsequent surgical dissection, the techniques and volume of RT are similar to those described for adjuvant therapy except that the superior border of the treatment volume may usually extend to midpelvis. Generally this will be done when preoperative RT or chemoRT is needed for a locally advanced vulvar primary and both groins should be included. The nodal bed including the deep femoral node depth should be confirmed by CT or US, particularly if techniques more sophisticated than parallel opposed AP photon fields are to be used. Conventionally, the CTV should be defined on the planning CT. The dose delivered must be substantially increased for patients with fixed or ulcerating (unresectable) lymph nodes. Although the optimal dose is not defined, a dose of 64 Gy to 67 Gy, usually in combination with multiple cycles of concurrent chemotherapy, may be necessary to provide the highest probability of locoregional control while remaining within the tolerance of adjacent normal tissues.

Several techniques have been used to minimize femoral neck dose (and risk of subsequent femoral neck fracture) include partial central transmission block technique; in dose to the deep groin nodes is prescribed through a large anterior photon field employing low-energy photons of 4 MV to 6 MV. Dose to deeper pelvic nodes and the vulva is calculated and supplemented by a smaller, opposed posterior pelvic field using photons of higher energy. A central partial transmission block is placed over the anterior field corresponding to the narrower posterior field that attenuates the contribution of the anterior field to the deep pelvic nodes and vulva, allowing better dose homogeneity. If the CTV is more superficial, dose may be further supplemented by administering a portion of the treatment with high-energy electrons. When abutting photon or photon and electron fields to encompass nodal tissue overlying the femoral necks, there is considerable potential for "hot" and "cold" spots. Hot spots may injure the femoral arteries as well as the femurs, and cold spots hazard disease recurrence within the CTV. Moving the field abutments once or twice during a course of treatment will serve to minimize these hazards.

Another technique used is the *modified segmental boost technique*. Right and left anterior oblique, partially beam-split photon fields are used to supplement groin node dose and is a technique suitable for any department with an isocentric linear accelerator with appropriate beam energies.[185,225] With this technique, the oblique fields are angled so the medial border of each anterior oblique field corresponds to the beam divergence of the lateral border of the posterior field, minimizing the potential for hot and cold spots. The tumor dose must be brought to the skin surface if there is evidence of cutaneous involvement. Bolus material may be required (Figure 60-10).



eFigure 60-15 A patient with regionally advanced squamous cancer of the vulva with necrotic (gauze packed) groin nodes ulcerating through skin. Concurrent 5-fluorouracil–based chemotherapy administration with radiation produced both rapid tumor involution at the primary site and groin nodes as well as accelerated reaction in surrounding skin. During treatment (electron boost therapy) previously unsuspected but subsequently biopsy confirmed discontiguous skin metastases *(white arrows)* were appreciated in skin of lower abdominal wall and upper lateral thigh documenting cancer progression while receiving chemotherapy in areas outside the irradiated volume.

Because vulvar neoplasia is often a field defect, second tumors may develop but are often labeled vulvar recurrences. New primary cancers often develop in sites remote from the initial tumor.[38] It is important, if possible, to differentiate a new occurrence of cancer from a recurrence because the latter would attribute a treatment failure to the original treatment modalities used and lead to an underestimate of the efficacy of the original therapy. Management of the groins is complex when a new cancer is detected and must depend on prior groin management.

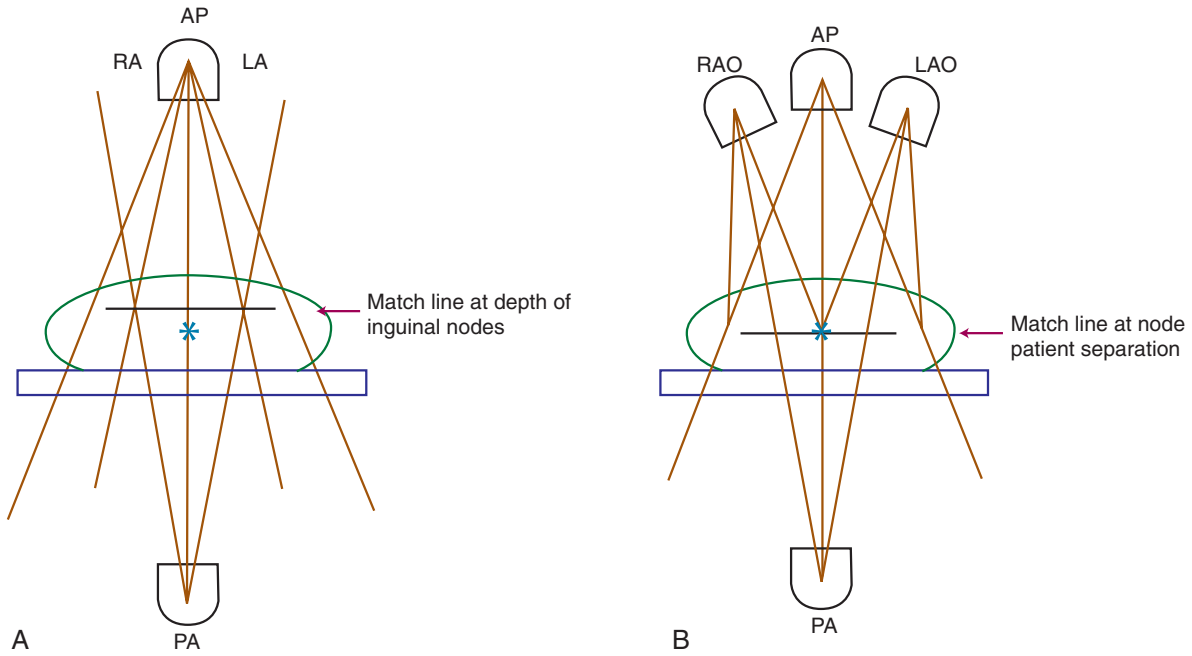


Figure 60-10 Treatment technique for irradiation of the pelvis and inguinal nodes. Beam arrangements for two techniques: segmental boost technique **(A)** and modified segmental boost technique **(B)**. *AP,* Anterior-posterior; *LA,* left anterior; *LAO,* left anterior oblique; *PA,* posterior-anterior; *RA,* right anterior; *RAO,* right anterior oblique.
Data from Moran M, Lund MW, Ahmad M, et al: Improved treatment of pelvis and inguinal nodes using modified segmental boost technique. Dosimetric evaluation. Int J Radiat Oncol Biol Phys 59:1523–1530, 2004.

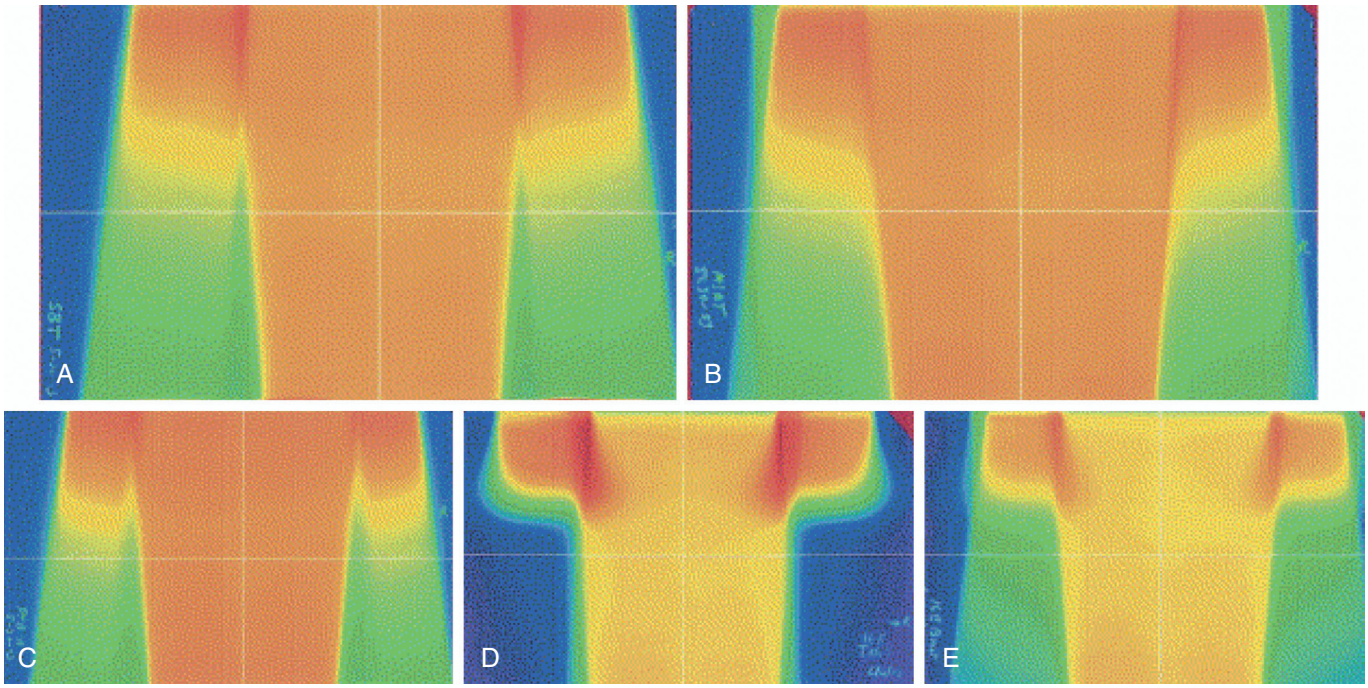
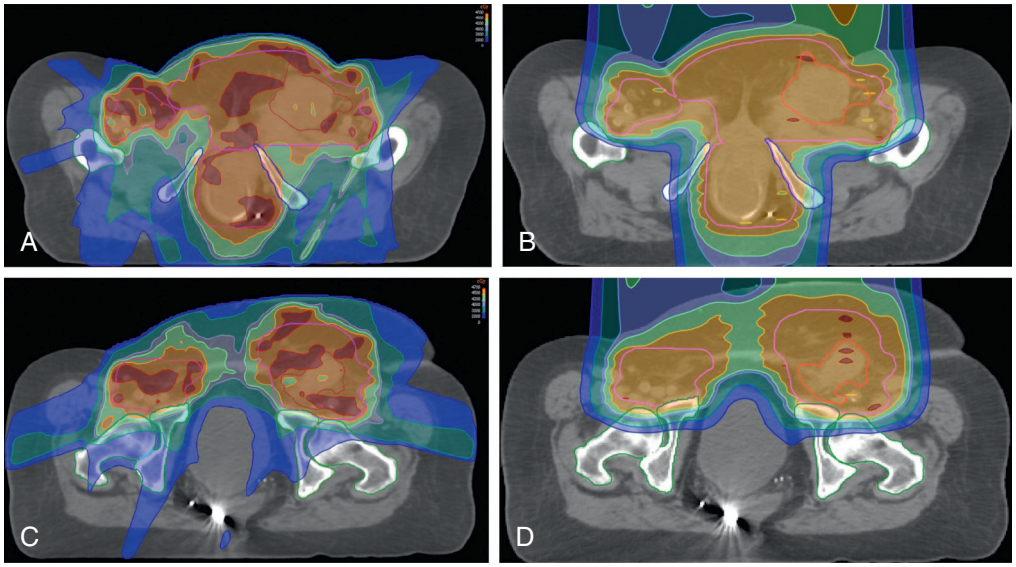


Figure 60-11 Comparative dose profiles for various techniques employed to treat the pelvis and groin nodes. Color rendering of axial dose distribution generated from vertical film irradiation in a plastic-water (PW) phantom using five different techniques for treating pelvis and inguinal nodes. High-dose areas are visible in field overlap regions. **A,** Segmental boost technique. **B,** Modified segmental boost technique. **C,** Partial transmission block technique. **D,** Photon with electron tag technique. **E,** Photon with electron boost technique.
Data from Moran M, Lund MW, Ahmad M, et al: Improved treatment of pelvis and inguinal nodes using modified segmental boost technique. Dosimetric evaluation. Int J Radiat Oncol Biol Phys 59:1523–1530, 2004.

Axial dose profiles employing various techniques are depicted in Figure 60-11, illustrating the magnitude of hot spots at the boundaries of treatment fields.

Depending on equipment availability, preferable technical alternatives include the use of IMRT. It is extremely important that the quality assurance measures are rigorous and oncologist technical expertise is satisfactory if IMRT is used. Patients appropriate for the substantially more conformal dose distributions that can be achieved with these alternatives should preferably be cooperative, thin, and amenable to precise and



eFigure 60-16 Dose distributions with intensity-modulated radiation therapy (IMRT) and intensity-modulated proton therapy therapy (IMPT) for 45 Gy to a clinical target volume (CTV) encompassing a recurrent squamous carcinoma of the vulva after wide local excision with a 7-mm surgical margin and a negative sentinel node biopsy. Recurrence was observed at 5 weeks following surgery with clinically rapid progression both in residual vulva and left groin. The advantage of IMPT is seen in reduced dose administered to femoral necks, ischial rami, and acetabular bone in anticipation of an ultimate requirement for high dose to be administered to both the left groin and the vulva. Comparative sparing of the boney structures underlying the left groin mass permits greater flexibility in administering boost radiation to this volume, which can also be carried out with proton beam. The IMRT plan was created using a seven-field (100 segments) beam arrangement with multicriteria optimization and collapsed cone algorithm. The proton beam scanning plan was generated using Astroid, an in-house treatment planning system at Massachusetts General Hospital. Protons in thousands of magnetically steered pencil beams are separately adjustable and optimized to achieve the prescribed dose. *Blue*, 20 Gy; *dark green,* 30 Gy; *grey,* 40 Gy; *light green,* 42 Gy; *orange,* 45 Gy (prescription dose); *red,* 47 Gy. Dose distributions courtesy of Peter Paetzold and Judith Adams, Division of Medical Physics, Department of Radiation Oncology, Massachusetts General Hospital, Boston, MA. **A,** IMRT dose distribution at the center of the groin mass and at the level of the distal vagina, inferior ischial rami, and lesser trochanters of the femurs. **B,** IMPT dose distribution at the center of the groin mass and at the level of the distal vagina, inferior ischial rami, and lesser trochanters of the femurs. **C,** IMRT dose distribution at the cephalad portion of the groin mass, femoral heads and acetabular regions with inguinal CTVs encompassing bilateral groins with generous margins. **D,** IMPT dose distribution at the cephalad portion of the groin mass *(red line)* with inguinal CTVs encompassing bilateral groins with generous margins *(pink lines)*.

reproducible daily setup because the potential for marginal miss is amplified by the tight tolerances used by these techniques. It is important that marginal miss is minimized by ensuring adequate planning target volume (PTV), even if doses to small volumes of normal structures approach those experienced with the old technique of a parallel pair. With IMRT, a somewhat greater degree of dose inhomogeneity within the target volumes is part of the price paid for more conformal therapy, which is more than offset by substantially reduced dose to tissues and structures not part of the target volumes.

A conformal dose distribution achievable with IMRT technique is seen in Figure 60-12. It is easily appreciated that the extra time and effort expended in planning and carrying out such treatment substantially reduces the dose to adjacent normal tissue, which are not included in the target volume. Arguably, absent the capacity or experience in sophisticated RT of this nature, facilities in the United States should refer patients for RT to suitably equipped and experienced tertiary centers capable of employing these more advanced techniques.

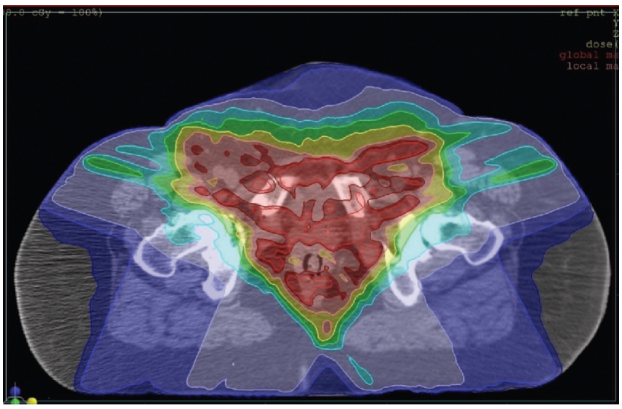


Figure 60-12 Intensity-modulated radiation therapy (IMRT) dose distribution for a patient with a posterior vulvovaginal cancer encroaching on the anal sphincter for whom the target volume included elective treatment of clinically and radiographically uninvolved inguinofemoral nodes. A small portion of the femoral heads receive up to 80% of the prescription dose. The femoral necks receive 70% to 25% of the prescription dose with a steep dose gradient between the subcapital proximal femoral neck and the femoral metaphysis. Coupled with the diminished impact of reduced total dose and dose per fraction, this technique is unlikely to result in radiation induced femoral insufficiency fractures. *Aqua,* 70% of prescribed dose; *blue,* 25%; *dark red,* 105%; *green,* 80%; *orange*, 100%; *purple,* 50%; *red,* 107%; *yellow*, 90%.

Under special circumstances, use of intensity-modulated proton beam (IMPT) can provide more conformal dose distribution than can be achieved by photon IMRT, which may be clinically advantageous when high-dose RT is required for tumors in close proximity to normal structures and surgery is not feasible (eFigure 60-16, *A-D*).

Guidelines for the treatment of primary vulvar cancers and regional nodes by IMRT are codified in GOG Protocol 279 and presented in abbreviated form in Tables 60-8 and 60-9.

It should be understood that selection of target volumes, choice of treatment technique, and prescription of RT dose and fractionation should be individualized based on tumor factors, patient comorbidities, availability of equipment, and sophistication of medical dosimetry support. Reference guidelines with respect to target volumes, dose, and dose limitations to volumes of organs at risk must be interpreted in the light of individual patient and tumor factors and should not be applied with uncritical rigidity. There can be no substitute for thoughtful consideration of all relevant clinical parameters and prudent deviation from guidelines when circumstances dictate this to be in the patient's best interest.

Adjuvant Postoperative Irradiation of the Vulva

When adjuvant irradiation to the vulva is indicated because of risk for local recurrence, an appositional perineal portal may be used with the patient in dorsal lithotomy position. Although often requiring daily physician verification of treatment setup, this permits precisely tailored volumes to be treated reproducibly. Just as surgical concepts are changing to limit radical excision to the site of the primary cancer rather than extirpation of the entire vulva, radiation volumes are also being modified. A localized field of radiation may be used to encompass the vulvar scar with an appropriate margin. This allows maximal sparing of uninvolved vulvar tissues from

TABLE 60-8 Target Volume Definitions from GOG Protocol 279

Vulvar Gross Tumor Volume (GTV)	Gross tumor as seen on radiographic imaging or as visible on clinical examination and delineated with surface markers on planning computed tomography
Inguinal Gross Tumor Volume (GTV)	Unresected or residual gross disease in the inguinalfemoral region as defined on any radiographic imaging
Vulvar Clinical Tumor Volume (CTV)	Vulvar GTV with 2-cm margin including skin and subcutaneous tissues but excluding bone unless bone involvement documented. When vulvar GTV involves vagina, a minimum of 2 cm of normal vagina to be included in CTV. When the vulvar GTV involves or extends to within 1 cm of the anal verge a minimum of 2 cm of anorectum to be included in CTV. When the vulvar GTV involves the urethra or periurethral tissue a minimum of 2 cm of urethra to be included in the CTV
Inguinal Clinical Tumor Volume (CTV)	In the absence of an inguinal GTV the CTV will extend 2.5 cm lateral and 3 cm medial to the nearest inguinal vessel as well as 2 cm anterior and 1 cm posterior to the vessels. The cephalad border is at the top of superior pubic rami. The caudal extent is the bottom of the lesser trochanter. Any postoperative changes from prior dissection should be included in the CTV. In the presence of inguinal GTV the CTV must include the GTV with a minimal expansion of 7 mm
Pelvic Nodal Clinical Tumor Volume (CTV)	Pelvic nodal CTV (when indicated) shall include bilateral external iliac, obturator, and internal iliac nodes defined by the vasculature of each region with a minimum 7-mm expansion
Planning Tumor Volume (PTV)	7-mm to 10-mm margin in all directions around vulvar, inguinal, and pelvic CTVs with bolus as needed to assure adequate skin dose

TABLE 60-9	Dose Constraints for Organs at Risk GOG Protocol 279
Small Bowel	<30% to receive 40 Gy or more Dmax 51 Gy or less
Anorectum	<80% to receive 40 Gy or more Dmax <65 Gy. This constraint should exclude any PTV that overlaps this volume
Bladder	<50% to receive 45 Gy or more Dmax 65 Gy or less
Femoral head/ neck	<50% to receive 45 Gy or more Dmax 55 Gy or less

Dose constraints are guidelines but cognizant of the fact that if following constraints rigidly tumor may be underdosed in which case adequate tumor dose is more important. In this circumstance the patient should be informed of increased risk of complications.

acute and late radiation reactions. This is in contradistinction to "guidelines" developed by the NRG, when RT to the entire vulva is suggested. When therapy is adjuvant, RT alone employing dose ≥56 Gy is recommended, depending in part on whether a margin is narrow or grossly contaminated, as well as on the health of the surrounding tissues. The role of concurrent chemoRT in this adjuvant setting is not established. The beam energy should be tailored to the estimated depth or thickness of the original lesion from the vulvar surface, with appropriate use of bolus to deliver the prescribed tumor dose to the skin of the vulva. Electron beam or a low-energy photon beam is employed.

Preoperative or Definitive Vulvar Irradiation

When initial RT is selected for primary management of a small or early midline vulvar primary, a technique of irradiation may be used similar to that described for adjuvant treatment (i.e., a perineal portal tailored to the depth and thickness and size of the lesion) if the groin nodes will not be treated. Alternatively, a small volume may be irradiated with IMRT technique. More commonly, the target volume will include the groin nodes bilaterally. The majority of vulvar cancers are radioresponsive, and visible response to RT is often apparent after a tumor dose of 30 Gy to 36 Gy in factions of 1.8 Gy to 2.0 Gy. Because available dose-control data for vulvar cancer are scant and seldom correlated with the volume of disease treated, and because it is unknown to what extent the addition of concurrent chemotherapy will modify the total dose required to sterilize disease, dosage guidelines are imprecise. In general, concurrent chemotherapy (weekly cisplatin or infusional 5-FU with or without cisplatin or mitomycin C) is recommended for definitive treatment. If primary tumors shrink and become resectable, a preoperative dose of 45 Gy to 57.6 Gy should suffice. For medically inoperable patients or primary tumors which remain unresectable by conservative surgery, tumor doses should be escalated up to as high as 67 Gy. Total dose will be contingent on the fractionation employed, the elapsed time to complete treatment, and whether or not concurrent chemotherapy is employed. As the dose is increased, the risk of skin atrophy, fibrosis, and bone insufficiency fractures increases, complications that can be debilitating.

Because of the complexity of the three-dimensional contours of the vulva, perineum, and groins, thermoluminescent dosimeters placed on the tumor and in the cleft between the labia are a simple mechanism to confirm actual absorbed dose at the vulva. This permits tailoring compensatory measures should the dose inhomogeneity be excessive.

Because of the exquisite radiosensitivity of most vulvar cancers, the potential negative impact of protracted overall treatment time may be less than for other tumors. Data from GOG 101 with a planned split course of RT with a 2-week break and overall dose of only 47.6 Gy still revealed an approximate 30% complete pathologic response in advanced disease. Although planned split-course irradiation is believed to be undesirable, most patients develop confluent moist desquamation and require a short rest to allow epithelial regeneration before completing a planned definitive course of chemoRT to the vulva. Use of twice daily fractionation schemes may reduce overall elapsed treatment time while maximizing radiation-drug synergism. Twice-daily fractionation during reduced volume boost radiation to gross disease or a concomitant small-volume boost may also reduce overall duration of treatment. Because volumes are small, this can be accomplished without unacceptable acute RT toxicity.

Interstitial RT implants have been used by some, particularly for boosting bulky disease or boosting vaginal extension.[226,227] No randomized data are available to evaluate the relative benefits and toxicities of interstitial versus external boost irradiation. Potential pitfalls of interstitial techniques include difficulty in achieving dose homogeneity, potential increased late effects consequent to the unavoidable hot spots in tissues in direct contact with interstitial sources, and variability in intersource separations with patient movement and leg positioning. An illustration of adverse late sequelae in a patient with vulvar cancer treated with interstitial technique is seen in eFigure 60-17.

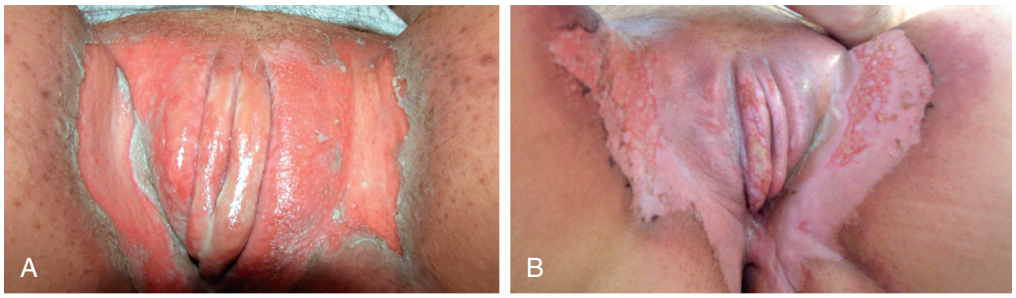
Radiation Tolerance and Treatment Sequelae

When vulvar radiation is used either as an adjuvant treatment to wide local excision or as definitive treatment, full tumor dose needs to be delivered to the skin and mucosal surfaces. Even when doses of 45 Gy to 54 Gy are given in the adjuvant setting, it is expected that almost all patients will experience some degree of desquamation. This may vary from patchy, moist desquamation to confluent, moist desquamation over the entire treatment volume. Generally, this reaction heals in the 2 weeks to 3 weeks after completion of RT. Because of the accelerated repopulation of normal squamous cells in the epidermis, healing of moist desquamation can be quite rapid (eFigure 60-18, *A* and *B*). The acute reaction is usually managed with symptomatic measures, including frequent sitz baths, exposure to air, application of topical ointments such as those used to treat superficial burns, and pain medication. In some situations, particularly in elderly, frail patients, hospitalization for skin care may be required. Many patients find sitz baths in reconstituted salt solutions of seawater particularly soothing. Irritation from passage of urine over the irradiated vulva can be avoided by voiding into water in a sitz bath. Depending on the volume treated, acute effects may include urethritis, cystitis, and proctitis. Watery diarrhea is unusual unless a full pelvic volume is irradiated, which is rarely appropriate.

The late effects of RT may include skin changes of atrophy or telangiectasis, which, in small volumes, are not usually functionally distressing. Some patients may experience more extensive skin atrophy and dense subcutaneous fibrosis (eFigure 60-5, *B*) depending on the volume necessarily carried to high dose. The development of mucosal or perineal ulcers is rare. Late effects on the vulva appear to be minimized by limiting the radiation fraction size to 1.6 Gy to 1.8 Gy and the volume of reduced target boost therapy. Inclusion of anorectum in boost volume treatment may result in chronic rectal bleeding (radiation proctitis) or fibrosis and stricture of the anal canal.



eFigure 60-17 Severe late radiation toxicity in a patient treated for locally advanced vulvar cancer with high-dose external and interstitial radiation exceeding 70 Gy. Although cancer was controlled, the patient required both urinary and fecal diversions for bladder and anorectal injury, and became narcotic dependent for control of perineal pain.



eFigure 60-18 **A,** Confluent moist desquamation in a patient whose treated volume encompassed the entire vulva. Photograph was taken 9 days after 47.6 Gy chemoradiation (5-fluorouracil/cisplatin regimen similar to GOG Protocol 101) when tiny islands of regenerating squamous epithelium are just beginning to appear. **B,** Six days later the desquamated area has largely reepithelialized. Of note, this patient was treated to a target volume (CTV) that would be considered excessive in the modern area, employing much less sophisticated techniques than are currently available (i.e., intensity-modulated radiation therapy).

Irradiation of the node-bearing areas may result in similar acute effects if full doses are required at the skin because of skin infiltration or ulceration, or when superficial groin nodes lie only millimeters below the skin in thin patients. Acute effects may vary from erythema to moist desquamation, particularly in intertriginous areas and along skinfolds.

The contribution of RT to the problem of leg edema induced by groin surgery is unknown. One series suggested that, after concurrent chemoRT, 4 of 14 surviving patients treated for advanced primary or recurrent disease experienced leg edema. In 2 patients this edema was minimal, not requiring treatment. Two patients did require treatment with compression and diuretics. Both had an inguinal lymphadenectomy before chemoRT.[166] Clearly the magnitude of the surgical intervention in the groins (sentinel node biopsy versus complete groin dissection) has major impact on the risk of lymphedema, with a 1.9% risk in patients undergoing only sentinel node biopsy compared to 25.2% in patients undergoing therapeutic inguinofemoral lymphadenectomy.[151] In a retrospective outcomes analysis, the extent of lymphadenectomy (gross total removal versus en bloc complete lymphadenectomy) did not appear to have a major impact on either disease control in the groin or survival when coupled with groin RT.[228] In the interests of minimizing the risk and severity of subsequent lymphedema and cellulitis, it seems prudent to limit groin dissection to removal of only grossly contaminated nodes when planned RT or chemoRT will follow.

RT to the groins may induce femoral neck fracture.[66,153] The risk of hip fracture may not correlate well with the dose delivered to the hips and may be more frequent in frail, elderly women with underlying osteoporosis.[229] Based on the anatomical study of sentinel node location by Rob et al,[122] a potential way to minimize the risk of this complication is to limit the groin target volumes laterally and use the planning CT to define the volume extending medially to the pubic tubercles when elective groin RT is performed in patients with clinically and radiographically negative groins. By excluding the lateral inguinal nodes as defined by Rob, the substantial majority of the femoral neck and metaphysis can be excluded from direct RT in most patients, when IMRT is not available to accomplish that objective.

Rarely, groin RT may induce hemodynamically significant femoral artery stenosis.[230] Fractures through the ischial rami may occasionally be seen in patients carried to higher RT dose for unresectable primary disease. RT insufficiency fractures are seen in eFigure 60-19.

Acute complications from chemoRT can be severe. Reviewing 5-FU with mitomycin-C or mitomycin-C alone used as concurrent radio-potentiators in the treatment of 17 patients with vulvar cancer, 35% developed grade-4 neutropenia and half of them developed neutropenic sepsis following their second cycle of chemotherapy.[231] About one quarter could not receive the second cycle of chemotherapy. Severe enterocolitis was a direct contributing cause of death in 2 patients. Skin toxicity necessitated treatment interruption in half of the patients at a median dose of 32.4 Gy (range 16.2 Gy to 48 Gy) and half required more than 9 weeks to complete therapy.[231] Because patients are often elderly, chemotherapy dose reductions should be considered for some.[232] Commonly most generally used concurrent chemotherapy is the familiar weekly cisplatin or 5-FU and cisplatin. Mitomycin-C has been associated with significant bowel toxicity and is rarely used.[224] Reduced bowel toxicity could be anticipated by the use of more conformal, contemporary RT techniques. Treatment interruption necessitated by severe acute RT dermatitis may delay treatment longer than the 7 days to 10 days generally needed. Usually chemoRT can be restarted when punctate epithelial islands are seen in areas of moist desquamation.

CHALLENGES, CONTROVERSIES, AND FUTURE POSSIBILITIES

Because of the diversity of clinical presentations, the relative rarity of the disease, and the availability of multiple effective treatment strategies, the systematic exploration of treatment options in Phase III clinical trials is difficult. For many questions, observational studies of outcomes after standardized therapy may be the best information available to guide future therapeutic choices. Several important questions remain to be addressed:

1. For resectable primary cancers involving the clitoris, lower urethra, or vaginal introitus, will primary surgery or primary chemoRT provide the best therapeutic ratio? Of particular relevance to this question would be a prospective comparison of both local cancer control as well as psychosexual and overall quality of life.
2. In advanced vulvar cancer, when chemoRT is selected for initial therapy, is it better to try to increase the RT dose sufficiently to eradicate disease, or is there less morbidity with a lower RT dose combined with planned conservative surgical removal of residual disease?
3. Does concurrent chemotherapy allow for the use of a decreased total RT dose or decreased RT dose per fraction with decreased late RT sequelae?
4. If concurrent chemotherapy is used, what agent(s) or combination of agents will provide the most effective radiosensitization with the least risk of serious acute toxicity?
5. Can appropriately planned chemoirradiation be used without compromising outcomes instead of complete inguinofemoral node dissection for patients with clinically and radiographically negative groin nodes or patients with microscopic nodal metastases detected by sentinel node biopsy?
6. When adjuvant groin and pelvic nodal irradiation is used, is it necessary to treat bilaterally if positive nodes are only unilateral?

An understanding of the answers to these questions will come from carefully documented reporting from centers where sufficient patients are treated in a uniform fashion and where techniques and doses of RT and the use of concomitant chemotherapy are carefully documented with respect to the site and extent of disease treated and the sites of cancer recurrence.

MISCELLANEOUS VULVAR MALIGNANCIES

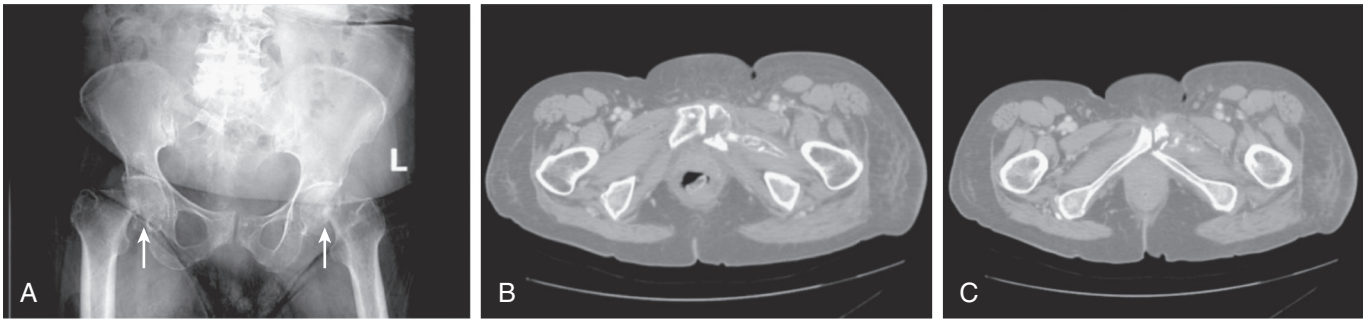
Verrucous Carcinoma

Verrucous carcinoma of the vulva represents a variant of squamous cell carcinoma. These lesions were originally described as occurring in the oral cavity but have also been described involving the vagina, cervix, and vulva.

Metastases to regional lymph nodes are rare and radical local excision is the standard treatment.[46-49] Fine-needle aspiration or excisional biopsy should be carried out if there are suspicious groin nodes. Usually enlarged nodes will be caused by inflammation, but groin node dissections are indicated if metastases are detected. Verrucous carcinoma has a reputation of being radioresistant, and reports of favorable outcomes after RT are uncommon. Surgery remains the treatment of choice whenever feasible, with the use of RT limited to circumstances in which potentially curative surgery cannot be performed.[233]

Melanoma of the Vulva

Melanomas of the vulva are rare and constitute about 10% of all vulvar malignancies but account for more than half of



eFigure 60-19 **A,** Bilateral subcapital femoral fractures *(white arrows)* following elective groin irradiation employing technique that did not use intensity-modulated radiation therapy, delivering excessive, avoidable dose to femoral necks. **B,** Displaced left superior pubus radiation insufficiency fracture. **C,** Radiation-induced insufficiency fracture through inferior ischial ramus and pubic symphysis.

Lesions may grossly resemble cauliflower (eFigure 60-20). Generally large, pearly gray to white in color, this cancer characteristically invades with a sharply circumscribed pushing margin. Clinically, these tumors are usually slow growing.

Melanocytes arise from the neural crest in embryonic life and migrate to a variety of sites including skin, mucosal membranes of the oral cavity nasal and paranasal sinuses, larynx, esophagus, large bowel, anus, leptomeninges, vulva, vagina, and the eyes. Mucosal or mucocutaneous melanomas comprise less than 2% of all melanomas in the United States.[234]



eFigure 60-20 Locally recurrent verrucous carcinoma following radical vulvectomy.

mucosal melanomas in women. Even large, tertiary cancer referral centers will treat only one or two such patients annually.[55,235,236]

Three basic histologic types exist: (1) superficial spreading melanoma is most common and tends to remain superficial in its early course; (2) lentigo malignant melanoma is a "flat freckle" that has a tendency to remain superficial; and (3) nodular melanoma is the most aggressive variety, carries the worst prognosis, and tends to invade deeply early.[235] Prognosis and staging are based on measurements of tumor depth of penetration as described by the melanoma staging systems of Clark, Breslow, and Chung.[53-55] In a study of 71 surgically treated patients with primary malignant melanoma of the vulva, the AJCC 1992 TNM clinical stage was the factor with the highest significant correlation with relapse-free interval. Absent AJCC staging, Breslow's depth of invasion was the most prognostically important factor (Phillips GT 1994).[74]

Treatment

Surgery is the most important management for vulvar melanoma. It has become more conservative as the scope of surgery has minimal, if any, impact on prognosis providing complete excision can be achieved.[237,240] Surgical management is being individualized to take into account identification of the depth of tumor invasion as well as tumor size and location. Wide local excision of vulvar melanoma is used increasingly.[241,242] PET/CT and sentinel node groin biopsies may be tools to aid in tailoring the extent of regional surgery. Systemic therapies for vulvar melanoma parallel systemic strategies for cutaneous melanomas arising at other primary sites. However, the presence of KIT mutations in some patients with mucosal melanomas has led to clinical trials of tyrosine kinase inhibitors that have shown clinically significant response rates including anecdotal durable responses in patients with measurable metastatic disease.[243-245]

Common sites of relapse include the groin, perineum, and vaginal urethral margin, which often predate the clinical appearance of hematogenous metastases.[55,235,246-248] However, in contrast to patients with squamous cancers of the vulva, patients who die of melanoma usually have widespread metastases to parenchymal organs.

At present, RT has no established role in the routine management of vulvar melanomas, although anecdotal information suggests that melanoma arising in this location may be more radiosensitive than melanoma from other cutaneous sites.[249] Given the high local-regional recurrence rate following surgery (often extensive, sometimes mutilating), prospective investigation of adjuvant regional RT or chemoRT, either preoperatively or postoperatively, is warranted. RT may be used for palliation of symptomatic recurrent disease and for patients initially unresectable or those declining surgery.

Although 5-year OS as high as 50% have been reported, most series report 5-year OS of 15% to 30% except for patients with stage I disease.[236] Patients with nodal spread are uncommonly cured.[55] The 5-year OS with negative and positive nodes is 38% and 13%, respectively.[250]

As with melanoma arising at other sites, the spectrum of biologic virulence is broad. Recurrence or metastasis 10 years or more after initial treatment is not uncommon.[55,235,246,247]

Sarcomas

Primary sarcomas of the vagina are extremely rare in adults. Characteristically, these will arise subcutaneously and involve overlying skin secondarily (eFigure 60-21). Often, because primary tumors are bulky, treatment by conservative primary excision is not feasible. Preoperative RT or chemoRT is favored to permit ultimate surgical treatment with less than conventional margins employed for sarcomas in other anatomical locations.

Bartholin's Complex Carcinoma

The Bartholin's complex comprises a duct that is lined by squamous epithelium as it enters the vaginal vestibule. The more proximal portions of the ductal system are lined by transitional epithelium and may be lined by columnar epithelium before branching into secretory glandular elements. Squamous carcinoma (arising in ductal epithelium) constitutes approximately 35% to 50% of cases of Bartholin's complex carcinomas; adenocarcinoma is slightly less common.[251-255] Adenosquamous carcinomas and transitional cell carcinomas make up a small minority of cases. Adenoid cystic carcinoma[56] represents a distinct subset thought to be less likely to spread to regional nodes and associated with a long natural history and late local or hematogenous relapse.[57] Perineural invasion is a characteristic histologic feature of these tumors, and their appearance and behavior closely resembles that of morphologically similar tumors arising in salivary glands.

Because of anatomic proximity of the complex to both the inferior ischial ramus and the anorectum, adequate surgical margins are rarely obtained and management frequently entails combinations of conservative surgery and RT or primary therapy with chemoRT.[256] Recurrences in the contralateral groin have been recorded in patients with negative ipsilateral groin nodes, suggesting that both groins be treated even for a lateralized primary cancer.[82]

Malignant melanoma of the vulva occurs predominantly in postmenopausal Caucasian women, with a peak incidence between the sixth and seventh decades; however, the ratio of white-to-black incidence in the United States is dramatically lower than for cutaneous melanoma and the pathogenesis is presumed to be unrelated to ultraviolet light exposure.[234] These lesions may arise de novo or from preexisting junctional or compound nevi.

Reinforcing the concept that mucocutaneous melanomas should be evaluated and potentially treated differently than cutaneous melanomas are the observations of different rates of driver mutations detected in these entities. BRAF (serine/threonine kinase) mutations are common in cutaneous melanoma but rare in mucosal melanoma. KIT (receptor tyrosine kinase) are significantly more common in mucosal melanoma than cutaneous melanoma.[237]

The AJCC 2009 cutaneous melanoma TNM staging formalism is depicted in eTable 60-1. As a rough approximation, prognosis of melanoma of the vulva parallels prognosis by stage of cutaneous melanomas, but overall prognosis is worse because of characteristically advanced stage at the time of diagnosis.[238]

Because of the clinical radioresistance of melanoma and the poor tolerance of the vulva and perineal skin to high-dose radiation, the addition of synchronous radio-potentiating chemotherapy to conventionally fractionated radiation would seem to merit investigation.

eTABLE 60-1 American Joint Commission on Cancer 2009 Cutaneous Melanoma[239]

Classification	Thickness (mm)	Ulceration Status/Mitoses
T		
Tis	NA	NA
T1	≤1.00	a: Without ulceration and mitosis <1/mm^2 b: With ulceration or mitoses ≥1/mm^2
T2	1.01-2.00	a: Without ulceration b: With ulceration
T3	2.01-4.00	a: Without ulceration b: With ulceration
T4	>4.00	a: Without ulceration b: With ulceration
N	No. of Metastatic Nodes	Nodal Metastatic Burden
N0	0	NA
N1	1	a: Micrometastasis* b: Macrometastasis†
N2	2-3	a: Micrometastasis* b: Macrometastasis† c: In transit metastases/satellites without metastatic nodes
N3	4 + metastatic nodes, or matted nodes, or in transit metastases/satellites with metastatic nodes	
M	Site	Serum LDH
MO	No distant metastases	NA
M1a	Distant skin, subcutaneous or nodal metastases	Normal
M1b	Lung metastases	Normal
M1c	All other visceral metastases Any distant metastasis	Normal Elevated

*Micrometastases are diagnosed after sentinel lymph node biopsy.
†Macrometastases are defined as clinically detectable node metastases confirmed pathologically.

Continued

eTABLE 60-1 American Joint Commission on Cancer 2009 Cutaneous Melanoma—cont'd

	Clinical Staging*				Pathologic Staging†		
	T	N	M		T	N	M
0	Tis	NO	MO	0	Tis	NO	MO
IA	T1a	NO	MO	IA	T1a	NO	MO
IB	T1b	NO	MO	IB	T1b	NO	MO
	T2a	NO	MO		T2a	NO	MO
IIA	T2b	NO	MO	IIA	T2b	NO	MO
	T3a	NO	MO		T3a	NO	MO
IIB	T3b	NO	MO	IIB	T3b	NO	MO
	T4a	NO	MO		T4a	NO	MO
IIC	T4b	NO	MO	IIC	T4b	NO	MO
III	Any T	N > N0	MO	IIIA	T1-4a	N1a	MO
					T1-4a	N2a	MO
				IIIB	T1-4b	N1a	MO
					T1-4b	N2a	MO
					T1-4a	N1b	MO
					T1-4a	N2b	MO
					T1-4a	N2c	MO
				IIIC	T1-4b	N1b	MO
					T1-4b	N2b	MO
					T1-4b	N2c	MO
					Any T	N3	MO
IV	AnyT	Any N	M1	IV	Any T	Any N	M1

**Clinical staging includes microstaging of the primary melanoma and clinical/radiologic evaluation for metastases. By convention, it should be used after complete excision of the primary melanoma with clinical assessment for regional and distant metastases.*

†Pathologic staging includes microstaging of the primary melanoma and pathologic information about the regional lymph nodes after partial (i.e., sentinel node biopsy) or complete lymphadenectomy. Patients with pathologic stage 0 or stage IA disease are the exception; they do not require pathologic evaluation of their lymph nodes.



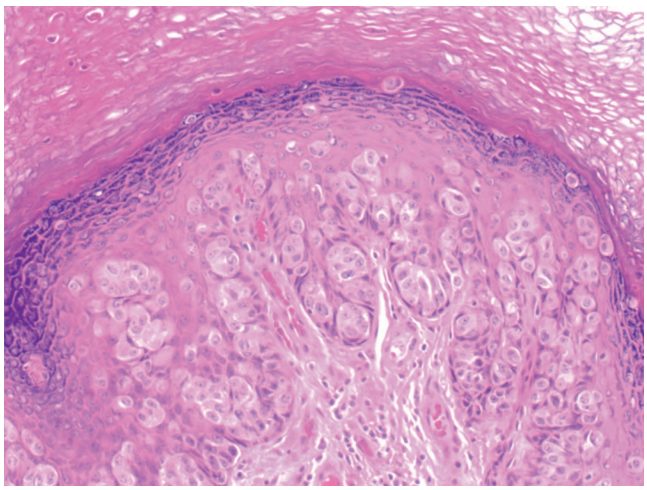
eFigure 60-21 Primary vulvar sarcoma. Epithelioid sarcoma of the vulva in a young woman arising subcutaneously in the right labia with secondary invasion and satellite lesions in skin. Prominent engorged tumor blood vessels can be seen through overlying skin. Successful local management was accomplished with preoperative chemoradiation and conservative surgery with extensive plastic reconstruction including rectus abdominis muscle flap.

Other than the special problems associated with treating tumors in proximity to multiple functionally important structures, there is nothing that distinguishes treatment of vulvar sarcomas from the treatment of soft tissue sarcomas at other sites.

Delay in diagnosis is common as Bartholin's complex cancers often present without as a mass without clinical involvement of the overlying vulvar skin and may initially be misdiagnosed as a Bartholin's gland cyst or abcess. Bleeding is usually a late symptom when cancer protrudes from the duct orifice in the vaginal vestibule.

Paget's Disease

Paget's disease of the vulva is a cutaneous change morphologically similar to Paget's disease of the breast (nipple) characterized histologically by large, vacuolated pathognomonic Paget's cells with bluish cytoplasm located in the basal layer of the vulvar epithelium (eFigure 60-22). Paget's disease often presents as an eczematoid "weeping" lesion that may be intensely pruritic. Paget's disease of the vulva is associated with an underlying in situ or invasive neoplasm in approximately 10% of cases. These include adnexal apocrine skin carcinomas, carcinomas of Bartholin's complex, and cancers of the urethra, bladder, vagina, cervix, endometrium, and rectum. Treatment is surgical, with cutaneous recurrences common. Negative surgical margins are difficult to obtain because "pagetoid" changes may extend microscopically in the epidermis well beyond the margins of what can be appreciated on clinical examination. Negative surgical margins have only limited correlation with freedom from local relapse. Micrographic (Mohs's) surgical technique has been advocated for Paget's disease as a means to achieve negative margins with less extensive surgical extirpation; however, this technique has not been proven to yield superior results.[257] Rarely, Paget's disease may become invasive, and metastases to groin nodes have been reported.[258-266] Management including RT has been reported with anecdotal favorable outcomes both in patients with invasive and noninvasive Paget's disease.[267-270] We recommend employing RT doses of 40 Gy to 56 Gy when surgery is medically unfeasible or could be functionally mutilating consequent to the location of the disease.



eFigure 60-22 Histopathology of extramammary Paget's disease of the vulva. Hematoxylin and eosin 20×.
Courtesy Rosemary Tambouret MD, Department of Pathology, Massachusetts General Hospital, Boston, MA.

CARCINOMA OF THE VAGINA

INCIDENCE

Vaginal cancer will account for about 4070 new cancer cases and 910 cancer deaths in the United States in 2015, comprising approximately 0.35% of all cancers in women, 3.1% of gynecologic malignancies, 0.31% of cancer deaths in women, and 3.0% of gynecologic cancer deaths. Seventy percent of patients are age 60 or older.

PATHOLOGY AND BIOLOGIC CHARACTERISTICS

The majority of lesions (80%) are squamous cell carcinoma. The second-most common type is melanoma. Sarcomas and lymphomas may be primary in the vagina. Adenocarcinomas are commonly metastatic from other primary sites (uterus, colon, ovary, kidney, breast) with the exception of primary clear cell cancers. True primary adenocarcinomas of the vagina are extremely rare.

STAGING EVALUATION

FIGO staging includes clinical assessment of the pelvis, chest radiograph, and renal evaluation. Depending on the clinical situation, CT, MRI, and PET/CT may be used to assess local and nodal extent of disease, but findings do not alter FIGO stage. Cystoscopy and proctoscopy may be appropriate when primary disease is extensive and involves the anterior vagina or rectovaginal septum. Patients with vaginal adenocarcinoma should be assessed for potential primaries arising in other organs. Patients with melanoma require systemic evaluation.

PRIMARY THERAPY

Patients with vaginal intraepithelial neoplasia (VAIN) may be treated with local excision, laser ablation, topical 5-FU, or RT.

Primary therapy for invasive disease usually consists of external and intracavitary or interstitial RT, except in highly selected early cases that may be treated surgically with local excision or with brachytherapy alone. Frequently, concurrent chemotherapy is administered, extrapolating from the beneficial results proven for patients with cancers of the cervix and anus.

Radical surgery, intended as monotherapy, may entail partial or total pelvic exenteration, and as such is generally reserved for salvage of isolated pelvic recurrence after RT and as primary therapy for patients with vesico-vaginal or recto-vaginal fistulas at diagnosis.

Five-year actuarial cancer-free survival in patients treated with RT alone or chemoRT with outcomes are similar stage for stage with those for cervical cancer; approaches 100% in stage 0, 85% in stage I, and 75% in stage II, but only 30% to 50% in stage III disease. Long-term cancer-free survival is rare for patients with stage IVA disease is anecdotal and generally less than 20%.

Patients who experience relapse usually do so within 2 years. Most patients will manifest local-regional persistence or recurrence as a component of the pattern of failure. Distant failure alone without antecedent local-regional failure is seen in less than 30% of relapsing patients.

ADJUVANT THERAPY

Concurrent chemotherapy with RT has been reported with favorable results in a small number of patients, paralleling similar treatment for anal, cervical, and vulvar cancers. Randomized, controlled trials comparing chemoradiation to radiation alone have not been performed.

SALVAGE

Radical surgery, usually exenterative, may be appropriate for persistent or locally recurrent disease, but the likelihood of salvage is low.

PALLIATION

Individualized irradiation may be effective to reduce local symptoms. Chemotherapy as with cervical cancer is generally minimally effective for disseminated disease.

Primary invasive cancer of the vagina is rare. According to the FIGO staging formalism, a cancer of the vagina that involves either the cervical os or the vulva must be classified as arising from that structure, even if the tumor epicenter appears to be in the vagina. Only if involvement of these adjacent organs can be excluded can an invasive cancer of the vagina be classified as primary. Because of the infrequency with which the disease occurs, standardized therapeutic approaches have not evolved, and few centers have extensive experience with these tumors.

Approximately 80% of vaginal malignancies are squamous cancers,[271] and the following discussion refers to squamous disease of the vagina except when otherwise stated.

ETIOLOGY AND EPIDEMIOLOGY

Approximately 70% of primary vaginal malignancies are detected in women 60 years of age or older and approximately 60% in patients older than 70 years of age.[271,272]

In a population-based case-control study of 156 women with VAIN or invasive vaginal cancer, number of lifetime sexual partners (>5), early onset of intercourse (age <17), and current smoking were identified as lifestyle risk factors. Antibodies to HPV 16 were much more common in VAIN and cancer patients than controls. Approximately 30% of patients had a history of treatment for a prior anogenital in situ or invasive malignancy, most commonly of the cervix.[273] Early hysterectomy appears to be a risk factor in some studies, but only if done for malignant or premalignant disease.[273,274]

In a review of recently published data, HPV DNA is detected in 64% to 91% of invasive vaginal cancers and 82% to 100% of VAIN grade 3.[275] HPV 16 serotype is the most common, detected in 55.4% of invasive cancers and 65.8% of VAIN grades 2 and 3.[276] Detection of HPV in invasive cancer has been reported to be associated in better DFS and OS independent of age and stage in patients with stages I and II disease.[277]

The criteria for considering a vaginal squamous carcinoma as primary include vaginal location (it should not involve the external cervical os or vulva) and a specified length of time. Approximately 5 years should have elapsed from a previous diagnosis of cervical or vulvar cancer.

Immunosuppression (e.g., among organ transplant patients) predisposes to lower genital tract intraepithelial neoplasia, including VAIN, although a higher incidence of invasive vaginal cancer has not been demonstrated. Previous ionizing radiation for prior malignancy may also predispose to VAIN or vaginal cancer, usually after a latent period of many years,[278] suggesting that RT may a contributing factor in some patients. Given the similarly increased incidence of

vaginal cancer after surgical treatment of cervical malignancy, multiple factors may contribute.

The natural history of VAIN is not precisely known and its potential to progress to invasive squamous malignancy is not known with precision. In most VAIN series there is a clinically significant incidence of subsequent invasive vaginal cancer. The congruence of risk factors for VAIN and invasive disease[273] and the younger average age of patients with VAIN in comparison to patients with invasive disease, gives credence to the theory that VAIN is a precursor lesion in some, if not all, patients with invasive disease.

Aho et al identified 23 patients with VAIN followed for at least 3 years without treatment.[279] The mean age was 41. Half of the VAIN lesions were multifocal and half were associated with either CIN or vulvar dysplasia. The spontaneous regression rate of VAIN was high (78%) including 4 of 5 VAIN grade 3 patients, but two cases (9%) progressed to invasive cancer. Three studies have shown that only 2% to 5% of patients with VAIN treated with various methods progress to having invasive vaginal carcinoma.[278-280]

The normal vagina does not contain glandular elements, thus primary adenocarcinomas of the vagina are rare. Most commonly, adenocarcinomas involving the vagina are metastases from other organs. Common primary sites include the uterine corpus, ovaries, kidneys, breast, colon, and rectum.[281] Direct extension from primary adenocarcinomas in the cervix, Bartholin's glands, or paraurethral Skene's glands may involve the vagina but should be clinically apparent on physical examination.

The clear cell variant of vaginal adenocarcinoma (CCAC) has been linked to in utero exposure to the synthetic estrogen diethylstilbestrol (DES) that was used in the late 1940s, 1950s, and 1960s to support high-risk pregnancies and prevent threatened spontaneous abortion.[282] Despite minimal evidence of efficacy, use was continued until it was banned for use in pregnancy in 1975. Vaginal adenosis, morphologically identical to rare cases of vaginal adenosis in women born before the DES era, has been detected in approximately one third of patients with in utero DES exposure. Three patterns of adenosis have been described: mucinous (resembling endocervical glands), tubo-endometrial, and embryonic.[283,284] Clear cell cancer of the vagina is associated with vaginal adenosis in as many as 95% of cases, most commonly the tubo-endometrial morphology, implicating adenosis as the cell-line of origin.[285,286] The Registry for Research on Hormonal Transplacental Carcinogenesis accessioned more than 580 cases of clear cell carcinoma of the vagina and cervix. In utero exposure to synthetic estrogens accounted for approximately two thirds of reported cases, leaving a significant number of cases unexplained. Work in the United States and the Netherlands suggested that the age distribution for clear cell adenocarcinoma of the vagina has two separate peaks.[287-289] The first peak contained women with a mean age of 26, and the second peak contained women with a mean age of 71 years.[289] The first peak contained all DES daughters, and the second peak contained women born well before 1950 and thus not exposed to DES. However, even when the DES daughters were excluded, a bimodal pattern was observed. The age range of DES-related clear cell adenocarcinoma is 7 years to 42 years. As gestational DES use was discontinued in 1975, it is probable that this peak in younger women will largely disappear. The actual risk of DES-exposed women developing clear cell adenocarcinoma is estimated at only 1 in 1000, with the highest risk in those women exposed before 12 weeks' gestation.[290] Rare patients with endometriotic implants in the vagina (seen after obstetrical or other injury, in an episiotomy scar, or in the vaginal apex scar after hysterectomy) may also develop clear cell cancer or other adenocarcinomas arising within the endometriosis.

PREVENTION AND EARLY DETECTION

Because of the strong evidence implicating HPV in the pathogenesis of most squamous cancers of the vagina and the predominance of the HPV 16 serotype, encouraging results from Phase III trials of HPV vaccines suggest that substantial reductions can be expected in the incidence of VAIN and in invasive vaginal malignancies if prophylactic immunization is widely implemented.[40]

Although many cases of VAIN spontaneously involute without therapeutic intervention, some do not. A policy of longitudinal surveillance and effective treatment for patients with persistent VAIN will likely reduce the risk of development of invasive cancer in those individuals in whom high-grade VAIN is a precursor lesion.

There is no consensus regarding the utility of routine vaginal vault screening after hysterectomy. Although early detection clearly benefits the woman in whom vaginal cancer is destined to develop, based on the low frequency of the disease and the limited apparent effectiveness of vaginal cytology to make the diagnosis, "there is insufficient evidence to recommend routine vaginal smear screening in women after total hysterectomy for benign disease."[291,292]

If a vaginal smear is done, the histologic and cytologic criteria for VAIN and invasive vaginal cancer parallel those for cervical lesions. In postmenopausal women or women with a history of vaginal RT related to prior treatment of cervical cancer, distinguishing dysplasia from inflammatory or post-RT changes can be difficult because atrophy and radiation effects can mimic the features seen in neoplasia. Topical estrogen therapy before sampling of the vagina may minimize atrophic and inflammatory changes and may facilitate more accurate assessment of specimens.

PATHOLOGY AND PATHWAYS OF SPREAD

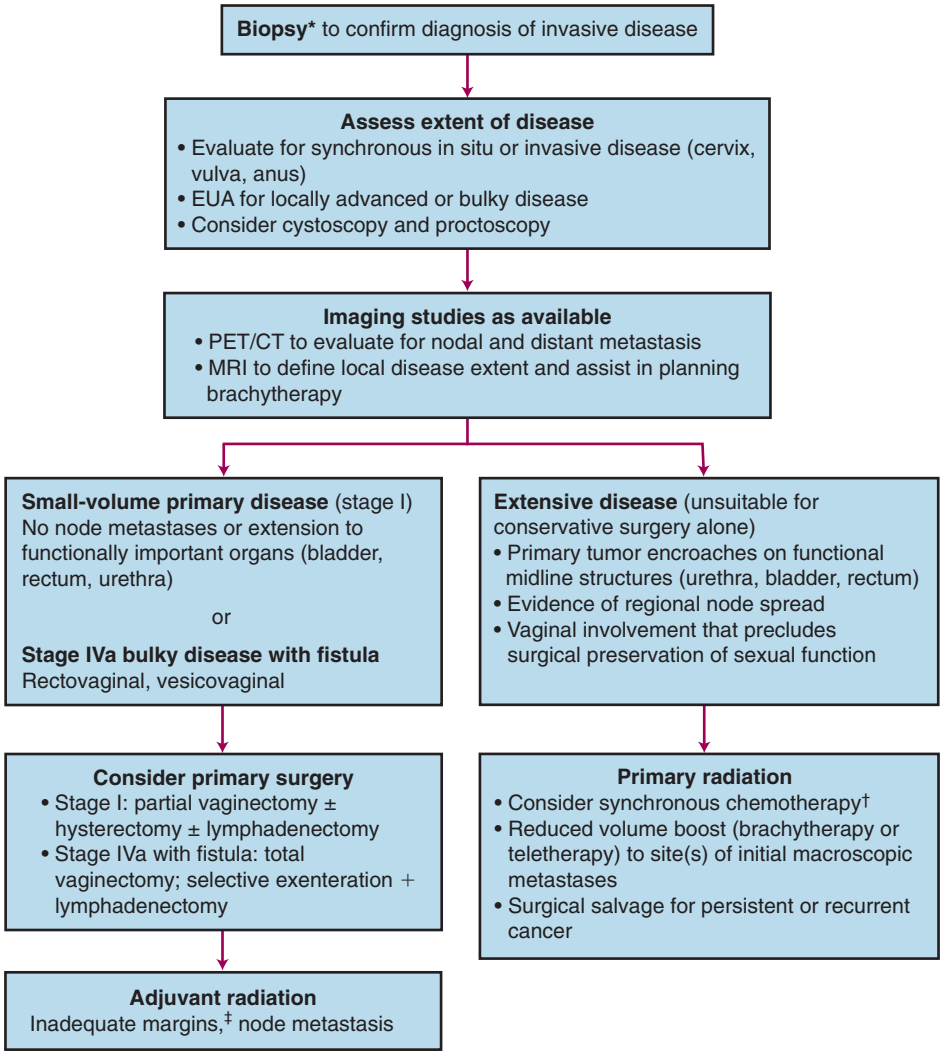
The majority of lesions (80%) are squamous cell carcinoma. The second-most common histology is melanoma. Sarcomas and lymphomas may be primary in the vagina. Adenocarcinomas are commonly metastatic from other primary sites (uterus, colon, ovary, kidney, breast) with the exception of primary clear cell cancers. True primary adenocarcinomas of the vagina are rare.

Most vaginal cancers involve the upper two thirds of the vagina where direct extension can involve the adjacent parametria, paracolpos, bladder, or rectum. Normal lymphatic drainage of the proximal third to one half of the vagina parallels that of the cervix: via the obturator nodes to the external iliac, internal iliac (hypogastric), and common iliac nodes. Lesions of the lower third of the vagina may follow vulvar lymphatic drainage patterns to the inguinal-femoral nodes and subsequently to the pelvic nodes. Lesions infiltrating the rectovaginal septum may spread to pararectal and presacral nodes. Interconnections between lymphatic channels do exist. Pathways of potential lymphatic metastases, however, may have been altered by prior surgery (e.g., hysterectomy with or without pelvic lymphadenectomy).

Hematogenous dissemination is rare at diagnosis except in patients with far advanced, neglected lesions.

CLINICAL MANIFESTATIONS, PATIENT EVALUATION, AND STAGING

Presenting symptoms of early disease include bleeding including contact bleeding, discharge, pruritus, and dyspareunia. Pain and alterations of urinary bladder or anorectal function are associated with locally advanced disease.



*Wide excisional biopsy: appropriate in small stage I lesions if not functionally deforming.
†Value of synchronous chemoradiation unproven for vaginal cancer at this time.
‡Margins ≤5 mm (arbitrary).

Figure 60-13 Diagnostic and therapeutic algorithm for invasive squamous cell cancer of the vagina. An *asterisk* indicates wide excisional biopsy that is appropriate for small stage I lesions if it is not functionally deforming; a *dagger* indicates that the value of synchronous chemotherapy (chemoradiation) is unproved for vaginal cancer; and the *double dagger* indicates margins of less than 5 mm (arbitrary measure). *CT,* Computed tomography; *EUA,* examination under anesthesia; *MRI,* magnetic resonance imaging; *PET,* positron emission tomography.

A diagnostic algorithm for invasive cancer of the vagina is depicted in Figure 60-13. Confirmation of invasive disease should be obtained by biopsy. In selected patients in whom excisional biopsy can be accomplished without functional compromise, wide local excision may be diagnostic and therapeutic in limited disease without risk factors.

Critical in planning therapy is definition of disease extent. Staging includes careful clinical examination of the vagina and pelvis, possibly under anesthesia, with careful examination of the cervix and vulva to exclude involvement of those sites. Colposcopy, cystourethroscopy, anoscopy, and proctoscopy will aid in the evaluation of primary disease extent and in screening for synchronous primaries of the cervix, vulva, and anus. Cystoscopy and proctosigmoidoscopy should be considered in women with locally advanced disease or with bladder or bowel symptoms.

Assessment of the pelvic and groin nodes by CT, MRI, or PET/CT is advisable to plan treatment in most cases of invasive disease, although results do not affect assignment of FIGO clinical stage. MRI may supplement physical examination in assessing primary disease extent and is superior to CT in distinguishing soft-tissue tumor extensions. Effective use of MRI requires contrast administration (gadolinium) and selection of the correct pulse sequences optimized for visualization of pelvic soft tissues. MRI findings may helpful in planning radiation dose distributions, particularly for brachytherapy techniques and in the design of reduced boost volumes for EBRT. Although the value of PET has not been investigated extensively in vaginal cancer,[293] its use to evaluate regional node metastasis and distant metastasis is rational, similar to that in cervical cancer. PET/CT is preferred to PET alone because of improved spatial resolution and ability to distinguish pelvic lymph node involvement from nonspecific fluorodeoxyglucose (FDG) activity in bowel. None of these imaging technologies will alter assignment of FIGO clinical stage. However, results of imaging may importantly

TABLE 60-10 Vaginal Cancer: Staging Systems

	AJCC TNM	FIGO	Definition
Primary tumor	Tx		Primary tumor cannot be assessed
	T0		No evidence of primary tumor
	Tis	0	Carcinoma in situ
	T1	I	Tumor confined to the vagina
	T2	II	Tumor invades paravaginal tissues but not to the pelvic wall
	T3	III	Tumor extends to the pelvic wall
	T4	IVA	Tumor invades mucosa* of the bladder or rectum or extends beyond the true pelvis
		IVB	Distant metastasis
Regional lymph nodes	Nx		Regional lymph nodes cannot be assessed
	N0		No regional lymph node metastasis
Upper 2/3rd vagina	N1		Pelvic node metastasis
Lower 1/3rd vagina	N1		Unilateral inguinal node metastasis
	N2		Bilateral inguinal node metastases
Distant metastasis	Mx		Presence of distant metastasis cannot be assessed
	M0		No distant metastasis
	M1		Distant metastasis

Modified from FIGO Committee on Gynecologic Oncology: Current FIGO staging for cancer of the vagina, fallopian tube, ovary, and gestational trophoblastic neoplasia. Int J Gynaecol Obstet 105(1):3–4, 2009 and Edge SB, Byrd DR, Compton CC, editors: Vagina: AJCC cancer staging manual, ed 7, New York, 2010, Springer, pp 387–389.[294,295]

**Presence of bullous edema is not sufficient evidence to classify as T4 or FIGO IVA.*

impact on selection, sequencing, and intensity of treatment modalities.

Patients are staged using the AJCC TNM formalism or, more commonly, the FIGO formalism (Table 60-10).

PRIMARY THERAPY

VAIN

VAIN may be multifocal in the vagina in up to 60% of patients,[296] and is best localized by colposcopy and iodine staining, with careful attention being paid to the vaginal vault angles, which are commonly distorted by previous hysterectomy. Among low-grade lesions, there appears to be significant spontaneous regression.

Treatments with surgical excision, laser vaporization, and intravaginal topical 5-FU have proven partially effective.[278,280,297] Local excision, when feasible without functional compromise, is the treatment associated with lowest risk of recurrence, but it is limited in applicability because the disease is so frequently multifocal. Recurrence following laser vaporization has been reported in 38% of cases, and recurrence after topical vaginal 5-FU in 59%.[296]

For selected cases, intracavitary brachytherapy alone may be employed,[280,298-301] but in general it should not be selected as first-line therapy because of the risks of long-term radiation effects including secondary carcinogenesis, particularly if considered for young patients. Usually RT is reserved for patients relapsing after conservative therapies. Control of VAIN by intracavitary brachytherapy alone approaches 100%, although late recurrences are occasionally observed.[301] Prospective data are not available regarding alterations in vaginal depth and diameter, elasticity, sexual function, and quality of life following vaginal brachytherapy.

Invasive Cancer

Primary vaginal malignancies are rare. Single-institution treatment outcome reports retrospectively analyze limited numbers of patients often spanning multiple decades during which diagnostic techniques and management philosophies have evolved rather than remaining static. Because of the correlation of prognosis with stage and tumor size and the fact that treatments feasible for earlier stage, smaller primaries without nodal spread may be quite different than management strategies for patients with more extensive disease, it is difficult to compare outcomes reflecting different therapeutic techniques and modalities. Treatment is often individualized using general principles of oncologic management with chemoRT or RT and tailored on the basis of tumor location and extent and the constraining comorbidities of an individual patient.

Rationale and General Principles

Radical irradiation constitutes the treatment of choice for most patients with vaginal cancer. Primary surgery is appropriate in the earliest of invasive lesions when curative or potentially curative resection can be achieved without exenteration or functionally morbid surgery. Generally this is feasible only for stage 1 lesions at or near the vaginal apex or well-laterized lesions in the distal vagina. Primary surgery may be appropriate for rare patients who present with primary disease–related fistulae that require surgery for restoration of continence. The magnitude of surgical intervention may be quite variable as reported from a single institution with a strong surgical bias[302] (Table 60-11).

Primary surgery may also be used in patients previously irradiated for other malignancies because further radical radiation is only rarely an option. Given the intimate proximity of bowel and bladder to the vagina, exenterative surgery is usually necessary to achieve clear margins and to promote postsurgical healing.

Tjalma et al[302] reported surgical results in 37 patients (26 stage I, 6 stage II, 2 stage III, and 3 stage IV) employing the surgical procedures detailed in Table 60-11. Seven patients received postoperative RT for incomplete excision or node metastasis. Five-year and 10-year OS were 92% and 74%, respectively, for patients managed with surgery alone, and 5-year OS was 71% for patients undergoing combined-modality therapy. Five of 37 patients (14%) in this surgical series were treated with exenterative procedures and may have

TABLE 60-11 Range of Surgical Treatments Used According to FIGO Stage[302]

FIGO Stage	Surgical Treatment
I	Partial or total vaginectomy Radical hystero/vaginectomy, ± pelvic ± paraaortic node dissection; inguinal node dissection for lower third of vagina
II	Partial or total vaginectomy + parametrectectomy + paracolpectomy + Pelvic ± paraaortic node dissection
III	Radical hystero/vaginectomy, + parametrectomy + pelvic/inguinal node, ± paraaortic node dissection
IV	Exenterative surgery, usually total with formation of urinary and bowel bypass

Reproduced from Tjalma WAA, Monaghan JM, de Barros Lopes A, et al: The role of surgery in invasive squamous carcinoma of the vagina. Gynecol Oncol 81:360–365, 2001.

TABLE 60-12 Results of Radical Radiotherapy for Previously Untreated Patients with Invasive Squamous Carcinoma of the Vagina, 1970-2000[308]

FIGO Stage	Patients	Pelvic Disease Control at 5 Years (%)	Disease-Specific Survival at 5 Years (%)
I*	50	86	85
II	97	84	78
III	39	69	n.s.
IVA	7	86	n.s.
III+IVA†	46	71	58

**18 patients had gross excision of their primary tumor before radiation, of which 10 were stage I.*
†5% of patients with stages III + IVA received neoadjuvant chemotherapy, and 17% received concurrent radiotherapy and cisplatin-based chemotherapy regimens.
n.s., *percentage not stated.*

been amenable to organ-conserving therapy with RT-based treatment with surgery reserved for salvage of persistent or recurrent disease. Three additional patients with stage IV disease had exenterative procedures.[302]

Eighteen patients in the series reported by Tjalma et al were managed with primary radiotherapy (1 stage I, 6 stage II, 4 stage III, and 7 stage IV) with 44% alive at 5 years and 35% alive at 10 years. These observational data do not permit comparison of the relative efficacy and morbidity of treatment modalities employed. Pelvic exenteration was employed to treat 2 patients with stage I disease and 1 patient with stage III disease in this series. Anterior exenteration was employed to treat 2 patients with stage II disease.

No widely accepted standardized treatment technique has been developed for RT treatment of vaginal cancer. Generally, brachytherapy may be employed alone in highly selected cases where the thickness and extent of disease may be encompassed by adequate tumoricidal dose; EBRT is often used in conjunction with a brachytherapy boost depending on the local and regional extent of disease. EBRT or concurrent chemoRT alone is employed for patients with locally extensive or bulky disease. Brachytherapy may include intravaginal sources such as a symmetrical cylinder or "Miami type" applicator or interstitial needle implants done freehand or with custom templates. Custom molds or partially shielded intravaginal cylinders can be used to selectively administer higher dose radiation to only a portion of the length and diameter of the vagina. Generally patients with early disease receive a higher proportion of their dose from brachytherapy, whereas those with more advanced pelvic disease receive a greater component of their dose from EBRT. Where the tumor volume cannot be encompassed with a brachytherapy boost a small volume IMRT field may be used to boost gross disease.

The principles of RT include treating the draining regional lymph nodes when there is a risk of nodal involvement. Because lesions of the lower third of the vagina have the potential to metastasize to inguinal lymph nodes, it is usual in this situation to electively include the medial inguinal lymph nodes in the RT volume. Relapse in nodes lateral to the femoral vessels is extremely rare. However, when groin nodes are involved, the entire inguinofemoral group of nodes may be irradiated employing techniques similar to those employed for groin irradiation in patients with primary vulvar cancers.

Usually 40 Gy to 50 Gy is delivered using EBRT to the whole pelvis, and intracavitary or interstitial irradiation is used to bring the primary tumor dose up to between 65 Gy to 75 Gy. A broad range of tumor doses are quoted in the literature, but it is important to understand which point or volume received the stated dose because there is a rapid fall-off in dose from intracavitary sources. For example, the brachytherapy dose at 5 mm depth may be 75% or less of the vaginal mucosal dose, accounting for at least some of the width of the spectrum of quoted radiation dose employed in patients treated for cure. Doses in excess of 80 Gy have been employed in some patients with increased risk of late complications, and a total dose between 70 Gy and 80 Gy has been recommended when radiation alone is employed, although obviously some tumor volumes are too large to encompass with more than 65 Gy to 75 Gy.[304]

Results

Series from single institutions often span multiple decades during which diagnostic assessments of tumor extent have changed, treatment strategies and techniques have changed and there is heterogeneity of cell type and tumor extent with some having prior treatment for other primary pelvic cancers. Outcomes analyses are thus challenging to interpret. Because treatment techniques (brachytherapy alone, EBRT alone, combinations of EBRT and intracavitary or interstitial brachytherapy) and total radiation dose appropriately vary with stage, disease distribution, and tumor size, it is difficult to make any statement regarding comparative efficacy of radiotherapeutic modalities, techniques, or doses.

In a series of 26 cases of non-diethylstilbestrol related adenocarcinomas of the vagina treated with radiation at the MDACC, Frank et al[305] reported statistically significantly lower rates of pelvic control (31% versus 81%) and OS (34% versus 58%) and higher rates of distant metastatic spread at 5 years (39% versus 15%) than in patients with primary squamous cancers treated at the same institution. Similarly, melanoma of the vagina is associated with a grim prognosis, and should not be pooled with squamous cancers in analyzing treatment efficacy and survival.[246,306,307]

Mature outcomes from an unusually large series of 193 patients with primary squamous cancers of the vagina spanning 30 years at the MDACC were reported with regard to pelvic control and DSS at 5 years (Table 60-12). This series consisted exclusively of previously untreated patients treated wholly, or predominantly, with RT.[308]

Neoadjuvant chemotherapy followed by surgery has been reported in a limited number of patients with stage II disease. Three cycles of paclitaxel and cisplatin given every 3 weeks were administered preoperatively to 11 patients with stage II disease before radical hysterectomy and vaginectomy.[303] Three patients achieved complete clinical response and 7 achieved partial response. Two patients subsequently relapsed. This approach has not been broadly adopted.

For squamous cancer, tumor stage is generally found to be the most important prognostic variable for local control and survival after treatment with irradiation. Tumor size (smaller or larger than 4 cm) and histologic grade may be influential,[304,309,310] as well as the presence of metastases in regional nodes. None of these factors is reflected directly in FIGO staging.

According to numerous analyses, almost all failures will occur within the first 5 years.[308-313] It is not currently feasible to distinguish potential second primary cancer in the vagina from possible marginal recurrence. Rare late failures in the vagina may reflect an underlying field defect rather than inadequate initial therapy.

Relapse is more likely to be pelvic than systemic. In the series from MDACC, 21 of 31 patients (68%) with stages I to II disease who relapsed had failure in the vagina or pelvis as all, or a component, of their relapse pattern, whereas 10 of 31 (32%) failed distantly only. Among patients with stages III to IV, 15 of 18 who relapsed (83%) had pelvic or vaginal recurrence as all, or a component, of their pattern of initial relapse. Three of 18 patients (17%) who relapsed had distant metastases only.[308] Rare relapse in inguinal nodes is seen in patients whose primary initially involved the distal one third of the vagina and in whom the inguinal nodes either were not included in the treatment volume or were grossly contaminated with metastatic disease at the time of diagnosis.[308,314] Patterns of relapse support more frequent use of concurrent chemoRT because only 17% of patients received combined-modality treatment during the 30-year span of the series.

Except for isolated vaginal recurrence in patients with VAIN or stage I disease, salvage therapy is generally ineffective. Surgical salvage implies partial or total exenteration in virtually all previously irradiated patients.

LOCALLY ADVANCED DISEASE AND PALLIATION

Because combined-modality treatment with concurrent chemoRT demonstrates improved outcomes in squamous cancers of the cervix, anus, and other sites, it is not unreasonable to extrapolate the use of synchronous treatment with concurrent chemoRT to similar patients with locally advanced vaginal cancer. This approach can be most easily justified for patients with stages III and IVA and bulky disease where results with RT alone are associated with substantial risk of local failure.[304,308,315] Consequent to the overall rarity of this disease, only limited numbers of patients have been reported using this approach.[194,304,308,309,316-321] It is unlikely that a prospective comparison of chemoRT and RT alone will be practically feasible. However, multivariate analysis of outcomes within a single institution comparing RT alone with chemoRT for vaginal cancer suggests that concurrent chemoRT confers an independent DFS advantage compared to RT alone.[321] This advantage may not be observed in institutions where chemoRT was preferentially administered to patients with multiple adverse prognostic factors.[304]

Analogous to the evolution of chemoRT in the treatment of cancer of the vulva, chemoRT for vaginal cancer may become more widespread. Drug regimens are similar to those used for vulvar and cervical cancers. No data are available to state which regimen is most effective. Assumptions about the preferential therapeutic ratio in vaginal and vulvar cancers associated with the use of chemoRT over RT alone are extrapolated from data on cervical and anal cancers.

Although anal canal cancers are amenable to cure with high-dose RT alone,[322] better local cancer control is achieved with chemoRT.[160,161] In addition, long-term complications are generally lower and functional results more satisfactory consequent to use of lower total doses of RT using fewer conventional fractions rather than reduced dose per fraction. Reduction in total RT dose from 65 Gy to 70 Gy to approximately 54 Gy has reduced the need for diverting colostomy or abdominoperineal resection for radiation complications in cured patients.

Concurrent chemoRT appears to significantly enhance RT effects on cancer and cycling epithelial cells but does not appear to proportionately increase late effects in normal tissues. Late complications in patients treated for cervical cancer with chemoRT are not dramatically different from those seen in patients treated with RT alone using comparable RT dose and fractionation regimens.[152,323,324] Concurrent chemoRT may increase acute toxicity, but late complications may be reduced if the total RT dose is reduced analogous to the anal canal cancers.

Most publications reporting treatment outcomes for patients with vaginal cancer report late bowel and urinary bladder complications, but few even comment on vaginal depth, diameter, elasticity, sexual function, and quality of life. No prospective evaluation of the impact of radical RT administered to the vagina has been undertaken. A potential benefit from integrating concurrent chemotherapy and implementing RT dose reduction to levels conventionally considered subtherapeutic (median cumulative dose of 63 Gy) may be in improved long-term vaginal function with reduced risk of severe atrophy or vaginal stenosis and fibrosis and reduced risk of severe complications including fistulae and radiation insufficiency fractures.[318] It seems appropriate to use concurrent chemoRT for tumors whose extent is more than superficial mucosal.

In the unusual setting of patients presenting with distant dissemination, local RT limited to areas of gross disease may palliate symptoms of discharge, bleeding, and pain. Systemic chemotherapy alone is minimally effective and characterized by a low probability of complete response and short duration of partial response. Results broadly parallel those for disseminated cervical cancer.

IRRADIATION TECHNIQUES AND TOLERANCE

Brachytherapy

Brachytherapy as monotherapy is appropriate for patients with VAIN, which has persisted despite less potentially damaging interventions, and for highly selected patients with small-volume, minimally invasive disease confined to the vaginal wall whose tumor volume can be encompassed without delivering unacceptable dose to the vaginal mucosal surface. Occasional patients treated thus may relapse in pelvic sites remote from the vagina.

More commonly, brachytherapy is used to supplement EBRT dose given to a large volume encompassing the primary disease, potential subclinical extensions of the primary cancer, and lymph node volumes at risk. Following 45 Gy to 50 Gy of conventionally fractionated EBRT, brachytherapy is employed to "boost" cumulative dose (EBRT plus low-dose rate brachytherapy dose) so that the gross tumor volume (GTV) is approximately 65 Gy to 75 Gy although in smaller tumors doses of 70 Gy to 82 Gy have been achieved when RT is employed as the sole modality of therapy.[304,308,321] The extrapolation of such high doses comes from the high "point A" dose prescription in cervical cancer, but it is important to realize that the entire cervical cancer does not usually receive the "point A" dose. Dose selection for vaginal cancers must include the entire

tumor volume and is therefore usually less than the quoted dose of 75 Gy.

Intravaginal irradiation is often accomplished using some form of vaginal cylinder. The largest possible diameter of cylinder is used to improve the ratio of dose to the tumor surface to dose at maximal tumor depth. Because of the rapid fall-off in dose with distance from intravaginal sources, it is inappropriate to use intracavitary brachytherapy to treat primary cancers that are more than 5-mm thick at the completion of EBRT.

When conventional low-dose rate intravaginal brachytherapy is employed, the labia may be sutured closed, securing the implant in place. When high-dose rate brachytherapy delivers treatment over a few minutes, fixation of the cylinder to a locking base-plate assures rigid immobility of the system. The cylinder should protrude beyond the labia to prevent dose build-up on the inner labial surface where the cylinder is loaded close to the introitus. With high-dose rate it is feasible to employ differential inclusion of the vaginal circumference with a Miami applicator or partial shielding with reproducible treatment of smaller lengths of the vagina. This may contribute to improvement in functional outcomes. Daily high-dose rate treatments may employ fractions as small as 3 Gy at a depth of 5 mm or less to a cumulative brachytherapy dose of 27 Gy to 30 Gy to supplement the EBRT dose of 45 Gy to 50.4 Gy.

For disease involving the upper vagina or vaginal fornices, an intrauterine tandem may be placed to function as an anchor for vaginal cylinders or spacers, while ensuring adequate dose at the proximal end of the vagina. Individual, custom vaginal moulds have been used to treat vaginal cancer.[325]

For cancers with more than 5 mm of thickness, deep paravaginal invasion, or parametrial extension, brachytherapy boosts may be delivered using isotopes such as iridium-192 in interstitial implants. Interstitial implants may be performed "free-hand" or through a template sutured to the perineum.[300,326-329] In patients with cancers involving a vaginal fornix or extending into the parametrium, interstitial needles will commonly penetrate into the peritoneal cavity. Particularly in the common setting of prior hysterectomy, loops of bowel may be adjacent to or adherent to the vaginal apex. Under these circumstances, needle placement may be safer with simultaneous laparoscopy or laparotomy to reduce risk of perforation of abdominal viscera and to assure accurate needle placement.[330,331]

Real-time image guidance (when available) by CT, MRI, or transrectal US may assist in accurate needle placement. Because of the rarity of these tumors and the high degree of technical skill and experience required to conduct interstitial brachytherapy, referral to a high-volume tertiary treatment facility with specialized clinical and medical dosimetry staff would seem prudent.

In the era when brachytherapy is increasingly administered with high-dose rate technique, integration of a variety of high-dose rate dose-fractionation schedules with EBRT is complex and a variety of regimens have been employed. Proposed dose schedules published by the American Brachytherapy Society (ABS) are a useful set of guidelines that can be applied to the care of an individual patient[329] (Table 60-13).

TABLE 60-13 Proposed Dose Schedules for HDR Interstitial Brachytherapy in Combination with EBRT

Dose of EBRT	HDR Dose to CTV (Gy)	EQD2 to CTV	D2 mL per fx to Rectum to Limit EQD2 to ≤70 Gy
36 Gy/18 fx*	5 × 6	72.9	≤4.1
	5.5 × 6	78.0	≤4.1
39.6 Gy/22 fx*	5 × 6	76.4	≤3.8
	5.5 × 6	8l.5	≤3.8
45 Gy/25 fx	3 × 9	73.6	≤3.55
	3 × 10	76.8	≤2.38
	4.5 × 5	71.5	≤3.75
	5 × 5	75.5	≤3.75
	5.5 × 5	79.8	≤3.75
	7 × 3	74.1	≤5.2
50.4 Gy/28 fx	4.0 × 5	72.9	≤3.25
	4.5 × 5	76.8	≤3.25
	5 × 5	80.9	≤3.25
	7 × 3	79.4	≤4.55

CTV, *Clinical target volume;* EBRT, *external beam radiation therapy;* EQD2, *equivalent dose in 2 Gy fractions;* fx, *fractions;* HDR, *high-dose rate.*
**Total pelvic: dose to 50.4 Gy with midline block after 36 Gy to 39.6 Gy.*

External Beam Radiation

External beam irradiation is similar to that given for carcinoma of the cervix with the exception that usually the full length of the vagina is included in the initial EBRT volume. Rare exceptions may include patients with unifocal disease less than 2 cm in length confined to either the vaginal fornices or the distal vagina. Parallel opposed AP and posterior-anterior (PA) pelvic portals rather than a four-field box technique may be employed for slender patients and when medial inguinal nodes are included for patients with involvement of the caudal third of the vagina. For larger patients, a four-field technique may be used in an effort to reduce total dose and dose per fraction to the bladder dome and anterior small bowel. Medial groin nodes may be treated with this technique by expanding the anterior-inferior portion of the lateral fields, provided that the dose to the proximal femurs is kept less than 45 Gy by excluding these structures to the maximal extent feasible on the anterior and posterior fields. Rarely, when inguinal nodes are involved at the time of diagnosis, techniques that are used to encompass the entire inguinofemoral node volumes in patients with cancer of the vulva may be successfully deployed for patients with vaginal cancer.

IMRT may be employed with beneficial dose reduction to adjacent organs at risk and has been reported to result in excellent local control.[304] However, enthusiasm for the use of increasingly conformal dose distributions must be tempered with the understanding that the upper vagina is a mobile structure whose position will vary daily with different degrees of urinary bladder and rectal distension. CT-based treatment planning can account for extremes of potential motion by scanning with bladder and rectum distended and undistended through the use of temporary bladder catheterization and rectal balloon placement at the time of simulation along with intravaginal contrast material so that delineation of target volumes can be designed accordingly.

It should be emphasized that the initial target volume should be influenced by the results of diagnostic imaging studies and that extended volumes may be appropriate for patients with pelvic nodal metastases. Conventionally, the superior extent of the EBRT volume has been at the L5-S1 interspace when there is no evidence of pelvic node metastases. This assures coverage of retroperitoneal nodes caudal to the bifurcations of the common iliac arteries in almost all patients and will include some distal common iliac nodes.[332,333] However analysis of sites of relapse in one clinical series suggested that this volume might be excessive for most patients, contributing to avoidable acute and delayed toxicities of

treatment.[314] As initial failures are predominantly in the vagina, paracolpos, and parametria, expanded volumes to electively encompass larger nodal volumes may not be routinely useful. In patients with negative imaging assessment (PET/CT or diffusion-weighted MRI) of regional nodes, a reduced volume with superior border 1 cephalad to the inferior margin of the sacroiliac joints may be sufficient to encompass obturator nodes and first echelon (distal) external and internal iliac nodes. Target volume for initial EBRT treatment remains controversial. In patients with documented node metastases, extension of the treatment volume to encompass the next echelon of clinically uninvolved nodes seems reasonable. As the accuracy of imaging technology improves, smaller EBRT volumes may be used safely.

For patients with bulky disease including patients with gross lymph node metastasis, boost therapy by intracavitary or interstitial brachytherapy techniques may not be useful. EBRT boost volumes should be based on clinical findings and results from diagnostic imaging studies. Tailored volumes may be treated to a cumulative dose between 65 Gy and 70 Gy using EBRT alone. Higher doses carry substantial risk of late RT complications in adjacent vulnerable normal tissues including urethra, bladder, rectum, and small bowel. Administration of concurrent chemotherapy may be particularly indicated when the EBRT dose is limited by the RT volume required. Rapid clinical tumor shrinkage, often seen in the setting of concurrent chemotherapy administration, may suggest the wisdom of repeat CT simulation before planning reduced volume EBRT boost treatment.

Treatment Tolerance and Complications

Acute effects in patients undergoing EBRT as all, or a major component of their treatment, may include radiation urethritis/cystitis with frequency, urgency, and dysuria. Oral anticholinergic and antispasmodic medications may be beneficial for patients in whom these symptoms are more than a temporary irritant, as well as a urinary tract analgesic.

Depending on the volume of small bowel included in the irradiated volume, most patients will experience some degree of erratic bowel function that will usually include more frequent and often unformed bowel movements that may progress to watery diarrhea. Dietary modification and medications such as loperamide hydrochloride or atropine with diphenoxylate hydrochloride (Imodium, Lomotil) are usually beneficial.

Acute effects on the anorectum may cause tenesmus and small volume blood loss. Topical medications such as those employed for the treatment of hemorrhoids can be beneficial to some patients and may be applied directly to the anal area externally or to the anorectum by suppository.

Vaginal effects may include serous discharge and pruritus, for which oral antihistamines and topical vaginal moisturizing agents (Replens) may provide some symptomatic relief.

Acute RT dermatitis may progress to moist desquamation on the vulva and portions of the perineum when the primary lesion involves the distal vagina. Soaks, air exposure, and topical balms and creams that may or may not include antibiotics such as 1% silver sulfadiazine cream may ameliorate symptoms. Occlusive dressings may be temporarily required for severe cases. Therapy generally parallels skin treatment for thermal burns.

Because of the paucity of large data sets reporting treatment outcomes and the variability in disease extent and the equipment, techniques, and doses of RT, it is difficult to predict the risk of serious late complications for an individual patient.

Complications of treatment have been reviewed in various publications. In a historic series, Dancuart et al treated a group of patients between 1955 and 1982. Reported late effects included vaginal fibrosis (10%) and cystitis, proctitis, or vaginal necrosis (12%). A further 5% of patients experienced rectal or sigmoid stenosis, hemorrhage, or multiple fistulas.[312] Over a similar time period in which patients were treated with radical irradiation from 1953 to 1991 Perez et al[313] reported late complications in 205 patients from an initial population of 212 patients with VAIN (20 patients) or invasive carcinomas of the vagina (192 patients). Twenty-five major local complications (12% crude rate) attributable, all or in part, to RT injury were observed, including six rectovaginal fistulae, three vesicovaginal fistulae, four bladder neck contractures or urethral strictures, two rectal strictures, two proctitis, and one instance each of rectal ulcer, vaginal necrosis, small bowel obstruction, cystitis, leg edema, neuritis, severe vaginal stenosis, and diverticulitis. Tewari et al[327] reported on complications in a series of 71 patients treated between 1976 and 1997 with interstitial brachytherapy alone (10 patients) or in combination with EBRT (61 patients) to a cumulative dose of 80 Gy. Nine patients had major complications including four necroses, four fistulae, and one small bowel obstruction, for a crude rate of 13%. Chyle et al at MDACC found that transperitoneal staging pelvic lymphadenectomy before RT contributed significantly to complications of therapy.[310] Imaging has largely replaced surgical staging for cervical and vaginal cancers.

A retrospective series from MDACC analyzed complication rates for 193 patients treated between 1970 and 2000 using the NCI Common Terminology Criteria for Adverse Events.[308] The cumulative rate of grade-3 or grade-4 complications was 10% at 5 years and 17% at 10 years. Twenty patients had a total of 25 major complications, 19 of which involved the gastrointestinal tract including proctitis requiring transfusion (7 patients), fistulae (5 patients), small bowel obstruction (4 patients), and large bowel obstruction, rectal ulceration, and fecal incontinence (1 patient each). Eight of 11 patients with major rectal complications had primary tumors involving the posterior vaginal wall. Genitourinary complications included vesicovaginal fistulae (2 patients), hemorrhagic cystitis (3 patients), and urethral stricture (1 patient). All major urinary tract complications were seen in patients with primary cancers involving the anterior wall of the vagina. With univariate analysis, the incidence of complications correlated with primary tumor stage and smoking history. Current smokers had a 25% incidence of complications, compared to 18% in former smokers who quit 6 months or longer before RT and 5% in patients who had never smoked.[308]

Vaginal fibrosis and stenosis with shortening and narrowing is probably the complication that occurs with greatest frequency but is underreported. The average age of this population, many of whom may not regularly have vaginal intercourse, probably both increases the likelihood of significant stenosis and decreases reporting of this functionally limiting complication. The morbidity of vaginal stenosis may be limited to difficulty and discomfort with subsequent vaginal examinations in patients who are not active sexually. Stenosis may compromise the early diagnosis and subsequent salvage of local relapse as well as prevent surveillance of the cervix in patients who have not had prior hysterectomy. Vaginal stenosis can be prevented with variable success with the use of vaginal dilators and topical intravaginal estrogen on a chronic basis. This is effective for vaginal mucosal atrophy and should be used in addition to systemic hormone replacement in younger patients in whom RT has ablated ovarian function. When the uterus remains intact, hormone replacement should be combined estrogen and progesterone to protect the hormonally responsive endometrium, which might result in hematometra or hematocolpos in the setting of vaginal stenosis. Because some intravaginal estrogen will be absorbed

systemically, the precise balance of oral or transdermal hormone replacement with vaginal estrogen administration will vary from patient to patient.

TREATMENT ALGORITHM AND FUTURE POSSIBILITIES

A treatment algorithm for invasive cancer of the vagina is depicted in Figure 60-13.

Patients with small-volume primary tumors confined to the vaginal wall that do not encroach on functionally important midline structures (urethra, bladder, rectum) may be treated with primary surgical excision if the surgery would not compromise sexual function. Adjuvant RT may be subsequently indicated. Rarely are patients with more extensive disease suitable for initial surgery. An exception relates to patients with stage IVA bulky central disease and fistula formation (vesicovaginal or rectovaginal fistulae). Total vaginectomy with selective or total exenteration may be necessary initial treatment for hygienic reasons. However, fistula formation is not the inevitable consequence of radiotherapeutic management of patients with stage IVA disease. Anecdotally, some patients presenting with small vesicovaginal fistulae will have urinary continence restored if the vaginal walls fuse after radical RT, effectively sealing the fistula. If that is the intent, use of a vaginal dilator after RT will be counterproductive.

Use of concurrent chemoRT is not of proven value for patients with vaginal cancer, but its use is rational given utility in primary cancers of the anus, cervix, and vulva. As in cervical cancer tumors of diameter >4 cm (IB2) may benefit from additional chemo. It is reasonable to consider in patients whose tumor volume is unlikely to be cured with RT alone in a tolerable dose. Because of the rarity of vaginal cancer, prospective, randomized clinical trials are unlikely in the context of decentralized cancer care. Progress in improving local and regional control may come from more precise definition of disease extent using sophisticated spatial and metabolic imaging modalities. With better knowledge of dose-control probabilities and more powerful treatment planning capabilities rendering tighter, elegant RT dose distributions, the therapeutic ratio should improve. Concurrent chemoRT should also improve outcomes.

NONSQUAMOUS VAGINAL MALIGNANCIES

Vaginal Melanoma

Melanoma accounts for approximately 3% of vaginal malignancies and is the second-most common histologic type of primary vaginal cancer. Bleeding or protrusion of a mass from the vagina is the most common presentation. Data regarding stage distribution are limited, but advanced stage appears common.[306]

Primary treatment includes radical surgery, radical RT, or combinations of RT and surgery. Modality of treatment does not appreciably affect survival.[306] The prognosis is grim. In a series of 37 stage 1 primary vaginal melanomas treated between 1980 and 2009 at MDACC employing a variety of therapeutic strategies, 5-year DFS was 9.5% and median time to recurrence was 17.4 months.[334] The majority of relapses are local or regional, often with distant metastases. The lung and liver are the most common remote organs affected.

The rate of survival is much lower than that for cutaneous melanomas but is consistent with survival at other mucosal sites and the generally large tumor burden at diagnosis. Because inadequate surgical margins are highly predictive of local relapse and salvage after relapse is unlikely, patients treated with primary surgery have sometimes undergone partial or total pelvic exenteration. Given the poor survival and the high morbidity of such procedures, thorough preoperative assessment for disease spread beyond the boundaries of surgical resection should be undertaken in each patient for whom such surgery is contemplated. Investigations may include whole-body CT, PET/CT, and possibly MRI of the brain. Surgical therapy must also be individualized in the context of patient comorbidities and the patient's willingness to undergo procedures that imply profound changes in quality of life in exchange for a slender prospect of cure.

Although melanomas have traditionally been considered radioresistant, there are a few long term who have been treated with RT. Local RT may provide palliation and growth restraint in patients with proven metastatic deposits and primaries for whom exenterative surgery is not appropriate. Adjuvant systemic therapy and treatment of disseminated melanoma parallels the treatment of melanoma of the vulva and melanoma arising in other mucosal sites.

Sarcomas

Vaginal sarcomas comprise 3% of primary vaginal malignancies. The majority of cases are leiomyosarcoma.[335,336] Other reported sarcomas include endometrial stromal sarcoma, malignant mixed müllerian tumor/carcinosarcoma, and rhabdomyosarcoma, among others. Surgical resection is the treatment of choice. RT may be employed preoperatively or postoperatively for inadequate surgical margins or regional spread in analogy to the treatment of extremity and truncal sarcomas although its value and that of chemotherapy is not precisely known.

Embryonal rhabdomyosarcoma is a highly malignant, rapidly growing sarcoma that occurs predominantly in children although sporadic case reports involve adults. The most common site in the pediatric age group is the vagina. This tumor generally presents as soft nodules that fill and protrude from the vagina or as abnormal bleeding. The prognosis for patients with this malignancy has improved dramatically with the use of multimodality therapy including surgery, polyagent chemotherapy, and radiation.[337]

Clear Cell Adenocarcinoma (CCAC) of the Vagina

Prognostic factors for all clear cell carcinomas of the vagina include stage at diagnosis, tumor size, and grade of the lesion, including architecture and nuclear grade, and appear to pertain equally to patients both DES-exposed and DES-unexposed. Among patients who were DES-exposed, young age was also found to be a poor prognostic factor. It appears from the Netherlands registry that DES-exposed vaginal CCAC cases were diagnosed after shorter durations of symptoms.[289] Possibly because of early occurrence of abnormal bleeding, the majority of cases were stage I or stage II at diagnosis.

Both surgery and RT/chemoRT have been used as primary treatment options. Approximately half of all patients with vaginal CCAC in the U.S. Registry for Research on Hormonal Transplacental Carcinogenesis were treated initially with radical surgery alone.[338] Radical RT is offered as primary therapy for patients with locally advanced disease and those who are not surgical candidates or decline radical surgery. RT may be given as adjuvant therapy for patients at high risk for pelvic relapse. RT may be used alone or in combination with surgical resection to treat locally recurrent disease. Optimal treatment of recurrent disease is not clear; in 1979 Herbst reported a 5-year OS after pelvic relapse of 40%.[339]

Of all melanomas in women, less than 1% arise in the vagina. Most of the literature consists of case reports or small case series. The incidence of vaginal melanoma from population-based data is 0.026 to 0.030 per 100,000 women per year. Its etiology unlike cutaneous melanoma is unclear. Melanomas arising are thought to originate from in situ melanocytes in areas of melanosis or atypical melanocytic hyperplasia. Incidence does increase with age. The population-based median age is approximately 70 years.[307] Approximately 20% are multifocal within the vagina. In contrast to squamous cancers, most (65%) arise in the distal third of the vagina.[306,334]

Most relapses are local or locoregional, although the incidence of distant relapse in CCAC is higher than in squamous vaginal cancers. In Waggoner et al's study, 9% of all patients with DES-exposed CCAC presented with lung or distant nodal metastases.[338] Among patients who were DES-unexposed, the rate of distant disease was 24%. Although most relapses occur within 3 years of treatment, later relapses, have been reported.[340]

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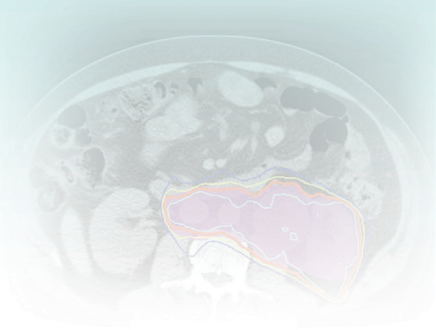
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CHAPTER

61 Ovarian Cancer



Danielle Vicus, William Small, Jr., and Allan Covens

INCIDENCE AND ETIOLOGY

Ovarian cancer constitutes 3% of all cancer diagnosed in women and 5% of all cancer-related deaths. In 2015 the estimated incidence of ovarian cancer in the United States was 21,290 cases with an estimated 14,180 deaths. The lifetime risk in the general population is 1.4%. The molecular events involved in the carcinogenesis of ovarian cancer are still unclear; however, environmental, hormonal, and genetic risk factors have been identified through epidemiologic studies.

PREVENTION AND EARLY DETECTION

The focus of ovarian cancer screening is to attempt to identify women with early-stage disease. The most common techniques used in screening are serum CA-125 and ultrasonography. Multiple trials have shown a low positive predictive value (PPV) of screening the general population and an expected higher PPV when screening high-risk populations. Until further evidence of the utility of screening is available it is not recommended for the general population.

Most hereditary ovarian cancer is associated with a germline mutation in the *BRCA1* or *BRCA2* gene. For patients with an identified *BRCA1* and *BRCA2* mutation, screening has been recommended, despite its unproven value. Prophylactic salpingo-oophorectomy at the completion of childbearing is recommended.

BIOLOGIC CHARACTERISTICS

Epithelial ovarian cancer comprises approximately 90% of all ovarian cancers, 75% of which are of serous histology. In the first two decades of life, ovarian germ cell tumors (GCTs) constitute almost 70% of all ovarian tumors, a third of which are malignant. Sex cord and stromal tumors are rare, although they account for 90% of all hormone-producing tumors.

STAGING EVALUATION

Ovarian cancer is staged surgically according to the International Federation of Gynecology and Obstetrics (FIGO) staging system based on the patterns of spread. In early-stage disease, comprehensive surgical staging is pertinent because the extent of disease determines indications for subsequent treatment. Advanced stage disease (III/IV) exists in 70% of patients at diagnosis.

PRIMARY THERAPY

The primary treatment for ovarian cancer is surgical. In early-stage disease a comprehensive surgical staging procedure is completed. In patients with epithelial stage IA or GCTs, fertility-sparing surgery may be performed. For patients with advanced stage, cytoreductive surgery is performed with the purpose of removing all macroscopic disease if feasible.

ADJUVANT THERAPY

Patients with early-stage, low-grade epithelial ovarian cancer do not benefit from adjuvant therapy. The current recommendation for all other patients is adjuvant combination chemotherapy (chemo) with carboplatinum and paclitaxel. Certain histologies such as clear cell may benefit from adjuvant radiation therapy (RT).

Patients with GCTs (other than stage I dysgerminoma and stage IA grades 1 and 2 immature teratoma) are commonly treated with bleomycin, etoposide, and a platinum-based regimen or with etoposide and a platinum-based regimen.

The benefit of adjuvant chemo for sex-cord and stromal tumors has not been proven.

ADVANCED DISEASE

Advanced ovarian cancer is treated with cytoreductive surgery and postoperative combination chemo. The most commonly used regimen is six cycles of carboplatin and paclitaxel. Intraperitoneal chemo (cisplatin with or without paclitaxel) and intravenous (IV) paclitaxel improves survival and should be considered in optimally debulked patients (<1 cm gross residual tumor), although the regimen for optimal therapeutic ratio is not defined. Maintenance chemo has not been shown to be beneficial and cannot be recommended. Maintenance bevacizumab has demonstrated a modest increase in progression-free survival (PFS) and no difference in overall survival (OS) or quality of life.

The majority of patients with ovarian cancer enter a state of remission on completion of surgery and postoperative chemo, but about 85% experience relapse and die of disease.

RADIATION THERAPY

Abdominopelvic RT is an effective adjuvant treatment for some well-defined patient groups with ovarian cancer, although platinum-based chemo has become the preferred modality. The role of RT in advanced stage disease as consolidation therapy sequential to surgery and chemo is controversial. Certain patients with early-stage disease and specific histologies may benefit from adjuvant RT. RT for palliation is effective and should be recommended in patients with localized symptoms.

PALLIATION

Because disease relapse is usually incurable, the principal aim is to prolong symptom-free survival and palliate symptoms. The benefit of second-line chemo is dependent on the disease-free interval from completion of treatment to relapse. Patients who experience relapse early, less than 6 months from completion of treatment, are "platinum resistant," and their response rates are low, whereas those who experience relapse with a longer treatment-free interval are "platinum sensitive" and have a higher response rate.

Secondary debulking, which is surgery performed to remove tumor relapse, is considered in patients with late relapse and resectable tumor. RT for palliation is an effective modality in patients with symptoms related to localized disease. Patients should be considered for clinical trials or symptomatic measures when a low probability of response to therapy is expected.

Ovarian cancer is the fifth-most common cause of cancer death among women, and the leading cause of gynecologic cancer-related death in the United States.[1] The incidence of ovarian cancer for 2015 in the United States was projected to be 21,290 cases, thus constituting 3% of all cancer diagnosed in women. The lifetime risk in the general population is 1.4%. In 2014 the expected number of deaths attributed to ovarian cancer was projected to be 14,180, accounting for 5% of all cancer-related deaths.[2]

Ovarian cancer is one of the most clinically challenging cancers to treat. Cure rates are low as symptoms are nonspecific and diagnosis is usually late in the disease course. It primarily spreads throughout the peritoneal cavity, and maximal cytoreduction, of proven benefit, often requires complex surgical procedures. The majority of patients experience relapse and will succumb to their disease, making ovarian cancer a psychologically and physically challenging disease for patients and their caregivers.

EPIDEMIOLOGY AND ETIOLOGY

Epidemiology

Ovarian cancer is infrequent before the age of 40, with a median age at diagnosis of 63 years. The age-specific incidence increases with age, reaching its peak in the eighth decade, with an incidence of 57 per 100,000 in the 70- to 74-year age group[3] (Figure 61-1). Incidence rates and the number of cancer-related deaths have been relatively stable over the past three decades.

Five-year OS is the typically reported end point for epithelial ovarian cancer and is approximately 45%. The survival is significantly better for the 30% of patients with localized disease, with 5-year OS of 93%. However, approximately 70% of women are diagnosed when disease has spread, with expected 5-year OS of 20% to 30%.[1,4-6] Women diagnosed younger than age 65 have higher 5-year OS (65.8%) in comparison to those older than age 65 (32.9%).

Etiology

The molecular events involved in the carcinogenesis of ovarian cancer are still unclear. However, environmental, hormonal, and genetic risk factors have been identified through epidemiologic studies.

Environmental Risk Factors

Country of residence and race has been associated with an increased risk of ovarian cancer. Women living in North America and in northern Europe have the highest risk. The incidence is highest among white women, is intermediate among black women, whereas Hispanic, Asian, and American Indian women have the lowest reported risk.[7] Many dietary factors have been evaluated in regard to the risk of ovarian cancer, including a diet high in meat and calories, antioxidant intake (e.g., vitamins A, C, and E), and lactose or coffee consumption, although none has consistently been shown to significantly alter the risk.[7-10]

Hormonal Factors

Hormonal factors including increased parity, age at first birth before age 25 years, history of breast-feeding, oral contraceptive use, and tubal ligation have been shown in multiple epidemiologic studies to decrease the risk of developing ovarian cancer by 25% to 60%.[11-13] Hormone-replacement therapy has been shown in the Million Women Study and in a more recent Danish cohort study to be a risk factor for ovarian cancer.[14,15] Both studies demonstrated a 1.5- to 2-fold increased risk of developing ovarian cancer in current users of hormone-replacement therapy. The protective effects of parity, multiple births, oral contraceptive use, and breast-feeding support the "incessant ovulation" theory, in which each ovulatory cycle causes damage to the ovarian epithelium and then the process of aberrant repair becomes an initial step in carcinogenesis.[16] Therefore, the more ovulatory cycles a woman has in her lifetime, the higher her risk of developing ovarian cancer. A second hypothesis attributes an increased risk to excessive

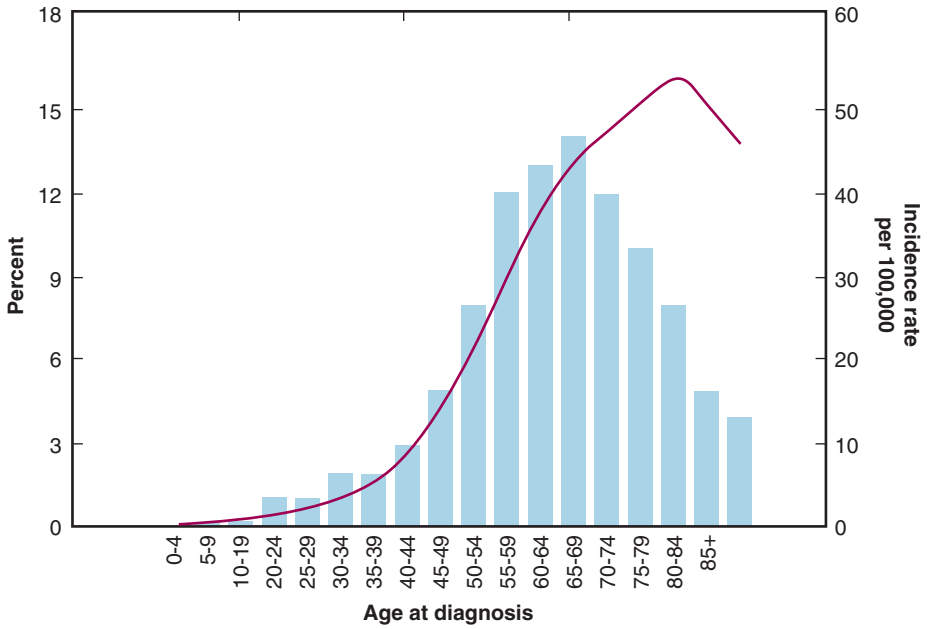


Figure 61-1 Incidence rates by age for ovarian cancer.
Data from Yancik R, Ries LG, Yates JW: Ovarian cancer in the elderly. An analysis of Surveillance, Epidemiology, and End Results Program data. Am J Obstet Gynecol 154:639–647, 1986.

gonadotropin secretion.[17] Because of the high concentration of gonadotropins, estrogenic stimulation occurs, leading to the entrapment of epithelial cells in inclusion cysts, which further leads to cell proliferation and malignant transformation.[17,18] Oral contraceptive use and pregnancy, in addition to stopping ovulation, lower gonadotropin levels; therefore, both traditional risk reducers are in concordance with both theories. Hence, patients treated for infertility with ovarian stimulation would be expected to have an increased risk of ovarian cancer. Although an increased risk of predominantly borderline tumors was reported in a cohort of women treated for infertility with prolonged use of the ovulation stimulator, clomiphene citrate, the data have not been consistent. Both a large Danish population-based cohort study and a retrospective cohort study of almost 10,000 U.S. women treated with a spectrum of infertility medications did not support the correlation between infertility medication and ovarian cancer.[19,20]

Genetic Factors

Only 15% of all ovarian cancers are attributable to known genetic mutations, that is, 13% to the hereditary breast and ovarian cancer syndrome (*BRCA1* and *BRCA2* germline mutations) and 2% to the hereditary nonpolyposis colon cancer syndrome (*MLH1, MSH2,* and *MSH6* mutations).[19,21,22] Women with hereditary nonpolyposis colon cancer (HNPCC) syndrome have an increased risk of developing multiple types of cancer, including colon, endometrial, and ovarian cancer. The lifetime risk of women with HNPCC of developing ovarian cancer is 15% to 25%.[23] The frequency of *BRCA* mutations differs among ethnic groups. Founder (recurrent) mutations have been identified in specific ethnic groups; for example, up to 40% of all women who are of Ashkenazi Jewish descent with ovarian cancer carry one of three founder mutations.[24] Additional founder mutations have been found among women who are Polish and French-Canadian.[25,26] Women who harbor a *BRCA1* mutation have a lifetime risk of 30% to 40% for developing ovarian cancer. Women with a *BRCA2* mutation have a 15% to 25% lifetime risk of developing ovarian cancer, depending on the location of the mutation in the genes; a higher risk is correlated with a mutation in the ovarian cancer cluster region.[27] Women with a *BRCA1* or *BRCA2* mutation also have an increased risk of fallopian tube cancer. The lifetime risk of breast cancer for carriers of *BRCA1* and *BRCA2* mutations is 50% to 85%.

PREVENTION AND EARLY DETECTION

Screening and Prophylactic Surgery

The majority of women with ovarian cancer presents with advanced disease and therefore has a poor long-term prognosis. In contrast, those patients who are diagnosed when the cancer is limited to the ovaries have a good prognosis, with a 5-year OS of 80% to 90%.[28] Unlike cervical cancer, it is unclear that there is an orderly progression from limited to extensive disease. Nevertheless, the focus of ovarian cancer screening is to identify women with early-stage disease. The most common screening techniques used to date are ultrasonography and serum CA 125. The latter is an antigenic serum tumor marker detected by radioimmunoassay that is elevated in 80% of epithelial ovarian cancers.

Two large randomized trials have addressed the question of the yield of screening for ovarian cancer: the U.S. National Institutes of Health (NIH) Prostate Lung Colorectal and Ovary Study (PLCO) and the U.K. Collaborative Trial of Ovarian Cancer Screening (UKCTOCS).[29,30] UKCTOCS randomly assigned 202,638 women who were postmenopausal to a control group (no screening) versus two different arms of screening (annual transvaginal ultrasonography or annual CA 125 screening and further transvaginal ultrasonography if results were elevated). To date only the prevalence data of UKCTOCS has been reported showing that the majority of cases diagnosed were at advanced stage. PLCO randomly assigned 39,115 women to screening (annual CA 125 and transvaginal ultrasonography) versus usual care (i.e., no screening). In 2011, the results of PLCO were published; 118 deaths caused by ovarian cancer were found in the intervention group and 100 deaths in the usual care group (relative risk [RR], 1.18; 95% confidence interval [CI], 0.82 to 1.71).[31] They found that 15% of women with false-positive results who underwent surgery experienced at least one serious complication and therefore concluded that this screening in the general population did not reduce ovarian cancer mortality and was associated with surgical complications. Although there are minor differences in trial design between the two aforementioned studies (including a stricter screening protocol, higher quality control, and the use of a trend in CA125 and not an absolute number in the UKCTOCS trial), at this point in time there is no proven survival benefit for screening the general population and it is not recommended.

Multiple trials have shown the expected higher PPV when screening high-risk populations.[32-37] For patients with an identified *BRCA* mutation, screening has been recommended at the NIH Consensus Conference on Ovarian Cancer despite the absence of proven survival benefit.[38]

New directions examining potential novel serum markers using proteomics and genomics are being explored.[39-41] The majority of studies are evaluating the sensitivity and specificity of combinations of markers. Visintin et al,[40] from Yale University, studied concentrations of a combination of six proteins, including leptin, prolactin, osteopontin, insulin-like growth factor 2, macrophage inhibitory factor, and CA 125 in 156 patients with newly diagnosed ovarian cancer and 362 healthy controls. They reported a sensitivity of 95.3% and a specificity of 99.4% for the detection of ovarian cancer. These promising results require additional validation studies.

The value of genetic counseling for patients with an identified *BRCA* mutation or HNPCC has been established because the management decision making is complex. Individualized recommendations are made based on the specific risk, patient age, and her reproductive goals. Prophylactic salpingo-oophorectomy in women with a *BRCA* mutation reduces the risk of gynecologic cancer (ovarian and fallopian tube) by 85% to 96%.[42-45] There remains an approximately 1% risk of primary peritoneal cancer.[42-44] In addition, the risk of developing subsequent breast cancer was reduced by 50% to 60%.[46] The NIH consensus panel in 1995 recommended prophylactic oophorectomy for women at high-risk at age 35 or after the completion of childbearing.[38] Because of the emerging evidence supporting the hypothesis that ovarian cancer originates in the fimbriated end of the fallopian tube, there is growing acceptance to perform bilateral salpingectomies at time of hysterectomy if oophorectomy is not indicated to potentially lower the risk of ovarian cancer. However, more data is needed before guideline recommendations can be made.

BIOLOGIC CHARACTERISTICS AND PROGNOSTIC FACTORS

Currently prognostic clinicopathologic and biologic variables are used to predict survival probability. It is hoped that molecular markers will soon be identified that better define risk.

Clinicopathologic Factors

The surgically determined stage of disease is directly correlated with survival. The Surveillance, Epidemiology and End Results (SEER) database, for patients diagnosed between 2006 and 2009, reported a 5-year OS of 44.2% for all stages; 91.9% for stage I, 72.0% for stage II, and 27.3% for combined stages III and IV.[47]

Histologic grade, based in the FIGO system on architectural features, that is, the ratio of glandular or papillary structures versus solid tumor growth within a tumor, is an important prognostic factor in epithelial ovarian cancer.[48-50] Patients with high-grade (poorly differentiated) tumors have worse outcomes than those with low-grade (well-differentiated) tumors. In patients with early-stage (IA to IB) low-grade tumors, a 94% 5-year OS has been reported with surgery alone.[51]

The effect of histologic cell type has generally been of less important prognostic significance than other factors although the stage distribution at presentation and response to chemotherapy differ markedly. However, it has been suggested that early-stage endometrioid and mucinous cell types have a better prognosis than serous and clear cell adenocarcinoma, but when grade and cell type are evaluated, histologic cell type has not been found to be an independent factor.[52,53]

In patients with advanced-stage disease, chemotherapy sensitivity is an important prognostic factor. Therefore, patients with serous histology have a better prognosis than those with the more chemoresistant tumors (e.g., mucinous and clear cell).[54]

Patient age at diagnosis and performance status are independent prognostic factors.[55,56] However, tumor size and bilaterality are not prognostic.

The volume of residual tumor at the completion of a cytoreductive surgery for advanced ovarian cancer is directly correlated with survival.[55] Chi et al[57] from Memorial Sloan Kettering Cancer Center have shown that an aggressive primary cytoreduction, including extensive upper abdominal procedures, resulted in increased optimal cytoreduction rates and significantly improved progression-free survival (PFS) and OS in patients with advanced ovarian carcinomas. However, it remains controversial whether it is primarily the aggressiveness of the surgery, the biology of the tumor, or both that contribute to prognosis.

Elevated preoperative and postoperative CA 125 levels, a reflection of volume of disease, and the time frame over which the level declines during chemotherapy have been shown to correlate with prognosis.[58]

Biologic Factors

The cellular DNA content, as determined by flow-cytometric analysis, is an independent prognostic factor. Aneuploid (versus diploid) DNA content in ovarian tumors is correlated with more aggressive biologic behavior and a worse clinical course.[59,60]

Molecular markers, including both abnormalities in oncogene products (e.g., ERBB2 [HER2/neu], ERBB3 [HER3]), and suppressor gene products (e.g., TP53) correlate with prognosis.[61,62] Many additional biologic markers, including markers of proliferation and of DNA repair, together with newer studies on loss of human leukocyte antigen class I, KLK6, and KLK13, have been reported,[63,64] although their significance has not yet been established.

PATHOLOGY AND PATHWAYS OF SPREAD

Pathogenesis

Ovarian cancers are classified by their histology. The largest categories are epithelial (approximately 80% of all ovarian cancers), germ cell, and sex cord and stromal. The traditional view of the pathogenesis of epithelial ovarian cancer asserts that all tumor subtypes share a common origin in the surface epithelium of the ovary, which is repeatedly disrupted by ovulation and consequent release of inflammatory cytokines, capable of damaging DNA.[65,66] This increases the susceptibility to malignant transformation. Moreover, numerous invaginations into the stroma develop as the ovary ages and these invaginations further form cortical inclusion cysts.[67] Epithelial cells in the cysts are exposed to high hormone levels that induce proliferation and are susceptible to malignant transformation if there has been previous DNA damage.

This putative mechanism of carcinogenesis has not been supported by identification of a precursor lesion in the ovary. Prophylactic surgery in patients with a genetic predisposition to breast and ovarian cancer has led to pathological evaluation of removed ovaries and fallopian tubes for the presence of early cancers or noninvasive lesions. Isolated foci of cancer have been seen in the fallopian tube but rarely have small isolated cancers been found confined to the ovary.[68-70] These observations led many authors to conclude that the fallopian tube may be the primary site of cancers, which if diagnosed later in the course of disease would have been classified as a primary ovarian cancer.[70-72]

Pathways of Spread

Epithelial ovarian cancer spreads through four mechanisms: (1) direct contiguous spread to adjacent organs, (2) transcoelomic in the peritoneal cavity, (3) lymphatic, and (4) hematogenous (rare).

Transcoelomic: The most common pattern of spread is through exfoliation of cancer cells into the peritoneal cavity. The cells move with the peritoneal fluid circulation from the pelvis into the right paracolic gutter to the upper abdomen and return to the pelvis through the left abdomen. The cells attach to the surface of intraabdominal organs and grow into masses. They uncommonly invade intraabdominal organs (e.g., the bowel, liver, or spleen).

Lymphatic: Lymphatic spread of cancer cells to the pelvic and paraaortic lymph nodes is common. Spread above the diaphragm to the supraclavicular nodes occurs through retroperitoneal dissemination.

Hematogenous: Hematogenous spread of ovarian cancer to the parenchyma of vital organs (e.g., liver or lungs) is rare at diagnosis, occurring in less than 5% of all cases. Systemic metastases can be seen at time of relapse, when disease is widespread throughout the pelvis and abdomen.

Direct spread: Ovarian cancer cells can spread through direct extension from the ovary to adjacent organs; the most common site being the fallopian tube.

Histologic Classification

Epithelial ovarian carcinomas are subclassified based on histologic cell type: serous, mucinous, endometrioid, clear cell, and transitional. They are also divided into borderline (also called tumors of low malignant potential) and invasive. Borderline tumors of the ovary are defined as those with epithelial atypia without stromal invasion. They generally are associated with an excellent prognosis, with a nearly 100% 5-year OS when diagnosed at stage I.[73] Borderline tumors occur primarily in women of a younger age in comparison with invasive cancer.

Serous carcinoma is the most common histologic subtype of epithelial ovarian cancer.[74] It is characterized histologically by broad, branching papillae covered with stratified epithelial

cells. High-grade serous carcinoma contains large pleomorphic nuclei with many mitoses. Papillary fenestrations with slit-like fenestrations are common, there may be large areas of necrosis, and psammoma bodies may be present.

Low-grade serous ovarian carcinomas (micropapillary carcinomas) are tumors with grade-1 nuclear atypia, low-grade architecture, and low mitotic activity.[75] They are associated with extensive papillary architecture and often contain an abundance of psammoma bodies. Low-grade serous carcinomas may arise in association with borderline tumors and are distinct from high-grade serous tumors because they do not behave aggressively. The low-grade and borderline serous tumors frequently have mutations in BRAF and KRAS and lack TP53 mutations. Borderline serous ovarian tumors clinically behave in an intermediate manner between benign and malignant; that is, there may be peritoneal implants but most are noninvasive. The 5-year OS of stage III borderline serous tumors is approximately 85%, whereas that of stage III invasive serous cancer is only 20% to 30%.[6,76] Long-term follow-up of 276 patients with ovarian serous tumors of low malignant potential identified unresectable disease and invasive implants as significantly associated with decreased survival ($p < 0.001$).[77]

Mucinous cyst adenocarcinomas are diagnosed when the majority of the epithelial cells contain mucin and comprise approximately 15% of ovarian tumors. The majority are benign (80%), approximately 10% are borderline, and 10% are invasive. Microscopically, the malignant areas show back-to-back glands with malignant cells and little or no stroma. The epithelial cells are columnar or polygonal with eosinophilic or mucinous cytoplasm. Goblet cells and signet ring cells may be present, although if they are abundant a metastasis from a gastrointestinal origin should be considered. Invasive mucinous carcinoma of ovarian origin is rare and is usually diagnosed at an early stage.[78] Molecular studies have shown a link between borderline and invasive mucinous tumors.[79] Unlike serous ovarian cancers, individual tumors frequently show heterogeneity with benign, borderline, and invasive areas. On gross examination they are the largest of all ovarian tumors, are commonly unilateral, have a smooth surface, and are multilocular.

Endometrioid carcinomas comprise approximately 10% of all epithelial ovarian cancers and commonly arise in extrauterine endometrial tissue. Approximately one third of the cases are associated with endometriosis.[80] Adenocarcinomas associated with endometriosis may develop in association with proliferative adenofibromas and frequently occur after de novo malignant transformation of the endometrial epithelium. They are composed of epithelial cells and patterns similar to endometrial hyperplasia and neoplastic changes of the endometrium. Early-stage endometrioid carcinomas are bilateral in approximately 15% of cases. They are both cystic and solid and often are seen near foci of endometriosis. The grading is identical to that of primary carcinomas of the endometrium. Endometrioid tumors of the ovary carry genetic alterations in the phosphatase and tensin homolog (PTEN) similar to those in the endometrium.

Clear cell carcinomas of the ovary are adenocarcinomas in which most of their epithelial cells have clear cytoplasm, predominantly owing to glycogen, although part may be from mucin. They are easily recognizable under low power because of their unique architecture. They primarily have a papillary pattern with hyalinized stroma, although they can also have a more cystic, glandular, or solid pattern. Clear cell carcinomas are uncommon, comprising approximately 5% of all epithelial ovarian tumors in North America, and almost half are associated with endometriosis. Unlike serous cancers, patients predominantly present with stage I disease (50% to 60%), and when compared stage for stage to serous ovarian cancer, the prognosis seems to be worse.[81,82] However, in Japan, clear cell carcinoma of the ovary represents more than 20% of all epithelial ovarian cancer.[83] The prognosis of stage I clear cell carcinoma in Japan has been shown to be superior to that of serous ovarian cancer. Ovarian clear cell and endometrioid cancers have been shown clinically to be associated with endometriosis; however, the molecular events associated with this transformation have only recently been identified by Gilks et al with regard to ARID1A mutations.[84] They identified ARID1A mutations in 55 of 119 ovarian clear-cell carcinomas (46%), 10 of 33 endometrioid carcinomas (30%), and none of the 76 high-grade serous ovarian carcinomas. They further saw that ARID1A mutations and loss of BAF250a expression was found in tumors and atypical endometriosis but not in endometriotic lesions. These data implicate ARID1A as a tumor-suppressor gene disrupted in endometriosis associated carcinomas and can potentially be an early event in the transformation of endometriosis into cancer.

Transitional cell ovarian carcinomas have epithelial cells that resemble transitional cells of the urinary tract. They include both Brenner tumors (benign, borderline, or malignant) and transitional cell carcinomas. They may be pure or a component of a mixed epithelial tumor. Brenner tumors are mostly arranged in a trabecular pattern, with lipid-rich cells in the stroma. The epithelial cells have a pale, oval nucleus with a longitudinal groove ("coffee bean" nucleus). They are high-grade epithelial tumors that, by definition, do not include the elements of Brenner tumors. The tumor resembles transitional cell tumors originating in the bladder with broad papillae containing highly stratified, crowded cells. The cells have eosinophilic or clear cytoplasm, and the degree of nuclear atypia varies. Transitional cell carcinomas are bilateral in up to 20% of cases.

CLINICAL MANIFESTATIONS, PATIENT EVALUATION, AND STAGING

Clinical Manifestations

More than 75% of epithelial ovarian cancers are diagnosed when disease has spread throughout the abdominal cavity. The most common presenting symptoms are abdominal discomfort, pain, or distension because of the presence of malignant masses or ascites throughout the peritoneal cavity. Gastrointestinal symptoms (e.g., nausea, early satiety, change in bowel habit/constipation, bloating) are also frequent at the time of diagnosis. Additional symptoms that may occur include fatigue, dysuria, and vaginal bleeding.

In patients with early-stage disease, symptoms are rare. Therefore, the diagnosis is predominantly made incidentally at the time of evaluation for nonrelated gynecologic complaints or by palpation of an asymptomatic ovarian mass. The majority of palpable ovarian masses in women who are premenopausal are benign. In contrast, any palpable mass in a woman who are postmenopausal has a high probability of being malignant.

Patient Evaluation and Diagnosis

Although the diagnosis of ovarian cancer is made at the time of surgery or by biopsy, benign diseases of the female genital tract such as functional cysts, endometriosis, and uterine myomas must be differentiated from ovarian cancer; therefore, patients who present with an adnexal mass must undergo a full evaluation, including history and physical examination. Pelvic ultrasonography and determination of CA 125 level are also used to assist in evaluating the malignant potential of the adnexal mass. A complex mass evident on ultrasound

evaluation containing irregular borders, solid elements with papillary projections, multiple irregular septa, and bilateral tumors is suggestive of malignancy. The use of additional abdominal and extra-abdominal imaging is dependent on the patient's specific complaints and the physical examination.

Serum CA 125 is elevated in 80% of women with epithelial ovarian cancer and is predominantly associated with serous ovarian cancer. It is seldom elevated in the mucinous subtype. In women who are postmenopausal aCA 125 higher than 65 U/mL was found to have a PPV of 98% and a negative predictive value (NPV) of 72%.[85]

Jacobs et al[86] proposed the "Risk of Malignancy Index" in 1990, estimating the risk of an adnexal mass being malignant in a specific patient. It has since been validated in many studies. The Risk of Malignancy Index incorporates the serum CA 125 level, ultrasound scan result (0, 1, or 3), and the menopausal state (0, premenopausal, 3, postmenopausal). These researchers defined a cutoff of 200 in which a sensitivity of 85% and a specificity of 97% for predicting malignancy were found.

Women who present with apparent advanced disease seen on ultrasonography or computed tomography (CT) need a full evaluation before deciding on optimal management. This includes a full personal and family history, physical examination, and assessment of surgical risk, which is pertinent to confirm the likely origin and probable extent of disease. Because most of the symptoms of advanced-stage ovarian cancer are nonspecific it is essential to confirm that the primary tumor is ovarian. Confusion with metastatic gastrointestinal tract malignancy can occur. Additional tests that may be required include serum CA 125 determination, imaging (e.g., chest radiography, CT, magnetic resonance imaging [MRI], barium enema), and upper or lower gastrointestinal endoscopies. Extensive disease may be judged initially unresectable and therefore indicate consideration of neoadjuvant chemotherapy rather than initial surgery.

Surgical Staging

Ovarian cancer is staged surgically according to the FIGO staging system, which was last revised in 1995. The patterns of spread and natural history of ovarian cancer form the basis of the system[28,87] (Table 61-1). The stage can be determined only after an exploration of the abdomen and pelvis, apart from the rare occasion in which stage IV disease may be documented by cytology positive pleural effusion, fine-needle aspiration of a supraclavicular node, or a liver metastasis. Comprehensive surgical staging is mandatory to determine subsequent treatment. When there is no macroscopic disease outside the ovary, an evaluation for microscopic disease must be performed. On entering the abdominal cavity, aspiration of ascites or peritoneal washings should be performed. The abdomen and pelvis should be thoroughly examined and palpated; any suspicious lesions should be sampled. The tumor should be removed intact if possible because spillage of malignant cells is suggested to worsen the prognosis.[88] The remaining ovary, uterus, and fallopian tubes should be removed unless fertility sparing is appropriate (premenopausal patient with a low-grade or borderline ovarian cancer). Pelvic and paraaortic lymph nodes should be systematically removed, an omentectomy performed, and random peritoneal biopsy specimens taken. Carnino et al showed that the detection of positive lymph nodes correlated with the number of lymph nodes removed (odds ratio [OR], 3.9 for more than 10 lymph nodes in comparison to 1 to 5; 95% CI, 1.0 to 15.4), therefore emphasizing the importance of systematic lymph node dissection.[89] Patients initially thought to have early-stage disease that undergo subsequent comprehensive surgical staging may be upstaged in up to 30% of the cases.[90]

TABLE 61-1 FIGO Staging for Carcinoma of the Ovary

Stage	Description
I	Growth limited to the ovaries
IA	Growth limited to one ovary; no ascites containing malignant cells. No tumor on the external surface; capsule intact
IB	Growth limited to both ovaries; no ascites containing malignant cells. No tumor on the external surface; capsule intact
IC	Tumor either stage IA or IB but with tumor on the surface of one or both of the ovaries; or with capsule(s) ruptured; or with ascites present containing malignant cells or with positive peritoneal washings
II	Growth involving one or both ovaries with pelvic extension
IIA	Extension or metastases to the uterus or fallopian tubes
IIB	Extension to other pelvic tissues
IIC	Tumor either stage IIA or IIB but with tumor on the surface of one or both of the ovaries; or with capsule(s) ruptured; or with ascites present containing malignant cells or with positive peritoneal washings
III	Tumor involving one or both ovaries with peritoneal implants outside the pelvis or positive retroperitoneal or inguinal nodes. Superficial liver metastases equals stage III. Tumor is limited to the true pelvis, but with histologically proven malignant extension to small bowel or omentum
IIIA	Tumor grossly limited to the true pelvis with negative nodes but with histologically confirmed microscopic seeding of abdominal peritoneal surfaces
IIIB	Tumor of one or both ovaries with histologically confirmed implants of abdominal peritoneal surfaces, none > 2 cm in diameter. Nodes negative
IIIC	Abdominal implants > 2 cm in diameter or positive retroperitoneal or inguinal lymph nodes or both
IV	Growth involving one or both ovaries with distant metastases. If pleural effusion is present, there must be positive cytologic test results to allot a case to stage IV. Parenchymal liver metastasis equals stage IV

It has also been shown that it is important that a gynecologic oncologist perform the operation. The percent of properly staged women varies by type of surgical qualification and is 97%, 52%, and 35% when the staging was performed by a gynecologic oncologist, obstetrician/gynecologist, or general surgeon, respectively.[91]

PRIMARY TREATMENT OF OVARIAN EPITHELIAL CANCER

The selection of treatment for each individual patient presenting with epithelial ovarian cancer should be based on the extent of disease, performance status, and individual patient characteristics. Therapeutic options include surgery, chemotherapy, radiation, or a combination of modalities. The identification of biomarkers and subsequent exploration of novel targeting molecular therapies constitute an important direction of research and potential therapeutic opportunity.

Early-Stage Disease: Surgery and Chemotherapy

There is consensus that all patients should undergo comprehensive surgical staging as their primary treatment. Approximately one third of patients with epithelial ovarian cancer present with apparent localized disease confined to the ovaries or to the pelvis. When all patients undergo surgical staging, however, this number decreases to 10% to 15%. Because the percentage of patients with early-stage disease is small and their prognosis is good, it is difficult to conduct studies evaluating the yield of adjuvant treatment for this group of patients.

Two randomized trials—International Collaborative Ovarian Neoplasm Trial 1 (ICON1) and Adjuvant ChemoTherapy In Ovarian Neoplasm Trial (ACTION)[92,93]—addressed the question of the efficacy of adjuvant chemo to improve survival in women with early-stage disease. Both trials randomized patients with early-stage disease to adjuvant platinum-based chemotherapy or no adjuvant treatment. The analysis of the combined trials showed an 8% difference in OS in favor of the adjuvant chemo arm (82% versus 74%, $p = 0.008$). Relapse-free survival (RFS) was also significantly better in the chemo arm of the trials (76% versus 65%, $p = 0.001$).

When the trials were analyzed separately, OS for all patients treated with chemo in comparison to those who did not receive adjuvant chemo in the ACTION trial was not found to be significantly better (hazard ratio [HR], 0.69; 95% CI, 0.44 to 1.08). On subgroup analyses, those whose disease was not surgically staged were found to significantly benefit from adjuvant chemo (OS HR, 1.75; 95% CI, 1.04 to 2.95). However in those optimally staged without evidence of metastatic disease, there was no benefit. This study was not powered to further analyze the influence of histology. Therefore, patients who do not have an optimal staging procedure should receive adjuvant chemotherapy. The benefit of adjuvant chemo in high-grade surgical stage I disease is unclear.

A literature review analyzed the results of 22 prospective randomized trials on the topic of benefit of adjuvant chemo in patients with early disease who had optimal surgical staging.[94] They concluded that adjuvant therapy is not advocated for patients with stage IA grade-1 tumors as their prognosis is excellent.[95] For patients with low-grade disease who did not have a comprehensive staging procedure, it is reasonable to offer completion of a staging procedure to avoid chemo in the proportion of patients shown to have no extra-ovarian disease. The alternative to avoid additional surgery is to give adjuvant chemo on the assumption that further disease is present in some patients.

Consideration of the prognostic factors (i.e., grade, stage, DNA ploidy, and CA 125 levels) may aid in assessing the probability of occult disease. For the clear cell subtype the acknowledged relative chemoresistance may suggest limited benefit from adjuvant chemotherapy.

Fertility-Sparing Therapy

Epithelial ovarian cancer occurs infrequently in women of childbearing age, with an estimated 8% of all malignant stage I epithelial cancers diagnosed in women younger than the age of 35.[96] Although there is relative consensus in regard to conservative surgical treatment (i.e., adnexectomy with comprehensive surgical staging), for patients with early-stage tumors of low malignant potential the literature is limited in regard to young patients with invasive epithelial tumors. Schilder et al[97,98] published a multiinstitutional study in 2002 on 52 women with stage IA ($n = 42$) or stage IC ($n = 10$) patients treated with fertility-sparing surgery and full surgical staging. Although all histologic cell types and grades were included, the majority of cases were mucinous ($n = 25$) and grade 1 ($n = 38$), and only 10 were of the serous cell type. Twenty patients received adjuvant chemo including all with stage IC grade 2 to grade 3. Five patients experienced relapse, and 2 died of their disease. The estimated 5-year OS was 98%, and the 10-year OS was 93%. Twenty-four patients, 6 who had received adjuvant chemo, attempted to conceive and 17 succeeded (71%). In a recent systematic review by Zapardiel et al, a total of 793 cases were reviewed and found to have a 5-year OS of 91%.[99] They further address the consensus in regard to fertility sparing in cases of stage I grade-1 and grade-2 ovarian cancer and the lack of consensus in regard to high-grade ovarian cancers. A study by Fruscio et al of 240 cases who underwent conservative treatment noted that although the tumor grade was the only independent predictor of poor prognosis the PFS and OS rates in the high-grade population is comparable to that shown in ICON1/ACTION trial where conservative treatment was not performed and therefore they conclude that conservative management does not seem to worsen prognosis.[100]

Young patients with stage IA disease can undergo fertility-sparing surgery and close follow-up without the need for adjuvant treatment. Patients with stage IC grade-2 to grade-3 disease can be managed with conservative surgery, but adjuvant chemo should be considered.

Radiation Therapy

Epithelial ovarian cancer is known to be a radiosensitive tumor. The benefit of adjuvant RT in patients with early-stage epithelial ovarian cancer has been evaluated in a series of studies.[101-103] Both intraperitoneal (IP) radioactive chromic phosphate suspension (^{32}P) and whole-abdomen irradiation (WAI) with a boost to the pelvis have been evaluated. Studies have suggested that the addition of RT to chemo for subsets of patients may have an expanding indication.[104-106]

Intraperitoneal Radioactive Chromic Phosphate Suspension (^{32}P)

Intraperitoneal instillation of radioisotopes, such as gold (^{198}Au) and chromic phosphate (^{32}P), have been studied in patients with ovarian cancer. It is now rarely used. Although the initial studies were performed using ^{198}Au, ^{32}P became the preferred isotope because of ease of handling, lack of gamma radiation, and a relatively low complication rate.[107] ^{32}P is a high-energy pure beta-particle emitter with a maximum energy of 1.71 MeV, a maximum penetration of 8 mm (average, 1 mm to 4 mm), and a half-life of 14.3 days. It can be used for intracavitary instillation at a dose of 10 mCi to 20 mCi. The majority of the ^{32}P is absorbed by the peritoneal surface via macrophages and then excreted through the lymphatic channels of the abdomen, that is, the thoracic lymphatics, and from there into the systemic vasculature where it is cleared by the liver. The retroperitoneal pelvic and paraaortic lymph nodes receive low doses of radiation. Because the main pattern of spread of ovarian cancer is transcoelomic, the IP instillation of radiocolloids, which deliver high doses of radiation to the peritoneal surfaces while minimizing systemic effect, would seem theoretically ideal. Gamma camera imaging of the abdomen has shown that the administration procedure including mobilization of the patients in the first 6 hours is critical for homogeneous dispersion of the radiocolloids on the serosal surfaces.[108] Dose calculations gave an estimated tissue surface dose of 30 Gy per 370 MBq of ^{32}P administered. The amount of ^{32}P in peripheral blood increased for 7 days after administration and was then followed by a continuous decrease. The estimated peripheral blood dose is 0.012 Gy, and the maximum bone marrow dose is 0.06 Gy.

TABLE 61-2 Early-Stage Ovarian Cancer: Randomized Trials of Whole-Abdomen Irradiation or ^{32}P

Trial/Author	Year	Stage	Study Design	No. Patients	5-Year Overall Survival (%)	Comments
NCIC/Klaassen[110]	1988	I, II	Pelvic RT + melphalan	106	61	^{32}P arm accrual closed early because of toxicity
			Pelvic RT + WAI	107	62	
			Pelvic RT + ^{32}P	44	66	
MDACC/Smith[103]	1975	I-III	WAI	51	71	<2 cm residual disease
			Melphalan	57	72	
PMH/Dembo[113]	1979	IB, II, III asymptomatic	WAI	76	64 (10-year)	$p = 0.007$
			Pelvic RT ± chlorambucil	71	40 (10-year)	
DACOVA/Sell[114]	1990	IB-IC, II	WAI	60	63 (4-year)	
			Pelvic RT + cyclophosphamide	58	65 (4-year)	
GOG 95/Young[51]	1990	IA-IBG3, IC, II	^{32}P	73	78	6% bowel obstruction in ^{32}P
			Melphalan	68	81	
NRH/Vergote[111]	1992	I-III	^{32}P or WAI	169	83	28 in ^{32}P arm treated with WAI
			Cisplatin	171	81	
GICOG/Bolis[112]	1995	IA-IB, IC	^{32}P	75	79	^{32}P not given in 20% of patients
			Cisplatin	77	81	
GOG 7602/Young[109]	2003	IA-IBG3, IC, II	^{32}P	110	78	3% bowel perforation in ^{32}P
			Cyclophosphamide + cisplatin	119	81	

Several randomized studies evaluating the efficacy of ^{32}P in early-stage ovarian cancer have been published[51,109-112] (Table 61-2). The earliest of the randomized trials was published in 1988 by the National Cancer Institute of Canada (NCIC).[110] Two hundred fifty-seven women with stages I to IIA high-risk ovarian cancer or with stage II disease were randomized to one of three trial arms: arm A, WAI (22.5 Gy in 20 fractions); arm B, melphalan; or arm C, ^{32}P. Surgical staging was not mandatory, and most patients' disease was not thoroughly staged. All patients were initially treated with pelvic RT (arm A: 22.5 Gy in 10 fractions; arms B and C: 45 Gy in 20 fractions). The ^{32}P trial arm was discontinued early because of increased bowel toxicity. No significant difference in survival was found.

In 1990 the Gynecologic Oncology Group (GOG) published a randomized controlled trial including 141 patients with stage I, grade-3 or stage II epithelial ovarian cancer randomly assigned to melphalan or a single dose of ^{32}P at the time of surgery.[51] With a median follow-up of more than 6 years the outcomes for the two treatment groups were similar with respect to 5-year disease-free survival (DFS) (80% in both groups) and 5-year OS (81% with melphalan versus 78% with ^{32}P; $p = 0.48$). They concluded that either treatment was a reasonable option.

In 1992, Vergote et al[111] published a randomized trial of 347 patients, stages I to III (no gross residual tumor), who were allocated to cisplatin (50 mg/m^2) every 3 weeks for six cycles or ^{32}P. Patients with intraabdominal adhesions allocated to IP administration of ^{32}P were treated with WAI (22 Gy to the whole abdomen in 20 fractions) followed by 22 Gy in 11 fractions to the pelvis. Patients did not undergo comprehensive staging because lymph node sampling was not performed. The estimated 5-year OS of patients with stage I disease were 82% for the ^{32}P arm, 94% for the WAI arm, and 79% for the cisplatin arm ($p = 0.79$, $p = 0.44$ compared with the cisplatin arm, respectively). Bowel obstruction occurred more frequently in those treated with ^{32}P (9%, $p = 0.02$) or WAI (21%, $p = 0.001$) in comparison with the cisplatin arm (2%). Because no survival benefit was shown, cisplatin was recommended as the standard treatment.

The Italian Gruppo Interregionale Collaborativo in Ginecologia Oncologica (GICOG) performed a randomized trial[112] of 152 women with stage IA grade 2, IB grade 2, and IC disease, comparing treatment with cisplatin with that with ^{32}P. Patients underwent a surgical procedure that did not include lymph node sampling. In 15 patients randomized to treatment with ^{32}P, the radioisotope was not delivered, owing to the development of abdominal adhesions. An improved 5-year PFS was reported for the cisplatin group in comparison with the ^{32}P group (85% versus 65%, $p = 0.008$) but without an OS difference (81% versus 79%, $p = 0.35$).

The latest randomized study was published by the GOG in 2003. Two hundred twenty-nine women with early-stage ovarian cancer at high risk for relapse (defined as stage IA or IB grade 3, stage IC, or stage II, no macroscopic residual) were assigned to treatment with ^{32}P or with cyclophosphamide and cisplatin.[109] The cumulative incidence of relapse at 10 years was 35% for the ^{32}P arm and 28% for the cyclophosphamide-cisplatin arm. Patients receiving cyclophosphamide-cisplatin had a relapse rate 29% lower than those in the RT arm ($p = 0.15$) and a death rate 17% lower than those in the RT arm ($p = 0.43$). The toxicity profiles of both regimens were reasonably well tolerated, although 3% of the patients receiving ^{32}P suffered perforation of the small bowel during the insertion of the IP catheter and 7% had problems with inadequate distribution. Grade-3 or grade-4 gastrointestinal toxicity was seen in 12% of patients treated with cyclophosphamide and cisplatin. The authors concluded that, although there were no statistically significant differences, the lower relapse rate seen in the chemo arm together with ^{32}P complications make platinum-based chemo the preferred adjuvant therapy.

External Beam Irradiation

WAI has generally been used in patients in whom the tumor was completely resected or in whom macroscopic disease is

<2 cm in diameter and located only in the pelvis. Adjuvant WAI has generally not been used to treat macroscopic extrapelvic residual disease because tolerable doses of radiation are generally insufficient to eradicate more than microscopic residuum except in the pelvis, where higher doses may be administered. Its advantage in comparison to ^{32}P is the ability to deliver a homogeneous dose to all areas of the abdomen and pelvis and the ability to encompass the pelvic and paraaortic lymph nodes. The disadvantage of WAI with conventional techniques is the dose-limiting acute and late toxicity related to the treatment, which is predominantly hematologic and gastrointestinal. The target volume includes the entire peritoneum, with the cephalad border being superior to the diaphragm and the caudal border the pelvic floor, thus encompassing peritoneal surfaces, pelvic and paraaortic lymph nodes, and the organs in the abdomen and pelvis. As the majority of relapses are confined to the abdominal and pelvic cavity, it is reasonable to expect that RT techniques that encompass the entire peritoneal cavity would be more likely to be curative. The total dose to the whole abdomen is limited to 25 Gy to 30 Gy, owing to the dose-limiting organs in the field, although the pelvis is usually given a total dose of 45 Gy.

Multiple randomized trials have been published evaluating the efficacy and toxicity of WAI in patients with early-stage ovarian cancer (see Table 61-2). Early studies established the inadequacy of treating the pelvis alone in patients with no gross residual disease.[113,115,116]

A trial from the Princess Margaret Hospital randomized 147 women with stages I to III disease comparing WAI and pelvic RT to pelvic RT alone or in combination with chlorambucil.[113] After a 7-year follow-up, the 10-year OS difference was significantly higher in the 76 patients treated with pelvic and WAI in comparison to the 71 patients treated with pelvic RT and chlorambucil (46% versus 31%, $p = 0.05$). The survival benefit was present only in patients with no gross residual disease or small volume pelvic residuum (<2 cm).

Hreshchyshyn et al[117] published a randomized trial of 86 patients who were clinical stage I (not surgically staged) randomized to pelvic RT, melphalan, or no additional treatment. They did not find a survival difference between observation and pelvic RT but did find a benefit for melphalan.

Several studies have compared chemo to RT, although only one incorporated a cisplatin-based regimen.[110,114,118,119] As previously noted, the NCIC randomized 257 women with stage I, IIA high-risk ovarian cancer, or stage IIB, and stage III to one of three trial arms: whole-abdomen/pelvic RT, melphalan, or ^{32}P.[110] No significant difference in survival was found. Smith et al[97] randomly assigned 149 patients with early-stage ovarian cancer to postoperative whole-abdomen/pelvic RT or melphalan. No survival difference was found between the groups.

The Northwest Oncologic Cooperative Group of Italy (NOCGI) conducted the only prospective randomized trial[119] in women with high-risk early-stage (stage I or II) ovarian cancer, comparing WAI with a cisplatin-based regimen. It was not completed. They randomized 70 women to cisplatin 50 mg/m^2 and cyclophosphamide 600 mg/m^2 or to WAI in an open technique, consisting of 43.2 Gy/24 fractions to the pelvis and 30.2 Gy to the upper abdomen. The study was closed early owing to multiple protocol violations (63% of patients were treated with chemo) and low accrual. With a median follow-up of 60 months, the 5-year OS was 71% for the cisplatin and cyclophosphamide arm and 53% for the WAI arm ($p = 0.16$). Although toxicity was well tolerated in the chemo arm of the study, in the WAI arm 28% of patients suffered from grade-3 to grade-4 acute diarrhea, two had severe enteritis requiring hospitalization, and one had late bowel obstruction requiring surgery.

In 1996, the GOG initiated a prospective randomized trial comparing WAI with platinum-based chemotherapy. Unfortunately the trial was not completed because of low accrual rates.

In the majority of studies looking at the efficacy of RT, all epithelial malignancies were included. There is some suggestion that certain histologic subtypes might benefit from the use of RT. Clear cell carcinomas particularly are typically chemotherapy resistant. Small studies have been conducted. Nagai et al[105] compared adjuvant platinum-based chemo to adjuvant WAI alone in 28 women with stages I to III ovarian clear cell carcinoma. Five-year OS and DFS in the RT arm were 81.8% and 81.2% versus 33.3% and 25% in the chemo arm ($p = 0.031$, $p = 0.006$), respectively. Locoregional control was also considerably improved with adjuvant RT. Only 1 of the 16 patients receiving RT had an isolated locoregional recurrence versus 7 who had locoregional recurrences in the 12 patients in the chemo arm. Dinniwell et al[104] performed a prospective, risk-stratified study of 29 patients with stages I to III epithelial ovarian cancer combining surgery, chemo, and adjuvant WAI. The subset of 11 patients with clear cell carcinoma and 5 with endometrioid histologies showed the greatest gains from this aggressive, multimodality approach, with a 4-year DFS of 77% compared with 27% for serous subtypes ($p = 0.01$). Finally, a retrospective but hypothesis generating study by Swenerton et al reported an improved survival in patients with stages I and II clear cell, endometrioid, and mucinous histotypes with the addition of adjuvant WAI to chemotherapy.[106] This group further published in 2012 a study on 241 stages I to II clear cell ovarian cancers comparing two groups; those treated with adjuvant chemo and RT and those treated with chemo only.[120] By physician choice, 211 were treated with chemo alone and 103 had the addition of pelvic and whole abdominal RT in a dose of 22.5 Gy to the pelvis in 10 fractions, followed by 22.5 Gy in 22 fractions to the whole abdomen. Although the groups were not randomly assigned, the stage distribution was comparable between the groups. They found no benefit for radiation in patients with stages IA and IC (rupture alone); however, a PFS benefit of 20% at 5 years in patients with stage IC and stage II was observed. For patients wit stage IC disease (cytology positive or surface involvement) this represents a RR reduction of 49% in those treated with radiation in comparison to those treated with chemo alone. The hypothesis generated from this observation was that improved pelvic control translated into a lower rate of relapse in this patient population. At this point in time there is limited data however. Given that clear cell cancers often are pelvic confined and that they are chemo resistant, an innovative research approach might consider examining a combination of novel targeting agents and pelvic RT in nonserous subtypes.

The trials cited in this section have demonstrated that radiation is an effective adjuvant modality for specific patients with ovarian cancer. However, currently it is used rarely and platinum-based chemo is considered the preferred modality. The role of adjuvant RT in certain early-stage nonserous histologies should be investigated.

LOCALLY ADVANCED DISEASE AND PALLIATION

Advanced-Stage Disease

The majority of cases of epithelial ovarian cancer are diagnosed when the tumor has spread throughout the abdomen and pelvis. Exploratory laparotomy is performed for the purpose of diagnosis, staging, and treatment.

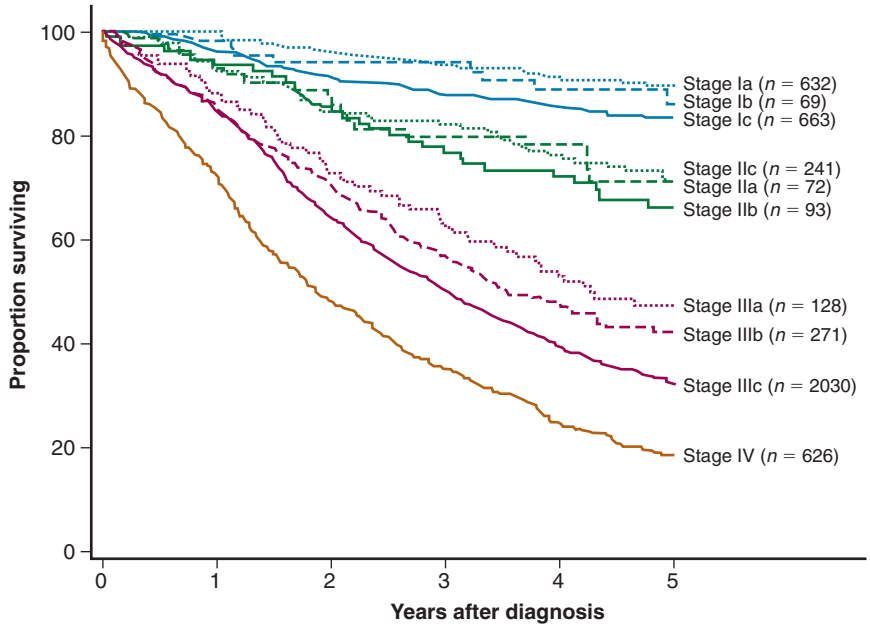
Epithelial ovarian cancer predominantly spreads throughout the peritoneal cavity and multiple masses are regularly

found at time of exploration. For most solid tumors, aggressive surgical resection is justified only if all known tumor can be excised; however, in ovarian cancer this is not the case. Cytoreductive surgery (known also as "debulking") is the standard. Munnell et al[121] were the first to introduce the concept of "maximum surgical effort" for ovarian cancer in 1968. They report on improved survival when patients had a maximum surgical effort in comparison to a biopsy or partial removal. Griffiths[122] was the first to show a significantly improved survival from this strategy in patients with residual disease less than 1.5 cm. Since then, "optimal debulking" has been defined as no tumor masses larger than 1 cm at the completion of surgery; however, the outcome is superior when there is no macroscopic residual.[123]

Hoskins et al reported on the effect of the maximum size of residual disease on the prognosis.[124] They found that among patients with suboptimal debulking (>1 cm residual disease), those with small-diameter residual disease (<2 cm) tended to survive longer than those who had larger residual disease. However, among those with larger residual disease, size did not affect prognosis appreciably. In 2006, Heintz et al[125] published an annual report on ovarian cancer. Five-year OS for the 2160 patients diagnosed with stage IIIC disease was 62.1% for no macroscopic, 32.9% for size less than 2 cm, and 24.8% for size greater than 2 cm. In concordance with the findings of Hoskins et al,[124] the most significant difference is between no macroscopic disease and any macroscopic residual disease (Figures 61-2 and 61-3).

These findings are important to guide management. Therefore, if disease cannot be cytoreduced to less than 2 cm, there is no survival advantage in proceeding with the debulking surgery, which can be a morbid procedure, especially if bowel resections, liver resections, and ostomies are added.

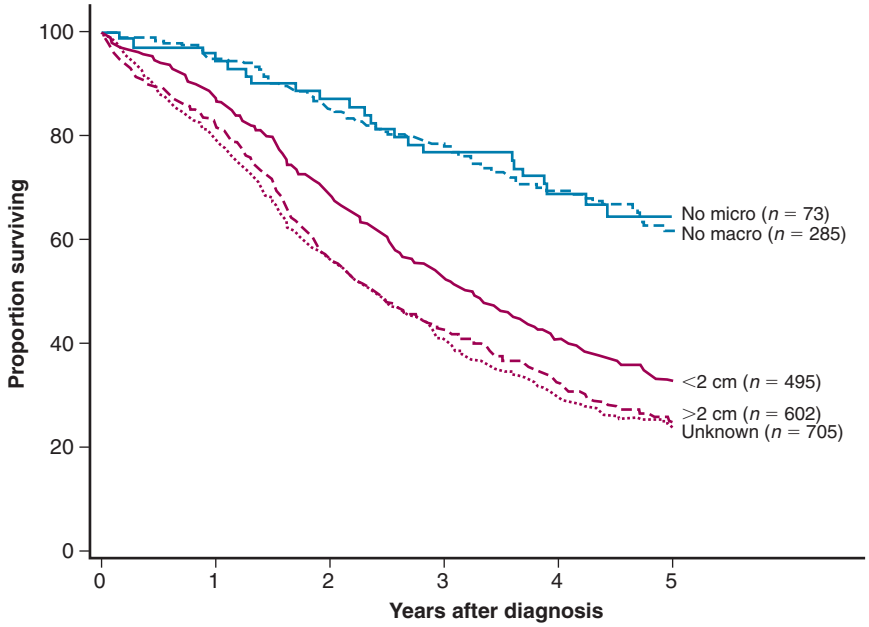
Patients presenting with stage IV disease have been included in most advanced ovarian cancer studies; precise data on their benefit from cytoreductive surgery are limited. Similar to the findings in stage III disease, retrospective studies have shown a statistically significant improvement in survival in cases in which optimal debulking is achieved.[126,127] Bristow et al[126] found optimal surgical debulking and performance status to be important determinants of survival. They showed that even in patients with unresectable liver metastasis,



Stage	Patients (*n*)	Mean age (yr)	Overall survival (%) 1-yr	2-yr	3-yr	4-yr	5-yr	Hazards ratio[a] (95% CI)
Ia	632	53.5	98.4	96.2	93.5	91.1	89.6	Reference
Ib	69	54.1	100.0	93.9	93.9	88.6	86.1	0.8 (0.4–1.6)
Ic	663	52.8	96.3	91.4	87.9	85.6	83.4	1.1 (0.8–1.4)
IIa	72	56.1	93.0	87.2	79.7	78.1	70.7	1.8 (1.1–3.0)
IIb	93	57.4	93.4	84.5	76.6	71.9	65.5	2.1 (1.4–3.1)
IIc	241	56.3	93.6	85.6	82.3	75.8	71.4	1.8 (1.4–2.5)
IIIa	128	57.1	88.1	72.6	63.1	52.8	46.7	4.0 (2.9–5.4)
IIIb	271	58.2	85.7	70.6	56.8	47.7	41.5	4.4 (3.4–5.7)
IIIc	2030	59.7	84.8	64.5	50.3	39.3	32.5	5.8 (4.7–7.0)
IV	626	60.4	72.4	48.4	35.2	24.8	18.6	8.9 (7.2–11.0)

[a]Hazards ratio and 95% confidence intervals obtained from a Cox model adjusted for age and country.

Figure 61-2 Stage and prognosis and residual disease and prognosis. Carcinoma of the ovary: patients treated from 1999 to 2001. Survival by FIGO stage, obviously malignant, *n* = 4825.
Data from Heintz AP, Odicino F, Maisonneuve P, et al: Carcinoma of the ovary. FIGO 6th annual report on the Results of Treatment in Gynecological Cancer. Int J Gynaecol Obstet 95(Suppl 1):S161–S192, 2006.



Residual disease	Patients (*n*)	Mean age (yr)	Overall survival (%) 1-yr	2-yr	3-yr	4-yr	5-yr	Hazards ratio[a] (95% CI)
No micro residual	73	55.8	94.4	87.1	76.8	68.6	63.5	Reference
No macro residual	285	56.3	95.0	85.0	77.9	69.3	62.1	1.0 (0.6–1.6)
≤2 cm	495	58.9	86.8	68.7	52.3	40.8	32.9	2.3 (1.5–3.5)
>2 cm	602	60.6	82.0	56.4	42.6	32.0	24.8	3.0 (1.9–4.5)
Unknown	705	61.1	79.6	56.3	40.7	29.3	24.1	2.9 (1.9–4.5)

[a]Hazards ratio and 95% confidence intervals obtained from a Cox model adjusted for age, stage and country.

Figure 61-3 Carcinoma of the ovary: Patients treated from 1999 to 2001. Survival in patients with stage IIIc disease by completeness of surgery, *n* = 2160.
Data from Heintz AP, Odicino F, Maisonneuve P, et al: Carcinoma of the ovary. FIGO 6th annual report on the Results of Treatment in Gynecological Cancer. Int J Gynaecol Obstet 95(Suppl 1):S161–S192, 2006.

optimal debulking of extrahepatic disease is associated with a significant survival advantage.

The success rate for optimal debulking varies widely between studies, from 20% to 85%.[128-130] This can be attributed to many factors, including the definition of optimal debulking, the expertise of the surgeon, the patient population (the percent of patients deemed unresectable before a surgical attempt), and probably the biology of the disease.

Because many patients cannot be optimally debulked initially, or the procedure needed to accomplish this is associated with a high risk of significant morbidity, neoadjuvant chemo to accomplish debulking has been introduced and studied. Several retrospective studies have reported survival results of patients treated with neoadjuvant chemo followed by interval debulking to be the same as for patients treated with primary debulking surgery.[131-134]

In the 1980s the European Organization for Research and Treatment of Cancer (EORTC) and the GOG (protocol 152) initiated two randomized trials to investigate the role of interval debulking in cases in which optimal debulking cannot be achieved at primary surgery.[135,136] The EORTC study included 278 women with suboptimally debulked disease (>1 cm residuum, FIGO stages IIB to IV). After completing three cycles of chemo (cisplatin-cyclophosphamide), the patients were randomized to an additional three cycles of chemo or to interval debulking followed by three more cycles of chemotherapy. The 2-year PFS and OS were significantly higher in the interval-debulking arm (OS, 56% versus 46%, $p = 0.01$). The difference in median OS was 6 months. After adjusting for other prognostic factors, interval debulking reduced the risk of death by 33%. GOG protocol 152 randomized 425 suboptimally debulked patients (>1 cm residual disease) who received three cycles of paclitaxel and cisplatin plus interval debulking (followed by three additional cycles of chemo) or three further cycles of chemo without surgery.[136] The median survival and PFS of the two groups was similar (32 versus 33 months and 10.5 versus 10.8 months, respectively). Their conclusion was that women who underwent an initial maximal but suboptimal debulking procedure did not benefit from interval debulking surgery. One of the main differences between the trials was that the initial surgery in protocol 152 was required to be appropriate ovarian cancer surgery (the majority performed by a gynecologic oncologist), whereas in the EORTC trial many of the patients had a minimal surgical effort at primary surgery by a general gynecologist. The majority consensus from these two studies is that debulking surgery should be performed by a gynecologic oncologist.[137]

Bristow and Chi[134] performed a meta-analysis including 22 studies. They concluded that neoadjuvant chemo is correlated with a worse prognosis than primary debulking surgery. The EORTC in collaboration with the NCIC in 2010 published the results of a prospective randomized trial including 718 patients with stages IIIC to IV ovarian cancer randomized to primary debulking surgery and six cycles of postoperative chemo or

to three cycles of neoadjuvant chemo followed by interval debulking and an additional three cycles of chemotherapy.[138] The results show a HR for death (intention-to-treat analysis) of 0.98 (90% CI, 0.84 to 1.13; $p = 0.01$ for noninferiority), and the HR for progressive disease of 1.01 (90% CI, 0.89 to 1.15) with a median PFS of 12 months in both groups. Complete resection of all macroscopic disease at surgery was the strongest independent variable in predicting OS. Importantly significant reduction in surgical complications in the interval debulking arm, including postoperative deaths (2.5% versus 0.7%), was noted. The results of this multiinstitution, multinational trial were not universally accepted. The rate of complete cytoreduction at primary surgery was low (19.4%) and remarkably variable with a range of 3.9% to 62.9%. This suggests a lack of surgical expertise and begs the question of generalizability of the results to centers with high surgical standards. In addition the survival of patients who underwent primary debulking was considered modest in comparison to other previous publications of nonrandomized data. Hence, in advanced stage ovarian cancer the decision between neoadjuvant chemo and interval debulking versus primary debulking surgery is still controversial.

Role of Chemotherapy

Surgery alone is not curative for advanced-stage ovarian cancer as microscopic residual disease is inevitable. Epithelial ovarian cancer is highly chemosensitive; therefore, standard postoperative treatment is combination chemotherapy. Platinum compounds are the most active agents and are the foundation of treatment. Their first use was reported in a small trial in 1982, which suggested a possible benefit to the addition of cisplatin to cyclophosphamide.

In 1986, the GOG published a randomized trial of 440 patients with advanced-stage ovarian cancer, comparing cyclophosphamide and doxorubicin with or without cisplatin.[139] The clinical complete response rate was 26% for cyclophosphamide and doxorubicin and 51% for the combination of cyclophosphamide, doxorubicin, and cisplatin ($p = 0.0001$). A survival benefit was seen for the platinum-based regimen in patients with measurable disease (median OS, 19.7 versus 15.7 months, $p < 0.03$), although not for patients without measurable disease. This and other trials lead to the use of platinum-based combination regimens as the standard of care. One of the important advances made in chemotherapeutic treatment of advanced ovarian cancer is the incorporation of the taxane, paclitaxel, into combination regimens. The GOG performed a randomized trial (protocol 111) comparing therapy with cisplatin and paclitaxel to that with cisplatin and cyclophosphamide.[140] Three hundred eighty-six suboptimally debulked (residual tumor > 1 cm) patients were randomized. Of the 216 with measurable disease, a superior response rate and survival was found for the cisplatin-paclitaxel trial arm (73% versus 60%, $p = 0.01$ and median OS, 38 versus 24 months, $p < 0.001$), respectively. The EORTC-NCIC performed an intergroup trial (OV-10) recruiting 680 women with broader inclusion criteria.[141] They included patients with stages IIB and IIC disease and optimal residuum and allowed for interval debulking. The overall response rate, PFS, and OS were statistically improved in the cisplatin-paclitaxel trial arm with median prolongation in OS of 10 months (35.6 versus 25.8 months, $p = 0.0016$). After the publication of these two Phase III randomized trials, the use of cisplatin-paclitaxel was established as the new standard of care.

Carboplatin, a second-generation platinum-based agent, is less nephrotoxic, neurotoxic, ototoxic, and emetogenic in comparison with cisplatin, although it is associated with a higher degree of myelosuppression, primarily thrombocytopenia.[142-144] Because of its renal excretion, patients with impaired renal function require individualized dose adjustment.[142] Multiple studies have shown equivalent efficacy between cisplatin and carboplatin and less toxicity for the latter. A meta-analysis of 12 randomized trials, including 2219 patients and 1745 deaths, confirmed this whether given as a single-agent or in combination regimens.[143]

The GOG performed a Phase III, noninferiority trial (protocol 158) of 792 women with small-volume stage III disease comparing cisplatin-paclitaxel and carboplatin-paclitaxel.[144] Median OS was 48.7 months for patients receiving cisplatin-paclitaxel arm compared with 57.4 months for those with carboplatin. The RR of death was 0.84 (95% CI = 0.70 to 1.02) for the carboplatin plus paclitaxel group. The GOG concluded that carboplatin plus paclitaxel resulted in less toxicity (gastrointestinal, renal, and grade-4 leukopenia) and was not inferior when compared with cisplatin plus paclitaxel. Combined therapy with carboplatin and paclitaxel is now considered the standard for first-line care of epithelial ovarian cancer.

The Gynecologic Cancer Intergroup (GCIG) evaluated the benefits of incorporating an additional cytotoxic drug or doublet with carboplatin-paclitaxel.[145] Women with stages III and IV epithelial ovarian cancer ($n = 4312$) were randomized to one of five trial arms (incorporating gemcitabine, liposomal doxorubicin, and topotecan) and compared to carboplatin-paclitaxel. There were no improvements in PFS or OS for the experimental regimens. Thus, the addition of these specific third chemotherapeutic drugs to the carboplatin-paclitaxel combination is not indicated.

Dose intensity of platinum regimens has been evaluated in numerous studies of different regimens.[146-148] There appears little evidence to support increased dose intensity of cisplatin and cyclophosphamide in regimens for advanced-stage epithelial ovarian cancer.[146] In 2009 Katsumata et al reported on a Phase III randomized controlled open label trial (JGOG 3016) of 637 patients with stages II to IV ovarian, fallopian tube or primary peritoneal cancer comparing a conventional regimen of six cycles of paclitaxel (180 mg/m^2; 3-hour IV infusion) plus carboplatin (AUC 6), given every 21-days to a dose-dense paclitaxel regimen (80 mg/m^2; 1-hour IV infusion) given on days 1, 8, and 15 plus carboplatin given on day 1 of a 21-day cycle.[149] They demonstrated a statistically significant improvement in median PFS (28 versus 17.2 months; HR, 0.71; 95% CI, 0.58 to 0.88) and 3-year OS (72.1% versus 65.1%; HR, 0.75; 95% CI, 0.57 to 0.98) for those who received the dose-dense regimen. Furthermore, in a subsequent publication looking at long-term results at a median follow-up of 6.5 years they reported a median OS of 100.5 months in the dose-dense treatment group and 62.2 months in the conventional treatment group (HR, 0.79; 95% CI, 0.63 to 0.99; $p = 0.039$).[150] Two large confirmatory trials of dose dense paclitaxel are under way: GOG 262 has completed accrual and results should be available soon and ICON8 completed accrual in the fall of 2014.

IP chemo has been evaluated in three large Phase III randomized trials.[151-153] Alberts et al published in 1996, a Phase III trial of IP cisplatin and IV cyclophosphamide compared with IV cisplatin and IV cyclophosphamide in 546 women with stage III optimally debulked (residual disease <2 cm) ovarian cancer.[152] Outcomes were improved for the IP arm and had less toxicity. However, because cyclophosphamide was no longer a standard regimen, additional studies were required to determine if the advantage was related to the route of administration when regimens incorporating paclitaxel were given.

In 2006, the GOG published a Phase III randomized trial (protocol 172) comparing IP cisplatin and paclitaxel compared with IV cisplatin and paclitaxel.[153] The median OS was found to be 49.7 months in the IV chemo arm and 65.6 months in the IP arm ($p = 0.03$). However, only 42% of patients allocated to

IP chemo completed all six IP cycles (primarily because of catheter-related issues and toxicity), in comparison to 83% allocated to IV chemotherapy. All patients who could not complete treatment in the allocated trial arm were switched to intravenous carboplatin. Quality of life was found to be significantly worse in the IP trial arm up to 6 weeks after treatment but returned to being equivalent to the IV arm 1 year after treatment.[154]

A systemic review of IP chemo identified seven randomized trials: three large Phase III trials and four smaller randomized trials.[155] All three large trials detected a statistically significant benefit in OS with IP cisplatin-based chemotherapy. A pooled analysis of six of the trials confirmed a survival benefit with IP cisplatin-based chemo (RR, 0.88; 95% CI, 0.81 to 0.95). Significant adverse effects including catheter-related complications were more common in the IP group.

In 2006 the U.S. National Cancer Institute (NCI) issued a clinical announcement advocating the use of IP chemo in the treatment of women with optimally debulked ovarian cancer.[156] Although the trials of IP chemo show a survival advantage, the incorporation of IP therapy into general practice is low. The reasons for the reluctance of practitioners include the high level of toxicity associated with the specific regimens showing benefit, the technical difficulties in delivery of the treatment, particularly the necessity for catheter placement and management, and the fact that no trial to date has compared IP chemo with the standard IV carboplatin-paclitaxel. Those using IP chemotherapy usually use lower doses than those reported in the positive trials. The GOG is currently performing trials of IP carboplatin-paclitaxel.

The majority of patients with ovarian cancer enter a state of remission on completion of surgery and postoperative chemotherapy. However, approximately 85% of patients in remission ultimately experience relapse; therefore, maintenance therapy has been proposed and investigated.

A GOG study (GOG 178) evaluated the efficacy of 12 versus 3 cycles of maintenance paclitaxel in patients who achieved a complete response to primary chemotherapy.[157] Because of an improvement in PFS with 12 cycles on an interim analysis (28 months versus 21 months, $p = 0.035$), the trial was closed. It was recommended that all participants then receive 12 cycles of paclitaxel. The difference in PFS did not translate into an OS benefit (median OS 53 versus 48 months for patients who received 12 versus 3 cycles of maintenance paclitaxel [$p = 0.34$]).[158] The proposed explanations behind the improved PFS without an improved OS include the high efficacy of treatment at relapse, crossover into the 12-cycle arm, and an insufficient sample size.

Currently, maintenance therapy with conventional antineoplastic agents is not recommended.

Molecular Targeting Agents

Molecular-targeted therapies have become the frontline of cancer research in many tumor sites and their investigation in ovarian cancer has evolved in the last 5 years. Two Phase III trials (GOG-0218 and ICON7) have evaluated the role of bevacizumab as concomitant and maintenance therapy in first-line therapy for ovarian, fallopian tube, and primary peritoneal cancers following surgical cytoreduction.[159,160] GOG 218, a double-blind, placebo-controlled Phase III randomized trial of 1873 stage III (incompletely resectable) or patients with stage IV ovarian cancer randomized to one of three arms; standard chemotherapy with placebo from cycles 2 through 22, standard chemotherapy with bevacizumab (15 mg/kg of body weight) from cycles 2 through 22 and standard chemotherapy with bevacizumab from cycles 2 through 6 and then placebo during cycles 7 through 22.[159] No difference in PFS was found between the control group and the arm treated with concomitant bevacizumab; however, a statistically significant increase in PFS was found between the control arm and the treatment arm of maintenance bevacizumab (10.3 months versus 14.1 months), with a HR of progression or death of 0.717 (95% CI, 0.625 to 0.824). No OS or quality-of-life differences were found between the three arms. Hypertension grade-2 or greater was more common with bevacizumab than with the placebo in a cost effectiveness evaluation by GOG. Because of the high drug cost, bevacizumab was not cost effective.[161] ICON7, a double-blind, placebo-controlled Phase II study, randomly assigned 1528 women after initial surgery to standard chemotherapy plus placebo or standard chemotherapy and bevacizumab (7.5 mg/kg for 6 cycles), followed by bevacizumab alone for an additional 12 cycles. The patient population in ICON7 differed from GOG 218 and included patients with early (9%) and advanced stage (70% had stage IIIC or IV) disease; 9% of patients had early-stage and 26% had residual tumor larger than 1 cm at completion of surgery. Median PFS was 17.3 months in the control group and 19 months in the group receiving bevacizumab. HR for progression or death in the bevacizumab group was 0.81 (95% CI, 0.70 to 0.94). There were more side effects in the bevacizumab arm including hypertension, thromboembolic events, and gastrointestinal perforations; however, no difference in quality of life was found. Both trials showed a modest increase in PFS with maintenance bevacizumab but no difference in OS or quality of life.

Additional molecular targeted treatments are currently under development for specific populations including a Phase III trial of maintenance poly ADP ribose polymerase (PARP) inhibitor in *BRCA* mutation carriers. The role of various novel molecular-targeted therapies in the adjuvant and the recurrent setting is an important question that needs to be addressed in the next decade. Careful cost-effective and patient-reported outcomes need to be incorporated into trial designs.

Role of Radiation Therapy

The role of "consolidation" RT in ovarian cancer as sequential to surgery and chemotherapy is controversial. Several publications have addressed the benefit of RT in multiple scenarios, although the limitations of the studies have made definitive conclusions difficult. Dembo et al[113] previously showed that WAI is an effective treatment of small residual tumor (<2 cm); therefore it seemed reasonable to suggest that there could be a benefit from administering WAI for consolidative treatment. In 1982 Fuks et al[162] proposed a new paradigm of treatment for stage III ovarian cancer, including initial surgery followed by aggressive combination chemotherapy, second-look laparotomy (to include cytoreduction), followed by WAI.

Several Phase III studies have since evaluated the efficacy of this multimodality treatment paradigm in comparison to postoperative extended chemotherapy (Table 61-3). Bruzzone et al[163] randomized 41 patients with no or minimal disease (<2 cm) at second-look laparotomy to an additional three cycles of platinum-based chemotherapy or WAI (total dose was 43.2 Gy/24 fractions to the pelvis and 30.2 Gy to the upper abdomen). Median survival and PFS were found to be 24 months and 16 months, respectively, in the patients in the RT arm of the study. In the chemotherapy arm, median survival and PFS were not reached at the time of publication. The trial was closed early owing to the superior survival of the patients treated with chemotherapy. In 1993 the North Thames Ovary Group study (NTOG)[164] randomized 117 patients with advanced ovarian cancer (stages IIB to IV) who had received postoperative carboplatin and were found to have minimal residual disease at second-look laparotomy to an additional five courses of carboplatin or WAI (24 Gy). No statistical difference was found in either DFS or OS between the groups.

TABLE 61-3 Randomized Trials of Consolidative WAI or ^{32}P

Trial/Author	Stage	Study Design	No. Patients	5-Year Overall Survival (%)	Bowel Obstruction
West Midlands/Lawton[165]	IIB residual, III, IV	WAI Chlorambucil	56 53	7 8	9%
Italy/Bruzzone[163]	III, IV minimal residual disease	WAI Chemotherapy	20 21	45 (3-year) 85 (3-year)	5%
NTOG/Lambert[164]	IIB-IV <2 cm residual disease	WAI Carboplatin	58 59	25 30	1.7%
Sweden-Norway/Sorbe[166]	III	WAI Cisplatin + doxorubicin/epirubicin Observation	32 35 31	56 (PFS) 36 (PFS) 36 (PFS)	10%
Germany/Pickel[167]	IC-IV no clinical disease	WAI Observation	32 32	59 33	3.1%
NRH/Vergote[168]	IAG2-3, IB, III	^{32}P Observation	25 25	95 (PFS) 82 (PFS)	4%
GOG 93/Varia[169]	III	^{32}P Observation	104 98	67 63	2.9%

PFS, *Progression-free survival;* WAI, *whole abdomen irradiation.*

Additional studies have shown mixed results when estimating a survival benefit for consolidation WAI.[165,170] Thomas[171] published a review in 1993 on the role for consolidation or salvage RT in advanced epithelial ovarian cancer. Twenty-eight studies with 713 patients were included. Overall, the evidence did not support an incremental curative benefit for WAI; however, because of the diverse inclusion criteria and the limited amount of patients in each trial, a decisive conclusion could not be made.

Two randomized trials published subsequent to this review have shown relatively optimistic results.[166,167] Pickel et al[167] performed a randomized study of 64 patients with stages IC to IV disease but without evidence of clinical disease after comprehensive surgical staging and platinum-based chemotherapy comparing WAI versus no further treatment. The 5-year DFS and OS of the patients who received WAI was significantly higher than those who were observed (49% versus 26%, $p = 0.13$, and 59% versus 33%, $p = 0.029$, respectively). This benefit was more obvious in patients with stage III disease (5-year OS, 59% versus 26%, $p = 0.012$). In 2003, group collaboration from Sweden and Norway published a randomized trial comparing consolidation treatment with RT or chemotherapy versus observation in 172 patients with stage III disease who underwent cytoreductive surgery and four cycles of platinum-based chemotherapy followed by second-look surgery.[166] Only patients with no macroscopic disease were included; patients with microscopic disease were randomized to chemotherapy or WAI, and patients with no microscopic disease were randomized to chemotherapy, WAI, or observation. Consolidation RT was a significant ($p = 0.050$) prognostic factor with regard to PFS in the subgroup with complete pathologic remission. In the subgroup with microscopic residual carcinoma, no differential benefit for RT or chemotherapy was observed. Late complications in the RT arm included four cases as grade 1 (diarrhea) and seven cases (10%) as grade 3 (intestinal obstruction).

Consolidative Intraperitoneal Radioactive Chromic Phosphate Suspension (^{32}P)

The role of ^{32}P as consolidative treatment after surgery and chemotherapy in advanced-stage ovarian cancer has been evaluated in several studies (see Table 61-3). The largest retrospective study from the University of North Carolina evaluated ^{32}P in 51 women with stages I to III disease.[172] They treated patients with no evidence of disease on second-look laparotomy with 15 mCi of ^{32}P. These patients were compared with 18 patients who had a negative second-look laparotomy but did not receive ^{32}P because of peritoneal adhesions, other protocols, or physicians' preference; with 15 who did not receive any additional treatment; and with 3 who received additional chemotherapy. After a median follow-up of 58 months, both an improved 5-year PFS (86% versus 67%, $p = 0.05$) and a 5-year OS (90% versus 78%) were noted in the ^{32}P group.

Two randomized trials of ^{32}P have been published.[168,169] The first was performed at the Norwegian Radium Hospital in which 50 patients with stage IA high-grade and stages IB to III disease were randomized after a negative second-look laparotomy to ^{32}P or no further treatment.[168] No significant survival difference was found between the groups; however, ^{32}P was associated with a considerable number of bowel complications. In 2003 the GOG (protocol 93) reported on a prospective randomized trial of 202 patients with stage III disease with a negative second-look laparotomy who were allocated to 15 mCi of ^{32}P or no further treatment.[169] After a median follow-up of 63 months, 5-year OS was 67% and 63% for IP ^{32}P and no further treatment groups, respectively. No significant difference in PFS or OS was found between the study arms. Three patients in the ^{32}P arm required surgery because of bowel obstruction. Thus, the data do not support the use of ^{32}P for consolidative treatment in ovarian cancer.

Recurrent Ovarian Cancer

Approximately 85% of patients with epithelial ovarian cancer will experience relapse. Recurrent or persistent ovarian cancer after first-line therapy is almost always incurable. The majority of the relapses (85%) are in the abdomen alone. Bowel symptoms are common. Treatment is generally aimed at prolonging symptom-free survival and palliating symptoms.

Patients with recurrent ovarian cancer are categorized by their "platinum sensitivity," which is primarily defined by the length of the treatment-free interval. Patients whose disease progresses during therapy or who experience a relapse less than 6 months from the completion of treatment are generally referred to as "platinum resistant," and their response rates and survival tend to be low and short. Patients presenting with early relapse are considered for second-line chemo

regimens or clinical trials. Many second-line chemo agents have been evaluated (liposomal doxorubicin, gemcitabine, topotecan, paclitaxel, and others), with response rates on the order of 10% to 15%.[173-176] In these patients, the median PFS is 3 months to 4 months and the median OS is 9 months to 12 months. Preliminary results of AURELIA, the first Phase III randomized trial of chemo with or without bevacizumab in patients with recurrent platinum-resistant ovarian cancer were presented in 2012.[177] The standard chemo group had an expected 12.6% response rate, whereas the response rate in the bevacizumab arm was significantly improved when measured by CA125 levels or RECIST criteria. Median PFS was 3.4 months in the control arm and 6.7 months in the bevicizumab arm ($p < 0.001$). The final results are pending. Other molecular targeting agents continue to be explored in recurrent, platinum-resistant disease. Because the chance of a meaningful disease-free interval is low, quality of life, treatment-related toxicity, and the patient's wishes are important issues to consider. Palliative RT to localized symptomatic masses produces high response rates even in chemoresistant disease.[178-181]

Patients who experience late relapse (i.e., more than 6 months from the completion of the initial chemo) are referred to as "platinum sensitive," and the probability of having a prolonged progression-free interval is good. The longer the initial treatment-free interval, the higher is the chance of response to second-line chemo, and probability of obtaining a meaningful disease-free interval.[182,183] Second-line chemo is usually retreatment with a platinum-based regimen. The estimated response rate is 30% to 70%.[184-186] Combination second-line chemo versus single-agent platinum has been compared in several studies.[184,185,187] ICON4/AGO-OVAR, a combined analysis of two parallel studies including 804 patients who were platinum-sensitive, compared carboplatin-paclitaxel to "conventional platinum-based chemotherapy" (single-agent carboplatin in the majority).[185] The median OS benefit for the combination was 5 months (29 months versus 24 months). CALYPSO, a randomized Phase III trial comparing pegylated liposomal doxorubicin (PLD) and carboplatin versus paclitaxel and carboplatin in patients who were "platinum-sensitive" with recurrent disease enrolled 976 people.[188] The trial, designed as a noninferiority study found PLD-carboplatin to have a superior PFS (11.3 months versus 9.4 months, HR, 0.821; CI 95%, 0.72 to 0.94) and had a superior toxicity profile including lower rates of severe and long-lasting neuropathy. The final results showed comparable median OS of PLD-carboplatin (30.4 months) and paclitaxel-carboplatin (33 months) (HR, 0.99; 95% CI, 0.85 to 1.16).[188]

Additional studies comparing platinum to platinum and gemcitabine or to platinum and epirubicin have all showed a superior response rate for the combination regimens.[189,190] Thus, the preferred regimen is platinum-based combination chemotherapy with a current recommendation for carboplatin-paclitaxel or PLD-carboplatin.

Molecular-targeting therapies have evolved as an important part of treatment in the recurrent setting. In 2012 the Ovarian Cancer Study Comparing Efficacy and Safety of Chemotherapy and Anti-Angiogenic Therapy in Platinum-Sensitive Recurrent Diseases (OCEANS) trial assessed the role of bevacizumab in the treatment of platinum-sensitive relapses.[191] This placebo-controlled, Phase III trial of chemotherapy (gemcitabine + carboplatin) with or without bevacizumab enrolled 242 patients with recurrent ovarian, primary peritoneal, or fallopian tube cancer. Median PFS was 12.4 months versus 8.4 months respectively in the bevacizumab and control arms. (HR progression, 0.484; 95% CI, 0.388 to 0.605). Bevacizumab-associated toxicities including hypertension were noted, but there were no cases of gastrointestinal perforations.

Additional studies are also exploring PARP inhibition specifically in women with *BRCA* mutations. Final results of a GOG Phase II study are pending (GOG 208). Initial results of 48 patients show 7% had a response; 21 were still receiving study drug.[192] Currently, a Phase III trial assessing the role of PARP inhibitors in *BRCA* carriers in the recurrent setting is open to recruitment.

Patients who do not respond to second-line carboplatin-paclitaxel are considered platinum resistant and have a low probability of responding to alternative regimens. Response rates to third-line chemotherapy including liposomal doxorubicin, topotecan, oral etoposide, and gemcitabine are 15% to 25%.[174,176,193,194]

Salvage WAI for ovarian cancer has also been reported. Sedlacek et al[195] evaluated WAI in 27 patients with recurrent ovarian cancer. Their treatment protocol included 30 Gy to 35 Gy, followed by a pelvic boost. OS at 1 and 5 years was 66% and 15%, respectively.

Secondary Cytoreductive Surgery for Disease Relapse

Technically, secondary debulking can be performed in 25% to 85% of patients.[196-198] It is commonly considered most likely to benefit patients with late relapse and resectable tumor, but the likelihood for and benefits of successful secondary debulking are not understood. Its intent is to remove recurrent tumor and thereby prolong the disease-free interval and survival.

Successful secondary debulking is limited. The Arbeitsgemeinschaft Gynaekologische Onkologie (AGO) DESKTOP OVAR trial is the largest series ($n = 267$ patients) published on the benefit of secondary cytoreductive surgery for recurrent ovarian cancer.[199] Complete resection was associated with significantly longer survival compared with surgery leaving any postoperative residuum (median 45.2 versus 19.7 months; $p < 0.0001$). Variables associated with complete resection were performance status, stage, residual tumor after primary surgery, and absence of ascites of more than 500 mL. An optimal resection was achieved in 79% of patients with all favorable prognostic factors. The EORTC attempted a randomized trial to evaluate the benefit of cytoreductive surgery in recurrent ovarian cancer, but it was closed because of poor accrual. A review of 17 publications of secondary cytoreductive surgery by Hauspy and Covens[200] concluded that patients with favorable characteristic (good performance status, long disease-free interval, and a single or few small intraabdominal sites of relapse) are the ideal candidates that may benefit from secondary cytoreductive surgery.

The most common site of relapse in ovarian cancer is IP with ascites and masses. Bowel complications frequently occur before general deterioration is profound. Comprehensive palliative care is required for all such patients. Partial bowel obstruction is treated conservatively with intestinal decompression and IV hydration. If bowel obstruction is complete or if conservative measures fail, palliative surgery performed to relieve bowel complications may be considered. In patients with an impaired performance status, extensive disease, and limited life expectancy, including multiple levels of obstruction, palliative measures without surgical intervention should be considered.

Intraoperative Irradiation for Locoregional Relapse

In patients with recurrent ovarian cancer localized in the pelvic sidewalls or paraaortic or pelvic lymph nodes, the use of aggressive surgery and intraoperative irradiation (IORT) alone or plus external beam irradiation (EBRT), appears beneficial when compared with "standard" EBRT salvage. Excellent results have been found in IORT series from both Mayo Clinic Rochester[201,202] and Stanford University.[203]

The Mayo Clinic Rochester (MCR) electron beam IORT (IOERT) series of 148 patients with gynecologic cancer included 16 with recurrent ovarian cancer.[201,202] In this highly select group of patients, 2-year OS was 61% and 5-year OS 54%. In an updated MCR analysis,[197] 20 patients with recurrent ovarian cancer received IOERT as a component of treatment and 16 of 20 also received perioperative EBRT (median 50 Gy, range 20 Gy to 54 Gy). With median follow-up of 76 months in surviving patients, 5-year OS was 49%.

Twenty-four patients had maximal resection of recurrent ovarian cancer followed by orthovoltage IORT at Stanford University, and 22 were evaluable for analysis.[203] Most had cytoreductive surgery plus chemotherapy at initial diagnosis; the mean disease-free interval was 48.2 months before resection or IORT. After maximal resection, residual disease was either microscopic (R1) or less than 0.5 cm (R2). The median IORT dose was 12 Gy (range, 9 Gy to 14 Gy). Postoperative EBRT (14 patients) or chemotherapy (6 patients) was given to 20 of 22 patients and was individualized based on sites of relapse and prior therapy (EBRT: abdominal/pelvic, 9; pelvic, 4; inguinal, 1). With median follow-up of 24 months, 5 patients remained free of disease. The 5-year OS was 22%, with a median survival of 26 months from the time of IORT.

Palliative Radiation Therapy

Palliative RT in ovarian cancer is effective in patients with symptoms because of localized disease. It is often a forgotten or ignored modality. In cases of vaginal bleeding, localized pain resulting from masses in the abdomen or retroperitoneum, or disseminated disease (e.g., brain metastases, supraclavicular nodes), RT can induce tumor regression and provide symptomatic relief.[180] Investigators from M. D. Anderson Cancer Center published a 55% response rate for pain palliation and 71% for vaginal bleeding with one to three fractions of 10 Gy.[181] However, 6 of 42 patients developed bowel radiation injury attributed to the large fraction size. A study from Fox Chase Cancer Center[204] reported the use of palliative RT in 33 patients with symptomatic ovarian cancer. Complete palliative response was noted in 51%, and the overall response rate was 79%. Vaginal bleeding and pain were controlled in 90% and 83% of patients, respectively. The median duration of palliation was 4 months, which reflected palliation until death in 90% of cases. In an additional study, from Memorial Sloan Kettering Cancer Center, the median duration of response was 11 months (range, 1 to 86) and closely approximated the survival rate. Additional studies show a similar benefit for palliative RT.[180,181,204,205] Recommendations on the optimal dose for palliation of soft-tissue masses are difficult to make because no comparative trials have been conducted and each center or oncologist uses different doses. No data support the common contention that palliation of symptoms or duration of symptom relief is greater with higher doses of radiation. However, it is obvious from the literature that RT is an effective modality in palliation for ovarian cancer even if the tumor is resistant to multiple lines of chemotherapy.

TREATMENT OF NONEPITHELIAL OVARIAN TUMORS

Ovarian Germ Cell Tumors

GCTs of the ovary are derived from the primordial germ cells of the ovary. They account for less than 5% of all ovarian malignancies and occur predominantly in young patients.[206] In the first two decades of life, GCTs account for two thirds of all ovarian malignancies and are rarely found in women older than the age of 30. The World Health Organization classification of GCTs includes dysgerminoma, yolk sac tumor, embryonal carcinoma, polyembryoma, nongestational choriocarcinoma, immature teratoma, and mixed GCTs. Dysgerminomas are the most common subtype, accounting for 40% to 50% of all GCTs. Immature teratomas and yolk sac tumors each comprise about 20%, and the other subtypes are extremely rare.

GCTs are rapidly growing tumors that frequently present as abdominal pain as a result of capsular distention, torsion, or hemorrhage or to menstrual irregularities. Physical examination and ultrasonography assist in making the diagnosis of an ovarian mass; differentiation between a benign and malignant mass can only be made by histology. Serum markers including β-human chorionic gonadotropin (β-hCG), lactate dehydrogenase (LDH), and α-fetoprotein (AFP) can be useful in helping to identify the presence of a GCT (eTable 61-1). Solid adnexal masses larger than 2 cm in premenarcheal girls or a growing mass with or without elevated tumor markers in menarcheal girls or young women is an indication for exploration. Ovarian GCTs (specifically gonadoblastoma and dysgerminoma) can be associated with dysgenetic gonads. Therefore, in premenarcheal girls with a gonadoblastoma or dysgerminoma, a karyotype should be obtained. Staging of GCTs is per the FIGO staging of epithelial ovarian cancer (see Table 61-1).

Because GCTs predominantly present in young women and are sensitive to postoperative chemo, fertility-sparing surgery is indicated even if the contralateral ovary is involved. The need for a staging procedure is controversial, particularly if adjuvant chemo will be recommended anyway. Many centers do consider careful inspection of the abdomen and pelvis by a trained gynecologic oncologist, with biopsy specimens taken from suspicious areas being adequate. Published recommendations for an appropriate staging procedure for ovarian GCTs[207] include peritoneal washings for cytology, a unilateral salpingo-oophorectomy, and biopsies of the omentum, contralateral ovary, and locoregional lymph nodes.[208] GCTs predominantly spread to retroperitoneal lymph nodes, in contrast to transcoelomic spread of epithelial ovarian cancer. A high proportion of the diagnoses are made after a gynecologist or general surgeon has performed surgery (usually unilateral salpingo-oophorectomy without staging). The value of reoperation is unclear. There is consensus that if observation without adjuvant therapy is adopted there is a need for close surveillance to detect and treat recurrence early. This includes frequent clinic visits and a combination of study of tumor markers and imaging.[208] The exact protocol differs among oncology centers.

Where there is no residual disease, the indication for and use of adjuvant chemo differs among oncology centers. The response to salvage chemo is good and survival rates appear comparable in many cases between those treated with adjuvant therapy versus treatment at the time of relapse. Serum tumor markers can assist in the early detection of recurrence in nondysgerminomas.[209]

Nondysgerminoma

The evolution of chemo for GCTs has been based on the successful treatment of similar histology and, more commonly, testicular GCTs. Initially, patients with advanced ovarian GCTs were treated with surgical debulking, followed by vincristine, dactinomycin, and cyclophosphamide chemotherapy (VAC regimen), with cure rates of approximately 50%.[210,211] As a result of the high cure rates achieved even in advanced testicular GCT using cisplatin, vinblastine, and bleomycin, the GOG evaluated a similar regimen in ovarian GCTs and noted a 70% 4-year OS.[211] Etoposide reduced toxicity and improved cure rates in testicular GCTs. Using three to four cycles of bleomycin, etoposide, and cisplatin (BEP regimen) led to its adoption as the standard regimen for ovarian GCTs, with a 79% to 83% PFS.[212,213] Patients who have no evidence of disease

eTABLE 61-1 Tumor Markers in Malignant Germ Cell Tumors of the Ovary

	AFP	β-hCG	LDH
Dysgerminoma	–	±	+
Immature teratoma	±	–	–
Yolk sac tumor	+	–	–
Choriocarcinoma	–	+	–
Embryonal carcinoma	±	+	–

AFP, *(α-fetoprotein);* β-hCG, *beta-human chorionic gonadotropin;* LDH, *lactate dehydrogenase.*

after surgical staging followed by three cycles of a BEP regimen can expect a 96% to 100% PFS.[208,214]

Most centers treat all tumors except stage IA grade-1 immature teratoma with postoperative chemotherapy. Recently, a large study of observation only for all stage IA GCTs showed a relapse rate of 36% for nondysgerminomatous tumors and 22% for dysgerminomas.[215] Relapse after observation has high salvage rates with the BEP regimen; all but 1 patient who experienced relapse was salvaged. As patients are young, and long-term risks from chemotherapy are relevant, a strong argument can be made for observation.

Disease relapse after primary chemo is treated primarily with second-line agents; infrequently, cure may require ablative regimens and bone marrow transplant. Palliative RT can be used in specific cases after chemo failure.

Dysgerminoma

Dysgerminoma, the most common of germ cell tumors, accounts for approximately 1% of all ovarian cancers. The majority occur between the ages of 10 and 30. Stage IA is the most common stage at diagnosis, representing 75% of all cases.[212] Ten percent may involve both ovaries. It predominantly spreads in an orderly progression to retroperitoneal lymph nodes, in contrast to the transcoelomic spread of epithelial ovarian cancer. LDH is a nonspecific tumor marker and is reported to be elevated in up to 95% of cases[209] β-hCG may be produced in low levels (<200 IU/L).

Young patients found to have stage IA dysgerminoma are usually treated with fertility-sparing surgery without adjuvant chemo or RT. Surveillance for clinical stage IA ovarian dysgerminoma is safe and effective in reducing unnecessary use of chemotherapy, with 10-year OS of 91% in the prechemo era, where relapse was commonly salvaged with RT, to which it is exquisitely sensitive.[216] Relapses usually occur within 2 years of diagnosis, and the relapse rate for stage IA is approximately 20%.[215]

Despite its radiosensitivity, extra-ovarian disease at diagnosis or relapse is usually treated with chemo because of the negative impact of RT on fertility. The BEP regimen and the EP regimen (etoposide/platinum) are the most common combination regimens used because they spare fertility; however, significant side effects do occur.[217,218] As all patients with an ovarian dysgerminoma are young, short- and long-term effects from chemo such as bleomycin-induced lung toxicity and secondary malignancies should be taken into consideration when deciding on treatment.[219-221]

Survival after diagnosis of ovarian dysgerminoma is good even when disseminated disease is found at time of diagnosis. The 5-year OS is higher than 90%.[222,223]

Immature Teratoma

Immature teratomas are composed of tissue that resembles embryonic elements, most commonly nervous system components, bone, cartilage, mucinous fluid, and hair, although any tissue may be seen. Microscopic examination reveals tissue from all three germ layers, with at least some of the components having an immature appearance. The majority of patients do not have an identified serum tumor marker; however, AFP can be elevated in cases with immature gastrointestinal elements.[224]

The treatment recommendation is an initial staging procedure for all patients; however, because most patients are only diagnosed after the final pathologic findings, reports of more limited surgery are common. Treatment decisions are commonly made based on pathology, imaging, and tumor markers.[225-227]

Immature teratomas are graded based on the amount of immature neural tissue they contain, and grade is correlated with prognosis. Norris et al,[228] in 1975, reported the prognosis of 58 patients with a pure immature teratoma treated with surgery: 16 patients were treated with RT or non–platinum-based chemotherapy either after surgery or at time of relapse. Survival of patients with grades 1, 2, and 3 were found to be 81%, 60%, and 30%, respectively. Patients with stage IA, grade-1 tumors can expect an excellent prognosis without the need for adjuvant chemo, and postoperative observation is recommended.

Yolk Sac Tumor (Endodermal Sinus Tumor)

Yolk sac tumors, also called endodermal sinus tumors, are derived from the primitive yolk sac. The majority of tumors secrete AFP, and there is a good correlation between the levels and the extent of disease.[209] Microscopically, Schiller-Duval bodies, a cystic space lined by endothelium with a central vascular area resembling a glomerulus, are characteristic. The median age at diagnosis is 17, with approximately one third of cases diagnosed in premenarcheal girls. Most patients present with stage I disease.[228]

Surgical treatment usually includes unilateral salpingo-oophorectomyas involvement of the contralateral ovary is rare. Although yolk sac tumors present at an early stage, the relapse rate is high. Therefore, some physicians advocate treating all patients with adjuvant chemotherapy.[229] Others believe it is reasonable to observe patients with stage I disease because AFP is elevated in the majority of cases and can be used as a serum tumor marker for early detection of relapse along with imaging. Serial AFP levels are used to monitor response to treatment.

Ovarian Sex Cord and Stromal Tumors

Sex cord and stromal tumors of the ovary account for approximately 5% of all ovarian malignancies. They can occur in patients of all ages, and a significant proportion is diagnosed in patients younger than 40 years old. The cells originate from the sex cords and mesenchyme of the embryonic gonad. Granulosa and Sertoli cells are derived from the sex cord cells; pleuripotential mesenchymal cells are the precursors of Leydig and theca cells, and fibroblasts. The most common type, granulosa cell tumors, constitutes 70% of all sex cord and stromal tumors.

Sex cord and stromal tumors have the ability to produce hormones, especially estrogen or testosterone. They account for 90% of all hormone-producing tumors. The presenting symptoms such as precocious puberty, virilization, or abnormal menstruation in the premenopausal age group or postmenopausal bleeding in the older group are the result of the hormonal elaboration from the tumor itself, or, in the majority of cases, as a result of a nonspecific stromal response in the ovarian tissue. Approximately 60%, of sex cord and stromal tumors, present as stage I.

Granulosa Cell Tumors

Granulosa cell tumors can occur at any age, with a peak in the fifth and sixth decades of life.[230] Two granulosa cell tumors have been separated into the adult type (95%) and juvenile type (5%) based on clinical and histologic characteristics. The main presenting symptoms are abnormal vaginal bleeding, abdominal pain, or distention. Tumors are frequently diagnosed at a large size, more than 10 cm in diameter. Because of the potential estrogen production of granulosa cell tumors, evaluation of the endometrium is important. Endometrial hyperplasia and cancer has been noted in up to 50% and 5% of patients, respectively, at diagnosis.[220] Microscopically, Call-Exner bodies (granulosa cells in rosettes around a central cavity resembling primordial follicles) can be seen. Granulosa

cell tumors spread by transcoelomic, lymphatic, and hematogenous routes, and metastases can develop in parenchymal organs (liver, brain, lungs). Inhibin is a tumor marker that is secreted by some granulosa cell tumors.[231]

The cornerstone of treatment is surgical resection. For women presenting at a young age, fertility-sparing surgery is an option after a negative endometrial biopsy. In a recent retrospective review[232] of 58 patients with sex cord and stromal tumors who underwent lymphadenectomy as part of their initial surgical procedure, none was found to have nodal involvement; thus, lymph node dissection seems unnecessary. Patients with granulosa cell tumors tend to experience relapse years after initial treatment. Because of late relapse, survival declines over decades; there is a significant difference between the 10-year and 20-year OS (90% and 50% to 75%, respectively).[233] In most stage IA cases, surgery alone is curative, although in patients with high-risk factors (large tumor size > 10 cm, tumor rupture, high mitotic index), adjuvant chemo may be considered, although its benefit is unproven.[234,235] Patients with disease spread outside the ovary (stages II to IV) are traditionally treated with postoperative adjuvant chemo, although benefits are unproven. Both chemotherapy and RT produce responses and are used in the recurrent setting.[234]

A Phase II GOG trial evaluated the efficacy of the BEP regimen in completely resected or recurrent sex cord and stromal tumors. Forty-eight of 57 patients had granulosa cell tumors. The response rate for primary disease was 69% (11 of 16), and for recurrent disease it was 51% (21 of 41).[236]

Pankratz et al[237] retrospectively evaluated the prognosis of 61 patients with granulosa cell tumors, 48 of who received postoperative RT. The patients who received postoperative RT had a lower mortality in comparison to those who were not treated with RT even though the stage distribution was in favor of the nonirradiated group. However, the improved OS was not statistically significant and specific data are lacking to make conclusions. Other studies have not shown a benefit of adjuvant RT.[220,234]

Relapses are often isolated intraabdominal or pelvic masses. Accordingly, further surgical resection or localized RT may control disease for protracted periods of years.

IRRADIATION TECHNIQUES

EBRT Technique

When used as a primary or consolidative adjuvant therapy, surgical staging information, as well as analysis of patterns of failure, suggests that to be effective the EBRT volume must include all peritoneal surfaces. Dembo et al[113] emphasized the necessity of covering the diaphragm with adequate margin during all phases of normal respiration.

In general, patients treated with WAI should undergo CT treatment planning in the supine position with arms placed on the chest, or above the head, with appropriate immobilization. Given the importance of treating the entire diaphragm, customized shielding above the diaphragm should allow full irradiation during all cycles of respiration but also attempt to minimize pulmonary and cardiac irradiation. The use of "four-dimensional" CT can allow customized shielding during all phases of quiet respiration. Alternatively, CT at full expiration will have the diaphragm at the most cephalad position, and if shielding is designed at that point in respiration, diaphragmatic coverage can be assured. This technique may result in increased pulmonary and cardiac RT. Coverage of the diaphragm at quiet respiration with four-dimensional CT is preferred.

The inferior edge of the field should be placed below the pelvic floor, generally below the level of the obturator foramen.

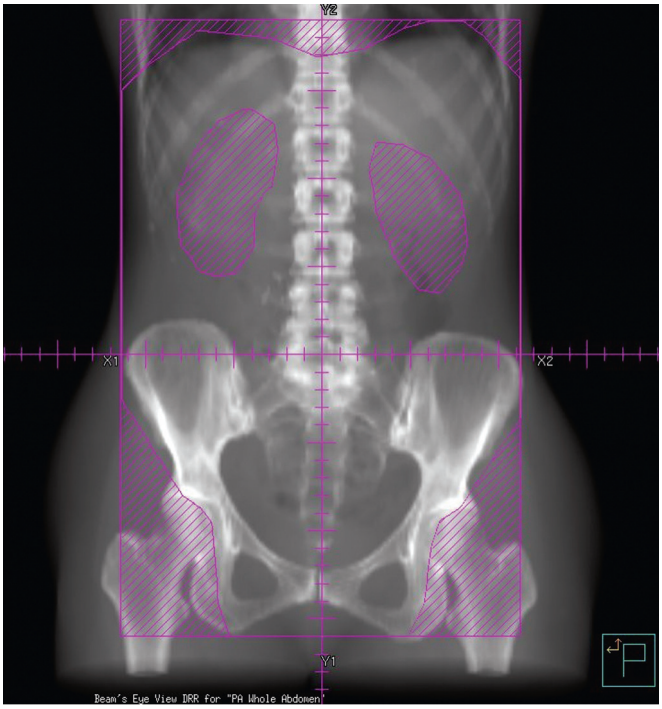


Figure 61-4 A typical whole-abdomen irradiation field.

The lateral edges of the field should be beyond the peritoneal reflection. Current WAI should be performed with an open-field technique, often at an extended source-to-skin distance. Previous use of a moving strip technique has been replaced with an open field technique, given the modern RT machines. The dose to the whole abdomen is generally limited to 22.5 Gy to 30 Gy in 1.0 Gy to 1.5 Gy per fraction. There is no obvious dose response, with a randomized trial noting no benefit to an abdominal dose of 27.5 Gy as compared with 22.5 Gy.[238] That being said, if doses above 25 Gy are used, there should be a consideration for liver shielding to keep the mean liver dose at approximately 25 Gy. In addition, the kidney dose should be limited to approximately 18 Gy. Given the use of the anterior-posterior/posterior-anterior (AP/PA) field, the most common technique is to use the PA shield for most or all of the PA treatments. Further shielding to block the bony pelvis and femoral heads, although delivering the full dose to the entire peritoneum, should be accomplished. Dose-volume histograms (DVH) should be obtained for the liver, kidney, and spinal cord to ensure that these organs are properly shielded. In addition, DVH analysis of the lungs and heart should also be accomplished with dosing to these organs minimized. Figure 61-4 depicts a typical WAI field.

In general, most studies have used a pelvic boost after WAI, for a total pelvic dose of 45 Gy to 50.4 Gy. This should be accomplished with standard pelvic RT techniques rather than IMRT to deliver tumor dose to all peritoneal surfaces. A repeat CT treatment planning session with the patient in a prone position, with a full bladder and possible abdominal compression, should be considered. Paraaortic boost for nodal disease or boost to residual disease should also be considered on an individual basis. If a paraaortic boost is accomplished, the spinal cord dose should be limited to 45 Gy.

Newer WAI treatment techniques have been developed to improve target coverage while reducing radiation to organs at risk, including the bone marrow. This can be particularly important in patients who are receiving chemotherapy and RT. Dosimetric studies have noted improved coverage of the

planning treatment volume and sparing of organs at risk with IMRT.[239] A recent Phase I study noted the feasibility of IMRT WAI as a consolidation after chemotherapy.[240] Helical tomotherapy also has been evaluated with improved dosimetric outcome.[241] All techniques must ensure delivery of tumor dose to the entire peritoneum.

Phosphorus-32

^{32}P is injected into the peritoneal cavity via an intraabdominal port or catheter. This is generally preceded by injection of contrast medium or a technetium-labeled radionuclide, followed by imaging to ensure adequate flow throughout the abdomen, including the cul-de-sacs and infradiaphragmatic region. After adequate flow has been determined, radioactive chromic phosphate ^{32}P (10 mCi to 20 mCi) is injected into the peritoneal cavity along with saline. Patients are then asked to move positions frequently to ensure good distribution through the peritoneal cavity.

TREATMENT ALGORITHMS, CHALLENGES, AND FUTURE POSSIBILITIES

Treatment Algorithm

The treatment of epithelial ovarian cancer is guided by the extent of disease at the time of diagnosis. Patients with disease confined to the ovary undergo a staging procedure to assess extent of microscopic dissemination that necessitates adjuvant chemotherapy. Certain early-stage histologies may benefit from adjuvant RT (clear cell, endometrioid, mucinous). Patients diagnosed with advanced disease undergo either a primary debulking procedure (to remove the maximum amount of macroscopic disease) or neoadjuvant chemo and interval debulking. The treatment algorithm presented in Figure 61-5 represents the current standard of care.

Challenges and Future Possibilities

Epithelial ovarian cancer remains a challenging cancer to treat as the majority of patients are diagnosed with advanced disease; although the response to chemo is high, most patients will eventually succumb to their disease. In the past decade, a modest improvement in survival has been demonstrated with the introduction of intraperitoneal chemotherapy. The specific timing and extent of debulking surgery together with the optimal chemo regimen are still controversial and will remain so until future results of current studies become available and the outcome becomes clearer. As technology improves, consolidative RT may play a role as the toxicity ratio is improved.

The role of RT for both early-stage and locoregional relapse needs to be clarified. Certain early-stage histologies (clear cell, endometrioid, and mucinous carcinomas) may benefit from adjuvant RT, as discussed previously, and this potential indication continues to evolve. The role of irradiation (EBRT, IORT,

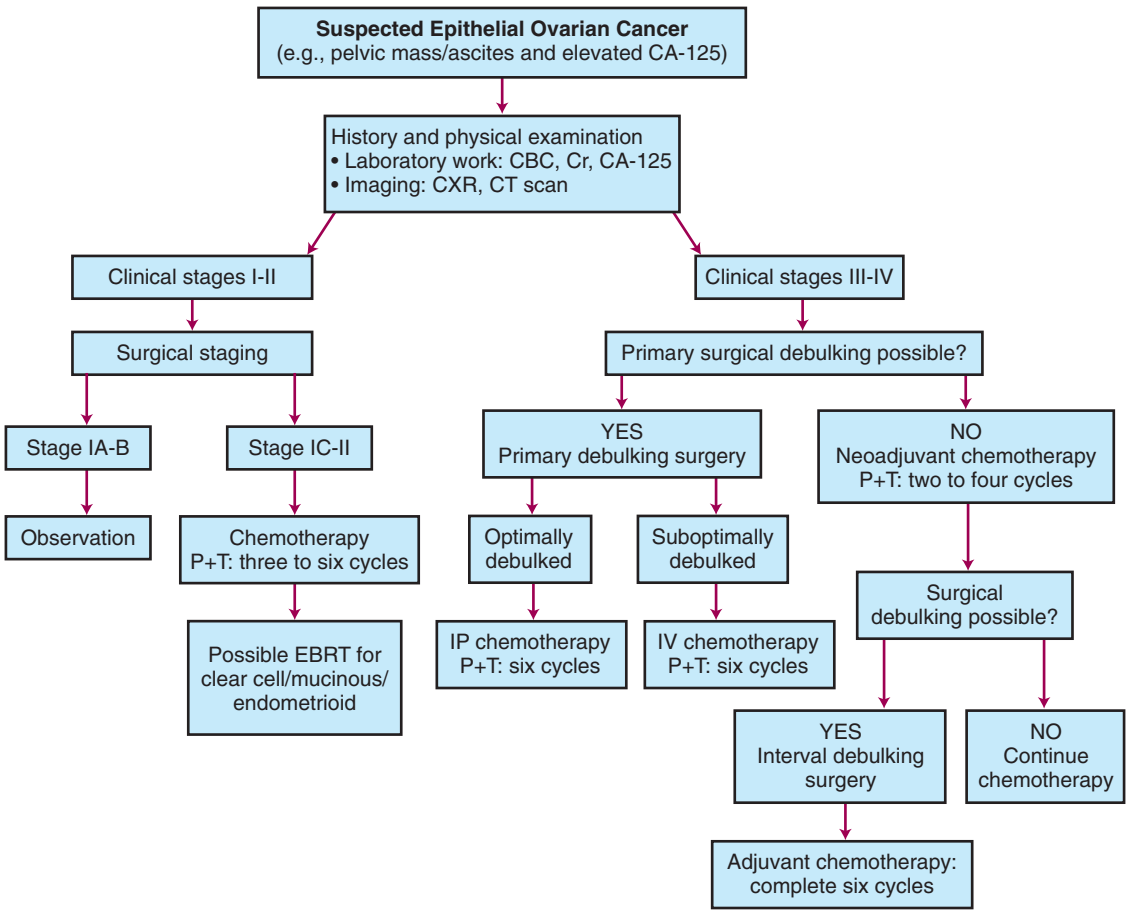


Figure 61-5 Treatment algorithm for epithelial ovarian cancer. *AFP,* α-fetoprotein; *β-hCG,* beta-human chorionic gonadotropin; *CBC,* complete blood count; *Cr,* complete response; *CT*, computed tomograph; *CXR,* chest x-ray; *EBRT,* external beam radiation therapy; *IP,* intraperitoneal; *IV,* intravenous; *P+T,* platinum plus taxane chemotherapy.

and even SBRT for localized masses) as a component of aggressive salvage treatment for select patients with locoregional relapse also needs to continue to be evaluated.

Multiple novel therapies, including PARP inhibitors and antiangiogenic drugs, have also shown promising results. The further understanding of the pathogenesis of ovarian cancer will potentially lead to the exploration and development of additional novel therapies based on the molecular signature of the tumor.

For specific patients who harbor a predisposition to the development of epithelial ovarian cancer, prophylactic surgery has been shown to prevent its development and should be recommended. Early detection has not yet been shown to be effective in high- or low-risk populations and should not be relied on at this time.

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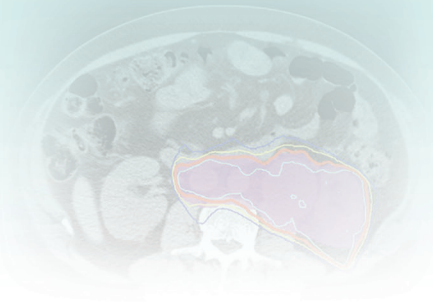
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Overview



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INCIDENCE AND MORTALITY

Breast cancer is the most common cancer in women, and it is estimated that one in eight women in the United States will develop breast cancer in their lifetime. Every year more than 40,000 women die from breast cancer, making it the second-leading cause of cancer-related deaths in women. Historically, the increase in breast cancer incidence was thought to be a reflection of changes in reproductive patterns, such as delayed childbearing and nulliparity, which are recognized as risk factors. Since the early 1980s, the incidence of breast cancer among older women was steadily rising because of improved early detection with the widespread use of mammography. The rates stabilized in the late 1990s and then started to decrease. In contrast the incidence of breast cancer in younger women has remained stable. With a rapidly aging population in the United States, the number of breast cancers is expected to increase over the next 20 years. Fortunately, screening, early detection, and advances in multidisciplinary treatment have led to continuous declines since 1990. Survivorship is a growing issue and research into the late effects of treatment will become even more relevant as the population of breast cancer survivors continues to increase. In this chapter, we will provide an overview and highlight the general considerations necessary in formulating a multimodality treatment plan for the management of a patient with breast cancer.

ETIOLOGY, RISK FACTORS, AND GENETICS

Breast cancer results from a series of genetic and epigenetic events that lead to dysregulation of cell growth, circumvention of apoptosis, and development of the ability to invade. The causes of these events remain largely unknown, although epidemiologic studies have implicated lifestyle, environmental, and germ-line genetic factors in predisposition to this disease.

Accepted risk factors for breast cancer include female sex, increasing age, personal or family history of the disease, exposure to ionizing radiation, nulliparity, hormone replacement therapy, alcohol intake, germ-line mutations in the *BRCA1* gene or *BRCA2* gene, and other more unusual inherited conditions. Up to 10% of breast cancers are caused by germ-line mutations that are passed down in families.

Advances in molecular genetics have identified several genes associated with an inherited susceptibility to breast cancer (i.e., *BRCA1, BRCA2, PTEN, TP53, CDH1*), and identification of a mutation has major implications for prevention, screening, and treatment. Formal risk assessment and genetic counseling takes into account a detailed family pedigree, an evaluation of the patient needs and concerns, past medical and surgical history, and any active cancer diagnoses.

PROGNOSTIC AND PREDICTIVE FACTORS

Several features help to predict the probability of successful outcome after treatment for breast cancer. The most powerful prognostic factor is disease stage at diagnosis, which is determined by the status of regional lymph nodes and the size of the primary tumor. Additional tumor-related prognostic factors include tumor grade, estrogen and progesterone receptor status, HER2/neu (ERBB2) status, and proliferative index. The most important patient-related factor is age, with young patients with breast cancer typically having the worst outcomes.

The genetic heterogeneity of breast cancer is increasingly being appreciated. New molecular tumor assays, including cDNA microarray classifications and molecular-based predictive assays, are enhancing the understanding of tumor biologic characteristics, prognosis, and predictors of treatment response. Several have moved into the marketplace and are used for treatment decisions (i.e., Oncotype-DX, PAM50, Mamaprint). Ultimately, it is hoped that continued research into the molecular biology of breast cancer will continue to identify new therapeutic targets and increase the personalization of breast cancer therapy.

TREATMENT

Breast cancer therapy requires a multidisciplinary team consisting of surgeons, medical oncologists, radiation oncologists, pathologists, radiologists, reconstructive surgeons, and supportive care personnel. Each aspect of multidisciplinary care should occur in a coordinated fashion. Most patients with breast cancer receive surgery, radiation, and systemic treatment. All three therapeutic specialties have seen significant advances, and each component of these treatments has been shown to independently offer survival benefit for selected patients. For patients with early-stage breast cancer, the outcomes associated with breast-conservation surgery, sentinel lymph node dissection, radiation, and systemic treatments are excellent. Treatment advances have also improved the prognosis for patients with more advanced disease at presentation. A particularly exciting advance has been the use of anti-HER2–directed therapies for patients with HER2-positive disease. In the future, additional molecularly targeted treatments are likely to further improve breast cancer outcomes.

INTRODUCTION

Breast cancer is one of the most common cancers seen and treated by radiation oncologists. Radiation plays an important role in the management of breast cancer at all stages, including ductal carcinoma in situ, early-stage disease (as a component of breast conservation), and locally advanced disease (as an adjuvant treatment after mastectomy). Radiation is also a highly effective palliative modality for patients with metastatic disease progressing within a localized area that adversely affects their quality of life.

This section of the textbook consists of this overview introduction, followed by chapters highlighting the role of radiation in ductal carcinoma in situ, early-stage disease, and locally advanced disease. This overview component reviews important aspects of breast cancer anatomy, breast cancer epidemiology and statistics concerning incidence and mortality, risk factors for the disease, screening, staging, prognostic and predictive factors, including the molecular classification of disease, and a summary of the role of surgery, radiation, and systemic therapies for breast cancer.

ANATOMY

A comprehensive understanding of the anatomy of the breast and its regional lymphatics is imperative for radiation oncologists to appropriately design radiation therapy fields that optimally cover targeted areas at risk for disease while sparing uninvolved normal structures. Historically, radiation treatment fields were designed based on standard external landmarks, but such techniques risked inadequate treatment of sites at risk of containing disease. Treatment planning based on computed tomography (CT) imaging has optimized the planning process and heightened the importance of radiation oncologists' familiarity with anatomy, particularly with respect to the breast's lymphatic drainage pathways.

The breast typically extends medially to the midline and laterally to near the midaxillary line. The cranial and caudal borders of the breast are typically the second and sixth anterior ribs, respectively, although the breast may extend higher into the axillary region (known as the *tail of Spence*). Breast parenchymal tissue is supported by fibrous septa (Cooper's suspensory ligaments) and connective tissue that contains blood vessels, nerves, lymphatics, and adipose tissue. The deep boundary of the breast is the fascia of the pectoralis major muscle. The chest wall, which consists of the rib cage and interosseous muscles and fascia, lies underneath the pectoralis major muscle. Microscopically, the breast parenchyma consists of lobules and ducts. The ductal system of the breast is divided into branching segments that converge into major lactiferous ducts near the nipple-areola complex. The interface between the lobules and the ducts, the *terminal ductal-lobular unit*, is the most common location for the development of breast cancer.

The breast has a rich lymphatic plexus that drains to lymph nodes of the axilla, internal mammary chain (IMC), and supraclavicular fossa (Figure G-1). Drainage can also occur to lymph nodes within the breast itself (intramammary nodes) and those between the pectoralis major and minor muscles (interpectoral or Rotter's lymph nodes). Sentinel lymph node surgery has helped to identify the most common drainage pathways of the breast lymphatics. Most individuals have lymphatic drainage to one or more lymph nodes in the low axilla. Axillary lymph nodes are customarily divided into three levels according to their anatomic location relative to the pectoralis minor muscle: level I axillary lymph nodes are located inferolateral to the pectoralis minor muscle; level II lymph nodes are beneath the pectoralis minor muscle; and level III lymph nodes (also called infraclavicular lymph nodes) are those superior and medial to the pectoralis minor muscle but below the clavicle. Figure G-2 shows an axial positron emission tomography (PET) image combined with a CT image of a patient with involvement of level I, II, and III lymph nodes. Patients with advanced disease are also at risk of having involvement of Rotter's nodes, an example of which is shown in Figure G-3.

Breast cancer can also involve lymph nodes within the IMC. Lymphatic channels that drain to internal mammary lymph nodes tend to run close to the pectoralis fascia, and therefore a sentinel lymph node procedure that is done with a superficial or subdermal injection of blue dye or radiocolloid will rarely reveal drainage to the IMC. To demonstrate drainage in such cases, these injections must be done within the tumor bed or deep near the pectoralis muscles. When breast cancer involves lymph nodes in the IMC, the nodes are usually within the first three intercostal spaces. These anatomic areas are easily visualized with CT scans, on which the internal mammary artery and vein are apparent just lateral to the sternum within the thoracic cavity. One study involving lymphoscintigraphy before sentinel lymph node surgery indicated that the frequency of drainage to the IMC was highest for lower inner quadrant tumors (43%), followed by lower outer quadrant tumors (32%) and central tumors (28%).[1] An axial PET/CT slice of a patient who presented with involvement of an internal mammary lymph node and concurrent disease within the ipsilateral breast and level I axilla is shown in Figure G-4. The frequency of internal mammary lymph node involvement depends on the status of the axillary lymph nodes and the anatomic location of the primary tumor. An important study from China reported the rates of IMC involvement in 2269 patients who had had dissection of this region as a component of an extended radical mastectomy.[2] The rates of IMC involvement were highest when axillary disease was also present (Table G-1).

Finally, breast cancer can also spread to the supraclavicular nodes, although this typically occurs only when axillary lymph nodes are also involved. The risk of supraclavicular lymph node involvement depends greatly on the number of positive axillary lymph nodes; clinical outcome data suggest that supraclavicular involvement for patients with one to three positive axillary lymph nodes is rare, but more than 15% of patients with four or more positive axillary lymph nodes

TABLE G-1 Pathologic Rates of Involvement of Internal Mammary Lymph Nodes According to Tumor Location and Pathologic Status of the Axilla

Tumor Location	Axillary Lymph Node (ALN) Status	Rates of Involvement of the Internal Mammary Lymph Node(s)
Medial/central	0 + ALN	6% (27/428)
	1-3 + ALN	26% (41/160)
	4-6 + ALN	43% (21/49)
	≥7 + ALN	40% (44/110)
Lateral	0 + ALN	3% (12/456)
	1-3 + ALN	14% (34/238)
	4-6 + ALN	20% (18/90)
	≥7 + ALN	43% (63/148)

Data from Huang O, Wang L, Shen K, et al: Breast cancer subpopulation with high risk of internal mammary lymph nodes metastasis. Analysis of 2,269 Chinese breast cancer patients treated with extended radical mastectomy. Breast Cancer Res Treat 107(3):379–387, 2008.

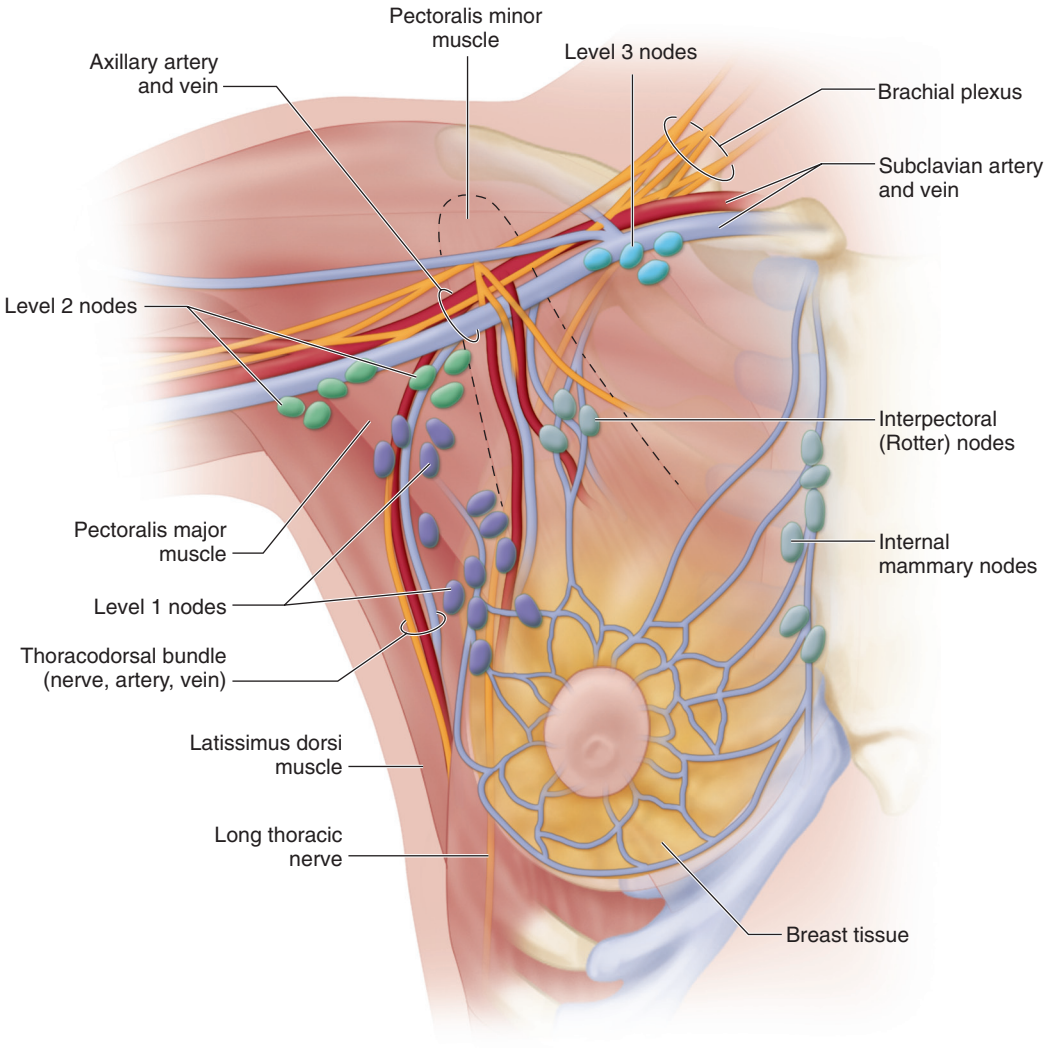


Figure G-1 Pictorial depiction of anatomic landmarks of the axilla and lymphatic drainage of the breast.

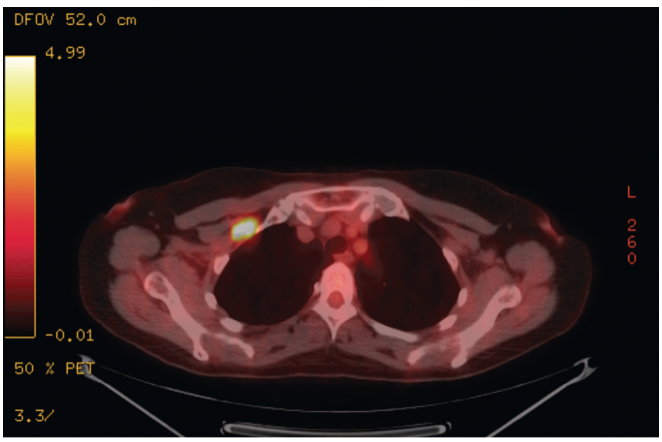


Figure G-2 Axial PET/CT slice of a patient with a right breast cancer that involved the level III axilla and infraclavicular fossa. The involved lymph node is below and medial to the pectoralis minor muscle. *CT,* computed tomography; *PET,* positron emission tomography.

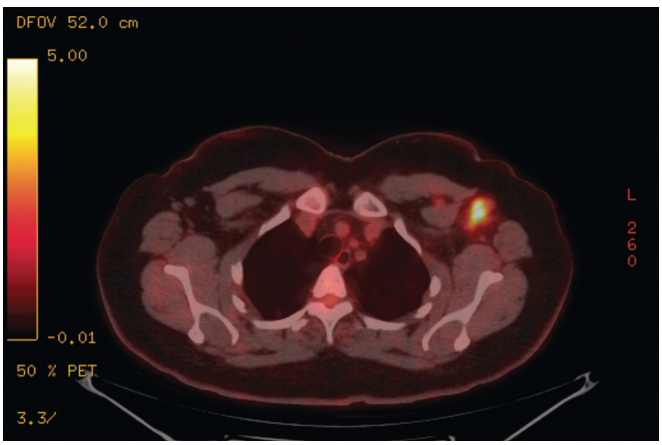


Figure G-3 Axial PET/CT slice of a patient with a left breast cancer that involved the level I axilla and Rotter's lymph nodes. The level I adenopathy is located lateral to the pectoralis minor muscle, and the involved Rotter's lymph nodes are anterior to the pectoralis major muscle. *CT,* computed tomography; *PET,* positron emission tomography.

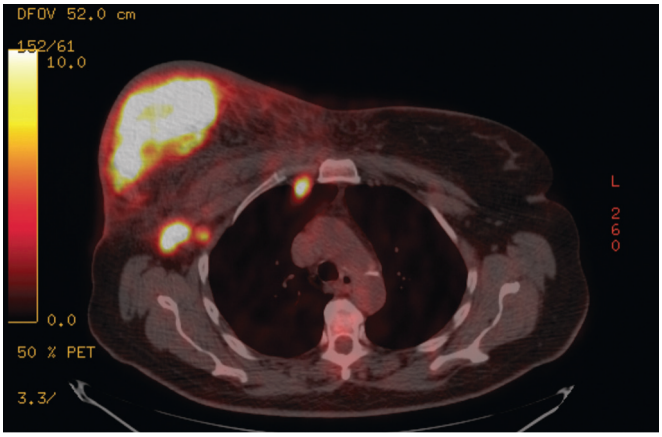


Figure G-4 Axial PET/CT slice of a patient with an inflammatory carcinoma of the right breast showing increased activity diffusely through the breast and involvement of both axillary level I and internal mammary lymph nodes. *CT*, Computed tomography; *PET*, positron emission tomography.

will have recurrence in the supraclavicular fossa if this region is not treated.[3] However, a recent study indicated that specific subsets of patients with one to three positive axillary lymph nodes may be at higher risk of recurrence in the supraclavicular fossa and may therefore benefit from treatment to this region. Those subsets include patients with high-grade disease, estrogen receptor–negative disease, and younger patients.[4] Disease that presents with involvement of supraclavicular lymph nodes at diagnosis has a particularly poor prognosis and represents the highest-risk category of nodal disease.

When designing radiation fields, a comprehensive understanding of anatomic relationships in the area to be targeted is essential for the radiation oncologist. Contouring, the process by which the target is delineated from normal tissue is subject to significant levels of inter- and intraobserver variability in terms of accuracy and reproducibility.[5] Guidelines have been developed for high-risk breast cancer to reduce this variability and to guide the delineation of the primary and lymph node clinical target volumes.[6] A recent advance in radiation treatment planning is the use of automated atlas based segmentation (AABS), a technology that uses CT-based atlases as a template to help delineate target volumes with more consistency.[7-9] This technology allows for increased reproducibility among radiation oncologists in delineating the regions of interest.

EPIDEMIOLOGY AND ETIOLOGY

Incidence and Mortality Rates

The American Cancer Society estimated that in 2013 an estimated 232,340 new cases of invasive breast cancer and 39,620 breast cancer deaths would occur[10] making it the second-leading cause of cancer-related deaths in women, exceeded only by lung cancer. Historically, the increase in breast cancer incidence was thought to be a reflection of changes in reproductive patterns, such as delayed childbearing and giving birth to fewer children, which are recognized as risk factors.

Starting in the early 1980s, the incidence of breast cancer among older women began rising as a result of improved detection with the widespread use of mammography. The rates stabilized in the late 1990s and then started to decrease; it has been hypothesized that the decline occurred because of a reduced use of hormone replacement therapy following the 2002 publication of the Women's Health Initiative randomized trial results.[11,12] In contrast the incidence of breast cancer in younger women has remained stable. Although breast cancer is a rare disease in young women, it is the most common cancer occurring in the age group. When it occurs in women younger than 35, it brings forth unique clinical challenges for the clinician and personal challenges for the patient, especially when associated with pregnancy.[13,14]

With a rapidly aging population in the United States, the number of breast cancers is expected to increase over the next 20 years. Fortunately, breast cancer mortality rates have declined continuously since 1990, probably because of screening leading to early detection and advances in multidisciplinary treatment.[15] Survivorship is a growing issue and research into the late effects of treatment is of relevance given that more than 2.9 million U.S. women with a history of breast cancer are expected to be alive in 2012.[16]

Risk Factors

The average lifetime risk of breast cancer for a woman in the United States has been estimated at 12.3% (1 in 8 women).[10] Table G-2 lists risk factors for developing breast cancer. The strongest risk factor for breast cancer is being female; only about 1% of all new breast cancer cases occur in men.[10] The second-most important risk factor is an individual's age, with 95% of all new breast cancer cases developing in women aged 40 years or older.[10] The annual risk of developing breast cancer increases exponentially from age 40 until menopause, at which time the rate of increase in annual risk slows considerably. After the age of 80, the annual incidence of breast cancer begins to show a slight decline. The risk of developing breast cancer as a function of age for females is shown in Table G-3.

The risk of breast cancer development is influenced by estrogen exposure over the course of one's life. Specifically, risk factors for breast cancer development include young age at menarche, nulliparity or older age at first pregnancy, and older age at menopause. In a large study of Swedish women, the risk of breast cancer increased approximately 13% for every 5-year increase in age at first birth.[17] Postmenopausal estrogen replacement therapy also has been shown to increase the risk of breast cancer. In a meta-analysis of 51 studies that included 52,705 women with breast cancer and 108,411 women without breast cancer, receipt of postmenopausal hormone replacement therapy was found to increase the annual relative risk of developing breast cancer by 2.3% for each year of hormonal therapy.[18] In 2000, a study of 46,000 women reported that the combined use of estrogen and progesterone increased the relative risk of breast cancer by 8% compared with the risk in nonusers, whereas the use of estrogen alone increased the relative risk by only 1%.[19] These data have been confirmed by two large prospective studies conducted through the Women's Health Initiative.[20,21]

Many patients and family members are interested in whether they can modify their risk for developing breast cancer through diet or exercise, or both. Evidence in support of any association between dietary fat content and breast cancer development has been weak and inconsistent.[22,23] Because of conflicting findings, it has been difficult to make strong nutritional recommendations for breast cancer prevention. Use of omega-3 polyunsaturated fatty acid (PUFA) supplements has gained attention in preclinical studies as a potential protectant against breast cancer.[24] In contrast, alcohol intake seems to be more consistently associated with increased breast cancer risk.[25,26] Exercise and body weight have a moderate impact on breast cancer risk. Relatively large studies have demonstrated that daily exercise, particularly early in life, can reduce the risk of breast cancer for both premenopausal and

TABLE G-2 Breast Cancer Risk Factors

Risk Factors Used in the National Cancer Institute Breast Cancer Risk Assessment Tool*	Other Known Risk Factors	Unlikely Risk Factors
Personal history of lobular carcinoma in situ or ductal carcinoma in situ	Female sex	Higher fat intake
Older age	Personal history of breast cancer	Fibrocystic breast disease
Family history of breast cancer and number of first-degree relatives with breast cancer	Germ-line mutation in *BRCA1* gene or *BRCA2* gene	Fibroadenoma
Nulliparity and age at first birth	Higher alcohol consumption	Simple breast cysts
Older age at menarche	Low amounts of exercise	Use of oral contraceptives
History of a breast biopsy and number of breast biopsies	Use of hormone replacement therapy	Use of tobacco
Personal history of atypical ductal hyperplasia	History of radiation treatments to the chest for Hodgkin's disease	
White race	Lack of breast-feeding	

*See also www.cancer.gov/bcrisktool.

TABLE G-3 Risk of Being Diagnosed with Breast Cancer in 10, 20, and 30 Years and in the Remaining Lifetime*

Current Age	+10 yrs	+20 yrs	+30 yrs	Eventually
0	0.00	0.00	0.05	13.39
10	0.00	0.05	0.49	13.54
20	0.05	0.49	1.95	13.57
30	0.44	1.91	4.57	13.59
40	1.49	4.18	7.64	13.31
50	2.79	6.36	9.77	12.21
60	3.83	7.49	9.63	10.11

yrs, *Years.*
**Given cancer-free status at the current age, lifetime risk (%) of being diagnosed with cancer was determined according to 12 Surveillance, Epidemiology, and End Results (SEER) areas; the lifetime risk of dying of cancer was 2.98% (determined for U.S. totals, 1999 to 2001).*

postmenopausal women.[27,28] Some recent evidence suggests that exercise and body weight can influence the outcome after breast cancer treatment as well.[29,30]

Genetic Factors and Breast Cancer Etiology

Breast cancer develops from breast epithelial tissue with abnormalities in several cellular processes as a result of genetic and epigenetic events. Some patients have inherited germ-line genetic conditions, such as a mutation in a relevant tumor suppressor gene, but in most cases the genetic events leading to breast cancer are somatic or sporadic. Approximately 20% to 25% of women diagnosed with breast cancer have a family history of the disease, and approximately 10% of patients have a family history showing an autosomal dominant pattern of breast cancer inheritance.

Epidemiologic studies of families with a history of breast cancer led to the discovery of germ-line mutations in two important tumor suppressor genes, the *BRCA1* and *BRCA2* genes. Individuals who inherit a mutation in the *BRCA1* gene or *BRCA2* gene from one of their parents have a high lifetime risk of developing a breast cancer that is associated with certain aggressive tumor characteristics. Mutation in the *BRCA1* gene is associated with triple negative cancers, medullary cancer, young age at diagnosis, and ovarian cancer.[31] Patients with mutations in the *BRCA2* gene more commonly develop ER-positive breast cancer, and although they are still at increased risk of ovarian cancer relative to the general population, this risk is less than for those with the *BRCA1* gene mutation. The *BRCA2* gene is also associated with male breast cancer.[31] Table G-4 highlights the main features of BRCA-linked tumors and the prevalence of second malignancies in *BRCA1* and *BRCA2* gene mutation carriers.[13,32-35]

The mutations of interest are point mutations that are found during traditional Sanger sequencing of the *BRCA1* and *BRCA2* genes. Large rearrangements in BRCA1 and BRCA2 (BART) occur in a small percentage (<1%) of all patients tested for hereditary breast or ovarian cancer syndrome.[36] Since 2008, BART testing has been included as part of Comprehensive BRCA*analysis* tests for patients with a strong personal and family history of breast and ovarian cancer and in individuals meeting criteria for automatic BART testing, the prevalence of mutations in a high-risk population is higher (7.5%) than in the normal population.[37]

For all patients diagnosed with breast cancer, a preliminary risk assessment should be performed to determine if a more formal evaluation is needed. The degree of risk for a familial syndrome increases with the number of affected family members, the closeness of the relationship, and the younger the age at diagnosis of the affected member.[38] Formal risk assessment and genetic counseling takes into account a detailed family pedigree, an evaluation of the patient needs and concerns, and the past medical and surgical history as well as any active cancer diagnoses.

The National Cancer Center Network (NCCN) panel recommends that patients with a personal history of breast cancer in addition to one or more of the criteria listed in Box G-1 should undergo testing. Furthermore, mutations should be suspected and tested for in cases of male breast cancer at any age, ovarian cancer at any age, and in high-risk ethnic backgrounds (e.g., Ashkenazi Jewish heritage). In addition to hereditary breast and ovarian cancer syndrome (BRCA1/BRCA2), advances in molecular genetics have identified several genes associated with an inherited susceptibility to breast cancer (e.g., *PTEN*, *TP53*, *CDH1*) and identification of a mutation has implications for prevention, screening, and treatment.[39]

New genetic testing panels use next-generation sequencing to detect hereditary breast, ovarian, and other cancer for patients who have tested negative for high penetrance genes such as *BRCA1* and *BRCA2* in light of a suggestive family history. These panels should not be routinely ordered without an expert cancer geneticist consultation as guidelines on risk assessment and management of variant mutations is not clearly defined.

Breast Cancer Screening

Breast cancer screening is performed in asymptomatic women so that disease can be detected earlier. Irrespective of risk level,

TABLE G-4 Features of BRCA-Linked Tumors

	BRCA1	*BRCA2*
Tumor biology	High proliferation rates Low differentiation Increased prevalence of grade-3 tumors Reduced ER/PR expression Increased rate of p53 mutations Higher degree of aneuploidy Reduced Her2/neu expression	Higher frequency of medullary tumor Increased rate of p53 mutation Higher degree of aneuploidy Reduced HER2/neu expression
Estimated lifetime breast cancer risk	47%-66%	40%-57%
Female breast cancer risk according to age	2% by age 30 20% by age 40 37% by age 50 55% by age 60	Same as *BRCA1*
Ovarian cancer risk	21% by age 50 40% by age 60	2% by age 50 6% by age 60

Adapted from references 13, 32, and 35.
ER, *Estrogen receptor;* HER2, *human epidermal growth factor receptor 2;* PR, *progesterone receptor.*

BOX G-1 Hereditary Breast and Ovarian Syndrome Testing Criteria

HEREDITARY BREAST AND OVARIAN SYNDROME TESTING CRITERIA (*BRCA1/BRCA2*)

A personal history of breast cancer plus one or more of the following:

1. Diagnosed at age 45 or younger
2. Having two breast primaries with the first breast cancer diagnosed at younger than age 50
3. Diagnosed at younger than age 50 with one or more close relative with breast cancer at any age.
4. Diagnosed with triple negative breast cancer at younger than age 60
5. Diagnosed at any age with two or more close relatives with breast cancer at any age; diagnosed at any age with one or more close relative with epithelial ovarian cancer diagnosed at any age
6. Diagnosed at any age with 2 or more close relatives with pancreatic or aggressive prostate cancer (Gleason ≥7) at any age

Adapted from Genetic/Familial High-Risk Assessment: Breast and Ovarian. NCCN Guidelines 2014. Accessed on 2/21/14.

a routine physical examination including a clinical breast examination (CBE) should be performed in all women. Following a complete medical history, women may be stratified into two risk groups: those at average risk and those at increased risk to determine further testing. Although controversies are unresolved regarding the timing interval of screening and the benefit of screening in particular age groups (i.e., ages 40 to 49), it is recommended that average risk women age 40 or older should undergo yearly screening bilateral mammogram based on a consensus statement from the American Cancer Society.[40-43] In the guidelines, there is no strict upper age limit for screening. However, if a patient has severe comorbidities that limit her life expectancy and if no intervention will be planned on the basis of the screening findings, then a recommendation should be made against screening in those clinical situations.

Much of the controversy over breast cancer screening stems from the concern that mammography may be overdiagnostic. This term refers to the fact that some cancers detected at screening may grow so slowly or not at all and that they may never result in death even if left undetected and untreated.[44] In these cases, patients are being subjected to unnecessary biopsies, surgeries, radiation therapy, and subsequent systemic treatments. This results in psychosocial and financial costs for patients, families, and society at large.

Table G-5 shows the recognized risk factors that place women at a higher risk of breast cancer and highlights the appropriate screening recommendations for them. The modified Gail model is a risk assessment tool, which calculates the 5-year and lifetime predicted risk of developing invasive breast cancer as a function of several known risk factors.[45,46] However, this risk tool should not be used in women with a predisposing gene mutation, a strong family history, a history of prior thoracic radiation, or for those with lobular carcinoma-in situ (LCIS). Additionally, models that rely on family history (i.e., Claus,[47] Tyrer-Cuzick,[48] and BRCAPRO[49]) can identify women with a greater than 20% lifetime risk of breast cancer based on these models and are instrumental in directing screening and identifying women who are candidates for risk reduction strategies.

The routine use of magnetic resonance imaging (MRI) screening for the general population is not recommended because of the high cost and high false-positive rate associated with MRI. Among the high-risk populations, clear evidence exists to recommend annual MRI screening in addition to mammography for BRCA carriers. In general, screening for hereditary breast cancer begins at age 25 and includes annual mammography, annual breast MRI, and biannual clinical breast exams. Because of the high incidence of "interval" cancers in BRCA carriers, alternating the imaging techniques (mammogram and MRI) every 6 months is suggested to attempt to provide more coverage. Women who received radiation treatment for prior diagnosis of lymphoma are screened similarly with mammography and MRI starting 10 years after completing radiation. Other high-risk characteristics such as a personal previous history of breast cancer, LCIS, or average familial risk do not warrant the adjunct use of MRI.

Breast Cancer Prevention Strategies

Women who are at increased risk of developing breast cancer can reduce this risk through prevention strategies. Specific lifestyle changes with the potential to modify risk include reducing or eliminating alcohol consumption, maintaining ideal weight, and exercising on a regular schedule. All women regardless of age or risk status should be recommended to

TABLE G-5 Breast Cancer Screening: Increased Risk Category

High-Risk Factor	Screening Recommendation
Prior history of breast cancer, Hx of lobular carcinoma in situ (LCIS) or familial risk	Encourage breast awareness, CBE every 6-12 months, annual mammography
≥35 years of age with a 5-year risk of invasive breast carcinoma ≥1.7% by Gail Model*	Encourage breast awareness, CBE every 6-12 months, annual mammography
Lifetime risk of breast cancer >20% based on family history models	Encourage breast awareness beginning at age 30, CBE every 6-12 months, annual mammogram; consider reduction strategies
History of previous therapeutic thoracic radiation (e.g., mantle radiation) between the ages of 10-30 years	Age ≥25: encourage breast awareness, annual mammograms, annual MRI as adjunct to mammograms, to be initiated 8-10 years after radiation exposure or at age 40, whichever comes first Age <25: encourage breast awareness, risk counseling, and annual CBE; annual mammography and MRI to be initiated 8-10 years after radiation exposure
Known genetic predisposition	Encourage breast awareness, CBE every 6-12 months, annual mammography, annual MRI; begin screening at age 25
Family history pedigree suggestive of genetic predisposition	Encourage breast awareness, CBE every 6-12 months, annual mammography, annual MRI; begin screening 10 years earlier than age of youngest woman in family diagnosed with breast cancer, but no later than age 40

From Breast Cancer Screening and Diagnosis. NCCN Guidelines 2014. Accessed on 2/21/14.
CBE, *Clinical breast examination;* Hx, *history;* MRI, *magnetic resonance imaging.*
**Risk Assessment by the Gail Model includes current age, age at menarche, age at first live birth or nulliparity, number of first-degree relatives with breast cancer, number of previous benign breast biopsies, atypical hyperplasia in a previous breast biopsy, and race.*

maintain a healthy lifestyle. Pharmacologic strategies that affect estrogen and progesterone signaling pathways can also reduce the risk of developing breast cancer. Risk reduction surgeries (i.e., bilateral total mastectomy or bilateral salpingo-oophorectomy) may be beneficial in select high-risk groups.

Risk Reduction Agents

Estrogen and the estrogen receptor (ER) are key regulators in the progression of breast cancer. Drugs that target ER are known as selective estrogen receptor modulators (SERMs) and were first approved as a treatment for metastatic hormone-receptor–positive breast cancer given its antagonistic effects on breast tissue. Tamoxifen is now routinely used to treat all stages of breast cancer. In adjuvant treatment trials, it has been noted that women who have been treated with tamoxifen for primary invasive disease have a lower incidence of ipsilateral and contralateral tumor recurrences.[50,51] This clinical finding as well as preclinical studies showing that tamoxifen has anti-initiator and antipromoter properties served as the basis for exploring the preventative effects of tamoxifen.[52,53]

The National Surgical Adjuvant Breast and Bowel Project (NSABP) P-1 trial was a randomized placebo-controlled study of tamoxifen that enrolled 13,388 women predicted to have a 1.67% or higher risk of developing breast cancer within 5 years. The results showed that tamoxifen reduced the rates of invasive and noninvasive ER-positive breast cancer by 49% and 50%, respectively.[54] In the International Breast Cancer Intervention Study I (IBIS-I) trial, women at high risk were treated with tamoxifen for 5 years and were found to have a reduced incidence in ER-positive breast cancer by 48% with a persistent benefit for at least 10 years after discontinuing therapy.[55,56] Although highly effective for breast cancer prevention, a side effect profile including hot flashes, night sweats, vaginal symptoms, and more serious effects such as endometrial cancer and thromboembolism has been associated with tamoxifen use. The rate of endometrial cancer was higher in women over the age of 50, and the risk for thromboembolism increased with age as well. Because of tamoxifen-related side effects, efforts were undertaken to consider alternative agents. Raloxifene (another SERM) was evaluated and found to reduce the rate of invasive ER-positive breast cancers becoming available as an alternative option in women who are postmenopausal.[57,58] Based on the collective results of the tamoxifen and raloxifene clinical prevention trials, the STAR (P-2) trial, conducted by the NSABP, compared the effectiveness of treatment with tamoxifen or raloxifene for 5 years on reducing breast cancer risk in 19,474 women who were postmenopausal and high risk.[59] The long-term follow-up of the STAR trial showed that although there were fewer cases of thromboembolism and uterine cancers in the raloxifene group, it was ultimately less effective at prevention of invasive breast cancer.[60]

More recently, the portfolio of choices for prevention strategies among patients who are high risk and postmenopausal has been further expanded. Aromatase inhibitors such as letrozole, anastrozole, and exemestane block the biosynthesis of estrogen from androgens by inhibiting the aromatase enzyme, which results in a decrease of circulating estrogen levels in the serum, tissue, and tumor cells.[61] Aromatase inhibitors have been shown to be more effective at preventing breast cancer recurrence and reducing second breast cancers than tamoxifen in the adjuvant setting.[62-64] These data led to the evaluation of aromatase inhibitors in the preventative setting. Two randomized placebo-controlled trials have demonstrated that exemestane (a steroidal aromatase inhibitor) and anastrozole (a nonsteroidal aromatases inhibitor) appear to be more effective than placebo at reducing the incidence of invasive and ductal carcinoma in situ cancers in women who are postmenopausal.[65,66] It is important to note, however, that the effects of tamoxifen have been shown to last for at least 10 years, and further follow-up is needed in the IBIS-II and MAP.3 trials to evaluate whether the effects of exemestane and anastrozole on breast cancer risk reduction will be sustained. At the current time, for women who are older than 35 years of age and who are at increased risk of breast cancer, oncologists may select among the available pharmacological strategies for breast cancer risk reduction based on the patient's hormonal status and the side effect profile of the drug.[67] Table G-6 highlights the available pharmacologic breast cancer risk reduction strategies.

The diagnosis of ductal carcinoma in situ (DCIS) has become a more common entity since the widespread use of screening mammography has been adopted, and it is recognized to be a risk factor for development of invasive breast

TABLE G-6 Highlights from Select Pharmacological Breast Cancer Prevention Trials

Trial	Study Design	Patient Population	Results	Toxicity Pearls
SELECTIVE ESTROGEN RECEPTOR MODULATORS (SERMS)				
Tamoxifen				
NSABP-P-1[54]	Tamoxifen vs. placebo	*N* = 13,388, HR, PPM	49% reduction in all BC	Decreased risk of bone fractures* Increased risk of thromboembolism† Increased risk of uterine cancer†
IBIS-I[55]	Tamoxifen vs. placebo	*N* = 7154, HR, PPM	27% reduction in all BC and 31% reduction in ER+BC	
Raloxifene				
MORE[57]	Raloxifene (60 or 120 mg) vs. placebo	*N* = 7705, NR, PM	65% reduction in all BC and 90% reduction in ER+BC	
CORE[58]	Extension of MORE	*N* = 5213‡	50% reduction in all BC and 66% reduction in ER+BC	
Tamoxifen vs. Raloxfene				
STAR-P-2[60]	Tamoxifen vs. raloxifene	*N* = 19,747, HR, PM	5 years: raloxifene = tamoxifen 81 months: raloxifene is 75% as effective as tamoxifen	Raloxifene: decreased risk of thromboembolism and uterine cancers compared to tamoxifen
AROMATASE INHIBITORS (AIS)				
Exemestane				
MAP3[65]	Exemestane vs. placebo	*N* = 4560, HR, PM	65% reduction in all BC at 3 years follow-up and 75% reduction in ER+BC	Increased risk of bone fractures, skeletal symptoms and vasomotor symptoms with AIs
Anastrazole				
IBIS-II[66]	Anastrazole vs. placebo	*N* = 6000, HR, PM	53% reduction in all BC at 5 years and 58% reduction in ER+BC	

AIs, *Aromatase inhibitors;* BC, *breast cancer;* ER+BC, *ER-positive breast cancer;* HR, *high-risk women;* NR, *normal-risk women;* PM, *post-menopausal;* PPM, *post-menopausal and pre-menopausal.*
**Tamoxifen has bone building effects.*
†*Increased risk of uterine cancer is more clinically relevant in older women (>age 50) with an intact uterus; increased risk of thromboembolism is worse in older age groups.*
‡*From MORE trial.*

cancer. It is unclear, however, which lesions will progress and develop invasive properties and which will not. Currently management of this entity includes a combination of surgical resection, radiation, and tamoxifen. For women with DCIS, the NSABP B-17 study reported a significantly better overall 5-year event-free survival attributed to a lower incidence of invasive and noninvasive ipsilateral breast cancer among women who underwent lumpectomy and radiation therapy compared to lumpectomy alone or lumpectomy and tamoxifen. The NSABP B-24 trial showed that the combination of lumpectomy, radiation, and tamoxifen was more effective in the prevention of invasive cancer in women with DCIS compared to lumpectomy and radiation alone.[68] A retrospective subset analysis of NSABP B-24 showed that women with ER-positive DCIS benefit from intervention with tamoxifen, whereas women with ER-negative disease do not.[69] Therefore, tamoxifen is recommended for women with ER-positive DCIS who have remaining breast tissue following locoregional management. Second-generation trials of endocrine therapy with aromatase inhibitors (NSABP-35 and International Breast Cancer Intervention Study II) have been limited to women with hormone-receptor positive DCIS.

Risk Reduction Surgeries

Bilateral risk-reduction mastectomy has a role in carefully selected patients after an appropriate workup, multidisciplinary consultation, and genetic counseling. Bilateral mastectomy is proven to be an effective risk reduction strategy for women with a germline mutation in the *BRCA1* or *BRCA2* gene.[70-72] When it is performed for the purpose of risk reduction, it should involve removal of all breast tissue. Axillary evaluation is not required unless there is invasive disease identified when the mastectomy specimen is evaluated pathologically.[73] For *BRCA 1* and *BRCA2* gene mutation carriers, prophylactic bilateral salpingo-oophorectomy is recommended after completion of childbearing as a highly effective preventative measure against ovarian cancer risk.[74]

Diagnostic Overview

In most cases, breast cancer is diagnosed after abnormalities are found on screening mammography or after detection of a palpable mass. Some patients may present with an isolated painless lump in the breast. Others may have discharge or bleeding from the nipple. In some, the mass may have gone unnoticed, ignored, or neglected for some time and the presenting signs and symptoms may include nipple retraction, pain, ulceration, inflammation, or malodor with fixation to the skin or chest wall on physical examination. All patients should undergo a careful history with attention given to risk factors and family history. Next, a detailed physical examination should be performed with focus on the involved breast, the opposite breast, all regional lymph node areas, the lungs, bone, and liver. Bilateral diagnostic mammography, including additional views that highlight the noted abnormality should be performed to assess the extent of involvement and to

evaluate for additional ipsilateral or contralateral disease. Most patients should also have diagnostic ultrasonography of the breast and regional lymph nodes to further delineate the locoregional extent of disease.

For patients with a suspicious abnormality on physical examination or on mammography or sonography, tissue from the abnormality should be obtained to rule out cancer. The recommended biopsy procedure is a percutaneous core biopsy usually done under sonographic guidance. For patients who present with suspicious calcifications that cannot be well visualized with sonography, a stereotactic biopsy is recommended. A stereotactic biopsy is done under mammographic localization. In any biopsy procedure, it is important to leave a clip or other marker near the abnormality to help localize the tumor bed for subsequent surgery. Once the diagnosis of breast cancer is established further pathological testing should be done on the tumor tissue to determine important features such as histology, grade, presence of lymphovascular invasion, and receptor status (ER), progesterone receptor [PR], and HER2/neu receptor). Fine-needle aspiration of any suspicious regional lymph nodes can also be valuable for determining the initial extent of disease. When indicated, appropriate staging studies should be performed to rule out the presence of distant metastatic disease. However, most patients with early-stage disease do not require staging studies.

STAGING

Breast cancer is staged according to the size and characteristics of the primary tumor (T), the involvement of regional lymph nodes (N), and the presence of metastatic disease (M).

Table G-7 shows the breast cancer staging system from the seventh (2010) edition of the *American Joint Committee for Cancer (AJCC) Staging Manual*.[75] That system comprises both a clinical staging system, based on physical examination and radiographic studies, and a pathologic staging system, based on examination of surgical specimens. Pathologic staging after initial systemic treatments before surgery should be annotated with a *yp* before the assigned stage. All practitioners involved in breast cancer care should be familiar with the AJCC staging

TABLE G-7 American Joint Committee on Cancer Staging System for Breast Cancer[75]

PRIMARY TUMOR (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
Tis (DCIS)	Ductal carcinoma in situ
Tis (LCIS)	Lobular ductal carcinoma in situ
Tis (Paget's)	Paget's disease of the nipple with no tumor[a]
T1	≤2 cm in greatest dimension
T1mi	Microinvasion 0.1 cm or less in greatest dimension
T1a	Tumor >0.1 cm but not >0.5 cm in greatest dimension
T1b	Tumor >0.5 cm but not >1 cm in greatest dimension
T1c	Tumor >1 cm but not >2 cm in greatest dimension
T2	Tumor >2 cm but not >5 cm in greatest dimension
T3	Tumor more than 5 cm in greatest dimension
T4	Tumor of any size with direct extension to (a) chest wall or (b) skin, only as described below
T4a	Extension to the chest wall, not including only pectoralis muscle invasion
T4b	Edema (including peau d'orange) or ulceration of the skin of the breast, or satellite skin modules confined to the same breast
T4c	Both (T4a and T4b)
T4d	Inflammatory carcinoma
REGIONAL LYMPH NODES (N)	
Clinical Disease	
NX	Regional lymph node(s) cannot be assessed (e.g., previously removed)
N0	No regional lymph node metastasis
N1	Metastases to movable ipsilateral level I to II axillary lymph node(s)
N2	Metastases in ipsilateral axillary lymph nodes fixed or matted, or in clinically apparent[b] ipsilateral internal mammary nodes in the absence of clinically evident axillary lymph node metastasis
N2a	Metastases in ipsilateral axillary lymph nodes fixed to one another (matted) or to other structures
N2b	Metastases only in clinically apparent[b] ipsilateral internal mammary lymph nodes and in the absence of clinically evident axillary lymph node metastasis
N3	Metastases in ipsilateral infraclavicular lymph node(s) with or without axillary lymph node involvement, or in clinically apparent[b] ipsilateral internal mammary node(s) and in the presence of clinically evident axillary lymph node metastasis; or metastasis in ipsilateral supraclavicular lymph node(s) with or without axillary or internal mammary lymph node involvement
N3a	Metastases in ipsilateral infraclavicular lymph node(s)
N3b	Metastases in ipsilateral internal mammary lymph node(s) and axillary lymph node(s)
N3c	Metastases in ipsilateral supraclavicular lymph node(s)

TABLE G-7 American Joint Committee on Cancer Staging System for Breast Cancer—cont'd

Pathologic Disease (pN)[c]			
pNX	Regional lymph nodes cannot be assessed (e.g., previously removed or not removed for pathologic study)		
pN0	No regional lymph node metastasis histologically, no additional examination for isolated tumor cells[d]		
pN0(i–)	No regional lymph node metastasis histologically, negative immunohistochemical staining		
pN0(i+)	Isolated tumor cells identified histologically or by positive immunohistochemical staining, no cluster >0.2 mm		
pN0(mol–)	No regional lymph node metastasis histologically, negative molecular findings (RT-PCR)[e]		
pN0(mol+)	No regional lymph node metastasis histologically or by immunohistochemical staining, positive molecular findings (RT-PCR)e		
pN1	Metastasis in 1 to 3 axillary lymph nodes and/or in internal mammary nodes with microscopic disease detected by sentinel lymph node dissection but not clinically apparent[f]		
pN1mi	Micrometastasis (>0.2 mm or >200 cells, none >2 mm)		
pN1a	Metastasis in 1 to 3 axillary lymph nodes		
pN1b	Metastasis in internal mammary nodes with microscopic disease detected by sentinel lymph node dissection but not clinically apparent[f]		
pN1c	Metastasis in 1 to 3 axillary lymph nodes[g] and in internal mammary lymph nodes with microscopic disease detected by sentinel lymph node dissection but not clinically apparent[f]		
pN2	Metastasis in 1 to 3 axillary lymph nodes or in internal mammary nodes with microscopic disease detected by sentinel lymph node dissection but not clinically apparent[f]		
pN2a	Metastasis in 4 to 9 axillary lymph nodes (at least one tumor deposit >2 mm)		
pN2b	Metastasis in clinically apparent internal mammary lymph nodes in the absence of axillary lymph node metastasis		
pN3	Metastases in 10 or more axillary lymph nodes, or in infraclavicular lymph nodes, or in clinically apparent[b] ipsilateral internal mammary lymph nodes in the presence of one or more positive axillary lymph nodes; or in more than 3 axillary lymph nodes with clinically negative microscopic metastasis in internal mammary lymph nodes; or in ipsilateral supraclavicular lymph nodes		
pN3a	Metastasis in 10 or more axillary lymph nodes (at least one tumor deposit >2 mm), or metastasis to the infraclavicular lymph nodes		
pN3b	Metastasis in clinically apparent[b] ipsilateral internal mammary lymph nodes in the presence of one or more positive axillary lymph nodes; or in more than three axillary lymph nodes and in internal mammary lymph nodes with microscopic disease detected by sentinel lymph node dissection but not clinically apparent[f]		
pN3c	Metastasis in ipsilateral supraclavicular lymph nodes		
DISTANT METASTASIS (M)			
MX	Distant metastasis cannot be assessed		
M0	No distant metastasis		
cM0(i+)	No clinical or radiographic evidence of distant metastasis but molecular or microscopically detected tumor cells in circulating blood, bone marrow, or other nonregional nodal tissue no larger than 0.2 mm in a patient without symptoms		
M1	Distant metastasis		
STAGE GROUPING			
Stage 0	Tis	N0	M0
Stage I	T1[h]	N0	M0
Stage IIA	T0	N1	M0
	T1[h]	N1	M0
	T2	N0	M0
Stage IIB	T2	N1	M0
	T3	N0	M0
Stage IIIA	T0	N2	M0
	T1[h]	N2	M0
	T2	N2	M0
	T3	N1	M0
	T3	N2	M0
Stage IIIB	T4	N0	M0
	T4	N1	M0
	T4	N2	M0
Stage IIIC	Any T	N3	M0
Stage IV	Any T	Any N	M1

From Edge SB, Byrd DR, Compton CC, et al, eds: AJCC cancer staging manual, ed 3, New York, 2010, Springer, pp 345–376.

[a]*Paget's disease associated with a tumor is classified according to the size of the tumor.*

[b]Clinically apparent disease *is defined as disease detected by imaging studies (excluding lymphoscintigraphy) or by clinical examination or is disease that is grossly visible pathologically.*

[c]*Classification is based on axillary lymph node dissection with or without sentinel lymph node dissection. Classification based solely on sentinel lymph node dissection without subsequent axillary lymph node dissection is designated (sn) for "sentinel node," for example, pN0(i+)(sn).*

[d]*Isolated tumor cells are defined as single tumor cells or small cell clusters ≤0.2 mm, usually detected only by immunohistochemical or molecular methods but which may be verified on hematoxylin and eosin staining. Isolated tumor cells do not usually show evidence of metastatic activity (e.g., proliferation or stromal reaction).*

[e]*Reverse transcriptase-polymerase chain reaction.*

[f]Not clinically apparent disease *is defined as disease not detected by imaging studies (excluding lymphoscintigraphy) or by clinical examination.*

[g]*If associated with more than three positive axillary lymph nodes, the internal mammary nodes are classified as pN3b to reflect increased tumor burden.*

[h]*T1 includes T1mic.*

system, and it is critical that each case be assigned a tumor-nodes-metastasis (TNM) stage before any treatment is begun. For patients with clinical stage I or II disease, the staging workup should include a physical examination, diagnostic mammography, ultrasonography, and routine serum studies. For patients with locally advanced disease, screening tests for metastatic disease should include a bone scan and liver imaging with CT or PET/CT.

The TNM staging of breast cancer has evolved over time. Some of the more important changes in recent staging systems have included:

- Considering the number of positive lymph nodes in assigning the pathologic N stage
- Considering the size of positive lymph node metastasis in assigning the pathological N stage (micrometastasis versus macrometastasis)
- Changing involvement of infraclavicular lymph nodes from N1 to N3 disease
- Changing involvement of supraclavicular lymph nodes from M1 to N3 disease
- Considering isolated tumor cells detected with immunohistochemical staining of sentinel lymph nodes, which is denoted as N0(i+)

Although it is important to establish the clinical stage before breast cancer, this is preliminary and following surgery a more definitive stage will be decided based on pathological examination of the postsurgical specimen. The pathologic stage is important for prognosis, to understand tumor biology, and to direct future systemic therapies. In up to one third of patients who have no clinically evident axillary nodes at diagnosis, histological examination of the nodes after surgery reveals cancer.

BREAST CANCER BIOLOGIC CHARACTERISTICS

Breast cancer is a biologically heterogeneous disease. Recent advances in genomics and molecular biology techniques have permitted more comprehensive assessments of its genetic heterogeneity. DNA microarray expression profiles have led to classification of breast cancer into molecular subtypes that correspond with distinct prognostic groups based on biology and aggressiveness of the disease.[76,77] Interestingly, these molecular classes are strongly influenced by the genes controlling expression of the ER and HER2/neu receptor.

Molecular Classification

The molecular profiles of estrogen-enriched cancers tend to be similar to those of luminal ductal cells, whereas estrogen-negative breast cancers have molecular phenotypes similar to cells in the basal layers of the breast ductal epithelium. Tumors that overexpress HER2/neu have unique signatures. Recent molecular classifications often group diseases into four classes that overlap but are not synonymous with variations in ER, PR, and HER2/neu status: luminal A tumors, which include most ER-positive, PR-positive, HER2-negative tumors; luminal B tumors, which include most ER-positive, PR-positive, HER2-positive tumors; HER2 tumors, which include most ER-negative, PR-negative, HER2-positive tumors; and, finally, basilar cancers, which overlap significantly with triple-negative (ER-negative, PR-negative, HER2-negative) breast cancers.

Luminal A disease expresses more ER-related genes, carries the best prognosis and predicts response to hormonal therapy. Luminal B tumors express more cellular proliferation and HER2-related genes and often have a higher grade and a worse prognosis compared to luminal A. A subgroup (30% to 50%) of basal-type cancer tends to be chemoresponsive but is nevertheless an aggressive molecular subtype with an overall poor prognosis. Finally, the inherent aggressive biology of HER2-positive disease has been transformed with the use of trastuzumab and other HER2-directed therapies—lapatinib, pertuzumab, and recently ado-trastuzumab. Increasing numbers of reports suggest that molecular subtypes and genetic factors can also affect the outcome after radiation and other locoregional treatments. For patients treated with breast conservation, recent studies from Harvard, British Columbia, and the M. D. Anderson Cancer Center suggest that triple-negative or basilar-like cancers are at increased risk of local recurrence after treatment with lumpectomy and whole-breast radiation.[78-80] These findings are consistent with reports from the Danish randomized trials and the M. D. Anderson Cancer Center indicating that triple-negative disease is also associated with locoregional recurrence after postmastectomy radiation.[81,82]

Predictive Markers and Selection of Therapy

In addition to classification, molecular markers are used to select patients for systemic treatment (e.g., chemotherapy, endocrine therapy, and targeted therapy) and to predict those who are most likely to benefit from the therapies. The quintessential example of a predictive marker is ER; since its discovery, all breast tumors are pathologically assessed for ER and patients with ER-positive tumors benefit from antihormonal treatments such as tamoxifen. A second important predictive factor was discovered in 1985 as the HER2 or erbB2 protein and is found to be amplified in 20% of breast cancers leading to protein overexpression.[83,84] HER2/neu is a transmembrane cell surface receptor with an internal domain that activates downstream signaling pathways. Overexpression has been associated with increased proliferative capacity, enhancement of metastatic potential, and increased rate of tumorigenesis. Trastuzumab is a humanized monoclonal antibody against the extracellular domain of the surface receptor and is an effective treatment in HER2–positive breast cancer in both the metastatic and adjuvant settings (adjuvant therapy as discussed later).[85] HER2 testing by immunohistochemistry to measure protein expression or fluorescent in situ hybridization (FISH) to measure HER2 gene copies is standard for all breast tumors and is predictive of response to targeted therapy.[86]

Furthermore, gene products may be combined to provide a picture of the molecular phenotype of the individual's cancer and thereby predict recurrence or response to chemotherapy. The Oncotype DX assay (Genomic Health) is a 21-gene recurrence score assay that was originally designed to predict the recurrence of ER-positive, node-negative breast cancer after treatment with adjuvant endocrine therapy. The test estimates 10-year risk of recurrence using formalin-fixed, paraffin-embedded tumor tissue. The gene expression is analyzed and a risk score (RS) is assigned based on a weighted algorithm. The assay was validated in 668 patient samples from patients treated with ER-positive, node-negative, tamoxifen who were enrolled in the NSABP B-14 clinical trial.[87] It has now been clinically adopted to determine whether women with high-risk, node negative, HER2-negative, ER-positive breast cancer should receive adjuvant chemotherapy in addition to endocrine therapy (see discussion in this chapter) as it is able to predict the magnitude of benefit.[88]

The assay categorizes patients into three risk groups: (1) A low-risk group (RS, 0-18), distant recurrence risk of less than 10%; (2) intermediate-risk group (18 < RS < 31), distant recurrence risk between 10% and 20%; (3) high-risk (RS > 31), distant recurrence risk greater than 20%. Chemotherapy is generally recommended for patients with intermediate and

high risk for recurrence.[89] Other multigene assays have been identified such as Mammaprint and PAM50; however, Oncotype-DX is widely used in the United States because of its practical attributes and ability to predict response to chemotherapy.

The prognostic and predictive capabilities of the Oncotype DX assay are continually being evaluated. In the prospective, randomized TAILORx clinical trial, patients assigned an intermediate RS were randomized to receive either chemotherapy and hormonal therapy or hormonal therapy alone. This trial enrolled more than 11,000 patients and closed to accrual in October 2010. Results are eagerly anticipated and will refine the utility of the test for the intermediate-risk group. A similar trial for patients who are node-positive (RxPONDER; SWOG S1007) is currently enrolling patients to determine whether there is a subset of patients who are node-positive, HER2-negative, hormone receptor–positive who may be spared from chemotherapy. As discussed later in this chapter, according to current guidelines, patients who are node-positive should be offered chemotherapy outside of a clinical trial.[89]

TREATMENT OVERVIEW

For invasive breast cancer in stages I to III, the goals of treatment are curative. Treatment decisions are ultimately made with regard to patient comorbidities, after weighing the potential benefits and harms of therapy, and based on the patient's personal preferences. Often, several extended discussions between the patient and a multidisciplinary team including medical oncology, surgical oncology, plastic surgery, and radiation oncology are needed to determine the best treatment plan. Multimodality therapy (Figure G-5) has had a profound impact on the outcomes of breast cancer because it has allowed for improved disease-free survival and overall survival.

Locoregional Treatments

Surgery and radiation have important roles in the curative management of most breast cancers and greatly determine the level of local control achievable. For patients with early-stage invasive disease, surgery can either be a breast-conserving resection of the primary tumor (e.g., a lumpectomy, segmental mastectomy, wide local excision) or a mastectomy. As highlighted in the subsequent chapter on early-stage breast cancer, numerous randomized prospective clinical trials have indicated that breast-conserving surgery with whole-breast radiation provides long-term outcomes equivalent to those of mastectomy. The goal of breast-conserving surgery should be to remove the primary tumor with surgical margins that are free from either invasive or in situ disease. A secondary goal is to provide the best possible cosmetic outcome, without retraction, nipple displacement, or excess volume loss from the procedure. For some women with larger breasts, several centers are now advocating oncoplastic surgery, in which local tissue rearrangements are performed at the time of surgical resection to maintain optimal breast aesthetics.[90,91]

Breast Surgery

Mastectomy is performed when the tumor is too large or locally advanced to allow breast conservation, although neoadjuvant systemic therapy can sometimes convert a patient into becoming eligible for breast-conserving surgery. Furthermore, mastectomy is indicated if the tumor is multicentric or multifocal, if the patient has a contraindication to radiation therapy, if the lesion is an ipsilateral recurrence in a previously irradiated breast, or if margin-free status cannot be achieved. Mastectomy is also a highly effective local treatment modality for early-stage disease and often precludes the need for radiation if the patient has lymph node-negative disease.

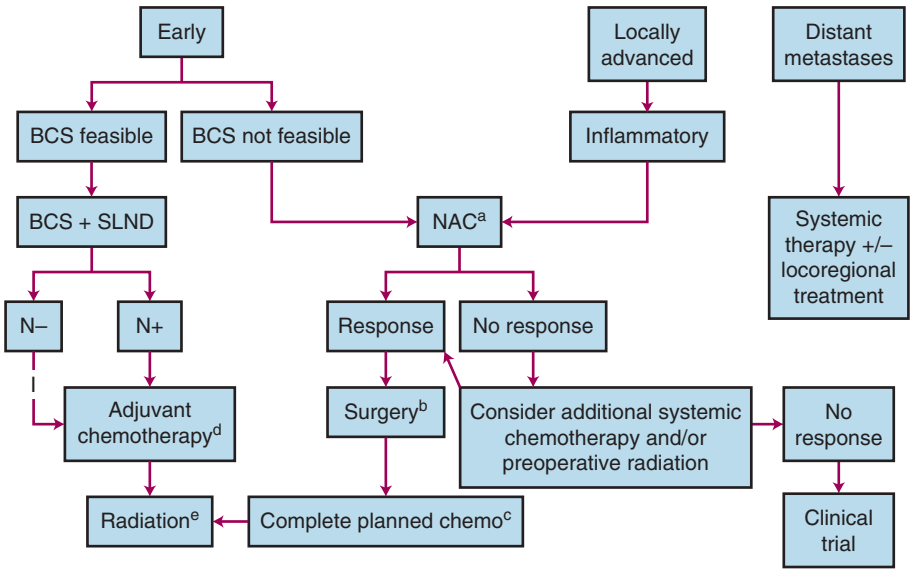


Figure G-5 Overview of multimodality therapy for breast cancer. *ALND,* axillary lymph node dissection; *BCS,* breast-conservation surgery; *ER,* estrogen receptor; *NAC,* neoadjuvant chemotherapy; *PR,* progesterone receptor; *SLND,* sentinel lymph node dissection. [a]Anthracycline- and taxane-based therapy is preferred. For Her2-positive tumor, add dual anti-HER2 blockade to the taxane portion. [b]The extent of surgery is determined by response but always includes an ALND. In inflammatory breast cancer, the surgery is always mastectomy + ALND. [c]Complete planned chemotherapy regimen if not completed preoperatively. Add endocrine treatment if ER-positive or PR-positive. Complete up to 1 year of trastuzumab in HER2-positive disease; may be administered concurrently with radiation therapy and with endocrine therapy if indicated. [d]Adjuvant chemotherapy is indicated in triple negative and HER2-positive tumors >5 mm. In hormone receptor–positive, HER2-negative tumors, chemotherapy is beneficial in patients with a high recurrence score on Oncotype-DX testing and is currently offered as standard of care in patients with intermediate recurrence score. [e]Whole-breast radiation with or without chest wall and lymph node basins as clinically indicated. For inflammatory breast cancer, radiation should include chest wall, level I/II axillary lymph nodes, supraclavicular nodes, and internal mammary lymph nodes if involved.
Adapted from NCCN guidelines and the ASCO-SEP Medical Oncology Self-Evaluation Program.

Skin-sparing mastectomy can preserve significant breast skin, which can allow plastic surgeons to use the breast's natural scaffolding to optimize the cosmetic results of an immediate reconstruction. If the normal inframammary sulcus is maintained, the breast can be reconstructed with excellent symmetry to the contralateral breast. Immediate breast reconstruction can be performed at the time of mastectomy for patients with noninvasive or early-stage disease and can be accomplished with tissue expanders and implants or autologous tissue flaps. Reconstruction may also be delayed for a period of up to 1 to 2 years.

Axillary Management

In addition to treating the primary breast tumor, surgery is important for staging and treatment of the axillary lymph nodes. For patients with invasive disease but no clinical evidence of spread to axillary lymph nodes, sentinel lymph node surgery is the gold standard approach for initial axillary disease staging. Sentinel lymph node biopsy is based on the concept that there is a reproducibly identifiable node (or nodes) that drains the breast and predicts the status of the remaining axillary lymph nodes.[92] This procedure entails injection of azusulfan blue dye or a radiocolloid, or both, into the periareolar or peritumoral subcutaneous tissue. Drainage to the first-echelon lymph nodes in the axilla is then detected by visual inspection of afferent lymphatic channels to a blue node or by use of a handheld gamma probe to detect lymph nodes showing radioactivity. Randomized trials have indicated that sentinel lymph node surgery is highly accurate, with identification and detection rates of 97%, equivalent to those of standard axillary dissection.[93] Axillary recurrence rates are less than 1% after a negative sentinel lymph node biopsy.[94] Currently, sentinel lymph node biopsy is the standard of care for staging the axilla in women with T1-T3, clinically node negative breast cancer.

The sentinel lymph node biopsy procedure represents a significant advance in surgical management that reduces the morbidity of axillary dissection in patients with node-negative disease by reliably differentiating between patients who are node-negative and node-positive disease. One of the main clinical questions after standardization of this approach is to ask whether there is a need for axillary dissection for local control and survival in the era of multimodality therapy. The ACOSOG Z11 trial randomized women with clinically node-negative with cancer <5 cm in size and positive sentinel lymph node(s) (<3 in number) treated with lumpectomy and radiation to completion axillary dissection versus no further surgery. At a median follow-up of 6 years, there were no differences in local control or survival between the groups.[95] Although these results are impressive, much discussion has occurred and the consensus is that further investigation is necessary. A key question is whether whole breast radiation played any role in the low recurrence rates and whether the axilla was actually untreated as all patients in the study received adjuvant breast radiation as a part of their breast-conservation surgery. Furthermore, long-term follow-up is needed as the majority of patients in the Z11 study had ER-positive, HER2/neu–negative postmenopausal disease making them more susceptible to late recurrences. Given that axillary burden is a reflection of tumor biology, these results should be applied within context and carefully to a select group of women who meet the Z11 criteria (Box G-2).[96] In patients who meet the strict criteria for the trial, discussion of these data should ensue with a focus on the questions that remain and the need for long-term follow-up.[97]

Radiation

The role of radiation in the locoregional management of breast cancer is reviewed in the three chapters on ductal carcinoma in situ, early-stage invasive disease, and locally advanced disease. Investigations of the use of radiation for breast cancer date back to some of the first randomized prospective trials in medicine, conducted during the 1950s and 1960s. As such, radiation is one of the most comprehensively investigated aspects of breast cancer care. A unique aspect of these investigations is that the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) in Oxford, England, which has done meta-analyses of the compiled data every 5 years, has centralized all of the data from each randomized trial investigating radiation treatments. Data from the EBCTCG analyses have yielded important and conclusive information about the benefits and risks of radiation treatments for breast cancer. For many decades, radiation was clearly shown to reduce the probability of locoregional recurrence for patients treated with breast-conserving surgery and for patients with positive lymph nodes who underwent mastectomy. The 2005 publication of the EBCTCG meta-analysis, which was able to assess 15-year outcome data, further demonstrated that use of radiation could reduce rates of breast cancer death and improve overall survival rates.[98] Included in that study were individual patient data from 42,080 patients with breast cancer treated in 78 clinical trials that investigated locoregional treatments between 1952 and 1995. Among those patients were 7311 patients treated in 10 trials comparing radiation versus no radiation after breast-conserving surgery and 9933 patients treated in 25 trials comparing radiation versus no radiation after modified radical mastectomy. In the trials that investigated radiation as a component of breast-conservation therapy, radiation was shown to reduce the risk of local recurrence by two thirds and to improve the absolute 15-year overall survival rate by 6% (41% versus 35%). Similarly, for patients with positive lymph nodes treated with modified radical mastectomy, radiation reduced the locoregional recurrence rate by 21% at 15 years (29% versus 8%), which was associated with a 5% decrease in the 15-year breast cancer mortality rate (60% versus 55%). A more recent update of these analyses continues to demonstrate locoregional and survival advantages for radiation therapy.[98]

The time course of the survival advantages from radiation is quite different than that seen from adjuvant systemic treatments. Specifically, survival advantages from systemic treatments tend to become evident within the first 5 years, probably reflecting the eradication of micrometastatic disease present at the time of adjuvant treatment. In contrast, the survival benefits from radiation reflect the eradication of persistent locoregional disease. For persistent locoregional disease to cause death, it must first repopulate and then successfully metastasize, after which the metastases must grow and become life-threatening. This concept is supported by data from the EBCTCG analyses; specifically, the locoregional advantages associated with radiation were found to occur early,

BOX G-2 ACOSOG Z0011 Criteria

"Z11 CRITERIA"[95,96]

Clinical T1 or T2 tumors
Clinically node negative
Breast conserving surgery and whole breast radiation
One or two positive sentinel lymph nodes
The following patients should be excluded:
Mastectomy
Breast conservation surgery with accelerated partial-breast radiation
Neoadjuvant chemotherapy
Three or more positive sentinel lymph nodes

with separation of the radiation versus no radiation curves developing during the first 5 years. However, the survival curves continued to overlap during these first 5 years, separating only later to become clearly evident by 15 years.[98,99]

The EBCTCG data also have been valuable in clarifying potential risks associated with radiation. Long-term outcome data from randomized trials indicate that coincidental radiation of the heart increased the risk of subsequent death from cardiovascular disease.[43] Indeed, in the first generation of randomized radiation trials, the percentage of patients dying from cardiovascular disease was roughly proportional to the decrease in risk of death from breast cancer after radiation therapy. These findings highlighted the importance of developing new radiation techniques to avoid irradiating the heart. Fortunately, with improvements in radiation techniques and improvements in the management of cardiovascular disease, the risk of cardiac toxicity associated with radiation has decreased over time.[100,101]

In general, the survival benefits associated with radiation treatments depend on four factors: (1) the risk of persistent locoregional disease after surgery and adjuvant systemic therapy; (2) the success of radiation in eradicating any persistent locoregional disease; (3) the risk of radiation-related death from normal tissue effects; and (4) the risk of dying of micrometastatic disease present at the time of locoregional treatment and outside of the radiation treatment volume. The success of radiation in eradicating persistent locoregional disease has increased and the risk of radiation-related toxicity has declined with the development of new treatment techniques that more accurately deliver the appropriate radiation doses to intended targets while avoiding radiation of normal tissues. Remarkably, the benefits of radiation have been relatively consistent over time: generally, radiation can reduce the risk of recurrence in all clinical settings by 65% to 75%.[98] In addition, with the advent of modern radiation techniques, the risk of radiation-associated death from normal tissue effects should be quite small.

Clinical research continues in attempts to identify, before treatment if possible, which patients will have clinically relevant persistent locoregional disease after surgery and adjuvant systemic therapy. The current standard is to recommend adjuvant radiation therapy for patients with invasive disease who are treated with breast-conserving surgery with the possible exception of women older than the age of 70 years with stage I ER-positive breast cancer. In addition, women with pathologic stage III breast cancer and some patients with pathologic stage II breast cancer who are treated with systemic therapy and surgery should receive postmastectomy radiation because of the clinically relevant risk of persistent locoregional disease. The risk of persistent disease is also interrelated with the risk of dying from micrometastatic disease that is present at the time of locoregional treatment and is outside of the radiation treatment volume. Specifically, having more than one involved lymph node and having an advanced primary tumor are predictive for both locoregional recurrence and distant metastases. Correspondingly, the probability of achieving a survival advantage with radiation may change over time as new systemic therapies are developed that have a much higher probability of reducing the competing risk of dying from micrometastatic disease.

Systemic Treatments

Systemic treatments are added to the treatment regimen of locally advanced or early-stage breast cancer based on a balance between the risk of distant metastasis and the benefit of therapies to reduce the risk of relapse early in the disease course (within the first 5 years). Data from a meta-analysis of adjuvant chemotherapy trials conducted by the EBCTCG indicate that systemic therapy provides a survival benefit for patients with lymph node-positive disease, those with lymph node-negative disease, and those with ER-positive tumors.[102] As you read further in this section, it will be helpful to refer to Figures G-5 and G-6. With increasing stage of disease, there is an associated increased risk in the development of systemic recurrence. In addition, to the extent of disease present at diagnosis, the underlying biological characteristics of the tumor are vital to determine the risk of recurrence or existence of micrometastatic disease. Age is an independent prognostic feature and younger women are at a higher risk of local and distant recurrence. In the setting of a young patient population, adjuvant systemic therapy is offered at a lower risk-to-benefit threshold. In comparison, for women older than age 70, there are no strict guidelines because few of them are included in clinical trials and decisions to proceed with systemic treatment should consider patient comorbidities and toxicity related to treatments. Treatment for breast cancer with cytotoxic agents may impair fertility and all patients who are premenopausal should be informed of the potential impact of chemotherapy on fertility. It is appropriate to consider fertility preservation before breast cancer treatment in young women who desire to bear children in the future.

Selection of Therapy

To help physicians and patients make treatment decisions and understand prognosis, Adjuvant! (www.adjuvantonline.com) was designed to determine the risk of relapse and death and to estimate the benefit of adjuvant systemic therapy based on patient age, comorbid conditions, tumor grade, ER status, tumor size, and the number of involved lymph nodes.[103] Systemic therapy should be considered for all patients when the tumor size is larger than 0.5 cm regardless of nodal status, or when there is lymph node involvement regardless of tumor size. The only patients who may not be at sufficient risk to warrant systemic treatment are those with small stage I tumors (<6 mm) that do not overexpress HER2/neu (Figure G-6).

The NCCN guidelines recommends consideration of Oncotype DX testing in patients with hormone receptor–positive, HER2/neu–negative, node-negative disease to help identify patients who are predicted to obtain the most benefit from adjuvant hormonal therapy alone and those who may or may not require adjuvant chemotherapy.[89] Tumors larger than 1.0 cm or tumors measuring 6 mm to 1.0 cm with unfavorable features including angiolymphatic invasion, high nuclear grade, or high histological grade, triple receptor negative and HER2/neu–positive should be considered for systemic adjuvant therapy, Tumors with a high RS (>31) have a predicted benefit from chemotherapy in addition to hormonal therapy. Patients in the low risk group (RS, 0-18) with a distant recurrence rate of less than 10% are predicted to have marginal benefit if any from adjuvant chemotherapy and should be offered hormonal therapy alone. Patients who are in the intermediate RS group (19-31) and those who are node positive (1-3) are currently being advised to receive chemotherapy followed by hormonal therapy; the clinical utility of Oncotype-DX test in these groups is being further defined in clinical trials (TAILORx and RxPONDER, respectively).

Cytotoxic Therapies

Several regimens are considered appropriate standard treatment for early and locally advanced disease (Tables G-8 and G-9). In general, a combination of two or more drugs is more effective than single agents. The NSABP B-18 trial showed that the administration of chemotherapy in the neoadjuvant setting did not improve or affect disease-free survival or overall survival in comparison to adjuvant administration.[124] Given that

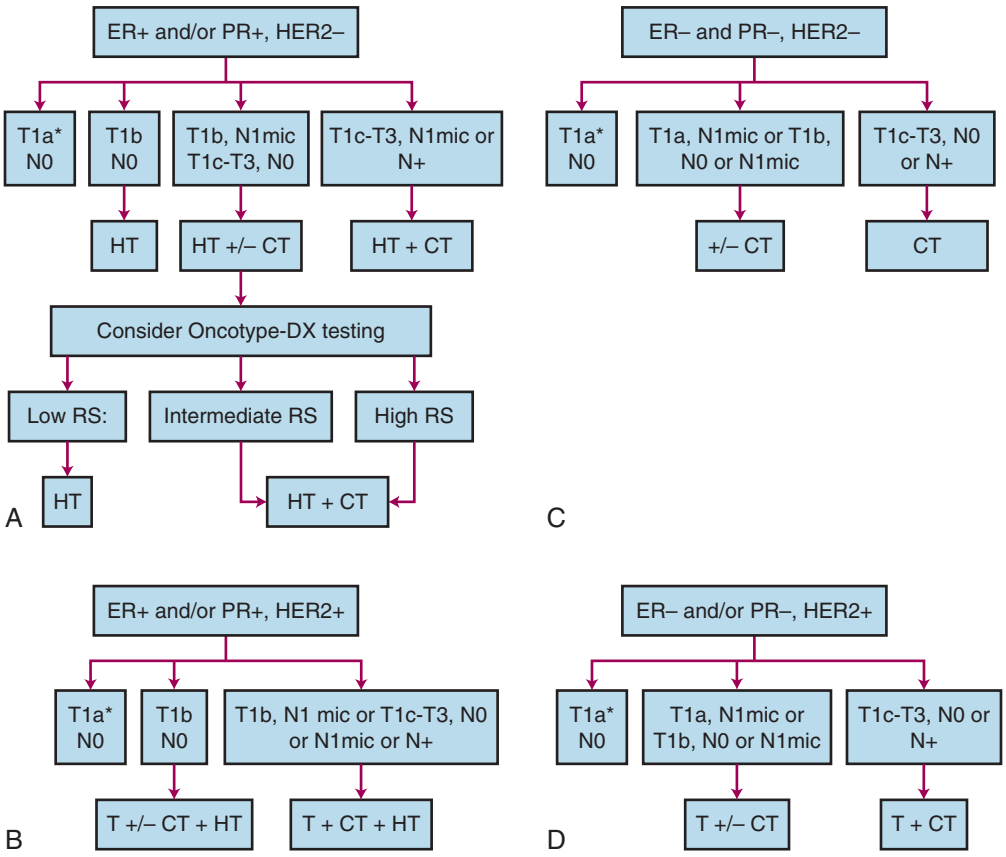


Figure G-6 Guidelines for adjuvant systemic therapy for **(A)** hormone receptor–positive, HER2-negative disease **(B)** hormone receptor–positive, HER2-positive disease **(C)** hormone receptor–negative, HER2 negative, and **(D)** hormone receptor–negative, HER2-positive disease. *CT,* Chemotherapy; *ER,* estrogen receptor; *HT,* hormonal therapy; *N+,* node positive; *PR,* progesterone receptor; *RS,* recurrence score; *T,* trastuzumab. *No adjuvant therapy; consider hormonal therapy in hormone receptor positive tumors for disease prevention.
Adapted from NCCN guidelines and the ASCO-SEP Medical Oncology Self-Evaluation Program.

TABLE G-8 Adjuvant or Neoadjuvant Chemotherapy Options

HER2-Negative Disease[a]	HER2-Positive Disease[c]
Adjuvant or Neoadjuvant	**Adjuvant**
Doxorubicin/cyclophosphamide (AC) × 4 cycles followed by 12 weeks of paclitaxel (p × 12)[b,104]	AC × 4 cycles followed by 12 weeks of paclitaxel and trastuzumab ± pertuzumab (pH ± P)[d] followed by trastuzumab (H) (over a 40-week duration)[114]
Dose-dense doxorubicin/cyclophosphamide (ddAC) × 4 cycles followed by dose-dense paclitaxel (ddp) × 4 cycles[105]	Docetaxel/carboplatin/trastuzumab ± pertuzumab (TCH ± P)[d] × 6 cycles followed by H (over a 34-week duration)[115]
Docetaxel/doxorubicin/cyclophosphamide (TAC) × 6 cycles[106]	Paclitaxel (p) and trastuzumab (H) (pH) × 12[e] followed by trastuzumab (H) (over a 40-week duration)[116]
Doxorubicin/cyclophosphamide (AC) × 4 cycles followed by docetaxel (D) ×4 cycles[107-109]	**Neoadjuvant**[d]
Other:	Non-anthracycline containing:
Docetaxel/cyclophosphamide (TC)[f] × 4 cycles[110]	Docetaxel/trastuzumab/pertuzumab (THP) × 4-6 cycles followed by adjuvant H (over a 40-week duration)[117]
Cyclophosphamide/methotrexate/fluorouracil (CMF)[g] × 6 cycles[111]	Docetaxel/carboplatin/trastuzumab/pertuzumab (TCHP) × 6 cycles followed by adjuvant H (over a 40-week duration).[118]
The following may be substituted for AC in the regimen AC × 4 → p × 12:	Anthracycline containing:
Fluorouracil/Adriamycin/cyclophosphamide (FAC) × 4 cycles[112]	AC/FAC/FEC/EC × 3-4 cycles, followed by preoperative THP × 3-4 cycles followed by adjuvant H (over a 40-week duration).[118,119]
Fluorouracil/epirubicin/cyclophosphamide (FEC) × 4 cycles[113]	

[a]*In Her2-negative disease, adjuvant systemic regimens are equally effective administered as adjuvant or neoadjuvant.*
[b]*The following substitutions may be made for AC: fluorouracil/epirubicin/cyclophosphamide (FEC); fluorouracil/adriamycin/cyclophosphamide (FAC).*
[c]*For patients with Her2-positive and axillary node-positive breast cancer, trastuzumab should be a component of their adjuvant systemic therapy. Trastuzumab should be highly considered for patients with HER2-positive node-negative tumors ≥1 cm. Trastuzumab given in combination with an anthracycline is associated with significant cardiac toxicity. Anti-Her2 therapy should not be given in combination with an anthracycline.*
[d]*A pertuzumab containing regimen should be administered to patients with HER2-positive breast cancer preferably in the neoadjuvant setting for tumors >2 cm that are locally advanced and operable. Patients who have not received a neoadjuvant pertuzumab-containing regimen may receive adjuvant pertuzumab.*
[e]*Paclitaxel with trastuzumab may be considered for patients with low-risk stage I, Her2-positive disease, particularly if not eligible for other standard adjuvant regimens because of comorbidities. Preliminary results from the Adjuvant Paclitaxel and Trastuzumab (APT) study were presented at San Antonio Breast Cancer Symposium 2013.*
[f]*Can be considered in patients who are low-risk and node negative; if node positive, anthracycline-containing regimen is preferred.*
[g]*Can be considered in patients who are low risk, those who have underlying cardiac dysfunction, or those with recurrent breast cancer or new breast primary who have previously received anthracycline-based therapy.*

TABLE G-9 Adjuvant Endocrine Therapy in Hormone Receptor-Positive Disease

Study	Endocrine Therapy/Duration	RR Recurrence	RR Mortality
	Primary Therapy		
EBCTC[120]	Tamoxifen (5 yrs)	0.61 (0.57-0.65)	0.70 (0.64-0.75)
ATAC[121]	Anastrozole vs. tamoxifen (5 yrs)	0.90 (0.82-0.99)	1.00 (0.89-1.12)
BIG 1-98[122]	Letrozole vs. tamoxifen (5 yrs)	0.88 (0.78-0.99)	0.81 (0.69-0.94)
	Sequential Therapy		
BIG 1-98	Tamoxifen/letrozole vs. letrozole Letrozole/tamoxifen vs. letrozole	1.05 (0.84-1.32) 0.96 (0.76-1.21)	1.13 (0.83-1.53) 0.90 (0.65-1.24)
	Extended Therapy		
NCIC CTG MA. 17[123]	Tamoxifen × 5 yrs followed by letrozole × 5 yrs	0.68 (0.55-0.83)	0.98 (0.78-1.22)

RR, *Relative risk;* yrs, *years.*

there is no efficacy advantage in progression-free or overall survival, systemic therapy regimens may be considered for administration in the adjuvant or neoadjuvant settings.[125] For locally advanced or inflammatory breast cancers, chemotherapy with or without targeted therapy is routinely administered in the neoadjuvant setting. The key advantages of neoadjuvant chemotherapy (NAC) include the ability to enable breast conserving surgery by downstaging tumors before surgery and the ability to assess in vivo response to chemotherapy.[126] In addition to increasing the likelihood of tumor control, more recently, a cited advantage of administering chemotherapy in the neoadjuvant setting has been accelerated drug approval. Pathological complete response has been proposed as a surrogate endpoint predictive of long-term clinical benefit and neoadjuvant trials allow for rapid assessment of drug efficacy.[127,128]

The most widely adopted regimens include combinations of an anthracycline and a taxane (either paclitaxel or docetaxel). This recommendation is based in part on an intergroup trial that randomly assigned patients who had been treated with four cycles of doxorubicin and cyclophosphamide (AC) to receive either four cycles of paclitaxel or no additional chemotherapy. Results of that trial showed a disease-free survival benefit for patients treated with paclitaxel.[129] These results are supported by those of a similar study conducted by the NSABP (the B-28 trial), which also found that patients who received four cycles of AC plus four cycles of paclitaxel had higher disease-free survival rates than those who received four cycles of AC alone.[130] Subsequent chemotherapy trials have investigated various combinations of taxane and anthracycline chemotherapy. An intergroup trial revealed that giving four cycles of AC followed by four cycles of paclitaxel in a dose-dense fashion improved disease-free survival rates relative to the usual 3-week dosing schedule of the same chemotherapy.[131] Finally, the Breast Cancer International Research Group conducted a trial that randomly assigned patients with lymph node-positive breast cancer to receive either six cycles of docetaxel, doxorubicin, and cyclophosphamide (TAC) or six cycles of fluorouracil, doxorubicin, and cyclophosphamide (FAC) and found an improvement in disease-free survival rates among those given TAC.[132] Collectively, these findings suggest that for patients with high-risk disease features (e.g., lymph node-positive disease, and node-negative with unfavorable features including large tumor size, high histological grade, triple receptor negative), any of the following third-generation chemotherapy regimens can be considered acceptable: dose-dense scheduling of AC with paclitaxel, weekly paclitaxel followed by AC, AC followed by docetaxel every 3 weeks, or TAC.[104,107,131,133,134] For patients with lower-risk breast cancer who desire a shorter course of chemotherapy, giving four cycles of docetaxel and cyclophosphamide (TC) has become more common after a recent randomized prospective trial found that this regimen produced better disease-free survival and overall survival rates than did four cycles of AC.[135]

Triple-negative breast cancer (TNBC) lacks expression of ER and PR and lacks overexpression or amplification of HER2 and is worth some focused attention because it is associated with a poor prognosis and poor overall response to standard anthracycline and taxane-based chemotherapy. Standard chemotherapy when administered in a neoadjuvant (NAC) fashion and results in a pathological complete response (pCR) of 20% to 34%.[128,136,137] A pCR is associated with increased survival and those who do not achieve this status are at high risk for disease recurrence.[138] Recent studies have shown that the pCR may be improved in TNBC with the addition of platinum-based NAC; however, this continues to be a topic of debate across TNBC.[139] Continued research efforts are under way to improve local and systemic control in this molecular subtype.

Endocrine Therapies

For most patients with ER-positive or PR-positive disease, hormonal therapy is indicated (Table G-9). Before selection of hormonal therapy, it is important to establish the patient's menopausal status. Premenopausal women whose ovaries continue to function after chemotherapy should receive tamoxifen for 5 years to 10 years as the preferred therapy.[140,141] Cytotoxic therapy may induce menopause; however, for the purpose of adjuvant hormonal therapy selection, the patient's menopausal status at the time of diagnosis is most relevant. Patients who were perimenopausal at the time of diagnosis should receive tamoxifen for 2 years to 3 years and may be switched to an aromatase inhibitor when they achieve menopause. For women who are postmenopausal, the use of an aromatase inhibitor is most effective. There are several options for patients who are postmenopausal, including an aromatase inhibitor for 5 years, initial tamoxifen for 2 years to 3 years followed by an aromatase inhibitor, aromatase inhibitor for 2 years to 3 years followed by tamoxifen for 2 years to 3 years or tamoxifen for 5 years followed by 5 years of an aromatase inhibitor.[142-144] Results of a recent EBCTCG meta-analysis of trials that compared breast cancer outcomes with adjuvant aromatase inhibitors versus tamoxifen for women who are postmenopausal with ER-positive breast cancer demonstrated that the use of aromatase inhibitors was associated with a breast cancer recurrence rate that was 3% lower than that with tamoxifen within 3 years to 5 years of follow-up.[64] A recent consensus statement from the American Society of Clinical Oncology that also reviewed published and ongoing trials of

adjuvant aromatase inhibitors recommends that women who are postmenopausal with ER-positive breast cancer consider incorporating an aromatase inhibitor at some point during adjuvant treatment.[145]

HER2 Targeting

The introduction of trastuzumab (Herceptin) for the adjuvant treatment of tumors with amplification of HER2/neu has been one of the most exciting advances in systemic treatment in the history of breast cancer. Randomized prospective trials demonstrated substantial improvements in disease-free and overall survival rates for patients with HER2/neu-overexpressing tumors when trastuzumab was added to adjuvant chemotherapy.[146-148] Specifically, the combined results from two randomized trials involving 3351 patients (94% of whom had lymph node-positive disease) indicated that four cycles of AC followed by weekly paclitaxel or 3-week paclitaxel with concurrent trastuzumab followed by 1 year of trastuzumab achieved a 52% reduction in the relative risk of recurrence compared with chemotherapy without trastuzumab.[147] The absolute reduction in risk of recurrence at 3 years was 12%. The European Herceptin Adjuvant (HERA) trial randomly assigned 5081 patients who had received at least four cycles of chemotherapy for HER2/neu-positive breast cancer (68% of whom had positive lymph nodes) to receive no further treatment, trastuzumab for 1 year, or trastuzumab for 2 years.[146] Trastuzumab reduced the relative risk of recurrence over chemotherapy alone by 46% (8.4% absolute reduction of the risk at 3 years). Finally, the Breast Cancer International Research Group trial 006 randomly assigned 3174 patients with HER2/neu-positive breast cancer (71% of whom had lymph node-positive disease) to receive chemotherapy with or without trastuzumab. That trial again confirmed that the addition of trastuzumab reduced the relative risk of recurrence or death over chemotherapy alone by 39%.[148] The incorporation of adjuvant trastuzumab based therapy has transformed the natural history of HER2-positive disease.

Neoadjuvant treatment with HER2 blockade has been found to significantly improve the pCR rate for patients treated with chemotherapy plus trastuzumab compared to chemotherapy alone.[149,150] More recently, neoadjuvant dual HER2 blockade has been evaluated.[117,118,151] The NeoSPHERE and NeoALLTO studies demonstrated that double HER2 blockade increased the pCR rate from 29% to 45% with pertuzumab plus trastuzumab and from 29% to 51% with lapatinib plus trastuzumab.[117,151] In NeoSPHERE, patients with hormone receptor–negative disease had a greater benefit when treated in the arm with dual HER2 blockade and chemotherapy. Of note, 17% of patients in the dual HER2 blockade–only arm achieved a pCR. It has recently been shown that achievement of a pCR specifically in the NeoALLTO study translates to an event-free survival and overall survival benefit.[152] In 2014 the results of ALTTO, NeoALTTO's "sister" trial in the adjuvant setting became available showing no additional benefit for the addition of lapatinib to trastuzumab in the adjuvant treatment of HER2 positive breast cancer.[152a]

For HER2-positive tumors that are large (>2 cm), operable, and locally advanced, the preferred treatment approach currently is dual HER2 blockade in the neoadjuvant setting with trastuzumab and pertuzumab in combination with a taxane with or without sequential anthracycline-based therapy.[117,118] Pertuzumab recently gained Food and Drug Administration (FDA) approval in the neoadjuvant setting in October 2013 and is recommended for use in one of the combinations as listed in Table G-8. A trial known as the Adjuvant Pertuzumab and Herceptin in Initial Therapy of Breast Cancer (APHINITY) will provide further data, disease-free survival, and results are eagerly anticipated in 2016. Further clinical investigation will be required to further examine the role of dual HER2 blockade alone and to identify the subset of patients that achieve pCR with a less toxic regimen.[117]

Sequencing of Therapies

The choice of sequence of systemic therapy in relation to surgery and radiation is optimally made by a multidisciplinary team. The decision is based on disease stage, the need for "up front" pathologic staging information, patient eligibility and desire for breast conservation, and coordination of the treating disciplines. Sequences in which chemotherapy is given before surgery (neoadjuvant therapy) are becoming increasingly more common for patients with stage II or III breast cancer. Trials investigating neoadjuvant hormonal therapy and chemotherapy with or without targeted therapy and its use to increase rates of breast conservation are reviewed in an upcoming chapter. For those patients who undergo surgery to be followed by adjuvant chemotherapy and adjuvant radiation, most centers in the United States recommend that the chemotherapy be completed first and then the radiation be given. A randomized prospective trial comparing 12 weeks of adjuvant chemotherapy given either before or after radiation for patients treated with breast-conservation therapy found no significant differences between the two treatment groups in time to any event, distant metastasis, or death.[153] The findings from this trial indicated that plans to delay radiation so that adjuvant chemotherapy could be completed first should be considered only for those patients with negative surgical margins. The sequencing of hormonal therapy and radiation has not been studied in a randomized comparative trial, but retrospective analyses suggest that concurrent and sequential treatments probably provide similar outcomes.[154-156] Finally, concurrent radiation and trastuzumab treatment also seems to be safe, although information on long-term outcome is not yet available. Randomized trials investigating the use of adjuvant trastuzumab have involved giving radiation and trastuzumab concurrently; findings from these trials on normal tissue effects, including short-term cardiac toxicity, suggest that giving trastuzumab concurrently with radiation does not increase the risk of injury.[157,158]

FINAL REMARKS

In the past 20 years, there has been tremendous growth in knowledge regarding the pathogenesis and treatment of breast cancer. Many of these advances have been possible because of collaborative focused efforts among radiologists, pathologists, genetic counselors, radiation oncologists, surgical oncologists, and medical oncologists. In this introductory chapter to the breast cancer section, we provide a broad overview that ranges from incidence and mortality to anatomy, biological characteristics, risk assessment, screening, diagnosis, staging, prognosis, selection of therapies, and multimodality treatment (surgery, radiation, and systemic therapy). We hope to have provided a strong foundation that will help you in your study moving forward. In the chapters to follow, there will be a more detailed discussion of early breast cancer, postmastectomy radiation, and DCIS from a radiation oncology focused perspective.

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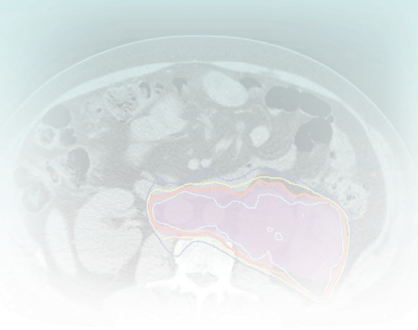
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CHAPTER

62 Noninvasive Breast Cancer



Chirag Shah, Douglas W. Arthur, and Frank A. Vicini

INCIDENCE

Noninvasive breast disease accounts for more than 20% of all breast cancers. Lobular carcinoma in situ (LCIS) represents less than 15% of these noninvasive cancers, whereas ductal carcinoma in situ (DCIS) represents 85% of noninvasive cancers. A third less common form of noninvasive disease, Paget's disease, accounts for 0.5% to 5% of all breast cancers.

BIOLOGIC AND PATHOLOGIC CHARACTERISTICS

LCIS is a noninfiltrating lobular proliferation exemplified by loose discohesive cells filling the acinar space. Lesions are frequently positive for estrogen receptor (ER) and progesterone receptor (PR), and loss of *E-cadherin (CDH1)* gene expression is characteristic. Overexpression of the c-*ERBB2* gene or mutation of the *TP53* gene may occur, but this is rare with the exception of pleomorphic LCIS.

In Paget's disease, Paget's cells are found in the epidermis with underlying malignant tissue found in more than 95% of cases.

DCIS is a noninfiltrating clonal proliferative process confined to the ductal lumens of the breast. DCIS may be a precursor to invasive disease. ER positivity is present in 70% of DCIS lesions; the rate of expression varies according to the grade of the lesion. The rate of expression is 90% in low-grade lesions and 25% in high-grade lesions. About 35% of DCIS lesions exhibit overexpression of the *HER2 (ERBB2)* gene and about 25% exhibit mutation of the *TP53* tumor suppressor gene.

STAGING AND EVALUATION

Staging and evaluation are accomplished with bilateral mammograms and excision with pathologic evaluation, which should determine the size and histologic type of the lesion, the ER and PR status, and the lesion's margin status. MRI is increasingly being used to help identify women with multicentric disease and those ineligible for breast-conserving therapy. In LCIS, the pathologic evaluation is limited to identification of the lesion and ER and PR status.

TREATMENT

For LCIS, treatment usually consists of observation. The rate of in-breast failure at 12 years is less than 15%. LCIS has a minimal impact on survival rates. Alternative approaches for high-risk disease have included tamoxifen versus bilateral mastectomy.

Treatment for Paget's disease usually involves breast-conserving therapy. Excision with negative margins is needed, followed by whole-breast radiotherapy. In-breast control rates are 87% to 95%. Patients with high-risk disease (i.e., diffuse disease with positive margins despite reexcision) should undergo mastectomy.

Breast-conservation therapy is also recommended for DCIS lesions. Excision with negative margins is followed by whole-breast radiation therapy with in-breast control rates of 85% to 95%. For low-risk disease (i.e., grade I lesions of <1 cm and negative margins of >1 cm), excision alone may be chosen. Mastectomy may be used for high-risk disease (i.e., diffuse disease with positive margins despite reexcision). More recently, data supporting the use of shortened radiation schedules as part of breast conservation has emerged in the form of accelerated partial breast irradiation and hypofractionated whole-breast irradiation.

INTRODUCTION

Noninvasive breast cancer is composed of three distinct histologic entities: LCIS, Paget's disease, and DCIS. As a result of the increased quality of and use of mammography, these three histologic types make up a larger percentage of all the breast cancer cases seen today.[1] Historically, mastectomy was frequently used as treatment for noninvasive disease, but with a better understanding of the natural history of these noninvasive disease processes, investigation has led to breast-conserving treatment options with regards to DCIS and Paget's disease and observation or risk-reduction for LCIS. Controversy regarding the optimal treatment approach continues to exist, and as a result, treatment recommendations range from observation to breast-conservation therapy to mastectomy. To appropriately formulate a patient's treatment options, it is important to understand the distinguishing pathologic appearances, biologic characteristics, and natural history of these three noninvasive breast disease entities.

LOBULAR CARCINOMA IN SITU

LCIS was first described as a pathologic entity by Foote and Stewart in 1941.[2] Microscopically, LCIS appears as a noninfiltrating process of lobular proliferation. LCIS has been reported to present with multicentric breast involvement in up to 90% of mastectomy specimens, with bilateral involvement documented in 35% to 59%.[3-6] Histologically, LCIS is characterized by loose discohesive epithelial cells filling the acinar space.[3-6] The degree of lobular involvement ranges from a simple filling of the ductal lumens to moderate distention to overt distention with extension into the adjacent extralobular ducts.[7] As a result of this spectrum of appearances, the lines of histologic delineation can become blurred between atypical ductal hyperplasia, LCIS, and when ductal extension is seen, DCIS. This introduces a source of complexity when comparing publications from varying institutions; even when using a proposed three-tier grading system, controversy still exists.[4-6,8]

Molecular markers have been suggested as a potential method of providing a technique for distinguishing LCIS in problematic cases.[5] LCIS cells are frequently ER-positive cells, and rarely overexpress c-ERBB2 or contain p53 mutations, with the exception of pleomorphic LCIS, which expresses high rates of Ki-67 and p53 positivity.[5,9-12] The loss of *CDH1* gene expression is documented in more than 95% of LCIS cases.[11,13] The *CDH1*gene is a calcium-dependent cellular adhesion molecule that is responsible for epithelial organization, and the absence of this adhesion molecule in LCIS may explain its discohesive morphologic characteristics.[11,13]

Publications on biopsy results report LCIS incidence rates to be 0.5% to 3.6%; these lesions represent less than 15% of all noninvasive lesions recorded, but recent population-based analyses suggest that this rate may be increasing.[6,14,15] Because there are no clinical or mammographic indicators, LCIS without additional histologic findings is typically an incidental finding when biopsy is performed for alternative reasons.[2-5,14] Although mammographically detected calcifications corresponding with LCIS have been reported, the calcifications are more commonly unassociated and are present in the adjacent tissue; therefore, if LCIS is identified on biopsy with a mammogram demonstrating calcification excisional biopsy is warranted.[14,16] In fact, DCIS or invasive disease, or both, is frequently identified in the subsequent lumpectomies performed (22% to 27% of cases) when LCIS is the sole histologic entity seen on core biopsy.[12,17,18] Criteria identifying those patients for whom observation only is sufficient following core biopsy showing LCIS have not yet been clearly specified.

Management considerations for LCIS differ depending on whether it is associated with a diagnosis of DCIS or infiltrative disease or whether LCIS is the sole histologic entity encountered. Only 5% to 12% of early-stage breast cancers have an associated component of LCIS.[19,20] Several institutional experiences have evaluated the potential impact of the presence of LCIS on breast-conserving treatment outcomes.[19-24] The number of patients included in these experiences is relatively small, and there are differences in these cohorts, including pathologic assessment, length of follow-up, and use of tamoxifen (Table 62-1). However, the majority of data suggest that no statistically significant difference exists when comparing rates of in-breast disease control, distant disease-free survival, and overall survival between patients with or without a component of LCIS.[19-24] The presently accepted treatment approach is to manage the breast according to the dominant histologic findings present (DCIS or invasive disease) and disregard the presence of LCIS. Additional surgery is not pursued to obtain LCIS clear margins. The need for the addition of tamoxifen or a more aggressive treatment approach in this group of high-risk patients is uncertain, and further study is necessary with no definitive evidence-based guidelines available.[25]

If LCIS is the sole histologic diagnosis, treatment recommendations range from observation to mastectomy. When first described as a pathologic entity, the significance of LCIS was unknown and mastectomy was consistently pursued.[2] Knowledge of frequent contralateral involvement extended treatment recommendations to random contralateral biopsy and bilateral mastectomy.[2,3] However, observational studies after lumpectomy only have led to a better understanding of the natural history of this disease, and a more conservative approach is now commonly practiced.[6,14] Although studies of *CDH1* and loss of heterozygosity (LOH) suggest that LCIS may be a precursor to invasive disease, LCIS has historically been considered a marker for an increased risk of developing invasive disease (9 to 12 times that of the normal population); this risk requires long-term follow-up exceeding 20 years.[4,26] More recently, population based data has found that 73% of patients undergo excision alone, 16% mastectomy, 10% biopsy, and 1% excision with radiation therapy.[15]

A range of ipsilateral and contralateral breast failure rates are reported following treatment. This variation is the result, in part, of differences in the length of follow-up, the definitions used for histologic classification (atypical lobular hyperplasia versus LCIS), and the extent of excision used in these observational studies.[27,28] In a 12-year follow-up publication on a 182-patient cohort treated with lumpectomy only for LCIS, the National Surgical Adjuvant Breast and Bowel Project (NSABP) reported a 14.4% in-breast tumor recurrence (IBTR) rate, and a 7.8% contralateral breast tumor recurrence (CBTR) rate.[28] Of the IBTRs, nine (34.6%, or 5% of the total cohort) were invasive malignant tumors and 17 (65.4%, or 9% of the total cohort) were noninvasive malignant tumors. Although the frequency of CBTRs was less than that of IBTRs, the frequency of invasive CBTRs (5.6% of the total cohort) was similar to that of invasive IBTRs (5% of the total cohort). All of the IBTRs were documented to be at the site of the index lesion except for one, characterized as pure LCIS, that was found at a remote site. This report continues to support the indolent nature of LCIS and a conservative management approach.

The impact of subsequent development of invasive disease on mortality risk has been estimated in earlier publications to

TABLE 62-1 Presence of LCIS versus in-Breast Failures in Breast-Conservation Therapy

Author	Median Follow-up Time	Disease Stage	No. Patients		Tamoxifen		In-Breast Failure Rate (%) at 10 yrs		*p* Value
			Positive for LCIS	Negative for LCIS	LCIS-Positive Receiving Tamoxifen (%)	LCIS-Negative Not Receiving Tamoxifen (%)	Positive for LCIS	Negative for LCIS	
Abner et al[19]	13.4 yrs	I-II	137	1062	2 overall		13*	12*	NS
Moran et al[20]	10.6 yrs	0-II	51	1045	20	20	23	17	NS
Jolly et al[21]	8.7 yrs	I-II	56	551	54	35	14	7	0.04
Sasson et al[22]	6.3 yrs	I-II	65	1208	40	35	29	6	0.0003
Ciocca et al[23]	6 yrs	0-II	290	2604	63.5	44.6	6	6	NS
Ben-David et al[24]	3.9 yrs	0-II	64	121 (matched pair)	48.5	39	0.9†	0†	NS

LCIS, *Lobular carcinoma in situ;* NS, *not statistically significant;* yrs, *years.*

**8 years.*

†5 years.

be 5% to 7% with a population study identifying the risk at 7.1% at 10 years.[14,29] However, with contemporary use of close mammographic and clinical follow-up leading to early detection of subclinical abnormalities, one would expect this mortality risk to be reduced. This reduction is reflected in the lower mortality risk (1%) reported by the NSABP.[28] Further, recent guidelines have not suggested an alteration in subsequent screening in those diagnosed with LCIS further supporting the reduced risk of mortality.[25]

Management options vary depending on individual risk assessment (Figure 62-1). Close observation with regular physical examinations and mammographic surveillance is the accepted management approach.[6,14,25,27,28] At present, there is no role for radiotherapy in the management of LCIS. Knowing that this is a bilateral breast disease process leaves a unilateral treatment approach inadequate (i.e., ipsilateral mastectomy).[25] Bilateral prophylactic mastectomy is thought to be excessive in all patients except those believed to be at higher risk (i.e., young patients, diffuse process, a significant family history of disease) for whom it could be considered.[25] A less radical approach to be considered is the use of tamoxifen. Indeed, a cohort of patients with LCIS was entered into the NSABP P-01 trial, which compared tamoxifen with placebo for breast cancer prevention. The 5-year risk of subsequent disease development was reduced with the use of tamoxifen by 56%, though patients with LCIS represented a small percentage of patients.[30]

Pleomorphic LCIS represents an emerging area of interest based on data demonstrating differences in molecular markers for this variant as well concern for underlying invasive malignancy with further sampling.[12,31] Data from Northwestern University found that variants of LCIS including pleomorphic LCIS were misinterpreted as solid DCIS in up to 15% of cases and that 20% of such cases had underlying lobular carcinoma at the time of surgery, which has been confirmed by other series.[31,32]

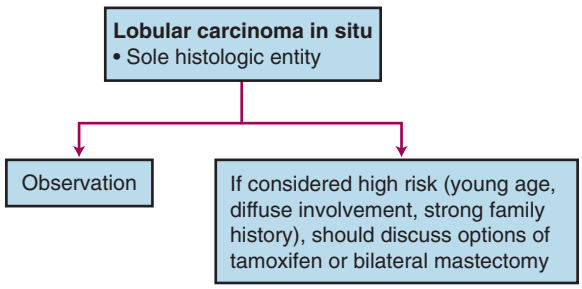


Figure 62-1 Treatment algorithm for lobular carcinoma in situ.

PAGET'S DISEASE

The clinical presentation of crusting, bleeding, and ulceration of the nipple was first described in 1856, but it was not until 1874 that the association with an underlying breast carcinoma was recognized by Sir James Paget.[33] Paget's disease of the nipple is characterized histologically by the presence of unique, clearly identifiable Paget's cells that are described as large, round to oval cells that contain hyperchromatic nuclei and prominent nucleoli with frequent mitoses noted. The Paget's cells occur singly or in clusters and are scattered throughout the epidermis.[34,35]

Reported in 0.5% to 5% of breast cancer patients, Paget's disease is an infrequent diagnosis.[33,36,37] It is most commonly unilateral, but reports of bilateral and male Paget's disease can be found.[38-40] Clinically, women describe itching and burning of the nipple and areola and crusting is often described. There is a slow progression toward an eczematoid appearance, which can extend to the skin. If neglected, bleeding, pain, and ulceration can occur.[37,38] The differential diagnosis includes superficial spreading melanoma, pagetoid squamous cell carcinoma in situ, and clear cells of Toker.[34-37] A palpable mass is detected in about 50% of patients at diagnosis. If there is a palpable mass, more than 90% will be invasive carcinoma. On the other hand, if no palpable mass is detected, 66% to 86% will have an underlying DCIS.[34-37] These adjacent, underlying malignant tumors are usually located centrally; however, they have also been located elsewhere in the breast.[33,37]

The appropriate management of Paget's disease remains unsettled; however, in concordance with physician and patient preference, attempts have been made to investigate the role of breast-conservation therapy. Because mastectomy was initially shown to be effective, the transition to breast-conserving treatment has been done cautiously because of the inability to accumulate a significant number of uniform patients similarly treated.[36,37] Recent data have demonstrated that based on pathological evaluation of mastectomy specimens, that breast-conserving therapy is feasible with appropriate margins and this is echoed in currently published treatment guidelines.[25,41] Limited series have described results with various forms of breast-conserving treatment, including limited surgical resection alone, radiotherapy alone, and limited resection followed by radiotherapy[42-47] (Table 62-2).

The combination of limited surgical resection and postoperative radiotherapy appears to be the most successful breast-conservation approach. Two collaborative studies have shown the successful use of breast-conservation therapy in Paget's disease of the nipple. The European Organization for Research and Treatment of Cancer (EORTC) Study 10873 was a

TABLE 62-2 Breast Conservation in Treatment of Paget's Disease

Author	No. Patients	Median Follow-up Time	Treatment Approach	Palpable Mass		DCIS Only		Actuarial Local Control Rate at 5 yrs
				Yes	No	With	Without	
Polgar et al[43]	33	6 yrs	Cone excision alone	91	9	91	9	71.6%
Stockdale et al[44]	19	5 yrs, 3 mos	Radiotherapy alone	30	3	30	3	84.2% (crude)
Bijker et al[45]	61	6.4 yrs	Cone excision + radiotherapy	3	97	93	7	94.8%
Pierce et al[46]	30	5.2	Excision + radiotherapy	59	2	57	4	91%
Marshall et al[47]	36	9.4 yrs	Excision* + radiotherapy	0	36	27	3†	91% (5-yr)‡ 87% (10-yr)‡ 87% (15-yr)‡

DCIS, *Ductal carcinoma in situ;* mos, *months;* yrs, *years.*
**Final margin status: 56% negative, 6% positive, 39% unknown.*
†6% DCIS and invasive disease, 3% invasive disease only, 16% no underlying pathology.
‡Breast as only site of failure.

multiinstitutional registration study reporting a 5-year local recurrence rate of 5.2% for a subset of 61 patients.[45] In this study, a complete excision with tumor-free margins of the nipple-areolar complex and underlying breast tissue was followed by whole-breast radiotherapy to 50 Gy. The median follow-up time was 6.4 years, and the majority of patients were found to have an underlying DCIS without a palpable mass.

The second study, a seven-institution collaborative review of 36 patients, included patients with Paget's disease without a palpable mass or mammographic density.[47] The median follow-up time was 9.4 years, and all had at least 12 months of follow-up. Patients underwent complete (69%) or partial (25%) excision of the nipple-areolar complex and underlying breast tissue, with 6% reported as a biopsy only. The final margin status was documented as negative in 56%, positive in 6%, and unknown in 39%. All received whole-breast irradiation at a median dose of 50 Gy, and the majority received an additional boost dose to the tumor bed. Actuarial rates of local in-breast failure as the only site of first recurrence were 9% at 5 years and 13% at both 10 years and 15 years. Despite the variation of clinical, pathologic, and treatment factors, statistical evaluation did not identify any factors that significantly predicted for risk of local recurrence. The findings from these studies have been confirmed by a large series from Sweden that evaluated 223 patients and found that type of surgery (BCS versus mastectomy) was not associated with breast cancer survival or disease free survival.[48]

On presentation, the workup and evaluation should include a bilateral breast examination, mammography, and full-thickness biopsy to confirm the diagnosis of Paget's disease and fully evaluate the extent of the underlying malignant disease.[25] In individuals with a positive biopsy for Paget's but no underlying mass, consideration for magnetic resonance imaging (MRI) is reasonable.[25] An individual's prognosis is not dependent on the diagnosis of Paget's disease but rather depends on the associated underlying malignant disease. Therefore, local treatment decisions as well as systemic and regional nodal disease risk management should be based on the underlying disease (Figure 62-2).[25] Standard breast-conservation therapy principles governing patient selection, surgical resection, and radiotherapy should be applied. Complete surgical resection of the disease process (i.e., nipple-areolar complex excision in conjunction with any underlying disease) with a negative microscopic surgical margin is then followed by standard whole-breast irradiation.

DUCTAL CARCINOMA IN SITU

Epidemiology

DCIS is represented by a heterogeneous spectrum of histologic appearances that all arise within and are confined to the ductal lumens of the breast. This clonal proliferation does not breach the epithelial basement membrane, and there is no evidence of invasion into the adjacent breast stroma.[49] DCIS lacks the ability to metastasize; the rarely reported axillary nodal metastasis or distant metastasis has been attributed to the probable presence of an undetected component of invasive carcinoma.[49,50]

Before 1980, the incidence of DCIS was low (i.e., only 1.4% of all breast biopsies and only 5% of all breast malignant tumors).[51,52] With the increased use of mammography and as pathologists began to recognize that DCIS was a distinct pathologic entity, the incidence of DCIS dramatically increased.[53] The incidence of DCIS has increased from 4800 cases reported in 1983 to more than 50,000 cases out of the estimated 230,000 new breast cancers diagnosed in 2013.[53] With this increase, there has been a corresponding change in the presentation of DCIS lesions from predominantly palpable to more than 90% of new lesions being nonpalpable.[54] Studies have shown that the rate of DCIS lesions detected by screening increases with age, whereas DCIS accounts for a progressively smaller percentage of the total cancers detected (i.e., invasive cancers plus DCIS).[55,56] The rate of DCIS detection has been shown to increase from 0.56 per 1000 mammograms among women aged 40 years to 49 years to 1.07 per 1000 mammograms among women aged 70 years to 84 years.[56]

Associated risk factors for the development of DCIS are similar to risk factors for invasive disease and include older age, benign breast disease, mammographic density, a family history of breast disease, and reproductive factors, including nulliparity or older age of pregnancy.[49,57-59]

Prevention and Early Detection (MRI)

Although successful treatment options are available, improved outcomes can be realized through both prevention of DCIS development and the early detection of new lesions. The role of tamoxifen in the prevention of disease development has been studied by the NSABP in a protocol that randomized patients at high risk for the development of breast cancer to either tamoxifen or placebo.[30] Patients eligible included those who were either 60 years of age or older, had a history of LCIS, or were between the ages of 35 and 59 years with a

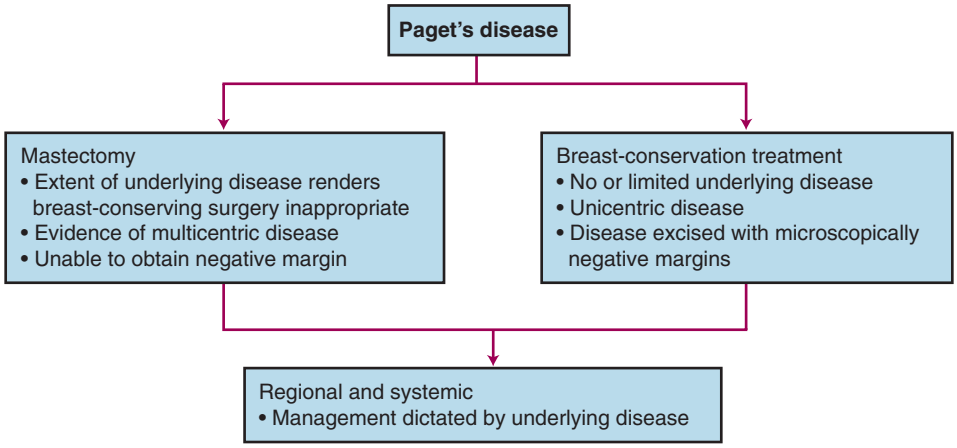


Figure 62-2 Treatment algorithm for Paget's disease.

5-year predicted risk for breast cancer, using the Gail model, of at least 1.66%. The 7-year follow-up data reveal that for noninvasive breast cancer, tamoxifen use was associated with a 37% reduction in risk. A subsequent randomized trial (NSABP P-2) randomized similar patients (woman who were premenopausal excluded) to tamoxifen or raloxifene. At 5 years, raloxifene was found to have a statistically nonsignificant increase in the incidence of noninvasive cancers than tamoxifen (relative risk, 1.40).[60]

Mammography plays an essential role in the early detection of noninvasive lesions, providing an opportunity for intervention early in the course of disease development. The distinctive mammographic feature of DCIS is the presence of microcalcifications, which has been reported in 84% to 98% of cases.[61,62] Seventy-two percent to 76% of DCIS lesions have microcalcifications as the sole mammographic finding, and an additional 12% have microcalcifications in combination with other mammographic abnormalities.[61,62] Beyond detection, several attempts have been made to correlate the mammographic appearance of the lesion with the histologic type, grade, and extent of disease. Linear branching microcalcifications have been reported to be associated with high-grade or comedo-type DCIS. Heterogeneous granular calcification is commonly associated with moderately differentiated DCIS and fine granular microcalcifications more typically with low-grade, non-comedo DCIS.[56,61,62] Although there is a degree of correlation between appearance and histologic type, there is considerable overlap, which limits the use of this information in clinical decision making. Microcalcifications are not always present throughout the histologic abnormality, and the estimated mammographic size and extent of disease frequently underestimate the true pathologic extent of the disease process. Although the mammographic extent can be used to guide the extent of surgical excision, caution should be exercised because the size is typically underestimated by 1 cm to 2 cm.[63,64] In patients presenting with nipple discharge with a negative mammographic evaluation, galactography may be helpful in distinguishing the presence of a papilloma from an underlying DCIS.[65]

More recently, MRI has emerged as another modality to help identify lesions. Its use has been suggested in patients with dense breasts as well as to identify multicentric disease and is increasingly being used in the noninvasive setting.[25] Further, recent studies have found that MRI has increased sensitivity to detect DCIS compared with mammography and can better identify those patients eligible for BCT.[66]

Biologic Characteristics and Molecular Markers

DCIS is a precursor lesion to invasive ductal carcinoma and exists along an evolutionary continuum that starts with benign breast tissue and ends with an invasive breast lesion.[67] This concept has been verified in several ways. For years, pathologists have recognized and documented confirmation of a histologic progression from benign breast cells to invasive breast cancer and realized that this histologic evidence was more commonly present where an invasive lesion was discovered. The evolutionary concept is further supported by the acknowledged association between the presence of DCIS and the subsequent increased risk of developing an invasive breast cancer.[49,68,69] In some series, a 10-fold risk of developing an invasive lesion has been reported. The presence of shared identical genetic abnormalities between DCIS and synchronous invasive breast cancer also suggests a clonal relationship of biologic progression.[49,68-70] This was noted in a recent study that found that the molecular phenotypes of coexisting DCIS within IDC were identical in 100% of cases.[71]

Documented genetic and molecular differences can differentiate DCIS from normal breast tissue. Genetic alterations have been evaluated with an analysis of LOH that has demonstrated gain or loss of multiple loci.[68-70] LOH is not seen in normal breast tissue but is present with an increasing frequency that correlates with histologic progression from benign to malignant tissue. In hyperplasias from noncancerous breasts, LOH is rarely documented; however, it is more commonly present (in 42% to 50% of patients) in atypical ductal hyperplasia. Among specimens harvested from cancerous breasts, 77% of noncomedo and 80% of comedo DCIS lesions share LOH with the synchronous invasive lesion in at least one locus.[70] Molecular markers have been studied and are found to have a heterogeneous distribution of expression.[49] The ER is present in 65% to 80% of DCIS lesions, but the rate of expression is high (90%) in low-grade lesions and is significantly less (25%) in high-grade lesions.[49,72] This trend is reversed with the *HER2/neu* proto-oncogene and the *TP53* tumor suppression gene. About 25% to 50% of DCIS lesions exhibit overexpression of the *HER2/neu*, with the *TP53* tumor suppressor gene mutated in 25% of cases. Both of these molecular markers are noted in less than 20% of low-grade lesions, but they are found in up to two thirds of high-grade lesions.[49,72]

Pathologic Characteristics and Pathways of Spread

The primary goal of pathologic assessment is to differentiate DCIS from invasive cancer because the presence of invasive disease alters the focus of treatment from the breast only to possible regional and distant metastases. Once DCIS has been identified, pathologic classification follows in an attempt to predict the clinical outcome and direct the treatment management. Historically, an architectural classification system has been used, dividing tumors into the five classic subtypes of comedo, solid, cribriform, papillary, and micropapillary cancers.[73-75] Less common subtypes have been described and include apocrine, neuroendocrine, signet-ring cell cystic, and hypersecretory carcinomas and clinging DCIS.[76] The difficulty with an architectural classification method is that there can be a mixture of architectural subtypes identified within the same lesion and that the reproducibility of classification is unreliable because pathologists apply various criteria.[77,78] Additionally, the value of an architectural classification system is questionable because the architectural subtypes do not correlate well with clinical behavior.[79] Although this was not an issue when mastectomy was routinely used, the ability to predict clinical behavior has become important now that breast-conserving approaches represent the standard of care in the management of DCIS.[25]

In an attempt to better predict clinical behavior, several classification systems have been proposed.[80,81] These are based on nuclear grade of the tumor cells and presence of comedo necrosis with and without architectural features. These characteristics appear to correlate with the risk of local recurrence.[79] In 1997, an international consensus conference was convened to discuss several pathologic aspects concerning DCIS, with the goal of reaching a consensus where possible.[82] Conference participants recognized that several classification systems had been proposed, and although a specific system was not endorsed, they recommended that four features be routinely described: nuclear grade, necrosis, polarization, and architectural pattern. They also recommended that several additional features be documented in the pathology report, including the margin status, size of the lesion, location of microcalcification in relationship to the DCIS lesion, and correlation of characteristics of the tissue specimen with radiographic and mammographic findings.[82]

Primary Therapy

Patient evaluation focuses on bilateral mammography, with which the presence of additional breast malignant lesions can be excluded and the extent of the DCIS process defined; MRI may also be useful to determine extent of disease and any multifocality or multicentricity.[25] After it is determined that DCIS is the only disease entity requiring treatment, the primary focus becomes local management of the breast. In concert with the spectrum of clinical presentations encountered with DCIS, there are several treatment approaches. They range from treatment of the whole breast to treatment of a partial breast target. On the one end of this spectrum, when multicentric disease or a diffuse DCIS process is documented, a mastectomy is considered to be the standard of care.[25] If a focal area of DCIS is confronted, then breast-conserving approaches are favored because of improved quality-of-life outcomes. Supported with Phase III trial data, the use of standard breast-conservation therapy with lumpectomy and standard whole-breast radiotherapy is most commonly recommended, and newer partial breast techniques (with and without radiotherapy) are now being offered with increased frequency based on emerging data.

All presentations of DCIS can be successfully managed with total mastectomy. This is supported by reports from mastectomy series showing disease control rates that approach 100% and cancer-specific mortality rates of less than 4%.[83-86] However, it is recognized that the availability of mammographic screening has shifted the most common presentation of DCIS from one of a palpable mass with advanced involvement to one of early-stage and limited-extent of disease for which a total mastectomy would intuitively appear to be excessive.[25,49] To promote mastectomy in the management of noninvasive disease would be in opposition to the increasing use of breast-conservation therapy for invasive disease. Although a Phase III trial comparing total mastectomy with breast-conservation therapy for DCIS has never been done, the psychological benefits of preserving the breast and the acceptable rates of local control achieved with breast-conserving therapy support the use of total mastectomy only when necessary. Total mastectomy is most commonly reserved for patients presenting with multicentric or diffuse disease, for patients in whom the use of radiotherapy is contraindicated, when an unacceptable cosmetic result is anticipated following appropriate surgical excision, or for salvage in the event of in-breast recurrence following standard breast-conservation therapy.[25,87]

Breast-conservation treatment consists of initial surgical excision of the primary lesion with a negative surgical margin followed by whole-breast radiotherapy delivered with standard accepted techniques, such as those used for early-stage invasive breast cancer. Literature supporting this approach is found both in retrospective series as well as in prospective Phase III trials comparing lumpectomy only with lumpectomy followed by whole-breast irradiation.[88-92]

Retrospective analyses of lumpectomy and whole-breast irradiation have reported 5-year cause-specific survival rates that approach 100% and local control rates that range from 85% to 95%.[88,93-98] Prospective randomized trials have been completed evaluating the role of postoperative radiotherapy and tamoxifen in breast-conserving management of DCIS (Tables 62-3 and 62-4). In a Cochrane Database review, postoperative radiotherapy for DCIS focused on four prospective randomized trials[99] (see Table 62-3). This meta-analysis confirmed a statistically significant benefit from the addition of radiotherapy for all ipsilateral breast events (hazard ratio [HR], 0.49; $p < 0.00001$), for DCIS (HR, 0.61; $p = 0.03$), and for invasive recurrence (HR, 0.50; $p = 0.0001$). This benefit was demonstrated in all of the subgroups evaluated, which included patients who underwent complete excision versus those who underwent incomplete excision, patients older than 50 years versus those younger than 50 years, patients with comedo necrosis versus those without comedo necrosis, and patients with lesions of 1 cm or larger versus those with lesions of less than 1 cm; these findings have also been confirmed by the Early Breast Cancer Trialists Group meta-analysis.[100]

The first of these four prospective randomized trials is the National Surgical Adjuvant Breast and Bowel Project (NSABP)

TABLE 62-3 Randomized Clinical Trials Evaluating the Role of Postoperative Radiotherapy in the Management of DCIS

			Local Recurrence (Cumulative %)				Overall Survival (%)		
Trial Group	No. Patients	Follow-up Time	Histologic Type of Recurrent Disease	Lumpectomy	Lumpectomy + Postoperative Radiation Therapy	*p* Value	Lumpectomy	Lumpectomy + Postoperative Radiation Therapy	*p* Value
NSABP B-17[89]	818	15-yr actuarial	DCIS	15.4	9.0	<0.001	84.2	82.9	NS
			Invasive	19.6	10.7	<0.001			
			DCIS + invasive	35.0	19.8	—			
EORTC 10853[90]	1010	15.8-yr median	DCIS	16.0	8.0	0.003	90	88	0.93
			Invasive	16.0	10.0	0.007			
			DCIS + invasive	31.0	18.0	<0.001			
UKCCCR[91]	1030	12.7-yr median	DCIS	9.7	3.8	<0.0001	90%	90%	—
			Invasive	9.1	3.3	<0.0001			
			DCIS + invasive	19.4	7.1	<0.0001			
SweDCIS[92]	1067	20-yr	DCIS	Absolute Difference: 10%		—			—
			Invasive	Absolute Difference: 2%		—			
			DCIS + invasive	Absolute Difference: 12%		—			

DCIS, *Ductal carcinoma in situ;* EORTC, *European Organization for Research and Treatment of Cancer;* NSABP, *National Surgical Adjuvant Bowel and Breast Project;* SweDCIS, *Sweden Breast Cancer Group DCIS trial;* UKCCR, *United Kingdom Coordinating Committee on Cancer Research;* yr, *year.*

TABLE 62-4 Randomized Clinical Trials Evaluating the Role of Tamoxifen in the Management of DCIS

Trial Group	No. Patients	Follow-up Time	Local Recurrence (Cumulative %)				Contralateral Recurrence (%)		
			Histologic Type of Recurrent Disease	Without Tamoxifen	With Tamoxifen	*p* Value	Without Tamoxifen	With Tamoxifen	*p* Value
NSABP B-24[89]	1799	15-yr actuarial	DCIS	7.6	6.7	0.33	2.8	1.6	—
			Invasive	9.0	6.6	0.03	5.3	3.3	—
			DCIS + invasive	16.6	13.2	—	8.1	4.9	0.33
UKCCCR[91]	1576	12.7-yr median	DCIS	12.1	8.6	0.03	1.3	0.3	0.08
			Invasive	6.9	6.8	0.79	2.7	1.5	0.03
			DCIS + invasive	19.6	15.7	0.04	4.2	1.9	0.005

DCIS, *Ductal carcinoma in situ;* NSABP, *National Surgical Adjuvant Bowel and Breast Project;* UKCCR, *United Kingdom Coordinating Committee on Cancer Research;* yr, *year.*

TABLE 62-5 Prospective Studies Evaluating the Role of Excision Alone

	Years	Number of Patients	Follow-Up (months)	Local Recurrence Rate (Time Point)
NSABP B-17[89]	1985-1990	403	207	35.0 (15 years)
EORTC 10853[90]	1986-1996	503	188	31% (15 years)
Swedish DCIS[92]	1987-1999	520	240	Absolute difference 12% (20 years)
UKCCR[91]	1990-1998	508	151	19.4% (12 years)
RTOG 9804[114]	1999-2006	298	78	3.2% (5 years)
Dana Farber[113]	1995-2002	158	132	13% (8 years)
ECOG E-5194[115]	1997-2002	670	104	15.4%/15.1% (low grade/high grade, 10 years)
University of Southern California[109]	1996-2009	604	75	VNPI 4-6: 5.4% (12 years) VNPI 7: 30% (12 years)

DCIS, *Ductal carcinoma in situ;* ECOG, *Eastern Cooperative Oncology Group;* EORTC, *European Organisation for Research and Treatment of Cancer;* NSABP, *National Surgical Adjuvant Breast and Bowel Project;* RTOG, *Radiation Therapy Oncology Group;* UKCCR, *United Kingdom Coordinating Committee on Cancer Research.*

protocol B-17, designed to evaluate the role of postoperative irradiation.[84,89-91] All 814 evaluable patients enrolled were initially diagnosed with DCIS and underwent lumpectomy achieving clear surgical margins (i.e., inked specimen margins that were tumor free on histologic testing). Patients were subsequently randomized to receive postoperative whole-breast radiotherapy or no radiotherapy. The radiotherapy guidelines used consisted of whole-breast tangential fields treated to 50 Gy as per previous NSABP studies; a boost to the surgical bed was not included. With 15 years of follow-up, the rate of in-breast tumor recurrence with lumpectomy only was 35.0%, as compared with 19.8% when irradiation was delivered. Nine pathologic features were evaluated for their ability to predict for in-breast recurrence: comedo necrosis remained as a significant predictor for recurrence.[101]

A second randomized Phase III trial evaluating the role of radiotherapy after complete local excision was completed by the European Organization for Research and Treatment of Cancer (EORTC 10853) enrolling more than 1000 patients.[90,92] All patients had histologically confirmed tumor-free margins, defined as no DCIS at the inked margin, and the prescribed radiotherapy consisted of whole-breast tangential fields treated to 50 Gy in 25 fractions. A boost dose was not advised, and only 5% received a boost to the surgical bed. At a median follow-up interval of 15.8 years, researchers reported a 31% in-breast failure rate with excision only and an 18% in-breast failure rate with excision plus radiotherapy.[90] Risk factors for recurrence were evaluated, and the relative benefit from the addition of radiotherapy was equivalent in all subgroups. It should be noted that there were two groups identified with an exceptionally low risk of recurrence of less than 10%. These groups were defined as those with well-differentiated DCIS with either a clinging or micropapillary growth pattern. The relative benefit of radiotherapy remained consistent in these patient groups, but the absolute benefit was reduced.[90,102]

The United Kingdom Coordinating Committee on Cancer Research (UKCCCR) DCIS Working Group and investigators from Australia and New Zealand have also conducted a randomized trial investigating the role of adjuvant irradiation (Table 62-5).[91] Within a more complex 2 × 2 factorial protocol design, the aim was to compare four treatment regimens: excision alone, excision plus tamoxifen, excision plus radiotherapy, and excision plus radiotherapy and tamoxifen. Tamoxifen was prescribed as 20 mg/day, and radiotherapy was delivered through whole-breast tangential fields to a total dose of 50 Gy. A boost was not recommended. A total of 1030 patients were enrolled in the radiation arm of the trial. With a median follow-up of 12.7 years, radiation therapy was associated with a reduction in ipsilateral invasive (HR 0.32, $p < 0.0001$) and noninvasive recurrences (HR 0.38, $p < 0.0001$). The addition of tamoxifen to radiotherapy offered minimal benefit toward the overall ipsilateral local control rates; however, it did appear to reduce the ipsilateral recurrence rate of DCIS (HR 0.70, $p = 0.03$) and contralateral events (HR 0.44, $p = 0.005$).[91]

The SweDCIS study from the Swedish Breast Cancer Group enrolled 1067 patients from 1987 to 1999, randomizing between lumpectomy followed by radiotherapy and lumpectomy only for treatment of DCIS.[92] Patients underwent a sector resection with the aim of achieving a 1-cm gross surgical margin; microscopic clear resection was not required. The majority of

patients received 50 Gy in 25 fractions to a whole-breast treatment target. A split course of 54 Gy in 2-Gy fractions delivered in two treatment series separated by a 2-week break was allowed. No boost dose was delivered. A recent 20 year update found the absolute difference in local recurrence to be 12% with an absolute reduction of 10% for DCIS recurrences and 2% for invasive recurrences. Subgroup analysis by age, lesion size, focality, completeness of excision, and the presence of a lesion detected by screening confirmed that all groups benefited in risk reduction with the addition of radiotherapy.[92]

In a trial asking a similar question of the role of tamoxifen and building on the results from B-17, the NSABP initiated a trial to determine if the addition of tamoxifen to lumpectomy and postoperative radiotherapy would be more effective than lumpectomy and postoperative radiotherapy alone.[89] All of the 1799 women underwent excision and were randomized to whole-breast irradiation and placebo or whole-breast irradiation followed by tamoxifen. The postoperative radiotherapy was delivered with standard tangential fields to a total dose of 50 Gy. The placebo or tamoxifen (10 mg twice daily) was continued for 5 years. At 15 years, the in-breast failure rate following lumpectomy, radiotherapy, and placebo was 16.6%, and it was reduced to 13.2% when tamoxifen was added to lumpectomy and radiotherapy. The occurrence rate of cancer in the contralateral breast was also reduced with the addition of tamoxifen from 8.1% to 4.9%.[89]

Risk factor assessment has been performed with the goals of determining which patients are ideal for breast-conservation therapy, which patients would be better treated with mastectomy, and which patients could be successfully managed with lumpectomy only. Single-institution studies and randomized studies have identified factors that predict for an increased risk of recurrence. Tumor size, the presence of comedo necrosis, the nuclear grade, young patient age, and the margin status have all been identified as factors associated with a higher risk of in-breast recurrence.[88-92,95,102-107] However, the addition of radiation therapy reduces the risk of recurrence in all cases; only when diffuse disease, signified by mammographic appearance or the inability to achieve clear surgical margins, is encountered is mastectomy the preferred method of surgical management.[25] In the absence of these high-risk factors, the prevalent question is whether a less-comprehensive treatment approach (i.e., wide excision only or lumpectomy and hypofractionated/accelerated partial breast irradiation) is sufficient. Although failure pattern data and retrospective analysis exist to confirm the validity of these more directed treatment approaches, confirmation by an appropriately designed clinical trial is lacking.[26,108]

The Van Nuys Prognostic Index is a proposed method of identifying patients whose risk of in-breast failure following lumpectomy is so low that adjuvant radiotherapy would be of minimal benefit.[108,109] This scoring index is based on tumor grade, tumor size, patient age, and surgical margin width. Achieving a clear margin of more than 1 cm has been determined to be an important predictor of this index. It is important to note that this determination is characterized by a comprehensive, exhaustive pathologic evaluation assuring that a 1-cm clear surgical margin is achieved in all directions. The scoring index was developed and evaluated at a single institution through retrospective analysis and has yet to be consistently independently validated.[110-112]

In a prospective single-arm study at the Dana-Farber/Harvard Cancer Center evaluating wide excision alone, 158 patients with grade I or II DCIS lesions of 2.5 cm or less were treated with wide excision with final surgical margins of 1 cm or more without further treatment.[113] Treatment with tamoxifen was not permitted. Presently accepted standard practice approaches to surgical resection and pathologic assessment were applied. The median follow-up time was 40 months. Accrual was prematurely closed after 13 patients developed local recurrence at an unacceptably high in-breast failure rate corresponding to a 5-year rate of 12%.[113]

The Radiation Therapy Oncology Group (RTOG) initiated a prospective randomized trial evaluating the need for radiotherapy in patients with low-risk DCIS. Following lumpectomy with clear margins of resection of 3 mm or more, patients were stratified according to age (<50 years versus ≥50 years), tumor size (≤1 cm versus >1 cm to 2.5 cm), margin status (negative reexcision versus 3 mm to 9 mm versus ≥10 mm), grade, and use of tamoxifen (at the discretion of the managing physician). After stratification, patients were randomized to whole-breast irradiation versus observation. This trial had a target accrual of 1800 patients but closed because of slow enrollment with 636 patients. At 5 years, the addition of radiation therapy significantly reduced local recurrence rates (0.4% versus 3.2%). Importantly, a patterns of failure analysis found that two thirds of recurrences in the observation-alone arm were true recurrences (in the same quadrant as the initial tumor), whereas none of the recurrences in the RT arm were true recurrences.[114]

In an intergroup trial run by the Eastern Cooperative Oncology Group (ECOG) and North Central Cancer Treatment Group, wide excision only in a population of conservatively selected patients with DCIS was evaluated.[104] Eligible patients included those with low- or intermediate-grade DCIS lesions measuring 2.5 cm or less or high-grade DCIS lesions measuring 1 cm or less. The microscopic margin width was required to be 3 mm or more with no residual calcifications on postoperative mammograms and 30% received tamoxifen. Six hundred and seventy patients were evaluable, and at 5/10 years, the rates of local recurrence were 6.1%/15.4% and 15.3%/15.1%, for the low- and intermediate-grade and high-grade cohorts, respectively.[115]

Alternatives to traditional whole-breast irradiation have emerged as modalities to shorten the duration of adjuvant radiation therapy. Accelerated partial breast irradiation allows for the delivery of treatment in 1 week or less. While waiting for results from NSABP B-39, multiple studies have emerged demonstrating low rates of local recurrence and excellent toxicity profiles in patients with DCIS.[116-118] Evidence-based guidelines allow for the use of partial-breast irradiation in patients with DCIS at this time off-protocol.[116-118] With regard to hypofractionation, increasing data has demonstrated equivalent efficacy to whole-breast irradiation though data is limited in the setting of DCIS.[119-121]

Recently, there has been renewed interest in identifying those patients with DCIS who may not benefit from adjuvant radiation therapy. Although previous approaches and trials used clinical and pathologic criteria, more recently data has emerged on the role of multigene assays in patients with DCIS. Solin et al evaluated 327 patients from the ECOG trial with adequate tissue for multigene assay using three risk categories: low (DCIS score <39), intermediate (39-54), and high risk (≥55). DCIS score, as a continuous variable, was found to be significantly associated with ipsilateral breast tumor recurrence after adjusting for tamoxifen utilization; on multivariate analysis, DCIS score remained significantly associated. By risk group, the 10-year rate of IBTR was 10.6%, 26.7%, and 25.9% for low, intermediate, and high-risk groups, respectively, and for invasive IBTR the rates were 3.7%, 12.3%, and 19.2%, respectively.[115] Further prospective study is required, although these data do suggest the possibility of tumor genetics identifying patients at low risk suitable for treatment with lumpectomy alone. However, there still remain concerns as the low-risk cohort still had a greater than 10% risk of recurrence.

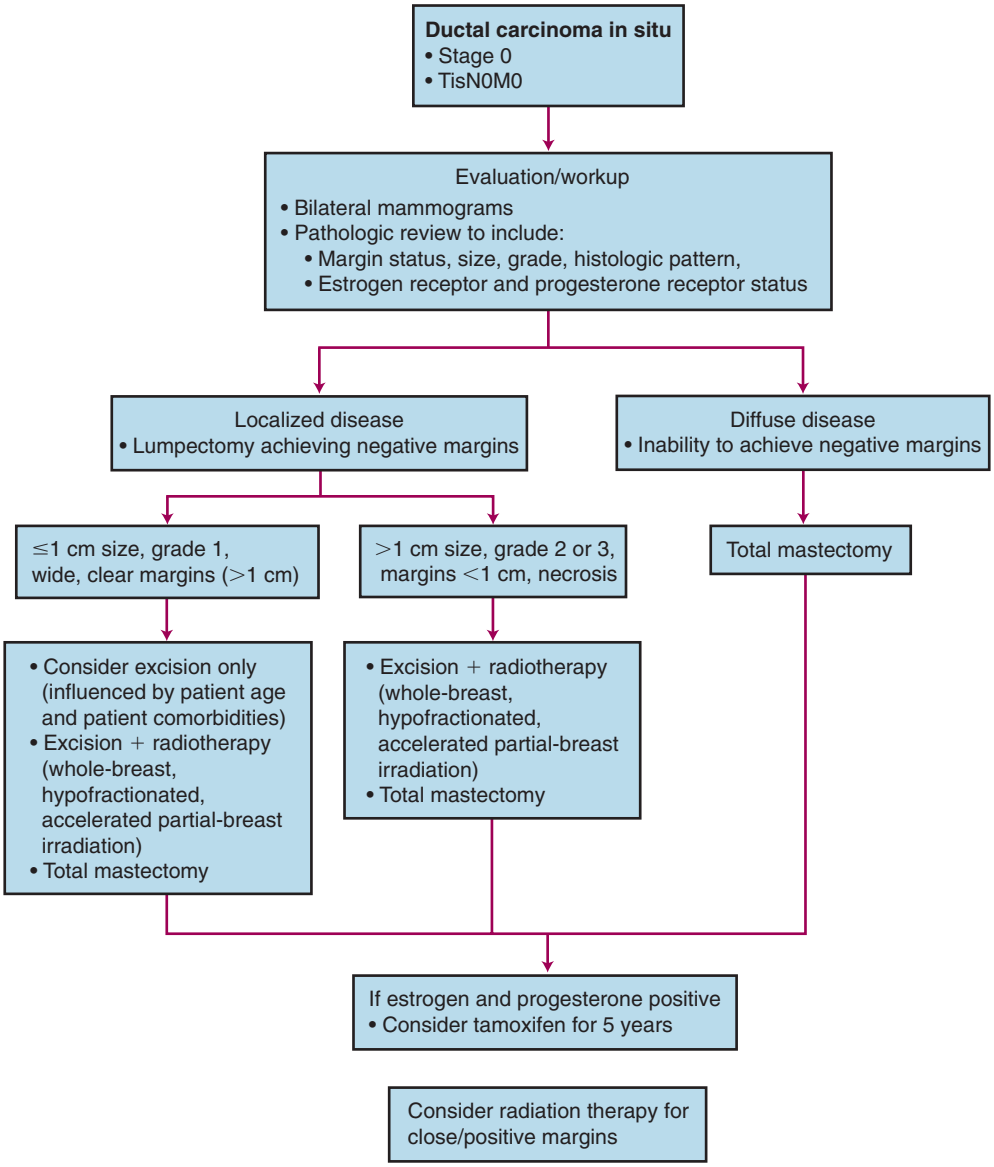


Figure 62-3 Management decision tree for ductal carcinoma in situ.

In summary, DCIS is a noninvasive malignant tumor that is managed successfully with treatment directed toward the breast only (Figure 62-3). Treatment approaches addressing the whole breast are considered the standard of care, although hypofractionated and partial-breast treatment (i.e., wide excision only versus lumpectomy plus partial-breast irradiation) techniques are being evaluated. Although mastectomy can always be considered a treatment option, breast-conservation therapy is the preferred treatment approach. When considering a patient for standard breast-conservation therapy, it is important to first ensure that clinical and mammographic information confirms that the lesion is unicentric. When surgical excision of the lesion is performed, negative pathologic margins should be established and an acceptable cosmetic result achieved. Postoperative irradiation should be delivered with whole-breast tangential fields to a homogeneous dose of 46 Gy to 50 Gy in 1.8 Gy to 2 Gy per fraction. An additional dose to the surgical bed plus the tumor margin (1 cm to 2 cm) typically follows, so that the total cumulative dose to the surgical bed is 60 Gy to 66 Gy.

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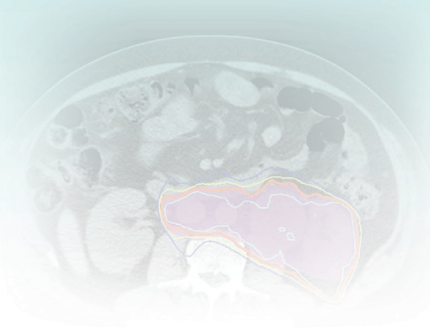
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CHAPTER

63 Breast Cancer: Stages I-II



Abram Recht

PATIENT SELECTION

The majority of individuals with stages I to II invasive breast cancer are candidates for breast-conserving therapy (BCT).

Treatment with conservative surgery (CS) and radiation therapy (RT) is absolutely or relatively contraindicated because of toxicity concerns for only a few patients. In some individuals the anticipated cosmetic results of CS and RT may be so poor that mastectomy with immediate reconstruction is a more appealing alternative.

Proper pretreatment evaluation is a critical aspect of deciding on the most appropriate treatment approach. Careful physical examination should be performed. All patients should have mammograms before biopsy and, in selected patients, after surgery to ensure the completeness of resection. The role of magnetic resonance imaging (MRI) is still unsettled and controversial. Specimen radiography should be performed routinely, including for patients who present with a nonpalpable mass without microcalcifications.

Careful evaluation of the tumor specimen is mandatory, especially with regard to the margins of resection. It is critical for the pathologist to note whether and how far tumor extends beyond the edges of any grossly apparent mass, and whether calcifications are associated with the tumor, benign tissue, or both. Detailed description of the size of the invasive component, histologic type, presence of an extensive intraductal component or lymphovascular invasion, grade, and other features of the lesion should be recorded.

TREATMENT

Some patients have a low risk of local recurrence when treated with CS and endocrine therapy without irradiation. However, there is no consensus on exactly which combination of patient, clinical, and histologic factors permit acceptable results with this approach.

There is no consensus on the minimum microscopic tumor-free margin width needed to offer patients BCT (either with or without RT). Though uninvolved margins are preferred, selected patients with involved margins have excellent local control with RT.

Most patients with uninvolved margins have excellent local control and cosmetic results when given whole-breast doses of approximately 45 Gy to 50 Gy in 2-Gy fractions or its biologic equivalent. Patients younger than age 50 years or those with certain histologic findings may benefit most from the addition of a boost dose to the tumor bed and surrounding area.

Three-dimensional compensation improves the homogeneity of radiation dose distribution within the breast. This results in fewer acute side effects and improved cosmetic outcome for many patients.

Accelerated partial-breast irradiation allows patients to undergo BCT more quickly than with conventional whole-breast irradiation. However, there are substantial uncertainties regarding its long-term efficacy and toxicity, selection of patients for this approach, and its technical details.

The value of RT directed at regional lymph nodes is uncertain. There is no consensus on when (and which) regional nodes should be irradiated.

FOLLOW-UP

The focus of follow-up should be on detecting potentially curable recurrences and new primary tumors in the ipsilateral and contralateral breasts.

The optimal follow-up schedule and testing regimen is unknown. Nonetheless, it is reasonable to perform biannual or annual physical examinations and annual mammograms indefinitely.

THERAPY OF LOCOREGIONAL RECURRENCE

Most patients with a local recurrence who have received prior RT should undergo mastectomy. Selected patients may have acceptable results with further BCT if careful clinical, radiologic, and pathologic evaluation shows the lesion to be limited in extent, and there is no evidence of multicentric disease.

Patients not previously irradiated are usually candidates for further BCT, including RT.

The value of further adjuvant systemic therapy for patients with local recurrence after BCT is uncertain.

INTRODUCTION

Approximately 70% to 80% of patients with stage I or II invasive breast cancers are technically candidates for BCT.[1,2] Six major randomized trials[3-9] using modern RT techniques (eTable 63-1) and a meta-analysis including additional studies[10] found no differences in disease-free survival (DFS) or overall survival (OS) between mastectomy and BCT.

Many questions remain regarding optimal patient evaluation and selection for BCT, RT techniques and doses, factors affecting complications and cosmetic outcome, follow-up, and treatment of locoregional recurrences. Several texts discuss these topics in greater depth.[11-14]

PRETREATMENT EVALUATION

Imaging

Mammography should always be performed, although it does not always accurately delineate the extent of disease. MRI finds additional ipsilateral foci in 5% to 10% of candidates for BCT and unsuspected contralateral disease in 3% to 5%.[15-17] Most abnormal findings near the index lesion are malignant, whereas those further away are likely to be benign.[18] Two randomized trials disagreed on whether preoperative MRI reduced the need for reexcision.[19,20] Two retrospective studies found a lower risk of local failure in patients undergoing

eTABLE 63-1 Randomized Trials Comparing Mastectomy to Breast-Conserving Therapy

Trial	Dates	Pts	FU (years)	Time-Point (yrs)	Distant Failure		Overall Survival	
					M	BCT	M	BCT
WHO[3]	1972-1979	179	22 (mean)	—	0.7 (04-1.2)*		0.7 (0.5-1.1)*	
Milan I[4]	1973-1980	701	20	20	24%†	23%†	41%	42%
NSABP B-06[5]	1976-1984	1406	20.7 (mean)	20	51%	54%	47%	46%%
US NCI[6]	1979-1989	279	25.7	20	29%‡	56%‡	44%	38%
EORTC 10801[7]	1980-1986	903	22.1	20	43%	47%	45%	40%
Denmark 82TM[8]	1983-1989	731	19.6	10/20	61%‡	60%‡	51%	58%

BCT, *breast-conserving therapy (included radiation therapy);* EORTC, *European Organization for Research and Treatment of Cancer;* FU, *mean or median length of follow-up, in months;* M, *mastectomy;* NSABP, *National Surgical Adjuvant Bowel and Breast Project;* US NCI, *United States National Cancer Institute;* WHO, *World Health Organization;* yrs, *years.*

**Odds ratio, BCT to mastectomy, with 95% confidence interval; exact rates not given, although illustrated in figures.*

†*Crude rate.*

‡*Total relapse rate; distant metastasis rate not given separately.*

Notes: Follow-up is median unless otherwise noted.

Rates given are actuarial, at time-point indicated, unless otherwise noted.

For the NSABP B-06 trial, comparison included only lumpectomy patients receiving radiotherapy.

MRI,[21,22] but two others did not.[23,24] MRI may be most valuable for patients with tumors larger than 2 cm or infiltrating lobular histology.[25]

Postoperative mammograms only rarely show residual calcifications or additional masses in patients with uninvolved microscopic margins.[26,27] Its use made no difference to the recurrence rate for patients with ductal carcinoma in situ (DCIS) in one series.[28] Postoperative MRI has limited accuracy in detecting residual disease.[29-31]

Pathologic Evaluation

The most common approach for microscopic margin assessment is for the surgeon to remove a single specimen that the pathologist rolls in India ink and sequentially sections perpendicular to its long axis ("bread-loafing"). Some pathologists "shave" each face of a specimen; the margin is considered involved when tumor is seen in one of the shaved margin slides. These approaches may have quite different clinical implications.[32,33] Some surgeons take additional "cavity" specimens after removing the main specimen.[34] The role of intraoperative margin assessment is uncertain.[35]

SURGICAL TECHNIQUES

Breast-Conserving Surgery

Technical aspects of breast surgery are discussed in depth elsewhere.[11,13,14] Patients with large cancers or lesions in areas where resection can cause substantial breast distortion may benefit from "oncoplastic" reconstruction.[36-38] Reduction mammoplasty at the time of excision may reduce the risk of retraction in patients with large breasts.[39]

Axillary Dissection

The classical three anatomic "levels" of the axilla are: level I, lateral and inferior to the border of the pectoralis minor muscle; level II, under the pectoralis minor; and level III (also called the "infraclavicular" nodes), medial and superior to the border of the pectoralis minor.[40] Randomized trials found no differences in axillary failure or survival rates between "limited" dissection (removal of level I or level I and II nodes only) and "complete" dissection (removal of levels I, II, and III), but limited dissection caused less morbidity.[41-43] Axillary failures are rare after technically adequate levels I to II dissection[40,44] unless there is extensive nodal involvement.[45]

Sentinel Node Biopsy

Sentinel node biopsy (SNB) uses injection of a radionuclide tracer or vital dye (or both) in the breast to guide the surgeon to the nodes to remove.[46] Immediate and long-term complications are lower for SNB than for levels I to II axillary dissection (AxD).[47-49] False-negative rates of SNB are 0% to 12% in different series, but the risk of axillary failure after a negative SNB is small.[50-53] OS and distant failure rates are the same after AxD and SNB for patients with clinically negative axillary nodes.[54-56]

BREAST-CONSERVING SURGERY WITH RADIATION THERAPY

The effectiveness and toxicities of BCT are affected by patient, clinical, and pathologic factors and treatment parameters.

Patient Factors

Pregnancy

Unterminated pregnancy is an absolute contraindication to breast RT because of the possible teratogenic and carcinogenic effects of scattered radiation on the fetus.[57]

Prior Treatment with Radiation Therapy

Most physicians recommend mastectomy for patients with prior thoracic irradiation.[58] However, there were no unusual acute or chronic sequelae among several small studies of women treated with CS and RT after RT for Hodgkin's disease or non-Hodgkin's lymphoma.[59-62] One such patient treated at Stanford University did develop severe soft-tissue necrosis.[63] Some individuals have been successfully treated with partial-breast irradiation, albeit with short follow-up.[64,65] Such patients should understand they may be at substantial risk of developing new breast cancers because of their prior exposure, which may affect their decision making.

Rheumatologic Disorders

The use of BCT in patients with rheumatologic disorders has been controversial. Three small studies found no clear increased risk of complications in patients with rheumatologic disorders to a matched "normal" population, except for scleroderma.[66-68]

Breast Size

Women with large breasts have more acute skin reactions and long-term retraction and fibrosis than patients with smaller breasts.[69,70] However, their results can be improved by using higher-energy photons,[71] 1.8-Gy daily fractions, three-dimensional compensation,[69] and treatment in the lateral decubitus or prone positions.

Prior Breast Augmentation

Patients with augmented breasts should have MRI, given the limitations of mammograms in this setting. Capsular fibrosis and other complications after RT occurred in half or more of patients in two series[72,73] but were much less common in several others.[74-76] Thus, it seems reasonable to offer such patients BCT.

Patient Age

Patients younger than 35 years to 40 years old at diagnosis have higher local recurrence rates than older patients in most series.[77,78] However, overall outcome is not superior after mastectomy.[79-83] Some studies have suggested margins smaller than 2 mm or high histologic grade increase young patients' risk of local recurrence,[84-86] but others have not.[87] Systemic therapy substantially reduces their local failure rates.[77,88]

Older patients tolerate RT well and have excellent local control rates.[89,90]

Genetic Factors

A family history of breast cancer by itself does not increase the risk of local failure following BCT (eTable 63-2).[91-95] Most[96-102] but not all[103-105] studies also found modest or no differences between patients with *BRCA1* and *BRCA2* mutations and unaffected patients (eTable 63-2). Recurrence in a different quadrant is more common in *BRCA1* and *BRCA2* mutation carriers than noncarriers, suggesting they have a higher risk of developing new primary cancers.[99] Tamoxifen or oophorectomy may reduce both ipsilateral local failure[99] and contralateral new primary cancers.[99,106]

Most studies do not show that ipsilateral mastectomy with or without contralateral prophylactic mastectomy improves long-term outcome for patients with *BRCA1* and *BRCA2*

eTABLE 63-2 Local Failure Rates after Breast-Conserving Therapy in Patients with Hereditary Breast Cancer

Location, Years	Risk Factor	Follow-up (months)	Calculation	LF: HBC	LF: Sporadic
Brisbane, 1982-1989[91]	Any FH	50	5-year	4% (85)	5% (418)
Philadelphia, 1977-1986[92]	Any FH	60	5-year	6% (264)	9% (517)
Houston, 1970-1994[93]	Any FH	106	Crude LRF	10% (32 of 308)	12% (80 of 677)
Chicago, 1977-1993[94]	1st degree FH	46 (mean)	5-year	5% (134)	3% (660)
Boston, 1968-1986 (age ≤36)[95]	1st degree: BC age <50 or OC any age	60 (min)	5-yr crude	3% (1 of 29)	14% (24 of 172)
Rotterdam, 1980-2001[96]	*BRCA1*	61	5-year	12% (76)	14% (241)
New York, 1989-1999[103]	*BRCA1/2*	50	Crude LRF	19% (4 of 21)	6% (13 of 220)
Rotterdam, 1980-?[97]	*BRCA1/2*	52/61	5-year	*BRCA1*: 12% (76); *BRCA2*: 17% (35)	12% (410)†
Montréal, 1986-1995[98]	*BRCA1/2*	77	5-year	6% (32*)	7% (170*)
Multicenter, ?[99]	*BRCA1/2*	95/80	10-year	12% (160)	9% (445)†
			15-year	24%	17%
Paris, 1981-2000[100]	*BRCA1/2*	105	Crude	24% (7/29)	19% (52 of 271)
Villejuif, ?[101]	*BRCA1/2*	114	10-year	*BRCA1*: 9% (37) *BRCA2*: 37% (16)	12% (43)
New York-Montréal, 1980-1995[102]	*BRCA1/2*	116	10-year	12% (57)	8% (440)
New York, 1980-1990[104]	*BRCA1/2*	124 (survivors)	5-year 10-year	15% (28) 22%	5% (277) 7%
New Haven, 1975-1998 (age <42)[105]	*BRCA1/2*	152 (mean)	5-year 10-year	22% (22) 41%	15% (105) 19%
Heidelberg, 1995-2002[107]	CHEK2	87	Crude	12% (3 of 25)	8% (10 of 125)

From Recht A: Radiation therapy and hereditary breast cancer, ASCO Educational Book, 2010, pp 16–18. With permission of the publisher.
FH, *Family history of breast cancer, unless otherwise stated;* HBC, *hereditary breast cancer;* LF, *local failure;* LRF, *locoregional failure;* min, *minimum potential follow-up time;* OC, *ovarian cancer;*
?, *Not reported or unknown.*
Notes: Follow-up is median unless otherwise noted. Number of patients in group in parentheses when actuarial failure rate given.
**Includes patients with mastectomy; 94% of patients in series treated with breast-conserving therapy, but exact number per risk group not reported.*
†*Sporadic cohort matched to HBC cohort by age and date of diagnosis.*

mutations or a family history of breast cancer compared to BCT,[97,108-111] though there are exceptions.[112] However, these studies usually contain small numbers of patients, there is considerable selection bias in treatment assignment, and follow-up is too short to detect late differences.

Syndromes associated with impaired radiation damage repair, such as ataxia telangiectasia, result in a substantial risk of complications from RT.[113] However, patients heterozygous for *BRCA1* and *BRCA2* mutations or with a single ATM mutation do not have increased toxicities.[99,114-116] Some studies suggested increased adverse results for patients with more than one ATM mutation,[117] those with particular single ATM mutations,[118,119] and those with polymorphisms of multiple radiation repair genes.[118,120-123]

In-field cancers have been reported to occur within a few years of RT in several patients with TP53 mutations, which causes the Li-Fraumeni syndrome.[124-126] RT does not increase contralateral breast cancer rates in patients with ATM[127-129] or *BRCA1* and *BRCA2* mutations.[111,130]

Clinical Factors

Means of Detection

Local recurrence rates are similar for patients with palpable and nonpalpable cancers.[131] Patients with nipple discharge do not have higher local failure rates than others.[132]

Tumor Size and Location

Tumor size does not influence local recurrence rates.[84] However, it is difficult to achieve both acceptable cosmetic results and negative margins in most patients with tumors larger than 4 cm to 5 cm without using neoadjuvant chemotherapy.

Patients with subareolar or periareolar lesions that do not directly extend to the nipple or areola have high local control rates following excision with negative margins without nipple-areolar resection.[133,134] Even when nipple-areolar resection must be performed, local control is high,[135] the appearance and texture of the remaining breast are at least as good as that following reconstruction procedures, and sensation is preserved.

Bilateral Breast Cancers

Patients with bilateral breast cancer (either synchronous or metachronous) can be treated successfully with BCT without increased complications,[136-138]

Multiple Ipsilateral Primary Cancers

Multiple synchronous ipsilateral breast cancers occur in only 2% to 4% of patients.[139-141] The majority of apparently independent lesions in one recent study were clonal, indicating a single site of origin.[142] Local failure rates are similar to those of patients with a single lesion when negative margins are achieved.[137,143-148]

Pathologic Factors

Margin Status

A "positive" or "involved" margin is defined as invasive cancer or DCIS present at an inked surface when a bread-loafing technique is used or having tumor anywhere in shaved margin specimens. Involved margins are associated with higher local failure rates than uninvolved margins, although the difference is much smaller in recent studies than older ones.[149] Invasive cancer and DCIS involvement have similar implications.[150,151] Studies differ on whether the presence of lobular carcinoma in situ (LCIS) at margins is a risk factor.[152,153]

The extent of margin involvement is important. In one study with a median follow-up time of 127 months, the crude 8-year local failure rate was 14% for 122 patients with focal margin involvement and 27% for 66 patients with extensive involvement.[150] In another study, the risk of local failure was 14% (10 of 70) for patients with a single positive margin, compared to 36% (17 of 47) for patients with multiple involved margins with a median follow-up of 72 months.[154]

TABLE 63-1 Tumor-Free Margin Width and the Risk of Local Failure Following Breast-Conserving Therapy with Radiation Therapy

	JCRT[150]	Tufts[85]	William Beaumont[156]
Median Follow-up (months)	127	121	103
Measure	8-yr crude	12-yr KM	12-yr KM
Margin Width (mm):			
Positive, NOS	18% (192)	17% (105)	30% (38)
0.1-1	7% (94)	—	14% (94)
1.1-2	6% (33)	—	18% (45)
0.1-2	7% (127)	9% (99)	—
>1 (NOS)	6% (186)	—	—
>2 (NOS)	6% (153)	—	9% (333)
2.1-3	—	—	15% (59)
3.1-5	—	—	13% (43)
2.1-5	4% (47)	5% (84)	—
>5 (NOS)	12% (56)	0 (69)	—
5.1-10	—	—	13% (90)
>10 (NOS)	—	—	5% (52)
No tumor on reexcision	8% (101)	6% (137)	2% (160)

Adapted from Recht A: Lessons of studies of breast-conserving therapy with and without whole-breast irradiation for patient selection for partial-breast irradiation. Semin Radiat Oncol 15:123–132, 2005, Table 1; with permission of the publisher.

CI, *Cumulative incidence;* JCRT, *Joint Center for Radiation Therapy, Boston;* KM, *Kaplan-Meier estimator;* NOS, *not otherwise specified;* yr, *year.*

Note: Number of patients in subgroup in parentheses.

Investigators often distinguish "negative" from "close" but uninvolved margins based on the tumor-free margin width.[155] However, there is no standard definition of these terms. Only three published studies with long follow-up examined outcome according to sequential margin intervals, rather than a single cut-point (Table 63-1).[85,150,156] They do not show a consistent relation between increasing margin width and lower local failure rates. A study from British Columbia also found a 4% local failure rate in both 170 patients with margins of 0.1 mm and 1 mm and 52 patients with 1.1-mm and 2-mm margins, with median follow-up of 62 months.[149]

Few data exist on other aspects of margins. A study from Scotland found that reexcision performed for an anterior margin of less than 1 mm found residual disease in only 4% of patients who had initial excision in the subcutaneous plane, compared to 24% of patients with a narrow posterior margin (originally taken to the pectoralis fascia) and 33% of those with a narrow circumferential (or radial) margin.[157] Margin direction did not affect local failure for patients with margins of less than 2 mm or those with positive margins in another study.[158] One study found that the volume of disease near uninvolved margins affected the risk of local recurrence.[156]

The number of excisions required to achieve uninvolved margins was not a risk factor for local failure in most,[159,160] but not all,[161] series. Studies also disagree whether finding residual

disease on reexcision modestly increases local failure rates, even with negative margins.[162-164]

Chemotherapy and tamoxifen substantially reduce failure rates in patients with uninvolved margins as a whole.[165,166] This effect may be proportionally greater for patients with margins narrower than 1 mm to 2 mm.[150,167]

Other Histologic Features

An infiltrating ductal carcinoma has an "extensive intraductal component" (EIC) when DCIS both comprises a prominent portion of the area of the primary mass and is present in grossly normal adjacent breast tissue, or when the tumor is predominantly noninvasive.[168] (Other definitions probably describe the same entity.) Tumors with an EIC extend more widely within the breast.[169] Its impact on local failure is uncertain when margin status is accounted for.[84,150,170] Patients with microinvasive cancers have the same risk of local failure as those with larger areas of invasion.[171]

The terms *multicentric* and *multifocal* are not standardized but commonly refer to the presence of cancer in more than one quadrant or in multiple areas within a single quadrant, respectively. Such findings do not affect the risk of local relapse.[172,173]

Lymphovascular invasion is an independent but small risk factor for local recurrence in most,[174-177] though not all,[91] studies.

Patients with infiltrating lobular carcinomas or mixed ductal and lobular features[178-182] or rarer histologic subtypes[181,183-187] have comparable local recurrence rates to patients with infiltrating ductal carcinomas.

One study found a substantial risk of residual DCIS or invasive disease on reexcision when atypical ductal hyperplasia was at or near the margins.[188] However, benign proliferative diseases do not appear to affect the risk of local failure.[189-191]

Studies conflict on whether the presence of LCIS does[192-194] or does not[153,195-197] increase local failure rates.

Biologic Markers of Tumor Behavior

Patients with tumors that express the estrogen receptor (ER) have modestly lower local recurrence rates than patients with ER-negative tumors when systemic therapy is not used.[198] Appropriate systemic therapy reduces this difference substantially.

Breast cancers can be grouped into "intrinsic subtypes" according to patterns of gene expression.[199] Most studies classify cancers with immunohistochemical assays of critical cell signaling receptors, rather than direct analysis of gene copy numbers. Subtypes are associated with marked differences in age at presentation, tumor size, histologic features, and the extent of lymph node involvement.[200,201] Patients with luminal A subtypes (ER-positive, progesterone receptor, or PR, positive, and c-*erb*B-2/neu, or HER2, negative) uniformly appear to have 10-year local relapse rates of 5% to 8% after BCT. Patients with basal (or "triple-negative") subtypes have similar local failure rates to patients with other combinations of ER, PR, and HER2 status in some studies[202-208] or modestly higher rates in others.[209-213] Local failure rates increased with HER2 overexpression in some series[201,209,212,214] but not others.[207,215] Trastuzumab may reduce this risk.[216]

Other gene expression profiles may also affect local control, but differences in outcome are small.[207,217,218] Intratumor heterogeneity must also be considered when using such panels for clinical decision making.[219]

Prognostic Indices

Several investigators have proposed using prognostic indices that combine patient-, clinical-, and tumor-related features to more accurately determine the risk of local failure after BCT.[220-222] Their ultimate role is not yet clear.

Conclusions

There are only a few patients for whom RT is absolutely or relatively contraindicated because of toxicity concerns. The anticipated cosmetic results may be so poor for some individuals that mastectomy with immediate reconstruction may be a more appealing alternative. Margin status is the most important determinant of local control, but other factors interact with it and each other in complex and poorly-understood ways. An uninvolved margin is sufficient to obtain excellent local control rates in the great majority of patients. Wider tumor-free margin widths might benefit certain patient subgroups (e.g., those younger than age 35 to 40, those with an EIC, or patients receiving RT after a long delay from surgery as a result of chemotherapy), but data are limited and contradictory. If margins are still involved microscopically after reexcision, then the patient should understand that she is at higher risk of local recurrence, although this may be reduced somewhat by systemic therapy.

BREAST-CONSERVING SURGERY WITHOUT RADIATION THERAPY

Results of Conservative Surgery with or without Radiation Therapy

eTable 63-3 summarizes the largest randomized trials comparing CS alone to CS with RT for relatively unselected patients, with respective local recurrence rates of about 15% to 40% and 3% to 20%, respectively.[5,223-228] However, more recent trials with more restrictive patient selection which routinely used endocrine therapy have considerably lower failure rates without RT (Table 63-2).[165,229-238] For example, in the NSABP B-21 trial, the local failure rate was 10% (19 of 197 patients) at median follow-up of 89 months for patients with a tumor 1 cm or smaller with known positive ER treated with tamoxifen without RT.[165,229] Giving RT changed rates of distant metastasis, breast cancer-specific mortality, or OS in the former studies but not the latter ones.

The use of RT improved recurrence-free, breast cancer-specific survival, and OS in both patients with negative and positive axillary nodes in the most recent meta-analysis of the Early Breast Cancer Trialists' Collaborative Group, which included trials begun before 2000.[241] The proportional reductions were greatest in patients with positive axillary nodes. The benefits of RT with respect to these endpoints were much more variable in patients with negative nodes in relation to patient age at diagnosis, tumor size tumor grade, ER status, and the use of systemic therapy. The investigators therefore created a model to further investigate the impact of RT on breast cancer-specific mortality for patients with pathologically uninvolved nodes. This resulted in three groups, based on how much RT would reduce the predicted 10-year risk of any recurrence: large (20% or more); intermediate (10% to 19%); and low (less than 10%). Ten-year risks of locoregional failure were reduced by RT by 24%, 13%, and 9%, respectively, and 15-year breast cancer death rates by 7.8%, 1.1%, and 0.1%, respectively (Figure 63-1).

Correlates of Local Recurrence in Patients Treated with Conservative Surgery and Endocrine Therapy without Radiation Therapy

Endocrine therapy seems needed to obtain acceptably low failure rates without RT.[230,234,242] There was no difference in

eTABLE 63-3 Randomized Trials Comparing Breast-Conserving Surgery Alone to Breast-Conserving Surgery and Radiation Therapy for Relatively Unselected Patients with Early-Stage Invasive Breast Cancer, with Median Follow-up Time Longer Than 5 Years

					Local Failure		Distant Failure or Breast Cancer Death		Death, All Causes	
Trial	**Dates**	**Pts**	**FU (months)**	**Time-Point (years)**	**BCS Alone**	**BCS & RT**	**BCS Alone**	**BCS & RT**	**BCS Alone**	**BCS & RT**
NSABP B-06[5]	1976-1984	1137	248 (mean)	20	39%	14%	42%*	35%*	53%	50%
Uppsala-Örebro[223]	1981-1988	381	103 (BCS alone)/ 109 (BCS & RT)	10	24%	9%	20%†	10%†	22%	22%
St. George/Royal Marsden[224,225]	1981-1990	400	164	Crude	41%	20%	28%†	26%†	34%	31%
Ontario[226]	1984-1989	799	91	Crude	35%	11%	30%†	23%†	24%	21%
Scotland[227]	1985-1991	585	68	Crude	24%	6%	20%*	13%*	0.98§	
Milan III[228]	1987-1989	567	109	10	15%	3%	16%*‡	12%*‡	23%	18%

See also Table e63-1; BCD, *Breast cancer death;* BCS, *breast-conserving surgery;* BCS & RT, *breast-conserving surgery and radiotherapy;* DF, *distant failure;* FU, *follow-up;* Pts, *patients.*

Note: Rates given are actuarial, at time-point indicated, unless otherwise noted.

**Breast cancer death.*

†*Distant failure.*

‡*Crude rate.*

§*Hazard ratio of BCS & RT to BCS alone; actual rates not reported.*

TABLE 63-2 Local Failure Rates in Randomized Trials Treating Selected Patients with Breast-Conserving Surgery and Endocrine Therapy with or without Radiotherapy

Study	Dates	Age	Nodes	Max Size (cm)	Other Selection Criteria	FU (mo)	No RT: LF	RT: LF
NSABP B-21*[165,229]	1991-1998	Any	pN0	1	None	134	20% (206) (14-yr)	10% (228)
GBSG V[230,231]	1991-1998	45-75	pN0	2	HG 1-2, EIC–, LVI–, ER+ or PRP+	119	8% (6/80)	5% (5/94)
Ontario-British Columbia[232,233]	1992-2000	≥51	pN0 or cN0	5	None	94	12% (383) (8-yr)	4% (386)
BASO II[234]	1992-2000	≤69	pN0	2	HG 1	121	8% (8/106)	0 (0/98)
CALGB 9343[235,236]	1994-1999	≥70	pN0 or cN0	2	ER+	151	9% (27/319)	2% (6/317)
ABCSG Study 8A[237]	1996-2004	Any	pN0	3	HG 1-2, ER+ or PR+	54	5% (19/417)	0.5% (2/414)
Italy†[238,239]	2001-2005	55-75	pN0 or pN1 (13%)	2.5	EIC–, LVI–	108	4% (16/376)	3% (12/373)
PRIME II[240]	2003-2009	≥65	pN0	3	HR+, not HG 3 with LVI (one alone acceptable), margins ≥1 mm	60	4% (668) (5-yr)	1% (658)

ASO, *British Association of Surgical Oncology;* CALGB, *Cancer and Acute Leukemia Group B;* cN0, *clinically-uninvolved axillary lymph nodes;* CT, *chemotherapy;* EIC—, *no extensive intraductal component;* ER+, *positive for the estrogen-receptor protein;* HR+, *positive for either the estrogen- or progesterone-receptor protein;* FU, *median length of follow-up (in months);* GBSG V, *German Breast Cancer Study Group Trial V;* HG, *histologic grade;* LF, *local failure rate (crude, unless otherwise specified);* LVI—, *lymphovascular invasion;* LVPI—, *no lymphovascular or perineural invasion;* Neg, *"negative" margins, not otherwise defined in the study;* NG, *nuclear grade;* NSABP, *National Surgical Adjuvant Breast and Bowel Project;* pN0, *pathologically uninvolved axillary lymph nodes;* PR+, *positive for the progesterone-receptor protein;* PRIME, *Post-operative Radiotherapy In Minimum-risk Elderly;* SPF, *S-phase fraction.*

Notes: Crude local failure rates are given, unless a time is given in parentheses, in which case the results are actuarial. All patients had uninvolved margins.

**Results given here for patients with centrally reviewed cancers.*

†*Systemic therapy given as appropriate for nodal status and tumor biology, but details not reported.*

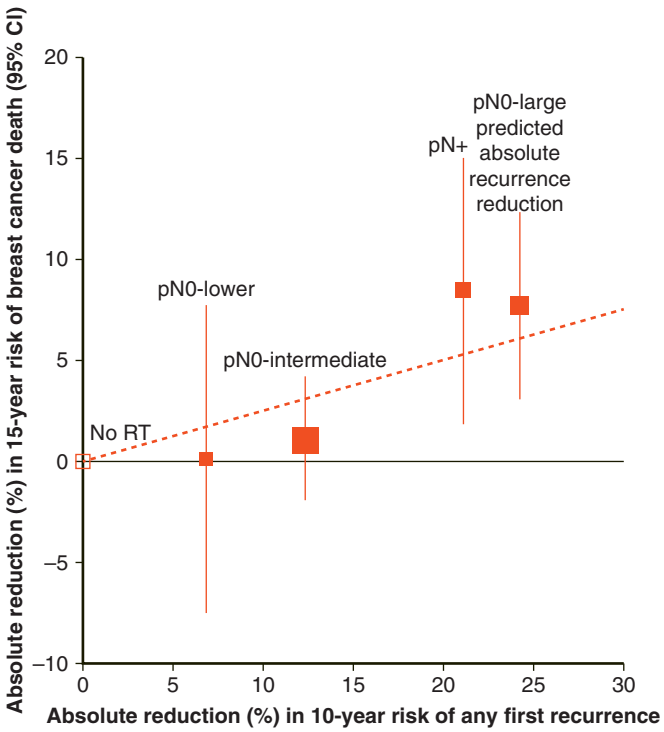


Figure 63-1 Relation between the absolute reduction in 10-year overall recurrence risk and reduction in 15-year breast cancer mortality.

From: Early Breast Cancer Trialists' Collaborative Group: Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10 801 women in 17 randomised trials. Lancet 378:771–784, 2011; with permission of the publisher.

local failure rates between patients ages 50 and 60 years, ages 60 and 70 years, or older than 70 years in a retrospective study in London employing tamoxifen[243] or between those ages 55 and 64 years and 65 and 75 years in a prospective randomized trial from Italy.[238] Age older than 65 years,[228] the absence of comedo or lobular features,[223] and low histologic grade[244] were associated with reduced failure rates in series not employing systemic therapy. In a study from Milan, patients with infiltrating lobular carcinomas had a slightly higher local failure rate (12%, or 9 of 72 patients) compared to patients with infiltrating ductal histology (8%, or 18 of 231 patients).[245] A study from Guy's Hospital, London of patients age 70 and older found that lymphovascular invasion and ER-negative status were associated with higher risks of locoregional recurrence.[246] Patients with grade 1 or 2 luminal A tumors demonstrated no difference in the 10-year local failure rates with or without RT in the Ontario-British Columbia trial (both 5%); patients with other subtypes had substantially higher local failure rates when RT was omitted.[247] In a retrospective study of patients older than 70 years treated in Nottingham, England, with median follow-up of 37.5 months local failure rates were 33% (4 of 12) for margin widths less than 1 mm, 12% (2 of 17) for margins of 1 mm to 5 mm, and 2% (1 of 54) for margins wider than 5 mm, respectively.[248]

Combinations may be more important than individual features in predicting local failure. In the Ontario-British Columbia trial, the actuarial 8-year local recurrence rate for 237 patients age 60 years or older with tumors 2 cm or smaller and positive ER or PR was 7% when treated with tamoxifen alone at a median follow-up of 94 months.[233]

Conclusions

There is no consensus on which patients are appropriate candidates for CS without RT. I feel it reasonable to offer such

treatment to those with all of the following characteristics: age 60 years or older (though many American radiation oncologists prefer a minimum age of 70 years); 2-cm or smaller ER-positive grade 1 or 2 tumor without an EIC or lymphovascular invasion; microscopic margins 5 mm or wider; pathologically negative axillary nodes (or clinically negative nodes for those age 70 or older); and willingness to take endocrine therapy. However, the effect of RT on patients' quality of life is brief and limited,[249] serious complications are rare, and some patients may prefer to reduce their risk of local failure yet further by being irradiated.[250,251] Decision aids may help patients make this choice.[252]

WHEN TO USE NODAL IRRADIATION

Axillary Irradiation

Some patients with clinically uninvolved (cN0) axillary nodes have a low risk of regional nodal failure without any axillary treatment.[233,236,245,253,254] Many studies using breast RT alone without axillary surgery also found a low risk[245,255-261] but others had much higher rates.[257,262] A trial at the National Cancer Institute of Milan randomly assigned 517 evaluable patients age 18 years to 65 years with clinical T1N0 cancers to breast irradiation plus axillary dissection (AxD) or breast RT alone.[262] The incidence of nodal involvement in the AxD group was 29%, with the latter group having an axillary failure rate of 9% (21 of 243 patients) with median follow-up of 10.6 years. However, the axillary failure rate was only 4% (4 of 110 patients) in an otherwise identical trial they performed for patients ages 65 years to 80 years.[263] Axillary plus breast RT results in failure rates of 1% to 3%.[258,264-266] Such treatment resulted in 1% to 2% lower failure rates than breast RT alone in two Italian trials.[267,268] Axillary RT is not as effective for patients with clinically suspicious (cN1) nodes,[40] who should undergo AxD.

Axillary failure rates after a positive levels I to II AxD are generally low if a minimum of 6 to 10 nodes are removed.[45,269] Failure rates may be 7% to 10% or higher in unirradiated patients with 8 or more positive nodes or T2-3 tumors with 4 or more positive nodes[45] or when a substantial proportion of removed nodes are involved.[270] In one series there were no axillary failures in patients with 10 or more positive nodes who received only supraclavicular irradiation after a complete axillary dissection.[271] Extracapsular tumor extension does not increase the risk of axillary failure.[269,272]

Three trials have compared AxD to breast RT only after a positive SNB. The American College of Surgeons Oncology Group Trial Z0011, conducted from 1999 to 2005, randomly assigned 891 patients with T1-2 tumors and one to two positive sentinel nodes. With median follow-up of 6.3 years, the crude risks of regional nodal failure in the AxD and SNB arms were 0.5% and 1%, respectively.[273] However, 20% of patients were lost to follow-up.[274] The International Breast Cancer Study Group 23-01 trial, conducted from 2001 to 2010, included 931 patients with micrometastases (0.2 mm to 2 mm). With a median follow-up of 60 months, crude axillary recurrence rates were 0.2% and 0.8% in the two arms, respectively.[275] A similar Spanish trial found an axillary recurrence rate of 1% (1 of 113 patients) in patients treated with BCT without AxD, with median follow-up time of 62 months.[276] Finally, the European Organization for Research and Treatment of Cancer (EORTC) AMAROS trial, conducted from 2001 to 2010, randomly assigned patients with a positive SLN to either AxD or breast plus axillary RT. With a median follow-up of 6.1 years, axillary failure rates in the two arms were 0.5% (4 of 744 patients) and 1% (7 of 681 patients), respectively.[277]

It is not known whether breast plus axillary RT is better than breast RT alone for certain patients with positive SLN(s). In a nonrandomized Dutch study of patients with sentinel node micrometastases, the 5-year axillary failure rate was 4% among 93 patients treated with CS and RT to the breast only,[278] compared to no failures in 94 patients treated with breast plus axillary RT.[279]

Supraclavicular Nodal Irradiation

Supraclavicular recurrences are often grouped with axillary apical or infraclavicular recurrences. They occur in only a few percent of patients with uninvolved or one to three positive axillary nodes.[44,45,280,281] Such failures occurred in 7% to 10% or more of patients with four or more positive axillary nodes in older studies,[45,269,282,283] but only 3% to 5% of patients in several recent studies.[284-286] Patients with a high proportion of involved nodes may also be at increased risk.[270]

The impact of other factors on supraclavicular relapse rates is uncertain. Some studies suggest that lymphovascular invasion increases the risk,[269,280,285] though others do not.[272,281] A study from Taiwan found that high tumor grade, having four or more positive nodes, and having positive nodes in axillary level II or III were associated with increased supraclavicular failure rates.[287] A study from Seoul, South Korea, found lymphovascular invasion, having two to three positive nodes, extracapsular extension, and involved nodes at level II or III to be independent risk factors. The 79 patients with two or more risk factors had a 5-year supraclavicular failure rate of 27%, compared to 3% for the 369 patients with one or no risk factor.[288] A study from London used tumor grade and the number of involved nodes to create three risk groups, with 10-year supraclavicular-infraclavicular failure rates of 1%, 10%, and 21%.[289] The British Columbia Cancer Agency found that patients with two or more of the findings of histologic grade 3, lymphovascular invasion, an ER-negative tumor, or three positive nodes had a 10-year regional nodal failure rate of 12%.[290] However, failure rates at specific nodal sites were not reported.

The impact of supraclavicular RT on overall outcome has never been examined in any randomized trial separately from internal mammary nodal irradiation.

Internal Mammary Nodal Irradiation

Internal mammary node (IMN) metastases occur in 5% or fewer of patients with pathologically negative axillary nodes and in 20% to 50% with positive nodes.[291,292] Tumor size and the number of involved nodes influence this risk.[44] Results of the largest such study are shown in eTable 63-4.[293] The location of the primary tumor has only a minor impact on this incidence when tumor size and axillary nodal status are accounted for.[293,294] It is common to see drainage to the IMNs when lymphoscintigraphy is performed for SNB,[294] but only 10% to 25% of such "hot spots" are involved pathologically.[295-298] Despite their frequent involvement, clinical IMN recurrence occurs in 1% or fewer patients in nearly all studies and is rare even when the nodes are shown to be involved by biopsy.[299]

The value of treating the IMNs prophylactically has thus been controversial for decades.[300] A trial conducted in France from 1991 to 1997 randomly allocated 1334 evaluable patients with positive axillary nodes or medial or central tumors with negative nodes after mastectomy and AxD to either chest wall and supraclavicular RT or the same plus IMN irradiation.[301] There was no significant difference between the two arms in 10-year DFS (50% and 53%, respectively) or OS rates (59% and 63%) at a median follow-up of 8.6 years. OS was worse in the IMN irradiation arm for patients with medial or central tumors

eTABLE 63-4 Incidence of Internal Mammary Node Involvement in Relation to Axillary Node Involvement and Tumor Size (Fudan University, Shanghai, China, 1956-2003)

Tumor Size, Involved Axillary Nodes	Patients	Internal Mammary Nodes Involved (%)
T1, N0	204	2.9
T2, N0	493	4.9
T3, N0	187	4.8
T1, 1-3	57	10.5
T2, 1-3	244	20.5
T3, 1-3	97	19.6
T1, 4-6	9	33.3
T2, 4-6	89	31.5
T3, 4-6	41	19.5
T1, ≥7	12	25.0
T2, ≥7	143	42.0
T3, ≥7	103	42.7

Data from: Huang O, Wang L, Shen K, et al: Breast cancer subpopulation with high risk of internal mammary lymph nodes metastasis: Analysis of 2,269 Chinese breast cancer patients treated with extended radical mastectomy. Breast Cancer Res Treat 107:379–387, 2008.

with negative axillary nodes (25% of the study population); the opposite trend was found for patients with positive axillary nodes. The MA.20 trial performed in Canada from 2000 to 2007 enrolled 1832 patients undergoing BCT with positive nodes (85% of the study population) or "high-risk" node-negative tumors to undergo either breast RT only or breast plus supraclavicular and IMN RT.[302] With a median follow-up of 62 months, there were statistically significant improvements in 5-year rates of locoregional failure (5% and 3% in the two arms, respectively), distant DFS (87% and 92%), and DFS (84% and 90%). The EORTC trial, conducted from 1996 to 2004, accrued 4004 patients treated either with BCT or mastectomy with either involved axillary nodes or medial or central tumors with negative nodes.[303,304] With a median follow-up of 10.9 years, the 10-year OS rate in patients receiving breast or chest-wall RT only was 80.7%, compared to 82.3% in patients also receiving supraclavicular plus IMN RT ($p = 0.056$); their respective 10-year rates of freedom from distant metastases were 75% and 78% ($p = 0.02$), and DFS were 69.1% and 72.1%.[305] Nodal irradiation had a greater effect on OS for patients with negative nodes (hazard ratio [HR], 0.79, with 95% confidence interval [CI] 0.61 to 1.02) than for patients with 1-3 positive nodes (HR 0.89; CI 0.73 to 1.09), 4-9 positive nodes (HR 0.85; CI 0.61 to 1.18), or 10 or more positive nodes (HR 1.0; CI 0.59 to 1.71).

Conclusions

There is no consensus on when axillary or supraclavicular RT should be given following levels I to II AxD when zero to three nodes are positive. I will generally add a supraclavicular field for patients with one to three positive nodes when there is LVI or a large primary. A supraclavicular field seems adequate for most patients with four or more involved nodes; a full axillary field may be useful for patients with extensive nodal involvement or a more limited dissection. Most patients with a positive SNB have a low risk of regional nodal failure when treated with breast RT only. It is not yet clear which patients have meaningfully improved results with AxD or breast plus axillary RT. The role of prophylactic IMN RT is still uncertain. Two of the three randomized trials on this topic were designed in a way that the impact of IMN RT could not be separated from that of supraclavicular irradiation. Subgroup analyses suggest that subtle differences of treatment technique and patient characteristics may determine whether individual patients benefit or not. Because IMN RT increases the irradiated volumes of lung or heart, in my view it is currently acceptable but not mandatory to give IMN RT to patients with positive axillary nodes.

TREATMENT TECHNIQUES

Patient Position and Immobilization

Patients are traditionally irradiated in the supine position. The lateral decubitus[306] and prone positions[307-309] may be especially useful for patients with large breasts because acute reactions are reduced by opening skin folds and long-term fibrosis lessened by decreasing separation (eFigure 63-1). The prone position results in anterior displacement of the heart,[310] which sometimes increases the irradiated heart volume,[311] though heart exposure is decreased for the majority of patients.[312] Some patients are unable to tolerate these positions.[308,313]

Immobilization techniques using specialized breast boards, custom-made foam cradles, and other approaches can achieve daily patient position reproducibility within 5 mm.[314-316] Set-up errors with prone positioning are comparable to supine treatment.[317,318] However, there is no fully satisfactory way to immobilize the breast itself, especially for large-breasted women. Netting is useful to move the breast tissue medially, and careful taping can help open skin folds. Using a bra increases skin reactions, though this may allow a reduction in intrathoracic normal-tissue exposure.[319]

Whole-Breast Irradiation

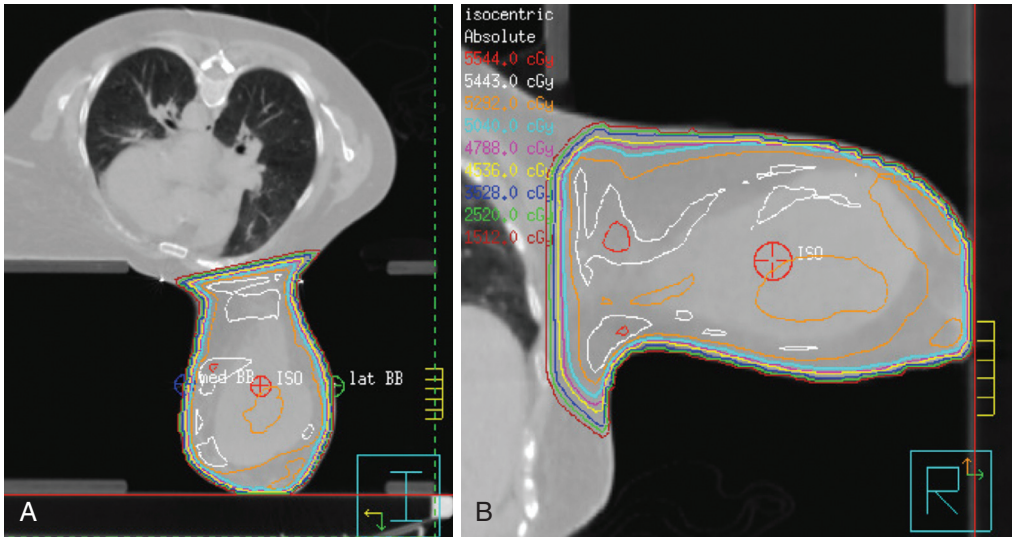
Traditional tangential field borders, created in the era of fluoroscopic simulation based predominantly on surface anatomy, include nearly the entire volume of the breast with adequate margin for daily set-up error (Box 63-1 and Figure 63-2). Three-dimensional CT-guided simulation has replaced fluoroscopic simulation. However, there is substantial interphysician variation in delineating the breast on CT.[320-322] Although interobserver variation may be reduced by the use of "standard" templates or atlases,[323,324] it seems unlikely such variations are of substantial clinical importance because the risk of local recurrence is quite low for patients planned based on surface anatomy. One advantage of CT-guided simulation is to allow greater accuracy in localizing the excision site. Because most recurrences occur at or near this area, deviating from the classical field borders for selected patients is likely to reduce toxicity without increasing local failure rates (e.g., moving the medial tangent entrance to left of midline laterally and using cardiac blocking in a patient with a small left upper outer quadrant lesion) (eFigure 63-2). Blocking or gantry rotation should be used to make the posterior tangent field edges coplanar to reduce normal-tissue exposure.

Most patients are best treated with 6-MV photons. It is preferable to use 10 MV or higher energies alone or in combination with 6-MV photons for patients with large breasts or medial-to-lateral separations (more than 22 cm to 24 cm) to keep the maximum inhomogeneity less than 110%. Skin failures are rare, regardless of treatment energy,[71] and bolus or a beam-spoiler should not be used routinely.

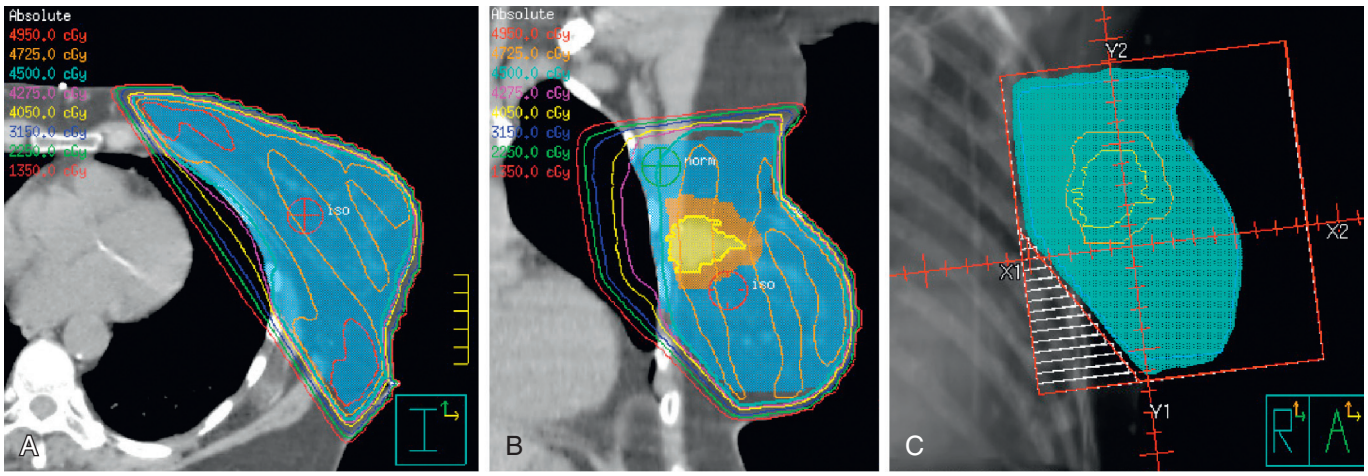
The breast-chest wall volume varies substantially in shape and transverse dimensions superiorly to inferiorly. Physical wedges generally result in satisfactory dose homogeneity in the central-axis plane, but there are often large and intense hot spots in the more superior and inferior planes. Inverse-planned intensity-modulated radiation therapy (IMRT)[325,326] with or without treatment of regional lymph nodes,[327-333] results in much more homogeneous dose distributions throughout the entire treatment volume. Several randomized[334-336] and retrospective and prospective studies[69,337-339] of three-dimensionally compensated breast RT found it reduces acute and chronic toxicities. These studies used simple forward-planned IMRT techniques with only a few additional segments (Figure 63-3 and eFigure 63-3). This approach produces nearly identical results to inverse-planned IMRT for the great majority of patients.[340-343] Elimination of a physical medial wedge also reduces scattered radiation exposure of the contralateral breast and other areas.[344,345] Hence, CT-guided simulation and three-dimensional treatment planning and compensation should be routinely used.

Respiratory excursion of the breast is 2 mm to 6 mm in different directions.[346] Daily set-up variation and respiratory motions have only a small impact on the cumulative dose distribution within the breast or near the excision cavity.[346-351] However, these can have a substantial effect on the IMN dose.[346,352]

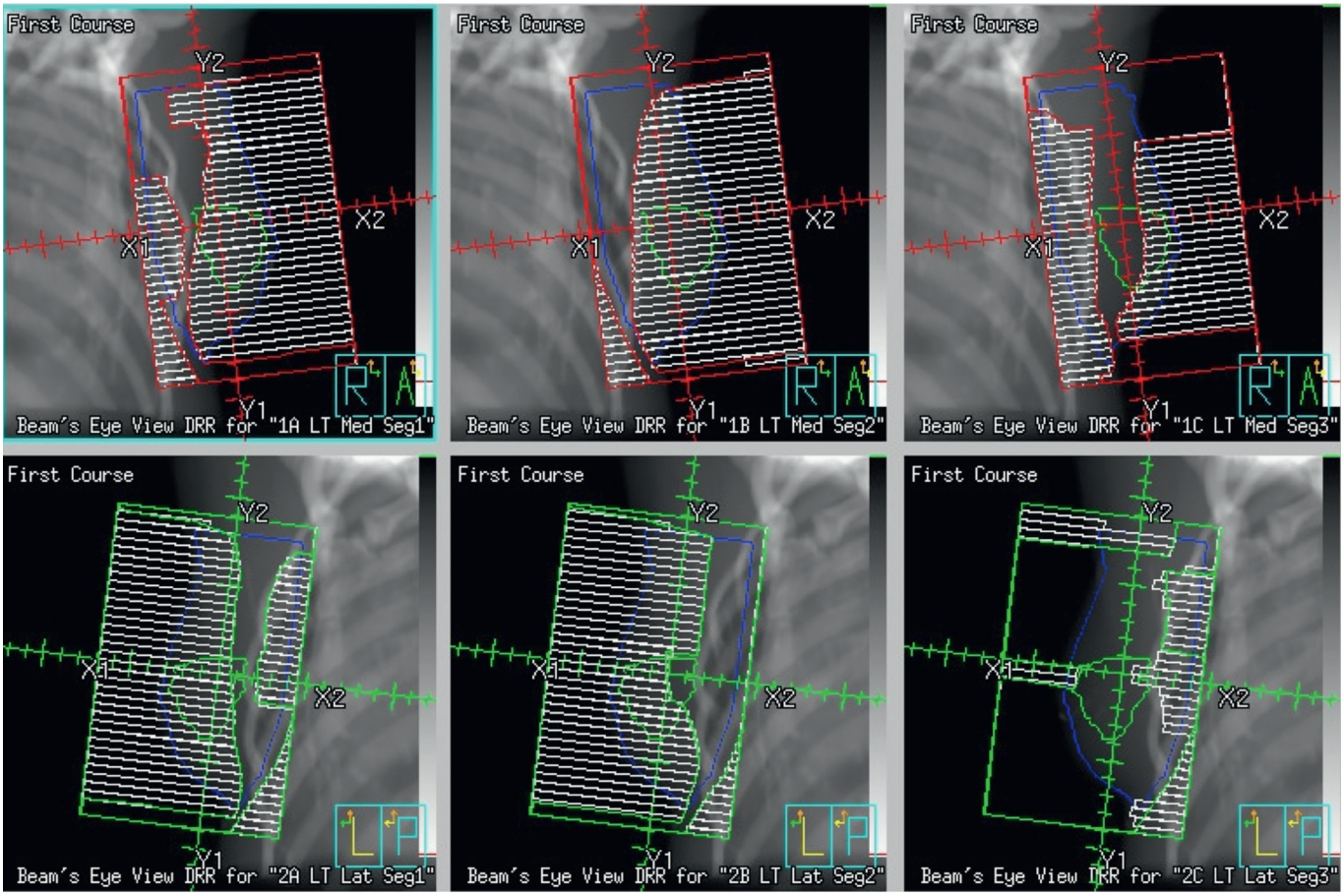
Respiratory gating or breath-holding during deep inspiration reduces the amount of heart irradiated.[315,346,352-358] Both deep-inspiration breath-holding and judicious cardiac blocking may be needed (eFigure 63-4). The left anterior descending coronary artery may move more than other portions of the heart, and therefore keeping the heart 5 mm or more from



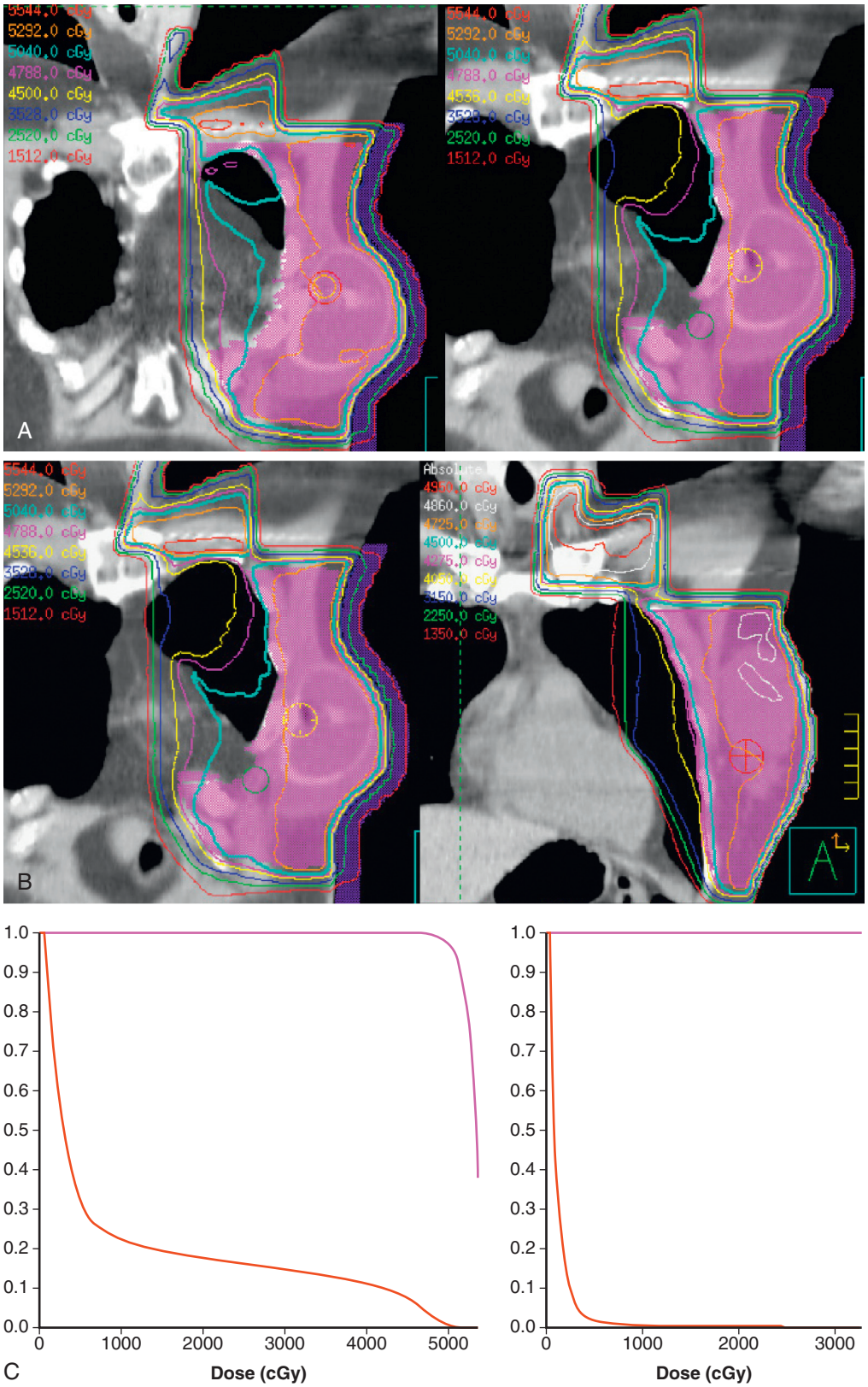
eFigure 63-1 Patient with large, pendulous breast treated in the prone position. **A,** Planning computed tomography. **B,** Detailed isodose distribution; prescription dose was 5040 cGy.



eFigure 63-2 Individualized tangential fields. Heart and lung exposure were reduced by placing the medial border to left of midline, using a steep gantry angle, and blocking the heart using multileaf collimators. **A,** Transverse dose distribution through central axis. **B,** Coronal dose distribution. **C,** Digitally reconstructed radiograph showing blocking of hear and 100% isodose "cloud" *(blue wash)* and excision site *(yellow)* with expansion for the boost planning target volume *(brown)*.



eFigure 63-3 Example of additional segments added to open tangents used for forward-planned intensity-modulated radiation therapy (IMRT).



eFigure 63-4 Effects of deep-inspiration breath-holding (DIBH) and cardiac blocking on heart exposure in a patient treated with mastectomy and immediate reconstruction using a tissue expander. Prescription dose is 50.4 Gy. **A,** Coronal views of dose distributions in free breathing (FB) on left and DIBH on the right without cardiac blocking. **B,** Coronal views of dose distributions for DIBH, without cardiac blocking on the left and with cardiac blocking on the right. **C,** Dose-volume histogram of heart exposure *(red lines)* for DIBH without cardiac blocking on the left and DIBH on the right with cardiac blocking. The pink lines are the dose to the reconstructed breast planning target volume.

BOX 63-1 Traditional Field Borders and Blocks

TANGENTS

Inferior: 1-cm margin inferiorly to the inframammary fold.

Superior: The margin of the breast is determined by palpation and is given a 1-cm margin. When a three-field technique is used, the placement of the match-line will depend on the location of the primary tumor as well as the breast tissue; ordinarily, the match-line will be at the second intercostal space or the second rib (radiographically, usually at the inferior edge of the sternoclavicular junction).

Lateral: Include all breast tissue with a 1-cm margin; this usually places this border at the posterior to midaxillary line.

Medial: At the midline in most patients. When the internal mammary nodes are to be included, then the medial border is best determined with the aid of lymphoscintigraphy or computed tomography; otherwise, the medial border is arbitrarily placed 3 cm across the midline. When the contralateral breast has been previously treated, or when both breasts are to be treated simultaneously, care should be taken to ensure that treatment fields do not overlap. A gap of 0.5 cm on skin between the medial borders of the two pairs of fields is adequate.

Anterior: 2-cm margin of light is given above the highest point of the breast.

Posterior: The deep edges of the tangents should be coincident; the medial and lateral borders determine their exact position.

Blocks: When the "corner-block" three-field technique is used, then a block is drawn along the hanging wire that defines the match-line at the superior border with the en face supraclavicular/axillary field. If a single-isocenter three-field technique or the primary collimators are used to match the superior border of the tangents to the nodal field, then blocking is used to define the posterior field borders of the tangents. Heart blocks may be used if needed for some patients with left upper-quadrant or central primaries.

BOOST

Include the breast tissue from approximately skin surface to anterior chest wall, with 1 cm to 2 cm around the excision cavity, as the planning target volume.

SUPRACLAVICULAR AND AXILLARY FIELD:

This field is angled approximately 5 degrees to 10 degrees from the vertical toward the medial side to avoid treating the cervical spinal cord.

Borders:

Inferior: Determined by the match-line with the tangential fields. With the Joint Center for Radiation Therapy (JCRT) technique, the central-axis plane is located here.

Superior: Radiologically, usually the superior-most portion of the first rib. Except in unusual situations, it is preferable not to clear skin (or "flash") in the supraclavicular region.

Lateral: Usually two thirds of the medial-to-lateral distance through the humeral head. In some patients with extensive axillary disease, it may be necessary to clear skin laterally.

Medial: Set up to the center of the suprasternal notch (midline), then angle the gantry.

Blocks: The inferior border is defined by a block through the central axis. In most patients the lateral third of the humeral head should be blocked; in some patients with extensive axillary disease, this may not be possible.

SUPRACLAVICULAR FIELD

Same borders as the full axillary and supraclavicular field, except the lateral field border is at the coracoid process.

EN FACE AXILLARY BOOST (EAB)

The couch, gantry, and collimator are angled to direct the beam from the axilla toward the supraclavicular nodes by aiming toward the suprasternal notch. The isocenter is placed at a point 3 cm to 4 cm lateral to the head of the clavicle, in the supraclavicular fossa. The field size will vary with the patient's body size, but will usually be on the order of 6 cm × 8 cm. The anterior border is set to run posteriorly to the anterior edge of the pectoralis major muscle, as determined visually and by palpation. The other borders are determined by the desired volume of treatment.

POSTERIOR AXILLARY BOOST (PAB)

Inferior: Block the field to match the superior border of the tangential fields.

Superior: Parallel the clavicle.

Medial: 2 cm into the lung tissue medial to the chest wall.

Lateral: At the middle of the humeral head.

EN FACE INTERNAL MAMMARY FIELD

Use computed tomography simulation to plan depth and width. Blocking is needed to avoid overlap with the tangential fields used to treat the breast and lateral chest wall.

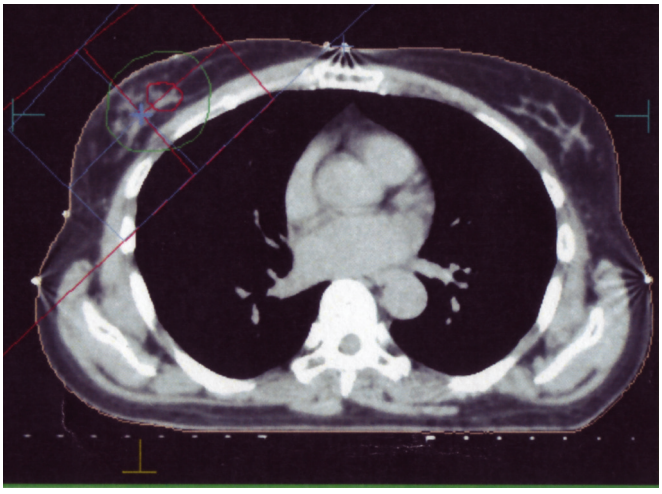
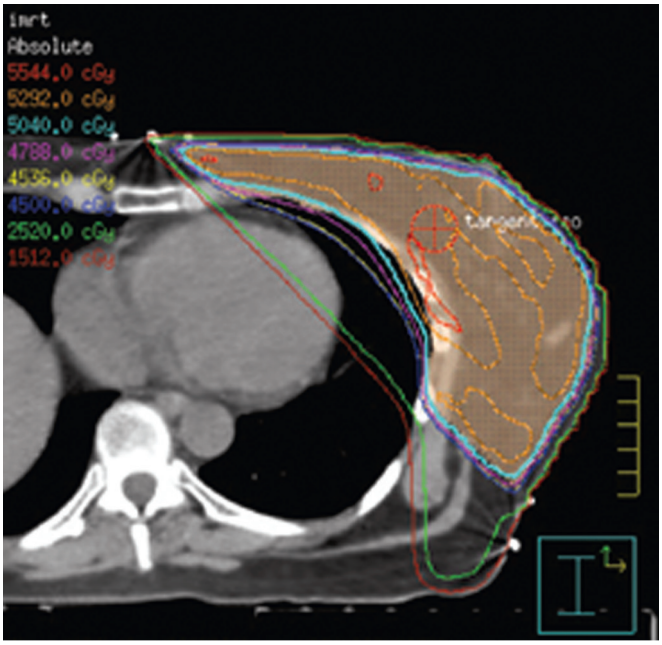


Figure 63-2 Transverse view of tangential fields without nodal irradiation. Gantry rotation is used to make the posterior field edges coplanar. (Excision cavity outlined in red, with green circle representing a 2-cm circumferential expansion.)

the field edge or block may be prudent.[359] However, patients cannot always comply with breath-holding, it does not always provide much heart sparing, or blocking cannot be used because of the location of the primary. Using additional gantry angles or helical tomotherapy may reduce heart dose (eFigure 63-5) but at the price of decreased coverage of the breast volume[360] or increased exposure of other normal tissues.[328,332,333,361,362]

Breast Boost Volume and Techniques

The optimal boost volume is unknown. In most institutions, the breast boost clinical target volume is defined by adding a 1-cm to 2-cm circumferential margins around the tumor bed, with the anterior boundary extending just below the skin and the posterior boundary at the anterior chest wall or pectoralis major muscle. The volume of the excision cavity decreases particularly within the first 1 month to 2 months after surgery and often further during RT.[363-370] There are no data whether local control or cosmetic results are changed if the boost is planned soon after surgery or just before the boost is to be given. Surgical clips help delineate the excision site compared to CT images



eFigure 63-5 Transverse dose distribution for a multiple-gantry angle intensity-modulated radiation therapy (IMRT) plan, used to reduce the heat dose. The prescribed dose was 5040 cGy in 28 fractions. Note how the 50% isodose line (2520 cGy) extends posteriorly, reflecting the use of a posterior field including the lateral portion of the breast.

alone,[371] but the volume defined by CT is generally larger than that defined solely by surgical clips.[372-374] It can be difficult to delineate the extent of the cavity on CT,[375-378] and there is no agreement on exactly what features should be included in the target volume. Variation between radiation oncologists in defining the lumpectomy site can be reduced by establishing common guidelines and training.[379,380] Nonetheless, small differences in the size or placement of the boost volume seem unlikely to have a major impact on the risk of recurrence.[381,382]

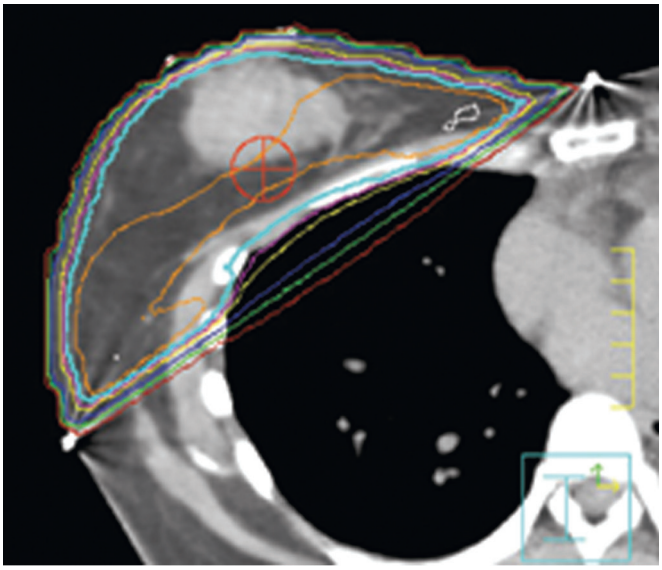


Figure 63-3 Dose distribution of tangential fields created using lung inhomogeneity corrections and forward planning, with additional medial and lateral segments added to improved homogeneity. The prescribed dose was 4500 cGy. Isodose color key: red, 30%; green, 50%; dark blue, 70%; yellow, 90%; magenta, 95%; light blue, 100%; orange, 105%; white, 109%.

Local control rates are similar with interstitial implantation, photons, or electrons, though there are conflicting data on whether their cosmetic results differ (eFigures 63-6 to 63-8).[383-388] Intraoperative photon and electron beams have also been used for this purpose.[389-392]

Supraclavicular and Axillary Nodal Irradiation

A slightly oblique anterior "third field" is generally used to treat the upper axillary and supraclavicular nodes, which are not adequately included in breast tangential fields.[393-396] Both multiple isocenter[397-401] and single isocenter[402,403] approaches have been employed to match this field to the tangents. The former use combinations of table, gantry, and collimator rotation and blocking to avoid hot spots because of field overlap or underdosing as a result of fields being too far apart (Figure 63-4). Nodal irradiation can also be given in the prone position.[404,405]

Nodal fields borders are often different at different institutions, though confusingly the same terms are used from one center to another. A *supraclavicular field* includes the level III axillary nodes, as well as the true supraclavicular nodes more medially. The inferior border is generally placed at the inferior edge of the clavicular head.[406] In most centers its lateral border is at the coracoid process or the medial border of the humeral head. A *full axillary field* (also called a *supraclavicular/axillary field*) extends the lateral border of the supraclavicular field to split the humeral head or, at some institutions, to extend laterally beyond the axillary soft tissue entirely. The superior border of these fields also varies between institutions, from the top of the first rib radiographically, to the top of the shoulder, to the superior border of the thyroid cartilage. The subclavian and axillary vessels are used as surrogates for the position of the axillary nodes in CT simulation, and the sternocleidomastoid, pectoralis minor and major, and anterior scalene muscles and the clavicle used to define the infraclavicular and supraclavicular nodal regions.[407] A block is usually placed along the transverse spinous pedicles to protect the spinal cord, larynx,

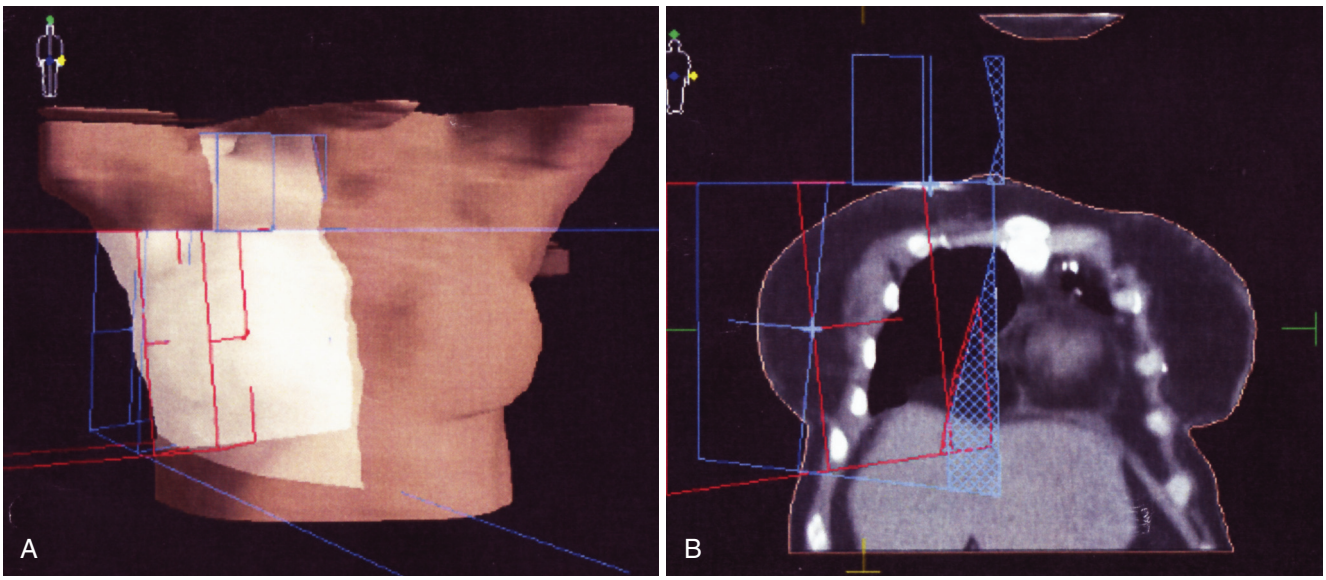
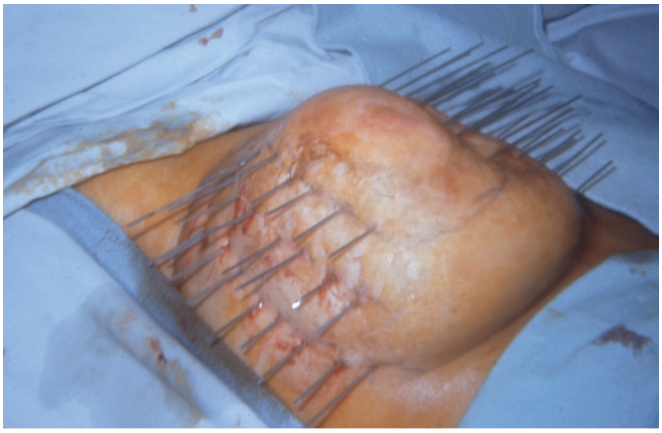
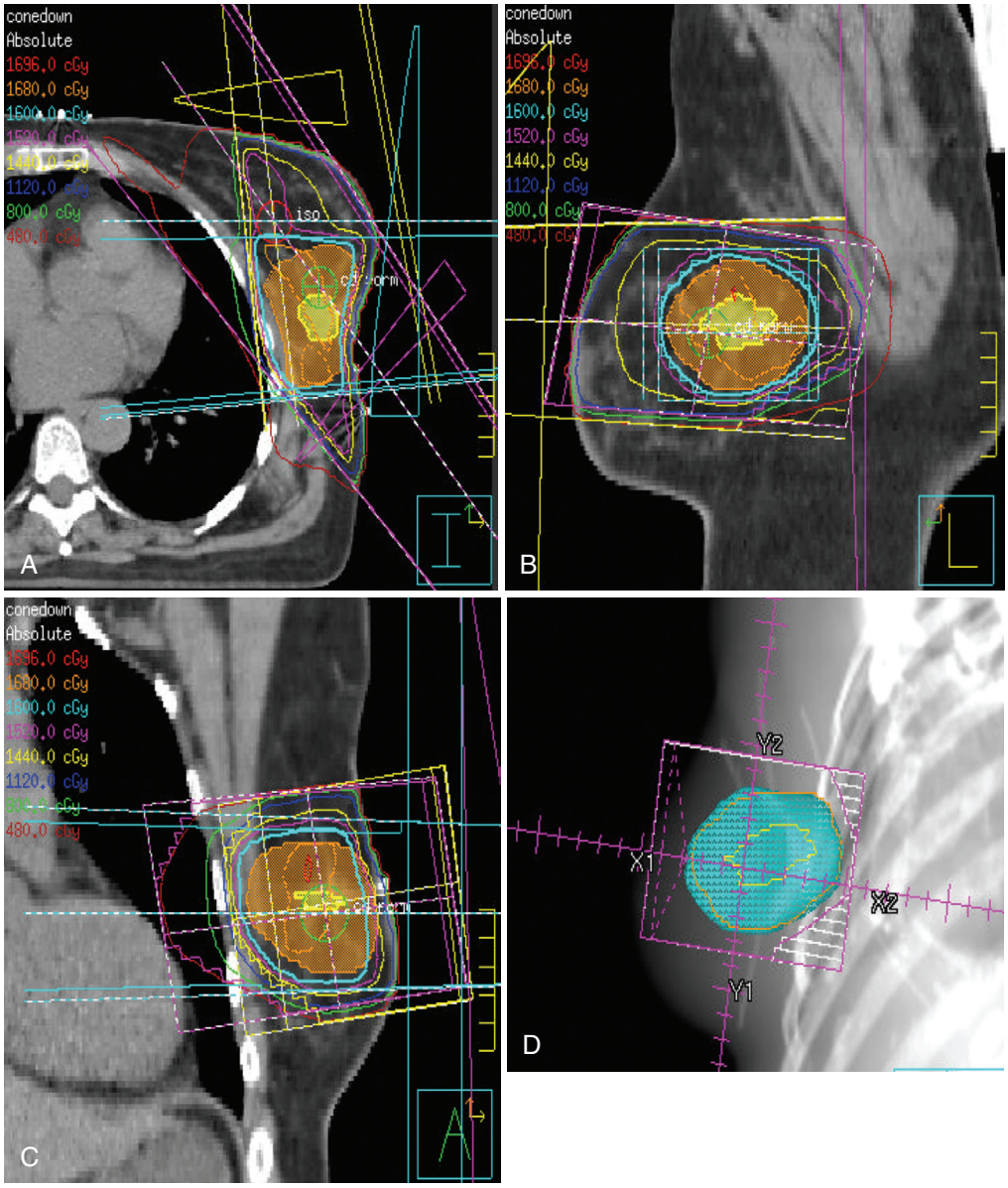


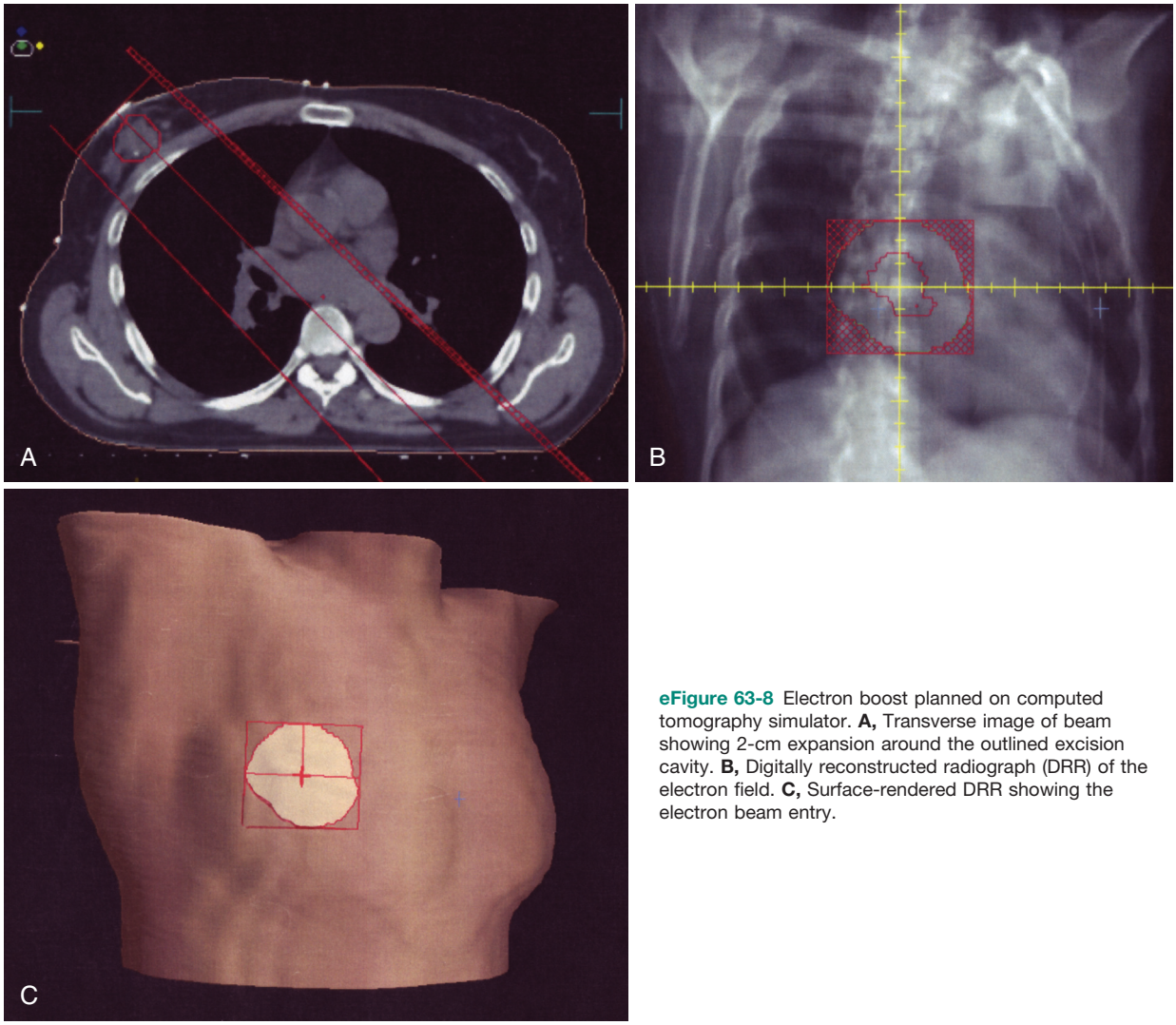
Figure 63-4 Multiple isocenter three-field match technique. **A,** Anterior surface-rendered digital reconstructed radiograph showing the match between the supraclavicular field and the tangential fields. Note the inferior divergence of the tangential fields from each other. **B,** Coronal computed tomography representation of intersections of the match between the supraclavicular field and tangential fields at the level of the isocenter of the tangents. Note the blocks on the medial *(red)* and lateral *(blue)* tangential fields, which define their posterior borders and a cervical spine block on the medial portion of the supraclavicular field.



eFigure 63-6 Placement of stainless-steel needles through the breast for interstitial implant boost. Plastic tubes are inserted through the needles, which are then removed. Metal buttons are then placed over the ends; after the radioactive material is inserted when the patient has returned to her room, these will be crimped to hold the implant securely in place. (The ends of the tubes have not yet been trimmed.)



eFigure 63-7 Three-field photon boost, using anterior, left lateral, and left posterior oblique fields. The excision cavity *(shown in yellow color wash)* was expanded by 2 cm to create the boost planning target volume *(orange color wash)*, which was edited to come no closer than 5 mm to the skin surface and no deeper than the anterior chest wall or pectoralis muscle. **A,** Transverse view. **B,** Sagittal view. **C,** Coronal view. **D,** Left posterior oblique beam's-eye view; 100% isodose surface in light blue.



eFigure 63-8 Electron boost planned on computed tomography simulator. **A,** Transverse image of beam showing 2-cm expansion around the outlined excision cavity. **B,** Digitally reconstructed radiograph (DRR) of the electron field. **C,** Surface-rendered DRR showing the electron beam entry.

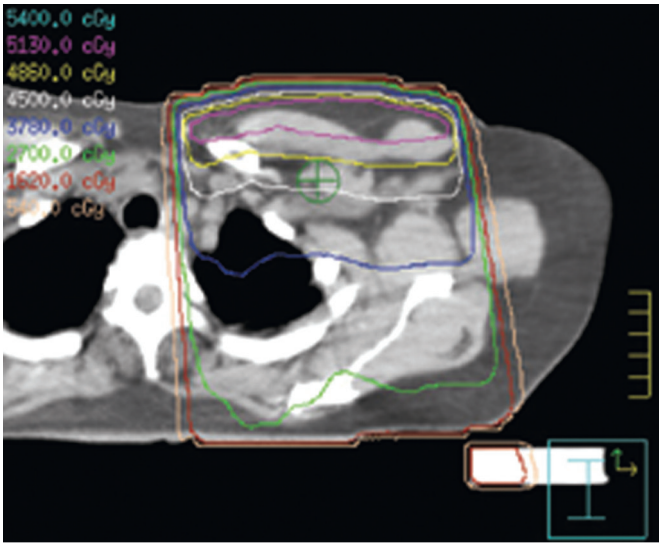


Figure 63-5 Dose distribution in a supraclavicular-axillary field, prescribed to 4500 cGy at a depth of 5 cm.

and esophagus, though some supraclavicular recurrences are close to the medial field border.[408]

Supraclavicular and full axillary field doses were traditionally prescribed to an arbitrary depth below the skin surface (3 cm and 5 cm, respectively). However, nodal depths vary substantially,[407,409-411] and CT should be used to define the prescription depth when possible (Figure 63-5). A single anterior oblique field is effective and safe for most situations. Opposed fields or three-dimensional conformal techniques may improve nodal coverage with acceptable inhomogeneity for patients with deep nodes or situations calling for doses above 45 Gy to 50 Gy.[412,413]

Internal Mammary Nodal Irradiation

The majority of IMNs lies in the first three intercostal spaces between the posterior edge of the sternum and the parietal pleura but may be as inferior as the sixth intercostal space.[414,415] The nodes themselves cannot be seen unless pathologically enlarged.[416] Their depth and location from the midline vary substantially.[411] Half to three quarters of nodes in the upper two to three intercostal spaces are located medial to the internal mammary vessels (usually visible at the sternal-pleural junction). Most (but not all) nodes in more inferior levels are lateral to the vessels.[415] However, the maximum distance of the IMNs from the vessels has not been described; hence the optimal expansions to define the clinical target volume are not known.

Anterior photon fields commonly used to treat the IMNs in the past increased the risk of late cardiac deaths.[417] Electron or mixed-beam direct internal-mammary fields reduce heart exposure,[418-420] but this approach requires substantial care to achieve an acceptable junction with the tangential fields. The "partially-wide tangent" technique includes the IMNs in the third interspace and above in tangential fields that cross the midline, with the inferior portions blocked posteriorly to reduce the irradiated volumes of lung and heart (eFigure 63-9).[421] However, such blocking may increase the risk of local failure for patients with inferiorly located tumors.[422] Coverage of the IMNs may be improved and normal-tissue doses reduced with IMRT.[412,423] Using protons may reduce cardiac and lung exposure even further,[424,425] but this modality is not widely available.

RADIOTHERAPY DOSE AND SCHEDULE PARAMETERS

Interval between Surgery and the Start of Radiation Therapy

Local failure rates do not increase when RT starts up to 4 months to 5 months after the last breast surgery in most,[426-432] but not all studies.[433] Prolonging the start of RT beyond this time increased failure rates for patients with close margins (1 mm or less) in one randomized trial of the sequencing of chemotherapy and RT.[434,435] The effect of the tumor-free margin width was not reported in other such randomized trials.[436-438]

Whole-Breast Fractionation

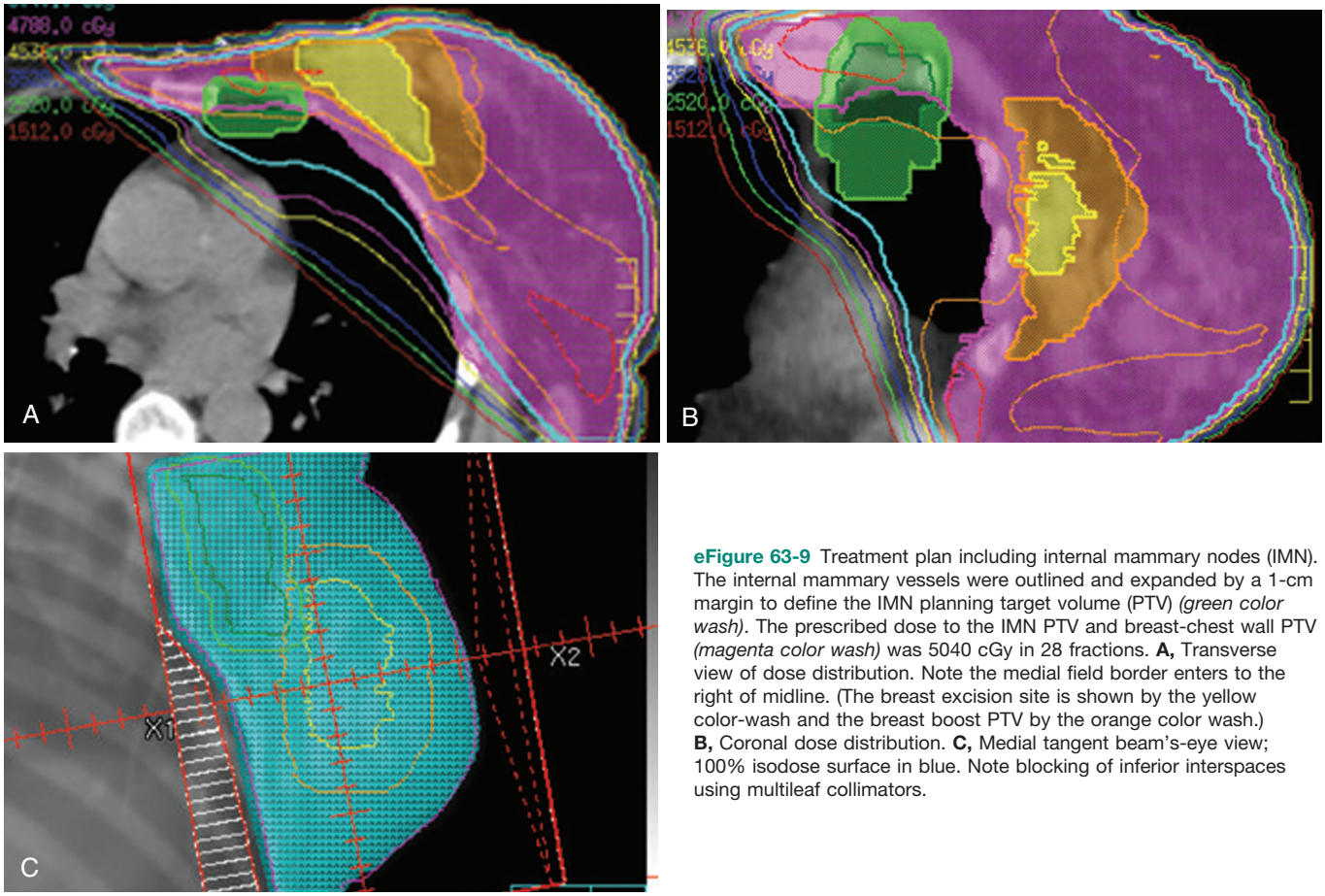
Conventions for prescribing dose to the breast or boost have varied substantially from one institution to another both in the "two-dimensional" era[439,440] and now. Hence, data on the dose-response must be interpreted with caution.

Most centers in the United States and Western Europe traditionally gave whole breast doses of 45 Gy to 50 Gy in 1.8-Gy to 2-Gy daily fractions given five times weekly.[441] Centers in the United Kingdom and Canada routinely used schemes with higher daily fraction sizes but lower total doses (for example, 40 Gy in 15 or 16 fractions over about 3 weeks). Several randomized clinical trials have compared these and other fractionation schemes.[442-450] Two are particularly important. A trial conducted from 1993 to 1996 in Canada assigned 1234 women to receive either 50 Gy in 25 fractions or 42.5 Gy in 16 fractions.[444,445,448] A boost was not given. With a median follow-up of 12 years, 10-year rates of local recurrence in the two arms were 6.7% and 6.2%, respectively. Seventy percent of patients in each arm had excellent or good global cosmetic outcome, with no difference in complication rates. The "START B" trial, conducted in the United Kingdom between 1999 and 2002, compared 50 Gy in 25 fractions to 40 Gy in 15 fractions in 2215 patients.[446,450] A boost of 10 Gy in 5 fractions was given to 43% of patients. With a median follow-up of 9.9 years, 10-year actuarial locoregional failure rates were 5.5% and 4.3% in the two arms, respectively. Cosmetic results were slightly better in the 40 Gy arm, with no difference in complication rates.[446,451] The Canadian trial found a higher local failure rate for patients with grade-3 tumors in the hypofractionated treatment arm than the prolonged arm,[448] but this was not seen in the START trials[452] or a retrospective study from British Columbia.[453] Subsequent central review of the pathology slides of patients in the Canadian trial also found grade no longer to be a factor in outcome.[453a]

Some groups have given RT once or twice weekly.[447,454-462] However, there are only limited long-term data on this approach.

Total Dose to the Primary Tumor Site and Overall Treatment Time

Four randomized trials have compared whole-breast RT alone to whole-breast RT plus a boost for patients with uninvolved margins.[463-468] Absolute differences in local control between the arms were only 2% to 3%. The largest trial, conducted by the EORTC, initially defined margin status only in relationship to the invasive component of the tumor.[466,468] A central pathology review including about one third of the entered patients (which did evaluate the margins for DCIS) found a boost benefited significantly only patients with margins wider than 2 mm, reducing the 10-year failure rate from approximately 14% to 7% when the distance to invasive disease was assessed and from about 17% to 5% when the distance to DCIS was assessed.[469] The boost also decreased local failure rates



eFigure 63-9 Treatment plan including internal mammary nodes (IMN). The internal mammary vessels were outlined and expanded by a 1-cm margin to define the IMN planning target volume (PTV) *(green color wash)*. The prescribed dose to the IMN PTV and breast-chest wall PTV *(magenta color wash)* was 5040 cGy in 28 fractions. **A,** Transverse view of dose distribution. Note the medial field border enters to the right of midline. (The breast excision site is shown by the yellow color-wash and the breast boost PTV by the orange color wash.) **B,** Coronal dose distribution. **C,** Medial tangent beam's-eye view; 100% isodose surface in blue. Note blocking of inferior interspaces using multileaf collimators.

significantly for patients with high-grade cancers or age younger than 50, but results were not described according to margin status and use of the boost simultaneously.

The EORTC trial also randomly allocated patients with positive margins to receive a boost to either 60 Gy or 76 Gy. Their 10-year local recurrence rates were 17.5% and 10.8%, respectively.[470] Thirteen percent of patients in the high-dose arm developed severe fibrosis in the boost region, compared to 3% of the control group.

A retrospective study from Istanbul, Turkey, suggested that treatment interruptions or breaks of 8 days or more significantly increased the risk of local recurrence in patients treated with whole-breast RT plus a boost.[471]

Many institutions have investigated "concurrent boost" techniques, in which IMRT is used to give a higher daily dose to the boost volume with either hypofractionated or 1.8-Gy to 2-Gy daily whole-breast doses.[472-479] Although well tolerated acutely, data on long-term efficacy and complications are limited. This approach is being evaluated by randomized trials in North America and Europe.[480,481]

Nodal Irradiation Doses

Doses of 45 Gy to 50 Gy or their hypofractionated equivalent result in a low incidence of nodal failure in patients with clinically uninvolved nodes or involved nodes following axillary dissection.[40,446,450,482,483] The dose-response relationship for control of suspiciously enlarged nodes or gross residual disease is unknown.

Conclusions

Whole-breast and nodal doses of 45 Gy to 50 Gy in 25 fractions or 40 Gy to 42 Gy in 15 to 16 fractions appear equally effective and safe for most patients, though it is not known whether some subgroups would have better results with one scheme or another. A boost dose to the excision cavity and its environs increases the local control rate modestly for patient populations as a whole. There is not consensus on which patient subgroups are most likely to benefit from a boost. When a boost is used, the total dose to the primary tumor site should be approximately 60 Gy to 65 Gy in 1.8-Gy to 2-Gy fractions or its biologic equivalent for patients with uninvolved margins. Higher doses may be appropriate for patients with involved margins, but the risk of toxicity is increased.

ACCELERATED PARTIAL-BREAST IRRADIATION

Introduction

As noted previously, occult synchronous primary cancers are rare in patients with clinically unicentric cancers. Most residual tumor cells are located within a few centimeters of the excision cavity[169] and within only 10 mm to 15 mm for those with small cancers with 1 mm to 2 mm microscopic margins.[484,485] Two thirds or more of local recurrences are at or near the site of the primary tumor, whether RT is used or not.[486] Hence, treatment of only a limited volume surrounding the tumor might be as effective as whole-breast irradiation (WBI) for many patients. This approach might reduce complications and allow treatment to be completed more quickly.[487] Techniques for "accelerated partial breast irradiation" (APBI) include: low- or high-dose rate interstitial implantation[488] (eFigure 63-10); high-dose rate brachytherapy using a balloon catheter with one or more source channels[489,490] (eFigure 63-11); permanent interstitial implantation of radioactive seeds[491] (eFigure 63-12); single-fraction intraoperative irradiation using 50 kV photons[492] (eFigure 63-13), high-energy electrons[493] (eFigure 63-14), or brachytherapy[494]; and three-dimensional conformal external-beam irradiation using photons,[495-497] mixed photons and electrons[498] (eFigure 63-15), or protons.[499,500]

Randomized Trials Comparing Whole-Breast and Accelerated Partial-Breast Irradiation

eTable 63-5 lists randomized trials comparing APBI to WBI.[501-511] Two trials did not assess microscopic margin status and used obsolete treatment techniques.[502,503] Efficacy results from three of the more recent trials have been published.

The National Institute of Oncology in Budapest, Hungary, conducted a trial from 1998 to 2004 that included 258 patients, all except one with microscopic margins 2 mm or wider.[504,505] Patients in the WBI arm received 50 Gy in 25 fractions without a boost, whereas patients in the APBI arm received either high-dose rate implantation (36.4 Gy in 7 fractions over 1.5 weeks) or (if technically unsuited for an implant) electrons (50 Gy in 25 fractions over 5 weeks). With a median follow-up of 10.2 years, the 10-year actuarial local failure rates in the two arms were 5% and 6%, respectively, with excellent or good cosmetic results in 63% and 81%, respectively.[505]

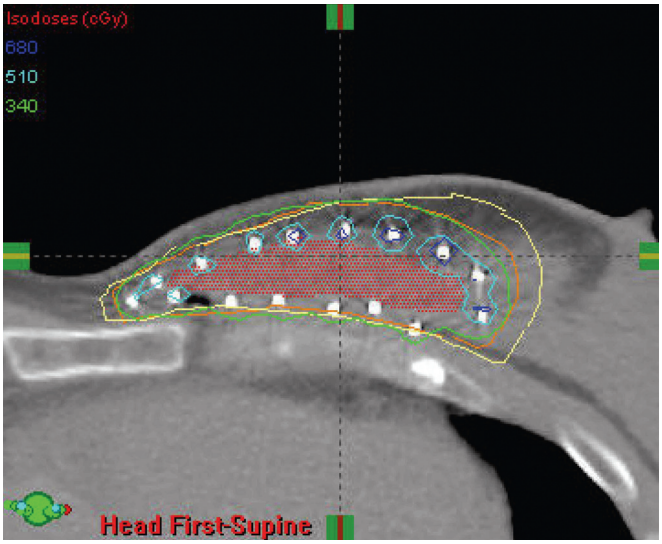
The international TARGIT-A trial randomly allocated 3451 patients from 2000 to 2012 to receive either WBI or a single dose of intraoperative radiotherapy (IORT) using an orthovoltage device delivering a dose of about 20 Gy immediately at the surface of the applicator and about 5 Gy at 1 cm.[507,508] Their 5-year local failure rates were 1.3% and 3.3%, respectively, with a median follow-up of 29 months. However, 14% of patients in the IORT arm received whole-breast irradiation because of histologic features following surgery or other reasons. Failure rates in the IORT arm were lower in patients having surgery simultaneously with IORT (2.1% at 5 years) than those having surgery, then IORT at a later date (5.4%).

The ELIOT trial, performed at the European Institute of Oncology in Milan, Italy, from 2000 to 2007, randomly allocated 1305 patients to receive WBI plus a boost or IORT using megavoltage electrons to give 21 Gy to the tumor bed. Their 5-year breast recurrence rates were 0.4% and 4.4%, respectively, with median follow-up of 5.8 years.[506] Patients with tumors larger than 2 cm, four or more positive nodes, ER-negative tumors, and triple-negative tumors had local failure rates of more than 10% after IORT.

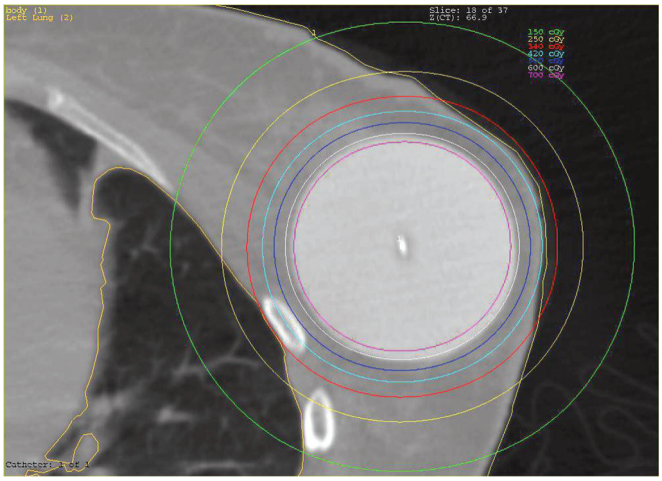
None of these trials showed differences between the arms in OS or breast cancer-specific mortality. However, cosmetic results were worse with external-beam APBI than for WBI in the Canadian RAPID trial[512] but better in the IORT arm of the TARGIT-A trials.[508] Most toxicities were lower in the IORT arm of the ELIOT trial than in the conventional arm, but the rate of fat necrosis was higher.[506]

Results of Nonrandomized Studies and Correlates of Local Recurrence

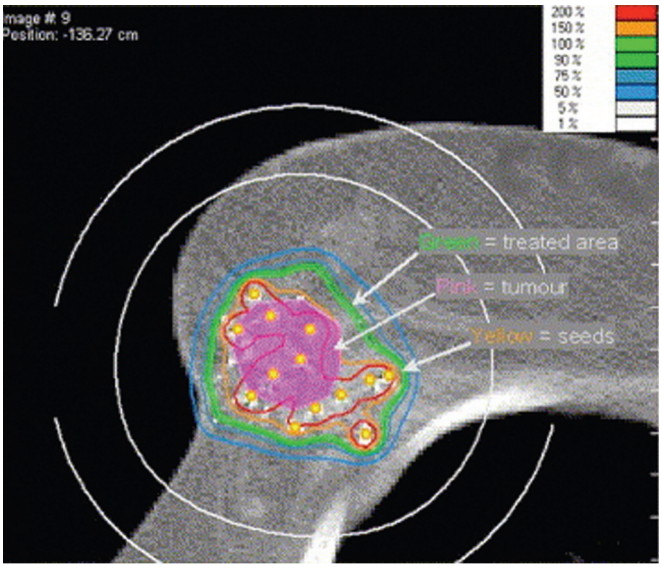
Local failure rates in most nonrandomized studies of APBI with median follow-up of 5 years or more were comparable to those achieved with WBI (eTable 63-6).[513-529] Several early series had much higher failure rates,[513,514,517] likely as of the result of different patient selection criteria and treatment technique. Several studies had higher local failure rates for women younger than age 50 than for older patients.[524,530,531] Patients with infiltrating ductal carcinomas and infiltrating lobular tumors had the same recurrence rates in the German-Austrian trial.[524] Several[528,529] but not all studies[532] found having a triple-negative or an ER-negative tumor was a significant risk factor. A tumor-free margin width of less than 2 mm appears



eFigure 63-10 Transverse computed tomography image of a volume interstitial implant for partial-breast irradiation, with target volume *(red color wash)* and superimposed isodose distribution.
From Vicini FA, Arthur DW: Breast brachytherapy: North American experience. Semin Radiat Oncol 15:108–115, 2005, Figure 3; with permission of the publisher.



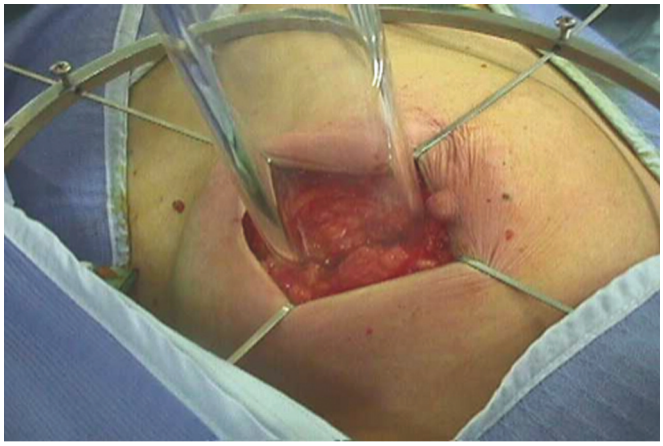
eFigure 63-11 Optimal placement of balloon brachytherapy device for partial-breast irradiation.
From Shah NM, Wazer DE: The MammoSite balloon brachytherapy catheter for accelerated partial breast irradiation. Semin Radiat Oncol 15:100–107, 2005, Figure 4; with permission of the publisher.



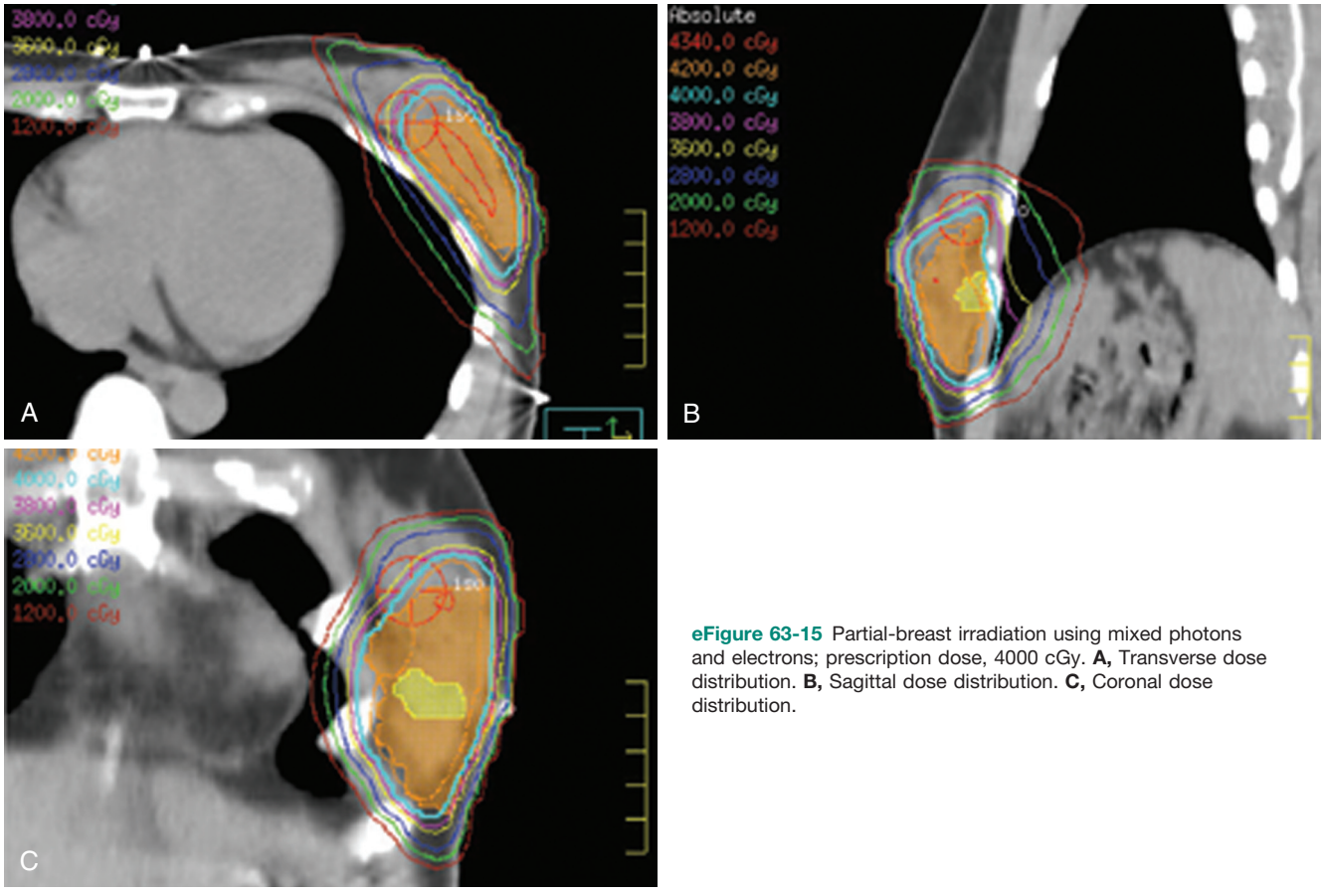
eFigure 63-12 Permanent palladium-103 seed implant for partial-breast irradiation, with superimposed dose distribution.
From Pignol JP, Keller B, Rakovitch E, et al: First report of a permanent breast 103Pd seed implant as adjuvant radiation treatment for early-stage breast cancer. Int J Radiat Oncol Biol Phys 64:176–181, 2006, Figure 3; with permission of the publisher.



eFigure 63-13 Intraoperative partial-breast irradiation using the 50-kV Intrabeam system, with the x-ray source in the breast wound *(inset)*.
From Vaidya JS, Tobias JS, Baum M, et al: TARGeted Intraoperative radiotherapy (TARGIT): An innovative approach to partial-breast irradiation. Semin Radiat Oncol 15:84–91, 2005, Figure 2; with permission of the publisher.



eFigure 63-14 Intraoperative electron applicator in position for single-dose partial-breast irradiation.
From Orecchia R, Veronesi U: Intraoperative electrons. Semin Radiat Oncol 15:76–83, 2005, Figure 2; with permission of the publisher.



eFigure 63-15 Partial-breast irradiation using mixed photons and electrons; prescription dose, 4000 cGy. **A,** Transverse dose distribution. **B,** Sagittal dose distribution. **C,** Coronal dose distribution.

eTABLE 63-5 Randomized Trials of Whole-Breast versus Partial-Breast Irradiation

Trial	Dates of Accrual	Patients/Accrual Goal	PBI Modality
Christie Hospital[501,502]	1982-1987	708	EB electrons
Yorkshire, England[503]	1986-1990	174	EB electrons/photons
Budapest[504,505]	1998-2004	255	Implant or electrons
ELIOT (European Institute of Oncology, Milan)[506]	2000-2007	1305	Intraoperative electrons
TARGIT-A[507,508]	2000-2012	3451	50 kV Intraoperative photons
GEC-ESTRO[509]	2004-2009	1233	Interstitial implant
NSABP B-39/RTOG 0413[488]	2004-2013	4500	Interstitial implant, intracavitary brachytherapy, EB photons
Florence, Italy[510]	2005-2013	520	EB photons
RAPID (Ontario-British Columbia)[512]	2006-2011	2135	EB photons
IMPORT LOW (United Kingdom)	2006-2010	2018	EB photons

EB, *External-beam therapy;* ESTRO, *European Society for Therapeutic Radiology and Oncology;* GEC, *Groupe Européen de Curiethérapie;* kV, *kilovolts;* NSABP, *National Surgical Adjuvant Breast and Bowel Project;* PBI, *partial breast irradiation;* RTOG, *Radiation Therapy Oncology Group.*

eTABLE 63-6 Results of Selected Nonrandomized Studies of Accelerated Partial-Breast Irradiation with Median Follow-up of 5 Years or Longer

Institution	Accrual Dates	Patients	Median Follow-up (months)	Local Failure Rate (%)
Guy's Hospital (IB, iridium-192)[513]	1987-1988	27	72	37
Guy's Hospital (IB, cesium-137)[514]	1990-1992	50	76	18
Ochsner Clinic (IB)[515,516]	1991-2001	163	65	3
London Regional Cancer Center (IB)[517]	1992-1996	39	91	15 (5-yr: 16)
William Beaumont Hospital (IB)[518]	1992-2001	199	146	5 (12-yr: 5)
Örebro, Sweden (IB)[519]	1993-2003	50	86	6 (7-yr: 4)
Budapest (IB)[520]	1996-1998	45	81	7
Massachusetts General Hospital (IB)[521]	1997-2001	48	134	12 (12-yr: 15)
RTOG 95-17[522]	1997-2000	99	84	6 (5-yr: 3)
Tufts-Brown Universities (IB)[523]	1997-2001	33	84	9 (5-yr: 6)
Budapest Trial (IB, EB)[504]	1998-2004	128	66	5
German-Austrian Trial (IB)[524,525]	2000-2005	274	64	3 (5-yr: 2)
New York University (EB)[526]	2000-2005	98	64	1 (5-yr: 1)
University of Wisconsin (IB, BB)[527]	2001-2006	322	60	2 (5-yr: 5)
MammoSite Registry (BB)Study[528]	2002-2004	1449	63	3 (5-yr: 4)
Dana-Farber/Harvard Cancer Center (EB)[529]	2003-2005	98	71	5 (5-yr: 5)

BB, *Balloon brachytherapy;* EB, *external beam;* IB, *interstitial brachytherapy;* IORT, *intraoperative radiotherapy;* RTOG, *Radiation Therapy Oncology Group;* yr, *year. Crude local failure rates given; actuarial rates within parentheses.*

associated with a high risk of local failure.[528,533-535] The Radiation Therapy Oncology Group (RTOG) 96-17 trial found a local failure rate of 14% (4 of 29) among patients not receiving systemic therapy, compared to 3% (2 of 70) among those who did.[522]

It is likely that combinations of features will predict more for local failure than any single factor. However, one scheme created by a consensus panel[536] has not generally been found to predict strongly for relapse.[527,531,537,538]

Conclusions

The optimal pretreatment evaluation, selection criteria, technical parameters, and choice between different modalities for APBI are not known. At present, I limit such treatment to patients age 50 or older with 2-cm or smaller grade-1 to grade-2 ER-positive invasive cancers or DCIS with microscopic margins 2 mm or wider, with negative axillary nodes if invasive.

ACUTE AND CHRONIC COMPLICATIONS AND COSMETIC RESULTS

Acute Reactions and Their Management

Two randomized trials found washing with soap and water reduced the severity of skin reactions, compared to not washing or using water alone.[539,540] Several trials showed no differences in reactions between patients using different skin care products compared to each other or when no products were applied.[541-545] One double-blinded trial suggested a cream containing hyaluronic acid was more effective in preventing severe skin reactions than one containing only the base.[546] Several trials found that applying a potent steroid cream from the beginning of treatment decreased the intensity of acute skin reactions.[547-549] However, there were no data whether this increased the risk of folliculitis or caused long-term skin changes. A randomized trial showed no difference in skin reactions whether aluminum-based antiperspirants were used during treatment or not.[550]

Moisturizers can substantially reduce itching and irritation once they occur. Applying these before RT does not appreciably increase the skin dose[551]; hence, patients may use such products whenever and as often as needed. Folliculitis can be treated successfully with chlorhexidine gluconate or other antibacterial soaps.

About 10% to 15% of patients develop moist desquamation (usually in the axilla or inframammary fold) during or shortly after completion of RT[434]; the rate may be 50% or higher for patients receiving concurrent chemoradiotherapy.[552] Such reactions are more common in large-breasted women, even with three-dimensional compensation.[69,553] Patients with only limited areas of moist desquamation can often continue RT without interruption; if necessary, treatment can often temporarily switch from tangential fields to the boost field. Reepithelialization need not be complete for RT to resume; hence, treatment breaks of more than 1 week are rarely necessary. Antibacterial soaps, moisturizers, and nonadherent dressings are helpful in reducing symptoms. In a randomized trial performed in Scotland, patients with moist desquamation took longer to heal when a hydrogel dressing was used than when a dry dressing was applied.[544]

Mild fatigue is common during RT. A prospective study in Munich, Germany, did not find any factors correlated with its development or severity.[554] A study in Newcastle, Australia, found that a higher baseline fatigue level and higher baseline neutrophil and red cell counts were predisposing factors.[555] Although fatigue usually resolves within 2 months following completion of RT, a prospective study in Caen, France, found some patients still reported fatigue 1 year later, which correlated with being depressed at initial evaluation.[556]

Myelosuppression of clinical significance is extremely unusual, and hence blood counts do not need to be routinely checked.

Postoperative cellulitis or abscess should be dealt with before RT is started if possible. If RT has started, antibiotics or surgical consultation should be initiated promptly, but it is probably not necessary to interrupt RT unless abscess drainage is required.

Subacute and Chronic Complications

Skin, Soft Tissue, and Bone

Skin thickening is common after BCT.[557] Hyperpigmentation may persist in some patients, particularly darker-skinned ones. Patients may develop telangiectasias years later. Rarely, patients develop postirradiation morphea or circumscribed scleroderma weeks to years following RT,[558-560] with patches of white or yellowish well-circumscribed sclerosis and induration (sometimes surrounded by a more highly pigmented, bruise-like area or preceded by erythema). Patients may develop a skin "radiation recall" reaction when chemotherapy (particularly doxorubicin) is given following RT (Figure 63-6). However, this is rare when chemotherapy begins more than 2 weeks after the completion of RT.[552]

Breast abscesses or cellulitis develop in 5% to 10% of patients at any time after surgery.[561,562] Cellulitis may be more frequent in patients with hematomas or seromas requiring drainage, large volumes of resected breast tissue, or breast edema.[563,564] Sometimes cellulitis or abscesses mimics an inflammatory-type recurrence,[561,565] although the presence of pain, possible systemic symptoms of infection, and the time-course of development usually make the distinction clear. Removing large volumes of breast tissue following RT is associated with a high risk of complications.[566]

Breast fibrosis can evolve over 5 years or more after treatment.[388,448,450] It is generally mild, but when severe can impair the cosmetic results. Some patients with severe fibrosis respond to treatment with pentoxifylline alone or in combination with vitamin E.[567,568] Other therapies, such as hyperbaric oxygen, have been inadequately tested.[569]

Soft-tissue necrosis is quite rare, even with outmoded RT techniques.[570] Some individuals develop fat necrosis, which typically causes a painful or painless mass, sometimes accompanied by thickening or retraction or dimpling of the overlying skin.[571,572] Mammography usually reveals a spiculated,



Figure 63-6 Moist desquamation in electron boost field after completion of radiotherapy. Such reactions are uncomfortable but rarely become infected.

often poorly defined mass that may contain punctate or large, irregular calcifications. Cystic degeneration may eventually result in a cavity that contains oily fluid or necrotic fat.

Milk production is substantially reduced after irradiation.[573,574] Nonetheless, a few patients have reported breastfeeding to a limited extent from the treated side.

Patients commonly have intermittent transient breast pain even decades after treatment, which can be sharp and shooting or dull and aching, usually lasting a few seconds or minutes though rarely longer. Younger patients seem more likely to experience pain than older individuals.[575,576] Patients treated with RT had more breast discomfort initially than those allocated not to receive RT in a randomized trial, but with further follow-up the degree of discomfort became equal in both groups.[577] Pain is generally mild or moderate, but for some it is sufficiently bothersome to require medication.[575]

The risk of rib fractures is related to the treatment energy and the total dose.[570] Its incidence should be less than 1% with current techniques.[578]

Arm Edema and Shoulder and Arm Function

Arm edema usually develops in the first 3 years after treatment.[579,580] About half of patients with mild edema will develop greater edema with time.[581] Symptomatic edema occurs in about 5% to 10% of patients treated with either SNB, levels I to II AxD, or RT alone; these cases are usually mild.[582] The incidence and severity of arm edema are substantially increased following a complete AxD,[42] especially when full axillary RT is also given.[583-585] However, full axillary RT does not increase the risk of arm edema for patients having limited surgery.[583-586] Arm edema rates were not increased in most retrospective studies by supraclavicular RT, even for patients having complete AxD,[587-590] though in other studies it has.[591-593] In the randomized MA.20 trial, supraclavicular RT increased the 5-year incidence of grade-2 or higher lymphedema from 4% to 7%.[302] A posterior axillary boost increases the risk of arm edema.[590,592,594-596]

Arm edema may cause psychological and functional morbidity, as well as predisposing patients to cellulitis. The risk of arm edema does not seem to be reduced by prophylactic manual lymphatic massage.[597] There is no agreement on a threshold to start treatment.[598] A meta-analysis of randomized trials suggested that manual lymphatic massage has some benefit in addition to compression bandaging.[599]

Axillary RT may cause changes in shoulder mobility or arm functioning.[600] These are rare in patients treated with doses of 50 Gy or less in 1.8-Gy to 2-Gy fractions or its equivalent.

Neurologic Injuries

The intercostal brachial nerve syndrome is characterized by fairly constant paresthesias and dull, aching, or burning pain of the upper arm, shoulder, and axilla, and occasionally of the more anterior chest wall. This syndrome may be permanent. Occasional patients respond to nerve blocks or topical measures.[601,602] Injury of the thoraco-dorsal, long thoracic, and pectoral nerves resulting in motor weakness is rare now.

Classic RT brachial plexopathy is a chronic, progressive syndrome whose onset can occur from as soon as 3 months to as long as 26 years after RT.[603] Patients usually present with sensory or motor symptoms in the ipsilateral limb. Pain can occur but is generally not prominent. A second, rarer type of radiation plexopathy appears more rapidly and usually resolves spontaneously.[604] The incidence of brachial plexopathy is 0% to 5% in patients receiving doses to the plexus of 50 Gy to 54 Gy in 1.8-Gy to 2-Gy fractions or 40 Gy to 45 Gy in fractions of 2.5 Gy to 3 Gy.[603] A pilot study combining pentoxifylline, vitamin E, and clodronate showed promise in treating patients with RT-induced lumbosacral radiculopathy.[605]

The presence of severe pain and an enhancing mass on MRI are the most helpful findings in distinguishing between radiation-induced and malignant brachial plexopathy.[606-609] Abnormal uptake of 18-fluorodeoxyglucose on positron emission tomography generally indicates malignancy.[610]

Pulmonary Effects

Radiographic infiltrates and localized interstitial fibrosis are common after RT.[611] These generally stabilize by 12 months after treatment, although some may resolve, and some may progress for 5 years or longer.[612,613] Patients' exercise tolerance or ability to engage in activities is very rarely affected.

Clinical radiation pneumonitis is characterized by nonproductive cough, fever, and nonspecific infiltrates inside the treatment fields.[611] It generally appears from 4 months to 9 months after completion of RT. Rarely, RT appears to precipitate a more generalized syndrome, bronchiolitis obliterans organizing pneumonia.[614,615] Either type of pneumonitis is rare in patients treated to the breast alone.[616-618] It occurs in fewer than 5% of patients treated with a third nodal field when the average lung distance is 3 cm or less.[618] Radiation pneumonitis has also been reported following external-beam APBI, which exposed large volumes of the ipsilateral lung to relatively low doses.[619] There are conflicting data on whether the risk of pneumonitis is increased by chemotherapy (particularly when given concurrently with RT)[552] or tamoxifen.[167,620] Prolonged courses of steroids are often needed to treat pneumonitis when symptoms are severe.

Cardiovascular Complications

RT may cause heart damage.[621-624] Acute and subacute complications, such as pericarditis, are rare.[570] The exact degree of long-term cardiac risk is uncertain. Such toxicity appears mainly as a result of coronary artery disease[625] and may have a latency period of 10 years or more. Early development of perfusion abnormalities on radionuclide imaging has not yet been shown to predict the long-term risk of clinical heart disease.[626] Meta-analyses and registry-based studies, which included patients treated mainly with outmoded techniques of RT or large daily fraction sizes, found increased mortality rates.[417,627-629] One such study suggested the risk was related to the estimated mean heart dose.[630] Other registry studies did not find such an effect or found substantial effects only for patients irradiated before about 1980 to 1985.[631-633] Several single-institution studies using modern RT techniques did not show increased cardiac morbidity or mortality at median follow-up times of 10 years to 20 years after RT,[634-638] although others have.[639,640]

Risk factors for cardiac complications of RT are not well understood. Preexisting ischemic heart disease was a risk factor in a study from Sweden and Denmark.[629] A study from the University of Pennsylvania found a statistically significant interaction between hypertension and left-breast irradiation in the development of coronary artery disease.[639] However, a study from Amsterdam and Rotterdam found that smoking was the only significant factor.[641] Of note, excess cardiac events in this study occurred in patients treated with postmastectomy RT (which generally included the IMNs) but not patients treated with BCT (which included only the breast). The volume of heart irradiated in the tangential fields was not a risk factor in another study from the Netherlands, with median follow-up 16 years.[640] Cardiac risk is similar between regimens using fraction sizes of 1.8 Gy to 2 Gy and those using fractions of 2.5 Gy to 3 Gy[642] but may be increased with fractions larger than 3 Gy.[643]

Anthracycline cardiac toxicity after commonly used drug doses is not increased by RT.[578,644-647] There is no evidence yet for a deleterious cardiac interaction between breast RT and

trastuzumab, but follow-up of these patients is still short.[648,649] It is uncertain whether irradiating the IMNs will increase this risk.[650,651]

Giving prophylactic RT to the supraclavicular nodes does not appear to increase the risk of stroke.[642,652-654]

Carcinogenesis

Patients age 40 years to 45 years or younger at initial diagnosis have a small increased risk of developing new contralateral primary cancers as a result of RT.[655-657] The relative risk was 1.21 at a dose of 1 Gy in a study using the Connecticut Tumor Registry.[655] Modern techniques result in contralateral breast doses of 0.5 Gy or less when physical wedges are not used.[658]

Most cancers developing within the RT fields are soft-tissue sarcomas or angiosarcomas. These may appear as soon as 1 year to 2 years after treatment but tend to occur after 8 years to 10 years or longer.[659-661] The excess incidence of soft-tissue sarcomas is 9 cases to 14 cases per 100,000 patient-years observation.[662-665] The excess incidence of angiosarcomas in patients treated with BCT is 5 cases to 13 cases per 10,000 treated patients.[659,665-667] Treatment outcomes are poor.[665,668-671]

Lung cancers following RT given for breast cancer are almost entirely limited to current or former smokers.[672-674] Postmastectomy RT was associated with an estimated excess of 7 to 8 cases per 10,000 women who survived more than 10 years from diagnosis in one study,[675] but studies following BCT found no increased risk,[676,677] perhaps because of the smaller irradiated lung volume. Esophageal cancer rates increased after RT in some studies,[678,679] which likely reflect direct exposure from en face supraclavicular and IMN fields.[680]

Radiation-induced leukemia is rare in patients not receiving chemotherapy.[578] Leukemia risk may be increased by 0.3% to 0.5% by RT in patients who receive standard-dose chemotherapy.[681,682]

Lymphangiosarcoma of the arm (or Stewart-Treves syndrome) is an extremely rare complication in patients developing arm edema.[683]

Cosmetic Results

Cosmetic results may evolve for more than 5 years from treatment.[388,448,450] Outcomes have improved over time as a result of changes in surgical and RT techniques (Figure 63-7). The great majority of patients treated now have acceptable results. There is no "standard" for describing cosmesis. Schemes for objectively measuring changes in breast size, shape, fibrosis, or contour have been devised,[388,684-686] but these are not widely used. They also may not capture skin changes and other significant sequelae. Patients tend to have more favorable views of cosmetic outcome than do physicians.[687,688]

Surgery is the most important factor affecting cosmetic outcome.[383,387] Radiation-induced fibrosis can lead to breast retraction and increased tissue firmness. Greater breast size has been associated with increased retraction after BCT (eFigure 63-16).[70,689-691] This problem can be at least partially overcome by the use of higher photon energies[71] and the prone or lateral decubitus position, or sometimes having breast reduction surgery at the time of tumor excision.[39] Doses to the entire breast much above 50 Gy in 2-Gy fractions seem to worsen results,[692] as do large fraction sizes when doses above 45 Gy are given.[693] Giving a breast boost worsens cosmetic results modestly because of fibrosis and skin changes such as telangiectasias.[388,468] The use of a hockey-stick field or other techniques resulting in imperfectly matched field edges can cause substantial fibrosis and skin changes at areas of overlap (eFigure 63-16).



Figure 63-7 This patient was treated for right breast cancer in 1974 and left breast cancer in 1991; the photograph was taken 2 years after the last treatment. The right side was treated using a 4-MV linear accelerator to a dose of 46.8 Gy to the breast and regional nodes, followed by an electron boost. The left side was treated on a 6-MV accelerator, giving 45 Gy to the breast only followed by an electron boost. On the right, she has substantial fibrosis and retraction of the breast superiorly, a hyperpigmented and fibrotic ridge superiorly as a result of match-line overlap between the tangential and supraclavicular/axillary fields, and substantial telangiectasias in the electron-boost field. In contrast, the cosmetic result on the left is good, with an easily visible surgical scar in the upper outer quadrant but few other changes. In later follow-up (February 1997), telangiectasias began to appear in the left-sided electron boost field also *(not shown)*.

Cosmetic results are similar whether chemotherapy is given before or after RT.[434] Cosmetic results tend to be inferior in patients receiving concurrent chemotherapy and RT compared to sequential regimens, although not all studies agree on this point.[552] Overall cosmetic results appear little affected by endocrine therapy or its sequencing with RT.[167,694-696]

Patients with poor cosmetic results can sometimes benefit from surgical correction.[38] However, such surgery can cause complications.

PATIENT FOLLOW-UP

Follow-up Visits and Testing

The major goal of surveillance following BCT is to detect ipsilateral local or regional recurrences and new ipsilateral or contralateral primary tumors sufficiently early to prevent the development of distant metastases. Imaging studies of other organs and serum tumor markers should not be routinely performed in asymptomatic patients.[697]

Patients commonly have an interval history and physical examination every 3 months to 4 months for the first several years after treatment and then every 6 months to 12 months indefinitely. However, there are no data showing this schedule to be superior to others. Randomized trials in Britain and Canada in patients with low risks of ipsilateral and contralateral breast cancer development found that follow-up by primary care physicians or telephone follow-up by nurses resulted in equal overall outcome as in-person follow-up by specialists.[698-700]

The optimal frequency of mammograms after BCT is not known. It is rare to find recurrence within the first year after treatment.[701] Some physicians recommend unilateral mammograms every 6 months for as long as 5 years after treatment.[702] However, there are no randomized trials on this issue, and most retrospective studies have not found a benefit to this approach.[703,704] A study at the Netherlands Cancer Institute in



eFigure 63-16 Example of a poor cosmetic result in a patient with large breasts as a result of excessive fibrosis and retraction. Note also the hyperpigmented and fibrotic ridges seen at the medial and superior borders of the left breast because of overlap between a hockey-stick field and breast tangential fields.

Amsterdam found no difference in rates of finding impalpable contralateral breast cancers or tumor stage whether mammograms were performed annually or every 2 years.[705]

MRI is more sensitive than other imaging modalities.[706-708] However, the low risk of recurrences or contralateral new primaries and high salvage rates imply that indiscriminate use of follow-up MRI will have little, if any, impact on OS.[709-711] Its use might be more beneficial for women age 40 years or younger at initial diagnosis.[712,713]

Presentation of Local Recurrence

Most local failures in the first 5 years to 10 years after initial therapy are in or near the tumor bed. A larger proportion occurs in other quadrants with longer follow-up.[193,714-719] This pattern suggests that "relapses" can be the result of either regrowth of tumor cells left following initial therapy or to new, unrelated primary tumors developing later. Location alone is not sufficient to distinguish between these two possibilities, as shown by molecular profiles.[720,721]

Roughly one third to one half of local recurrences in older studies were detected solely by mammography, with the rest divided nearly equally between those found on physical examination without radiologic signs and those detected both by both.[722] In more recent studies a higher proportion of recurrences were detected only with mammography.[723,724] The physical and radiologic characteristics of the recurrence differ from those of the original presentation in a substantial proportion of patients.[725] Hence, patients presenting with radiologically occult primaries should be followed with mammography as well as physical examination, and vice-versa.

Physical examination following treatment usually shows only mild thickening without a mass effect. However, either surgery or RT may cause masslike fibrosis that may occasionally be difficult to distinguish from a local recurrence. Changes that occur more than 1 year to 2 years following the completion of RT can be the result of benign causes (e.g., fat necrosis) but must generally be viewed suspiciously. Recurrences may be especially difficult to detect for patients with infiltrating lobular carcinomas, which often produce only minimal thickening or retraction at the biopsy site without a mass. In rare patients, the only sign of recurrence may be diffuse breast retraction. Recurrence in the nipple alone, presenting as Paget's disease, seem rare.

Mammographic changes may take 2 years to 3 years to reach their final state.[726] There is substantial overlap in appearance between benign and malignant lesions.[727] Microcalcifications that develop in a quadrant different from the initial tumor have a high likelihood of being malignant.[728] Recurrences of infiltrating lobular carcinomas are particularly likely to be radiographically occult.

Differential Diagnosis and Further Evaluation

The most common benign cause of suspected recurrence is probably fat necrosis. Biopsy is often required to confirm the clinical impression. Sarcomas are fortunately rare in this patient population but must be kept in mind.

Ultrasound may sometimes be helpful in distinguishing benign and malignant lesions. Significant early contrast enhancement with gadolinium is seen on MRI in nearly all patients with recurrent cancer but can also occur with fat necrosis and fibrosis.[729,730] However, in general negative imaging studies should not prevent early fine-needle aspiration cytology or core biopsy of ambiguous or clinically worrisome lesions.

It is sometimes difficult to distinguish between radiation-induced cellular atypia and malignancy, even on open biopsies.[731] In turn, a negative minimally invasive biopsy should not stop further pursuit of a suspicious lesion.[732]

TREATMENT OF LOCOREGIONAL FAILURE

Five percent to 10% of patients with a recurrence in the treated breast present with concurrent distant metastases.[733,734] Positron emission tomography with FDG may find more sites than CT and bone scan.[735] A similar proportion of patients will have either locally extensive recurrences or concomitant inoperable regional nodal recurrences that preclude surgery. It is rare that axillary exploration finds nodal tissue in patients who have had prior dissection,[736] and hence redissection or SNB does not seem warranted in the absence of suspicious adenopathy. Repeat SNB is feasible for those who have only had SNB before.[737] Aberrant lymphatic drainage is common in patients who had prior AxD or SNB.[737-739]

Five-year relapse-free survival rates after salvage mastectomy for patients with an isolated operable breast relapse are 60% to 80%, with OS and cause-specific survival rates of 80% to 85%.[733] Ten-year rates are about 20% lower. Postoperative complications are rare. Chest-wall recurrence occurs in 10% or fewer patients following salvage mastectomy; most such patients will develop progressive local disease despite further treatment. The ultimate risk of distant relapse following local failure appears similar after either initial treatment with CS alone or CS and RT.[740]

Several factors correlate with outcome after salvage mastectomy. Subsequent failures are rare in patients with noninvasive recurrences but occur in 30% to 50% of patients with invasive cancers.[741-744] Patients with smaller invasive recurrence have better outcome than patients with larger tumors or diffuse recurrences.[745] Lymphovascular invasion, high tumor proliferation rate, and triple-negative receptor phenotype at the time of recurrence are also associated with a worse outcome.[746-748] Patients with multiple adverse factors do worse than those with none or one.[748] Patients who recur in the skin alone or with an inflammatory-type picture have a poor prognosis.[745,749,750] The longer the time to failure after initial therapy, the better the prognosis, although this has not been true for all series.[745] Patients with likely new primaries rather than a true recurrence may also do better.[751]

Numerous studies have used further CS with or without additional RT in patients with a local failure after initial CS and RT.[752,753] Overall outcome has generally been comparable or superior to that for patients treated with mastectomy, but this approach has usually been used predominantly for smaller, more favorable tumors.[754] Second local failure rates have been 20% to 30% in most studies,[755,756] though some have lower rates.[757] Many groups have given localized RT following excision with variable results, although the risk of serious complications appears low.[472,758-766] A European trial found a 5-year second local failure rate of 6% in 217 patients treated with lumpectomy and brachytherapy, with median follow-up of 3.9 years.[766] High histologic grade was the only significant risk factor on their multivariate analysis, though age 55 years or younger and negative hormone receptors were also significant on univariate analysis. A study at the European Institute of Oncology of 161 patients found the 5-year second local failure rate was still 15% for their "favorable" group (patients with a tumor 2 cm or smaller relapsing more than 4 years after initial treatment).[756] A study from Osaka, Japan, found a much lower rate of second breast relapses in patients with ER-positive tumors (12%), compared to patients with ER-negative tumors (45%),[765] but this was not found in the Milan study (27% and 30%, respectively).[756]

Breast-conserving salvage therapy has been performed in 30% to 70% of patients initially treated with CS alone.[223,226,228,767] In a series from Women's College Hospital, Toronto, the 5-year actuarial second local recurrence rate was 69% for patients treated with further BCS alone and 11% for 14 patients treated with BCS and RT.[768]

An international randomized trial found chemotherapy benefitted patients with ER-negative tumors but not those with ER- or PR-positive ones following isolated local or regional recurrence after either BCT or mastectomy.[769,770] However, results were not stratified by the initial surgery and type of recurrence.

About half of patients with isolated axillary recurrences can be cured by surgery or additional RT. However, few if any patients with supraclavicular or internal mammary nodal recurrences are long-term survivors.[166,722,771-774]

CONCLUSIONS

BCT provides highly satisfactory cosmetic results without compromise of local tumor control or survival for the great majority of patients with early-stage breast cancer. This approach has been one of the great success stories of modern oncology. Cooperation between surgeons, radiologists, pathologists, medical oncologists, and radiation oncologists is critical in achieving this goal.

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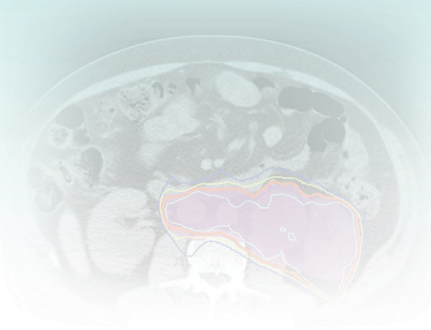
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CHAPTER

64 Breast Cancer: Postmastectomy Radiation, Locally Advanced Disease, and Inflammatory Breast Cancer



Benjamin D. Smith

INCIDENCE

Locally advanced breast cancer accounts for approximately 12% to 15% of invasive breast cancers diagnosed in the United States, with an age-adjusted incidence of approximately 16 cases per 100,000 women per year.

BIOLOGIC CHARACTERISTICS

Locally advanced breast cancer represents a heterogeneous collection of disease. Some are neglected primaries that have slowly progressed to an advanced stage whereas others result from rapid disease growth as a result of an aggressive biology. Neglected primaries are more common in unscreened patients and are characteristically low to intermediate nuclear grade cancers that are hormone receptor–positive and HER2/neu-negative. In contrast, locally advanced breast cancers diagnosed between screening intervals or shortly after the first sign or symptom of the disease commonly have high-grade and high-proliferative indices. These cancers are commonly estrogen and progesterone receptor–negative and may have amplification of HER2/neu. Inflammatory breast cancer is the most aggressive subgroup of locally advanced breast cancer presenting with rapid disease growth and involvement of the dermal lymphatics. Inflammatory breast cancer has a high propensity for metastatic spread and carries a relatively poor prognosis.

STAGING EVALUATION

All patients with locally advanced breast cancer should undergo a history and physical examination, diagnostic mammography, and serum studies. To evaluate extent of locoregional disease, imaging modalities such as chest computed tomography (CT), breast magnetic resonance imaging (MRI), or ultrasound are often helpful, with ultrasound identifying clinically relevant extraaxillary adenopathy in 37% of patients. Screening for distant metastasis should be conducted using either a combination of chest and abdomen CT plus bone scan or fluorodeoxyglucose-positron emission tomography (FDG-PET)/CT.

THERAPY

Locally advanced breast cancer requires multimodality treatment that includes multiagent chemotherapy, surgery, radiation therapy, and endocrine therapy when indicated. Neoadjuvant chemotherapy plays an important role in shrinking initially unresectable disease so that it becomes resectable. In addition, neoadjuvant chemotherapy may allow carefully selected patients to undergo breast-conserving surgery. After chemotherapy and surgery, all patients with locally advanced breast cancer should receive radiation to the breast or chest wall and the undissected regional lymph node basins (axillary apex, supraclavicular, and, in general, internal mammary). Patients with ER+ disease should also receive tamoxifen or an aromatase inhibitor for a minimum of 5 years. All patients with HER2/neu-positive disease should receive trastuzumab.

RESULTS

The outcome for patients with locally advanced breast cancer has significantly improved over the past two decades, with overall 5-year survival of 70% in the general population of patients with tumors >5 cm or four or more involved nodes. Long-term locoregional recurrence rates after surgery and radiation therapy for patients with locally advanced disease range from 10% to 25%, depending on the particular features of the disease.

INTRODUCTION

There is no single accepted definition of locally advanced breast cancer. The term is most often used to refer to a patient with clinical stage III breast cancer (see Staging) whose disease is unresectable at the time of diagnosis because of extension of the primary tumor to the skin or chest wall or extensive regional lymph node metastases. However, patients with resectable disease that is either large (>5 cm) or involves four or more axillary nodes are often also included in the definition of "locally advanced." This chapter will draw the distinction between locally advanced breast cancer that is unresectable at diagnosis and that which is resectable. It will also discuss postmastectomy radiation therapy (PMRT), including considerations of PMRT for patients with stage II disease that is not locally advanced.

Locally advanced breast cancer was once considered a fatal disease. Before the routine use of chemotherapy, the vast majority of patients developed distant metastases and died.[1-3] In the past, locoregional treatments such as mastectomy alone, radiation therapy alone, or combined surgery and radiation therapy were used, but outcomes were generally poor.[1-3] Fortunately, with integration of chemotherapy and endocrine therapy with appropriate surgery and radiation therapy, locoregional control, distant disease-free survival, and overall survival have improved substantially.[4,5] This improvement in

distant disease-free survival has also heightened the survival benefit of radiation conferred by achieving locoregional control.[6] Accordingly, care for locally advanced breast cancer requires careful coordination of a multidisciplinary team of specialists to achieve optimal results.

EPIDEMIOLOGY

With introduction of screening programs, a modest reduction in the incidence of locally advanced breast cancer was noted through the 1980s and 1990s.[7] It is not entirely clear whether the incidence has continued to decline in the 2000s. Estimates provided by the American Cancer Society indicate that the incidence of regional stage breast cancer in white women decreased by approximately 1.6% per year between 2006 and 2010, whereas incidence remained stable in black women.[8] However, analysis of Surveillance, Epidemiology, and End Results (SEER) data indicates that the incidence of locally advanced breast cancer (defined as size >5 cm or four of more involved lymph nodes, and no distant disease) was stable between 2004 and 2010, with an age-adjusted incidence of approximately 16 cases per 100,000. SEER data further indicate that locally advanced breast cancer accounts for approximately 12% to 15% of all invasive breast cancers.

There are still subgroups of patients in the United States for whom locally advanced breast cancer remains an epidemiological problem. For example, the incidence of tumors greater than 5 cm is approximately 40% higher in African American women than white women.[8] There are many possible reasons for the higher incidence of locally advanced breast cancer in African Americans, including decreased access to medical care, less use of screening mammography, and biological differences in the cancer. Specifically, breast cancers in African American women tend to be of higher grade and more often lack estrogen receptors (ERs) compared to white women.[9,10] In the developing world, approximately half of patients present with locally advanced disease.[11,12]

BIOLOGIC CHARACTERISTICS AND MOLECULAR BIOLOGY

Locally advanced breast cancer can result either from rapid disease growth with early spread to the lymphatics or from a delay in diagnosis. A thorough patient history and physical examination combined with an assessment of the tumor's biological features can help to distinguish these two categories. Typically, rapid disease growth occurs in the setting of high-grade tumors with high proliferative indices; such tumors are more likely to be ER–negative disease or overexpress HER2/neu. These tumors may develop during the interval between screening mammograms. In contrast, a high percentage of locally advanced breast cancers are of low or intermediate grade and are hormone receptor–positive. Oftentimes, such patients have not undergone screening and may present for medical care months after their first breast symptom.

Inflammatory breast cancer, a subcategory of locally advanced disease, has a unique clinical presentation and biological traits. The diagnosis of inflammatory carcinoma is made on the basis of the clinical history and physical examination findings. The clinical history of a patient with inflammatory breast cancer should include a description of breast erythema, warmth, and heaviness that have a relatively rapid onset and progression (typically progress over a period of 3 months or less). On physical examination, brawny edema of the breast is present, which may or may not be associated with a breast mass. It is important to distinguish inflammatory breast cancers from neglected breast primaries that slowly progress over many months to up to a year. Neglected locally advanced cancers typically present as a large breast mass or advanced adenopathy resulting in secondary inflammatory changes in the breast that may mimic those of inflammatory breast cancer.

Histopathologically, inflammatory breast cancer is most commonly characterized by high histological grade, a high percentage of cells in the S phase, aneuploidy, absent ER expression, and high expression of *p53* and epidermal growth factor.[13] Some authors have found that HER2/neu is not more commonly overexpressed in inflammatory breast cancer than in noninflammatory advanced disease,[13,14] although more recent studies have reported higher rates of HER2/neu overexpression.[15] The potential higher rate of both HER2/neu and epidermal growth factor receptor has permitted new opportunities for clinical trials investigating targeting these tyrosine kinase receptors.

One of the pathological hallmarks of inflammatory breast cancer is invasion into the dermal lymphatics and erythema of the skin, which may in part be representative of tumor angiogenesis. Shirakawa et al found inflammatory breast cancer xenografts to have a particular pattern of neovascular growth, in which blood vessels within cancer tissue did not have a lining of endothelial cells.[16] In addition, human inflammatory breast cancer specimens have been noted to have a higher microvessel density pattern compared to noninflammatory breast cancer.[17,18]

The most important advance in understanding the underlying biology of breast cancer, including locally advanced disease, is the growing appreciation of the importance of molecular subtype as a tool to predict benefit from targeted therapies such as endocrine therapy or trastuzumab and to prognosticate outcomes. As initially described by Perou et al, breast cancers may be broadly classified into four categories: Luminal A (classically ER positive, HER2/neu negative), Luminal B (classically ER+, HER2/neu positive), HER2-enriched (classically ER-, HER2/neu positive), and basal-like (classically ER-, HER2/neu negative).[19,20] In patients with locally advanced breast cancer treated with mastectomy and radiation, these categories predict likelihood of locoregional control, with basal-like and HER2-enriched tumors experiencing the highest risk of locoregional recurrence and luminal A/B tumors experiencing the lowest risks.[21-23]

PATHOLOGY AND PATHWAYS OF SPREAD

The majority of locally advanced breast cancers demonstrate invasive ductal histology. Invasive lobular histology may also be seen, particularly because tumors of this histology may progress to a large size before becoming clinically or radiographically apparent. Favorable breast cancer histologies such as tubular, medullary, or mucinous rarely present with locally advanced disease.

The pathways of spread of locally advanced breast cancer are most commonly through the regional lymphatics. Involvement of the axillary levels I and II lymph nodes is common for patients presenting with a T3 or T4 primary. In addition, such patients are at risk for disease in the level III axillary, infraclavicular, supraclavicular, and internal mammary lymph nodes.[24] Disease can further spread along nodal channels to nodal basins outside the classic boundaries of regional disease, for example, the anterior mediastinum, ipsilateral cervical nodal basin, or even the contralateral axilla. Figure 64-1 shows common clinical and radiographic findings in locally advanced breast cancer and the associated stage of disease. Patients with locally advanced disease are also at risk of hematogenous spread, most commonly to the lung, liver, bone, and brain.

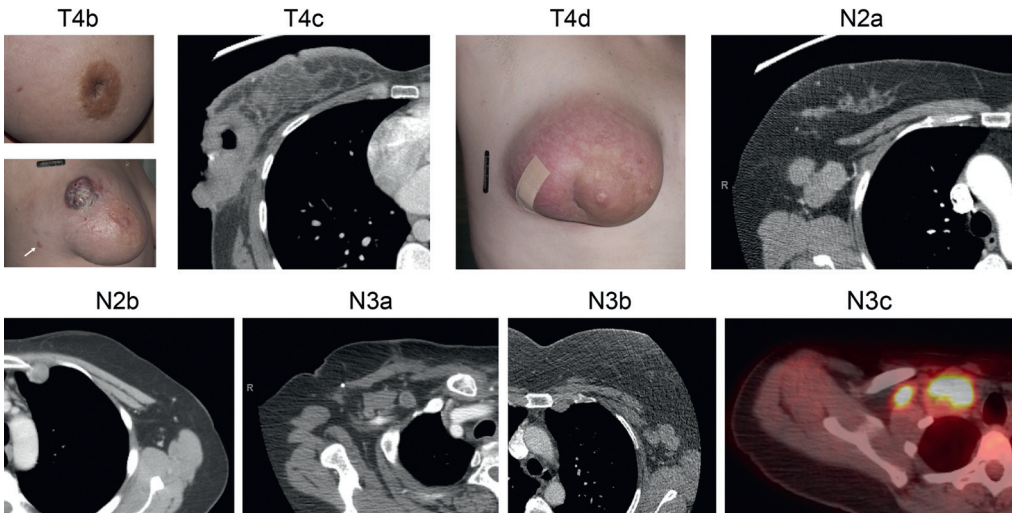


Figure 64-1 T4b, The top photograph depicts a patient with skin edema. Note the peau d'orange changes with increased visibility of the skin pores, edema of the areola, and retraction of the nipple. The bottom photograph depicts a patient with all three findings that can indicate T4b disease: skin edema, ulceration, and a satellite lesion *(see arrow)*. This patient had a neglected breast cancer with an ulcerating mass in the upper outer quadrant that became superinfected, developed into an abscess, and required surgical drainage. T4c, This computed tomography (CT) image shows an ulcerating mass that is extending to involve the serratus anterior muscles of the chest wall. T4d, This patient presented with rapid onset of diffuse breast erythema and was diagnosed with inflammatory breast cancer. N2a, This CT image shows a conglomerate of axillary lymph nodes that are adherent to one another. This is the radiographic correlate of the clinical finding of matted lymph nodes. Classically, this clinical and radiographic finding is the result of the extranodal extension of the tumor resulting in adherence of lymph nodes to one another. N2b, This patient had clinical involvement of the left internal mammary chain in the absence of axillary involvement. N3a, This patient had a necrotic, biopsy-proven lymph node in the infraclavicular space, which is the space medial to the medial margin of the pectoralis minor muscle and tracks along the subclavian artery and vein. N3b, This patient had involvement of both the axillary and internal mammary nodal basins. N3c, This patient had involvement of the supraclavicular nodal basin noted on positron emission tomography/CT.

CLINICAL MANIFESTATIONS, PATIENT EVALUATIONS, AND STAGING

Patients with locally advanced breast cancer commonly present after detecting a breast mass on self-examination. For noninflammatory cancers, there is often a significant interval from the period of first noticing the breast abnormality to the time of presentation for medical care. During this interval, the breast mass usually increases in size. After a long delay before seeking treatment, patients can present with a bleeding or ulcerative mass that occupies the majority of the breast. Over time, some breast cancers can involute or even autoamputate the breast. Superinfection and abscess may occur.

In most cases, regional adenopathy is evident at the time of diagnosis of T3 or T4 primary breast cancers. Pain, limited range of motion, edema, and weakness or numbness of the arm is possible in patients with advanced axillary or supraclavicular adenopathy.

In contrast to the relatively slow progression of noninflammatory locally advanced breast cancer, patients with inflammatory breast cancer most frequently describe a rapid onset of breast erythema and increasing breast size or heaviness. Often, these changes progress over days to weeks and are frequently misdiagnosed as breast cellulitis. Figure 64-1 shows a photograph of the presenting appearance of the breast in a patient with inflammatory breast cancer. The history of presenting signs and symptoms is the critical determinant in classifying a breast cancer as inflammatory.

All patients presenting with locally advanced disease require a comprehensive initial history and physical examination. It is critical to establish the time course of presenting signs and symptoms because these elements are necessary to distinguish inflammatory breast cancer from other T4 tumors. In addition to breast symptoms, the history should include questions concerning changes in general health and questions specifically relating to symptoms possibly due to metastases (e.g., bone pain or change in neurological status).

The initial physical examination is of critical importance in patients with locally advanced breast cancer. Unlike patients with early-stage disease, the majority of patients with T3 or T4 tumors are treated with neoadjuvant chemotherapy. This treatment significantly shrinks the tumor in most patients, and careful documentation of the pretreatment extent of disease is important for determination of subsequent locoregional therapies. The breast examination should document breast asymmetry, mass size, and whether the mass is freely mobile, skin erythema or edema, and skin or nipple retraction. Mobility of the primary mass should be tested with the pectoralis major muscle contracted and relaxed to distinguish chest wall invasion from invasion into the pectoralis muscle. Skin edema is best assessed with the patient in the supine position. Edema of the skin causes thickening, which makes the hair follicles more prominent, resulting in the classic "peau d'orange" appearance. This can best be appreciated by gently pinching the affected skin between the thumb and first finger. Figure 64-1 shows a patient who presented with T4 primary disease and was found to have peau d'orange on initial examination. The axilla and infraclavicular and supraclavicular fossae should be examined with the patient upright, and regional adenopathy should be described to include the size, consistency, and mobility of axillary, infraclavicular, and supraclavicular lymph nodes. The internal mammary lymph nodes are infrequently palpable, even when involved with disease. Despite this, the parasternal area should be examined for asymmetrical prominence with the patient supine.

After completion of an examination, the primary tumor and nodal basin should be assigned a clinical T and N stage, based on the physical examination findings supplemented by

relevant imaging findings and results of any needle biopsies. Based on clinical grounds, stage III breast cancer is established by any of the following: advanced T stage (T4 based on invasion of the chest wall excluding pectoralis muscles [T4a]; skin involvement including edema, ulceration, or satellite lesion [T4b]; both chest wall and skin involvement [T4c]; or inflammatory cancer [T4d]) or advanced N stage (N2 based on matted axillary nodes [N2a] or clinically involved internal mammary nodes in the absence of axillary nodes [N2b] or N3 based on involvement of the infraclavicular [N3a], internal mammary plus axillary [N3b], or supraclavicular nodes [N3c]). It should be noted that clinical stage III breast cancers are often considered unresectable at diagnosis and require neoadjuvant therapy to facilitate complete surgical resection. Patients staged as clinical T3 N1 are also classified as clinical stage III, although such patients' tumors may be resectable without neoadjuvant therapy.

Patients with clinical stage I or II breast cancer may undergo initial surgery and then be upstaged to pathologic stage III, most commonly because of the finding of four or more involved axillary nodes on review of the axillary dissection specimen. Such patients may be considered to have locally advanced breast cancer by some authors, but nevertheless have initially resectable disease even without neoadjuvant therapy because of a lower presenting clinical stage. The seventh edition of the American Joint Commission clinical and pathological staging system is provided in the breast cancer overview chapter.

All patients with locally advanced disease should be staged using bilateral diagnostic mammography, basic serum chemistry tests and blood counts, a CT scan of the chest and abdomen, and bone scan. FDG-PET fused with a CT is increasingly used as an alternative to bone scan and axial CT. As shown in Figure 64-2, FDG-PET may have value in guiding radiation field delineation in patients with inflammatory breast cancer by demonstrating the location and extent of regional adenopathy.[25] Patients with skin involvement should have pretreatment photographs to document extent of involvement. In addition, in our institution we routinely use ultrasonography to assess the extent of disease in the regional lymph nodes and have reported that ultrasound detected additional involved nodes beyond the levels I and II axilla in 37% of patients with locally advanced breast cancer.[24] Although not required, breast MRI can be helpful in patients where there is uncertainty regarding invasion of the chest wall or pectoralis or to identify otherwise occult primary tumors in patients with a clinical suspicion for inflammatory breast cancer.[26] Serum tumor markers such as carcinoembryonic antigen (CEA), CA15.3, and CA27-29 are used by some practitioners but are currently not recommended as standard of care.[27]

TREATMENT OVERVIEW

Patients with clinical stage III disease are optimally treated with a combined-modality approach. The incorporation of systemic treatments into the management of locally advanced disease, along with improvements in surgical and radiation therapies, have significantly improved the outcomes of patients with advanced disease. For example, early studies in which patients with advanced disease were treated with mastectomy or radiation therapy reported 5-year survival rates of only 25% to 45%.[1-3] In contrast, recent SEER data have shown that patients with advanced-stage disease, when treated with a combination of surgery, radiation therapy, and

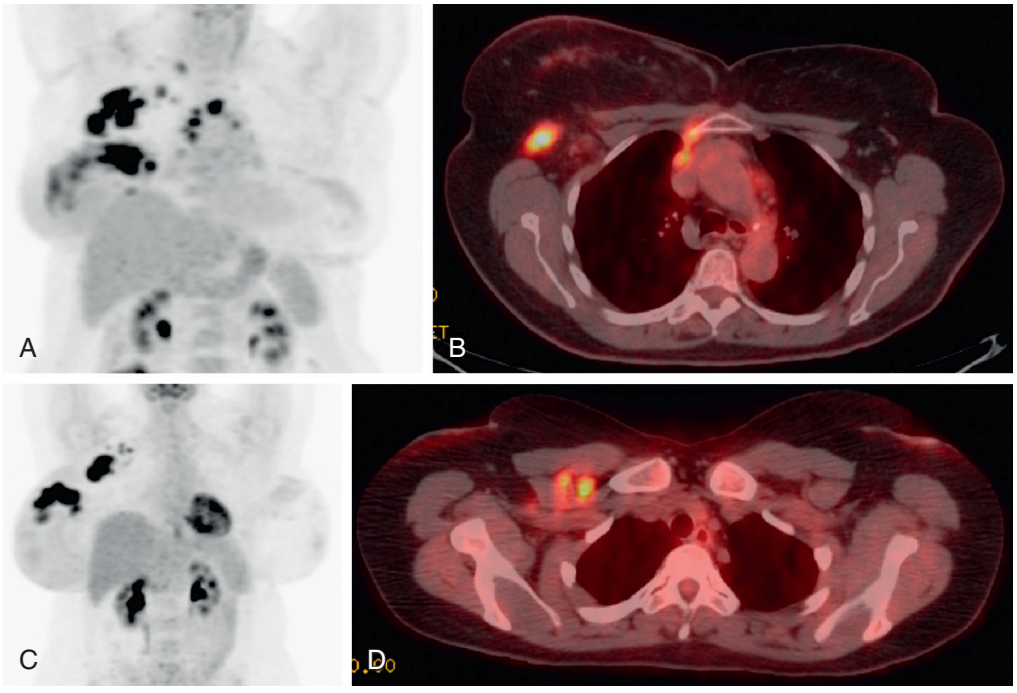


Figure 64-2 This figure depicts the positron emission tomography–computed tomography (PET-CT) findings from patients with inflammatory breast cancer. Panels **A** and **B** depict a triple negative inflammatory breast cancer with involvement of the ipsilateral axillary, infraclavicular, supraclavicular, internal mammary, and mediastinal nodal basins. Panels **C** and **D** depict an ER-, HER2/neu-amplified inflammatory breast cancer with involvement of the ipsilateral axillary and infraclavicular nodal basins. Both patients experienced major responses to chemotherapy, underwent modified radical mastectomy, and received postmastectomy radiation therapy to 51 Gy at 1.5 Gy per fraction delivered twice daily, with an additional boost, most commonly 15 Gy at 1.5 Gy per fraction delivered twice daily to the chest wall and the initially involved nodal basins. The PET-CT findings were helpful in delineating both the initial and boost fields.

chemotherapy, have 5-year survival rates of approximately 70%. In our institutional experience, we have reported a 5-year survival rate of 80% for patients with stage IIIA disease and 45% for patients with stage IIIB disease.[4]

Combined-modality treatments are best administered with input from a coordinated multidisciplinary team of surgeons, medical oncologists, and radiation oncologists. For patients with advanced but resectable breast cancer, mastectomy followed by adjuvant chemotherapy and radiation therapy is an acceptable therapeutic approach. Equally appropriate is to use chemotherapy as the first therapeutic intervention (called *neoadjuvant chemotherapy*). For patients with unresectable disease at the time of diagnosis as a result of T4 primary tumors or advanced lymph node disease, neoadjuvant chemotherapy is considered the standard of care.[28]

Treating patients with chemotherapy prior to surgery has several potential advantages. One advantage is that it gives selected patients with T3 or T4 tumors the option of being treated with breast-conserving surgery. Indeed, numerous studies have indicated that neoadjuvant chemotherapy achieves a substantial reduction in the size of the primary tumor and nodal metastases in more than 80% of cases, which often permits a breast-conserving approach that achieves an acceptable esthetic outcome.[29-32] A second advantage is that neoadjuvant chemotherapy allows for assessment of the primary tumor's response to a particular chemotherapy regimen. For the minority of patients whose disease does not respond or progresses, this assessment facilitates a change to a different regimen, allowing for the most effective chemotherapy to be given as early as possible and also avoiding unnecessary toxicity from an ineffective therapy. A third advantage is that the extent of residual disease informs prognostication[33] and may influence locoregional treatment decisions. A final advantage of neoadjuvant chemotherapy is that it facilitates expeditious testing of promising new agents because the Food and Drug Administration has recently approved the use of pathologic complete response as an endpoint to support accelerated approval of new agents.

One desired advantage of neoadjuvant chemotherapy that has not been realized is the hope that earlier administration of chemotherapy would increase the probability of eradicating preexisting micrometastatic disease. Unfortunately, the two largest trials that compared neoadjuvant and adjuvant chemotherapy found that delivering chemotherapy before surgery provided no overall survival advantage compared to delivering chemotherapy after surgery. Specifically, the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-18 randomized 1523 patients with early-stage, operable breast cancer to receive four cycles of doxorubicin/cyclophosphamide (AC) either before or after surgical treatment. After long follow-up, the overall survival and disease-free survival rates were nearly identical between the two groups.[34] Interestingly, there appeared to be an advantage for neoadjuvant chemotherapy for the younger patients and an advantage for the adjuvant chemotherapy in the older patients. A second large, randomized, prospective trial conducted by the European Organization for Research and Treatment of Cancer (EORTC) also demonstrated equivalent rates of survival and distant metastases between pre- or postoperative chemotherapy treatment with four cycles of fluorouracil, epirubicin, and cyclophosphamide (FEC).[31,35]

The increasing use of neoadjuvant chemotherapy has raised many questions concerning the surgical and radiotherapeutic management of patients with locally advanced breast cancer. Accordingly, it is best to have surgeons, radiation oncologists, and medical oncologists participate in decisions regarding treatment sequencing and provide the necessary multidisciplinary coordination to address the added complexity that neoadjuvant chemotherapy brings to the treatment of patients with locally advanced breast cancer.

LOCOREGIONAL TREATMENT OF PATIENTS WITH ADVANCED PRIMARY DISEASE

Breast Conservation after Neoadjuvant Chemotherapy

Historically, all patients with advanced primary breast cancers underwent mastectomy and postmastectomy radiation therapy as the preferred locoregional treatment. However, the high response rates associated with neoadjuvant chemotherapy have allowed for breast conservation in selected patients with advanced disease. The NSABP and EORTC trials comparing neoadjuvant chemotherapy with adjuvant chemotherapy in patients with stage II or III breast cancer found that breast-conservation rates were higher in the neoadjuvant chemotherapy arms.[29,31] This increase was directly because of a greater percentage of patients with T3 disease being offered breast conservation after first responding to chemotherapy. One concern over using chemotherapy before breast-conserving surgery is that many advanced breast cancers do not shrink concentrically to a solitary nidus in response to neoadjuvant chemotherapy. In such cases, surgery directed at the primary core may leave a high burden of microscopic disease around the tumor bed site, which may lead to higher likelihood of local recurrence.

Some clinical data indeed indicate that patients with advanced tumors who have been treated with breast-conserving surgery after neoadjuvant chemotherapy have higher rates of breast cancer recurrence. For example, in the NSABP B-18 trial, the local recurrence rate in patients with large primary tumors in whom a response to neoadjuvant chemotherapy allowed a breast-conserving surgery was twice that in patients with smaller tumors who were treated with surgery first (15.7% versus 7.6%, respectively).[29] Other series have also shown relatively high local recurrence rates in patients who receive neoadjuvant chemotherapy.[36,37] From these data it is clear that breast-conserving procedures after neoadjuvant chemotherapy are more complex, that multidisciplinary coordination is important, and that proper patient selection for breast conserving procedures is critical. Carefully planning for breast conserving surgery by, for example, placing a clip in the tumor at the time of initial biopsy and diagnosis, may facilitate localization of the tumor after chemotherapy and improve long-term local control.[38]

With appropriate patient selection and multidisciplinary management, the outcome of breast conservation for selected patients with locally advanced breast cancer can be excellent.[39,40] Investigators from M. D. Anderson have developed and validated a prognostic index to predict likelihood of long-term locoregional recurrence in patients treated with neoadjuvant therapy and breast conserving surgery. The prognostic index assigns a point for each of the following variables: clinical N2/3 disease, lymphovascular invasion, residual pathologic tumor size >2 cm, and multifocal residual disease. For patients with 0, 1, or 2 points, 5-year risk of locoregional recurrence is only 7%. In contrast, for patients with 3 or 4 points, 5-year risk of locoregional recurrence is 31%.[40] Accordingly, this prognostic index can be used to select patients who are most appropriate for breast conservation after neoadjuvant chemotherapy. For patients with a high prognostic score who are motivated for breast conservation, consideration should be given to more extensive surgery or more intensive imaging, such as MRI, to guide the surgical resection volume.

TABLE 64-1 10-Year Locoregional Recurrence and Overall Survival Rates in Randomized Trials Investigating Irradiation after Mastectomy and Systemic Treatments

Trial	No. Patients	Treatment Arm	Locoregional Recurrence	Overall Survival
Danish 82b[39] (10-year data)	1708	Irradiation	9%	54%
		No irradiation	32%	45%
Danish 82c[40] (10-year data)	1375	Irradiation	8%	45%
		No irradiation	35%	36%
Danish 82b/c[42] (18-year data)	3083	Irradiation	14%	37%
		No irradiation	49%	27%
Vancouver[44] (20-year data)	318	Irradiation	10%	47%
		No irradiation	26%	37%

Mastectomy and Postmastectomy Radiation Therapy

A modified radical mastectomy (resection of the breast, pectoralis fascia, and levels I and II axillary lymph nodes) remains the most common surgical treatment for patients with locally advanced breast cancer. Nevertheless, risks of locoregional recurrence after this surgery remain high if radiation is not also given. Postmastectomy radiation therapy (PMRT) benefits this cohort of patients by reducing locoregional recurrence and thereby improving overall survival.

Despite the fact that postmastectomy radiation has been evaluated in more than 25 trials conducted over 40 years, there remain a number of significant controversies over its use. Historically, it was questioned whether the benefits of postmastectomy radiation were offset by its associated toxicity. Specifically, in 1987, Cusik et al published the first meta-analysis of data from PMRT trials and reported that radiation use was associated with a poorer overall survival rate.[41] In a subsequent analysis, Cusik et al reported that PMRT decreased the breast cancer death rate but increased the nonbreast cancer death rate,[42] which resulted in equivalent overall survival rates between the two groups.

The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) has performed a more recent and comprehensive meta-analyses of trials investigating postmastectomy radiation therapy.[43] The 2005 publication of this meta-analysis included data from 9933 patients treated on clinical trials with mastectomy, axillary clearance with or without PMRT. The results of this study clearly demonstrated that PMRT reduced isolated locoregional recurrence rate for patients with lymph node-positive disease treated with mastectomy. Specifically, PMRT decreased the 15-year isolated locoregional recurrence rate for patients with lymph node–positive disease from 29% to 8%.[43] The more revolutionary finding was that this significant absolute improvement in locoregional control reduced the 15-year breast cancer mortality rate from 60% (no radiation) to 55% (radiation). This finding was particularly important in that previous meta-analyses suggested that the benefit of adjuvant radiation was limited to locoregional control.

It is important to recognize that the benefits of adjuvant radiation for patients with locally advanced disease may be greater than that reported in meta-analyses. Many of the trials included in meta-analyses included patients at low risk for locoregional recurrence, used unconventional radiation doses, fractionation patterns, and radiation field designs, and enrolled patients in a much earlier era where systemic therapies were either less effective or entirely omitted. To minimize these confounding effects, Van de Steene et al conducted a similar meta-analysis but excluded trials that began before 1970, trials with small sample sizes, trials with relatively poor survival rates, and trials that used radiation fractionation schedules that are no longer standard practice.[44] When these less-than-optimal studies were excluded, PMRT significantly improved overall survival, reducing odds of death by 12.4%. In addition, Whelan et al performed a meta-analysis of the published PMRT trials that included systemic therapy in both treatment arms. In this analysis, the addition of radiation after mastectomy was also shown to reduce the risk of any recurrence (odds ratio, 0.69) and mortality (odds ratio, 0.83).[45]

The most recent Phase III randomized trials investigating PMRT were initiated almost three decades ago but remain relevant in that they used more modern radiation treatment techniques and dose fractionation and included some form of systemic therapy for all patients. Table 64-1 displays the results from these trials. The Danish Breast Cancer Cooperative Group (DBCCG) 82b trial randomized 1708 premenopausal women with stage II or III breast cancer to receive mastectomy followed by nine cycles of cyclophosphamide/methotrexate/5-fluorouracil (CMF) chemotherapy or mastectomy, radiation therapy, and eight cycles of CMF chemotherapy.[46] The simultaneously run DBCCG 82c study randomized more than 1300 women who are postmenopausal to receive mastectomy and tamoxifen or mastectomy, tamoxifen, and radiation therapy.[47] Patients randomized to receive radiation therapy in these studies had a lower 18-year rate of locoregional recurrence and a higher 18-year overall survival rate.[48,49] A smaller trial, conducted in Vancouver, British Columbia, randomized 318 women who are premenopausal with lymph node-positive disease to receive mastectomy and CMF chemotherapy with or without PMRT.[50,51] Again, patients who underwent radiation therapy had lower 20-year rates of locoregional recurrence and similar improvement in the 20-year overall survival rate.

Exploratory analyses of the Danish trials classified the impact of PMRT on both locoregional control and survival stratified by molecular profile of the treated tumor.[21,22] Several interesting conclusions may be drawn from these studies. First, long-term risks of locoregional recurrence were similar regardless of ER or HER2/neu status in patients who did not receive PMRT. It should be noted, however, that endocrine therapy was not used in the DBCG 82b and only 1 year of tamoxifen was administered in 82c. It is likely that patients with ER+ positive disease receiving optimal endocrine therapy may have lower locoregional recurrence risks even without radiation than reported in these studies. The relative benefit of radiation in reducing locoregional recurrence, however, did vary by tumor molecular profile. Specifically, patients with ER+ disease experienced a greater than 90% relative reduction in risk of locoregional recurrence when treated with PMRT, whereas patients with triple-negative disease experienced a 67% relative reduction and patients with ER-, HEr2/neu-positive disease experienced a 50% reduction. With regard to survival, PMRT significantly improved long-term overall survival for patients with ER+ disease, but failed to improve overall survival for those with either triple-negative disease or ER-, HER2/neu-positive disease. These findings underscore the

TABLE 64-2 10-Year Locoregional Recurrence Rates in Clinical Trials That Used Mastectomy and Systemic Treatments without Irradiation

Trial	No. Patients	Systemic Therapy	Locoregional Recurrence	
			Patients with 1-3 Positive Lymph Nodes	Patients with >3 Positive Lymph Nodes
Recht et al[56]	2016	CMF	13%	29%
Katz et al[54]	1031	Doxorubicin-based	10%	21%
Wallgren et al[57]	5352	Varied	14% 19% to 27%*	24% 24% to 34%*
Taghian et al[58]	5758	Varied	13%*	24% to 32%

CMF, *Cyclophosphamide, methotrexate, 5-fluorouracil.*
**Higher rates were associated with high-grade disease and lymphovascular space invasion.*

potential heterogeneity underlying the relationship between locoregional recurrence benefit and survival benefit of PMRT. It is hoped that introduction of more effective systemic therapies for HER2/neu-positive and triple-negative breast cancer will not only improve overall outcomes for these patients, but also, through controlling distant micrometastatic disease, allow such patients to experience a meaningful survival benefit from radiation.

There is significant current controversy over whether PMRT is indicated for patients with stage II breast cancer with 1 to 3 positive lymph nodes. The majority of the patients enrolled in the Danish and British Columbia randomized trials had 1 to 3 positive lymph nodes, and based on the positive findings from these studies, many feel that all patients with lymph node–positive disease should receive radiation treatments. The difficulty in interpreting these data, however, is that many patients in these trials did not undergo formal levels I and II axillary dissection. The median number of axillary lymph nodes resected was only 7, with 76% of the patients having fewer than 10 lymph nodes removed and 15% having 3 or fewer lymph nodes removed.[46] This diverges from standard U.S. practice in which the median number of nodes removed is approximately 15.[52] Accordingly, some of the patients reported to have 3 or fewer positive lymph nodes likely would have had 4 or more positive lymph nodes if a more extensive surgical procedure had been performed. Correspondingly, their risk of a chest wall or supraclavicular recurrence would be higher than that estimated for patients with only 1 to 3 positive nodes based on more thorough, and thus more accurate, axillary lymph node dissection. In addition, failure to remove these additional involved axillary lymph nodes would predispose patients to axillary recurrence, which could be avoided by a more complete axillary dissection. Indeed, in an earlier publication of the Danish 82b trial, it was reported that 45% of all locoregional recurrences occurred in the axilla.[53] The Danish group reanalyzed their data and evaluated only the patients with 1 to 3 positive lymph nodes who had at least 8 lymph nodes removed at the time of mastectomy. This publication still demonstrated a significant reduction in locoregional recurrence with the use of radiation (27% to 4%) and also continued to demonstrate an absolute 9% survival advantage for radiation in this cohort.[54]

The most recent analyses from the EBCTCG comparing mastectomy with levels I and II axillary dissection with or without adjuvant radiation also evaluated the benefit of radiation according to the number of positive lymph nodes.[55] This analysis included data from approximately 8135 patients treated in 22 trials that were started between 1964 and 1986 and demonstrated a significant benefit in locoregional recurrence (20% versus 4% at 10 years) and survival (47% versus 38% at 15 years) for the patients with 1-3 positive lymph nodes, in addition to noting benefits for the patients with 4 or more positive lymph nodes and no measurable benefit for patients with node-negative disease.

Based on these data it would appear that PMRT is warranted for all patients with lymph node-positive disease. However, a number of studies performed in the United States suggest that patients with one to three positive lymph modes have a much lower risk of locoregional recurrence after mastectomy and chemotherapy. These data are summarized in Table 64-2. In general, these data suggest that the 10-year locoregional recurrence risk for patients with one to three positive lymph nodes is approximately 12%, which is almost three times lower than the locoregional recurrence rate in the no radiation arms of the Danish trials. Correspondingly, the expected locoregional control benefit to be gained from the addition of PMRT would be much less.

Two nonrandomized institutional studies suggest this. An analysis from M. D. Anderson found that the use of PMRT reduced the 10-year locoregional recurrence risk for patients with stage II disease and one to three positive lymph nodes from 13% to 3%.[56,57] Similarly, investigators from Massachusetts General Hospital found that PMRT reduced the 10-year risk of locoregional recurrence from 11% to 0% for patients with one to three positive lymph nodes.[58] Whether this degree of benefit is clinically meaningful with respect to patient survival remains a matter of controversy. Another important consideration is that locoregional recurrences after mastectomy can develop after 10 years of follow-up. Therefore, the 10-year data presented in Table 64-2 may underestimate the true percentage of patients with persistent locoregional disease after surgery and chemotherapy. Specifically, in the 20-year update of the Vancouver, British Columbia, randomized trial, approximately 20% of the total number of locoregional recurrences in the group randomized to no PMRT developed after 10 years of follow-up.[51]

Some series have identified subgroups of patients with stage II breast cancer and 1 to 3 positive lymph nodes that have higher risks of locoregional recurrence.[56,57,59-62] Factors that identify these subgroups include young age, the presence of extracapsular extension greater than 2 mm, tumor size larger than 4 cm, positive or close (<2 mm) surgical margins, lymphovascular space invasion, invasion of the skin, nipple, or pectoralis muscle, fewer than 10 lymph nodes resected, and a 20% or greater proportion of involved to dissected lymph nodes. It is important to recognize that these factors were identified in retrospective subset analyses and are not prospectively validated.

The ASTRO and ASCO consensus statements regarding PMRT recommended that an additional trial be performed to further clarify the benefit of PMRT for women with stage II disease and one to three positive lymph nodes.[63,64]

Unfortunately, an Inter-Group trial designed to determine the benefits of PMRT for these patients closed owing to poor accrual. Prospective trials evaluating the benefits of regional lymph node irradiation in primarily N1 patients have been conducted in Canada (MA.20) and Europe (EORTC 22922/10925) but results are not yet published. Findings from these large randomized trials are likely to significantly influence our understanding of the benefits of regional lymph node irradiation and PMRT in patients with one to three positive nodes.

Postmastectomy Radiation Therapy after Neoadjuvant Chemotherapy

As previously highlighted, the use of neoadjuvant chemotherapy has significantly increased in recent years, particularly for patients with advanced primary tumors. One of the most important questions raised by this increased use concerns the indications for PMRT. In patients treated with mastectomy first, the decision to administer radiation therapy is made on the basis of the pathological extent of disease. This is because pathological quantification of disease is much more precise than clinical and radiographic examinations. Accordingly, the ASTRO and ASCO consensus statements regarding PMRT have recommended that treatments be based in large part on the pathological determination of disease extent in lymph nodes.[63,64]

Neoadjuvant chemotherapy changes the extent of pathological disease in 80% to 90% of cases. Thus, data elements available to the clinician in generating a recommendation for or against PMRT in the neoadjuvant setting include the initial clinical stage, the final pathologic stage after delivery of chemotherapy, and the degree of difference between the two, which indicates the response, or lack thereof, to neoadjuvant chemotherapy. Prospective trials to determine whether response to chemotherapy may be used to inform decisions regarding radiation therapy are under way.[65] In the meantime, indications for PMRT following neoadjuvant chemotherapy and mastectomy must be based on the available nonrandomized literature.

For example, the largest study to assess locoregional recurrence rates after neoadjuvant therapy included 3088 patients treated on NSABP B-18 and B-27, two trials which used neoadjuvant chemotherapy and prohibited radiation after mastectomy. The key finding from these studies was that response to neoadjuvant chemotherapy correlated with risk of locoregional recurrence, supporting the hypothesis that chemotherapy response may also predict which patients do and do not require radiation therapy. Specifically, patients with a pathologic complete response to neoadjuvant chemotherapy in both the primary tumor and the axillary nodes experienced the lowest risk of locoregional recurrence, whereas patients with residual invasive disease in the breast who were pathologically node-negative had an intermediate risk of locoregional recurrence and patients with residual positive lymph nodes had the highest risk of locoregional recurrence. For example, in patients treated with mastectomy without radiation who were found to have residual nodal positivity, the risk of locoregional recurrence ranged from 11.2% to 22.4%. This risk was thought to be sufficiently high to justify consideration of PMRT. In contrast, for patients who converted from node-positive to node-negative after chemotherapy, locoregional recurrence risk was 0%, suggesting that PMRT may be safely omitted if a nodal pathologic complete response is achieved.[66]

To date, only one published study has evaluated the efficacy of PMRT in comparison to no PMRT in patients treated with neoadjuvant chemotherapy. This study compared the outcomes of 579 patients who received neoadjuvant chemotherapy, mastectomy, and radiation therapy with those of 136 patients who were treated with neoadjuvant chemotherapy and mastectomy alone.[67] All patients included in this study were treated on prospective trials at M. D. Anderson Cancer Center, but it is important to recognize that radiation therapy was not a randomized variable in any of these trials. Therefore, there were significant imbalances in the prognostic factors between the two groups, with those being referred for radiation therapy having more extensive disease. Despite the imbalances in both T and N clinical stage, the locoregional recurrence rate was significantly lower in the patients treated with PMRT than in those treated with neoadjuvant chemotherapy and mastectomy alone (10-year locoregional recurrence rates were 8% and 22%, respectively, $p = 0.001$). More importantly, as indicated in Table 64-3, treatment with radiation therapy was associated with better overall and cause-specific survival rates in selected groups of patients with high-risk disease. In addition, multivariate analysis showed that PMRT was independently associated with improved cause-specific survival, (HR = 0.49; 95% CI, 0.34 to 0.71; $p < 0.001$) and locoregional recurrence-free survival (HR = 0.21; 95% CI, 0.12 to 0.37; $p < 0.001$).

TABLE 64-3 10-Year Locoregional Recurrence and Overall Survival for Selected Subgroups of Patients in the M. D. Anderson Cancer Center Series Investigating the Efficacy of Postmastectomy Irradiation after Neoadjuvant Chemotherapy[60]

Characteristic	Treatment	Locoregional Recurrence	Cause-Specific Survival
T4 disease	Irradiation	15%	45%
	No irradiation	46%	24%
N2/N3 disease	Irradiation	12%	49%
	No irradiation	40%	27%
IIIB/IIIC disease	Irradiation	15%	44%
	No irradiation	51%	22%

That paper also addressed the question of whether PMRT is still needed in patients with clinical stage III breast cancer who achieve a pathologic complete response to neoadjuvant chemotherapy. For such patients, the locoregional recurrence rate was 3% if PMRT was given compared to 33% if PMRT was omitted ($p = 0.006$). In addition, using a broader definition of favorable response as having less than 5 cm of disease and fewer than four positive lymph nodes, similar benefits were noted. For those with stage III disease who achieved a favorable response using these criteria, the locoregional recurrence rates were 9% for those receiving radiation therapy versus 20% for those not receiving radiation therapy.[67]

On the basis of these data, it is reasonable to recommend PMRT for all patients with clinical T3 or T4 tumors or clinical stage III disease regardless of their response to neoadjuvant chemotherapy. In terms of clinical stage I or II breast cancer, PMRT should be recommended for patients with four or more positive lymph nodes after chemotherapy and for the unusual patient in whom the disease progresses and the primary tumor exceeds 5 cm in diameter. On the basis of the NSABP B-18 and B-27 data, it is also reasonable to consider PMRT for patients with only one to three involved nodes, although this remains an area of controversy and merits further study. These recommendations were articulated in a National Cancer Institute Statement of Science publication on this topic.[28]

A framework for radiation therapy decision making in patients treated with neoadjuvant chemotherapy and mastectomy was also recently created by the Athena Breast Health

Network based on the results of a systematic literature review.[68] This framework defined a select group of patients expected to have a risk of locoregional recurrence less than 10% without PMRT, defined as older than 40 years, clinical stage I/II (T1-2 N0-1), ER+, no lymphovascular space invasion, no extracapsular extension, and after neoadjuvant chemotherapy either a pathologic complete response or only one to three residual involved lymph nodes. The authors correspondingly recommended withholding postmastectomy radiation for such patients, although as mentioned previously, PMRT may be considered in light of the B-18/B-27 data. For all other patients, locoregional recurrence risk is expected to be higher and PMRT is generally warranted.

TECHNIQUES OF IRRADIATION

Radiation treatment plays a critical role in the management of locally advanced breast cancer, and as such the design of treatment fields is of critical importance. For patients with stage III disease, the initial target volume should include the breast and chest wall and draining lymphatics. At a minimum, the undissected axillary apex and the supraclavicular fossa lymph nodes should be included. In our institution, we also include the internal mammary lymph nodes as a therapeutic target. One rationale for including these structures is that the internal mammary lymph nodes frequently contain disease in patients with locally advanced disease, particularly those with medial and central tumors.[69]

A variety of techniques can be adopted to include these targets in the radiation field. Initially, patients should be immobilized with their ipsilateral arm abducted (90 degrees to 120 degrees) and externally rotated. In assessing arm position, it is important to have the soft tissues of the arm cranial to the junction of the tangent and supraclavicular fossa field to avoid unnecessary irradiation of the proximal arm. In addition, skin folds within the supraclavicular fossa should be flattened as much as possible. After positioning and immobilization, patients are placed on a 5-degree to 15-degree angle board to flatten the slope of the chest wall in the region of the sternum. This enables an electron field treating the internal mammary nodes to be as appositional as possible, which improves dosimetric coverage and decreases skin dose.

In our institution, a CT simulator, specially equipped with a large bore to accommodate the patient arm position, is used. Radioopaque wires are placed on the surgical scar(s), drain sites, and clinical treatment borders. The interface border between the chest wall and breast field and the supraclavicular field is typically placed at the bottom of the clavicular head, which ensures adequate coverage of the typically undissected axillary apex lymph node region.[70] A scout view of the patient is obtained to assess positioning. If the projection of the supraclavicular field is estimated to include a large volume of apical lung, then the patient may be repositioned at a lower slant angle or the junction between the supraclavicular field and breast and chest wall fields may be raised to decrease anticipated radiation of the lung from the supraclavicular field. CT images are then acquired and the appropriate isocenters are determined and marked along with appropriate set-up points. Areas of interest are then contoured on the CT slices. Typically, we contour the tumor bed (for cases of breast conservation), the internal mammary artery and vein in the upper three interspaces (i.e., from the caudal edge of the first rib to the cranial edge of the fourth rib), and the undissected level III axillary apex lymph nodes. Regions of any residual involved lymph nodes are also contoured.

For patients treated with breast-conserving surgery, the breast is typically treated with medial and lateral tangent photon fields. These fields are created with matched, nondivergent deep and cranial borders. A nondivergent cranial border is created through rotation of the couch. The nondivergent deep border is typically achieved by overrotating the gantry or a half-beam block. The collimators are rotated to match the chest wall slope, and any volume that extends cranially above the match line into the supraclavicular field is blocked. For patients with advanced disease or tumor located in the central or medial breast, we attempt to include the contoured internal mammary structures by widening the deep border in the upper half of the field (often called *deep tangents* or *half-wide tangents*). CT-simulation allows physicians to assess a variety of gantry angles for these tangents and pick the optimal angle that minimizes lung volume while avoiding irradiation of the contralateral breast.

Figure 64-3 shows an example of a deep tangent field that includes the upper internal mammary lymph nodes in the field. A supraclavicular and axillary apex field is matched to the tangents with a nondivergent half-beam block. The gantry of this field is rotated 10 degrees to –20 degrees to be off the spinal cord and esophagus yet still afford adequate coverage of the medial supraclavicular nodes.[71] For patients with advanced disease, we typically place the lateral border of the

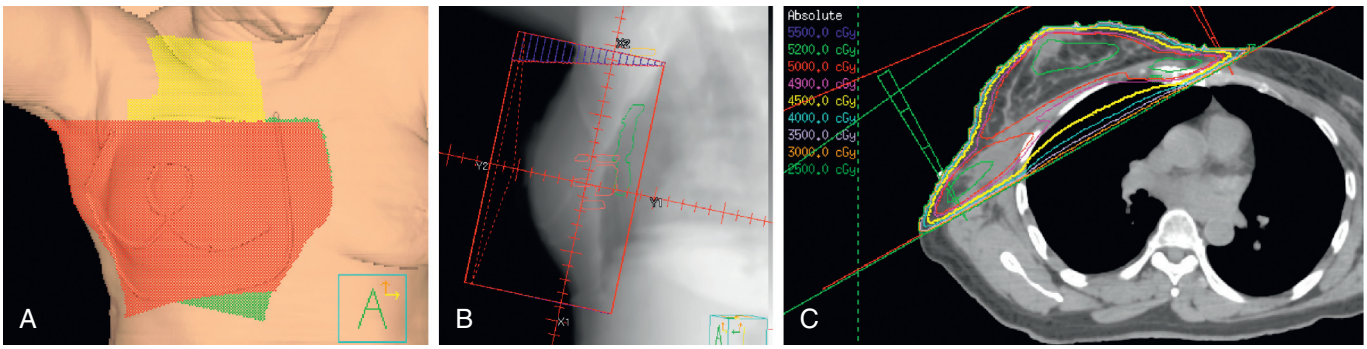


Figure 64-3 This patient had a triple negative cancer of the lower outer quadrant of the right breast with six radiographically suspicious axillary nodes on ultrasound, clinical stage T1c N1a. She received neoadjuvant chemotherapy followed by breast conserving surgery with reduction mammoplasty and axillary lymph node dissection, revealing a pathologic stage of ypT0 N1mic. She received radiation to the right breast using partially wide tangents to encompass the ipsilateral internal mammary nodes and a supraclavicular field to encompass the ipsilateral supraclavicular and infraclavicular nodal basins. Panel **A** shows the skin rendering for her treatment fields. Panel **B** shows the digitally reconstructed radiograph for the medial tangent, illustrating the "partially wide" technique which encompasses the internal mammary nodal chain as shown in green. Panel **C** shows the axial dose distribution, with the breast tissue covered by the 49-Gy isodose line *(shown in purple)* and the internal mammary nodal chain *(shown in green)* covered by the 45-Gy isodose line *(shown in yellow)*.

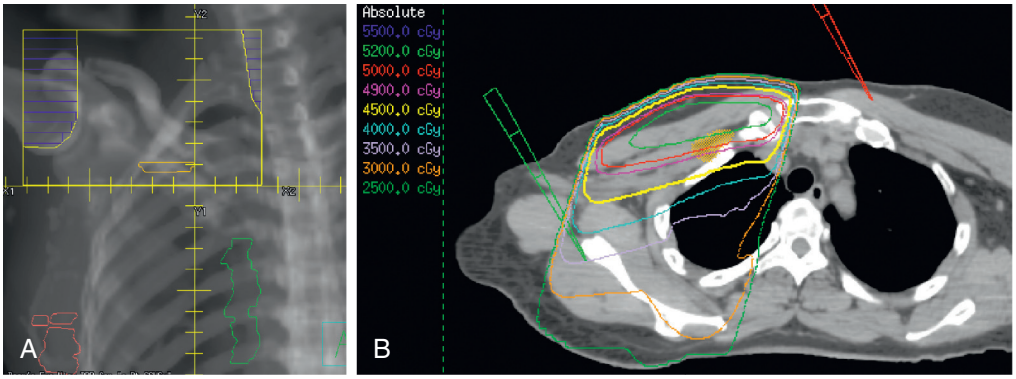


Figure 64-4 This figure shows the supraclavicular field used to treat the patient described in Figure 64-3. The superior border is set approximately at the level of the cricothyroid membrane, the medial border abuts the trachea, the lateral border is set at the lateral margin of the pectoralis major, and the inferior border is set at the inferior margin of the clavicle. The level III axillary and infraclavicular nodal basin is contoured *(shown in orange)*. A mix of lower and higher energy photons, each prescribed to their respective depth of maximum dose, is selected to ensure adequate coverage of the contoured level III axillary nodal basin with a dose of 45 Gy *(shown in yellow)*.

supraclavicular field at the lateral margin of the pectoralis major muscle to facilitate coverage of Rotter's space and the anterior soft tissues of the breast and chest wall and axilla. Figure 64-4 shows an example of such a field. A supplemental photon beam directed toward the region of underdosed axillary target is used to ensure the targeted axilla receives a minimum dose of 45 Gy in the following situations: axillary dissection was not performed, gross disease remaining in the axilla, or high burden of disease in the levels I and II axilla.

For patients treated after mastectomy, we typically target the chest wall and draining lymphatics with a four-field technique. The supraclavicular and axillary apex field is identical to that described previously. The lateral chest wall is treated with an opposed tangent technique similar to that used for a breast. The medial chest wall and internal mammary lymph nodes are treated with a medial electron field that includes the contoured internal mammary vessels and is angled 15 to 30 or more degrees. The angle is selected to minimize the cold triangle at the junction between the electron and tangent fields, with coverage ≥35 Gy at the cold triangle considered acceptable in our practice. This field is matched to the tangents on the skin for patients without T4 disease and overlapped by 3 mm in patients with T4 disease. Figure 64-5 shows examples of such fields. One advantage of this technique is that it provides relatively broad circumferential coverage of the chest wall, something that is important, particularly for patients with T4 tumors. In addition, the technique allows for exclusion of the cardiac silhouette from the high-dose region.

We treat our initial targets to a total dose of 50 Gy in 25 fractions over 5 weeks, but accept coverage of our contoured nodal targets with the 90% isodose line. For patients treated with mastectomy, we use a 3-mm to 5-mm bolus over the chest wall every other day for 2 weeks and then as needed to assure that a brisk radiation dermatitis develops (Figure 64-6). However, this dermatitis should not lead to a treatment interruption and moist reactions are to be avoided if at all possible. After completing a course of treatment to 50 Gy, we treat the chest wall with a generous boost of electron fields for an additional 10 Gy in five fractions (typically a combination of a medial and lateral electron field with a hinge angle ≤35 degrees and encompassing 5 cm to 10 cm beyond the mastectomy scar and the tumor bed location of the original primary) (Figure 64-7). In addition, we treat all sites of unresected but initially involved adenopathy in the internal mammary, infraclavicular, and supraclavicular regions with a radiation boost. If ultrasonography or other imaging has shown a resolution of disease in these areas, we deliver an additional boost of 10 Gy in five fractions. If gross residual disease persists on imaging, we increase the boost treatment to 16 Gy in eight fractions (Figures 64-8 to 64-10).

In our institution, we treat most patients with inflammatory cancer with an accelerated radiation schedule, based on a retrospective study that suggested that this schedule improved the outcome compared to a historical data set.[72] The initial target volumes are treated to 51 Gy in 1.5-Gy fractions given twice a day for 17 treatment days. Subsequently, the boost fields are treated with an additional 15 Gy in 1.5-Gy twice-daily fractions over 5 treatment days. We have found that this fractionation schedule is associated with an improved rate of locoregional control and has an acceptable toxicity profile.

Treatment plans showing radiation dose in multiple off-axis slices should be used to determine optimal beam parameters. Tangential photon fields are delivered using a forward-planned, field-in-field technique to achieve optimal three-dimensional dose homogeneity. CT treatment planning with heterogeneity correction factors is also used to improve dose modeling. Electron energies for the medial chest wall and internal mammary lymph node fields should ensure that the 90% isodose line covers the contoured volume and avoids irradiation of the heart. In addition, photon energies for the supraclavicular field should be chosen to ensure that the 90% isodose line fully covers the contoured, undissected level III axilla. It is frequently necessary to split the electron internal mammary field into two different fields, a higher energy field to cover the contoured lymph nodes, and a lower energy field caudal to the contoured nodes, to prevent excessive exit of dose into the heart or lung.

Dose-volume histogram (DVH) criteria for evaluating treatment plans remain an area of investigation, with little available data to discriminate a safe from nonsafe plan. Population-based data support a linear, no-threshold relationship between mean cardiac dose and cardiac event risk, suggesting that cardiac dose should be kept as low as reasonably achievable.[73] In our practice, respiratory gating with deep inspiration breath-hold is commonly used to reduce incidental cardiac irradiation, and most patients with left-sided breast cancers treated with radiation to encompass the ipsilateral internal mammary lymph nodes have a mean heart dose less than 4 Gy. For right-sided patients, mean heart dose is typically <2.5 Gy. Regarding lung irradiation, a reasonable target is to keep the ipsilateral lung V20 ≤ 35%, although in select

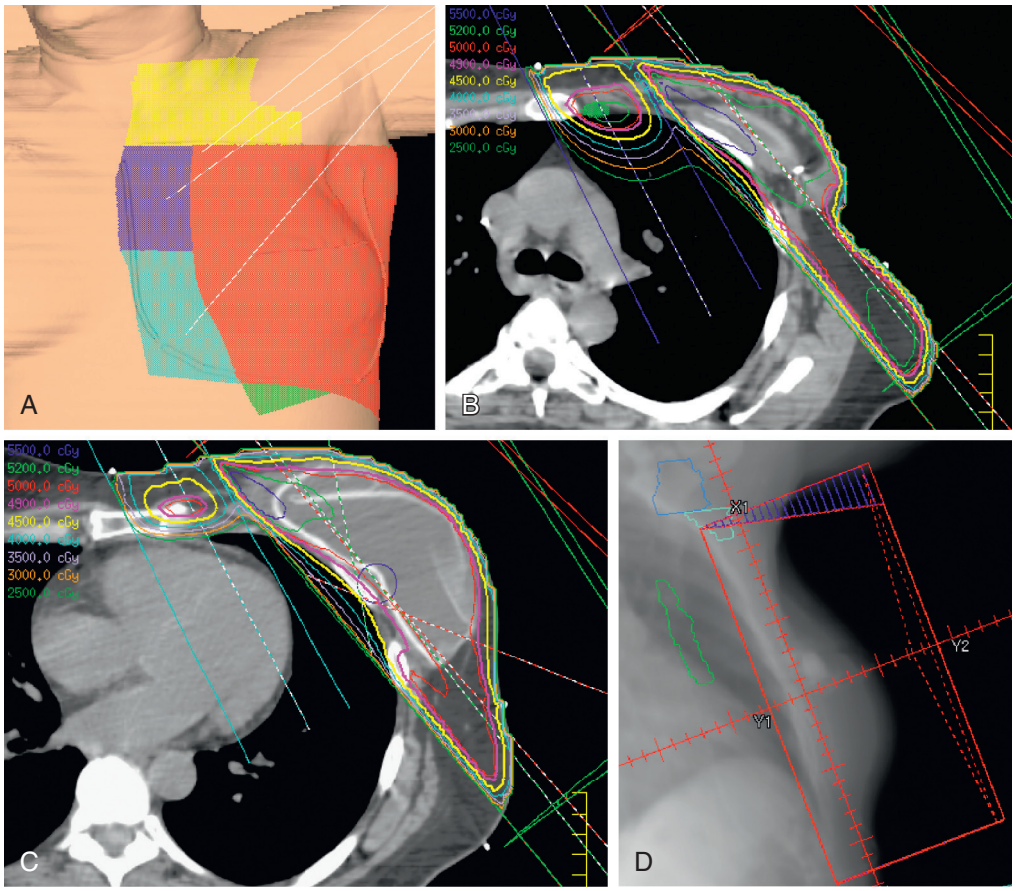


Figure 64-5 This patient had a T3 N1 left breast cancer treated with upfront skin-sparing mastectomy and axillary lymph node dissection with placement of a submuscular tissue expander. The expander was inflated during adjuvant chemotherapy and then deflated one day before simulation to a fill volume of 300 ml. Panel **A** shows the skin rendering of the various treatment fields, Panel **B** the axial dose distribution at the level of the contoured internal mammary lymph nodes, Panel **C** the axial dose distribution at the level of the heart, and Panel **D** the digitally reconstructed radiograph for the medial tangent field. The internal mammary nodal target is covered by the 45-Gy isodose line, as shown in yellow. In this case, the internal mammary electron field was split into two fields, a 12-MeV field to cover the contoured first three interspaces *(purple color in Panel **A**)*, and a 9-MeV field to cover just the lower medial chest wall and avoid the heart *(shown in light blue)*. This patient was treated in breath hold to optimize cardiac sparing. Her mean heart dose was 305 cGy and her ipsilateral *(left)* lung V20 was 24%.

cases the ipsilateral lung V20 may be higher. It is important to underscore that there is not a strong correlation between lung DVH parameters and risk of pneumonitis, and that plans should be optimized as carefully as possible given a patient's underlying anatomy and disease. A higher lung or heart DVH may be permissible in a patient with aggressive locoregional disease for whom radiation is essential to long-term disease control and survival.

INCORPORATION OF POSTMASTECTOMY RADIATION AND BREAST RECONSTRUCTION

Advances in breast reconstruction have significantly improved the quality of life for many patients who undergo mastectomy. However, when considering breast reconstruction, it is critical that surgical oncologists, plastic surgeons, and radiation oncologists work together to coordinate PMRT and reconstruction. This is because radiation often affects the cosmetic outcome of reconstruction and reconstruction can adversely affect the optimal design of radiation fields.

One important consideration is the timing of breast reconstruction. Immediate breast reconstruction has the advantage of permitting a skin-sparing mastectomy, which can preserve the native scaffolding of the breast contour and enhance the final cosmetic outcome. However, skin-sparing mastectomy may be contraindicated for some cases of locally advanced disease, such as inflammatory breast cancer or locally advanced disease involving the skin, where skin that might be spared during a skin-sparing mastectomy is at risk of harboring disease. Moreover, radiation treatments of a reconstructed breast have been shown by numerous authors to adversely affect the cosmetic outcome. A series from M. D. Anderson Cancer Center reported a 42% rate of implant failures when treated with PMRT compared to a 10% failure rate in patients who did not require PMRT.[74] Another series noted a 5-year complication rate of 27% in patients who had their tissue expanders or implants irradiated.[75] These complication rates are higher with longer follow-up times. Radiation also has adverse effects on autologous tissue reconstruction. In a series of 41 patients who underwent an immediate TRAM flap reconstruction and then received radiation, 78% experienced a volume loss, 56% had firmness within their flap, and 24% required an additional flap.[76]

Immediate reconstruction can also affect radiation field design. An interesting study evaluated PMRT fields in a cohort of 106 patients who had undergone immediate reconstruction and compared the field design to a matched control set of patients without a reconstruction at the time of treatment.[77]

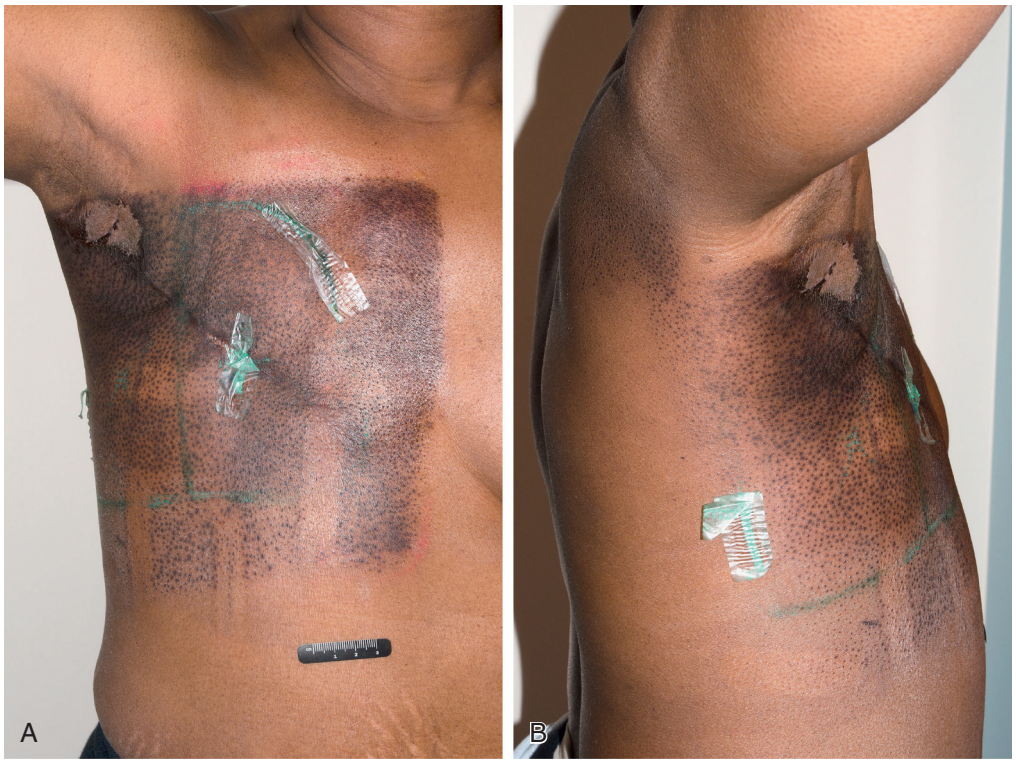


Figure 64-6 Anteroposterior **(A)** and lateral **(B)** views of a patient at the completion of 60 Gy in 30 fractions for a locally advanced breast cancer (50 Gy in 25 fractions using photon-electron technique to the chest wall and undissected nodal basins followed by 10 Gy in 5 fractions of an appositional electron boost using medial and lateral electron fields). The borders for her electron boost fields are outlined in green. This patient developed a grade 2 dermatitis with brisk erythema and hyperpigmentation that were essentially confluent across the chest wall and centered in follicles. There was no moist reaction. For patients with locally advanced breast cancer, this degree of skin reaction is appropriate. Care should be taken not to exceed this amount of skin reaction, thereby avoiding need for a treatment break before reaching the prescription dose.

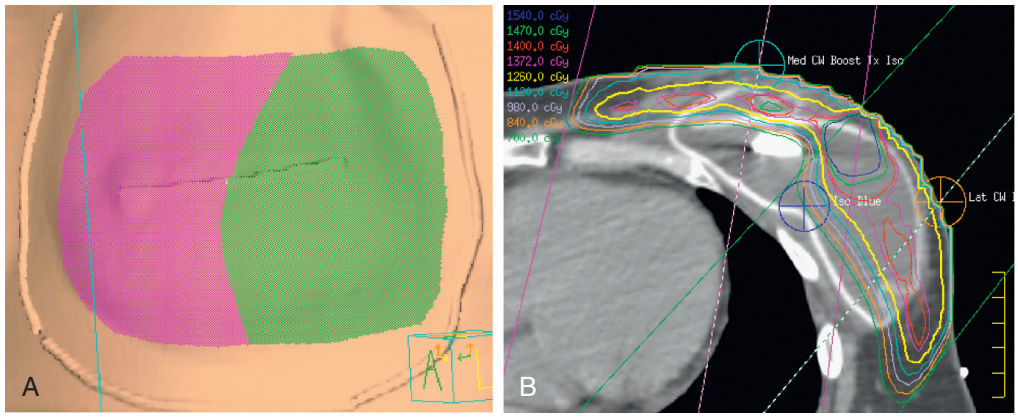


Figure 64-7 The chest wall boost fields used for the patient in Figure 64-5. The medial electron field was 6 MeV and the lateral was 12 MeV. She has a close (<2 mm) deep margin in the upper outer quadrant, so a higher energy for the lateral electron field was selected to ensure deeper coverage. The dose was 14 Gy in 7 fractions. Boost treatment was delivered in free breathing as breath-hold did not confer any additional benefit. Panel A shows the skin rendering, illustrating that the boost fields were designed to cover the skin flaps overlying the tissue expander. Panel B shows the axial dose distribution, with the 90% isodose line shown in yellow.

The authors reported that in 52% of the reconstruction cohort, a compromise had to be made in the treatment planning process compared to only a 7% rate for the control group. These compromises included inferior coverage of the chest wall, increased volume of lung or heart included in the radiation field, or inability to cover the internal mammary lymph nodes.

Accordingly, some patients with locally advanced disease may be best served by having a delayed reconstruction. Following radiation of the chest wall, it is often difficult if not impossible to undergo tissue expansion and placement of an implant such that most patients who undergo a delayed reconstruction require an autologous tissue flap. For selected cases that are candidates for a skin-sparing mastectomy, one can also considered a delayed-immediate reconstruction. In this procedure, a skin-sparing mastectomy is performed with placement of a tissue expander. The expander is inflated in the postoperative period but then partially deflated just before simulation to allow for optimal geometric design of the fields. After the acute skin reaction subsides, the expander

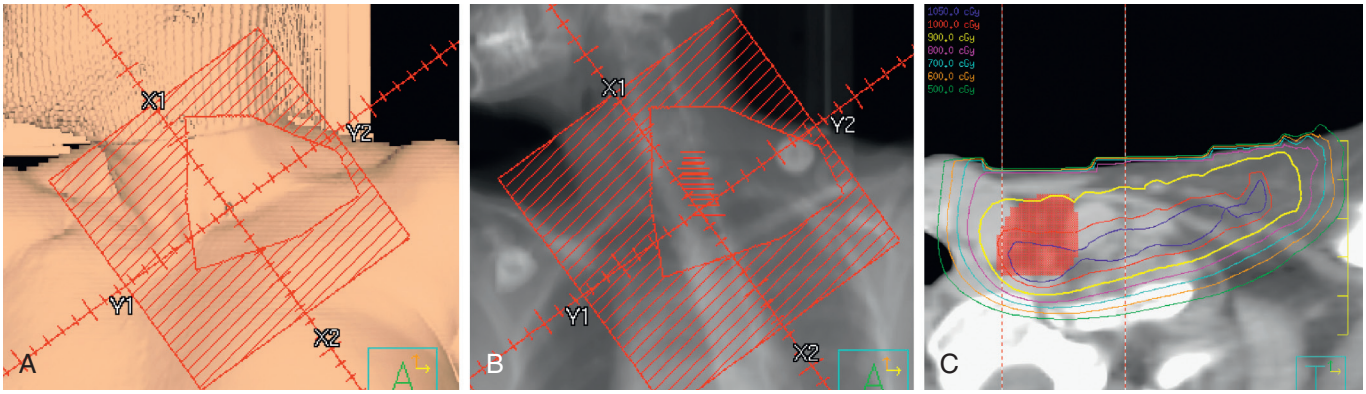


Figure 64-8 This patient had an ER+, HER2/neu-amplified left breast cancer, clinical stage T2 N3c, with biopsy-proven ipsilateral axillary and supraclavicular adenopathy. Her supraclavicular adenopathy was not palpable but was visualized on ultrasound. She responded to neoadjuvant chemotherapy and never had any cross-sectional imaging to document the precise location of initial involvement of the supraclavicular basin. She received a supraclavicular boost of 10 Gy in five fractions which resulted in long-term disease control and no major toxicity to the neck, although she did develop upper extremity lymphedema. Panel **A** shows the skin rendering for the supraclavicular boost field, Panel **B** the digitally reconstructed radiograph, and Panel **C** the axial dose distribution. The red contour is the medial supraclavicular nodal basin which was contoured to assist in treatment planning. The patient was treated in the open neck position with an aquaplast mask to unfold skin folds and improve coverage of the lateral low neck.

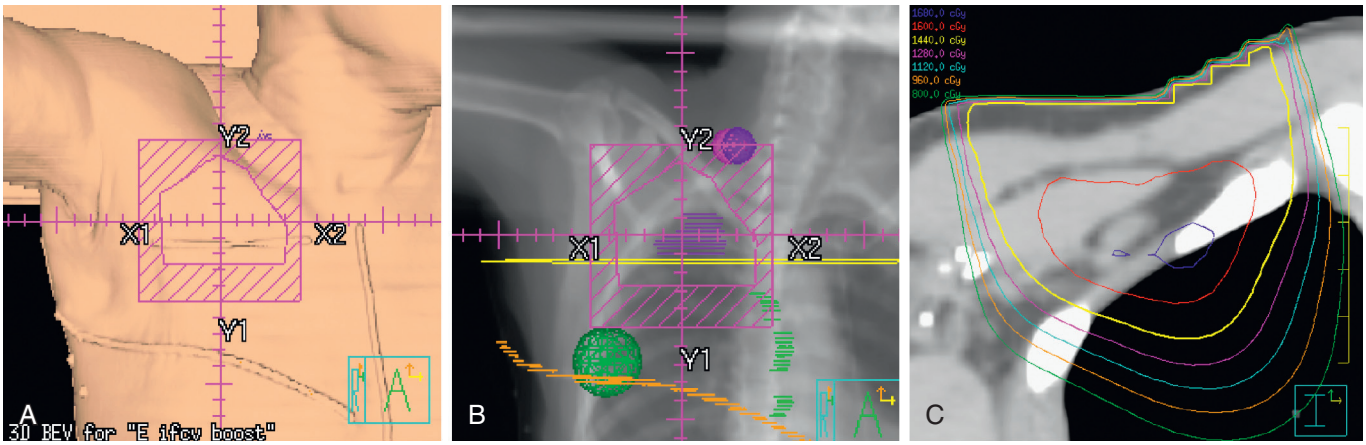


Figure 64-9 This is a patient with biopsy-proven infraclavicular and level II axillary disease that was treated with neoadjuvant chemotherapy and modified radical mastectomy. However, her level II lymph node was not resected at the time of modified radical mastectomy and remained grossly involved based on postoperative ultrasound. A dose of 16 Gy in eight fractions was delivered as an "infraclavicular" boost to encompass the levels II and III axillary nodal basins. (It should be noted that the terms *level III axilla* and *infraclavicular* are used synonymously in this chapter.) Panel **A** shows the skin rendering for the infraclavicular boost field, Panel **B** the digitally reconstructed radiograph, and Panel **C** the axial dose distribution. The yellow isodose line is the 90% isodose line; 16-MeV electrons were used to ensure that the 90% isodose line covered the involved level II axillary node. Note that the involved level II axillary node can be seen deep to the pectoralis minor on Panel **B**. It is important to carefully evaluate the postoperative anatomy at the time of simulation for any residual lymph nodes that may be involved. Postoperative ultrasound can be helpful to establish pathologic involvement and facilitate biopsy if indicated. When in doubt, integrating a boost confers relatively little morbidity and can help to eradicate residual macroscopic disease. For example, this patient's lymph node completely responded to her radiation and assumed a benign appearance within 3 months of completing radiation.

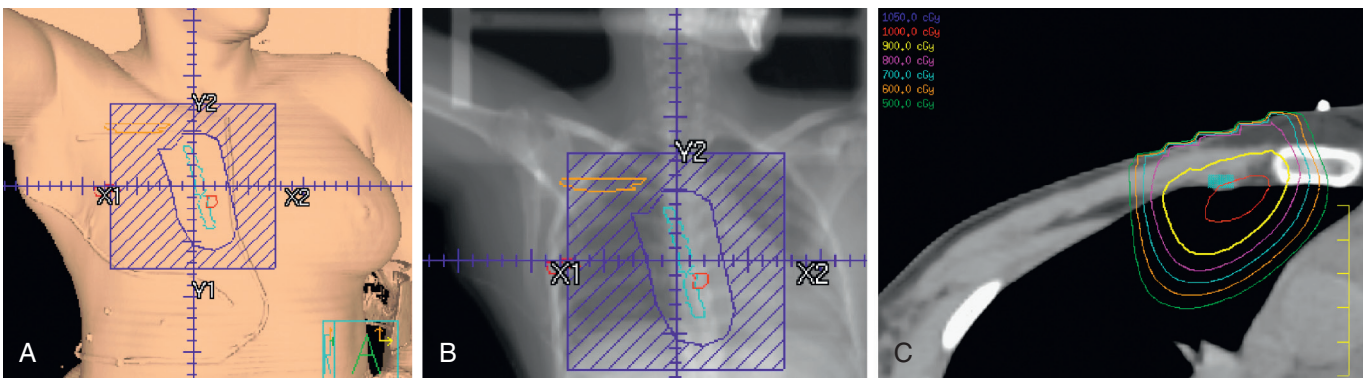


Figure 64-10 This is the internal mammary boost field used for the patient with T4c disease shown in Figure 64-2. She initially had involvement of a lymph node in the third internal mammary interspace, but this completely resolved during neoadjuvant chemotherapy based on serial ultrasound. Panel **A** shows the skin rendering for the internal mammary boost field, Panel B the digitally reconstructed radiograph, and Panel **C** the axial dose distribution. The red wireframe structure in Panel **B** is the area where the node was initially located, and the green indicates the internal mammary nodal chain in the first three interspaces. The prescription dose is 10 Gy in five fractions, but we attempt to cover the contoured target with the 90% isodose line, shown in yellow in Panel C. Seven-MeV electrons were used. Of note, this patient also required an infraclavicular boost, so the superolateral margin of the internal mammary boost field is modified to prevent overlap with the infraclavicular nodal field.

may be reinflated and, ultimately, replaced with an autologous tissue flap. Early results using this approach have been promising.[78]

OUTCOME

The routine use of chemotherapy and hormonal therapy has significantly improved the outcomes for patients with stage III breast cancer. Before the use of systemic treatments, few patients survived 10 years after surgery or radiation therapy.[1-3] In comparison, 67% of patients with stage IIB or IIIA disease and 33% of patients with stage IIIB/C disease survive 10 years if treated with anthracycline chemotherapy, surgery, radiation therapy, and hormonal treatments.[4] For patients with locally advanced breast cancer diagnosed in the early 2000s, SEER data indicate that 5-year survival is approximately 70%.

Multimodality treatment has also been able to improve long-term locoregional recurrence rates. For patients treated with chemotherapy, appropriate surgery, and endocrine therapy when indicated, combined with high quality radiation therapy planned in the three-dimensional era, 5-year locoregional recurrence risk is less than 5%.[67,79]

The subgroup of patients with locally advanced breast cancer who respond poorly to initial neoadjuvant chemotherapy remains a therapeutic challenge. It is clear that patients with a significant volume of residual primary disease or four or more lymph nodes after neoadjuvant chemotherapy have a poor prognosis, with disease-free survival rates of only 25% and locoregional recurrence rates as high as 25%.[67] New therapeutic approaches are needed for this cohort.

INFLAMMATORY BREAST CANCER

Inflammatory breast cancer is a unique and aggressive subgroup of locally advanced breast cancer manifested by rapid disease onset and the clinical findings of skin erythema, edema (peau d'orange), breast induration, warmth, and asymmetric enlargement. Typically, there is extensive lymphovascular invasion by tumor emboli that involve the superficial dermal plexus of vessels in the papillary and high-reticular dermis.

Inflammatory breast cancer comprises 1% to 6% of primary breast cancers.[80] There are no randomized prospective clinical trials that have specifically evaluated treatments in patients with inflammatory breast cancer. M. D. Anderson has one of the largest single-institution experiences in the treatment of inflammatory breast cancer, with a multidisciplinary clinic dedicated to the management of this disease. For patients managed in this multidisciplinary clinic who typically received both anthracycline- and taxane-based chemotherapy and HER2/neu-directed agents when indicated, 3-year overall survival was 82%, compared with 63% for patients treated in a previous era.[81] This finding underscores the importance of aggressive polychemotherapy, targeted therapy, and coordinated, multidisciplinary care to optimize outcomes for patients with inflammatory breast cancer.

The current standard of care for patients with inflammatory breast cancer is initial neoadjuvant chemotherapy followed by mastectomy, if feasible, and PMRT. In our institution, we have used an accelerated radiation schedule, giving patients twice-daily treatments (1.5 Gy twice daily to a total dose of 51 Gy to the chest wall and draining lymphatics, followed by a boost to the chest wall of an additional 15 Gy). In an initial retrospective analysis, this twice-daily schedule to 66 Gy total dose was associated with a locoregional recurrence rate of 16%, which was much lower than the 42% rate during the era when treatment was given to 60 Gy or when once-a-day radiation schedules were used.[72] An update of this experience reported that the majority of patients continued to have a benefit from the higher 66 Gy dose but that this dose was also associated with a 17% rate of grade 3 or greater toxicity. Patients who were older than age 45 and had favorable pathological responses to neoadjvuant chemotherapy and negative surgical margins were found to do equally well with the 60-Gy dose, and as such in this selected cohort the higher toxicity with 66-Gy does not appear to be warranted.[82]

Patients who do not respond favorably to neoadjuvant chemotherapy have a poor prognosis and may require locoregional therapy with preoperative radiation therapy or definitive radiation therapy alone. For patients with inflammatory breast cancer who present with distant metastases, recent data indicate that patients with a major response to chemotherapy who go on to receive mastectomy and PMRT can do relatively well, with 50% 5-year overall survival and 32% 5-year disease-free survival.[83] This finding suggests that aggressive local therapy may specifically benefit patients with metastatic inflammatory breast cancer provided they experience a major response to chemotherapy; further research is indicated to corroborate these findings.

TREATMENT ALGORITHMS

Figures 64-11 and 64-12 show treatment algorithms for patients with locally advanced breast cancer and patients with inflammatory breast cancer, respectively.

NEW THERAPEUTIC APPROACHES

The current era is arguably the most exciting in the history of breast cancer therapeutics. Development of novel therapies that target the estrogen receptor pathway and the HER2/neu pathway has already revolutionized treatment, and additional active agents seem to appear on an almost yearly basis. Given the demonstrated synergy between radiation and systemic therapy with regard to improving survival outcomes, it is likely that the introduction of newer agents may actually increase the survival benefit conferred by radiation.

Triple-negative, chemotherapy-refractory locally advanced breast cancer remains an area of considerable therapeutic challenge. Platinum agents have shown activity in triple-negative breast cancer and may begin to play an increasingly important role for this subtype.[84] In addition, for patients with either unresectable disease or those at high risk for locoregional recurrence after resection, it is possible that concurrent chemoradiation may become an important component of therapy. At present, data are limited but experiences exist to support consideration of concurrent taxane- or platinum-based chemoradiation.[85-87] Our own experience with concurrent capecitabine and radiation has shown mixed results, with some long-term control in patients who are estrogen receptor–positive, but uniformly poor outcomes for triple-negative disease.

Finally, technological advances in radiation therapy continue to influence how breast cancer radiation is delivered and planned. Many centers are increasingly using intensity-modulated radiation therapy or arc-based therapy, yet the long-term implications of low dose radiation exposure to the entire thorax remain an area of active debate.[88] The increasing dissemination of proton therapy may also influence treatment approaches to locally advanced breast cancer, particularly in patients with unfavorable anatomy for standard approaches or with extensive disease extending into the mediastinum (Figure 64-13). Given the prevalence of breast cancer and the societal imperative to control growth in healthcare spending, there will likely be growing pressures to develop and embrace effective yet economical radiation treatment strategies for locally advanced breast cancer.

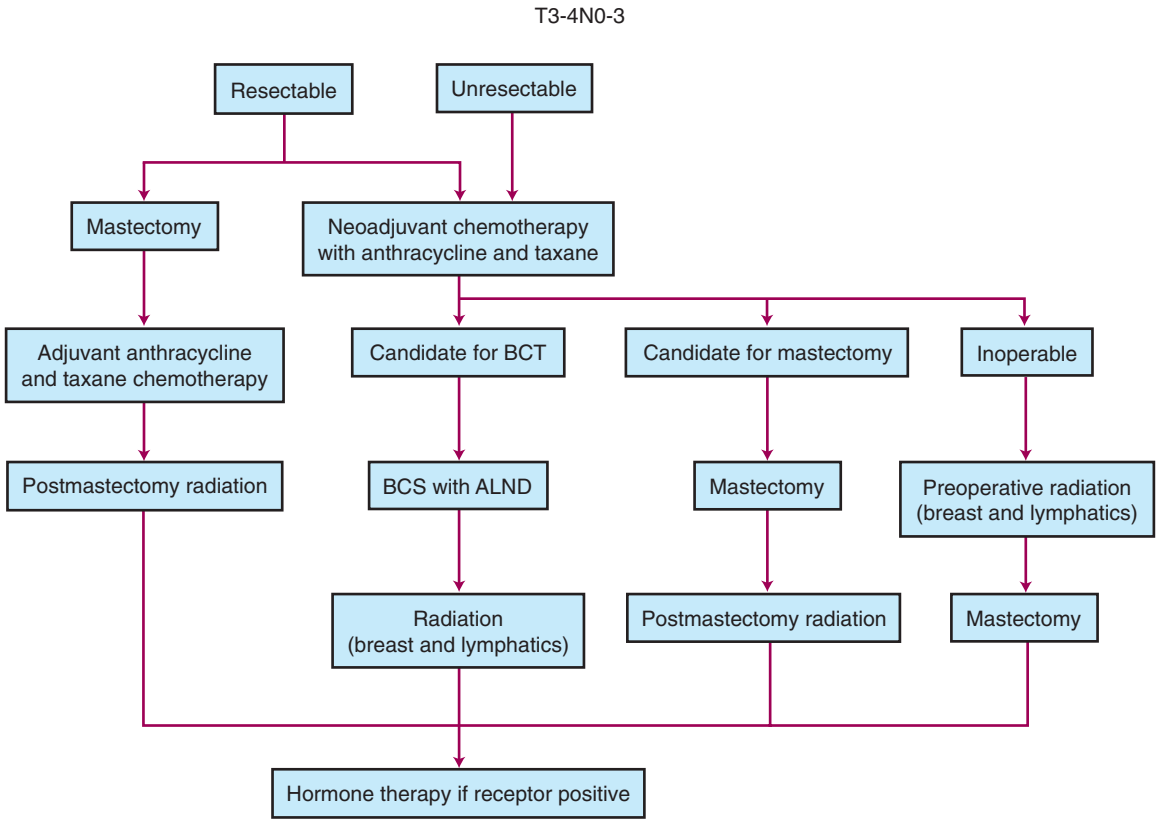


Figure 64-11 **A treatment algorithm for patients with locally advanced breast cancer.** *ALND,* Axillary lymph node dissection; *BCT,* breast-conserving therapy.

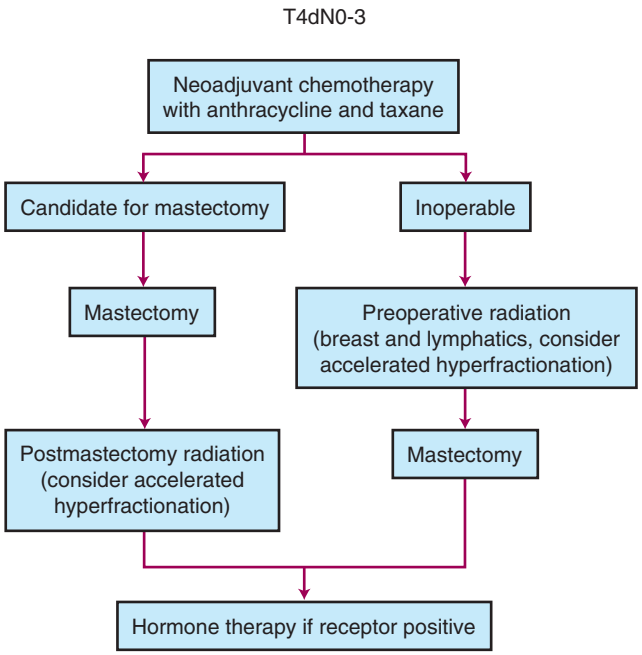


Figure 64-12 **A treatment algorithm for patients with inflammatory breast cancer.**

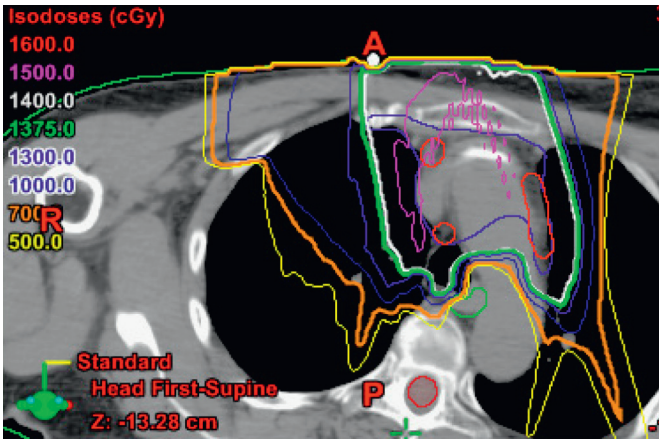


Figure 64-13 This patient had triple negative inflammatory breast cancer; her initial positron emission tomography–computed tomography (PET-CT) is shown in Figure 64-2, **A-B**. She experienced a major clinical response to neoadjuvant chemotherapy and underwent modified radical mastectomy showing minimal residual disease. She received postmastectomy radiation therapy with a photon field directed to her involved mediastinal nodes for the first 51 Gy delivered at 1.5 Gy twice a day. She then received a proton boost as shown in this figure to the supraclavicular, infraclavicular, internal mammary, and anterior mediastinal nodal basins. A dose of 14.4 Gy in eight fractions delivered once daily was used. She did well with no major pulmonary or cardiac toxicity and remains alive without evidence of recurrence several years after completing radiation.

CONCLUSIONS

Radiation therapy plays a vital role in the management of locally advanced breast cancer, synergizing with optimal surgery, and systemic therapies to optimize long-term locoregional control and survival. Thoughtful multidisciplinary integration of radiation with the other members of the breast cancer multidisciplinary team is vitally important to optimize cure rates and patient quality of life after treatment. Future improvements in biologic understand of breast cancer and systemic treatments should synergize with radiation to further improve outcomes for patients with locally advanced breast cancer.

CRITICAL REFERENCES



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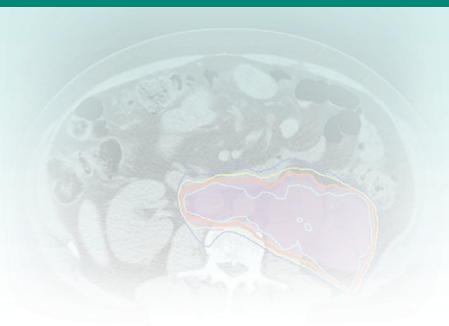
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CHAPTER 65

Soft-Tissue Sarcoma



Kaled M. Alektiar

EPIDEMIOLOGY AND PATHOLOGY

Soft-tissue sarcomas (STS) account for approximately 1% of adult cancers in the United States. The estimated number of newly diagnosed cases in the year 2014 was projected to be 12,020, with a slightly higher male-to-female ratio and 4,740 deaths. The peak incidence of STS is the fifth decade of life, but histology such as rhabdomyosarcoma has a peak incidence in the first decade of life. The most common site is the extremity (40%) followed by visceral (22%), retroperitoneal and intraabdominal (16%), trunk (10%), and other (12%). There are about 50 histologic types of STS, the most common being liposarcoma, undifferentiated pleomorphic sarcoma and myxofibrosarcoma, synovial sarcoma, and leiomyosarcoma. About 65% of STS are high grade and 35% are low grade.

BIOLOGIC CHARACTERISTICS

About 30% of STS have signature translocations, such as *SS18-SSX1* or *SS18-SSX2* in synovial sarcoma or t(12;16) in myxoid liposarcoma. Other sarcomas have oncogenic mutation such as *KIT* in gastrointestinal stromal tumor (GIST). The large majority of STS exhibit more complex genomic patterns. These molecular studies are having a significant impact on our understanding of the pathogenesis of STS and are providing more refined tools for classifying these tumors.

STAGING EVALUATION

Lesion size, mobility, relationship to the investing fascia, and adjacent neurovascular structures or bone are important parts of the tumor assessment. All soft-tissue masses deep to the fascia should be considered sarcoma until proven otherwise. Histologic confirmation, typically with core biopsy, is necessary. For extremity STS, imaging includes magnetic resonance imaging (MRI) of the extremity and chest computed tomography (CT). In patients with low-grade and small lesions, a plain chest radiograph may be sufficient. Imaging of the spine is important in patients with myxoid liposarcoma. For intraabdominal STS, CT chest, abdomen, and pelvis is preferred for assessment of the primary tumor as well as potential spread to lung, peritoneum, or liver. Major prognostic factors are pathologic grade, tumor size, and depth of involvement. These factors, combined with the presence of nodal involvement (rare except in certain histologic subtypes), and distant metastases, comprise the TNM stage classification.

PRIMARY THERAPY

Surgery is the main treatment for all STS. The role of adjuvant radiation therapy (RT) is well-established in extremity STS. One randomized trial showed that when RT was added to limb-sparing surgery, the results were equivalent to amputation in terms of survival. Two other trials showed that adjuvant RT significantly improved local control in the setting of limb-sparing surgery. RT is mainly external beam radiation therapy (EBRT) either preoperatively or postoperatively. A randomized trial comparing the two sequences showed significantly higher rate of wound complication with preoperative EBRT, but fewer long-term complications. Typical dose for preoperative EBRT is 50 Gy at 2 Gy per fraction, and for postoperative EBRT, 63 Gy at 1.8 Gy. Clinical target volume (CTV) is generated by expanding gross tumor volume and tumor bed by 4 cm longitudinally and 1 cm axially (except near bone, where no margin is added). The role of adjuvant chemotherapy remains controversial. For nonextremity sites, the role of adjuvant RT is less clear, and treatment recommendations need to be individualized.

PALLIATION

The main treatment for most metastatic STS is chemotherapy. Combination doxorubicin and ifosfamide provide higher rate of response than doxorubicin alone but without significant impact on survival and with higher toxicity rate. Treatment should be individualized; synovial sarcomas tend to respond better to combination chemotherapy, angiosarcomas to paclitaxel, and leiomyosarcomas to gemcitabine and docetaxel. Resection of lung metastasis is appropriate in patients with good performance status and limited extent of metastatic disease. There is an emerging role for stereotactic body radiation therapy (SBRT) in the treatment of lung or spinal metastasis.

STS account for approximately 1% of adult cancers in the United States. The number of newly diagnosed cases in year 2014 was projected to be 12,020, with a slightly higher male-to-female ratio; 6550 in males and 5470 in females. The estimated number of deaths was 4740.[1] These tumors can arise from any part of the body and can affect all age groups. Based on 10,000 cases of STS from Memorial Sloan Kettering Cancer Center (MSKCC), the most common site is the extremity (40%) followed by visceral (22%), retroperitoneal and intraabdominal (16%), trunk (10%), and other (12%). In general, the peak incidence of STS is the fifth decade of life, but histology such as rhabdomyosarcoma, tends to occur in young patients where

the peak incidence is in the first decade of life. About 65% of STS are high grade and 35% are low grade. Tumor size distribution is as follows: large (≥10 cm) in 38% of patients, medium in 31%, and small (≤5 cm) in 31%. Depth (with respect to the superficial fascia) is considered deep in 87% of cases and superficial in 13%. The three most-common histologic types are liposarcomas, undifferentiated pleomorphic sarcomas (previously known as malignant fibrous histiocytoma), and leiomyosarcomas.

The predominant form of relapse for STS is distant, mainly to lungs for extremity STS, and lung and liver for retroperitoneal and intraabdominal as well as visceral STS. In retroperitoneal and intraabdominal STS, local recurrence (LR) is more common than distant recurrence, whereas the opposite is true for extremity and visceral STS. Extremity and trunk STS have the highest rate of survival, about 60% disease-specific survival at 10 years, whereas retroperitoneal and visceral have the lowest, 40% at 10 years.

ETIOLOGY AND EPIDEMIOLOGY

Environmental Factors

The majority of STS develop without having clear predisposing factors. In some patients environmental, immunologic, and familial factors have been reported. Among environmental factors, exposure to radiation is one of the most commonly cited risk factors. The exact mechanism of radiation-associated sarcomas is not clear. It is possible that the genetic defect that may have led to the development of the first cancer for which RT was administered, may in turn, have led to the induction of the RT-associated sarcoma.[2] An example is the risk of secondary cancers in hereditary as opposed to nonhereditary retinoblastoma. In a study of 1604 patients with retinoblastoma who survived at least 1 year after diagnosis, the cumulative incidence of a second cancer at 50 years after diagnosis was 51% for hereditary retinoblastoma and 5% for nonhereditary retinoblastoma. The conclusion from this study was that genetic predisposition has a substantial impact on risk of subsequent cancers in patients with retinoblastoma.[3] The incidence of radiation-associated STS is not well established because in part of a long latency period. In a study from Finland of 295,712 patients with cancer treated with radiation and/or chemotherapy, 147 sarcomas were found compared with 88.5 expected. STS comprised 86% of the sarcomas. At 10 years of follow-up, the cumulative incidence of sarcoma was 0.03% (95% confidence interval [CI], 0.017% to 0.037%) among patients who received radiotherapy and 0.02% (95% CI 0.017% to 0.032%) among patients who did not receive radiotherapy.[4] The prognosis of RT-associated STS is significantly worse than sporadic STS independent of histologic type.[5]

The exposure to chemical carcinogens, including Thorotrast, vinyl chloride, and arsenic, have been linked to hepatic angiosarcomas. Workers exposed to phenoxyherbicides, chlorophenols, and dioxins had higher mortality rates from cancer compared with controls, and the increase was highest for STS.[6-8] There have been conflicting reports about occupational exposure to phenoxyacetic acids detectable in chlorophenols (frequent in wood preservatives) and certain herbicides.[9-12] Trauma is not considered a risk factor for STS; often a minor trauma draws the attention to the lesions. The question of whether the trauma from orthopedic surgery may increase the risk of sarcoma was addressed in a study from the Finnish Arthroplasty Register. A cohort of 24,636 patients with primary osteoarthritis and metal-on-polyethylene total hip arthroplasty who had been entered in the Finnish Arthroplasty Register were assessed for cancer risk. The mean follow-up time was 13 years. The numbers of cancer cases observed were comparable to the incidence in the general population.[13]

Immunologic Factors

Systemic or regional immunologic factors have been linked to STS. For systemic factors, HIV-related Kaposi's sarcoma, which is linked to human herpes virus 8, is well documented. Patients who are immunosuppressed such as patients who have undergone transplants are also at increased risk of smooth muscle tumors that are linked to Epstein-Barr virus. Chronic lymphedema, which could be considered a regional immunodeficiency phenomenon (Stewart-Treves syndrome), has been implicated in the development of lymphangiosarcoma in patients with breast cancer treated with radical mastectomies and axillary lymph node dissection.[14] It is important to note that this sarcoma is not directly linked to radiation exposure because some of these patients did not have radiation and even those who did, many developed their lymphangiosarcoma outside the radiation field.

Hereditary Factors

STS are occasionally associated with inherited genetic conditions. Neurofibromatosis type I is an autosomal dominant disorder with deletion or loss of function of *NF1* on chromosome 17. The product of *NF1* is neurofibromin, which generally suppresses RAS activity. The risk of developing a malignant peripheral nerve sheath tumors in these patients is about 10% over a lifetime.[15] Li-Fraumeni syndrome is another autosomal dominant hereditary cancer syndrome with a spectrum of tumors including breast cancer (most common), sarcomas (second-most common), leukemia, brain tumors, and adrenocortical carcinomas.[16,17] The underlying abnormality is germline deletion of the *p53* suppressor gene. The function of *p53* is to guard the integrity of the genome against DNA-damaging agents or hypoxia. When normal *p53* is activated, it leads to cell cycle arrest at G1 and induction of DNA repair. Gardner's syndrome, a subset of familial adenomatous polyposis, is associated with the development of intraabdominal desmoids.[18] In these patients there is loss of expression of the adenomatous polyposis coli (APC) gene.

PREVENTION AND EARLY DETECTION

General screening for sarcoma in the population at large is problematic given its rarity. Patients at increased risk for sarcoma require a more detailed clinical evaluation at a lower threshold of intervention than one might use in general practice. Deep lesions always require investigation, especially if there is a history of growth, and any superficial or deep abnormality of skin or soft tissues in patients with a history of prior RT requires careful evaluation. Predisposing genetic tendencies should be considered.

Unfortunately, in the clinical management context, the cause of an individual sarcoma is of limited significance because it generally does not affect therapeutic decision making beyond the fact that patients who have sarcomas arising in a previously irradiated field cannot easily receive further RT, and there may be limitations in surgery as well.

BIOLOGIC CHARACTERISTICS AND MOLECULAR BIOLOGY

Considerable progress has been made in the field of molecular genetics of STS. To some extent STS can be divided into two

genomically distinct groups: sarcomas with specific genetic alterations and sarcomas with complex genetic alteration.

Sarcomas with Specific Genetic Alterations

This group includes STS with either a reciprocal chromosomal translocations, which account for 30% of sarcomas (e.g., *SS18-SSX1* or *SS18-SSX2* in synovial sarcoma), or specific-activating mutation (e.g., *KIT* in gastrointestinal stromal tumors). Most translocation-associated sarcomas arise de novo and seem to maintain their simple genetic abnormality throughout their clonal evolution.[19] The karyotypes of these tumors are simple and near diploid. The fusion genes resulting from the translocations can encode abnormal transcriptional proteins, growth factors, or tyrosine kinases. An example of aberrant transcriptional protein is FUS-CHOP protein resulting from t(12;16) in myxoid liposarcoma. The FUS-CHOP oncoprotein regulates transcriptions of adipocytic maturation factors as well as angiogenic and proinflammatory factors. An example of growth factor abnormality, involves upregulation of platelet-derived growth factor-B (PDGFB) when fused with collagen 1 alpha 1 (COL1A1), resulting from t(17;22) as seen in dermatofibrosarcoma protuberans. Oncogenic mutation in *KIT*, and to a lesser extent in platelet-derived growth factor receptor-α (PDGFR-α), is an example of mutation in a driver gene.

Sarcomas with Complex Genetic Alterations

The majority of STS belong to this group. The karyotypes of these sarcomas are complex with a great deal of genomic instability including changes in chromosome number, unbalanced translocations, genetic deletions, and amplifications.[20] Several genes responsible for maintaining the integrity of the genome such as *TP53, NF1, PTEN, CDKN2A, CDKN2b,* and *RB1* are often deleted in these sarcomas. These tumors contain several genomic aberrations in the genome of a single tumor and heterogeneity of aberrations across tumors of a given type.[19] Most of these tumors arise de novo, but a subset show histological progression (e.g., progression of well-differentiated to dedifferentiated liposarcoma) that is accompanied by increasing genetic complexity.

The better understanding of sarcomas at the molecular level is having an impact on our understanding of its pathogenesis, is improving our diagnostic accuracy in a group of tumors known for histological complexity, and is beginning to give us new insights on how to treat some of these tumors. The therapeutic implications and the improved classifications of sarcomas will be discussed later in the chapter.

Molecular pathogenesis of sarcomas can be viewed in three broad categories. Transcriptional target dysregulation results from abnormal fusion proteins in translocation-associated STS. Mutations in key genes and signaling pathways constitute another mechanism in sarcomagenesis. As mentioned previously, oncogenic mutation in *KIT* or in PDGFR-α is an example of mutation in a driver gene. Most sarcomas, however, including those that are translocation-associated, do not have a well-defined driver mutation. Some of the common mutations in signaling pathways include *TP53, NF1,* and *PI3K*. *TP53* mutations are seen in about 17% of pleomorphic liposarcomas, *PI3K* mutations in 18% to 20% of myxoid and round cell liposarcomas, and *NFI* in 8% to 11% of myxofibrosarcomas and pleomorphic liposarcomas. A DNA copy number alteration is the third mechanism in sarcoma pathogenesis. This is the hallmark for sarcomas with complex genetic alterations. However, even within this group, the complexity varies, with some sarcomas being moderately complex as seen in some dedifferentiated liposarcoma (Figure 65-1).

PATHOLOGY AND PATHWAYS OF SPREAD

Pathology Classification

Pathologic classification of STS is challenging. There are about 50 histologic types of STS. Traditional approaches relied heavily on trying to match the morphology of STS with what is thought to be the soft tissue of origin of the sarcoma. Such an approach has its limitations, for example, synovial sarcomas do not arise from the synovium per se. Malignant fibrous histiocytoma (MFH), considered one of the most common histologies, was thought to derive from histiocytes. Not only was that derivation unfounded, the term *MFH* itself is questionable because on reexamination many of these tumors could be classified along other lineages.[21]

The current emphasis in pathologic classification of STS is more on the line of differentiation of the tumor, such as adipocytic (e.g., liposarcomas), fibroblastic and myofibroblastic (myxofibrosarcoma), smooth muscles (leiomyosarcoma), skeletal muscles (rhabdomyosarcomas), nerve sheath (malignant nerve sheath tumors), undifferentiated (undifferentiated pleomorphic sarcoma), and uncertain differentiation (synovial sarcoma). Light microscopic examination plays a significant role in assigning histologic type and grade.

Grading of STS is critical; in fact, the staging system is primarily driven by it. There are several grading systems in use: at MSKCC a two-tier system is used (high versus low), the American Joint Committee on Cancer (AJCC) staging system uses a three-tier system (grades 1, 2, and 3). Irrespective of the system, grade is highly predictive of outcome, in terms of LR, distant spread, and survival. These different grading systems rely, to a varying degree, on tumor differentiation, mitosis, degree of necrosis, and histologic subtypes. No grading system is perfect; at MSKCC the two-tier system is preferred because of its simplicity. Low grade is equivalent to grade 1 in the three-tier system, and high grade is equivalent to grade 2 or 3.

In addition to morphology, there has been a great emphasis on using immunohistochemistry to better assign a line of differentiation. Some of the common markers used to determine line of differentiation include desmin, vimentin, cytokeratin, and S-100 to name a few. Newer markers are being used to detect specific molecular aberrations such as MDM2/CDK4 amplification in well-differentiated and dedifferentiated liposarcomas to separate them from benign lipomatous tumors. Perhaps the biggest improvement in STS classification has been through molecular testing. For example, signature translocations such as t(X; 18) is diagnostic for synovial sarcomas. STS rank second to hematological malignancies in the number of signature translocations (Table 65-1). The molecular tests used to detect a translocation generally include reverse transcriptase-polymerase chain reaction (RT-PCR), and fluorescence in situ hybridization (FISH). The 2013 World Health Organization (WHO) classification of soft-tissue tumors relies on morphology, immunohistochemistry, and genetic features[22] (Box 65-1).

Selected Pathologic Subtypes

Liposarcoma

Liposarcoma is the most common histology when all sites are considered. In the 2013 WHO classification, there are four subtypes of liposarcoma: myxoid, dedifferentiated, pleomorphic, and not otherwise specified. Atypical lipomatous tumor and well-differentiated liposarcoma are considered intermediate (locally aggressive) in the WHO classification. Most well-differentiated liposarcomas (WDL) occur in the fifth to seventh decades of life. Extremity is the most common location (about 75%) followed by retroperitoneum. These low-grade tumors

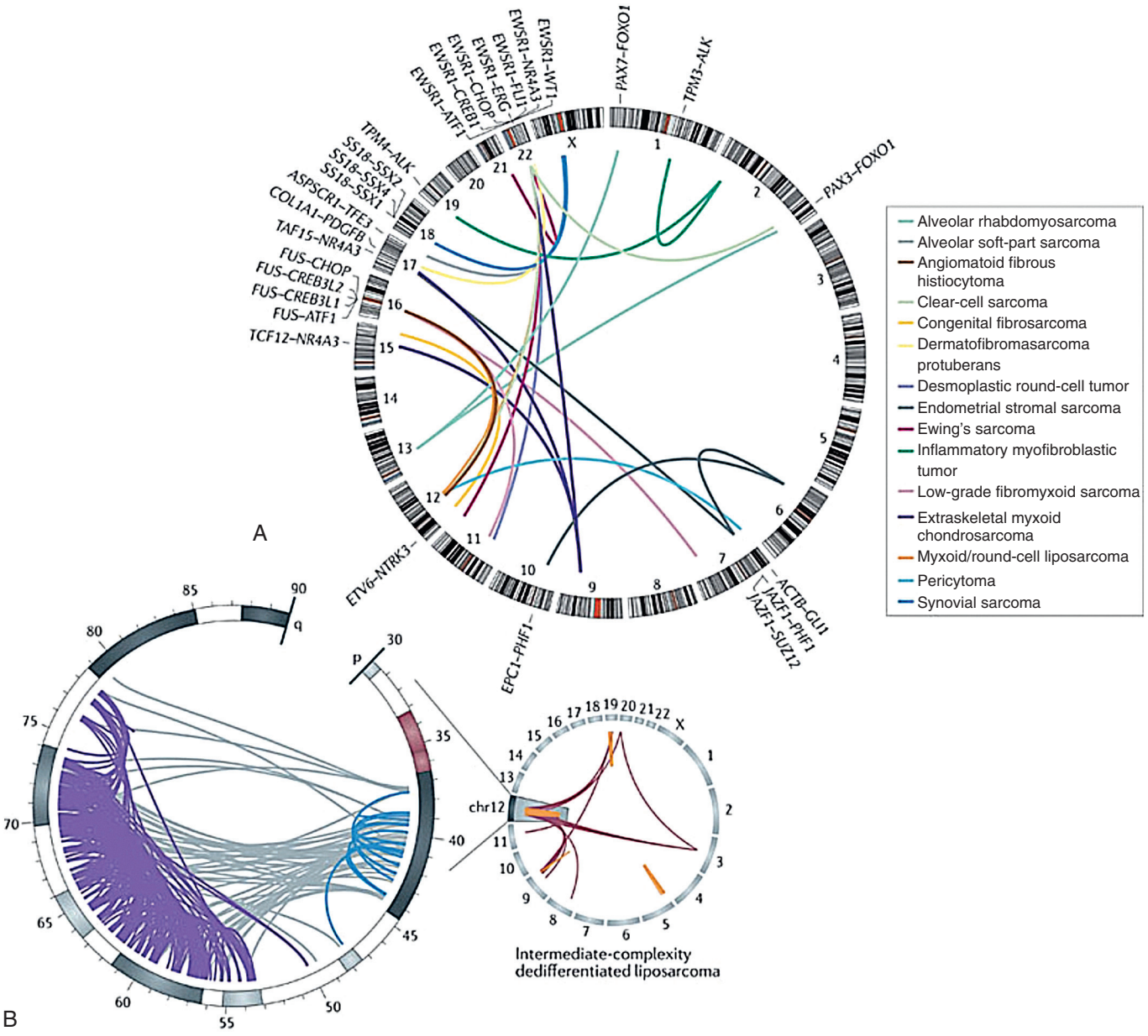


Figure 65-1 The structure of sarcoma genomes. **A,** Common translocations in soft-tissue sarcomas. The ring represents the whole genome from chromosome 1 to 22 as well as *X* chromosome. Example, translocation between chromosome 18 and chromosome X in synovial sarcomas. **B,** The right panel shows somatic structure of an intermediate-genomically complex sarcoma, a dedifferentiated liposarcoma. There are interchromosomal rearrangements shown in dark red and intrachromosomal rearrangements are shown in orange. The left panel shows the pathognomonic chromosome 12q amplifications in greater detail.
From Taylor BS, Barretina J, Maki RG, et al: Advances in sarcoma genomics and new therapeutic targets. Nat Rev Cancer 11(8):541–557, 2011. With permission.

tend to have an indolent course with low risk for distant recurrence irrespective of site. Extremity WDL can recur locally, but the risk is relatively low to justify routine use of adjuvant RT, especially in the primary setting. In contrast, WDL in the retroperitoneum tends to recur often.

Myxoid liposarcoma has a signature translocation[19,20] at t(12:16) in 90% of cases and t(12;22) in less than 5%. They are predominantly seen in extremity sites (most common liposarcoma in extremity) and affect younger patients usually in the third to fourth decades of life. The term *round cell* is no longer used in association with myxoid liposarcoma based on the 2013 WHO classification; these tumors are graded to reflect the spectrum of their behavior. Recognizing myxoid liposarcoma has significant clinical implications for radiation oncologists because these tumors are exquisitely radiosensitive[23,24] (Figure 65-2). In addition they tend to metastasize to unusual sites for STS, such as the spine.[25]

Dedifferentiated liposarcomas are often seen in the retroperitoneum (75%), but other sites include spermatic cord, trunk, and head and neck. It commonly affects older patients and on imaging, the tumors can have a mixture of solid masses (similar to other STS), mixed with areas of "fatty-looking"

tissues. Microscopically this is represented by a mixture of WDL and dedifferentiated liposarcomas.

Pleomorphic liposarcomas are the least common liposarcomas. They can arise in an extremity or the retroperitoneum. They are high-grade lesions with aggressive behavior. At MSKCC, a nomogram has been developed to predict the outcome of liposarcoma across different sites.[26]

TABLE 65-1 Translocation-Associated in Selected Soft-Tissue Sarcoma

Histologic Subtype	Translocations	Genes Involved
Alveolar sarcoma of soft parts	t(X;17)(p11;q25)	*TFE3-ASPL*
Clear cell sarcoma	t(12;22)(q13;q12)	*EWSR1-ATF1*
Desmoplastic small round cell tumor	t(11;22)(p13;q12)	*EWSR1-WT1*
Ewing's	t(11;22)(q24;q12) t(21;22)(q22;q12)	*EWSR1-FLI1* *EWSR1-ERG*
Myxoid liposarcoma	t(12;16)(q13;p11) t(12;22)(q13;q12)	*FUS-DDIT3* *EWSR1-DDIT3*
Rhabdomyosarcoma (alveolar)	t(2;13)(q35;q14) t(1;13)(p36,q14)	*PAX3-FOXO1* *PAX7-FOXO1*
Synovial sarcoma	t(X;18)(p11;q11) t(X;18)(p11;q11)	*SS18-SSX1* *SS18-SSX2*

Undifferentiated Pleomorphic Sarcoma

MFH used to be the most common type of STS. Several studies, however, have shown that many of such pleomorphic tumors, using immunohistochemistry and other ancillary studies, could be assigned a line of differentiation, such as liposarcomas, leiomyosarcomas, and rhabdomyosarcomas.[21] The 2013 WHO classification does not recognize MFH as an entity; instead many such tumors now belong to a category called *undifferentiated/unclassified sarcomas*. Within this new category there are several subtypes: pleomorphic, spindle, round cell, epithelioid, and not otherwise specified.

Undifferentiated pleomorphic sarcomas (UPS) generally affect older patients typically in the sixth and seventh decades of life. Most patients present with deep lesions in the extremity, especially thigh. Retroperitoneal location is not common; pleomorphic sarcoma morphology in this location is more likely to be dedifferentiated liposarcoma. These tumors are high grade and exhibit complex genetic alterations. The natural history is extraordinarily variable, reflecting the heterogeneity of these lesions. The most common site for metastases from pleomorphic sarcomas is the lung (90%), bone (8%), and liver (1%), with rare regional lymph node metastases.[27]

Myxofibrosarcoma

These tumors used to be considered a subtype of MFH, myxoid MFH. In the WHO classification, myxofibrosarcoma is recognized as its own entity, belonging to the fibroblastic and myofibroblastic tumors category. Myxofibrosarcoma often arise in

BOX 65-1 Histologic Classification of Soft-Tissue Sarcoma (Selected Histologies)

FIBROBLASTIC AND MYOFIBROBLASTIC TUMORS

Intermediate (Locally Aggressive)

Desmoids-type fibromatoses.
Intermediate (rarely metastasing)
Dermatofibrosarcoma protruberans
Solitary fibrous tumor

Malignant

Adult fibrosarcoma
Myxofibrosarcoma
Low grade fibromyxoid sarcoma
Sclerosing epithelioid fibrosarcoma

ADIPOCYTIC TUMORS

Intermediate (Locally Aggressive)

Atypical lipomatous tumor
Well-differentiated liposarcoma

Malignant

Myxoid liposarcoma
Dedifferentiated liposarcoma
Pleomorphic liposarcoma
Liposarcoma–not otherwise specified

SMOOTH MUSCLE TUMORS

Leiomyosarcoma

SKELETAL MUSCLE TUMORS

Malignant
Rhabdomyosarcoma
Embryonal rhabdomyosarcoma
Alveolar rhabdomyosarcoma
Pleomorphic rhabdomyosarcoma
Spindle cell and sclerosing rhabdomyosarcoma

VASCULAR TUMORS

Epithelioid hemangioendothelioma
Angiosarcoma of soft tissue
Kaposi's sarcoma

PERIVASCULAR TUMORS

Malignant glomus tumors

NERVE SHEATH TUMORS

Malignant peripheral nerve sheath tumor (MPNST)
Malignant triton tumor
Glandular MPNST
Epithelioid MPNST
Malignant granular cell tumor

TUMORS OF UNCERTAIN DIFFERENTIATION

Alveolar soft part sarcoma
Clear cell sarcoma
Epithelioid sarcoma
Desmoplastic small cell tumor
Extra-skeletal Ewing's sarcoma
Extra-skeletal myxoid chondrosarcoma
Neoplasms with perivascular epithelioid cell differentiation (PEComa)
Synovial sarcoma

UNDIFFERENTIATED/UNCLASSIFIED SARCOMAS

Undifferentiated pleomorphic sarcoma (UPS)
Undifferentiated spindle cell sarcoma
Undifferentiated round cell sarcoma
Undifferentiated epithelioid sarcoma
Undifferentiated sarcoma–not otherwise specified

GASTROINTESTINAL STROMAL TUMORS

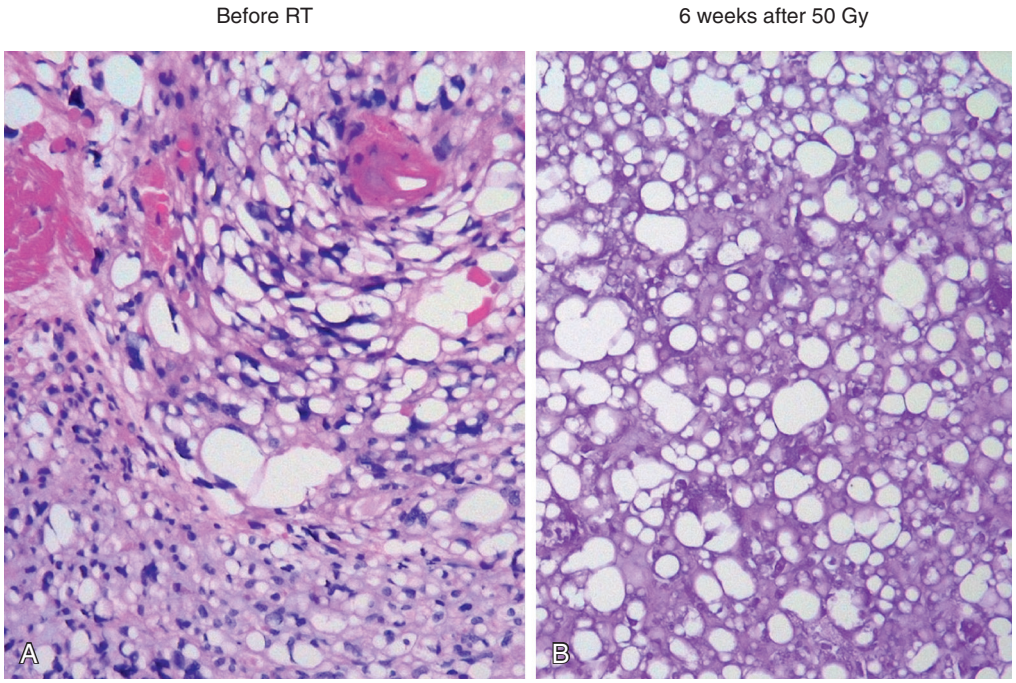


Figure 65-2 Demonstration of the exquisite radiosensitivity of myxoid liposarcoma to radiation. **A,** Before radiation therapy (RT); **B,** Approximately 95% necrosis after 50 Gy of RT.

extremity sites especially in older patients and is considered one of the most common histology in this patient population. These sarcomas have no distinct genetic abnormalities. The majority are high grade. It is an important histological subtype for radiation oncologists to recognize because of its propensity for LR. Some of the myxofibrosarcoma present as diffuse superficial lesions, making it difficult to appreciate the true extent of the disease on imaging and at time of surgical resection. This could explain the high rate of LR even when adjuvant radiation is given. However this should not be considered as a sign of radioresistance. Mutter et al compared high-grade leiomyosarcoma (n = 88) to high-grade myxofibrosarcoma (n = 144) in the setting of primary nonmetastatic extremity lesions.[28] Myxofibrosarcoma presented more frequently with tumors larger than 5 cm ($p < 0.001$), deep location ($p = 0.03$), upper extremity site ($p = 0.015$), and higher rate of positive and close margins ($p < 0.001$). The 5-year LR rate was not significantly different, 14.6% for myxofibrosarcoma compared with 13.2% for leiomyosarcoma ($p = 0.5$). What was different was the pattern of LR; of 17 myxofibrosarcoma LRs, 47% occurred out of field compared to 8% for leiomyosarcoma ($p = 0.04$). In addition once LR developed in patients with myxofibrosarcoma, many (35%) went on to develop subsequent and sometimes multiple LRs compared with no subsequent LRs in the leiomyosarcoma group ($p = 0.05$). Thus, it is important to separate the rate of initial LR in myxofibrosarcoma, which seems to be similar to other histologies such as leiomyosarcoma, from the repeated subsequent recurrences in the same index case, giving the impression that most myxofibrosarcomas recur after radiation.

Leiomyosarcoma

Leiomyosarcomas (LMS) affect women more often than men even after accounting for gynecologic LMS. By far the most common site is the retroperitoneum; other sites include gastrointestinal viscera, extremity, vessels (e.g., leiomyosarcoma of inferior vena cava), and skin. Site plays an important role in prognosis, with cutaneous LMS having the best prognosis. LMS often presents as a small nodule with low-grade features, and generally wide excision is sufficient treatment. In contrast, retroperitoneal and vascular LMS have much worse prognosis. LMS are genomically complex; there is an amplification of myocardin (MYOCD) in about 70% of retroperitoneal LMS.[29] When high-grade LMS were compared to high-grade myxofibrosarcomas in primary extremity lesions,[28] the 5-year rate of distant metastasis was significantly higher in LMS (54.1% versus 24.3%; $p = 0.014$).

Synovial Sarcoma

Synovial sarcomas are high-grade tumors that tend to affect young adults and adolescents. Like other sarcomas, extremity is the most common site, but head and neck is a relatively common site. Calcifications on plain films or CT scan can be seen in some synovial sarcomas. The two main histological types are the monophonic and the biphasic, with the monophonic type being the most common. In biphasic synovial sarcomas there is a mixture of epithelial and spindle cell components. Synovial sarcomas[19,20] have a distinct translocation t(X; 18). The fusion involves of SS18 from chromosome 18 and either SSX1 (two thirds of cases) or SSX2 (one third of cases) on the *X* chromosome.[30,31] At MSKCC, there is a synovial sarcoma–specific nomogram to help predict outcome in this group of tumors.[32]

Gastrointestinal Stromal Tumors

Gastrointestinal stromal tumors (GISTs) are thought to originate from intestinal cells of Cajal. In the past, many of these tumors were classified as LMS. GISTs affect mainly adults and can arise anywhere in the gastrointestinal tract with stomach and small intestine being the most common sites. In a small number of cases they arise from the mesentery, omentum, or retroperitoneum. A common presentation for GISTs is a GI bleed or an abdominal mass. Metastases occur predominantly within the peritoneal cavity and the liver. The molecular understanding of GISTs has revolutionized how GISTs are diagnosed and treated, which will be discussed later in the chapter.

These tumors have oncogenic mutations in the *KIT* or PDGFR-α genes in 85% and 5% of cases, respectively.[33,34] *KIT*

and *PDGFR*-α mutations are mutually exclusive. These mutations are driver mutations, which explain the great success in treating them with the tyrosine kinase inhibitor imatinib.[35,36] The most common location of KIT mutations are exon 11 in about two thirds of cases and exon 9 in 10%. Having an exon 9 mutation seems to infer worse tumor response to imatinib than an exon 11 mutation.[37] About 10% of GISTs do not exhibit *KIT* or *PDGFR*-α mutation and are called wild type. Some of these wild-type GISTs have BRAF mutations, NF1 mutations, succinate dehydrogenase subunit mutations, and RAS-family mutations.[20]

Clear Cell Sarcoma

These sarcomas used to be called malignant melanoma of soft parts because of some histological similarity with melanomas (intracellular melanin and immunoreactivity for S-100 and HMB45). However, these tumors have a signature[19,20] translocation t(12;22) seen in 70% of cases, which is not observed in cutaneous melanomas. They affect young adults mainly in the second to fourth decades of life and have predilection for distal lower extremity sites (ankle and foot). These tumors are considered high grade and have high propensity for spread including to lymph nodes. Sentinel lymph node biopsy or positron emission tomography/computed tomography (PET/CT) should be considered at time of initial evaluation.

Epithelioid Sarcoma

There are two types of epithelioid sarcomas: classic type, and proximal type. Classic type affects patients mainly in the third decade of life, with preference for distal upper extremity sites (hand and forearm). They present as a slow growing nodule and in some cases they can be multinodular, making it difficult to assess their true extent. They are high grade and have a high propensity for LR as well as regional lymphatic spread. The use of sentinel lymph node biopsy or PET/CT should be considered at time of initial evaluation. The patterns of local recurrence are challenging because some may occur quite a distance away from the primary site. The proximal type, tend to affect older patients than the classic type. Most common location is pelvis, including perineum and genital tract. These tumors are highly aggressive.

Pathways of Spread

Local Disease

Most extremity STS tend to spread in a longitudinal direction within the muscle groups where they originated. As they extend, lesions invade muscle and contiguous structures and occasionally envelop major neurovascular structures. The extending border comprises an outer perimeter of edematous tissue intermixed with a reactive zone of neovascularity with interspersed tumor satellites and pseudopodia. This surrounding area is generally termed the *pseudocapsule* and may encourage erroneous interpretation of anatomic disease containment and encourage enucleation. Such operations, frequently called *shell outs*, almost invariably mean that residual disease remains.

STS generally respect barriers to tumor spread in the axial plane of the extremity such as bone, interosseous membrane, and major fascial planes, and this feature should be exploited in planning tissue-preserving approaches to management. Thus, the margins of RT should be wide in the cephalocaudal direction but in the cross section there may be much greater security in defining nontarget structures. The importance of the osteo-fascial compartments of the extremities is that, from an anatomic standpoint, they operate as functional units and are protected from each others' risks of tumor contamination in the absence of inappropriate violation of the subdividing fascial septa. The latter may occur with misplaced surgical intrusion, including inappropriate placement of drain or biopsy tracts.[38]

The fascial structures are also important because they guard tumors arising superficial to the fascia investing the muscles of the region from the deeper structures. Tumors arising in subcutaneous tissues are staged differently to those arising deep to the fascia. In the event that the fascia has been disrupted, as is often the case after an "unplanned" sarcoma resection with positive margins, it may provide a route for deep contamination by tumor.

Extremity lesions arising in extracompartmental spaces such as the axilla, femoral triangle, sartorial canal, and popliteal space have the ability to extend proximally and distally at considerable distances with less anatomic restraint and early involvement of the neurovascular bundle.[39] For nonextremity lesions, the direction of sarcoma growth is also along the involved musculature, but care must be taken to ensure that the fascial planes are appropriately recognized and encompassed in surgical or RT target volumes.[40]

Regional Lymph Node Involvement

In STS there is generally no need for any specific regional lymph node treatment. Important exceptions to this generalization include epithelioid sarcoma, clear cell sarcoma, angiosarcoma, and rhabdomyosarcoma[41,42] (Table 65-2). Traditionally, lymph node involvement has been associated with an adverse prognosis rivaling that of distant metastasis. However, data suggest that isolated lymph node metastasis may not be as deleterious a factor.[43-45] This is reflected in the most recent version of the TNM staging system (see later section on staging).[46]

Distant Metastasis

Most sarcomas present with localized disease, and overt metastasis is present in only 10% of cases at diagnosis. Typically, the patient is asymptomatic and staging investigations are required to demonstrate metastases. The predominant risk is to the lungs. Spread to bone can be seen with myxoid liposarcoma, where it may be the first site of relapse. Myxoid liposarcoma also has the unusual characteristic of developing isolated soft-tissue metastases. In patients with retroperitoneal sarcoma and intraabdominal visceral sarcomas, the liver is a more common site of first metastasis.

CLINICAL MANIFESTATIONS, PATIENT EVALUATION, AND STAGING FOR EXTREMITY STS

Clinical Manifestations

About 40% of all STS originate in the extremities; of these about 60% are thigh STS. The most common presentation of extremity STS is a painless mass. If pain or other symptoms are evident, it usually indicates origin from or invasion of neurovascular structures. Erythema and warmth may be evident depending on the vascular and tissue response. Some patients will present with large, slow-growing lesions that may restrict joint motion; and larger tumors may ulcerate skin or invade adjacent compartments. In general, superficial lesions are smaller than those deep to fascia, and upper extremity lesions tend to be smaller than those in lower extremity.

Patient Evaluation

The overall initial evaluation of a patient with STS is summarized in the diagnostic algorithm (Figure 65-3). Clinical assessment should include history and clinical examination, with particular attention to the relationship to the investing

TABLE 65-2 Histologic Type of Sarcomas and Lymph Node Metastasis*

	Mazeron 1987 Series[41]		Fong 1993 Series[42]	
Histologic Subtype	***n***	**%**	***n***	**%**
Alveolar soft part	3/24	12.5	0/13	0
Angiosarcoma	—	—	5/37	13.5
Chondrosarcoma	—	—	1/46	2.2
Clear cell sarcoma	11/40	27.5	—	—
Epithelioid sarcoma	14/70	20	2/12	16.7
Fibrosarcoma	54/215	4.4	0/162	0
Hemangiopericytoma	—	—	0/21	0
Leiomyosarcoma	21/524	4.0	9/328	2.7
Liposarcoma	16/504	3.2	3/403	0.7
Lymphangiosarcoma	—	—	1/4	25.0
Malignant fibrous histiocytoma	84/823	10.2	8/316	2.6
Neurofibrosarcoma/ MPNST	3/476	0.6	2/96	2.1
Osteosarcoma	—	—	0/11	0
Rhabdomyosarcoma (embryonal)	—	—	12/88	13.6
Rhabdomyosarcoma (other)	201/1354	14.8	1/35	2.9
Synovial sarcoma	117/851	13.7	2/145	1.4
Undifferentiated spindle cell	—	0	0/42	—
Vascular	43/376	11.4	—	—
Other	—	—	0/27	0
Total	567/5257	10.8	47/1772	2.6

Data from Mazeron JJ, Suit HD: Lymph nodes as sites of metastases from sarcomas of soft tissue. Cancer 60:1800–1808, 1987, summarizing literature studies and Fong Y, Coit DG, Woodruff JM, et al: Lymph node metastasis from soft tissue sarcoma in adults. Analysis of data from a prospective database of 1772 sarcoma patients. Ann Surg 217:72–77, 1993, from a single institution.
MPNST, *Malignant peripheral nerve sheath tumor.*
**Number (n) of patients with nodal metastases and sarcoma in two studies and proportion (%) of all lesions.*

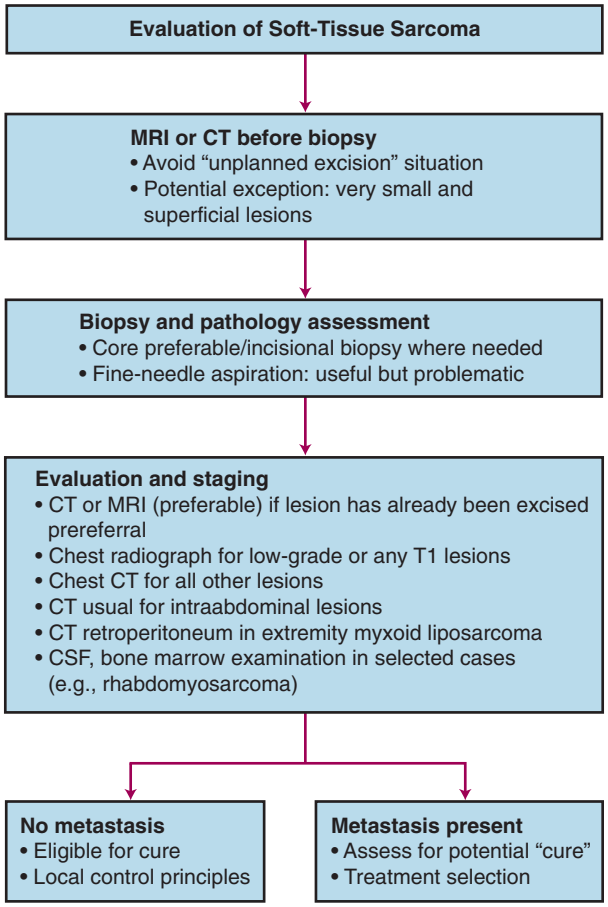


Figure 65-3 Diagnostic algorithm for the initial evaluation of a patient with soft-tissue sarcoma. All soft-tissue masses deep to the investing fascia should be considered sarcomatous until proven otherwise. Emphasis is needed on the type of biopsy and pathologic assessment. Most patients require computed tomography (CT) or magnetic resonance imaging (MRI) for the local disease assessment, and most patients require CT to exclude metastatic disease. Cerebrospinal fluid (CSF) analysis for tumor cytology is indicated in parameningeal rhabdomyosarcoma.

fascia deep to the subcutaneous fat (i.e., whether superficial versus deep) and adjacent neurovascular structures or bone as well as lesion size and mobility.

All soft-tissue masses deep to the investing fascia should be considered to be sarcoma until proven otherwise. A prior inappropriate excision may jeopardize the form and outcome of local treatment by contaminating tissues that were uninvolved initially. Thus, to minimize the risk of undesirable outcome, prebiopsy imaging is necessary.

Imaging of Primary

MRI is considered the optimal imaging modality to assess the primary lesion in extremity STS. Most STS will appear as low-signal intensity on T1-weighted images and high-signal intensity on T2-weighted images. MRI is highly accurate in delineating the extent of a soft-tissue abnormality and peritumoral edema. It is important to note, that although MRI is a highly sophisticated imaging modality, it is not diagnostic of STS and pathological confirmation is required before initiation of therapy.

Critical aspects to ascertain from an MRI include size of the lesion, its relationship to the investing fascia (superficial or deep), and proximity to neurovascular structures and bone (Figures 65-4 and 65-5). The multiplanar imaging and soft-tissue detail rendered by MRI makes this modality ideal for treatment planning of STS of the extremity.

A CT of the extremity is a reasonable substitute for MRI. A "blinded" study by the Radiation Diagnostic Oncology Group[47] that compared MRI and CT in patients with malignant bone and soft-tissue tumors showed no specific advantage of MRI over CT. Although CT has lower soft-tissue resolution than MRI, it has an advantage over MRI in assessing bone involvement. Plain x-rays are of little value in the evaluation of STS other than detecting calcifications or bony involvement.

PET/CT is being used increasing in STS, but its role in assessing the primary tumor is not well defined. There are some suggestions that it could be used to predict early response to chemotherapy.[48]

Establishing the Diagnosis

The biopsy should be carefully designed to facilitate subsequent surgical removal and adjuvant therapy. Core needle biopsy is the most commonly used approach nowadays and

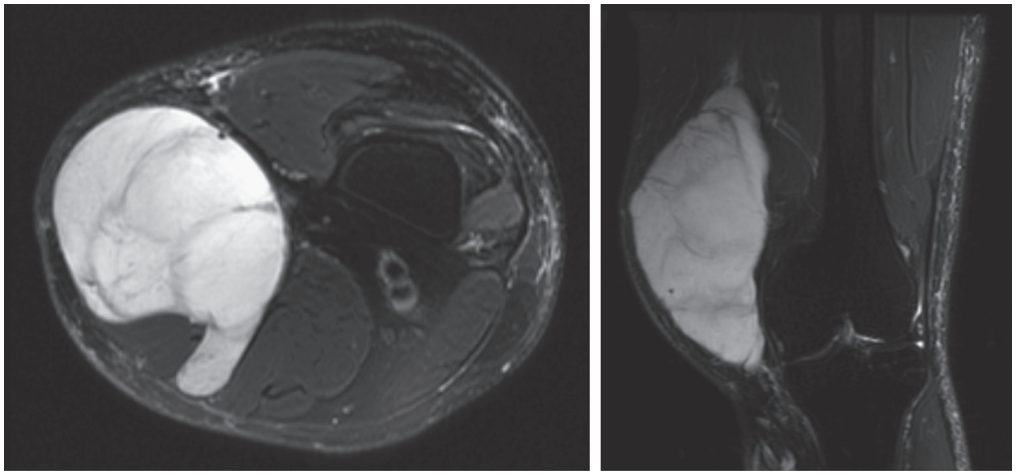


Figure 65-4 Magnetic resonance imaging of the knee.

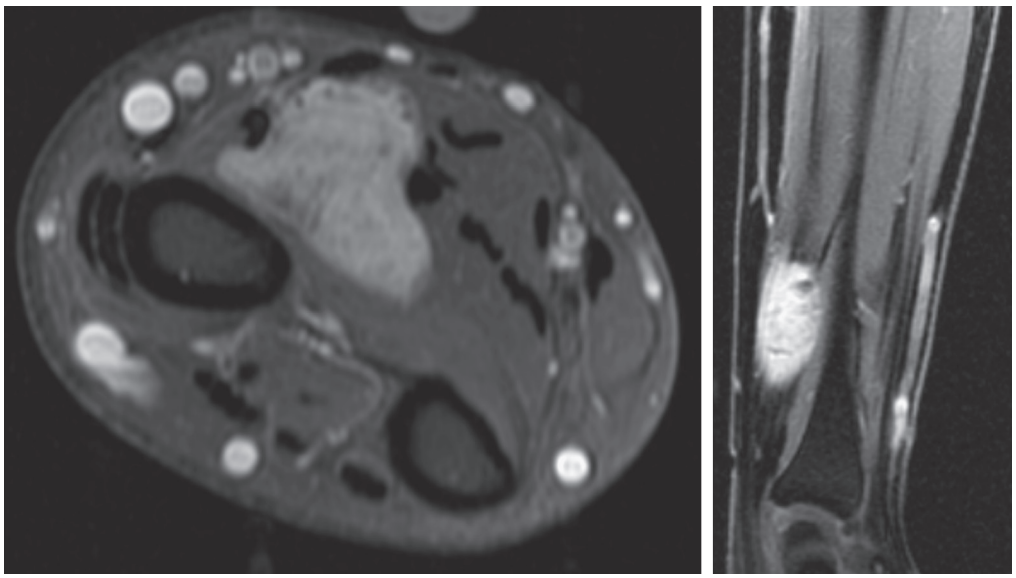


Figure 65-5 Magnetic resonance imaging of the forearm

its accuracy is well established. In a report on 530 patients, core needle biopsy could differentiate STS from benign soft-tissue tumors with an accuracy of 97.6%. High-grade sarcomas were differentiated from low-grade sarcomas with an accuracy of 86.3%. Tumor subtype was accurately assigned in 88.0% of sarcomas.[49]

An incisional biopsy provides the highest yield because sufficient tissue for additional immunohistochemistry, electron microscopy, molecular assessment, and cytogenetics is made available. Disadvantages of this approach may include complications and potential delay in initiation of neoadjuvant therapies if there are wound problems. Excisional biopsy should be avoided to the extent possible because of its potential impact on subsequent therapies including definitive surgery and radiation. If the orientation of an excision is perpendicular to, rather than along, the long axis of the extremity, the reexcision will be challenging. The role of fine-needle aspiration biopsy (FNAB) is controversial in making initial diagnosis of STS.[50] FNA however, has an important role in establishing the presence of recurrence, both local and distantly.

Exclusion of Metastasis

The most common site for metastasis in extremity STS is the lungs. Either chest x-rays or CT could be used. Although chest CT is considered the gold standard, it is not clear if it is needed for all STS of the extremity. In a report on 1170 patients with newly diagnosed STS, the efficacy of chest x-rays in identifying pulmonary metastatic disease was compared with CT of the chest. The incidence of lung metastasis on CT was 8.3%. The accuracy of chest x-ray was 96.9% compared to 99.6% for CT. The stage of STS (tumor size, grade, and depth), influenced the yield. If the chest x-ray was used as the only imaging tool this would results in lung metastasis being missed in 4.9% of stage III disease (>5 cm, deep, and high grade). In contrast, less than 0.5% of metastasis would be missed if patients with stage IA (≤5 cm, low grade, and superficial) had chest x-rays alone.[51] Spinal metastasis with or without lung metastasis can be seen in patients with myxoid liposarcoma (Figure 65-6). Therefore, spinal MRI is sometimes recommended for these patients.[52] In a study of 109 adult patients with STS who



Figure 65-6 Spinal magnetic resonance imaging showing metastasis in myxoid liposarcoma.

TABLE 65-3 TNM Classification of Soft-Tissue Sarcomas

PRIMARY TUMOR (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor 5 cm or less in greatest dimension
T1a	Superficial tumor*
T1b	Deep tumor
T2	Tumor more than 5 cm in greatest dimension
T2a	Superficial tumor*
T2b	Deep tumor
REGIONAL LYMPH NODES (N)	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1†	Regional lymph node metastasis
DISTANT METASTASIS (M)	
MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

STAGE GROUPING				
Stage IA	Grade 1	T1a, T1b	N0	M0
Stage IB	Grade 1	T2a, T2b	N0	M0
Stage IIA	Grade 2-3	T1a, T1b	N0	M0
Stage IIB	Grade 2	T2a, T2b	N0	M0
Stage III	Grade 3	T2a, T2b	N0	M0
Stage III	Any grade	Any T	N1	M0
Stage IV	Any grade	Any T	Any N	M1

From Sobin LH, Gospodarowicz MK, Wittekind C: TNM classification of malignant tumours, ed 7, Oxford, 2009, Wiley-Blackwell.
**Superficial tumor is located exclusively above the superficial fascia without invasion of the fascia; deep tumor is located exclusively beneath the superficial fascia, superficial to the fascia with invasion of or through the fascia, or both superficial yet beneath the fascia.*
†Presence of positive nodes (N1) in M0 tumors is considered stage III.

underwent PET/CT as part of their initial staging, only 5 (4.5%) were upstaged. Of the 5 patients, 3 had extrathoracic metastasis, 1 had both thoracic and extrathoracic, and 1 had lung metastasis not identified on chest CT.[53] It is unclear if routine use of PET/CT is indicated in the initial staging of STS. Perhaps the exception would be for histologies with a high rate of nodal metastasis or nonthoracic spread patterns.

Staging

The Union for International Cancer Control (UICC)/AJCC TNM (seventh edition) staging system[46] is the most widely employed staging system for STS and is unusual within the overall TNM classification system in that it incorporates histologic grade with anatomic disease characteristics. The system is based on grade (three-tiered system), size partitioned at the 5-cm break point, and lesion depth as "a" (superficial tumor arising outside the investing fascia) or "b" (a deep tumor that arises beneath the fascia or invades the fascia) (Table 65-3). All STS subtypes are included except hollow visceral sarcomas, Kaposi's sarcoma, fibromatosis (desmoid tumor), and sarcoma arising from the dura mater, brain, and parenchymatous organs. Some aspects of the AJCC seventh edition differ from the previous edition. Tumor grade uses three-tiered system and tumor depth is reported but it does not change stage grouping. Nodal involvement without distant metastasis is considered stage III.

PRIMARY THERAPY FOR EXTREMITY STS

Surgery

General treatment principles for nonmetastatic extremity are shown in Figure 65-7. Surgical resection in the form of limb-sparing surgery is the main treatment for extremity STS. The aim is to try to get about a 2-cm margin of normal tissue around the gross tumor. The important aspects of such surgery, especially as it pertains to the radiation oncologist, include the following: was complete gross resection achieved, were adjacent major nerve or bone manipulated, and what type of wound closure was performed? Complete gross resection with an adequate margin is important to ensure that the resection went beyond the pseudocapsule of the tumor. Having said this, the size of the margin need not be 2 cm all around. Often fascia, bone, and neurovascular structures represent a natural barrier to STS local spread. If the tumor was close to bone or major nerve, striping the periosteum or neurolysis is considered an adequate margin. Such manipulation of bone or nerve, however, increases the risk of fracture or neuropathy when adjuvant RT is used. Occasionally cortical bone resection or resection of major nerve is required if the STS invades them. For wound closure, it is important to know if it was a primary skin closure or required tissue transfer in the form of skin graft or myocutaneous flap because of its potential impact on wound complications especially when RT is being considered.

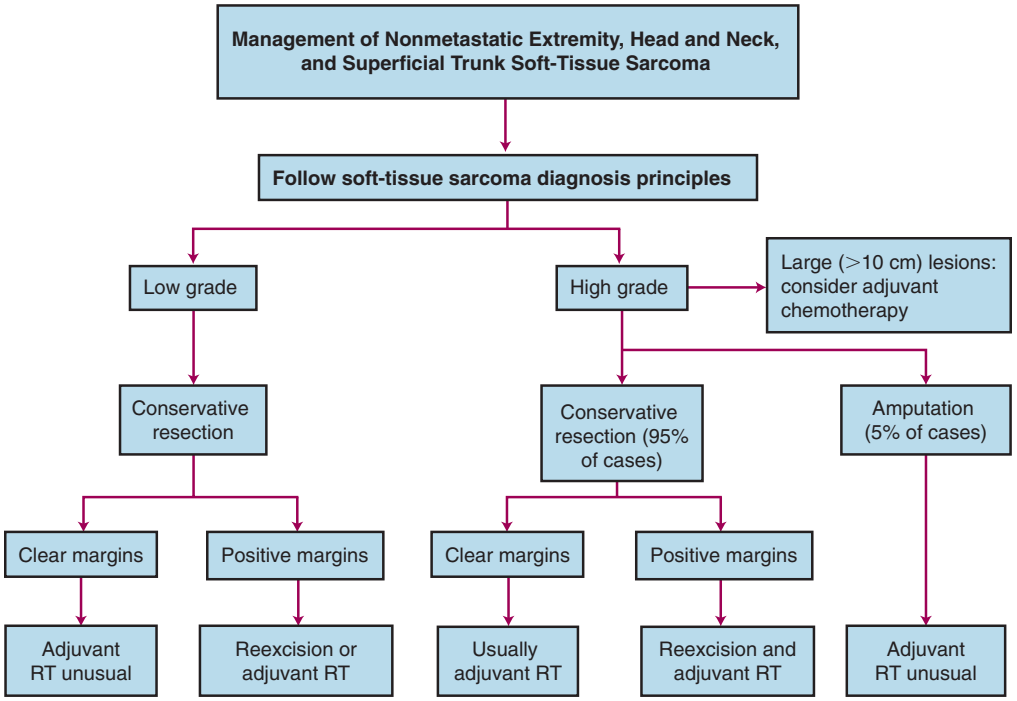


Figure 65-7 The focus of this schema predominantly addresses the local treatment of these lesions and recognizes that systemic chemotherapy is controversial. In unfavorable presentations in a fit patient, chemotherapy may be considered, although in general this is an institution-specific preference. Of note, the predominant approach involves tissue preservation with conservative surgery and adjuvant radiation therapy (RT). Selected patients may be treated with surgery alone, and rarely, patients (5% of cases) require amputation.

The use of amputation as the initial surgical treatment in STS should be rare. The notion that unless amputation is performed, the sarcoma will spread have been address by a randomized trial from the National Cancer Institute (NCI). The trial compared amputation ($n = 16$) to wide local excision and postoperative external beam radiation ($n = 27$) in patients with high-grade STS of the extremity. There were four local recurrences in the limb-sparing group and none in the amputation group ($p = 0.06$). However, there were no differences in the 5-year disease-free survival (DFS) rates (71% and 78%; $p = 0.75$) or overall survival (OS) rates (83% and 88%; $p = 0.99$) between the limb-sparing group and the amputation treatment groups.[54] At MSKCC[55] the rate of amputation is only 5% to 10% since the 1980s. Amputation should be considered only[56,57] where the tumor involves several compartments or invades major nerves (thigh STS involving both sciatic and femoral nerves). Another scenario would be a distal lower extremity lesion when a below-knee amputation prosthesis may provide better functional outcome than a limb damaged by tumor, extensive surgery and RT.[58]

Role of Adjuvant Radiation

Before discussing the role of RT in the management of STS, it is important to differentiate between radiosensitivity and radioresponsiveness. Radiosensitivity refers to the inherent response of cancer cells to radiation, and radioresponsiveness refers to how quickly a tumor regresses after radiation. These two parameters do not always correlate. The slow rate of regression of STS after RT, an example of poor radioresponsiveness, is often mistaken for radioresistance. The benefit of adjuvant RT in terms of local control has been demonstrated in two randomized trials. The first trial from MSKCC randomized 164 patients after limb-sparing surgery to radiation in the form of brachytherapy (BRT) or no further radiation. There were 78 patients in the adjuvant BRT arm and 86 patients in the no further RT arm. With a median follow-up time of 76 months, the 5-year actuarial local control rates were 82% and 69% in favor of brachytherapy ($p = 0.04$). This improvement in local control was most evident for patients with high-grade histology; local control for the BRT arm was 89% compared with 66% for surgery alone ($p = 0.0025$). There was no improvement in local control for patients with low-grade tumors. The 5-year freedom-from-distant-recurrence rates were 83% and 76% in the BRT and no BRT groups ($p = 0.6$), respectively. The 5-year disease-specific survival rates were also not different; 84% compared with 81% ($p = 0.65$), respectively.[59]

The second trial, from the NCI, was similar to the MSKCC trial except that EBRT was used instead of BRT. Ninety-one patients with high-grade lesions were randomized; 47 to receive EBRT and 44 to not receive EBRT. With a median follow-up of 9.6 years, a highly significant decrease ($p = 0.0028$) in the probability of LR was seen with radiation, but no difference in OS was shown. Of 50 patients with low-grade lesions (24 randomized to resection alone and 26 to resection and postoperative radiotherapy), there was also lower probability of LRs ($p = 0.016$) in patients receiving EBRT, again, without a difference in OS.[60]

As mentioned previously, some histologic subtypes such as myxoid liposarcoma are exquisitely sensitive to adjuvant RT, with 5-year local control rates in the range of 97%.[61,62] Other histologies may not be as radioresponsive as myxoid liposarcomas and local control may vary, but there is no evidence that certain histologic subtype are resistant to radiation. Italiano et al[63] reported on 237 primary resected synovial sarcomas. The use of adjuvant RT was associated with significant reduction in the rate of LR (hazard ratio [HR]: 0.43; $p = 0.026$). In another study of 83 extremity synovial sarcomas, the 10-year

local control was 86% for upper-extremity lesions and 80% for lower-extremity lesions.[64] Clearly adjuvant RT plays a significant role in the treatment of STS of the extremity. Nonetheless, there is still considerable debate about indications, timing, type, volume, dose, and morbidity profile.

Indications for Adjuvant RT

Who should receive adjuvant RT? Based on the results of aforementioned two trials, it is clear that addition of RT to limb-sparing surgery significantly improves local control in extremity STS. Yet there has been several attempts to try to identify a subset of patients in whom adjuvant RT could be omitted.[65] In a report from MSKCC, patients with small (<5 cm) high-grade STS who had negative margins after oncologic resection had equivalent local control whether adjuvant RT was used or not. However, even within this favorable group of patients, age more than 50 years (relative risk [RR] = 6; 95%; p = 0.001), and central (groin, axilla) tumor location (RR = 3; p = 0.005) were highly predictive of LR.[66] This indicates that one or two prognostic factors such as size or grade may not be adequate to determine who should receive adjuvant RT. At MSKCC, a nomogram was developed to try to estimate the risk of LR in patients with primary nonmetastatic STS treated with limb-sparing surgery alone.[67] There were 684 patients with a median follow-up of 58 months; the 3-year and 5-year actuarial local recurrence rates were 11% and 13%, respectively. Factors included in the nomogram were age (≤50 versus >50), size (≤5 versus >5 cm), margin status (negative versus close/positive), grade (low versus high), and histology (atypical lipomatous tumor and WDL versus other). The STS nomogram predicted the LR rate with a C-index of 0.73. Such a nomogram can serve as a valuable clinical tool for assessing an individual patient's risk of LR and guiding adjuvant treatment decisions (Figure 65-8).

Timing of Adjuvant RT

The National Cancer Institute of Canada (NCIC) conducted a randomized trial in extremity STS comparing preoperative (n = 94) to postoperative EBRT (n = 96). With 3.3 years median follow-up, there was an identical local control between the two arms with an early improvement in OS (p = 0.0481) in the preoperative RT arm[68] that was not substantiated with 5-year results.[69] The 5-year results for preoperative versus postoperative RT, respectively, were: local control, 93% versus 92%; metastatic relapse free, 67% versus 69%; recurrence-free survival, 58% versus 59%; OS, 73% versus 67% (p = 0.48); and cause-specific survival, 78% versus 73% (p = 0.64). Only resection margin was significant for local control. Tumor size and

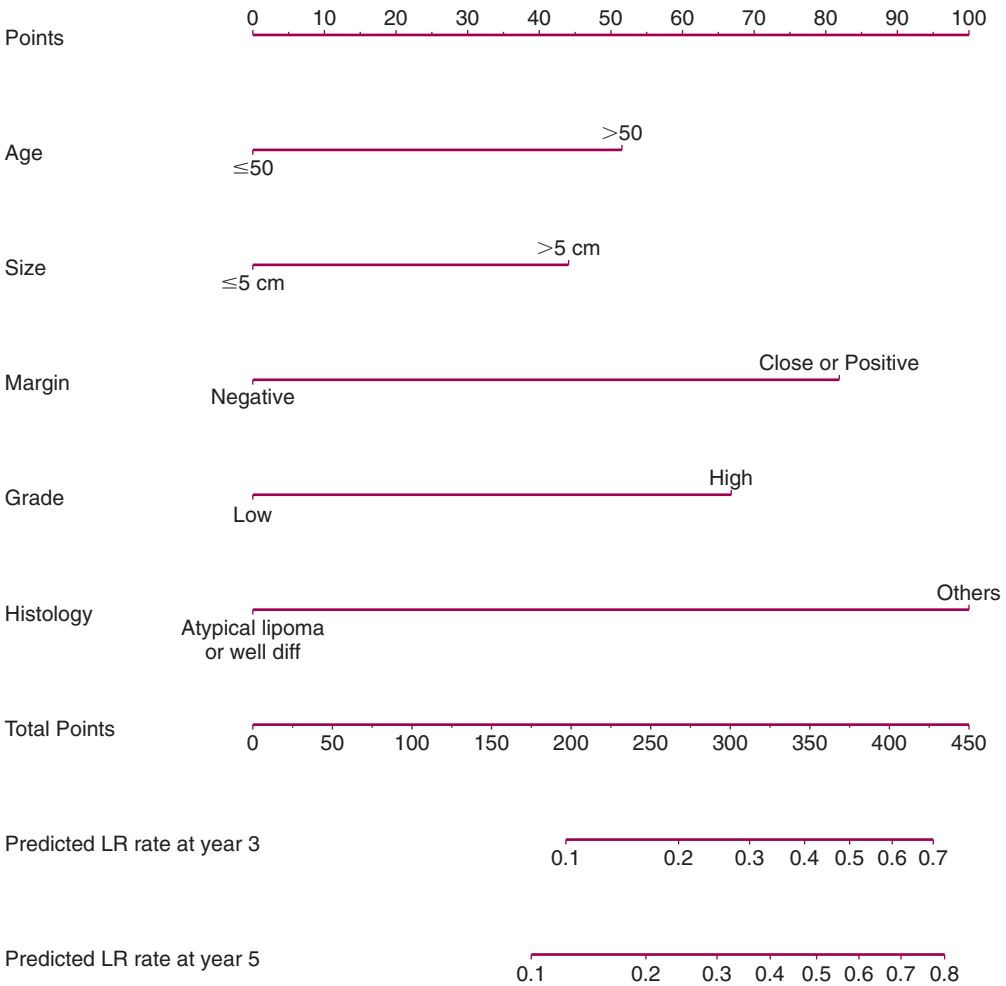


Figure 65-8 Nomogram for predicting risk of local recurrence (LR) at 3 years and 5 years in primary soft-tissue sarcomas of the extremity after surgery alone.

grade were the only significant factors for metastatic relapse, OS, and cause-specific survival. Grade was the only consistent predictor of recurrence-free survival.[69]

A literature-based meta-analysis of oncologic outcomes of preoperative versus postoperative EBRT analyzed a total of 1098 patients from five eligible studies. The risk of LR was somewhat lower after preoperative RT, but even more importantly the risk of metastatic spread did not increase with the delay in surgical resection with preoperative EBRT.[70] The latter finding is an important one to highlight to patients, who are often concerned about the delay in initiating surgery. Furthermore, Sampath et al[71] assessed the impact of RT sequencing on OS and cause-specific survival using the National Oncology database and found 1087 patients who received RT with surgery. OS was significantly improved with preoperative RT versus postoperative RT, with a median survival of 124 months and 90 months, respectively ($p = 0.02$).

Type of Adjuvant RT

There are several radiation modalities that could be used in the treatment of STS of the extremity (Figure 65-9). The most common one is conventional EBRT as employed in the NCIC trial.[68] Other modalities include BRT as used in the MSKCC trial,[59] but there has never been a head-to-head comparison of BRT to conventional EBRT. More recent techniques include intensity-modulated radiation therapy (IMRT) and image-guided radiation therapy (IGRT).

Brachytherapy

BRT has several advantages; patients usually leave the hospital having completed all their treatment in about 2 weeks compared to a 5- to 7-week course of EBRT. The evaluation of the tumor bed at the time of the operation by both the surgeon and the radiation oncologist can far exceed any imaging modality in its accuracy, and the rapid dose fall off with BRT spares more normal tissue than EBRT. There are also some limitations to BRT. Based on the MSKCC trial[59] the benefit of BRT in terms of local control was limited to high-grade STS. For patients with low-grade STS[72] LR occurred in 5 of 23 patients (22%) in the no-BRT group and 6 of 22 patients (27%) in the BRT group ($p = 0.60$). In a subsequent report from MSKCC limited to patients with primary nonmetastatic high-grade STS treated with adjuvant BRT ($n = 202$), the 5-year local control was 84 % with a median follow-up of 61 months. The local control was not uniform across disease sites; it was 91% for lower-extremity lesions, 76% for nonshoulder upper extremity, and 44% for shoulder location ($p < 0.001$). One possible explanation for poor results with BRT in the shoulder location is tumor bed geometry.[73]

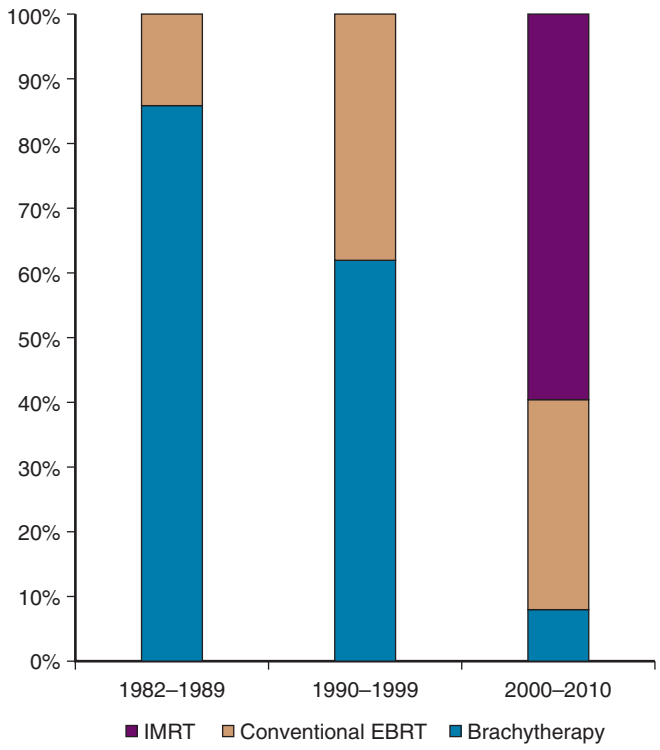


Figure 65-9 Trends of the type of adjuvant radiation therapy in primary soft-tissue sarcomas at Memorial Sloan Kettering Cancer Center. *EBRT*, external beam radiation therapy; *IMRT*, intensity-modulated radiation therapy.

Intensity-Modulated RT

IMRT can provide improved dose distribution in STS of the extremity because of steep dose gradients between target and normal tissues trial.[74] Preliminary results of IMRT in 31 adult patients with primary nonmetastatic extremity STS, who were treated at MSKCC were encouraging in terms of morbidity, despite the locally advanced nature of patients included in that study.[75] The question was whether the high conformal nature of IMRT may adversely impact local control. In a subsequent report from MSKCC on 41 patients (median follow-up: 35 months), the 5-year local control was 94%. This was achieved despite having a positive or close (<1 mm) margin in 51% of patients.[76] In a comparison between BRT ($n = 71$) and IMRT ($n = 63$) in primary nonmetastatic high-grade extremity STS, IMRT provided significantly better local control. With a median follow-up of 46 months, the 5-year rate of local recurrence was 8% for IMRT compared to 19% for BRT ($p = 0.04$). That difference retained its significance on multivariate analysis ($p = 0.04$). Of note, there were significantly more patients with positive and close margins ($p = 0.006$), and tumor >10 cm ($p = 0.005$) in the IMRT group than the BRT group.[77] In a separate report IMRT ($n = 164$) was compared to conventional EBRT ($n = 155$), in primary nonmetastatic extremity STS. With a median follow-up 49 months, the 5-year rate of local recurrence was 7.6% with IMRT as opposed to 15.1% with conventional EBRT ($p = 0.05$). That difference retained its significance on multivariate analysis ($p = 0.02$). There were significantly more patient with positive and close margins ($p = 0.04$) in the IMRT group.[78]

Image-Guided RT

In a Phase II trial using image-guided IMRT, O'Sullivan et al[79] reported on 59 patients with lower-extremity STS. The main purpose of the study was to evaluate whether this technique would influence the rate of wound complications with preoperative radiation (these results will be discussed later). With a median follow-up of 49 months, the 5-year local control rate was 88.2%. The RTOG-0630 Phase II trial using preoperative IGRT in extremity STS was recently completed. It defined the preoperative RT volume for intermediate- to high-grade tumors larger than 8 cm, as the clinical target volume (CTV) including the gross tumor and clinical microscopic margins with suspicious edema as defined by MRI T2-weighted imaging, plus 3-cm margins in the longitudinal dimension. The volume could be shortened to include only the end of a compartment. The radial margin was defined as 1.5 cm, including any portion of the tumor not confined by an intact barrier to spread. For lower-grade tumors the CTV still included the gross target volume (GTV) and suspicious edema, plus 2-cm margins in the longitudinal directions. The radial margin from the lesion was 1 cm, including any portion of the

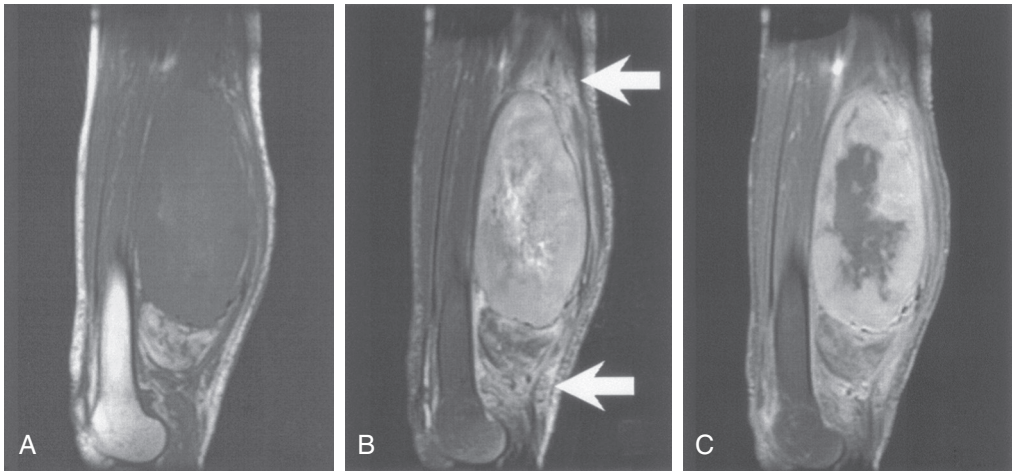


Figure 65-10 Sagittal T1-weighted **(A)**, fat-suppressed fast spin-echo T2-weighted **(B)**, and contrast-enhanced fat-suppressed T1-weighted **(C)** magnetic resonance images of a liposarcoma of the posterior thigh. Peritumoral increased T2-weighted signal intensity *(arrows)* seen both proximally and distally to tumor periphery on T2-weighted image **(B)**, with mild corresponding enhancement on contrast-enhanced T1-weighted image **(C)**.
Adapted from White LM, Wunder JS, Bell RS, et al: Histologic assessment of peritumoral edema in soft tissue sarcoma. Int J Radiat Oncol Biol Phys 61:1439–1445, 2005.

tumor not confined by an intact barrier to tumor spread. Of the 79 evaluable patients who underwent preoperative IGRT, 5 did not have subsequent surgery. Local control was achieved in 69 of 74 patients who underwent resection.[80]

RT Target Volume

In the era of CT and MRI, the RT target volume has undergone significant modifications. The need to cover muscles, within a compartment, from insertion to insertion is no longer needed. Therefore, accurate delineation of tumor volume is critical especially in the setting of preoperative EBRT. The Radiation Therapy Oncology Group (RTOG) performed a study to determine potential variation in delineating GTV in STS of the extremity. There was almost perfect agreement between experts in GTV delineation for upper- and lower-extremity STS.[81] In a subsequent report, the RTOG consensus was to delineate GTV as the gross tumor defined by T1 contrast-enhanced MRI.[82]

Although GTV delineation with the aid of MRI seems straightforward, how much margin to include beyond the GTV, to create the clinical target volume (CTV), is more challenging. The local growth characteristics of STS have suggested that tumor cells may be located in the surrounding soft tissues at some distance from the main tumor mass.[83] The original observation led to the development of the concept of a "reactive zone" surrounding the lesion, situated between the tumor edge and adjacent normal tissues. In a report from Princes Margret Hospital (PMH) on 15 patients, sarcoma cells were identified histologically in the tissues beyond the tumor in 10 of 15 patients who had not received previous RT. In six cases, tumor cells were located within 1 cm of the tumor margin, and in four cases malignant cells were found at a distance greater than 1 cm and up to a maximum of 4 cm. The location of tumor cells beyond the margin did not correlate with tumor size, nor did it correlate with the location or extent of peritumoral changes[84] (Figure 65-10).

The RTOG consensus regarding CTV was that it should include the GTV plus 3-cm margin in the longitudinal directions and 1.5 cm radially.[82] But the concern was whether a mere 3-cm expansion is sufficient to cover peritumoral edema. Therefore, in a subsequent study, the GTV and CTV were outlined, and then areas of suspicious edema on T2-weighted images were outlined separately. The median volume of suspicious edema not included in the CTV was only 0.3 cm^3. Thus, the conclusion was that CTV, formed from GTV expansion of 3 cm longitudinally and 1.5 cm radially, is likely to include peritumoral edema in the majority of cases. However, the CTV should be manually altered to include any area of suspicious edema that is not already included in the CTV.[85]

At MSKCC, a 4-cm expansion in the longitudinal directions is often used to keep in line with volumes from randomized trial data,[68] especially NCIC where the margin was 5 cm from GTV to field edge (equivalent to 4-cm expansion from GTV to CTV). This expansion margin however could be shortened if it extended beyond the compartment. The radial expansion margin is often 1 cm to 1.5 cm excluding skin surface, intact fascial barriers, and bone. The planning target volume (PTV) at MSKCC is created by adding a 1-cm uniform expansion margin to the CTV.

Immobilization is critical to minimize setup errors in general but especially when using IMRT. How to position the treated extremity is critical. Ideally the extremity should be placed as close to neutral anatomical position as possible while trying to limit "spill over of radiation" to normal tissues and structures outside the treated target. With conventional EBRT sometimes it is a compromise, but with IMRT it is often possible to place the treated extremity in a neutral anatomic position because several beams are generally used. Another important aspect of immobilization is to minimize rotational setup variations. For example, when treating a thigh STS, immobilization of the foot is more critical than the thigh itself. When IMRT is combined with daily IGRT and a clinically proven immobilization method,[86,87] the CTV to PTV expansion can be decreased from 1 cm to 0.5 cm.

For patients treated with postoperative EBRT, the starting point is the tumor bed rather than GTV. However, it is recommended that the original tumor extension (the resected GTV) should be recreated within the planing CT. Placing surgical clips at the boundaries of the tumor bed, at time of resection, is extremely helpful. On CT simulation axial cuts, the tumor bed often is manifest as a hypodense region compared to adjacent normal muscle. Inclusion of the scar as well as drain

site in the tumor bed is important as long as they are in close proximity. To create the CTV, a similar expansion margin to that with preoperative radiation is used (i.e., 4 cm in longitudinal directions and 1 cm to 1.5 cm axially from tumor bed). In the event that the surgical scar and drain sites extend far beyond the tumor bed, simply including them within CTV (minimal margin) should be sufficient. Adding 4-cm expansion margins to scar or drains that extend far beyond tumor bed might be prohibitive from a normal tissue tolerance point. In the postoperative setting, a cone down is often employed after 45 Gy to 50 Gy. The CTV is created from tumor bed plus 1 cm to 1.5 cm in long axis and 1 cm radially. PTV is created by adding a 1-cm margin uniformly. A review by Haas et al[88] outlines the steps of volume creations and CTV and PTV expansion in preoperative as well as postoperative settings (Figures 65-11 and 65-12).

There is an ongoing trial by the National Cancer Research Network (NCRN) in the United Kingdom that is comparing a 5-cm longitudinal margin from GTV or 1 cm from the surgical scar, whichever is longer, versus a 2-cm longitudinal margin (axial margin is 2 cm in both arms), to assess if a reduced volume of postoperative RT will increase limb function without compromising local control.

When using BRT in extremity STS at MSKCC, single-plane implant is often used. Catheters are placed parallel along the long axis of the extremity and are sutured to the tumor bed to provide stability. The distance between catheters should be about 1 cm. The starting point is the tumor bed defined by surgical clips. In the longitudinal margin, 2 cm is added, and axially, 1 cm is added. No attempts are made to cover scar or drain sites.

Radiation Doses

For patients treated with preoperative EBRT, the typical dose is 50 Gy in 25 fractions. One of the debatable areas is whether

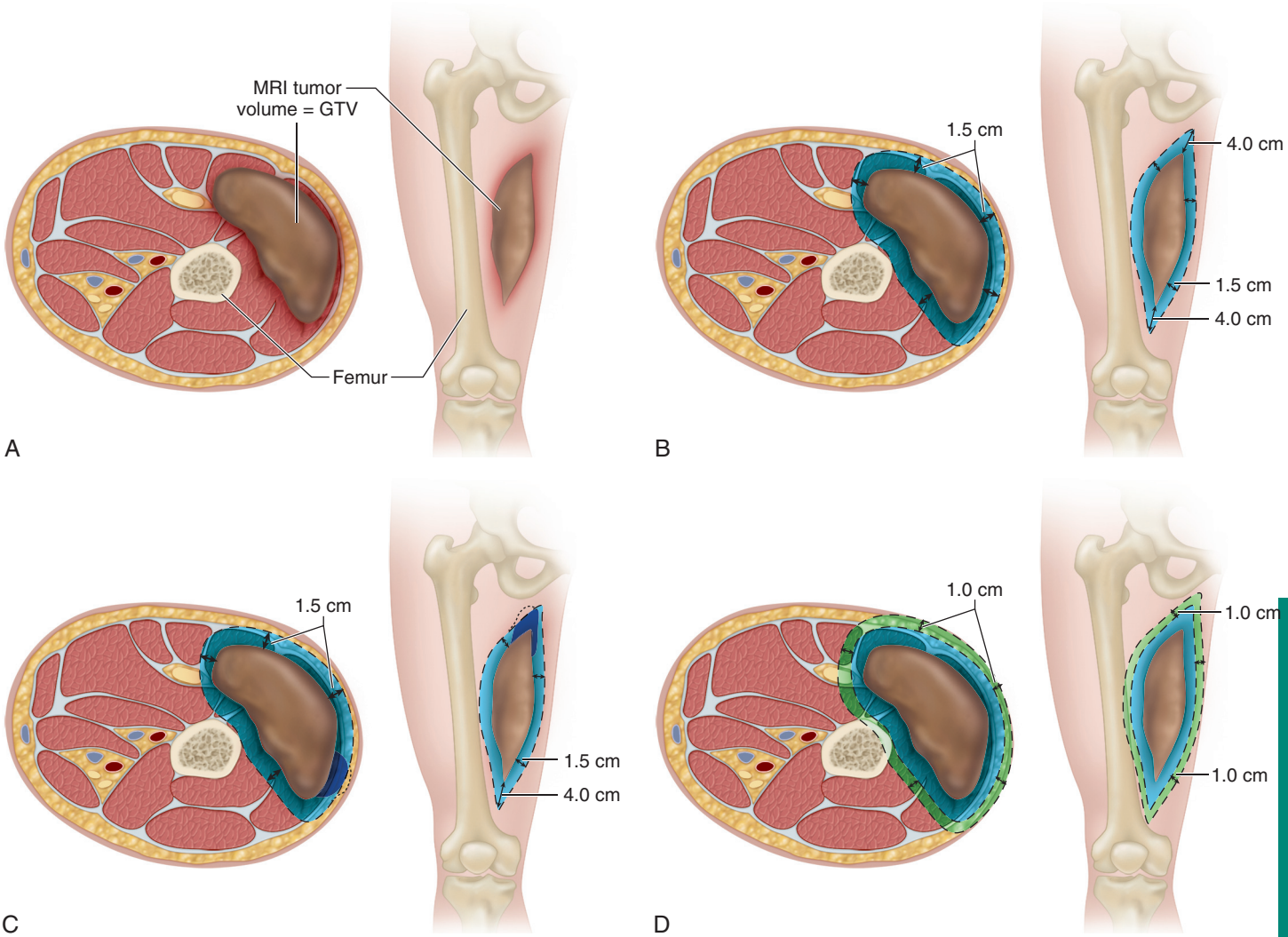


Figure 65-11 Target definitions in the preoperative setting. **A,** Patient to be treated with preoperative radiation therapy. Sarcoma delineated using T1-weighted, postgadolinium magnetic resonance imaging (MRI) scan fused to planning computed tomography (CT) scan. This gross tumor volume (GTV) does not include peritumoral edema, generally best seen on T2-weighted MRI scan. **B,** GTV transversely expanded with 1.5 cm but constrained at surfaces of fascia and bones, unless invaded. Longitudinally, expansion was 4 cm. Note: this was a sarcoma case without peritumoral edema. **C,** Sarcoma case with peritumoral edema with GTV also transversely expanded with 1.5 cm and constrained at surfaces of fascia and bones, unless invaded. Longitudinally, expansion was 4 cm. Note: CTV has been manually edited (bold dashed line) to encompass edema zone in both transverse and coronal planes. Peritumoral edema indicated by striped zone. **D,** Delineation of final preoperative planning target volume (PTV) by expansion of CTV with 1 cm in all directions, although PTV can vary by local institutional protocols. Obtained with permission.

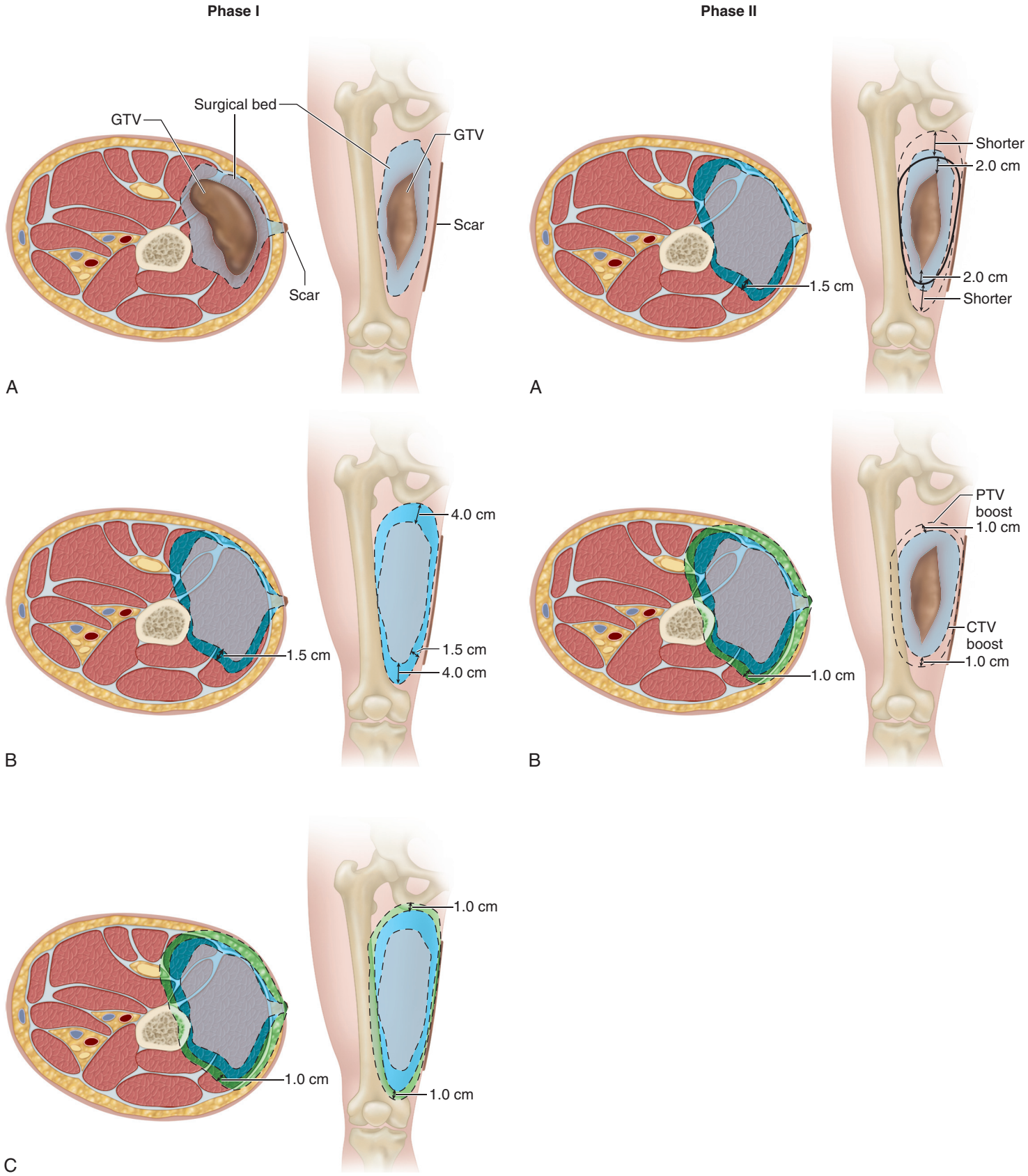


Figure 65-12 Phase I: Target definitions for postoperative radiation therapy (RT). **A,** Patient to receive postoperative RT. Both original sarcoma extensions (gross tumor volume [GTV]) visualized, as well as surrounding surgical bed. **B,** Margins for postoperative RT elective clinical target volume (CTV) are shown; these margins were 1.5 cm in transverse plane onto, but constrained at, surfaces of bones and fascia, unless involved with tumor at surgery. Note: elective CTV remains inside the skin. Furthermore, the elective CTV is longer than the marker of the skin scar. If 4-cm expansion of reconstructed surgical volume in longitudinal direction is shorter than surgical scar, elective CTV will need to be expanded to include the surgical scar. **C,** Expansion of 1 cm in all directions to produce postoperative elective planning target volume (PTV), although PTV can vary by local institutional protocols. Phase II: Target definitions for postoperative RT boost. Postoperative boost CTV was the same volume as the postoperative elective CTV, except craniocaudally **(A)**. In longitudinal direction, elective CTV is 2 cm longer on both sides than the reconstructed sarcoma GTV before surgery. **B,** Expansion of 1 cm in all directions of boost CTV to produce boost PTV, although PTV can vary by local institutional protocols. Obtained with permission.

additional RT is required for patients who undergo oncologic resection after preoperative radiation and were found to have positive surgical margins. In a study from PMH, 52 patients were treated with preoperative RT alone (50 Gy), whereas 41 received preoperative RT plus a postoperative cone down to a total of 66 Gy. The 5-year local control was 90.4% for those treated to 50 Gy alone compared with 73.8% for those who received additional postoperative cone down ($p = 0.13$). Although this data cannot be considered conclusive, it is important to balance the potential added advantages of more radiation beyond 50 Gy, to potential disadvantages in terms of morbidity.[89]

With postoperative EBRT, typically initial volume is treated to 45 Gy to 50 Gy followed by a cone down to bring the total dose to 63 Gy to 66 Gy depending on tumor grade, margin status, and location (normal tissue tolerance). For patients with positive microscopic margins after an oncologic resection, the use of adjuvant radiation has been shown to reduce the risk of LR at 5-year from 46% with surgery alone to 26% with the addition of radiation.[90] But it is clear that the risk of LR is still high in these patients, even when RT is added. The question then is, should the dose of radiation be escalated? Delaney et al[91] advocated for a dose higher than 64 Gy and reported a 5-year local control rate of 82%. Yet it is important to note that not all positive margins are created equal. In a report from PMH,[92] the 5-year local control rate was 85.4% in patients where a positive margin was anticipated at the time of oncologic resection. It seems that a small, isolated positive resection margin, planned from the outset with the intention of sparing a critical structure (major nerve or bone), has a favorable outcome, provided adjuvant RT is appropriately applied. In contrast, those with unanticipated positive margins at the time of oncologic resection had a local control rate of 63.4%. A third positive margin category in that report was for patients who had prior unplanned excision and were found to have positive margins at time of reexcision. Their 5-year local control was 78.9%. Patients who underwent prior unplanned excision represent a challenge, regarding whether to perform a reexcision and with regard to the role of radiation because many of these patients may have residual disease after the unplanned excision.[93,94] At MSKCC, all such patients undergo an oncologic reexcision. Occasionally, the reexcision reveals no residual sarcoma on pathologic examination. In a report from MSKCC, 200 such patients with primary nonmetastatic STS were assessed.[95] None of these patients received adjuvant RT. At 5-year, the risk of LR was 9%. However, for patients who were older than 50 years, the rate was 15% compared to 5% for those who were younger than 50 ($p = 0.001$). Similarly the rate for stage III was 26% compared to 7% for stages I to II ($p < 0.001$).

From the preceding discussion it is clear that margin status should not be looked at in isolation. Having a pathologically negative reexcision is no guarantee for excellent local control in patients older than 50 years or those with stage III disease. Conversely, having a positive margin is not always an indication for radiation dose escalation especially for patients with low-grade WDL, where an argument could be made that they do not need any radiation. For patients with gross residual disease after an oncologic resection, the dose should be 66 Gy to 70 Gy as long as it does not exceed normal tissue tolerance.

When using BRT at MSKCC, the dose is prescribed to the median peripheral dose rate (MPDR). The distance from the catheters to the MPDR is ideally 0.5 cm. With low-dose rate (LDR) BRT, the dose rate is typically 9 Gy to 10 Gy per day over 4 days to 5 days to a total of 45 Gy. Care should be taken to avoid hot spots in skin. With high-dose rate (HDR) BRT, the dose is typically 36 Gy given twice daily in 10 fractions over 5 days. The American Brachytherapy Society recently published a consensus regarding the role of BRT in sarcoma. Recommended dose is 45 Gy to 50 Gy with LDR when given alone and 15 Gy to 25 Gy when given with EBRT (45 Gy to 50 Gy). For patients treated with pulse dose rate, the doses are similar to those with LDR. For HDR, when used alone the dose is 30 Gy to 54 Gy, and 12 Gy to 20 Gy when combined with 45 Gy to 50 Gy of EBRT.[96]

Morbidity of Radiation

The aim of adjuvant RT in STS is limb preservation oncologically and functionally. The most common acute side effect of adjuvant RT in extremity STS is dermatitis. With conventional EBRT, it is not uncommon to develop moist skin desquamation, especially around skin folds (axilla and groin) or when the radiation beams angle is tangentional with skin surface. Moist desquamations can often lead to treatment interruption. The rate of grade-2 or higher radiation dermatitis in the postoperative arm of NCIC[68] was 68% compared to 36% with preoperative RT ($p < 0.0001$). This is not surprising because the dose of radiation as well as the volume irradiated is significantly less with preoperative EBRT.

When IMRT was compared to conventional EBRT, grade-2 or higher radiation dermatitis with IMRT[78] was significantly less (31.5 versus 48.7%, $p = 0.002$). The mean duration of treatment interruption in the IMRT group was 0.8 days, compared with 2.2 days in the conventional EBRT group ($p < 0.001$).

Another common acute side effect is wound complications. In the NCIC trial,[68] the primary endpoint was significant wound complications defined as needing reoperation, deep wound packing for more than 120 days, or wound infection requiring intravenous antibiotics. The rate was 35% in those treated with preoperative EBRT compared to 17% for those treated with postoperative EBRT ($p = 0.01$). It is important to note that although wound complications are a common side effect with radiation, they are not unique to radiation. In the MSKCC trial[97] comparing surgery alone to surgery and BRT, the rate of significant wound complication was 14% in the surgery alone arm compared with 24% with BRT ($p = 0.13$). In addition the rate of wound complications are not the same across extremity sites. In a separate report from MSKCC,[98] comparing upper- to lower-extremity STS, the rate of wound complications requiring reoperation was 1% for upper extremity compared with 11% for lower extremity ($p = 0.002$). In the NCIC trial the largest number of wound complications was seen in thigh STS.[68] Even within the thigh, rate of wound complications differ; in a report from MSKCC on 255 primary STS of thigh treated with adjuvant RT,[99] the rate of wound complications requiring reoperation was 4.9% in anterior compartment lesions as opposed to 14.6% for medial and posterior compartments ($p = 0.014$). Data regarding wound avoidance using IGRT, revealed a rate of 30.5% significant wound complications, which were not statistically different than the rate in the NCIC trial.[79] In some STS of the extremity, tissue transfer in the form of skin graft or myocutaneous flap are required. In a report on 43 patients who did have tissue transfer, the rate of reoperation was only 6% when postoperative RT was administered, indicating that once the tissue transfer is healed, it tolerates postoperative RT well.[100]

With regard to late toxicity, subcutaneous fibrosis is rather common. In the NCIC trial, the rate of grade 2 or higher was 31.5% in the preoperative RT arm compared to 48.2% for the postoperative arm. The corresponding rates for joint stiffness were 17.8% in the preoperative RT arm and 23.2% in the postoperative arm, respectively.[101] Edema is another potential long-term side effect of adjuvant RT. In the NCIC trial, grade-2 or higher edema was seen in 15.1% of patients treated with preoperative RT compared to 23.3% for those treated

TABLE 65-4 Results of IMRT in Extremity Soft-Tissue Sarcomas

	# of pts	Median F/U	Size >10 cm	5-year LC	Grade 2 ≥ edema	Grade 2 ≥ stiffness
MSKCC78*	165	42 mo	44%	92.4%	7.9%	14.5%
PMH79†	59	49 mo	44%	88.2%	11.1%	5.6%

F/U, *Follow-up;* LC, *local control;* MSKCC, *Memorial Sloan Kettering Cancer Center;* PMH, *Princess Margaret Hospital.*
**P only.*
†Limited to lower extremity.

postoperatively.[101] Some of the predictors of lymphedema include tumor size more than 5 cm and deep locations.[102] The site of STS also plays an influence on the rate of edema. In patients with thigh STS, the rate of lymphedema is 25.7% for medial thigh compartment tumors compared to 9% for primaries of the anterior and posterior compartment ($p = 0.005$), reflecting the rich lymphatic in the medial compartment.[99] The use of IMRT[78] seems to have a beneficial impact on lymphedema in extremity STS. The rate of grade-2 or higher edema is 7.9% for IMRT compared to 14.9% for conventional RT ($p = 0.05$).

Peripheral neuropathy can occur in the setting of adjuvant RT in extremity STS. In thigh STS[99] the rate of neuropathy is higher for posterior compartment lesion than anterior and medial (21.1% versus 3.5%, $p < 0.001$). Another predictor in that study was neurolysis where the rate was 27% as opposed to 5.2% for those who did not have neurolysis ($p = 0.0003$). For patients treated with BRT it is important to make sure that the radioactive sources are not in close proximity to a major nerve.

The rate of bone fracture is not that high (about 4% to 5%) when all extremity sites are combined. However, in patients who develop fractures, most of them occur in the lower extremity.[103,104] Dickie et al reported on 21 patients with lower-extremity STS who developed fracture and matched them with a random sample of 53 patients who did not develop fractures.[105] The risk of fracture was lower when V40 <64%, mean dose <37 Gy, or D-max anywhere along the length of bone was <59 Gy. Because most fractures in the lower extremity are femoral, the group at PMH developed a nomogram to assist in predicting the risk of femoral fracture. Important predictors include female gender, older age, anterior compartment location, extent of periosteal stripping, large tumor size, and high dose of RT.[106] The use of IMRT may provide a dosimetric advantage in reducing the dose to the femur when treating thigh STS. Folkert et al reported[107] on 82 primary thigh STS treated with adjuvant IMRT. With a median followup of 55 months, the risk of femoral fracture was 7.4%. This rate was much smaller than the expected rate (26.4%) from the PMH nomogram. Late toxicity (grade 2 or higher) data from the Phase II trial assessing IGRT in lower-extremity STS[79] showed subcutaneous fibrosis (9.3%, joint stiffness, 5.6%, and edema, 11.1%). Preliminary data from the RTOG 0630 Phase II trial are also encouraging in terms of late toxicity. Of 57 evaluable patients, the 2-year rates of grade-2 or higher late toxicity were subcutaneous fibrosis 5.4%, joint stiffness 5.4%, and edema 5.2%, respectively.[108]

In summary, when weighing risks and benefits of adjuvant RT in extremity STS, it is important to take into consideration the uniqueness of each anatomic region. Patients with upper-extremity STS are ideal candidates for preoperative RT because the rate of wound complications is relatively low. Thus, the patient gains all the benefits of a low rate of late toxicity without incurring a high risk of wound complications. But even within lower-extremity STS, a medial thigh STS may benefit from the lower dose of RT with the preoperative approach, rather than compounding an already high risk of edema with the high dose of RT required in the postoperative setting. Modern techniques of RT such as IMRT (Table 65-4) and more recently IGRT seem to have a favorable morbidity profile.

RT Alone

RT is most effective when used with surgery. Occasionally patients may not be a good candidate for surgery because of advanced age or comorbidities. Tepper et al[109] treated 51 patients with definitive photon beam irradiation to a total dose of 64 Gy to 66 Gy. The 5-year local control and survival rates were 33% and 25%, respectively. Local control was better for tumors <5 cm (87.5%) than in tumors 5 cm to 10 cm (53%) or larger than 10 cm (30%). In an update by Kepka et al on 112 patients who underwent RT for gross disease, local control at 5 years was 51%, 45%, and 9% for tumors <5 cm, 5 cm to 10 cm, and >10 cm, respectively. Patients who received doses less than 63 Gy had inferior 5-year local control (22% versus 60%); DFS (10% versus 36%), and OS (14% versus 52%). Although higher dose of RT was associated with better outcome, those who received more than 68 Gy were more likely to develop complications.[110] Another strategy to employ when giving definitive RT is radiosensitization. Rhomberg et al reported the results of a randomized trial comparing RT alone to RT and radiation sensitizer razoxane. In the subset of patients with gross disease ($n = 82$), the razoxane/RT arm demonstrated improved local control (64% versus 30%, $p < 0.05$). Acute skin reactions were enhanced in the "sensitizer" arm, but late toxicity was not increased.[111]

Chemotherapy for Nonmetastatic Extremity STS

The need for effective chemotherapy in primary high-grade STS of the extremity is clear, based on high risk of developing distant metastasis (up to 50% for high-grade large lesions). Unfortunately, data from several randomized trials have been inconclusive at best.

Adjuvant Chemotherapy

Doxorubicin has been extensively used in the treatment of STS, including several randomized trials comparing resection to resection followed by chemotherapy. In a meta-analysis[112] of 1568 patients (886 extremity sites), adjuvant chemotherapy had a significant impact on DFS but not OS. The 10-year DFS rate was 55% with chemotherapy compared to 45% with surgery alone ($p = 0.0001$). OS rate, however, was 54% with chemotherapy compared to 50% with surgery alone ($p = 0.12$).

This meta-analysis was criticized for including some patients with low risk of distant metastasis, and the chemotherapy regimen in many of the trials was considered suboptimal. A study from Italy limited to high-grade tumors randomized patients after surgery to observation ($n = 51$) or chemotherapy ($n = 53$) consisting of five cycles of epirubicin and ifosfamide.[113] Initial results showed significant improvement in DFS as well as OS; however, on longer follow-up the difference in OS was no longer statistically significant.[114] One

explanation for the loss of significance was small sample size. A recently completed European Organisation for Research and Treatment of Cancer (EORTC) 62931 trial randomized 351 patients with high-grade STS (about 80% were located in extremity or limb girdle) after resection to observation (176) compared with five cycles of doxorubicin and ifosfamide. The 5-year OS rates were almost identical; 66.5% in the chemotherapy arm and 67.8% in the observation arm. The corresponding 5-year relapse-free survival rates were 54.9%, and 52.9%, respectively. The cumulative incidence of metastasis was 35% in both groups.[115]

Neoadjuvant (Preoperative) Chemotherapy

There are several theoretical advantages of neoadjuvant over adjuvant chemotherapy. First, early initiation of systemic therapy; second, an unfavorable response to chemotherapy early on may obviate the need of more therapy; and lastly, it may have local response advantages, rendering subsequent surgery less radical. There are no randomized trials comparing the two approaches. A randomized trial by the Italian and Spanish Sarcoma Groups, compared three cycles of preoperative epirubicin and ifosfamide (n = 164) to the same chemotherapy followed by two more cycles postoperatively (n = 164). Of the 328 patients on this trial, about 90% had tumors in the extremity or limb girdle. With a median follow-up of 63 months, the 5-year OS was 68% for patients who were treated preoperatively and 71% for those treated preoperatively as well as postoperatively. Patients with extremity site did not fare better than the whole cohort. Five-year OS for the cohort was 69.7% and for extremity subset it was 68.6%. The 5-year cumulative incidences of distant metastasis were 32.6% and 33%, respectively.[116] Of note, the 5-year cumulative incidence of distant metastasis in the surgery alone arm of the EORTC 62931 trial[115] was also 34%.

Because of the inability to mount a large randomized trial addressing the role of chemotherapy in the adjuvant or neoadjuvant setting, several attempts have been made to pool data from large established cancer centers in the United States. One such study included all patients treated or not treated with adjuvant or neoadjuvant chemotherapy at M. D. Anderson Cancer Center (MDACC) and MSKCC; it showed no statistical difference in OS for patients treated with chemotherapy versus no adjuvant chemotherapy. There was a suggestion that chemotherapy delayed the manifestation of distant metastasis but did not prevent it.[117] Another comparison of data from the University of California–Los Angeles (UCLA) and MSKCC showed that adjuvant chemotherapy may be useful for synovial sarcomas.[118] A third comparison, this one between MSKCC and the Dana-Farber Cancer Center institutional databases[119] suggested a significant improvement in disease-specific survival in patients with high-grade extremity STS greater than 10 cm. In interpreting such data it is important to recognize biases that may exist, and it seems clear that randomized trials are sorely needed in the United States.

Combined Radiation and Chemotherapy

There are several approaches to combining radiation and chemotherapy depending on the setting. Regarding the postoperative setting, in the chemotherapy arm of the EORTC 62931, chemotherapy was delivered first followed by postoperative RT. In the control arm, postoperative RT had to start within 6 weeks of surgery. The 5-year cumulative incidence of locoregional relapse was 18.9% in the chemotherapy arm compared to 23.7% in the control arm. This showed that a delay in starting RT in the setting of adjuvant chemotherapy did not adversely impact local control. However, it is important to note that both the surgeon and radiation oncologist had to agree to delay RT for a patient to be eligible.[115]

In the preoperative setting, the group at Massachusetts General Hospital (MGH) developed a strategy of using three cycles of doxorubicin, ifosfamide, mesna, and dacarbazine (MAID) interdigitated with two 22-Gy courses of preoperative RT (11 fractions each) for a total dose of 44 Gy in localized, high-grade, large (>8 cm) extremity and truncal STS. This was followed by surgical resection. Postoperatively, three more cycles of MAID were given and an additional 16 Gy (8 fractions) boost dose was given for patients with positive margins. In the most recent update of their experience, 63 patients were evaluated. With a median follow-up of 46 months, the locoregional and distant 5-year recurrence-free survival rates were 91% and 64%, respectively. The 5-year OS and disease-specific survival rates were 86% and 89%, respectively. Thirty-four (52%) patients had grade-3 or grade-4 acute hematologic chemotherapy-related toxicity. There were no treatment-related deaths or secondary myelodysplasia.[120]

The RTOG performed a Phase II trial based on this regimen. In the most recent update of this trial,[121] 64 patients were analyzed. With a median follow-up of 7.7 years in surviving patients, the 5-year rates of locoregional failure (including amputation) and distant metastasis were 22.2% and 28.1%, respectively. Estimated 5-year rates of DFS, distant disease-free survival, and OS were 56.1%, 64.1%, and 71.2%, respectively. Ninety-seven percent experienced grade-3 or higher toxicity, including three deaths (two as a result of acute myelogenous leukemia). Other investigators, when using preoperative chemotherapy opted to deliver the radiation postoperatively[122] or in a concurrent fashion. Fakhrai et al[123] reported on a randomized trial comparing preoperative chemotherapy (six cycles of doxorubicin and ifosfamide) and RT to preoperative RT alone. In the chemotherapy arm, preoperative RT was given in accelerated fashion (3 weeks) to a total dose of 51 Gy in twice a day fractions of 1.7 Gy. This course of RT was administered with cycles three and four during which, only ifosfamide was given. The rate of LR was 13% in the chemoradiation arm and 22% in the preoperative RT alone arm (p = 0.38).

In summary, large randomized trials have failed to show a significant improvement in OS for patients with nonmetastatic STS receiving chemotherapy including doxorubicin and ifosfamide. However, when combined with other smaller trials, there may be a marginal benefit in term of OS. Therefore, it is not unreasonable to offer chemotherapy to younger patients with relatively sensitive subtypes such as high-grade myxoid liposarcoma and synovial sarcoma chemotherapy.

INTRAABDOMINAL STS

Retroperitoneal Sarcomas

STS of the retroperitoneum represent about 15% of all STS. Liposarcomas (mainly well-differentiated and dedifferentiated subtypes) are the most common histologic type (42%) followed by LMS (29%).[124] Most of these tumors are large in size at time of presentation,[125] with 60% of them being larger than 10 cm and only 6% being less than 5 cm. Some of these tumors may grow to an enormous size, especially WDL, without symptoms. Typical symptoms when present include nonspecific abdominal pain, anorexia, and weight loss.

Metastasis to lungs but also to liver may occur in retroperitoneal STS, thus initial assessment should include CT of chest, abdomen, and pelvis. Core biopsy with image guidance is preferred over blind core biopsy because of significant heterogeneity within many of these tumors, where solid areas representing dedifferentiated liposarcoma are intermixed with WDL. Retroperitoneal sarcomas are currently classified by the TNM system. However, another classification system has been developed based on grade, completeness of resection, and

distant metastases.[126] For class 1 (low grade, grossly complete resection, and no metastases) the stage-specific 5-year survival rate was 89%. For class 2 (high grade, grossly complete resection, and no metastases) the 5-year survival was 40%. For class 3 (any grade, incomplete resection, and no metastases) it was 26%; and for class 4 (distant metastases) it was 17%.

The management of a suspected retroperitoneal sarcoma is summarized in Figure 65-13, and the mainstay of treatment is complete surgical resection. Adjuvant RT could be recommended, but the benefits unlike in extremity STS are uncertain. In addition, when evaluating patients for these treatments an important component should include the determination of vital organ function that may be compromised by RT and surgery. Of particular importance are the functional capacity of the liver and the differential function of the kidneys because one may need to be resected or irradiated. Chemotherapy has not shown benefit.

Surgery for Retroperitoneal Sarcoma

The optimal primary treatment of retroperitoneal sarcoma is en bloc excision of the tumor with adjacent involved viscera and a margin of uninvolved tissue.[127-132] Achieving a complete gross resection is critical. In a report from MSKCC[125] ($n = 278$), the most important predictor of poor disease-specific survival was incomplete gross resection (RR: 4; $p = 0.001$). It is not necessary to remove adjacent organs, unless these organs are involved. The rate of complete gross resection is improving. In a recent report from Italy, Gronchi et al[133] reported a 90.8% rate of complete gross resection in 523 patients with primary retroperitoneal STS. However, the 5-year rate of LR was 31.1%, DFS was 39.4%, and OS was 56.8%. Of the 523 patients (36.9% received adjuvant RT), 128 developed LR as a first event, and 93 developed distant metastasis. Such patterns of relapse highlight the challenge of retroperitoneal STS, where the LR rate is higher than the distant metastasis rate even when 90% complete gross resection is achieved.

Adjuvant RT

The high risk of local failure after surgery has made additional RT an attractive option for retroperitoneal sarcoma, but its role is controversial. Unlike in extremity STS, there are no randomized trials comparing surgery to surgery and radiation. Doses of radiation given in extremity STS may exceed tolerance especially when given postoperatively. There have been several strategies to address the dosimetric challenges when treating retroperitoneal STS. Although the debate about preoperative versus postoperative RT in extremity STS may not be answered to everyone's satisfactions, there is no question that preoperative RT is the preferred approach in retroperitoneal STS. The typical large tumor mass in retroperitoneal STS often serve as an in situ tissue expander that displaces small bowel and other radiosensitive viscera from the radiation field. There are several reports in the literature about preoperative RT in retroperitoneal STS. Pawlik et al[134] reported long-term results of two prospective trials using preoperative RT to 45 Gy to 50 Gy followed by resection in 72 patients. When the analysis was limited to the 54 patients who had preoperative RT and underwent complete gross resection (22 patients receive intraoperative radiation), the 5-year rate of local control was 60%, DFS 46%, and OS 61%. Gronchi et al reported on a Phase I-II trial using preoperative RT to 50.4 Gy given concurrently with three cycles of high-dose long infusion ifosfamide.[135] Of the 83 patients enrolled, 79 underwent surgery. With a median follow-up 4.8 years, the 5-year DFS was 45% and OS 59%. The cumulative incidence of LR was 37% and distant recurrence 26%.

Other strategies included adding intraoperative radiation (IORT) to EBRT with encouraging results.[136-138] The main advantage of IORT is to be able to dose escalate, while physically or with the help of shielding, to reduce the dose to adjacent normal structures. Typical dose of external beam is usually 45 Gy to 50 Gy and that of IORT 10 Gy to 15 Gy (Table 65-5). At MSKCC, HDR IORT is used, whereas at MGH and Mayo Clinic it is mainly electron IORT. The target to be treated with IORT is mainly the posterior structures (paraspinal tissues and vessels) where surgeons have difficulty obtaining wide negative margins. The reported 5-year local control with such an approach ranges from 59% to 83%. At the Mayo Clinic, 3 of 43 patients (7%) with primary disease developed LR as opposed to 17 of 44 patients (49%) who were treated for locally recurrent disease.[137] The reported 5-year OS ranges from 48% to 74%, again with better results in patients with primary disease. Moderate to significant complications are not infrequent.[136-138] Special consideration should be given to peripheral neuropathy because it is a dose-limiting toxicity of IORT. The rate ranges from 6% up to 37%, and it is influenced by the type of IORT. Patients treated with HDR IORT have a low rate of peripheral neuropathy (6%) compared with 15% to 37% with electron IORT.[136-138]

The use of proton therapy and IMRT has been investigated at MGH.[139] They reported on 28 patients; 75% received preoperative IMRT or protons and 11 received additional IORT. With a median follow-up of 33 months, the 3-year local control was 90% for primary lesions ($n = 20$) and 30% for recurrent. Dose-painting IMRT has been suggested as an alternative to preoperative RT plus IORT. The rationale being, that what needs dose escalation is not the whole target volume, but instead the posterior structures (vessels and paraspinal tissues) as is used with IORT. Tzeng et al[140] reported on 16 patients treated with such an approach to a total dose of 57.5 Gy. Complete gross resection was achieved in 14 of 16 patients. With a median follow-up of 28 months, the 2-year local control was 80%, and the rate of late gastrointestinal toxicity was 6%. At MSKCC, the current approach for adjuvant RT when needed is the dose-painting approach. The expansion margin around the GTV to create a CTV is typically 1.5 cm. The expansion margin from CTV to PTV is 1 cm. This volume is treated to 50.4 Gy in 28 fractions. Posterior structures are dose painted to 60.2 Gy at 2.15 Gy per fraction (Figure 65-14). Some have taken this concept one step further and limited the radiation to the posterior structures only. Bossi et al reported on 18 patients with retroperitoneal liposarcomas treated to 50 Gy preoperatively with such an approach. With median follow-up of 27 months, there were two LRs and one distant relapse.[141]

In summary, the management of retroperitoneal STS is challenging. Even in modern surgical series where in 90% of

TABLE 65-5 Outcome with Resection: IORT with or without EBRT in Retroperitoneal STS

	n	F/U	EBRT	IORT	5-y LC	5-y OS	GI toxicity	Neuropathy
MGH136	16	38 mo	Preop	10-15 Gy	83%	74%	10%	15%
Mayo137	87	42 mo	Preop	12-15 Gy	59%	48%	18%	37%
MSKCC138	32	33 mo	Postop	12-15 Gy	66%	64%	19%	6%

F/U, *Follow-up;* EBRT, *external beam radiotherapy;* IORT, *intraoperative radiotherapy;* LC, *local control;* OS, *overall survival;* GI, *gastrointestinal;* MGH, *Mass General Hospital;* MSKCC, *Memorial Sloan Kettering Cancer Center.*

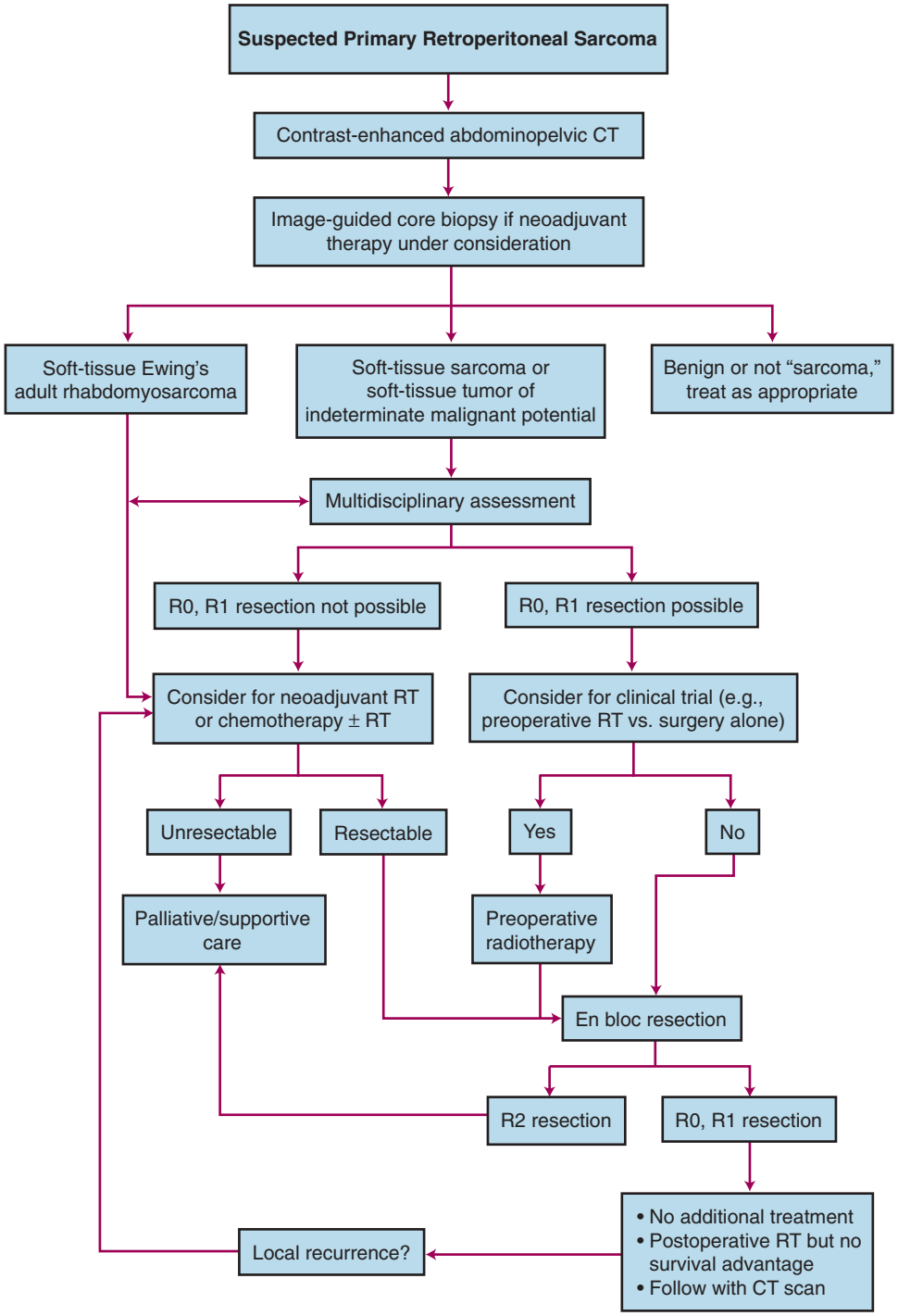


Figure 65-13 Treatment and diagnostic algorithm for a suspected retroperitoneal soft-tissue sarcoma. These lesions are often low-grade liposarcomas and resemble mature fat, presenting difficulties for the pathologist in ascertaining a pathologic diagnosis of sarcoma even when multiple image-guided biopsies are attempted. The clinician may need to determine the appropriate choice of treatment even when the diagnosis is clinically highly suspicious, but biopsy sampling artifact may make confirmation of pathologic diagnosis improbable without definitive resection. The place of induction approaches, especially preoperative RT, needs to be considered on an individual basis in such cases. Not included in the algorithm is the critical necessity to evaluate the functional capacity of the patient, which should especially include differential evaluation of both kidneys before resection or irradiation (see text). *CT,* Computed tomography; *R0,* microscopically clear resection; *R1,* microscopically positive but grossly clear resection; *R2,* resection with macroscopic gross residual disease; *RT,* radiation therapy.

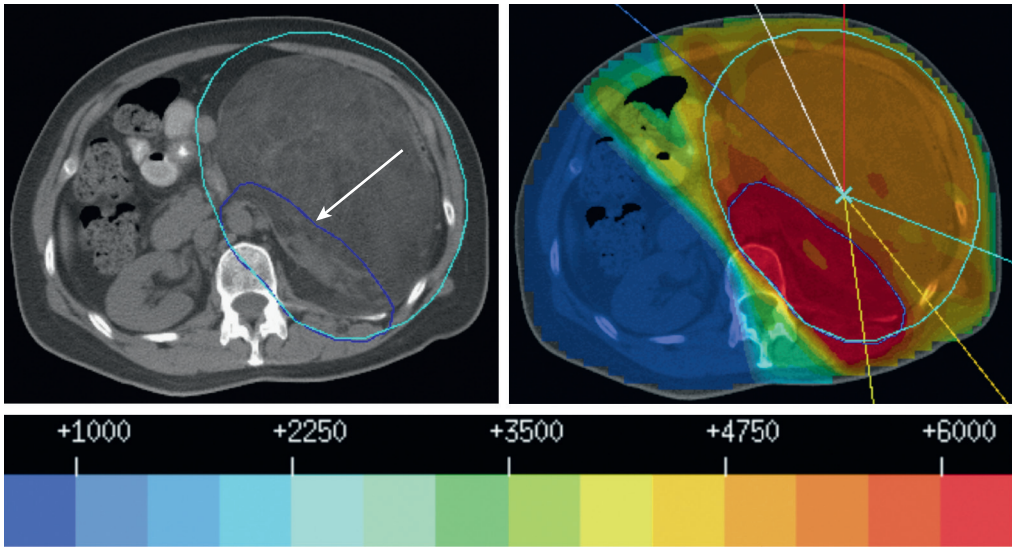


Figure 65-14 Dose-painting preoperative intensity-modulated radiation therapy in retroperitoneal soft-tissue sarcomas. Arrow indicates posterior structures. Orange zone is 50.4 Gy and red zone is 60.2 Gy (bowel excluded).

cases complete gross resection was obtained, the 5-year risk of LR was about 30%. The typical pattern of relapse was more local than distant suggesting a potential role for adjuvant RT. But unlike extremity STS, there are no prospective randomized trials to support its role and the toxicity is not minimal. If adjuvant RT is to be used, preoperative RT to 45 Gy to 50 Gy is preferred over postoperative RT. There are several approaches to dose escalation. IORT for 10 Gy to 15 Gy in addition to 45 Gy to 50 Gy EBRT have been used with good outcome. It seems that those with primary disease are the one who benefit the most. Data on dose-painting IMRT are preliminary but encouraging.

Primary Gastrointestinal Stromal Tumors

GISTs are the most common mesenchymal tumors of the gastrointestinal tract. The incidence is on the rise in part because of better recognition of these tumors using immunohistochemistry and molecular diagnostics.[142] With an incidence of 4000 cases per year in the United States, GISTs are now considered the most common type of sarcoma.[143] As mentioned previously, these tumors have oncogenic mutations in *KIT* or PDGFR-α. They typically affect patients in their fifth and sixth decades of life. The primary treatment is surgical resection. Tumor size, mitotic index, tumor location, and tumor rupture during surgery are independent predictors of recurrence after complete resection.[144] The modified National Institutes of Health (NIH) criteria use tumor size (three breakpoints: 2 cm, 5 cm, and 10 cm), mitotic count, and location (gastric versus nongastric) for risk stratification after surgery.[145] For patients with high-risk disease, the 10-year recurrence-free survival is 36.2%, for intermediate risk, 86.9%, low risk, 89.7%, and for very low risk, 94.9%.

Management of GISTs has dramatically changed with the use of imatinib, a selective tyrosine kinase inhibitor of *KIT* and PDGFR-α. The median survival of patients with metastatic GIST treated with this agent improved on average, from 9 months to more than 4 years.[143,145-147] Imatinib was also found effective in the adjuvant setting for patients with high-risk disease.[148]

Most of the current research focuses on the duration of treatment and correlation of kinase genotypes and outcome. Imatinib 400 mg daily is considered adequate for most patients with metastatic disease. Treatment should be continued on a lifelong basis. A randomized trial from the French Sarcoma Group[149] reported 2-year progression-free survival of 80% in patients randomized to continue on imatinib after 3 years of therapy as opposed to 16% in the group randomized to discontinue therapy after 3 years ($p < 0.0001$). The location of *KIT* mutation on exon 11 compared with exon 9 seems to influence the response to imatinib.[150] Patients with exon 9 mutations do worse; therefore, in the metastatic setting, a daily dose of 800 mg instead of 400 mg is recommended. In the adjuvant setting, a randomized trial[151] showed that compared to 1 year of adjuvant imatinib, 3 years of imatinib improved DFS and OS.

STS OF UNCOMMON SITES

Head and Neck STS

Head and neck STS comprise only about 5% of STS. They may originate within the upper aerodigestive tract or in the subcutaneous tissues of the scalp, facial tissues, or neck. Presentations vary in tumor size and locations, ranging from a superficial mass to upper aerodigestive tract obstructive symptoms, cranial nerve dysfunction, or proptosis.

They differ from extremity STS in several aspects. They tend to be smaller at presentation, have relatively high rate of aggressive histologies, such as angiosarcomas, and the risk of local recurrence exceeds that of distant spread.[152] Mattavelli et al[153] reported on 127 patients with STS of the head and neck who underwent surgical resection. Of the 127 patients, 122 (73%) were smaller than 5 cm. The rate of positive margins was 32%. Adjuvant RT was given to 36% of patients and chemotherapy to 26%. With a median follow-up of 66 months, the 5-year LR rate was 17% and distant recurrence 11%. The 5-year OS was 73%. Adjuvant RT should be considered because of the tight surgical margins. O'Sullivan et al[154] reported on 40 consecutive patients treated with preoperative RT to 50 Gy. The

actuarial 2-year local relapse-free rate was 80%, and the metastatic relapse-free rate was 85%. Major wound complications occurred in 8 of 40 patients (20%) within 120 days of surgery.

Cutaneous angiosarcoma of the head and neck region, which is most common site for this histology, deserves special consideration. These tumors occur in the dermal tissues of the head and neck, typically on the scalp (about 50% of cases) or facial skin. It is a disease of elderly patients who are Caucasian and is rarely seen in patients of African origin.[155] These lesions commonly present as purple, bruiselike lesions, with time progressing to ulceration and chronic bleeding. The multifocal nature of these angiosarcomas represents a significant challenge for local therapies. Lateral extension through the dermis makes assessment of the surgical margins difficult. Pawlik et al reported on 29 patients with scalp angiosarcomas in whom clear margins of resection were achieved in only 21.4% of patients.[156] Guadagnolo et al[157] reported on 70 patients: 20 (29%) were treated with surgery alone, 27 (39%) with RT alone, and 23 (33%) with surgery and radiation. Chemotherapy was given to 44 patients. Median follow-up was 2.1 years. The OS rate was 43% at 5 years, and local control was 43%. Of the 50 patients who received RT (median dose 60 Gy), 22 (44%) developed LR (68% in-field, 23% marginal, and rest outside field). Those treated with surgery and radiation had significantly better local control than those treated with surgery or RT alone (84% versus 24%, $p < 0.0001$).

Postoperative RT with wide margins to minimize marginal recurrences is recommended, but RT techniques remain challenging because of the large convex surface of the scalp and the desire to avoid irradiating underlying brain beyond tolerance. Newer approaches that combine IMRT with other techniques are now available.[158] Metastasis is common and occurs mostly in regional lymph nodes and the lung. Patients with advanced disease have a poor prognosis, but there can be dramatic responses to chemotherapy in a minority of patients, with paclitaxel being the most promising.[159,160] A Phase II trial with sorafenib, a tyrosine kinase inhibitor of vascular endothelial growth factor receptor that also blocks *RAF* signaling, has shown significant activity against angiosarcoma.[161]

Breast Sarcomas

Primary breast sarcoma is rare, but histologic subtypes are diverse, ranging from phyllodes tumors (the most common) with relatively good prognosis to radiation-associated angiosarcomas on the other end of the spectrum. Most patients present with a breast mass, although RT-associated angiosarcomas may also present as purple skin discoloration. Treatment recommendations are a hybrid between extremity STS and adenocarcinoma of the breast. Unlike breast adenocarcinomas, breast STS tend to be larger; thus, mastectomy is used more often. Axillary lymph node dissection is not routinely needed because of a low risk of nodal involvement. Breast-conserving surgery can be attempted as long as adequate negative margins are obtained.

Treatment of phyllodes tumor is based on the degree of malignancy. Those with benign tumors generally do not require adjuvant radiation. For patients with borderline or malignant phyllodes, the need for RT depends on whether the patient underwent mastectomy or lumpectomy. Belkacemi et al reported 5-year local control of 91% with mastectomy alone and 92% with mastectomy and RT, indicating that RT is not needed after mastectomy unless there are positive margins.[162] Pezner et al[163] reported on 169 patients with malignant phyllodes tumors who underwent lumpectomy alone. With a median follow-up of 64 months, the 5-year local control was only 79.4% and other studies confirm a LR rate of about 20% with lumpectomy alone.[164] In contrast, Barth et al reported on a prospective study of 46 patients who had negative margins after lumpectomy and received postoperative radiation to 50.4 Gy. With a median follow-up of 56 months, the 5-year local control was 100%. These results favor the use of postoperative RT after lumpectomy. The role of chemotherapy in the management of this disease is limited.[165]

Radiation-associated angiosarcomas deserve a special consideration. It is a potential long-term sequela after breast irradiation, with an estimated cumulative incidence of 0.3% at 15 years after treatment.[166-168] But this histology is not uniquely radiation related. Radiation naïve patients can develop angiosarcoma in the breast.[169] RT-associated angiosarcomas tend to occur in older patients and involve the dermis, as opposed to sporadic cases, which present as a parenchymal mass in younger patients. The prognosis of RT-associated angiosarcomas is poor; Torres et al[170] reported on 95 patients (95.7% with localized disease), the 5-year local control was 50.7% and OS 53.5%.

Thoracic STS

Thoracic STS are a heterogenous group with lesions arising from the chest wall, mediastinum, or pleura. Durani et al[171] reported on 337 patients with localized disease. The mean age was 50 years and median size was 8 cm. Location was soft tissue and chest wall in 85.5%, mediastinum 9.5%, and pleura 5%. Adjuvant RT was given to 51.4% of patients and chemotherapy to 40.7%. With a median follow-up of 4.7 years, the 5-year rate of LR was 14%, and, 90.8% (306 of 337) in the subset of patients with primary disease. The use of RT was associated with significant improvement in local control. The 5-year distant relapse rate was 17% and OS was 65%. Chest wall STS are often treated in a similar fashion to extremity STS. The preoperative approach should be encouraged to limit the volume of lung receiving a high dose of radiation.

ATYPICAL-BEHAVING STS SUBTYPES

Pediatric-Type STS in Adults

Certain histologic types of STS such as rhabdomyosarcoma and Ewing's sarcoma are seen predominantly in children, but they can still occur across the age spectrum.[172] When such histologies are encountered in adult patients it raises the issue of how they should be treated. In pediatric STS, there is heavy reliance on chemotherapy but less so in adults, and the dose of RT in pediatric STS is less than what is used in adult STS.

Rhabdomyosarcoma

Rhabdomyosarcoma (RMS) in the 2013 WHO classification includes the following main subtypes: embryonal, alveolar, and pleomorphic.[22] Alveolar RMSs have distinct translocations that help distinguish it from other RMSs. There is signature translocations in t(2;13) in 60% of cases and in t(1;13) in 20% of cases. Embryonal RMS is characterized by loss of heterozygosity (LOH) at chromosome 11p15.5. Embryonal and alveolar RMSs are predominantly seen in children but they can occur in adults up to the age of 45. Pleomorphic RMS display complex genetic alterations and tends to occur in adults older than 45 years.

RMS is one of the sarcomas associated with a risk of lymph node metastasis. RMS is divided into four groups, and three risk categories that take into account not only typical TNM findings but also tumor site and histology.

The prognosis of adult RMS is worse than in children. Whether this is a reflection of different biology or

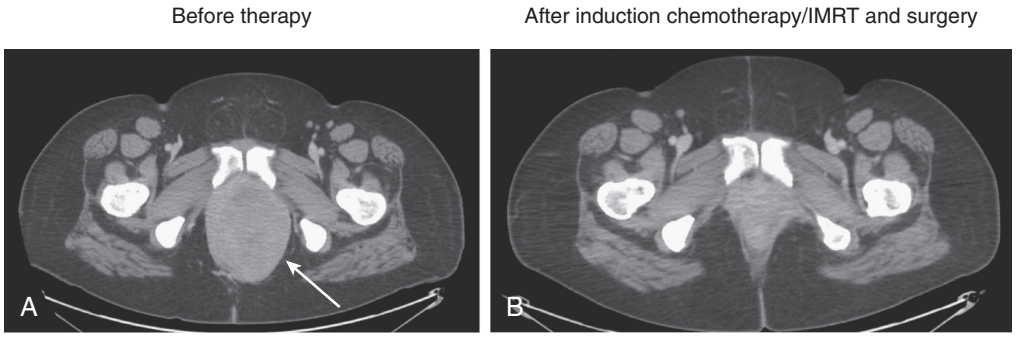


Figure 65-15 Ewing's sarcoma of the perirectal region: **A,** Tumor mass at presentation *(arrow)*, **B,** after induction chemotherapy, preoperative intensity-modulated radiation therapy (IMRT) to 50.4 Gy and surgery. Pathology at surgery did not reveal any residual disease.

aggressiveness of treatment is not entirely clear. In a report from MSKCC[173] of 148 patients (16 years old or older) with RMS, the patients treated on or according to RMS protocols had better OS (54% versus 36%; $p = 0.03$). RT to the primary site was given to 65% of patients. In the subset of patients with nonmetastatic disease ($n = 94$), the 5-year LR rate was 34% and the 5-year OS was 45%. It could be argued that the aggressive multimodality approach, as used in pediatric RMS, is warranted in adults as well. The doses of postoperative RT in pediatric RMS are modest, usually 36 Gy to 41 Gy. It is unclear if such doses are adequate for adults with RMS. Certainly, for patients with pleomorphic RMS the postoperative RT dose should be 63 Gy to 66 Gy, similar to other adult STS.

Extraskeletal Ewing's Sarcoma

Most Ewing's sarcomas in children are primary bone sarcomas, whereas most adult Ewing's sarcomas arise in soft tissue (about 75%). The most common site is the lower extremity (25%) followed by upper extremity (18%). These tumors have signature translocations t(11;22) in 90% of cases and the second-most common translocation is t(21;22). Martin et al[174] reported on 46 adult patients with primary disease, and with a median follow-up of 29 months, the 5-year survival was 60%. The general treatment guidelines follow those with bone Ewing's sarcoma including the use of systemic chemotherapy and radiation (Figure 65-15). Again the typical postoperative dose of RT for pediatric Ewing's sarcomas is 45 Gy to 50 Gy, and whether that is adequate for adults is unclear.

Dermatofibrosarcoma Protuberans

Dermatofibrosarcoma protuberans is a superficial tumor that often manifests as a deceptive dermal, raised, purple or red lesion(s) in the lower neck, upper chest, and shoulder girdle regions, although any site may be involved. This tumor arises from the dermis and exhibits a characteristic slow but persistent growth over many years. It affects mainly patients of middle age. More than 90% of these tumors are characterized by the t(17;22)(q22;q13) reciprocal chromosomal translocation that is now becoming the hallmark feature of the diagnosis. The main treatment is surgical resection with wide margins. Another approach is Mohs's micrographic surgery. Paradisi et al[175] pooled results from the literature and reported six recurrences in 463 cases for Mohs's surgery (1.3%), as opposed to 288 recurrences in 1394 cases for wide local excision (20.7%).

Castle et al[176] reported on 53 patients treated with surgery and radiation (median dose 60 Gy for postoperative RT and 50 Gy for preoperative RT). With a median follow-up of 6.5 years, the 5-year local control was 98%. The authors recommended that adjuvant RT should be considered for patients with large or recurrent tumors or when attempts at wide surgical margins would result in significant morbidity. Imatinib has demonstrated antitumor effects in advanced disease harboring t(17;22). Data from two Phase II trials of imatinib showed objective response rate approaching 50% in locally advanced or metastatic dermatofibrosarcoma protuberans.[177]

Aggressive Fibromatosis

Also referred to as extraabdominal desmoid tumors, aggressive fibromatosis is a benign neoplasm capable of local infiltration and destruction. It affects young adults and can arise anywhere in the body but predominantly in extremity girdles, abdominal wall, and extremity. Wide surgical excision is the treatment of choice. But recurrence is frequent; the treatment should be individualized because this tumor is benign, patients are relatively young, and it is advisable to withhold or delay RT and systemic treatments if at all possible.

Gronchi et al[178] reported on 203 patients treated with surgery the 5-year DFS was significantly better for primary compared to recurrent lesions (81% versus 59%, $p < 0.01$). In the subset of patients with primary disease ($n = 128$; 15.6% received adjuvant RT); the 5-year DFS for those with positive margins was not significantly different than those with negative margin (79% versus 82%, $p = 0.5$). The corresponding figures in the subset of patients with recurrent disease ($n = 75$; 26.7% received adjuvant RT) were 47% versus 65%, but that difference did not reach statistical significance ($p = 0.17$). This data indicate that adjuvant RT may not be required in primary disease even with positive margins. In contrast, data from MDACC showed that if resection margins were positive after surgery alone, the 10-year recurrence rate exceeded 50% but was reduced to 31% in patients who received RT ($p = .007$). In addition, in patients treated with RT for gross disease, the 10-year actuarial relapse rate was 24%, making this a viable option for such patients.[179] In a subsequent report they recommended that for patients who have undergone surgery with positive resection margins, postoperative RT to a total dose of 50 Gy in 25 fractions with a 5-cm to 7-cm margin on gross tumor was advised. For unresectable gross disease, RT alone to a total dose of 56 Gy in 28 fractions delivered via a shrinking field technique after 50 Gy was recommended.[180]

Imatinib has demonstrated clinical activity in recurrent or advanced nonresectable aggressive fibromatosis. The French Sarcoma Group reported the results of a Phase II trial using imatinib for progressive and recurrent aggressive fibromatosis.[181] Forty patients were treated with imatinib (400 mg/day for 1 year) with 1 complete response, 3 partial confirmed

responses, 28 cases of stable disease, and 3 cases with progressive disease observed. The 2-year progression-free rate was 55%. Recent data seem to indicate even better activity of sorafenib against these tumors.[182]

SALVAGE TREATMENT AND PALLIATION

Local Recurrence

General management approaches for locally recurrent STS are summarized in Figure 65-16. For patients who develop LR (nonmetastatic) and are radiation naïve, they should be treated in a similar fashion to primary disease. For previously irradiated lesions, greater individualization is needed. BRT in addition to surgery is often an option. Torres et al[183] reported on 62 patients with locally recurrent STS after prior RT; 25 were treated with surgery alone and 37 with surgery and reirradiation. The types of reirradiation were as follows: LDR BRT to 45 Gy to 50 Gy in 33 patients, 3 preoperative RT to 45 Gy to 50 Gy, and 1 postoperative RT to 64 Gy. The overall 5-year local control was 51%; 39% in the surgery alone group compared with 58% for surgery and reirradiation ($p = 0.4$). Complications requiring outpatient or surgical management were more common in patients who had undergone reirradiation (80% versus 17%, $p < 0.001$). Thus, the additional morbidity with reirradiation has to be weighted against potential benefit.

Metastatic Disease

Surgery

With the propensity for isolated lung metastasis in STS, consideration of pulmonary metastasectomy is always warranted. The International Registry of Lung Metastases reported 5206 patients with pulmonary metastases resection, 2173 of whom had bone sarcomas or STS. Patients with single metastases and long disease-free intervals were recognized as having the best outcome.[184] The importance of achieving complete resection was highlighted by Billingsley et al. In the 719 patients with lung metastasis from STS, the OS rate was 25%. In the group that underwent complete resection, the 3-year survival rate was 46%. In contrast, those who underwent incomplete resection did not fair much better than those who did not have resection.[185]

Radiation

Until recently, radiation played only a minor role in the management of metastatic STS. But with the advances in SBRT, a

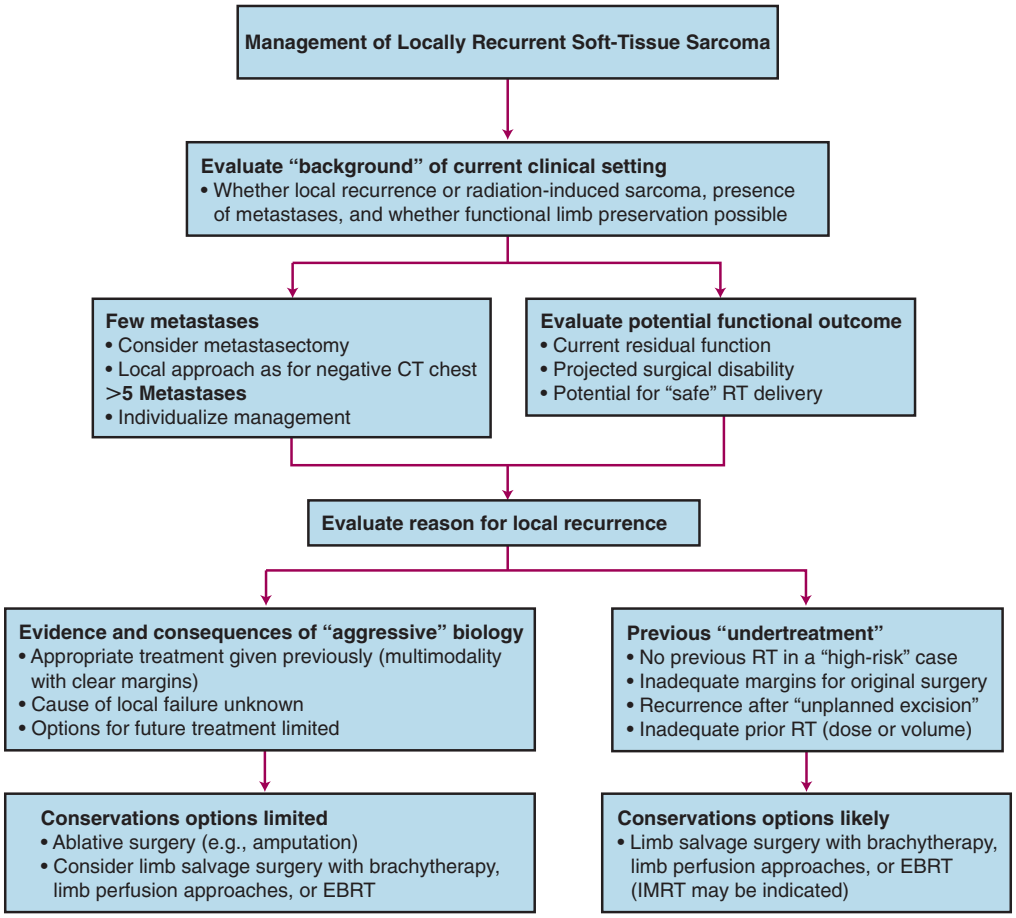


Figure 65-16 Management algorithm for the treatment of locally recurrent soft-tissue sarcoma. These lesions are complex to manage, and the clinician must consider various elements that include the potential that the lesion may be an irradiation-induced sarcoma, appreciating the reasons underlying the recurrence, the impact of concurrent metastases on decision making, and the options for protecting functioning tissue at the site of the recurrence. *CT,* computed tomography; *EBRT,* external beam radiation therapy; *IMRT,* intensity-modulated radiation therapy; *RT,* radiation therapy.

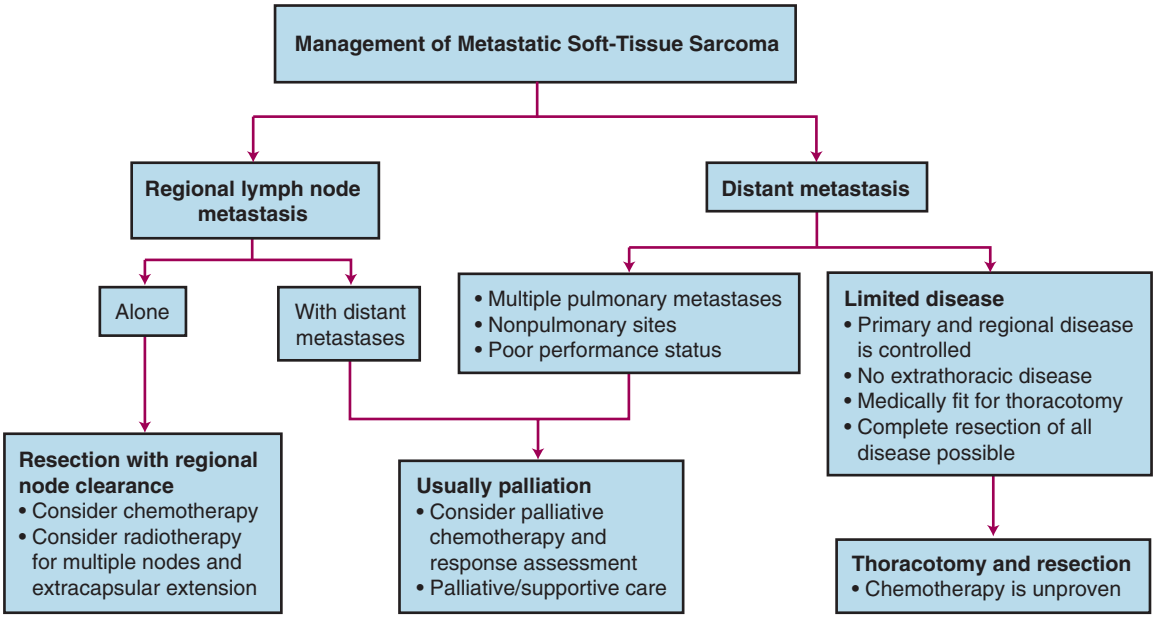


Figure 65-17 Management algorithm for the treatment of metastatic soft-tissue sarcoma. Patients with these lesions have potentially salvageable disease that requires careful selection before initiating intensive treatment approaches.

subset of patients with limited metastatic burden and good performance status seems to benefit from it. Dhkal et al[186] reported on 15 patients with lung metastasis who underwent SBRT, generally 50 Gy in 5 Gy fractions. The 3-year local control was 82%. In a report from UCLA,[187] 16 patients were treated with SBRT to a median dose of 54 Gy in three to four fractions. With a median follow-up of 20 months, the control rate was 94%. In a systematic literature review regarding hypofractionated SBRT in variety of metastatic tumors to lung including STS, the 2-year local control and OS for the single-fraction therapy were 78.6% and 50.3%, respectively, and with the fractionated therapy they were 77.9% and 54%. Reported toxicities were low.[188]

For patients with spinal metastasis SBRT is an attractive option. In a report from MSKCC,[189] 88 patients were treated with hypofractionated or single-fraction SBRT. Local control at 12 months was 87.9%. Those treated with single fraction (median dose 24 Gy) did better ($p = 0.007$). Grade-3 late toxicity was 4.5%.

Chemotherapy for Metastases

General management principles for metastatic STS are highlighted in Figure 65-17. A complete and durable response to systemic chemotherapy in metastatic STS is uncommon. Single-agent doxorubicin is the most commonly used drug in the first-line treatment of metastatic STS[20] and produce response rates ranging from 12% to 24%. The response rate with single-agent ifosfamide[20] is higher typically ranging from 20% to 25%. Bramwell et al performed a meta-analysis on data on 2281 participants from eight randomized controlled trials comparing single-agent doxorubicin to doxorubicin-based combination chemotherapy and concluded that single-agent doxorubicin was the optimal therapy.[190] Median survival ranged from 7.7 months to 12.0 months with single-agent doxorubicin and was 7.3 months to 12.7 months with combination chemotherapy.

In a recent randomized trial,[191] 228 patients were randomized to doxorubicin alone and 227 to doxorubicin and ifosfamide. All patients had metastatic or unresectable disease. There was no significant difference in OS between the groups; median OS was 12.8 months in the doxorubicin group compared with 14.3 months in the doxorubicin and ifosfamide group (HR: 0.83; $p = 00.076$). More patients in the doxorubicin and ifosfamide group than in the doxorubicin group had an overall response (26% versus 14%; $p < 0.0006$). The most common grade-3 and grade-4 toxic effects were all more common with doxorubicin and ifosfamide than with doxorubicin alone, and they included febrile neutropenia (46% versus 13%), anemia (35% versus 5%), and thrombocytopenia (33% versus <1%), respectively.

Individualization of treatment is important because certain histologies respond differently. In a retrospective review of EORTC chemotherapy trials, ifosfamide-containing regimens provided better response rate than doxorubicin in patients with synovial sarcomas. Conversely, patients with LMS were less responsive to ifosfamide-containing regimens.[192] Thus, ifosfamide is not typically recommended for LMS, instead gemcitabine and docetaxel are often used. Maki et al reported on a Phase II randomized trial comparing gemcitabine and docetaxel to gemcitabine alone in patients with metastatic STS; the combination yielded superior progression-free survival and OS especially for patients with LMS.[193] As mentioned previously, patients with metastatic angiosarcomas seem to respond well to paclitaxel.[194]

Pazopanib, a multitargeted tyrosine kinase inhibitor, has been used in nonlipomatous STS. In a recent trial,[195] 369 patients with metastatic STS, progressing despite previous standard chemotherapy, were randomly assigned in a 2:1 ratio to receive pazopanib ($n = 246$) or placebo ($n = 123$). Median progression-free survival was 4.6 months for pazopanib compared with 1.6 months for placebo ($p < 0.0001$). OS was 12.5 months with pazopanib versus 10.7 months with placebo ($p = 0.25$). As we begin to unlock the pathways involved in sarcomatogenesis (Figure 65-18), newer targeted therapies based on the specific genomic alterations will be used.[196,197]

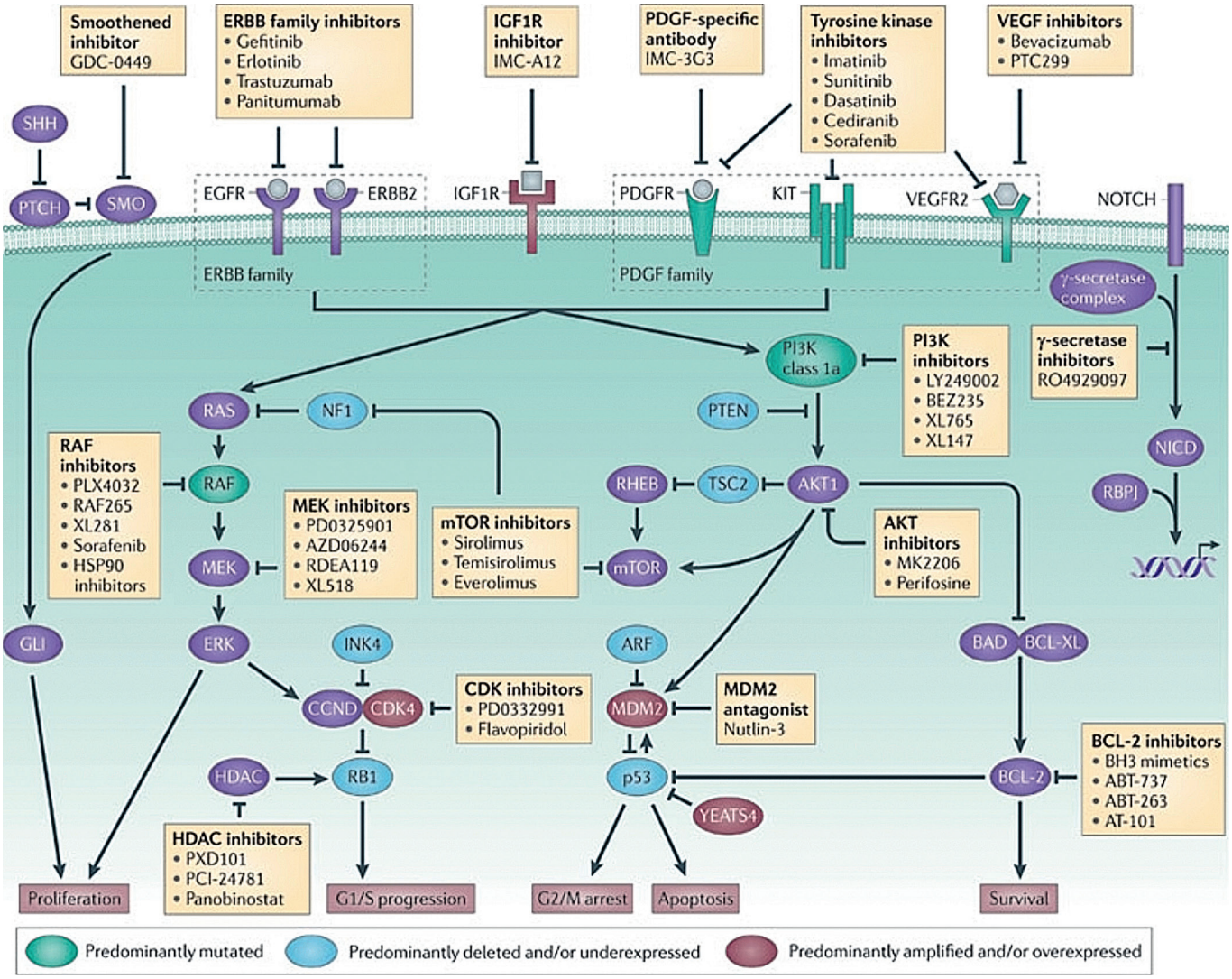


Figure 65-18 Pathways for targeted therapy in sarcoma. Subsets of nodes are colored by their dominant alteration type (mutated, deleted, or amplified). Yellow boxes indicate targeted agents in clinical use or early development.
From Taylor BS, Barretina J, Maki RG, et al: Advances in sarcoma genomics and new therapeutic targets. Nat Rev Cancer 11(8):541–557, 2011. With permission.

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CHAPTER

66 Benign Diseases

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DEFINITION AND CLASSIFICATION OF BENIGN DISEASES

Many diseases that are pathologically benign (nonmalignant) do not act clinically benign, causing significant symptoms or dysfunction to the patient. A number of these entities can be successfully treated with ionizing radiation. The use of irradiation for benign diseases dates back centuries, with initial uses coming from results obtained using x-rays for experimental purposes. Sokoloff reported positive results in radiotherapy of painful "rheumatoid diseases" as early as 1898.[1] The traditional classification of benign diseases amenable to radiotherapy as inflammatory, degenerative, hyperproliferative, functional, and other types of disorders is currently outdated. Worldwide, irradiation of benign diseases has become more important, although indications and treatment concepts have changed considerably with increasing information regarding acute and late effects of radiation therapy. Today, clear differences between countries do exist regarding radiation therapy use in nonmalignant conditions because of historical clinical traditions and differences in training.[2-6]

Indications for the Implementation of Radiotherapy

Benign diseases have several features that may justify the use of radiotherapy. They can grow invasively and aggressively. For example, desmoids (aggressive fibromatoses) and keloids can be cosmetically disfiguring and functionally disturbing. Endocrine orbitopathies may be life threatening. Refractory hepatic hemangiomas (Kasabach-Merritt syndrome) or juvenile angiofibromas in facial regions of children or adolescents may require radiotherapy. There may be an indication for irradiation when benign diseases have a lasting effect on quality of life by causing pain or other serious symptoms, or if other therapeutic options are not available, have failed, or may induce more side effects. Overall, however, radiotherapy is *rarely* the first option for treatment of most nonmalignant diseases. Therefore, the process leading up to informed consent must be especially thorough. Particular attention should focus on the risk for long-term consequences, such as the induction of secondary malignancies, including solid tumors or leukemia.

Long-Term Risk for Tumor Induction

Considering international data about the emergence of tumors and leukemias after whole-body exposure to ionizing radiation (United Nations Scientific Committee on the Effects of Atomic Radiation [UNSCEAR], Biological Effects of Ionizing Radiation [BEIR]), the risk for tumor induction can be calculated on gender- and age-related bases.[7] The average lifetime risk for exposure to radiation is lower in men (9.5%) than in women (11.5%). Table 66-1 summarizes the age- and gender-specific risks for tumor induction.

Principles of Irradiation of Benign Diseases

The principles of irradiation of benign diseases can be summarized in 10 statements (Box 66-1). These should be carefully considered for each patient in whom irradiation is being evaluated.

RADIOBIOLOGIC ASPECTS

The radiobiologic mechanisms, known from the treatment of malignant disease, and the identified proliferating target cells are only partially applicable to benign diseases. Other radiation-sensitive target cells and cellular and functional mechanisms should be considered as target points for ionizing radiation. However, radiotherapy is probably not working via one particular mechanism but rather through a complex interaction of different effects.

Reactions in Connective Tissue

Several mechanisms are triggered by ionizing radiation in connective tissues. Following any trauma or acute or chronic inflammation, several cell systems regulate the repair process where fibroblasts play a central role, particularly during the reparative phase, which is characterized by high cell production and stimulation of specific growth factors. Furthermore, ionizing radiation also has a pivotal influence on cellular differentiation.[8,9]

For some hyperproliferative events, fibroblast overreaction is responsible for the disease process (e.g., during the early stage of Dupuytren's contracture, during the early phase of Peyronie's disease, in keloids, and in the progression of aggressive fibromatosis [desmoid]). The increase in fibroblast production can be modified by ionizing radiation, which influences differentiation and suppresses cell proliferation.

Reactions in the Vascular System

The endothelial cells of the capillaries and the larger arterial and venous blood vessels possess a high proliferative potential and are the origins of various cytokine-mediated cellular reactions. Intercellular adhesion molecule 1 (ICAM-1), a mediator of the leukocyte-endothelial interaction, is induced by low radiation doses.[10] Similarly, selectins mediate the penetration of mononuclear blood cells into the interstitial tissue. Endothelial prostaglandin release is also modulated by ionizing radiation.[11] Cellular and membrane functions can be modified when they are exposed to radiation.

Large single or total doses may cause endothelial damage, leading to sclerosis and obliteration of small blood vessels. Higher fractionated doses or single doses are used for cerebral arteriovenous malformations (AVMs) or symptomatic vertebral hemangiomas, and lower single and total doses are applied to reduce inflammatory processes such as endocrine orbitopathy and pseudotumor orbitae.

TABLE 66-1 Tumor Induction Depending on Age and Gender: Relative Lifetime Risk

Age-group (Years)	Men (%/Sv)	Women (%/Sv)
≤10	25.0-26.0	32.0-33.0
11-20	15.0	19.0
21-30	13.0-14.0	17.0
31-40	7.0	8.0
41-50	5.0	6.0
51-60	4.5	5.0
61-70	3.5	4.5
71-80	2.5	3.0
>80	1.0	1.5

From Jansen JTM, Broerse J, Zotelief J, et al: Assessment of carcinogenic risk in the treatment of benign disease of knee and shoulder joint. In Seegenschmiedt MH, Makoski H-B, editors: Kolloquium Radioonkologie/ Strahlentherapie, Radiotherapie bei gutartigen Erkrankungen, Vol 15, Altenberge, Germany, 2001, Diplodocus Verlag, pp 13–15.

BOX 66-1 Principles of Irradiation of Benign Diseases

1. Estimate the natural course of disease without therapy.
2. Consider the potential consequences of nontreatment of the patient.
3. Review data about alternative therapies and their therapeutic results.
4. Conduct a risk-to-benefit analysis compared with other possible measures.
5. Prove that the indication is justified if conventional therapies have failed, if risks and consequences of other therapies are greater, and if nontreatment would have more dramatic consequences than irradiation for the patient.
6. Consider the potential long-term radiogenic risks to the individual patient.
7. Inform each patient about all relevant details of radiotherapy: target volume, dose concept (single and total dose), duration of single session and whole irradiation series, relevant radiogenic risks, and side effects.
8. Obtain written consent from the patient following thorough patient education.
9. Ensure long-term aftercare to document results.
10. Request a competent second opinion in case of doubt and if the provided patient's data or treatment decisions are uncertain.

Data from Seegenschmiedt MH, Katalinic A, Makoski H, et al: Radiation therapy for benign diseases. Patterns of care study in Germany. Int J Radiat Oncol Biol Phys 47:195–202, 2000; Micke O, Seegenschmiedt MH: The German Working Group guidelines for radiation therapy of benign diseases. A multicenter approach in Germany. Int J Radiat Oncol Biol Phys 52:496–513, 2002.

Reactions in Painful Processes

Degenerative processes in hypotrophic tissues such as tendons, ligaments, and joints can cause pain by chronic inflammation and trigger various forms of functional impairment of the musculoskeletal system. Radiation does not influence the degenerative process but may reduce inflammation and as a consequence, improve function of affected joints and limbs and achieve pain relief.[12,13]

Mechanism of Action

To know individual target cells and potential pathogenic mechanisms of the various benign diseases also means to coordinate the radiation therapy concepts accordingly and consistently. The dose concepts applied in benign diseases differ greatly from each other because of other potential mechanisms of action (Table 66-2).

TABLE 66-2 Mechanisms of Action and Dose Concepts

Mechanisms of Action	Single Dose (Gy)	Total Dose (Gy)
Cellular gene and protein expression (e.g., eczemas)	<2	<2
Inhibition of inflammation in lymphocytes (e.g., in pseudotumor orbitae)	0.3-1	2-6
Inhibition of fibroblast proliferation (e.g., in keloids)	1.5-3	8-12
Inhibition of proliferation in benign tumors (e.g., in desmoids)	1.8-3	45-60

BENIGN DISORDERS OF THE HEAD AND NECK AND CENTRAL NERVOUS SYSTEM

Benign tumors of the central nervous system (CNS) can lead to severe, life-threatening symptoms resulting from local expansion and pressure on neighboring normal structures. Depending on the growth rate, the surrounding normal tissues can potentially adapt and delay symptoms and the subsequent clinical diagnosis.

Pituitary adenomas, meningiomas, vestibular schwannomas, craniopharyngiomas, and chordomas are important benign CNS tumors treated with irradiation. These are covered fully in Chapters 23, 28, 29, and 30 and will not be discussed here.

Arteriovenous Malformation

Definition and Clinical Features

Intracranial AVMs are rare vascular abnormalities consisting of widened arteries with connections to the normal capillary bed that enables oxygenated blood to enter directly into the venous system. Approximately 80% of AVMs are located supratentorially. The incidence of AVMs is unknown. Its prevalence is below 0.01% (≈18:100,000) in the Western hemisphere. Most AVMs are discovered at the age of 20 years to 40 years. AVMs can extend to aneurysms and rupture (2% to 5% per year).[14] Neurologic symptoms associated with AVMs include headaches, hemorrhage, and cramp attacks, which may culminate in sudden death through bleeding. Increased risk of hemorrhage includes prior hemorrhage, exclusive deep venous drainage, associated aneurysms, and deep location, which can influence surgical and or radiosurgery decision making.[14,15] Lethality after the first bleeding episode occurs in up to 30%; 10% to 20% of survivors have long-term neurologic defects. Spontaneous regression is rare.[15] Diagnosis of AVMs is made with imaging techniques such as angiography and magnetic resonance imaging (MRI).

The aim of therapy is the prevention of bleeding by complete obliteration of the nidus, the improvement of neurologic malfunctions, if feasible, and preferably, minimal therapy-induced side effects. For this purpose, the options of minimally invasive endoscopic surgery, endovascular embolization, and stereotactic radiosurgery (SRS) are available. For therapy

TABLE 66-3 Arteriovenous Malformations: Obliteration Rate and Rate of Radiation Side Effects after Radiosurgery

Study (Chronological)	No. Patients	Obliteration (%)	Moderate Side Effects (%)	Severe Side Effects (%)
Steiner et al[19]	247	81	8	1
Engenhart et al[20]	212	72	4	4
Colombo et al[21]	153	80	6	2
Deruty et al[22,23]	115	82	10	Not stated
Flickinger et al[24]	197 351	72 75	5	3
Miyawaki et al	73	64	13	5
Chang et al[25]	254	79	3	2
Schlienger et al	169	64	4	1
Shin et al[26]	100	95 (5-year)	Not stated	4
Friedman et al[27]	269	53	4	1

planning, precise knowledge regarding the size, location, arterial feeders, and venous drainage of the nidus is required.

Surgical Treatment

The therapy of choice is the elective complete excision of the AVM vascular abnormality. Particularly with small AVMs in superficial, noneloquent regions of the brain, microsurgery results in high cure rates. Larger AVMs are treated initially with embolization before surgery or SRS. Only in special cases is surgery performed under emergency conditions to remove life-threatening brain hemorrhages.

Irradiation Options

Arteriovenous malformations are irradiated with SRT/SRS with a linear accelerator or Gamma Knife (see Chapters 7 and 23).

Stereotactic radiosurgery for AVMs dates back to the 1970s. The mechanism of action of SRT/SRS is linked to injury to the vascular endothelium, which causes proliferation of smooth muscle cells and the elaboration of extracellular collagen causing progressive stenosis and obliteration of the AVM.

Fractionated radiation with total doses of up to 60 Gy produced inadequate results.[16-18] Depending on the size and location of the AVM, a single dose of 15 Gy to 30 Gy is required to the periphery of the nidus. If therapy is successful, complete obliteration of the nidus will occur usually no sooner than 2 years from treatment, with many taking 3 years or longer. This delay in obliteration does leave the risk of bleeding until complete obliteration occurs. The obliteration rate after SRT or SRS is 65% to 95% (Table 66-3).

The side effects of SRT/SRS are mostly chronic and follow the time course of AVM obliteration: focal radionecroses or leukoencephalopathies occur 9 months to 3 years after SRT, but they may also appear after several weeks.[17,21,22,24,25,28-36] The risk correlates strongly with the irradiated brain volume, location of the AVM, and the total dose.[37-39] The brain volume irradiated with more than 10 Gy is an important predictive factor.[40,41]

Whether unruptured AVMs should be treated or observed has been a matter of debate. The ARUBA trial, a randomized trial of unruptured brain AVMs compared the risk of death and symptomatic stroke. Patients were randomized to either medical management for symptoms treated with pharmacologic agents alone or medical management with interventional therapy including neurosurgery, stereotactic radiotherapy, or embolization, alone or in combination. The trial was halted early because of the superiority of the medical management group because the risk of death or stroke was significantly lower compared to the intervention group.[42]

Glomus Tumor or Chemodectoma

Definition and Clinical Features

Glomus tumors (synonyms are chemodectomas or nonchromaffin paragangliomas) are rare benign tumors that can occur in multiple anatomic locations:

1. Paragangliomas occur at the carotid glomus, along the carotid, mostly near the bifurcation.
2. Jugular paragangliomas are found near the skull base in the region of the jugular bulb.
3. Paraganglioma of the tympanic glomus occurs in the region of the tympanum.
4. Other paragangliomas occur at the larynx, near the aorta, in pulmonary locations, and in the orbital cavity.

Approximately 50% of tumors are located near the skull base in the jugular fossa. The age peak is 45 years. The tumors are usually unilateral; only 10% to 20% are bilateral or multiple.[43] They grow slowly, rarely have endocrinologic activity, and degenerate into malignant forms in 5% to 10% of patients. They can also infiltrate bone, vessels, the middle ear, and cranial nerves (CN). The main symptoms are headaches, CN failure (CN V to XII), dysphagia, pulsatile tinnitus, vertigo, and hypacusis. Without therapy, there is the risk for CN injury; the swelling can be so extreme as to be life threatening. The diagnosis is made clinically and with high-resolution computed tomography (CT) and MRI.

Surgical Treatment

Although glomus tumors grow slowly, they can cause severe problems and, therefore, must be treated. In the carotid region, primary tumor resection after previous embolization is the therapy of choice. At the skull base or at the tympanum, neurosurgical interventions carry more risk, and therefore, fractionated radiation is often favored. In the case of incomplete surgery, the patient should initially be observed, and further treatment should only be started if the tumor grows.

Irradiation Options

Depending on the size and location of the lesions, the indication for RT may be either *primary* irradiation in the case of functional or other inoperability (mostly, jugular paragangliomas) or *adjuvant* irradiation for R1 to R2 resections or irradiation of *recurrence* if there is progression after surgery. Conventional fractionated three-dimensional (3D) conformal radiation therapy with 45 Gy to 55 Gy is the norm. The clinical target volume (CTV) is restricted to the tumor region with a safety margin to cover microscopic extensions.

Irradiation of paragangliomas produces control rates as good as or even better than surgery.[44] Even in large, diffusely growing or multiple tumors, radiation produces a local control rate of 88% to 100%.[26,27,44-46] Kim et al noted a recurrence rate of 22% with doses of less than 40 Gy, whereas recurrences occurred in only 1.4% with doses of more than 40 Gy.[45] Frequently, tumor rests are detectable on imaging for several years. Therapeutic success is usually assessed in terms of the regression of CN failures and the lack of tumor progression. A dose of 45 Gy to 50 Gy does not complicate surgery that might become necessary later.

Stereotactic single-dose radiation and Gamma knife therapy have efficacy in the treatment of paragangliomas.[26,27,44-51] The results are favorable compared to fractionated radiation, with excellent local control rates and acceptable side effects. Sheehan et al reported data regarding 134 patient procedures from eight Gamma knife centers including prior resection in 51 patients. The median tumor margin dose was 15 Gy. With a median duration of follow-up of 50.5 months (range, 5 months to 220 months), overall tumor control was 93% at last follow-up with an 88% actuarial tumor control 5 years after surgery. Worsening CN function was seen in 11% of patients despite radiological evidence of control.[52] No secondary malignancies were noted.

Irradiation of paragangliomas of the carotid glomus can acutely cause pharyngeal mucositis and chronically may lead to skin fibrosis and dryness of the pharyngeal mucosa on the irradiated side. Irradiation of jugular or tympanic paragangliomas can lead to acute skin reactions in the external acoustic canal, tube ventilation dysfunction, reduced sound conduction, and salivary retention may occur on the ipsilateral side.

Juvenile Nasopharyngeal Fibroma

Definition and Clinical Features

Juvenile nasopharyngeal fibromas (JNFs), which is a synonym is angiofibromas, are rare, benign, strongly vascularized tumors in the head and neck region, affecting mainly male juveniles. JNFs develop in the sphenoethmoidal suture and can spread from the epipharynx and the main nasal cavity via the sphenopalatine foramen and into the pterygopalatine fossa. After bony destruction, there is spread into the paranasal sinuses, the infratemporal fossa, the orbital space, and the middle cranial fossa.

Intracranial spread occurs in about 25% of cases. Typical symptoms are epistaxis and impaired nose breathing. Depending on the pattern of spread, facial swelling as well as orbital (e.g., blindness) and intracranial symptoms (e.g., CN failure) may occur. A biopsy can cause massive bleeding so that histologic confirmation of diagnosis is often not performed. The presence of hormone receptors shows the influence of androgynous hormones. Spontaneous remission after puberty is possible, but therapy can hardly be delayed when the symptoms increase and when complications are threatening.[53,54]

Surgical Treatment

In JNF, the main emphasis is placed on surgery combined with embolization to decrease the size of the tumor.[55,56] Small tumors that are restricted to the posterior nasal cavity and the nasopharynx can be completely removed after embolization. A JNF with lateral spread is also an indication for surgery. Endoscopic surgical approaches have been used in treating these tumors as a means of decreasing morbidity.[57,58] Through surgery, the local control rates for most JNFs without intracranial spread range up to 100% with minimal toxicity.[53,54,57,58]

Irradiation Options

Radiotherapy is an effective treatment for JNF. In locally advanced disease, complete resection is often not possible, and tumors with intracranial spread should receive primary irradiation. Other indications for radiation are tumor rests, inoperability, or local recurrence after initial surgical resection. With modern CT-based treatment planning, high control rates are achieved in locally advanced JNF as well. Intensity-modulated radiation therapy (IMRT) is often recommended.[59]

Total doses of 30 Gy to 55 Gy (1.8 Gy to 2 Gy per fraction) are said to be effective, but for large tumors, doses of 40 Gy to 46 Gy are currently recommended.[60-64] With conventional fractionated radiation, control rates of 80% to 100% can be reached. Remission of JNFs after radiation often requires several months[61]; sometimes, complete remission, as detected by imaging techniques, does not occur even after years, although there is no further growth.

Radiation side effects include mucositis, xerostomia and caries, dysfunction of the pituitary gland, CN failure, temporal lobe necrosis, osteoradionecrosis, growth impairment of the facial skull, cataract, glaucoma, and atrophic rhinitis, but these can be limited through careful radiation planning and highly conformal radiation. Radiation-induced tumors occur in up to 4% of cases, particularly in young patients; this has to be weighed against the risk for sudden death or severe morbidity after surgery.

BENIGN DISORDERS OF THE EYE AND ORBIT

Macular degeneration and endocrine orbitopathy (Graves' disease) are important benign diseases of the eye or orbit that are treated with irradiation. They are discussed in detail in Chapter 31 and will not be covered here.

Pterygium

Definition and Clinical Features

Pterygium is a wing-shaped fibrovascular proliferating tissue originating at the lens epithelium at the border between the conjunctiva and the cornea. It normally extends from the medial (nasal) corner of the eye to the cornea and beyond. The highest incidence occurs in hot, dusty, dry, and sun-exposed regions (desert belts). In such areas, even people in their 20s and 30s can be affected.[65,66] Typical symptoms are the sensation of having a foreign body in the eye and tearing. Motility problems are sometimes present. If the cornea is affected, vision may be impaired.

Surgical Treatment

Surgery is the mainstay of treatment, with treatment indicated if vision is threatened by the pterygium growing toward the pupil or if cosmesis is affected. Historically, the initial approach was bare sclera excision, which removes the pterygium from the cornea and conjunctiva, leaving the bare sclera exposed. Absent adjuvant therapy, recurrence rates have been reported to be as high as 88%.[67] Currently accepted therapeutic strategies include conjunctival or limbal autografts with or without mitomycin C intraoperatively or postoperatively. Amniotic membrane grafting has been used, but appears to be inferior to conjunctival or limbal autografting. With the use of the aforementioned adjuvants, recurrence rate reduction (compared to bare sclera excision alone) in both primary and recurrent cases is in the range of 40% to 95%. Vision-threatening and non-vision-threatening complications are relatively rare but can include scleral thinning or ulceration, delayed

conjunctival epithelialization, iritis, corneal edema, corneal perforation, symblepharon, corneal dellen, astigmatism, pyogenic granuloma formation, ocular pain, photophobia, and foreign body sensation.[67-70]

Irradiation Options

Radiotherapy is indicated after local resection of a recurrent pterygium, but some centers also report success with primary or preoperative radiation of the pterygium.[71] Besides rare orthovoltage therapy,[72] brachytherapy with beta radiators and eye applicators is usually employed. Normally, radionuclide strontium-90, a fission product of uranium-235 (half-life period, 28 years), which decays to yttrium-90 (half-life period, 64 days) is used. Strontium-90 radiation has a maximum energy of 0.546 MeV; for yttrium-90 it reaches 2.27 MeV.[73] The eye applicators have an effective diameter of 8 mm to 12 mm. The affected lesion is generously covered by the applicator for a certain time. If lesions are large, they are treated with a circular motion toward the corneal limbus.[74]

Most clinical studies have used postoperative radiation for recurrence prophylaxis with subsequent relapse rates of 1.5% to 11%. Van den Brenk[75] observed only 1.4% recurrences in 1300 treated pterygia (1064 patients). Irradiation was carried out once a week (days 0, 7, and 14 postoperatively). Paryani et al[74] achieved a recurrence rate of only 1.7% in 825 eyes with 60 Gy in six fractions of 10 Gy (once a week). Wilder et al[65] report a recurrence rate of more than 11% in 244 eyes after 24 Gy in three fractions of 8 Gy (once a week). In comparison to placebo irradiation, a Dutch double-blind randomized study with one fraction of 25 Gy showed significantly lower recurrence rates (local relapse in the irradiation arm in only 3 of 44 tumors and in the placebo arm in 28 of 42 tumors).[76]

Radiogenic consequences such as severe scleromalacia and corneal ulcerations occur in up to 4% to 5% of cases after application of higher total doses and after single-dose radiation of 20 Gy to 22 Gy.[77,78]

Choroidal Hemangioma

Definition and Clinical Features

Choroidal hemangiomas are slowly growing benign vascular tumors originating from the vessels of the choroid. The *diffuse type* (ages 5 years to 10 years, almost always associated with Sturge-Weber syndrome) and the *local type* (ages 30 years to 50 years) can be distinguished.[79] Symptoms are determined by the size and location of the tumor. If the hemangioma is located close to the papilla or macula, vision changes, metamorphopsia, and secondary retinal detachment are observed. In case of direct macular involvement, chronic glaucoma frequently develops. A threat to vision can occur and is the main indication for therapeutic intervention. On ophthalmoscopic examination, hemangiomas appear as a red-orange swelling with concomitant clinical phenomena (e.g., glaucoma, retinal detachment). Further diagnostic procedures are ultrasound, fluorescence angiography, CT, MRI, and scintigraphy (phosphorus-32).[80]

Nonradiotherapeutic Treatment

Indications for therapy depend on the progression of the lesion and the severity of symptoms (visual impairment, retinal detachment, or secondary glaucoma). Small lesions outside the field of central vision are treated with photodynamic therapy, photocoagulation, or transpapillary thermotherapy (e.g., to prevent retinal detachment).[81,82] Lesions near the macula or papilla are not coagulated because there is a risk for central scotoma. The same holds for incomplete retinal detachment and for the diffuse type (Sturge-Weber syndrome). In general, the currently favored therapeutic intervention is photodynamic therapy. Intravitreal bevacizumab alone, or in combination with local therapy, has also been used.[83-86] Patients with small, well-circumscribed lesions and patients with a history of longstanding visual loss can potentially be observed.[87,88]

Irradiation Options

Irradiation can be delivered by photons, protons, or brachytherapy. It is typically indicated in cases of no or minimal response to other local therapies and particularly in cases of critical proximity to the macula or papilla because invasive measures can threaten vision.[80] After successful irradiation, the primary lesion flattens, the retina reattaches partially, or perhaps, completely, and the eye and vision are maintained. Visual acuity is often improved. A loss of visual acuity affects almost exclusively eyes with existing location-dependent maculopathy. Early initiation of radiation can potentially lead to better long-term results.[89,90]

Schilling et al[90] irradiated 36 localized and 15 diffuse hemangiomas with 20 Gy in 10 fractions of 2 Gy. After 5 years, 23 eyes (64%) of the localized type achieved complete retinal reattachment. Visual acuity was stable in 50% and improved in 50%. Favorable results were also achieved for the diffuse type. In locally advanced cases, irradiation of the hemangioma cannot conserve visual acuity but can often maintain the eye as a whole.

Radiation with photons or protons is typically conventionally fractionated (1.8 Gy to 2 Gy per fraction) to total doses of 18 Gy to 20 Gy (local type) or 30 Gy (diffuse type). In cases of unilateral location, a lateral stationary field that tilts slightly posterior is used to protect the other eye and the chiasm. In bilateral disease, opposing lateral fields with lens protection are used.

Brachytherapy is carried out in localized hemangiomas with eye plaques, with iodine-125 seeds being the preferred source. Doses from the apex to the base of the lesion vary between 30 Gy and 240 Gy. Results are excellent in the sense of a permanent resorption of the subretinal edema, complete retinal attachment, and maintenance of vision.[89,91-94]

Potential radiogenic side effects are retinopathy and papillopathy with doses of more than 30 Gy. Despite lens-protecting radiation techniques, cataracts occasionally develop as well. With external beam techniques, protons may have the additional benefit of minimizing the risk of secondary malignancy induction compared to photons, which is an issue of particular relevance in pediatric cases.[95-99]

Idiopathic Orbital Inflammation or Pseudotumor Orbitae

Definition and Clinical Features

Lymphoid diseases of the orbit are rare and have a broad range, including pseudotumor orbitae (PO) and malignant lymphomas.[97,100] There are three possible nonmalignant causes: (1) an infectious process, for example, in transmitted sinusitis; (2) an autoimmune process; or (3) a fibroproliferative process.

PO typically occurs in patients of middle age, with clinical signs and symptoms that can result in a broad differential diagnosis. Thus, other causes of orbital space involvement such as granulomatous diseases (e.g., sarcoidosis, Wegener's granulomatosis), local infections, malignancies, or autoimmune diseases have to be excluded. Frequently, the acute onset of symptoms, unilateral disease, and impaired eye motility point to pseudotumor. On imaging, the infiltrates appear in retrobulbar adipose tissue (≤80%), enlarged eye muscles (≤60%), thickening of the optic nerve (≤40%), and proptosis (≤70%). On the basis of clinical diagnosis and diagnostic imaging, it can be difficult to differentiate between

benign and malignant changes; therefore, biopsy is essential.[101]

Nonradiotherapeutic Treatment

Surgical excision can be used in accessible lesions, but recurrences are frequent.[102] Corticosteroids are the most important component of medical therapy, but up to 50% do not respond adequately.[96,103] Some patients are forced to discontinue corticosteroid use secondary because of untoward side effects.[94,104] Beyond corticosteroids, there is increased interest in nonspecific as well as targeted immunomodulatory therapies in the management of PO. However, there are a limited number of studies demonstrating overt clinical benefit with these agents in patients not responding to initial corticosteroid therapy.[96] Without therapy, visual acuity can deteriorate seriously and permanently. The potential for malignant transformation of orbital pseudotumors is unclear.

Irradiation Options

Irradiation is typically reserved for patients who have not responded to initial corticosteroid therapy. As noted by Lambo et al, radiotherapy has response rates of 70% to 100%.[100,101,104-107] Recommended doses vary between 0.5 Gy and 3 Gy per fraction and total doses of 20 Gy to 35 Gy.

In Europe, a treatment attempt with a low dose of two fractions of 0.5 Gy per week up to a total dose of 5 Gy (first series) has been used.[107] In the case of nonresponse after 4 weeks, irradiation is changed to daily 1.5 Gy to 2 Gy fractions up to 30 Gy to 40 Gy as a total dose (second series). In the United States, most patients are treated with initial doses of approximately 20 Gy to 30 Gy at standard fractionation.[108]

Irradiation Technique

After CT planning, patients are treated via anterior and lateral fields with 1:3 weighting and wedged filters for dose homogenization while the patient's eyes are open. In bilateral disease, parallel opposing lateral fields with a half-block technique[102] or two anterior electron fields are used.

Irradiation Side Effects

With careful treatment planning, serious radiation-related side effects are rare (keratitis, retinopathy, cataracts, etc.).

BENIGN DISEASES OF JOINTS AND TENDONS

Dose Concepts

It has been known since the beginning of the 20th century that low doses of ionizing radiation may have analgesic and anti-inflammatory effects.

Nonradiotherapeutic Treatment

Numerous conservative measures, such as oral, local, or systemic application of medications, lifestyle modifications, physical therapy, and so on are the mainstay of management. Radiation therapy is rarely used in the United States for primary management of these diseases, but its use is certainly more common in other countries.

Irradiation Options

In Germany, guidelines and dose concepts for radiotherapy of benign diseases were developed during the past 10 years to 15 years, where a dose per fraction of 0.5 Gy to a total dose of 6 Gy can, and has been, used.[2,3,109] Conditions that have been treated include bursitis, tendonitis, subacromial syndrome (rotator cuff syndrome), tennis elbow (epicondylopathia humeri), calcaneodynia (heel spur), and degenerative joints with cartilaginous destruction (osteoarthritis).[108,110-115]

BENIGN DISEASES OF CONNECTIVE TISSUE AND SKIN

Desmoid (Aggressive Fibromatosis)

Definition and Clinical Features

A desmoid is a benign growth of connective tissue originating in the deep muscular-aponeurotic structures in the region of muscle fascias, aponeuroses, tendons, and scar tissue. The incidence of new cases is two to four per 1 million inhabitants per year. Women are affected twice as frequently as men (1:1.5 to 2.5). Desmoids occur most frequently during the third and fourth decades of life, but children can be affected as well. Mesenteric desmoids are commonly associated with the *APC* gene mutation as in Gardner's syndrome.[116]

Desmoids are differentiated into extraabdominal (≈70%) and intraabdominal (≈10%) desmoids and those located in the abdominal wall (≈20%). Extraabdominal forms tend to recur locally. Intraabdominal forms are associated with the autosomal dominantly inherited Gardner syndrome. Histologically, desmoids are similar to low-grade (G1), highly differentiated fibrosarcomas. Mitotic activity is low, and cellular atypia is rare. Locally infiltrating growth and nonencapsulation has earned the name of "aggressive fibromatosis" for this disease. Local recurrences after resection alone are quite common particularly after marginal or intralesional excision.[117,118] Pretreatment imaging with MRI is used to estimate the size and infiltration into other organs and incision biopsies are performed to distinguish benign from malignant lesions. Although prognosis for survival is good, these lesions may impair function, impact quality of life, and cause life-threatening events.

Nonradiotherapeutic Treatment

Desmoids can regress spontaneously or they can grow to a huge size, but they rarely cause death.[119] Surgery with a safety margin of 2 cm to 5 cm is considered the gold standard. After R0 resection, no adjuvant therapy is usually required. After R1 resection, treatment options include observation if the lesion is in a site where re-resection is feasible; if not, postoperative radiation is reasonable. Good long-term control can be achieved by resection alone, but up to 50% of patients develop local recurrence, which requires surgical and other measures subsequently.[120] Hormonal intervention with tamoxifen, progesterone, and toremifene can exert growth inhibitory effects.[121-123] Overall antiestrogens produce an effect in approximately 50% of patients as determined by systematic review.[124] Nonsteroidals, vitamin C, and chemotherapeutic agents have been tested.[125,126]

Irradiation Options

Radiotherapy is indicated in cases of local inoperability and after R2 resection and in R1 resection if repeated surgery would not be feasible or has already been performed for local recurrence. Radiotherapy is often used adjuvantly or as primary treatment. Adjuvant radiotherapy significantly reduces local recurrence rates compared with surgery alone. With total radiation doses of more than 50 Gy, the local recurrence rate decreases from 60% to 80% with surgery alone to 10% to 30% after adjuvant RT. With normal fractionation and single doses of 1.8 Gy to 2 Gy, a total dose of 50 Gy to 55 Gy is recommended postoperatively. For inoperable or recurring desmoids, some recommend a total dose of 60 Gy to 65 Gy.

After primary radiotherapy, the local control rate does not differ substantially from that after adjuvant irradiation.[3,117,120,127-133] A recent Phase II pilot study evaluated the response of patients with inoperable progressive disease of primary, recurrent, or incompletely resected desmoids receiving 56 Gy in 28 fractions and demonstrated a 3-year local control rate of 81.5%.[134]

Irradiation Results

In most studies, tumor size has no prognostic influence on local control rates. According to a meta-analysis (698 cases in 13 studies), the local control rate after R0 resection and radiotherapy was improved by 17% compared with that of surgery alone. For macroscopic (R2) and microscopic (R1) tumor residual, patients treated with adjuvant radiotherapy had even better results.[135,136] In 2001 to 2002, patterns of care study on the use of radiotherapy for treatment of desmoids were carried out in Germany; 345 patients were subjected to evaluation. The desmoids were distributed in the extremities (81.2%; 280 tumors), the trunk (13.9%; 48 tumors), and the head and neck region (4.9%; 17 tumors). A total of 204 patients (59%) were irradiated for locally recurrent or unresectable desmoids: 141 (40.8%) for high-risk situations postoperatively, 44 for unclear resection status, 49 after R1 resection, and 28 after R2 resection. Most patients were intensively pretreated, on average with two (range, one to five) operations. The median time of observation after therapy was 43 (range, 4 to 306) months. A total of 67 recurrences (19%) were seen after radiation. The long-term local control rate was 81.4% after primary radiotherapy of nonresectable desmoids and 79.6% after postoperative irradiation of resected desmoids. A precise topographic analysis of recurrences was possible in 124 patients or 22 recurrences (18%); 12 (54%) of the recurrences were located within and 10 (46%) were located outside the target volume or at the edge of the field.

Peyronie's Disease

Definition and Clinical Features

Peyronie's disease is a chronic and mostly progressive inflammation and connective tissue excrescence of the tunica albuginea in the cavernous bodies of the penis.[137] It usually affects men between the ages of 40 years to 60 years. Its cause is unknown. Strands of scar lead to the typical bending of the penis, which may cause severe pain during erections. Spontaneous remission is described only rarely.

Nonradiotherapeutic Treatment

There is no simple and successful standard treatment. Vitamin E, para-aminobenzoate, and steroids are said to have a favorable influence during the early phase. There are also local therapeutic attempts with ultrasound or shock waves as well as with corticoid, procaine, and hyaluronic acid injections. Surgery is the standard of care for stable Peyronie's, disabling deformity, or erectile dysfunction unresponsive to drug therapy. Several different surgical procedures are used including tunical shortening or lengthening and the use of penile prostheses. Each surgical procedure comes with potential complications and differing levels of postoperative satisfaction; thus, no one surgical treatment is considered standard.[138]

Irradiation Options

Although radiation therapy has been used in the treatment of Peyronie's, results have been mixed. Low-dose radiation appears to be effective in early stages in patients with painful erections not improving over time or by using oral or intralesional methods. Ionizing radiation can delay further induration and lead to softening of lumps and strands that cause pain, bending, and functional problems of the penis. Radiotherapy can be used during the early stages of Peyronie's disease, but in the later stages, there are hardly any radiosensitive fibroblasts and inflammatory cells left. Irradiation is carried out with gonadal protection (lead apron or capsule), and the glans penis is spared. The nonerect penis is pulled forward manually by the patient and is irradiated via a dorsal stationary field with orthovoltage or electrons up to 6 MeV with a 5-mm to 10-mm bolus.

Conventional fractionation is 20 Gy in 2-Gy fractions, but it is possible to use hypofractionation with a single dose of 2 Gy to 4 Gy two to three times per week up to a total dose of 12 Gy to 15 Gy.[139-142]

However, the actual effectiveness of radiation is unknown because of the absence of criteria for success. As well, randomized, controlled trials comparing interventions do not exist. This leads some to recommend that radiation not be used in this setting.[138]

Irradiation Results

Within 12 months to 24 months, radiotherapy leads to an improvement of symptoms in two thirds of all patients with early-stage disease. Local pain and associated clinical symptoms decrease in up to 75%. Angulation (25% to 30%) and dysfunction of the penis (30% to 50%) show less response because these symptoms often indicate that the disease is already in a more locally advanced stage.[140-142]

Dupuytren's Contracture (Morbus Dupuytren) and Morbus Ledderhose

Morbus Dupuytren (MD) (Dupuytren's contracture) and morbus Ledderhose (ML) are two spontaneous connective tissue diseases in which the palmar or plantar aponeurosis is affected. Two thirds of patients show bilateral involvement. The disease is more common in the hands (MD) than in the feet (ML). It mostly appears from the age of 40 years onward. Depending on geographic region and racial factors, its prevalence is 1% to 3%. Initially, subcutaneous lumps with skin fixation appear; later, there are strands that may reach as far as the periosteum. With increasing connective tissue hardening, flexion contractures develop in the metacarpophalangeal or proximal interphalangeal joints, and grabbing (MD) or walking (ML) is impaired. Mostly, the fourth and fifth phalanges of the hand (MD) or the first and second toes of the foot (ML) are affected. The extent of the extension deficit determines clinical staging in MD.

Nonradiotherapeutic Treatment

Spontaneous regression is initially possible. Without therapy, more than 50% of people affected show disease progression after 5 years. Surgery is indicated if there is functional impairment.

Irradiation Options

Radiotherapy can be considered during the early stages of disease. The target cells are the strongly proliferating radiosensitive fibroblasts and inflammatory cells. The aim of therapy is to avoid further progression. Normal fractionation is 2 Gy per fraction to a total dose of 20 Gy or 3 to 4 Gy per fraction to a total dose of 12 Gy to 15 Gy.

Irradiation Results

Many studies demonstrate a good response to radiotherapy in the form of stabilized disease (70% to 80%). Only a small number of patients with early-stage disease, however, experience degeneration of lumps and strands (20% to 30%). Only a

few studies have controlled long-term observation for more than 2 years.[143] Betz et al reported the results of long-term results of 208 hands irradiated in 135 patients treated with orthovoltage therapy.[143] Patients received 30 Gy in 10 fractions treated split course with a 6- to 8-week break between courses. Patients were staged according to a modified version of staging described by Tubiana et al.[144] In this staging system, patients with stage N/I had clinical symptoms in addition to minor defects in extension (1 degree to 5 degrees). Eighty-seven percent of patients with stage N and 70% of patients with stage N/I stabilized or regressed. With more advanced stages, disease progression was seen in 62% of stage I patients (clinical symptoms with extension deficits of 6 degrees to 45 degrees), and 86% of stage II patients (clinical symptoms with extension deficits of 46 degrees to 90 degrees). No benefit was seen in patients with more advanced extension deficits. Also, the time period from first recognition of symptoms to radiation therapy onset influenced success, with better long-term results seen when irradiation was used within the first year of diagnosis versus those treated after 48 months ($p < 0.001$). Long-term relief of such symptoms as pruritus and scratching, tension, pressure, and burning occurred in 66% of patients. There was no increase in postsurgical complications, and only 32% of patients experienced minor late toxicity such as dry desquamation or skin atrophy. No evidence of secondary malignancy was seen. The authors concluded that radiation therapy is effective in the prevention of progress and relief of patient symptoms in early-stage contracture.

Keloids and Hypertrophic Scars

Definition and Clinical Features

Keloids are excessive tissue excrescences in the region of scars, and they may occur in case of skin injury from surgery, burns, chemical burns, or inflammation (e.g., acne) or even spontaneously. They differ from hypertrophic scars by their infiltrating character, causing local pain and inflammation reactions or even triggering long-term progression. Hypertrophic scars show thickening without surrounding reaction and can flatten spontaneously.

Keloids appear mostly in the upper body and in regions with high skin tension (e.g., above the sternum, at the earlobes, and in the joint regions). The cause of the disorder is still undetermined, but there is a genetic and race-specific predisposition.

Nonradiotherapeutic Treatment

Besides surgical excision of hyperplastic tissue with cosmetic disfigurement and functional disruptions, it is possible to use a conservative procedure with pressure and silicon bandages, steroids, plant extracts, or steroid injections for smaller lesions. In more than 50% of cases, there is local recurrence after excision of keloids alone.

Irradiation Options

Indications for irradiation are either demonstrated recurrences postoperatively or a high-recurrence risk (e.g., marginal resection borders, wider spread, unfavorable location). Fibroblasts, mesenchymal cells, and inflammatory cells are the target cells. Prophylactic irradiation immediately after excision of the recurrence is most effective. The local recurrence rate after postoperative irradiation is 20% to 25%.

Irradiation is initiated 24 hours after surgery at the latest. Orthovoltage (70 kV to 150 kV), electrons (<6 MeV), and brachytherapy with iridium-192 implants or with strontium-90 dermaplate are used.[145-148] The target volume is limited to the scar plus a 1-cm safety margin. The recommended dose is 12 Gy to 25 Gy, typically with 3-Gy to 4-Gy fractions.[109,147,149-152] Single-dose irradiation with 7.5 Gy to 10 Gy is effective.[153] Keloids in certain areas such as the chest wall tend to have a higher risk of recurrence, possibly because of tension placed on the tissue after surgical excision. Data from Ogawa et al suggest that doses of 20 Gy in 4 fractions should be considered for these areas. Recurrences on the chest wall decreased from 39% with 15 Gy in 3 fractions to 14.3% with 20 Gy.[149]

Other Diseases of Connective Tissue and Skin or Cutaneous Appendages

Acute and chronic inflammatory changes of the skin (furuncle, carbuncle), of the nailbed (paronychia), and those that affect the sweat glands of the armpit and groin (hidradenitis suppurativa) can lead to chronic and therapy-refractive inflammation that is painful and can seriously impair the function of those affected by the disease. If all local treatment measures are exhausted, if there is a confirmed resistance to antibiotics, and if further surgical measures are rejected, irradiation can be implemented with single doses of 0.5 Gy to 1 Gy daily up to a total dose of 10 Gy.

Gynecomastia

Radiotherapy for gynecomastia, a benign proliferation of breast tissue, is most commonly used in the setting of hormonal therapy for prostate cancer as either a prophylactic measure or as a treatment for painful gynecomastia in patients. The prevalence of gynecomastia in patients undergoing complete hormonal blockade is 15%, increasing to 75% with antiandrogen monotherapy.[154] Radiotherapy, when used prophylactically, appears to significantly decrease the incidence of gynecomastia but does not appear to relieve mastodynia.[155,156] Bilateral radiotherapy of the mammary region is performed with 8-MeV to 12-MeV electrons. Historically, four to five fractions of 3 Gy, up to a total dose of 12 Gy to 15 Gy, have been used to prevent pain or further growth of the mammary gland.[157] More recently, studies have evaluated the use of single-fraction radiation therapy.[154,158] Tyrrell et al published the results of a randomized, sham-controlled, double-blind, parallel-group multicenter trial involving 106 men with prostate cancer and no gynecomastia/or breast pain.[158] Patients received either a single dose of 10-Gy electron beam radiotherapy or sham radiotherapy. Bicalutamide was administered for 12 months from the day of radiotherapy. Physician-assessed gynecomastia was significantly lower with radiation therapy compared with sham radiotherapy (52% versus 85%; $p < 0.001$) with the incidence of ≥5 cm gynecomastia (measured by calipers being 11.5% with radiation therapy versus 50.0% for sham radiotherapy). More patients in the sham group experienced moderate to severe gynecomastia compared to the radiation therapy group (48% versus 21%). Radiation therapy also slowed the development of gynecomastia. There was no statistical difference in the incidence of breast pain with radiotherapy (83%) and sham radiotherapy (91%). There was a nonsignificant reduction in patients experiencing breast pain with prophylactic radiation therapy.

However, radiotherapy cannot reverse gynecomastia.

Plantar Warts

Plantar warts can be painful and functionally as well as cosmetically disturbing. In older studies, control rates of more than 80% were achieved with orthovoltage irradiation (10 Gy in one fraction, or 15 Gy in five fractions of 3 Gy). The warts fell off without consequences after several weeks.[159] Over the past several decades, the use of radiation for plantar warts has declined, so it is rarely used.

BENIGN DISORDERS OF BONY TISSUES

Aneurysmal Bone Cysts

Definition and Clinical Features

Aneurysmal bone cysts are benign vascular cystic lesions in the metaphasis of bones, which can cause functional impairment, pathologic fractures, and damage to neighboring structures. They can infiltrate the surrounding soft tissue. Despite their nonmalignant character, cysts can lead to bone destruction and thus lead to serious problems, which is why treatment is recommended once a cyst has been diagnosed, particularly if the vertebral column is affected.[160-162]

Surgical Treatment

Therapy is primarily surgical (resection or curettage with or without bone grafting) as long as this does not lead to a considerable functional impairment. Following curettage alone, cysts recur in up to 60% of patients, with lower rates reported in patients with allografting.[163,164] After complete resection, the risk of recurrence is minimal.[160-162]

Irradiation Options

Radiotherapy can be used in patients with cysts that cannot be treated by surgery or if curettage is difficult because of the size or location of cysts. Cyst progression or repeated recurrences are also indications for radiotherapy. Because more than 50% of patients are 10 years to 19 years old, radiation doses should be kept as low as possible, with strong consideration for the utilization of protons if at all possible.[95] Nobler et al[165] reported one recurrence in a total of 11 patients who were irradiated with total doses of 12 Gy to 31.6 Gy. A dose of 10 Gy to 30 Gy in 1.8-Gy to 2-Gy fractions over 1 week to 3 weeks seems to be adequate to control aneurysmal bone cysts reliably.[166-168]

Pigmented Villonodular Synovitis

Definition and Clinical Features

Pigmented villonodular synovitis (PVNS) is a rare proliferative disease affecting the synovia of joints and the tendon sheaths.[169] There are two types of disease: the strictly localized and the diffuse involvement of synovial membranes.[170] In most cases, the lesion is restricted to one joint, though can spread to muscles, tendons, and skin.

Surgical Measures

Surgical excision normally consists of synovectomy, which is rarely complete, particularly in large joints such as the knee.[171] Joint replacement has also been used.[172] Recurrence is seen in up to 45% of patients[173]; therefore, the addition of perioperative or postoperative irradiation is appropriate in patients with high-risk disease.[174,175]

Irradiation Options

O'Sullivan et al[170] reported on 14 patients who were irradiated with 30 Gy to 50 Gy in 15 to 35 fractions at Princess Margaret Hospital. The patients had different risk factors: microscopic residual tumor (7), macroscopic tumor (7), tumor more than 10 cm (5), tumor 5 cm to 10 cm (7), recurrences (8), and skin infiltration with ulceration (2). During an average observation period of 69 months (13 months to 250 months), 1 patient had persistent tumor 8 months after radiotherapy with 30 Gy in 15 fractions. All but 2 patients had tumor control. On the basis of the Princess Margaret Hospital results, radiation with a dose of 40 Gy in 20 fractions has been recommended.

Other institutions have evaluated their results with adjuvant irradiation after surgical resection and have achieved similar results. The German Cooperative Group on Radiotherapy in Benign Diseases (GCG-BD) conducted a pattern-of-care analysis of the results of postoperative RT for PVNS in 41 patients from 14 institutions.[174] The radiation dose ranged from 30 Gy to 50 Gy (median, 36 Gy; median single dose, 2 Gy). Local control was achieved in 95% of patients.

Vertebral Hemangiomas

Definition and Clinical Features

Vertebral hemangiomas are benign vascular lesions that can lead to a resorption of the affected bone.[176-178] Normally, only one vertebral body is affected. Hemangiomas are usually diagnosed by their radiologic picture of rarefaction with vertical, dense trabeculae in a honeycomb pattern. Most lesions require no therapy. In most cases, symptoms occur during the fourth or fifth decade of life.[179-182] Women are affected more frequently than men.[183] Spread of the tumor into the extradural space, hemorrhage, or rare compression fractures can lead to bone marrow compression.

Surgical Treatment

Surgical relief can become necessary, but it can be difficult owing to the danger of hemorrhage.[184-187] In most cases, only partial resection is possible, and postoperative irradiation can be considered.[176,177] Recently, less radical options such as vertebroplasty have been effectively used.[188-190]

Irradiation Options

The GCG-BD evaluated the results of radiation for vertebral hemangiomas in 84 patients from seven German institutions.[191] The RT dose ranged from 4.5 Gy to 45 Gy (median, 34 Gy; median single dose, 2 Gy). The overall response (complete plus partial response) was 90.5%, with long-term local control of 80.9%.

Rades et al[192] analyzed data from 339 patients with symptomatic vertebral hemangiomas from publications of the past 50 years. There were 222 patients who had to be excluded, either because surgery was part of the treatment (98 patients) or because the data were incomplete (124 patients). Of the remaining 117 patients, 54 patients received 36 Gy to 44 Gy (group A) and 62 patients 20 Gy to 34 Gy (group B). After a median observation period of 36 months (range, 6 months to 312 months), 39% of group A and 82% of group B patients had complete pain relief. The researchers recommend a total dose of 40 Gy.

Heterotopic Ossification

Definition and Clinical Features

Heterotopic ossification (HO) can appear following trauma or surgery of the hip (total hip replacement) in 10% to 80% of cases, and with varying degrees of severity. HO consists of real bone and is located in the periarticular soft tissues.[193] Ten percent develop extensive HO, causing pain and functional impairment. Patients with HO frequently complain of pain only a few days after surgery. Radiologic studies detect calcified structures with blurred contours 3 weeks to 6 weeks postoperatively.

The etiology of HO is only partially known. It is assumed that the pluripotent mesenchymal cells, which are present ubiquitously in periarticular soft tissue, develop into osteoblastic stem cells under certain conditions.[194]

For all patients with an indication for a hip replacement, there should be an individual estimation of the risk of HO before carrying out surgery. Patients who already have ipsilateral or contralateral HO carry the greatest risk. After a second surgery, 90% to 100% of those patients redevelop HO.[195-197]

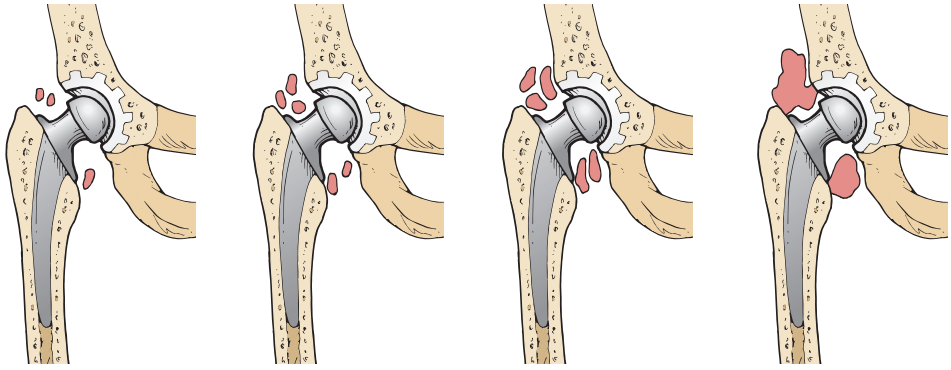


Figure 66-1 Staging of heterotrophic ossifications. **Grade I,** Bone islands within soft tissue around hip. **Grade II,** Exophytes of pelvis or proximal femur end with a minimum distance of 1 cm. **Grade III,** Exophytes of pelvis or proximal femur end with a distance of less than 1 cm. **Grade IV,** Bony ankylosis between proximal femur and pelvis.
From Brooker AF, Bowerman JW, Robinson RA, et al: Ectopic ossification following total hip replacement. J Bone Joint Surg 55A:1629–1632, 1973.

Patients with moderate or severe osteophytes at the femoral head and socket also have a high risk for HO, with an incidence of more than 50%.[198,199] After acetabular fractures, HO appears in 90% of hips. Fifty percent of those patients develop HO with clinical pathology.[200,201] Ankylosing spondylitis and the (rare) idiopathic hyperostosis of the skeleton are other influencing factors.

Diagnosis and Classification

Extensive ossifications lead to mobility impairment of the hip joint and cause pain. If HO is suspected, radiographs of the hip should be taken. Discrete changes in the radiograph can be seen at 2 weeks after surgery at the earliest. The literature provides a multitude of staging approaches. The most frequent one is the classification of HO according to Brooker et al[193] (Figure 66-1). To keep it simple, HO grades III and IV, according to Brooker et al, are designated as severe or clinically relevant, although there may not be any pain or mobility impairment.

Nonradiotherapeutic Treatment

Surgery

Clinically relevant (i.e., usually ankylosing) HO that has appeared after surgery should be removed to mobilize the joint and to remove pain. Complete removal of HOs is not essential if this is difficult and burdened with a higher risk. Most authors consider it necessary to wait for maturation of the forming ectopic bone and to reoperate only after 6 months to 1.5 years.

Medical Therapy

A number of medical options have been evaluated as prophylaxis against the development of HO. Although ethane hydroxy-diphosphates (EHDPs) have been used as prophylaxis, the treatment results are not convincing.[202-205] In contrast, some studies show that nonsteroidal anti-inflammatory drug (NSAID) use (indomethacin being the most commonly used), is effective in patients with a high risk of HO, with one meta-analysis noting that perioperative NSAID use resulted in a one half to two thirds reduction in the risk of HO development.[206-212] Selective cyclooxygenase-2 inhibitors have been tried, with promising results; though the concern for potential cardiovascular toxicity has tempered their use, particularly in patients with preexisting cardiovascular disease.[205]

Irradiation Options

Radiotherapy for prophylaxis of HO has been employed since the late 1970s and has proved to be effective. The initial dose was 20 Gy in 10 fractions.[213-218] Multiple dose schedules have been used. Various authors have pointed out that radiotherapy should be started no later than day 4 after surgery.

In three randomized studies, a dose of 10 Gy was compared with 20 Gy,[216] or with 17.5 Gy in five fractions,[219] and a single fraction of 8 Gy versus 10 Gy.[220] There was no significant difference between the effectiveness of high and low doses. Severe ossification occurred in 7% of patients with low and 5% of patients with high irradiation doses. No difference could be observed between fractionated and single-dose irradiation.

Preoperative radiation treatment with 7 Gy to 8 Gy in one fraction has been used successfully in patients with high-risk disease.[221] There appears to be no significant difference in clinically relevant HO compared with patients who are irradiated postoperatively.[222]

The relative roles of RT, indomethacin, and other NSAIDs for HO prophylaxis have been discussed by Pakos et al.[223-226] In a 2004 meta-analysis of seven randomized trials by Pakos et al,[223] irradiation was demonstrated to be more effective than NSAIDs for HO prophylaxis in preventing grade-3 to grade-4 ossification, but the absolute risk difference was only 1.2%. Pakos et al[225] subsequently reported a randomized trial in 96 patients comparing postoperative radiation (7 Gy in a single fraction) plus indomethacin (first 15 days postoperatively) to indomethacin alone (same 15 days) for HO prophylaxis. Patients receiving the combined treatment of radiation plus indomethacin had a lower rate of subsequent HO (4 versus 13 patients; $p < 0.05$). A systematic review of studies comparing indomethacin to radiation prophylaxis by Blokhuis and Frolke demonstrated an overall HO rate of 8.3% (5 of 60 patients) with radiation versus 8.9% (20 of 224 patients) with indomethacin. Although small, this difference was statistically significant.[227]

Irradiation is tolerated well. Neither fractionated irradiation nor high-single doses lead to an increased frequency of wound-healing disturbances, and there have been no documented cases of radiation-induced malignancies after prophylactic radiation.[228] Because radiation-induced tumors appear rarely and only after latencies of 10 years to 30 years, this risk is virtually irrelevant for most patients because the median age of patients is 65 years.

Irradiation Technique and Procedures

The irradiation field contains the typical localizations of periarticular ossifications, where the cranial field border is located approximately 3 cm above the acetabulum, and the irradiation field includes about two thirds of the implant shaft. Normally, the field size is 14 cm × 14 cm.

The effect of radiotherapy on the ingrowth of bone and fixation of noncemented implants was investigated in dogs[221] and rabbits.[229] After irradiation with 10 Gy (in five or four fractions), the fixation was significantly decreased within 2 weeks to 6 weeks.[229,230] Sumner et al[231] were also able to show that irradiation initially decreases the grade of fixation during the early postoperative phase, but after 4 weeks, the implants in irradiated and nonirradiated bone had the same strength.

In clinical application, the protection of the hip prosthesis with blocks as recommended by Jasty et al,[232] and the use of smaller blocks restricted to acetabular and femoral parts of the prosthesis can lead to ossifications underneath the block. Inadequate irradiation fields led to HO in 13 of 18 hips (76%) after irradiation with 7 Gy.[233] An open irradiation field covers the entire periarticular risk region more completely. Nonfixation of cementless implants was not observed after 6 Gy in one fraction,[234] after 7 Gy in one fraction,[235] or after 17.5 Gy in five fractions.[219,236,237] Because of the animal experimental and clinical studies, there appears to be no objection to irradiating hips with noncemented prostheses without a block. Strong consideration should be given to the utilization of testicular shielding in men interested in fertility as shielding can reduce testicular dose.[238]

Radiation for HO prophylaxis has also been used in patients with elbow trauma requiring surgical fixation. Although it does appear to be safe, a small prospective randomized study did note a significant difference in the nonunion rate between patients who received radiation and those who did not (38% versus 4%, $p = 0.007$).[239-241]

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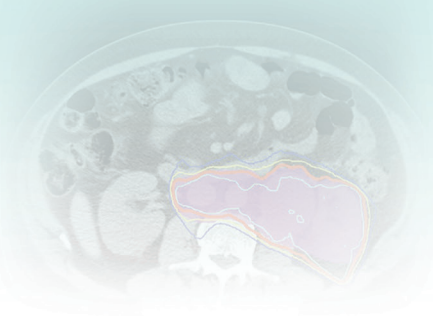
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Overview



Larry E. Kun

CANCER IN CHILDREN

An estimated 15,780 newly diagnosed children (10,450 in birth to 14 year olds) and adolescents (5330 in 15- to 19-year olds) were diagnosed with cancer in the United States in 2014.[1] Cancer remains the most-common disease causing death in children; it is second to accidents in all causes of death between birth and 14 years of age. Approximately 1900 cancer deaths occur annually in children and adolescents.[1,2] After a plateau in pediatric cancer survival, the rate of decline in cancer mortality in this age group over the past decade has resumed the progress noted previously in the evolution of combined-modality therapy.[2]

For children ages 1 to 14 years old, the most-common cancers are leukemias and central nervous system (CNS) tumors, together accounting for more 50% of cancers in children. Acute lymphoblastic leukemia (ALL) alone accounts for 26% of cases in children; acute myeloid leukemia (AML), 5%. The other most frequent types are neuroblastoma, non-Hodgkin's lymphomas, and Wilms' tumor. For adolescents 15- to 19-years old, the most-common cancers include Hodgkin's lymphoma, thyroid cancer, CNS tumors, germ cell tumors (especially testicular); other relatively common types include non-Hodgkin's lymphomas, bone tumors, and melanoma (Table I-1).[1] Between 2001 and 2009 epidemiology studies showed a stable overall incidence of cancer in children and adolescents with a noteworthy increase in thyroid and renal carcinomas; a significant increase in overall cancer rates in African American children and adolescents; and a decrease in the incidence of melanoma and extracranial-, extragonadal-germ cell tumors.[3]

With contemporary therapies, long-term disease control—*in most tumor systems tantamount to cure*—is achieved in approximately 80% of children and adolescents; 5-year relative survival increased from 58% for children 1- to 14-years old diagnosed between 1975 and 1977 to 83% for those diagnosed from 2003 to 2009.[1] Survivors of childhood cancer often have physical and functional limitations that prevent them from achieving their full potential and compromise quality of life. Late mortality (30% among those surviving at least 5 years post-diagnosis) is increasingly related to secondary neoplasms and cardiac or pulmonary deaths as a result of treatment, rather than to recurrent cancer.[4,5] The cumulative incidence of second cancers at 30 years following initial diagnosis in childhood was 20.5% in the Childhood Cancer Survivors Study analysis.[6,7] Current strategies and clinical investigations seek to maintain or improve disease control, while reducing therapeutic interventions associated with long-term morbidity and mortality; identifying local-regional and overall disease control achievable with radiation therapy is often weighed against specific radiation-related late morbidities and secondary malignant neoplasms (SMN), in particular.[6-8]

Genetically defined cancer susceptibility or predisposition syndromes are known to account for approximately 10% of pediatric cancers; a recent study suggests that more than 25% of patient with pediatric cancer may have an inherited genetic cause based on a strong family history of cancer, cancer types strongly associated with hereditary cancer, history suggestive of a genetic diagnosis, or family history of another medical condition associated with genetic cancer.[9,10] Many cancer predisposition syndromes have implications not only for primary tumorigenesis but also for enhanced radiation sensitivity related to secondary carcinogenesis and, less frequently, somatic effects.[8,11] Retinoblastoma is the "classic" autosomal dominant hereditary cancer associated with the *RB1* tumor suppressor gene and a high rate of SMNs: a cumulative risk of 36% SMN by 50 years post-diagnosis, data showing a three-fold higher risk following orbital radiation therapy compared to those treated without irradiation.[12-14] Li-Fraumeni syndrome is caused by heterozygous germline mutations in the *TP53* tumor suppressor gene.[15] The syndrome is associated with an increased risk of cancer in children and young adults, especially bone and soft-tissue sarcomas, adrenocortical carcinomas, choroid plexus carcinomas, and frequent multiple primary tumors in a given patient.[16] Aside from the classic neurofibromas and optic nerve/optic tract gliomas associated with neurofibromatosis type 1 (NF1), malignant peripheral nerve sheath tumors, low-grade gliomas outside the visual pathways, and pheochromocytomas occur rather commonly in children and adolescents with NF1.[17] The number of inherited cancer predisposition syndromes related to pediatric oncology is impressive, as is the increasing recognition of late radiation effects in such cohorts.[8,11,17,18]

Approximately two thirds of children with cancer in North America are treated on clinical protocols, primarily studies coordinated by the Children's Oncology Group (COG), one of the pediatric disease-specific consortia (New Approaches to Neuroblastoma Therapy, NANTS; Pediatric Brain Tumor Consortium, PBTC; Therapeutic Advances in Childhood Leukemia and Lymphoma, TACL), and independent trials at the few major institutions able to mount clinical trials. Challenges remain in ensuring appropriate multimodality therapy for adolescents and young adults with pediatric types of cancer, as well as the enormous lack of resources for treating children with cancer in the developing world.[2,3,19,20]

Radiation therapy is a major component of coordinated, multimodality therapy for children. In the most common childhood cancer, ALL, the prior use of preventive cranial irradiation was initially associated with then remarkable cure of ALL, but more recently recognized primarily in

TABLE I-1 Common Neoplasms Occurring in Children and Adolescents

Disease Type	Childhood Cancers (%)	Role for Radiation Therapy
Acute Leukemias	**24**	
• Acute lymphoblastic (ALL)	*18*	1. Limited number may benefit from preventive cranial irradiation (high-risk T-cell, <5% ALL cases) 2. Therapeutic CNS-RT for CNS relapse 3. Total-body irradiation (TBI) or total lymphoid irradiation (TLI) in bone marrow transplantation (BMT) for recurrent/high-risk ALL
• Acute myeloblastic (AML)	*5*	1. TBI in BMT
Central Nervous System	**18**	
• Glial tumors	*12*	1. Local RT for many low-grade presentations, often at progression 2. Local RT for all high-grade presentations
• Ependymomas	*1*	1. Local RT for virtually all presentations
• Craniopharyngiomas	*1*	1. Local RT for incompletely resected or progressive/recurrent tumors
• Medulloblastomas and other embryonal CNS tumors	*3*	1. Systematic craniospinal irradiation + local boost for children ≥ 3 years 2. Local RT in children < 3 years (investigational)
• CNS germ cell tumors	*1*	1. Ventricular RT with local boost and chemotherapy vs. ventricular or craniospinal RT for germinomas 2. Ventricular or craniospinal RT plus chemotherapy for "malignant" germ cell tumor
Malignant Lymphomas	**15**	
• Hodgkin's lymphoma	*9*	1. Local (involved field) in combined modality therapy 2. TLI or TBI in transplantation settings for recurrent disease
• Malignant lymphoid tumors	*6*	1. Local RT for symptom control or recurrent disease
Neuroblastoma	**5**	1. Local regional RT for regionally advanced disease 2. Palliative RT (bone; soft tissue) 3. TBI in high-dose therapy/stem-cell rescue regimens (investigational)
Wilms' Tumor	**4**	1. Local/regional RT in advanced disease or unfavorable histology 2. Visceral RT in metastatic disease
Retinoblastoma	**3**	1. Ocular RT in consolidative or progressive/recurrent settings
Soft-Tissue Sarcomas	**6**	
• Rhabdomyosarcomas	*3*	1. Local/regional RT for most (intermediate/advanced or alveolar histology) presentation
• Other soft tissue	*3*	1. Local/regional RT based on histology, site, size, and age
Bone Sarcomas	**6**	
• Osteosarcoma	*3*	1. Limited postoperative use in central sites
• Ewing's sarcoma	*2*	1. local RT for "nondispensable" primary site 2. Local postoperative RT following marginal resection 3. Visceral and bone RT in metastatic disease
Hepatic Tumors	**1**	1. Limited postoperative or palliative RT
Germ Cell Tumors	**5**	1. Limited local/regional RT

Modified from SEER Cancer Statistics: http://seer.cancer.gov; Ward E, et al: Childhood and adolescent cancer statistics, 2014. CA Cancer J Clin 64(2):83–103, 2014, and Smith MA, et al: Declining childhood and adolescent cancer mortality. Cancer 120(16):2497–2506, 2014.
CNS, *Central nervous system;* RT, *radiation therapy.*

unique association with late morbidities. Current therapeutic approaches largely obviate irradiation except for instances of CNS relapse or in the context of bone marrow transplantation for relapsed, refractory, or genetically virulent forms of ALL, where total body or total lymphoid irradiation is a part of the conditioning regimen.[21-25]

Data from St. Jude Children's Research Hospital show the proportion of newly diagnosed children who receive irradiation for all forms of cancer has increased over the past 18 years from approximately 40% to nearly 60%, even with the elimination of preventive cranial irradiation in institutional ALL protocols.[22] A retrospective study of NCI's SEER database reports significant reduction in radiation therapy, though, between 1973 and 2008 for children with ALL, non-Hodgkin's lymphoma, and retinoblastoma, with modest declines in brain cancer, bone cancer, Wilms' tumor, and neuroblastoma; whether SEER reporting is accurate reradiation utilization is questioned.[26] In major referral centers for pediatric cancer, pediatric cases have increased, particularly in CNS tumors (reported at 25% to 65% of cases undergoing radiation therapy) and for tumors requiring abdominal and pelvic and head and neck irradiation.[27]

Increased utilization of radiation therapy in regional and national referral centers reflects improvements in diagnostic imaging for tumor mapping and in dose conformality with intensity-modulated radiation therapy (IMRT) photon irradiation and the availability of proton beam radiation therapy (PBRT; evolving from standard double scatter technology toward intensity modulated proton therapy with spot beam technology)—all enabling significant reduction in radiation exposure to critical normal structures. Interest in PBRT has been particularly noted in CNS tumors and sarcomas where

dose reduction in neuroanatomic regions related to neurocognitive development and in anatomic sites related to somatic and visceral growth and function has driven centralized referral patterns based on technology.[28-33] Such technologies have favored judicious radiation intervention even in the more vulnerable younger children where rebalancing efficacy and tolerance are critically important, as in CNS atypical teratoid/rhabdoid tumors (AT/RT) and genitourinary rhabdomyosarcomas in girls.[30,34,35] The defensive posture of the radiation oncologist has been replaced by the knowledge base required in clinical and biologic understanding of pediatric cancers, common and evolving drug therapies, and the application of sophisticated radiation technology.

Key radiation parameters are critically important in pediatric therapy, where the relative radiation sensitivities of pediatric cancers compete with the added vulnerabilities of the growing, developing child or adolescent. There are increasing studies in most pediatric CNS tumors, sarcomas, and other common solid tumors showing disease control with diminishing target volumes, essentially shrinking the clinical target volume (CTV) expansion of the tumor volume to take further advantage of three-dimensional treatment planning and more conformal radiation delivery.[35-39] As target volumes are progressively tighter, quality control becomes more critical both at institutional and cooperative group levels. Target volumes in unique tumor settings may actually need to be larger, as with alveolar rhabdomyosarcoma and the potential value of nodal irradiation.[40,41] As well, there have been progressively lower radiation doses shown to be effective in rhabdomyosarcoma, Ewing sarcoma, medulloblastoma, CNS germ cell tumors, and other settings where either (1) combinations of pre- or postirradiation chemotherapy provide an additive effect or (2) postchemotherapy surgery provides microscopic disease only.[35,38,42,43]

Molecularly targeted agents have increasingly been investigated in combination with radiation therapy. Several classes of drugs have shown radiosensitizing potential in preclinical studies and have completed Phase I and Phase II studies in pediatrics (e.g., platelet derived growth factor [PDGF] inhibitors, farnesyl transferase inhibitors [FTI], histone deacetylase inhibitors [HDAC], and Poly[ADP-ribose] polymerase [PARP] inhibitors). The ultimate utility of molecularly targeted agents and the interactions with irradiation will be apparent in tumor systems where specific molecular targets and available pharmacotherapeutics allow prospective clinical trials.

Radiation-related late effects are often more pronounced in children than in adults, especially in somatic changes (growth and development of musculoskeletal tissues) and functional effects (neurocognitive, auditory, endocrine).[6,21,28,32,39,44] Infants and young children are particularly vulnerable to the effects of both irradiation and chemotherapy agents (e.g., alkylating agents, cis-platinum, Adriamycin).[44-46] Alterations in bone growth, muscle development, and intermediate-size arterial caliber tend to be more prevalent in younger patients than in adolescents or adults.[47,48] Threshold radiation levels are recognized for epiphyseal growth, but even low dose exposures can be correlated with changes in height and bone development (both contour and integrity).[48] It is not clear whether visceral tolerances are significantly lower in the younger age group, although the frequent use of combined chemoradiation therapy introduces added concerns regarding radiation tolerance for the heart and lungs, the liver and the kidneys.[49,50] Intermediate-size vessels, particularly at the circle of Willis, show reduced caliber and flow after irradiation in a high proportion of children younger than 1 to 3 years of age, whereas major extracranial vascular effects are otherwise most noteworthy in coronary vessels.[47,51] A high proportion of children evidence hypothyroidism after even low-dose irradiation to the neck; manifestations of reduced testosterone and estrogen levels following low-dose pelvic irradiation are noted after irradiation in childhood or adolescence.[52-54]

Neurocognitive effects of brain irradiation have been well described and correlated with radiation dose, volume, and patient age. Concerns regarding limited life potential attendant to diminished learning and IQ have driven protocol-based attempts to limit radiation use as well as introducing volume and dose constraints in treating children with CNS tumors over the past three decades.[5,21,28,32,39,46,55] Experience with narrow targets to rather high subtotal posterior fossa doses have shown preservation of intellectual function in children as young as 12 months of age in ependymomas.[39,55] Prospective measurements of learning disabilities are key to further assessing the impact of contemporary radiation therapy in localized brain tumors. Clinical trials suggest specific interventions (i.e., pharmacologic and cognitive rehabilitation) may ameliorate some of the learning problems associated with cerebral irradiation.[56]

In pediatric radiation therapy, one must always consider the risk of secondary carcinogenesis, an overall risk that is at least 5% to 10% over three decades of follow-up. The long survival intervals of successfully treated children and the added risks of SMN in the growing or developing tissues (e.g., the pubescent and adolescent breast) and in several of the cancer predisposition syndromes require exquisite balance in indications for radiation therapy and in selecting techniques that might limit carcinogenesis.[4-7,12-14]

The following chapters outline the biology, clinical features, and outcome of the more common pediatric cancers, summarizing the current and evolving roles of radiation therapy in the current approach to childhood cancer and consider the available data and ongoing trials related to radiation modalities and parameters of volume, dose, and fractionation.

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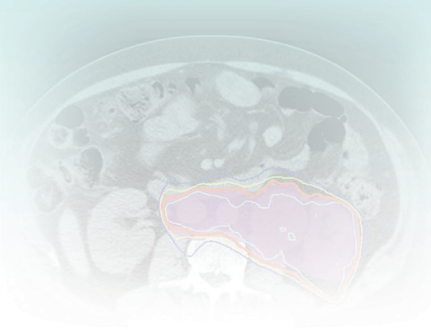
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CHAPTER

67 Central Nervous System Tumors in Children

Shannon M. MacDonald



INCIDENCE AND OVERALL SURVIVAL

The overall incidence of childhood brain tumors is 5.05 per 100,000 person-years for children birth to 19 years and 4.92 per 100,000 person-years for children less than 15 years of age. Brain tumors are the second-most common childhood malignancy and the most-common primary solid tumor. Pediatric brain tumors are a diverse group of tumors and outcomes are dependent on histologic subtype and treatment. Approximately 75% of children diagnosed with pediatric brain will experience long-term disease-free survival (DFS).

ETIOLOGY

At present, the etiology of most pediatric brain tumors is unknown. Genetic syndromes that may predispose children to certain subtypes of brain tumors include neurofibromatosis, Li-Fraumeni, Gorlin's syndrome, Turcot's syndrome, and ataxia-telangiectasia.

HISTOLOGIC SUBTYPES

- Embryonal tumors
  - Medulloblastoma
  - Supratentorial primitive neuroectodermal tumor (includes pineoblastoma)
  - Atypical teratoid rhabdoid tumor
  - Embryonal tumor with abundant neuropil and true rosettes
- Astrocytic tumors
  - Pilocytic astrocytomas (World Health Organization [WHO] grade 1)
  - Astrocytoma (WHO grade 2)
  - Anaplastic astrocytoma (WHO grade 3)
  - Glioblastoma multiforme (WHO grade 4)
- Ependymoma
  - Myxopapillary (WHO grade 1, usually of spine)
  - Classic/differentiated (WHO grade 2)
  - Anaplastic (WHO grade 3)
- Craniopharyngioma
- Germ cell tumors
  - Pure germinoma
  - Nongerminomatous germ cell tumors
    - Embryonal
    - Yolk-sac
    - Choriocarcinoma
    - Immature teratoma
    - Mixed germ cell tumors (NGGCT components ± germinoma)
  - Mature teratoma
- Choroid plexus tumors

EVALUATION

- History and physical examination
- Magnetic resonance imaging (MRI) of the brain and spine
- Lumbar cerebrospinal fluid (CSF) for patients with embryonal tumors, germ cell tumors and ependymomas α-fetoprotein and β-human chorionic gonadotropin tumor markers in both serum and CSF for germ cell tumors

INTRODUCTION

Childhood central nervous system (CNS) tumors are second in frequency only to leukemia and represent the most-common solid tumor in children.[1] At the time of this writing, the incidence of pediatric brain tumors is 5.05 per 100,000 person-years and only 7% of all brain tumors occur in children. Despite the relative infrequency of this disease, patients with pediatric brain tumor often require radiation therapy and they comprise a large proportion of the overall population of children seen by a radiation oncologist.

The diagnosis of a brain tumor in a child is devastating for both the child and their family. Although many brain tumors are curable, it is always at a cost, and caregivers are often forced to make difficult decisions to determine a treatment course with the best chance of survival, balanced with a side effect profile that will provide an acceptable quality of life for the patient. Technological advances in radiation therapy and surgery, along with biological advances in medicine, have led to marked improvements in the therapeutic ratio for pediatric brain tumors. Progress is also largely attributable to the cooperative nature of pediatric oncology and, critically, the willingness of parents to have their children receive their cancer treatment as part of a clinical trial. Despite major improvements over the past few decades, there is room for further development and advancement in care. Cure is not within reach for all childhood brain tumors, and, for these tumors, improved cure rate remains the focus of research. For highly curable brain tumors, maintaining cure rates and decreasing side effects is the goal of many clinical trials. Current research seeks to better characterize the biology of this group of diseases and to provide and improve curative treatment while preserving function.

MODERN PEDIATRIC RADIATION DELIVERY

Radiation plays a central role in the cure of many brain tumors; however, there is a cost to this curative treatment for most patients. Because of fear of sometimes-substantial late complications, attempts have been made to avoid radiation for some young patients with brain tumors, often with inferior outcomes. Technical advances in both diagnostic and therapeutic

radiology have allowed for major changes in the way we deliver radiation. Targets are now well defined, smaller and allow for a great deal of sparing of the normal healthy brain. Modern treatment allows for even young children to receive localized treatment with reasonable expectations of enjoying healthy and fulfilling lives. Although delay or omission of radiation is reasonable to consider for selected patients, physicians should also consider the consequence of tumor progression, additional chemotherapeutic agents and surgeries, and crucially, the possibility that radiation targets may be larger at the time of eventual treatment if radiation is delayed.

Three-Dimensional Treatment Planning

Most of the major advances in radiation oncology over the past few decades were made possible by developments in diagnostic radiology. Before the advent of computed tomography (CT) and magnetic resonance imaging (MRI), radiation planning was performed using x-rays, referred to as two-dimensional planning. Visualization of the target and adjacent uninvolved structures in three dimensions was not possible. Therefore, treatment generally consisted of generous, simple fields that delivered high dose to areas uninvolved by tumor, and in some cases tumor volumes may not have been adequately covered. Modern planning uses CT and MRI and most departments obtain a CT scan in the treatment position and fuse diagnostic MRI sequences for treatment planning. The most useful MRI sequences for an individual child's brain tumor are tumor type and patient dependent and best determined after careful review with a pediatric neuroradiologist. Because tumor extent is better visualized, margins for error around this volume can be made smaller, thereby allowing for full coverage of the tumor with improved avoidance of the surrounding healthy tissues.

IMRT

With the development of more sophisticated treatment planning software, the ability to simulate plan modification and complex photon beam arrangements became possible. Intensity-modulated radiation therapy (IMRT) refers to highly complex photon radiation planning that delivers small beamlets of photon radiation of various intensity from multiple angles to best shape high dose to the target volume while avoiding high and moderate dose radiation to normal healthy structures. For IMRT planning, the physician defines all structures and inputs the desired target dose and dose and volume limitations for normal structures and prioritizes these goals. The software program then runs multiple iterations of the treatment plan until it finds the best possible plan. Figure 67-1 demonstrates IMRT delivery for a child with an ependymoma. IMRT allows for the most conformal photon plan with high-dose isodose lines closely surrounding the target volume. Although IMRT plans decrease high and moderate dose to nearby structures, these plans typically result in the delivery of low dose radiation to a larger volume of tissue outside of the target. While this may be a little consequence in terms of function, second malignancy is a risk for even low dose radiation.

SRS/SRT

The term *stereotactic radiation*, in part borrowed from neurosurgical localization systems, refers to high-precision radiation therapy using a three-dimensional coordinate system. Stereotactic radiosurgery (SRS) refers to the delivery of a single treatment, whereas stereotactic radiation therapy (SRT) refers to fractionated stereotactic treatment. SRS is accomplished by delivering multiple small beams of radiation to deliver the prescription dose to the target, but a much lower dose to the surrounding tissues. Precision is of paramount importance for SRS and typically rigid frames and fiducial markers are used. Many delivery systems exist for photon based stereotactic treatments and protons can also be used. The rigid frame and immobilization required may be too difficult for many children to tolerate without sedation.

Proton Radiation

Proton radiation has become a more widely used radiation modality for pediatrics over the last decade. Proton radiation is a form of particle radiation that allows for complete sparing of tissue beyond the target volume for a given beam as well as often less dose proximal to the target compared to photon radiation.[2] Proton radiation can be delivered using three-dimensional conformal proton radiation (3DCPT), also referred to as *double-scattered proton technique*. For this treatment, individual proton beams of the required energies are stacked to create a modulated beam or Spread Out Bragg Peak (SOBP). This beam is passed through a brass aperture to shape the beam to the outline of the tumor and a Lucite compensator to allow the beam to conform to the distal edge of the tumor. Protons can also be delivered using a scanning technique.[3] For this treatment individual proton beams are scanned across the tumor in the required location and depth. Scanning can improve conformity and this treatment creates minimal scatter radiation (Figure 67-2). Up until 2006, only 3 proton centers existed in the United States. At the time of this writing, 14 centers exist and many others are in either construction or planning phases despite the high-capital costs involved with

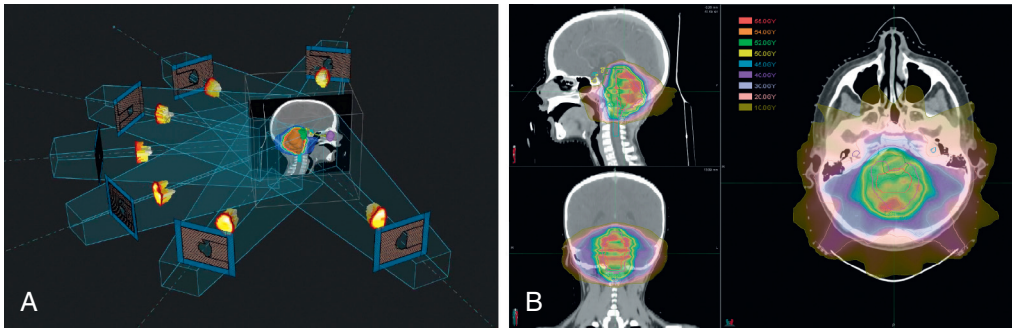


Figure 67-1 Intensity-modulated radiation therapy (IMRT) delivery and plan for a child with an infratentorial ependymoma. IMRT involves the use of highly sophisticated treatment planning software to run multiple iterations of plans involving multiple fields with varied intensity in segments of each field resulting **(A)** in a radiation treatment plan that is highly conformal to the target volume and spares critical nearby structures from high-dose radiation **(B)**.

building a center.[4] Pediatric brain tumors are considered one of the best indications for this type of treatment given the importance of sparing developing tissue from radiation. Although clinical experience is still limited, many publications have supported disease outcomes that are comparable to photons and early indications that morbidity may be less.[5-7] It is important to continue to collect data to confirm both efficacy and improved outcomes to justify increased costs. Although the upfront costs of protons are indeed greater than those of photons, modeling studies have predicted that protons will be cost-effective for selected pediatric brain tumors.[8,9]

Young patients with pediatric brain tumors should receive treatment in facilities with capabilities for anesthesia and preferably with child life specialists on staff. Immobilization and reproducibility are critical to any radiation delivery and can be a challenge for young children. Sedation is necessary for young children who are unable to cooperate, particularly for long treatments. We recommend consideration of anesthesia for children under the age of 7, but even older children may require sedation, especially for treatments longer than 20 or 30 minutes. If it is unclear if sedation is necessary, we recommend a trial run in the treatment room to better assess the child's ability to remain still. Image-guided radiation therapy with daily KV quality images or cone-beam CT is generally used to allow for a small set up margin and to improve accuracy.

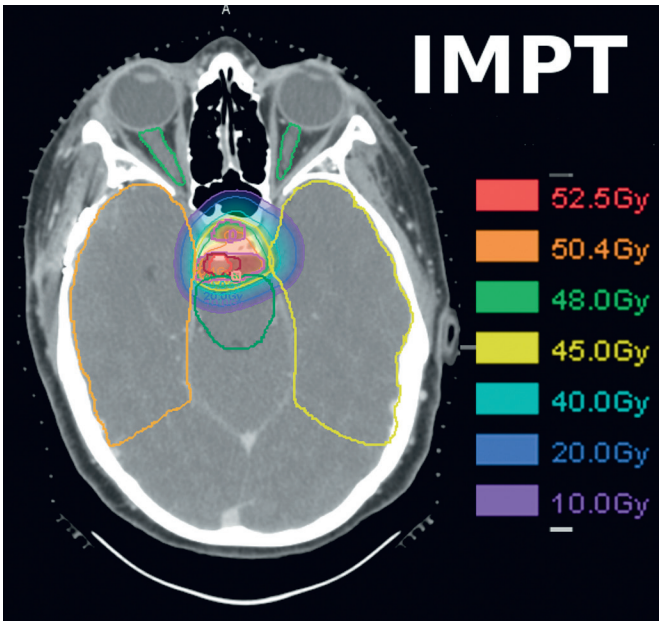


Figure 67-2 Proton beam scanning (PBS) for craniopharyngioma compared to other modalities. PBS is a way of delivering proton therapy with individual Bragg peaks rather than double scattered spread out Bragg peak (SOBP). This leads to improved normal tissue sparing for some tumors and decreases scatter radiation.

EMBRYONAL TUMORS

Embryonal tumors are the most common brain tumors in children under the age of 5, and second in frequency overall, to only low-grade gliomas.[1] Subtypes of embryonal tumors include medulloblastoma, supratentorial primitive neuroectodermal tumors (SPNET), atypical teratoid rhabdoid tumors (ATRT), and the relatively recently described embryonal tumor with abundant neuropil and true rosettes (ETANTR). These tumors are densely cellular, highly malignant small round blue cell tumors that have a propensity to spread through the CSF. Although grouped under embryonal tumors, these subgroups show distinct gene expression profiles, carry different prognoses, and have different patterns of relapse.[10] Although treatment regimens differ, intensive treatment with surgery, radiation, and chemotherapy is indicated for all embryonal tumor subtypes.

MEDULLOBLASTOMA

Medulloblastoma is the most common embryonal tumor that is, by definition, located in the cerebellum. Children are generally young at diagnosis, with a median age at onset of 5 years to 6 years.[11] Approximately 540 cases are diagnosed per year. Children generally present with headache, ataxia, nausea, vomiting, or cranial nerve deficit. Work-up includes a MRI of the brain that characteristically shows a mass in the cerebellum filling the fourth ventricle and obstructing the flow of CSF (Figure 67-3). The differential diagnosis for a tumor in this location in a child includes medulloblastoma, ependymoma,

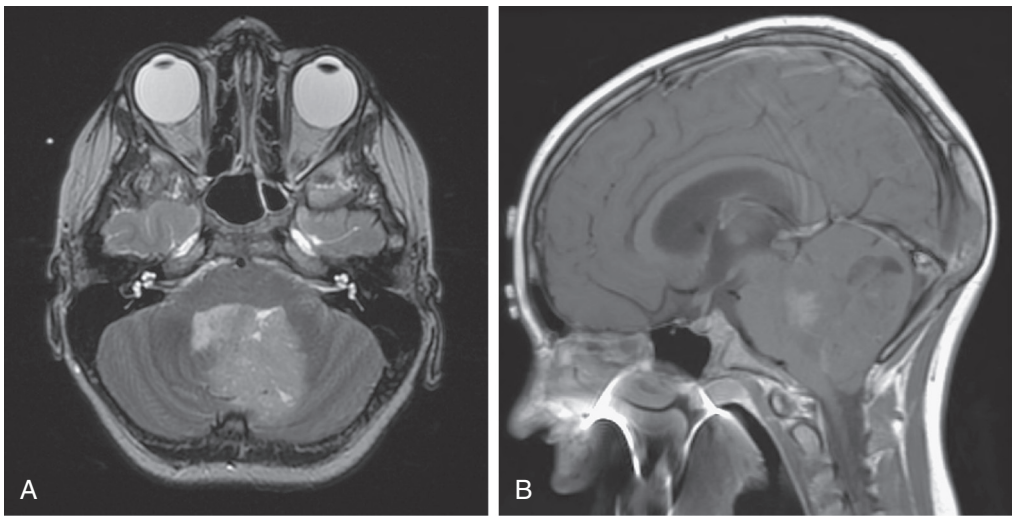


Figure 67-3 Medulloblastoma. Axial T2 **(A)** and sagittal T1 postcontrast **(B)** images showing a partially enhancing T2 bright medulloblastoma centered in the IVth ventricle in the posterior fossa and causing hydrocephalus.

low-grade glioma, and ATRT. Maximal safe resection is recommended for relief of symptoms and as a component of definitive treatment. Additional work-up includes MRI of the spine and a lumbar puncture to obtain CSF. MRI of the spine may be performed before surgery or 10 days to 14 days after surgery, but lumbar puncture should be performed 10 days to 14 days after surgery. Attempting to perform a lumbar puncture before surgery may result in herniation. Medulloblastoma has three main histopathologic subtypes: desmoplastic, classic, and anaplastic/large cell anaplastic. Desmoplastic tumors carry a more favorable prognosis, while frankly anaplastic tumors carry a poorer prognosis.[12,13] Regardless of pathological distinction; all medulloblastomas are considered WHO Grade IV.

At present, a risk-stratification system based on clinical factors divides patients into two risk groups, "high-risk" and "standard-risk," with standard-risk defined as children older than the age of 3 with ≤1.5 cm^2 of residual disease following surgery and no metastatic disease (grossly or in CSF) and all others considered high risk. Approximately 30% of patients will have metastatic disease at diagnosis.[8,9] The Chang staging system is often referred to for description of the extent of metastatic disease; M0, no evidence of metastasis; M1, cells in CSF; M2, seeding in intracranial subarachnoid or ventricles; M3, gross seeding of spine; and M4, extraneural metastasis.[14] The prognosis is worse for patients with gross metastatic disease, but the impact of microscopic disease in the CSF alone less clear.[8,15] In recent years, diffuse anaplastic/large cell histologies have been found to portend a poor prognosis.[13,16] The Children's Oncology Group determined that patients with otherwise standard risk disease but anaplastic histology should be treated on the high-risk COG study ACNS 0332 rather than the low-risk study ACNS0331.

Off-study, we generally make treatment decisions in the setting of a multidisciplinary conference, weighing the risks and benefits for this group of patients considering age and other clinical factors. The DFS for a patient with standard-risk disease treated with chemotherapy and radiation exceeds 80%.[13] Cure rates for high-risk disease are less favorable, but fall between 50% and 70%.[15,17] Children with standard-risk disease with anaplastic histology have a DFS in between these two groups of approximately 73%.[13]

The risk stratification system currently used evolved based on data from the pre-MRI era; it is now quite dated and may not adequately determine risk for all patients. It is likely that a new classification system for medulloblastoma will evolve in the relatively near future. A tremendous amount of convincing data for the use of gene expression profiles to determine prognosis for patients with medulloblastoma has been published over the past decade.[18-21] These data reveal that histologically similar tumors can be grouped into four distinct molecular subgroups with vastly different prognoses.[18] These four core groups, of decreasing disease outcomes, include WNT (wingless), SHH (sonic hedgehog), Group 3, and Group 4.[18] It is almost certain that in the future molecular stratification will play a role in the determination of treatment for all children with this disease. However, at present, it is recommended that this information be used for risk stratification only in the setting of a clinical trial. Institutional trials have already begun to use this information and the next Children's Oncology Group Trial will use molecular profiles in some way. In addition to risk stratification, newly discovered molecular pathways hold promise for more efficacious and less toxic targeted therapies.

Current standard treatment for medulloblastoma consists of treatment to the entire craniospinal axis to a dose of 23.4 Gy, usually with concurrent vincristine, followed by additional radiation to the posterior fossa or tumor bed, plus a margin (involved field) to bring the total dose to this region to 54 Gy.[22] Radiation should commence approximately 31 days after surgery and additional chemotherapy is delivered following radiation. Although involved-field radiation boost as opposed to a boost to the whole posterior fossa is conventional at many institutions, it is not yet considered to be standard of care as results from the COG study, ACNS0331, are not yet available. Several nonrandomized series suggest excellent outcomes without increased rates of failure in the posterior fossa.[23,24] It is important to note that the whole posterior fossa received 36 Gy for most patients studied.

In addition to randomizing patients to involved-field radiation versus whole posterior fossa, ACNS0331 also asked the question of reduced-dose craniospinal irradiation (CSI) (18 Gy) for children 8 years of age or younger with standard-risk medulloblastoma. The use of 18 Gy was based on favorable results from a small series combined with the desire to decrease radiation side effects for these young children.[25] At present, 23.4 Gy is standard for children of all ages, but results from ACNS0331, when available, may show that it is safe to deliver a lower dose for young children. For children with high-risk medulloblastoma, treatment consists of radiation with a CSI dose of 36 Gy followed a boost to 54 Gy to the posterior fossa with chemotherapy. Gross metastatic lesions should receive 45 Gy. The current COG protocol, ACNS0332, is evaluating the addition of daily carboplatin concurrent with radiation and posttreatment isotretinoin.

Management for children under the age of three is a bit more heterogeneous and generally consists of maximal safe resection followed by chemotherapy followed by delayed and usually localized radiation therapy. The radiation volume is often limited to the involved-field for children with localized disease or sometimes even omitted.[26,27] Outcomes are inferior, perhaps to a large extent because of the omission, deferral, or alteration of radiation therapy. The Head Start Trials have reported good outcomes for regimens including intensive chemotherapy and high-dose chemotherapy followed by stem cell rescue (HDCSCR).[26] The current COG study, ACNS0334, delivers intensive chemotherapy including high-dose chemotherapy and stem-cell rescue with or without methotrexate. Radiation is optional on this trial, and when used it calls for delivery of radiation to the involved field to a dose of 50.4 Gy to 54 Gy. With highly conformal treatments such as IMRT or proton radiation, localized treatment provides benefit to the area at highest risk of recurrence without the substantial late effects that delivery of radiation to the entire brain and spine would have for these young children. Children with desmoplastic nodular histology or extensive nodularity have a favorable prognosis and the current COG study ACNS1121 studies the use of intensive chemotherapy without radiation.[28]

The craniospinal volume includes the entire brain and spine. Care should be taken to ensure coverage of the cribriform plate and to give a margin of approximately one vertebral body below the thecal sac, which is typically located near S2 (Figure 67-4). Because it is critical to adequately cover these areas, it is best to confirm the location of these regions with a neuroradiologist. Most CSI treatments are delivered with the patient in the prone position, and most techniques involve field matching with fields matched anterior to the spinal cord, which creates a small area of underdosing in the cord but avoids any areas of overlap. Most centers place the match-line anterior to the cord to prevent hot spots in the cord (demonstrated in Figure 67-5). Care should be taken to minimize hot and cold spots and to "feather" fields to decrease uncertainty. The use of IMRT and scanning proton techniques allow for treatment without matching of fields; because of the lack of exit dose protons avoid exit dose to the thyroid, heart, lungs, abdominal organs and ovaries (Figure 67-6).



Figure 67-4 Care should be taken to carefully identify and ensure adequate coverage of the cribriform plate **(A)** and the thecal sac **(B)**.

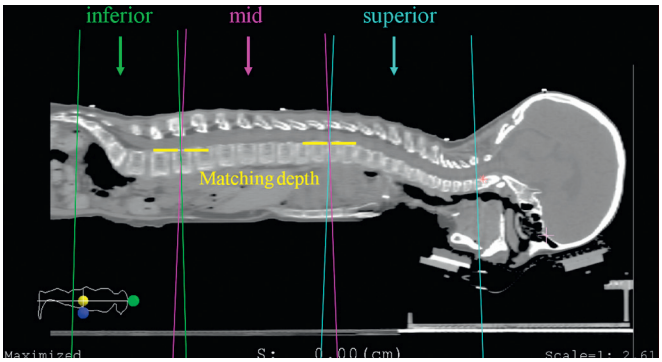


Figure 67-5 Prone CSI field set up demonstrating matching of spinal fields anterior to cord.

The posterior fossa volume is considered as CTV. This volume extends from the tentorium superiorly to C1 inferiorly. Laterally the posterior fossa volume includes the entire cerebellum and extends to the bony occiput and anteriorly this volume includes the brainstem and lower midbrain. The involved field volume GTV should include the tumor bed (anything in contact with the initial tumor before surgery) and any residual gross disease. Care should be taken to account for anatomical shifts following surgery. An expansion of 1 cm to 1.5 cm is typically used to form the CTV for the involved field boost (Figure 67-7).

SUPRATENTORIAL PRIMITIVE NEUROECTODERMAL TUMORS

Supratentorial PNETs are less common than medulloblastomas and account for 2% to 3% of primary brain tumors.[29] The metastatic potential of SPNET is similar to medulloblastoma, but the prognosis as a whole for patients with this disease is worse.[30,31] All patients with SPNETs are therefore considered to have "high-risk" disease and they are eligible for the same COG protocol that enrolls high-risk medulloblastoma patients (ACNS0332). Patients with pineoblastoma older than the age of 3 and patients without metastatic disease, however, seem to have a better prognosis.[30,32-34] Studies of patterns of relapse indicate a higher proportion of local failures for SPNET (other than pineoblastoma) when compared to medulloblastoma. Young children with SPNET/pineoblastoma treated without radiation therapy have dismal outcomes and focal radiation should be strongly considered for children under the age of three.[33,35,36]

The standard CSI dose for this disease is 36 Gy. Although local recurrence is most common for localized disease, no studies have explored lower CSI doses because of the less favorable outcome for this disease. A dose of 54 Gy is delivered to the tumor bed plus a margin of approximately 1 cm within anatomical boundaries. For children under the age of 3, involved-field radiation to 50.4 Gy to 54 Gy is generally recommended.

ATYPICAL TERATOID RHABDOID TUMOR

AT/RT rare malignancies that typically affect young children.[37] Although AT/RT accounts for 1% to 2% of childhood tumors in the brain, it may comprise more than 20% of CNS tumors in infants. These tumors have a mutation that results in a deficiency of INI-1 protein.[37] It is now routine to test all pediatric embryonal CNS tumors for loss of INI-1 to establish the diagnosis of AT/RT.[38,39] Before the discovery of this mutation, many patients with AT/RT were misdiagnosed as having medulloblastoma or SPNET. The prognosis for AT/RT is inferior to that for medulloblastoma and SPNET; however, recent studies with more aggressive chemotherapy have shown improved 2-year progression-free survival (PFS) and OS rates of 53% and 70%, respectively.[40] For patients with localized disease, cure is attainable with aggressive multimodality therapy. Disseminated disease still carries a dismal prognosis with a small chance of cure.

The treatment of AT/RT includes maximal resection of primary disease, intense induction chemotherapy including intrathecal chemotherapy, high-dose chemotherapy followed by stem-cell rescue (HDCSCR) and radiation therapy. For children under the age of 3, localized radiation is recommended. For older children, CSI followed by additional involved field radiation is favored because of risk of dissemination and poor prognosis, but some protocols use involved field RT even for older patients. Early timing of radiation also seems important. The tumor bed and any gross residual disease with a margin of approximately 1 cm should receive a dose of 50.4 Gy to

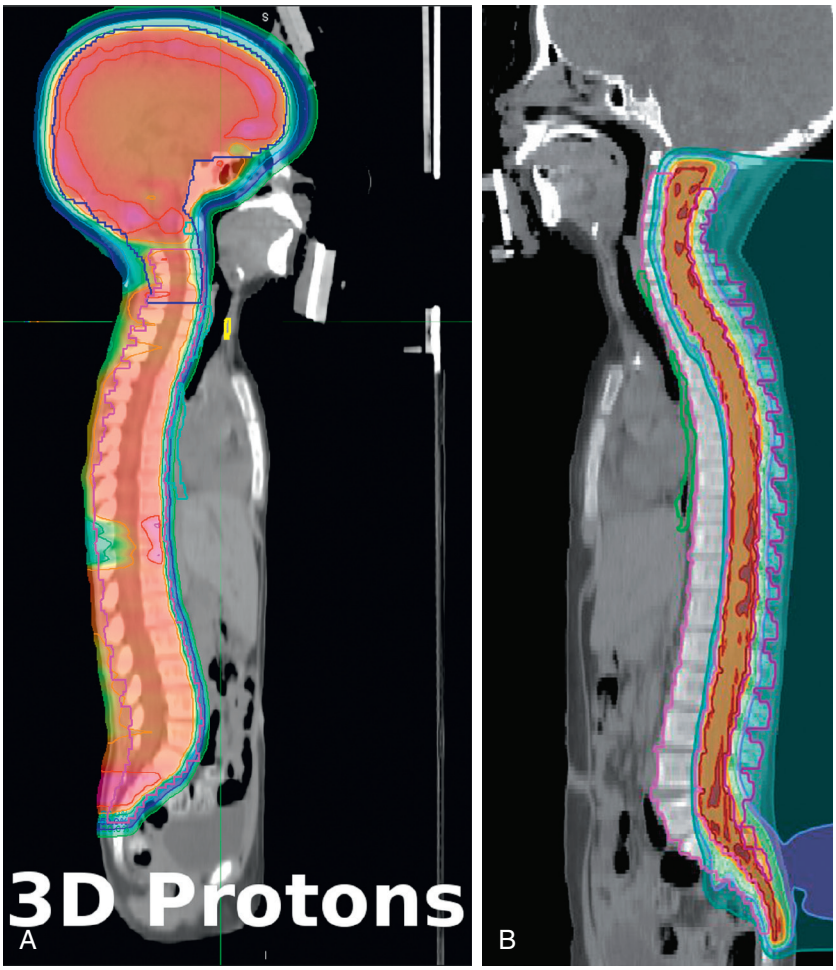


Figure 67-6 Proton radiation for CSI delivering demonstrating the ability to avoid organs anterior to the vertebral bodies. For growing children, the entire vertebral body is included in the target volume to avoid asymmetric growth from partial vertebral body treatment. **A** shows a three-dimensional conformal plan and **B** demonstrates a proton beam scanning technique that avoids hot/cold spots that may be introduced by field-matching.

54 Gy. Although there are limited data on effective CSI dose, given the more aggressive nature of this disease, 36 Gy is most standard for CSI.

ETANTR

Embryonal tumor with abundant neuropil and true rosettes (ETANTR) is a rare and relatively recently described subtype of embryonal tumor with approximately 50 reported cases.[41,42] This tumor usually occurs in young children younger than the age of 4 and is more common in females. Most are supratentorial, but they can occur in the infratentorial region. MRI appearance is similar to that of other embryonal tumors and dissemination is also through the CSF. Management is similar to the management of high-risk medulloblastoma and SPNET. Prognosis is poor and median survival short. Gessi et al reported 75% of patients dead of disease at 9 months; however, long-term survival is possible with one report describing one patient with long-term DFS of 7 years.[43,44]

EPENDYMOMA

Intracranial ependymomas are brain tumors that originate from ependymal cells lining the ventricles or from ependymal cell rests located in the brain parenchyma. They represent 5% to 8% of pediatric brain tumors and approximately 200 to 250 cases are diagnosed per year. Two thirds of these tumors occur in the fourth ventricle; the remainder of ependymomas occurs in the supratentorial compartments of the brain. These children are usually young because ependymoma is most commonly diagnosed in children under the age of four.

Presentation is dependent on location. Children with infratentorial tumors most often present with signs of hydrocephalus and/or cranial nerve deficits (similar to medulloblastoma). Children with supratentorial tumors can present with a variety of symptoms dependent on tumor location. Diagnostic workup includes MRI of the brain and spine and CSF sampling. Localized disease is most common, but metastatic disease can be seen elsewhere in the brain or spine. The diagnosis of metastatic disease based on CSF alone for ependymoma is extremely rare.[45]

Histopathology of ependymomas will reveal classic/differentiated (WHO grade II) or anaplastic (WHO grade III) tumors. Most studies, but not all, indicate that anaplastic tumors have inferior outcomes. The lack of consistency for this prognostic factor may be because of difficulty in assigning tumor grade or the small size of most studies.

The initial treatment is complete surgical removal. Removal of the entire tumor is critical for a favorable outcome and this has been demonstrated clearly in multiple series.[5,46] The 3-year to 5-year PFS rates are on the order of 51% to 88% for gross total resection and from 0% to 54% for subtotal resection.[5,47,48]

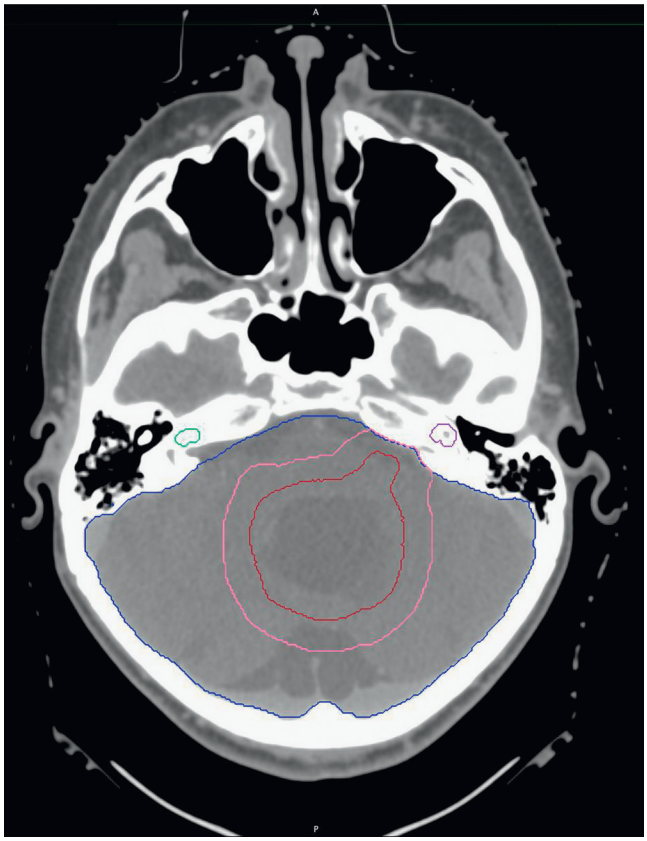


Figure 67-7 Involved field boost *(magenta)* compared to whole posterior fossa boost *(dark blue)*. The involved-field boost decreases the amount of cerebellum and usually brainstem in the treatment field. For many tumors, the distance from the cochlea, temporal lobes, and neuroendocrine structures is greater for the involved-field boost allowing for decreased high dose to these critical structures.

If complete removal is achieved, radiation to the tumor bed plus a margin is recommended. If resection is incomplete, a short course of chemotherapy followed by a second look surgery in attempt to achieve a gross total resection before radiation is favored. Chemotherapy alone is not an option for infratentorial disease as outcomes are dismal with a 5-year event-free survival of only 27%, and all patients alive at this time had received radiation at diagnosis or at time of failure.[49,50]

Although there are concerns about irradiating young children, Merchant et al proved this treatment to be safe and effective and the current and prior COG protocols deliver RT to children as young as 12 months of age. Survival was once thought to be inferior in children under the age of 3, but the St. Jude's experience showed that this was not the case if radiation was delivered, indicating that omission of radiation was the likely reason for reports of inferior outcomes. Because of the relatively young age of these children, highly conformal techniques such as IMRT or proton therapy should be strongly considered.

Infratentorial ependymomas are notorious for extension through the foramina of Luschka and Magendie (Figure 67-8). It is critical to review imaging with neuroradiology to determine the original tumor extension into these regions. Fast imaging employing steady state acquisition (FIESTA)/constructive interference in steady state (CISS) MRI images show CSF and parenchymal interfaces well and may be useful for defining extent of the original tumor or detecting small amounts of residual disease. These images can clearly show cranial nerves and the small amounts of disease spread so often seen with ependymomas.

For radiation therapy, the GTV should include any surface contacted by the original tumor as well as any gross residual disease. Although there will be shifts in tissue position following surgery, it is still useful to fuse the preoperative scan and to contour this volume to become familiar with both the anatomical location of the tumor as well as ependymal and CNS structures in contact with the tumor. This volume serves as a useful guide in contouring the GTV. The CTV expansion should be 5 mm to 10 mm with constraints for anatomical boundaries. The recommended dose to this volume is 54 Gy to 59.4 Gy in 30 fractions to 33 fractions. The recently closed and current COG protocols (ACN0121 and ACNS0831, respectively) prescribe a total dose to 59.4 Gy, but ACNS0831 requires

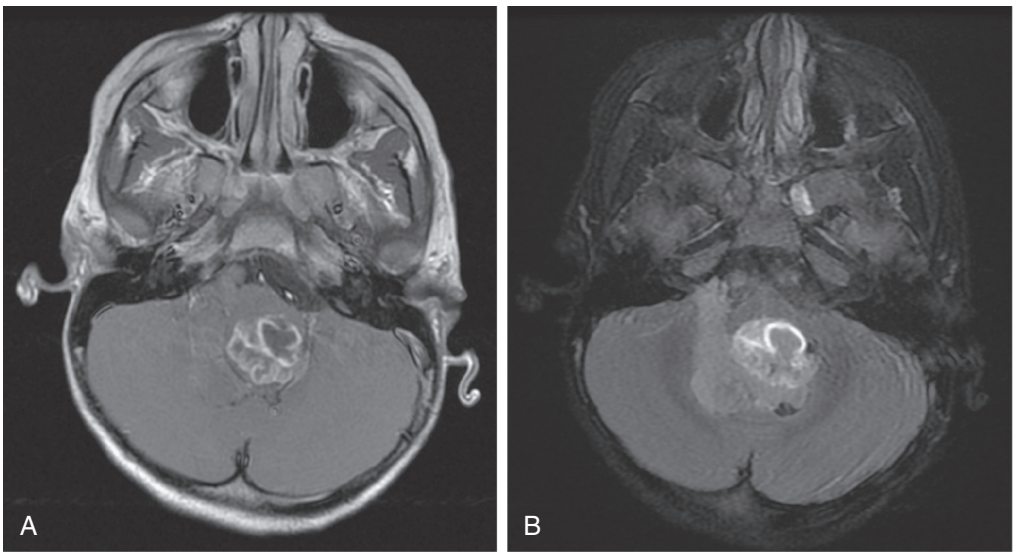


Figure 67-8 Infratentorial ependymoma. Axial images depict an infratentorial ependymoma with extension through the left foramen of Luschka and involving the vertebral and basilar arteries. T-1 post-gadolinium image **(A)** and T2 FLAIR image **(B)** show that this tumor is partially enhancing.

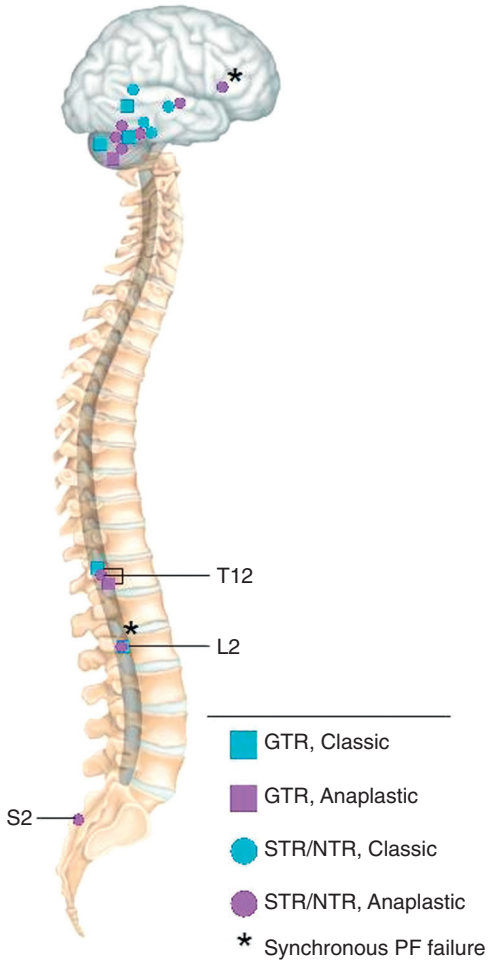


Figure 67-9 Patterns of relapse following involved field radiation for localized ependymoma.

that critical structures (the spinal cord and optics) outside of the area of highest risk be blocked after 54 Gy.[51] Children younger the age of 18 months or with known brainstem injury should receive a total dose of 54 Gy. Off protocol, a dose of 54 Gy to 59.4 Gy is typically used. Some clinicians recommend only delivering dose beyond 54 Gy to residual disease because of brainstem tolerance, whereas others feel the risk of local recurrence for this disease warrants a dose >54 Gy.

Recent studies have shown a proportional increase in distant relapses, owing to improved local control likely attributable to advances in surgical and radiation techniques (Figure 67-9).[5,52] ACNS0831 randomizes children to maintenance chemotherapy with vincristine, cisplatin, etoposide, and cyclophosphamide (VCEC) after radiation to explore in a randomized fashion whether or not additional chemotherapy will improve outcomes and determine how it will be tolerated. Supratentorial WHO Grade II tumors that are completely resected may be observed without radiation on ACNS0831. The last COG study also enrolled a small number of these patients on an observation arm. Off-trial, radiation is standard.

Similar to embryonal tumors, molecular profiling of ependymomas show distinct patterns for supratentorial and infratentorial tumors and indicate that these tumors may be genetically distinct entities. For rare cases of ependymoma that present with metastatic disease, CSI to 36 Gy followed by a localized boost to 54 Gy to 59.4 Gy is recommended unless the child is younger than 3 years of age. Outcomes are generally poor for patients with metastatic disease.[53] Ependymoma recurrences following radiation therapy are challenging to manage, but accumulating data suggests that reirradiation is of benefit for some patients, particularly those with isolated local recurrences.[54,55] Retreatment carries substantial and life-threatening risks, but alternative treatment options are quite limited. These cases should always be thoroughly discussed in a multidisciplinary setting and the risks and benefits of reirradiation thoroughly discussed with the family.

LOW-GRADE ASTROCYTOMA

Low-grade gliomas are the most common pediatric CNS malignancy. Though they may occur anywhere in the brain, the most-common locations are the cerebellum and cerebral hemispheres. Tumors in these locations can usually be treated by surgery alone with excellent long-term DFS; 90% for complete resection in modern series.[56] Additional locations less amenable to surgery include the hypothalamus, thalamus, tectum, optics, and brainstem. For these tumors, chemotherapy or radiation is typically required.

Histological subtypes of pediatric low-grade gliomas include pilocytic (WHO grade I) and diffuse (WHO grade II), with pilocytic astrocytomas accounting for the majority of tumors in young children. Presentation is dependent on location and may be slow to progress because these tumors are slow growing. Diagnostic work-up includes MRI of the brain. Although dissemination is rare in this disease, MRI of the spine is usually obtained at the time of diagnosis. Radiographically, low-grade gliomas may or may not enhance and can have cystic components. When complete surgical resection is not an option, management can be complex and treatment is best determined in a multidisciplinary setting. Biopsy is recommended for most sites to confirm pathology but is not considered necessary for optic and hypothalamic gliomas or tectal gliomas that have a classical appearance on MRI. Surgical intervention may also be needed to relieve pressure on critical structures. Tumors in these locations are almost always pilocytic astrocytomas and biopsy may carry a higher risk of morbidity.

Historically, radiation including a 2-cm to 3-cm margin around visible tumor was the standard of care for low-grade gliomas. Although favorable disease control was reported, late neurotoxicity, particularly for young patients, led investigators to explore chemotherapeutic options. Packer et al reported a 68% 3-year PFS rate for children treated with carboplatin and vincristine. The only significant prognostic factor for this cohort of 78 patients was age, with children 5 years of age or younger having a 3-year PFS of 74% and children older the age of 5 having a 3-year PFS of 39%.[57] The use of chemotherapy to delay radiation has since been widely adopted for children age 5 and younger and is often considered for children under the age of 10. Additional chemotherapeutic agents have since been studied. The multiagent therapy using thioguanine, procarbazine, Lomustine (CCNU), and vincristine has shown promising results as have other regimens. The 5-year PFS for thioguanine, lomustine, carboplatin, vincristine (TPCV) was 48% versus 35% for carboplatin and vincristine, although this difference was not statistically significant.[58]

The toxicity of a particular chemotherapy and also the cumulative morbidity of multiple regimens must be considered. Chemotherapy may have a substantial impact on these children both during the years of treatment as well as subsequently. Chemotherapy typically delays progression, which can be beneficial in providing time for brain development, but radiation therapy is usually still required for definitive treatment. When determining the appropriate therapy, one must also consider the risks of functional loss from progression of tumor. Merchant et al reported 10-year PFS rates of 74% for conformal focal radiation.

Bithalamic low-grade gliomas carry a much poorer prognosis, more similar to high-grade gliomas, with a poor median and OS.[59] This should be taken into consideration when making management decisions for this disease.

Treatment planning for low-grade gliomas has evolved greatly. It is now recognized that these tumors are not highly infiltrative. Modern series and protocols define the GTV as visible tumor that must include enhancing and nonenhancing or cystic tumor plus a small margin of 5 mm. Standard radiation doses range from 50.4 Gy to 54 Gy. If tumors contain a cystic component, it is important to include this portion of the tumor in the GTV and to monitor the cystic component for changes during radiation therapy and adjust the plan as needed. For rare cases of disseminated low-grade glioma, radiation volumes usually encompass the entire craniospinal axis to a dose of 36 Gy followed by involved field treatment to 45 Gy to 54 Gy depending on tumor location.

HIGH-GRADE ASTROCYTOMA

Unlike adults, high-grade gliomas are relatively uncommon in the pediatric population, representing 8% to 12% of pediatric brain tumors, and although they still carry a poor prognosis, long-term DFS is seen in approximately 20% of patients.[45,60] These tumors can occur at any location in the brain; symptoms are dependent on location and MRI usually shows an enhancing mass with surrounding vasogenic edema. The vast majority of tumors are localized and spread is local, but extent of local disease likely to be more extensive than that seen for other pediatric brain tumors. Maximal safe resection with attempt to preserve function should be attempted. Radiation is standard after surgery. Chemotherapy has been studied extensively but without great success. Although temozolomide has been successful for adult tumors, it shows minimal efficacy in children.[61,62] Despite limited efficacy, at present, temozolomide is often used as a first-line chemotherapy concurrent with radiation therapy and following radiation therapy. Efforts to discover a new and more effective agent are under way.

For treatment planning, one must be careful to include areas of contrast enhancement and T2 FLAIR signal abnormality for the initial GTV. This volume plus a generous margin is usually treated to 45 Gy. The enhancing area plus a margin should receive a boost dose to bring this region to a dose of 54 Gy to 59.4 Gy. Although anatomical boundaries such as bone and tentorium should be respected when defining the CTV, these tumors often cross white matter tracts, and it is important to consider this when defining tumor margins to account for microscopic spread of disease (Figure 67-10). These volumes are large compared to other pediatric tumors but considered necessary for disease control.

DIFFUSE PONTINE GLIOMA

Diffuse infiltrating pontine gliomas (DIPG) are high-grade tumors arising in the pons of the brainstem. These tumors have a characteristic appearance on MRI of a nonenhancing T2 bright lesion that expands the pons. Biopsy is not indicated when this classic pathognomic radiographic appearance is seen; however, for some clinical trials, pathology is obtained for molecular profiling.[63] Children typically present with a short duration of symptoms that most often includes ataxia, nausea/vomiting, and cranial neuropathies. Radiation is indicated to the tumor with a margin to a dose of approximately 54 Gy. Symptoms generally resolve with treatment. Unfortunately, duration of symptom relief is usually short lived, on the order of 6 months. This disease is uniformly fatal, and the median survival for these children is 1 year. Dose escalation and altered fractionation radiation therapy failed to improve outcomes and chemotherapy has not been terribly effective.[64-66] Genetic aberrations and molecular targets are currently under investigation and will hopefully improve outcomes for this disease.[63,67]

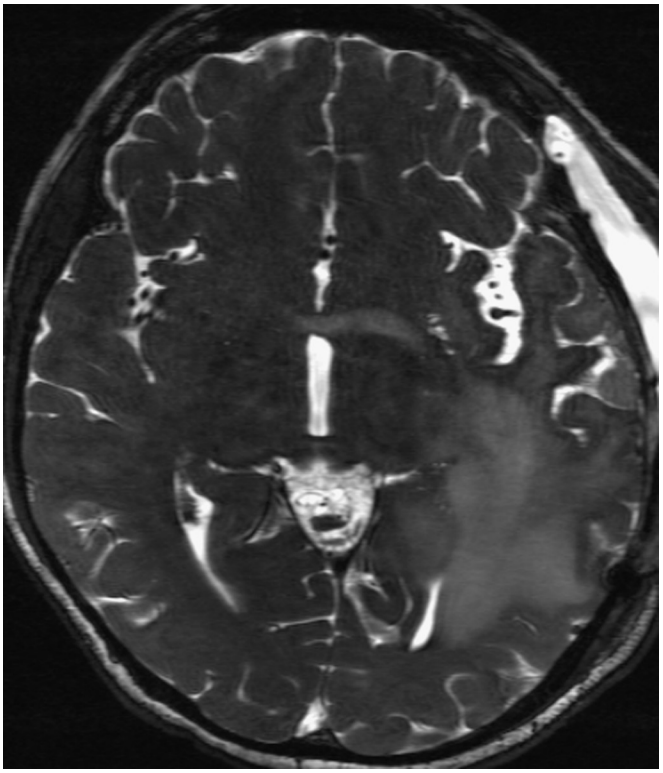


Figure 67-10 High-grade glioma showing a component of the tumor crossing the anterior commissure. Care should be taken to be sure this component crossing into the contralateral hemisphere is included in the gross tumor volume.

GERM CELL TUMORS

Pediatric intracranial germ cell tumors represent only 2% to 3% of childhood CNS neoplasms in North America, but they make up 10% to 11% of pediatric CNS tumors in Japan in the Far East.[68] These tumors occur most often in adolescents, but they can be seen in young children and adults. CNS germ cell tumors (GCTs) usually occur in the pineal gland and infundibulum and suprasellar region but may occur in other locations of the brain, such as the basal ganglia. A male predominance is seen for pineal gland tumors (5:1), but there is no sex predilection for suprasellar tumors. Disease is found in both the pineal gland and suprasellar region in 5% to 10% of cases and GCTs can occur elsewhere in the brain less frequently.

Patients typically present with symptoms of increased intracranial pressure as a result of blockage of CSF flow from the third to fourth ventricle or Parinaud's syndrome (decreased pupillary light reflex, impaired upward gaze, and convergence nystagmus) from compression of the superior colliculus of the tectum. Patients with suprasellar disease usually present with diabetes insipidus, decreased growth, or other endocrinopathy. Suprasellar tumors may also involve the chiasm or optic nerves causing visual impairment. It is not uncommon to see a patient with suprasellar GCT with a long history of symptoms before diagnosis.[69]

When a GCT is suspected by MRI findings, serum tumor markers, α-fetoprotein (AFP) and β-human chorionic gonadotropin β-HCG), should be obtained. If a lumbar puncture can be safely performed, CSF should be obtained for cytology and tumor markers. Although ventricular fluid is often obtained at time of biopsy or shunt placement, lumbar CSF 10 days to 14 days after a procedure is the gold standard.[70] MRI of the spine is also required to ensure disease is not disseminated.

GCTs are a heterogeneous group of tumors and are classified into two main groups that have prognostic and treatment implications, pure germinomas and non-germinomatous germ cell tumors (NGGCT). NGGCT include the subtypes embryonal, immature teratoma, choriocarcinoma, and yolk sac/endodermal sinus tumors. North American guidelines consider any abnormal elevation of AFP (≥10 or institutional norm) or elevation of β-HCG ≥100 to indicate a NGGCT. They children do not require biopsy for diagnosis. Mild elevation of β-HCG may be seen with pure germinomas. If tumor markers do not clearly indicate a NGGCT, biopsy is recommended to confirm diagnosis.

In North America, surgery is typically performed with the intent of obtaining tissue for diagnosis. For pineal region tumors, an increasingly common procedure accomplishing both diagnosis and relief of hydrocephalus is a third ventriculostomy. For this procedure, an endoscope is inserted through the lateral ventricles. Inspection of the lateral and third ventricles is performed to ensure no MRI-occult metastases are present. The pineal gland can be biopsied and an opening in the floor of the third ventricle is created permitting flow from the third ventricle to the prepontine space. This procedure is highly effective in relieving hydrocephalus without the need for an external drain or shunt.

Pure germinomas are highly curable tumors with DFS rates in excess of 90% for both localized and disseminated disease.[6,71,72] In the United States, chemotherapy followed by reduced-dose radiation is usually recommended for pure germinomas, although radiation alone is still considered an acceptable standard of care. Two to four cycles of platinum based therapy, usually carboplatin and etoposide is delivered. If a complete response is achieved, a dose of 21 Gy to the whole ventricles followed by a boost to 30 Gy to 40 Gy to the primary tumor region is delivered. If a complete response is not achieved, a second-look surgery is recommended (if this can be safely performed) to ensure that a nongermininomatous component is not present or higher doses of radiation may be recommended. If radiation alone is used, a dose of 24 Gy is usually delivered to the whole ventricle volume followed by a dose of 45 Gy to 50 Gy to the primary tumor bed. Patients with disseminated disease are treated in a similar manner, but CSI is used for the initial treatment volume rather than the whole ventricular volume.

Several studies have explored the use of chemotherapy followed by involved-field radiation to 30 Gy to 40 Gy.[73] Early reports showed promising results, but higher rates of ventricular relapse were later reported by Alapetite et al, resulting in a shift back to whole ventricular RT followed by an involved-field boost.[74] The current COG protocol, ACNS1123 is investigating the use of preradiation therapy chemotherapy with four cycles of carboplatin and etoposide followed by very low-dose whole ventricular radiation to 18 Gy and a boost to a total of 30 Gy to the primary tumor for localized pure germinomas following a complete response to chemotherapy.

NGGCT have a much poorer prognosis and multimodality therapy is always recommended. The addition of platinum-based chemotherapy has led to marked improvements in outcomes and recent studies show long-term disease free survival rates of 70% to 80%.[75] The standard chemotherapeutic regimen in the United States consists of six cycles of alternating carboplatin/etoposide and ifosfamide/etoposide. Patients with a complete response by MRI and normalization of tumor markers are then treated with radiation. Those who do not have a complete response should undergo a second look surgery. Although no viable tumor is found in some cases, residual tumor or mature teratoma may be present and is likely to grow at a later time. Although risks must be taken into consideration, removal is considered best if at all possible.

Radiation volumes and doses are somewhat controversial. The last COG protocol, ACNS0122, delivered CSI to 36 Gy followed by a boost to the tumor volume to 54 Gy. The results of this trial have not yet been published in manuscript form, but 5-year EFS and OS rates of, 84% and 93%, respectively, have been reported (personal communication, Stuart Goldman). International Society of Paediatric Oncology (SIOP) has reported excellent outcomes for chemotherapy and involved field RT. They found a dose less than 50 Gy to the involved field to result in inferior outcomes. The current COG protocol, ACNS1123, examines a middle ground radiation volume delivering 30.6 Gy to the whole ventricles followed by a dose of 54 Gy to the involved field following six cycles of carboplatin/etoposide alternating with ifosfamide/etoposide (identical to ACNS0122) for patients with localized NGGCT.

For treatment planning, it is important to assess carefully pre- and postchemotherapy imaging. It should be determined if tumor appeared invasive of brain parenchyma or if tumor is only displacing the adjacent brain parenchyma. These tumors are often large at diagnosis, but often regress completely with chemotherapy. It can sometimes be challenging to determine if there has been a complete response. Posttreatment MRI's almost always show some residual tissue that may be scar tissue, but this tissue should be evaluated carefully with pediatric neuroradiologists familiar with this disease to ensure residual tumor is not present. Pre- and postchemotherapy scans should also be reviewed to rule out any occult disease. A decrease in size of the infundibulum or pineal gland after chemotherapy should lead to suspicion of occult disease. If this is suspected, both regions should be included in the boost volume. The involved-field volume should also be determined at the time of planning CSI or whole ventricle treatment planning to ensure the CTV boost volume receives full dose. GCTs can involve the optic nerves and hypothalamus in areas that are not part of classic CSI or whole ventricle volumes (Figure 67-11). As the whole ventricular volume is somewhat difficult to contour consistently and is used on for all patients on the ACNS1123, guidelines to assist in contouring the whole ventricular volume are available on the QARC website (Figure 67-12).

CRANIOPHARYNGIOMA

Craniopharyngioma is a relatively uncommon brain tumor, with less than 100 cases diagnosed in the United States per year. Despite being considered a "benign" and highly curable disease, it remains one the most difficult and controversial brain tumors in terms of management. The controversy lies in the high risk of morbidity for these patients. Although complete resection is curative for these tumors, the most common adamantinomatous type of craniopharyngioma is often too adherent to critical structures to allow for a minimal-risk resection. It is critical that these cases be seen by experienced pediatric neurosurgeons and pediatric radiation oncologists, and that the risks and benefits of treatment are carefully considered in a multidisciplinary setting.

Craniopharyngiomas arise from remnants of Rathke's pouch in the sellar/suprasellar region intimate with neuroendocrine structures, the optic apparatus and the medial

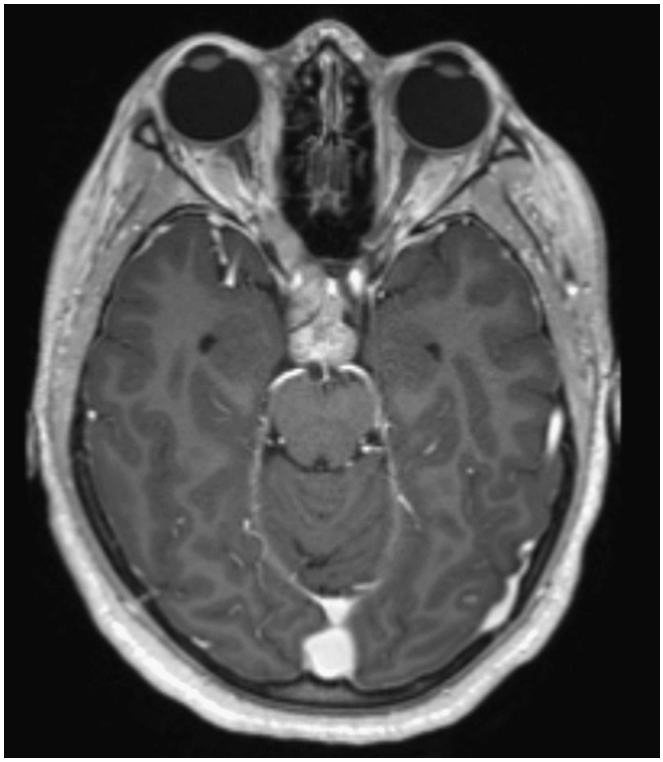


Figure 67-11 Germinoma with optic nerve involvement. Care should be taken to include this region in both the whole ventricle volume (or CSI volume) and the boost volume. The boost volumes should always be contoured at the time of initial volume planning.

temporal lobes. Complete resection is curative, but seldom achievable without great morbidity. For some young children or those with a large cystic component, cyst decompression and partial resection with close observation may be the best management. These children will require RT at some point and careful and frequent observation is required. Limited surgery followed immediately by radiation is our preference for most patients. This treatment was first shown to be an effective treatment for craniopharyngioma by colleagues at St. Georges and Royal Marsden Hospital in 1961.[76] Since their early reports, additional studies have confirmed excellent disease outcomes, with progression free survival ranging from 72% to 100%, for this combined treatment.[76-78] Although less data for IMRT and proton radiation is available, published studies have reported excellent outcomes.[78,79] Given the high likelihood of survival, minimizing late morbidity is of paramount importance. These modern modalities are therefore favored for treatment in attempt to decrease long-term morbidity (Figure 67-13). Fractionated SRS plays a role in the management of small tumors. SRS has a limited role given the close proximity of these tumors to the optic structures, but it may have a role for small solid tumor components that are not adjacent to optic structures or small recurrences.

Intracavitary radiation is another modality that can be an effective treatment option for the cystic component of craniopharyngiomas, but because of limited penetration, this treatment is not useful for treatment of the solid component of craniopharyngiomas.[80,81] For this reason, it is generally used only for cystic recurrence. For this procedure, beta emitting particles (P32 or Y90) are administered by stereotactic cannulation of the cyst or via an Ommaya reservoir in a joint procedure by a radiation oncologist and neurosurgeon.

For any tumor that has a cystic component, cyst growth, or less often reduction in cyst size, may occur during radiation therapy. Because of the cystic portion of the tumor is also targeted in treatment, it is crucial to make appropriate adjustments in the radiation plan during the course of radiation. We

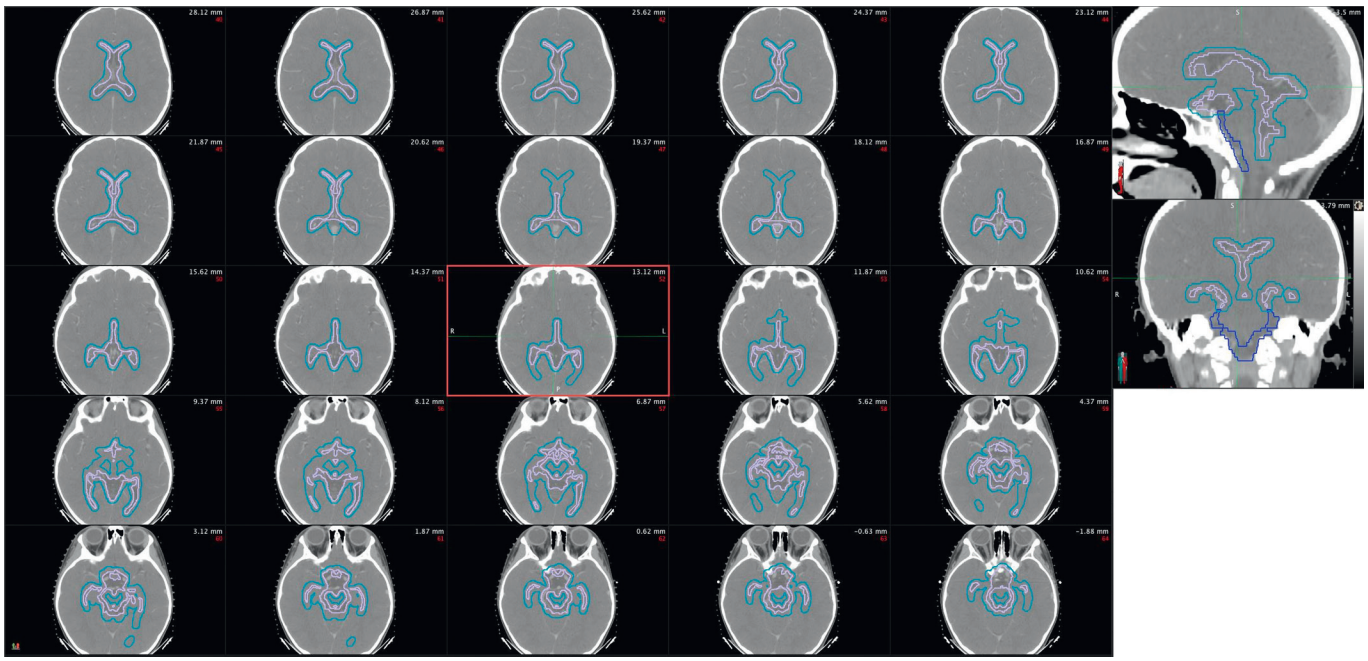


Figure 67-12 Whole-Ventricle Volume. Axial slices showing whole ventricular volume contours. The whole-ventricle volume includes the lateral third and fourth ventricles. Purple (WVV), blue (WVV PTV), dark blue (pre-pontine space). (Atlas is available on qarc website. http://www.qarc.org/cog/ACNS0331Atlas.pdf)

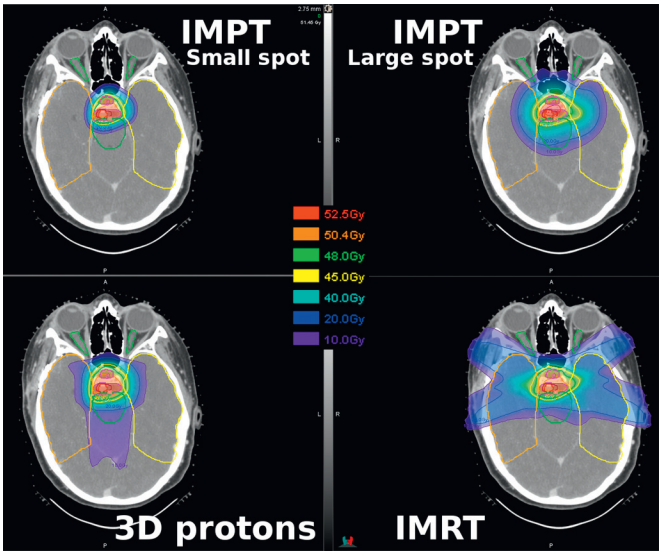


Figure 67-13 Modern modalities for localized treatment of craniopharyngioma.

recommend obtaining a CT or T2-weighted noncontrast MRI every 7 days to 14 days for cyst monitoring. If the initial MRI does not show change, subsequent MRIs during treatment are less likely to show change. The use of cone-beam CT is particularly desirable for image guidance for craniopharyngiomas because it may provide additional information about cystic changes on a daily basis.

The GTV for craniopharyngiomas includes both solid and cystic components. A small margin of 3 mm to 5 mm around the GTV should be given for the CTV volume. A dose of 50.4 Gy to 54 Gy at daily fractions of 1.8 Gy is recommended. Some series have used higher doses of radiation, but because of optic structure tolerance and lack of evidence that a greater dose provides improved tumor control, higher doses are not generally recommended.

CHOROID PLEXUS TUMORS

Choroid plexus tumors are rare and typically occur in young children, usually under the age of 2. Choroid plexus papillomas can be cured with surgery alone. Choroid plexus carcinomas carry a less favorable prognosis and in addition to maximal resection, chemotherapy and radiation are recommended.[82,83] Choroid plexus carcinoma has been associated with *p53* mutations.[84] A dose of 50.4 Gy to 54 Gy is used for the tumor bed. If the child is older and metastatic disease is present, CSI should be considered.

SPINAL CORD TUMORS

Primary spinal cord tumors are rare in children. Presenting symptoms include pain, weakness, altered sensation, sphincter dysfunction, and scoliosis.[85] Complete resection is recommended if this can be performed without loss of neurological function and is often required to relieve pressure on normal spinal cord. Pathologies include ependymoma (usually myxopapillary, WHO grade I), low-grade astrocytoma, and less often high-grade astrocytoma. Radiation is used for tumors that recur or cannot be completely resected. The recommended dose is 45 Gy to 54 Gy depending on the location in the spinal canal. A dose of 50.4 Gy is most often used in attempt to allow for durable control while minimizing, though not obviating, risk of spinal cord injury. Treatment is delivered to the visualized tumor usually with a margin of at least one vertebral body above and below the tumor. Care should be taken to provide an even dose to bone to prevent scoliosis or growth abnormality in children that have not reached their full height.

NORMAL TISSUE TOLERANCE AND SIDE EFFECTS

Toxicities related to radiation are usually divided into acute, subacute, and late effects according to the timing of the complications. Acute effects, which are usually temporary, occur during or shortly after irradiation. Subacute toxicities occur usually up to 6 months and occasionally even a year after the completion of radiation and late effects may develop after only 6 months but may also take years to manifest. A thorough discussion about the long-term side effects of cranial irradiation is a pivotal part of the initial consultation with a child and his and her parents, and it sometimes plays a role in decisions regarding the use of radiation therapy for a child. It is a good idea to first approach the parents to determine together how much information should be discussed with the child in attendance. Although some children benefit from hearing the whole discussion and knowing that nothing is being hidden from them, others may be scared or traumatized by the potential side effects of treatment.

ACUTE AND SUBACUTE TOXICITY

The most-common acute reactions to radiation for CNS tumors are nausea/vomiting, fatigue, headache, decreased appetite, temporary alopecia, and less commonly recurrence of symptoms initially caused by the tumor from swelling induced by radiation. Nausea and vomiting are usually effectively treated with antiemetics such as ondansetron or similar serotonin antagonists. For persistent vomiting despite these medications, lorazepam dronabinol or corticosteroids may be of benefit. The majority of acute toxicities resolve after the completion of chemoradiation, though fatigue, nausea, and decreased appetite may persist. When fatigue worsens several weeks after radiation, this is considered a subacute effect referred to as somnolence syndrome.[86] The most striking symptom of somnolence syndrome is marked fatigue, but headache, nausea, and vomiting may accompany fatigue. Symptoms typically peak after 4 weeks to 6 weeks and typically resolve by 4 months to 6 months after radiation. Low-dose corticosteroids or neurostimulants, such as modafinil or methylphenidate are typically used to alleviate symptoms. Duration of treatment is typically 1 months to 2 months.

NEUROCOGNITIVE TOXICITY

Cognitive impairment is among, if not the most, devastating and feared side effect in survivors of childhood primary brain tumors. This complication takes months to years to manifest and has been determined to be a failure of development rather than a decline in existing ability. The degree of impairment has been correlated to age at the time of radiation, volume of brain receiving radiation and radiation dose.[87] Radiation-induced cognitive decline is best studied in patients who have undergone radiation to the whole brain.[88] The loss in full-scale intelligence quotient (FSIQ) correlate with both dose and age at the time of irradiation. In a study of 48 patients with either acute lymphocytic leukemia or medulloblastoma, Silber et al found that the follow-up FSIQ in patients who received whole-brain radiation to a dose of 36 Gy was 8.2 points lower than the FSIQ of a patient who received 24 Gy, and 12.3 points lower than the FSIQ of a patient who received 18 Gy.[89] In contrast to

patients treated with whole-brain radiation, patients treated with involved field radiation may experience relative stability of FSIQ.[90] Merchant et al studied the cognitive outcomes in 78 patients with low-grade glioma treated with involved field radiation.[91] Fifty-five patients were evaluated on at least two occasions. The estimated FSIQ at 60 months (average 95.4) was not significantly changed from baseline (98.96). Analogous results were reported for 123 patients with ependymoma.[92] Longer follow up is needed to confirm this stability of neurocognitive function in these patients. Although Merchant et al have reported that the supratentorial brain seems more important for cognitive outcomes, more detailed neuropsychological testing is needed to determine what areas of the brain may be most critical for preserving overall cognitive function.[93]

NEUROENDOCRINE TOXICITY

Growth hormone deficiency (GHD) is the most common and best-characterized endocrine complication of radiation therapy.[94] In children, GHD limits growth and can lead to weight gain. In both children and adults, GHD alters body composition and lipid profile, decreases bone mineral density, and may affect cognitive ability and quality of life.[95,96] GHD is associated with many pretreatment variables, including tumor location and size as well as hydrocephalus.

Merchant et al performed provocative testing of GH secretion on 192 patients with primary brain tumors before and after involved-field radiation.[97] At a dose as low as 5 Gy, the 5-year risk of GHD was 23%. The cumulative dose associated with a 50% risk of GHD at 5 years was 16.1 Gy. Higher doses to the hypothalamus shortened the time to the development of GHD; patients who received greater than 60 Gy developed GHD by 12 months, whereas patients who received 15 Gy to 20 Gy developed GHD by 60 months.

Central hypothyroidism may also occur as a result to injury to the pituitary or hypothalamus from radiation or from mass effect from tumor or surgery. Although less common than GHD because of the higher dose required to induce central thyroid deficiency, rates close to 70% are seen for doses exceeding 40 Gy.[98,99] Symptoms include fatigue, lethargy, and weight gain. Replacement with levothyroxine is usually effective and well tolerated.

Radiation may affect gonadotropins. Relatively low doses of radiation can result in precocious puberty, especially in females. For doses between 18 Gy and 24 Gy, the mean age at menarche is earlier in females.[100,101] In children treated with doses between 25 Gy and 47.5 Gy, the average onset of puberty is early in both genders. It is much rarer for radiation to cause gonadotropin deficiency, but at doses greater than 50 Gy, this can be seen.[102] Merchant et al reported the cumulative risk of gonadotropin-replacement treatment at 10 years to be 14.1%. In contrast, the 10-year cumulative incidence of GnRH agonist use was 34.2%, but this is likely an overestimation of precocious puberty because some patients received growth hormone replacement.[91]

Adrenocorticotropic hormone (ACTH) deficiency causes nausea/vomiting, decreased appetite, hypoglycemia, fatigue, and hypotension. It may become life-threatening at times of stress if replacement is not given. It is rare that radiation alone results in deficiency.[98] Prolactin deficiency is rare, though hyperprolactinemia is possible.[99] Diabetes insipidus and hypothalamic obesity should not occur from radiation alone and are usually attributed to tumor mass effect or surgery.

OTOTOXICITY

Sensorineural hearing loss may occur as a result of radiation to the cochlea. Hua et al correlated mean dose to the cochlea with the risk of hearing loss.[103] They found that high-frequency hearing loss was 0% at 30 Gy, 2% at 35 Gy, 4% at 40 Gy, 5% at 45 Gy, 11% at 50 Gy, 24% at 55 Gy, and 37% at 60 Gy. Intermediate- and low-frequency hearing loss was not seen at doses less than 40 Gy. Although longer follow-up is needed, it seems that dose less than 35 Gy should minimize hearing loss from radiation therapy. This risk of ototoxicity is greater for patients who receive cisplatin-based chemotherapy, though it is unclear if this is because of independent risks of radiation and cisplatin or if there may be some synergistic effect of both therapies.[104]

VASCULAR COMPLICATIONS

Vascular complications as a result of radiation are rare, but do occur. Moyamoya syndrome may be seen after radiation.[105] Patients may present with seizures and ischemic events due to occlusion of vessels in the Circle of Willis. This syndrome is seen most often in patients with optic gliomas or craniopharyngiomas because of the tumor's close proximity to these vessels. The estimated prevalence following radiation is 3.5%, most diagnosed in patients with optic gliomas. Risk factors for Moyamoya syndrome include neurofibromatosis type 1, high dose to the circle of Willis, and young age at the time of radiation.

Brain tumor survivors are also at slightly higher risk for stroke than the general population. The 25-year cumulative incidence of stroke in brain tumor survivors is reported to be 6.9% for those who received radiation and 2.85% for those who did not receive radiation.[106]

Cavernous hemangiomas are benign vascular malformations that can develop months to years following radiation.[107] Most cavernomas are asymptomatic, but hemorrhage can occur. MRI surveillance is generally recommended, but surgical intervention is required if symptomatic hemorrhage occurs and may be indicated of if radiographic characteristics suggest that hemorrhage is imminent and may lead to morbidity.

VISUAL OUTCOMES

The optic nerves, chiasm, lenses, and retina may receive radiation dose from the treatment of CNS malignancies. Cataracts are a relatively common side effect of CSI and low doses may result in cataracts.[108] Lens replacement is generally successful. Optic neuropathy is rare at doses less than 55 Gy delivered with fraction sizes of less than 2 Gy per fraction.[109,110] The retina should not receive in excess of 45 Gy to avoid retinopathy, but this is easily accomplished for most brain tumors.

RADIATION NECROSIS AND PSEUDO-PROGRESSION

Radiation necrosis is a rare but devastating side effect of high-dose radiation (typically >55 Gy) that results in permanent death of brain tissue. Although most cases present within a year of treatment, cases have been reported as late as 6 years to 7 years after treatment.[111] It can be difficult to distinguish tumor progression from radiation necrosis or pseudoprogression by MRI and this should be considered. Decadron is often administered for patients who are symptomatic. Bevacizumab reduces vessel permeability and may lead to relief of symptoms and decreased steroid requirements.[112,113] Hyperbaric oxygen has also been investigated for the treatment of radiation necrosis.[114]

LEUKOENCEPHALOPATHY

Leukoencephalopathy is a rare but potentially devastating complication of radiation or methotrexate. Clinical symptoms

include lethargy, seizure, loss of motor function, ataxia, and spasticity. MRI will typically show extensive periventricular white matter destruction and areas of hypodensity attributed to lacunar infarcts. It is unusual to see this complication for patients treated for primary brain tumors and is best described in children with acute lymphocytic leukemia treated with brain radiation and high dose methotrexate.[115]

SECOND MALIGNANCY

Development of a second tumor following the treatment of a primary tumor is among the most devastating potential complications of radiation therapy. For patients who receive cranial irradiation, the risk is low, but increases with time from radiation. Most occur after 10 years. The Childhood Cancer Survivors Study reported 76 subsequent neoplasms among 1877 survivors of CNS malignancies at a median of 16 years from diagnosis.[116] Meningioma is the most common radiation induced malignancy for this group followed by gliomas.

CONCLUSIONS

A great deal of progress has been made in the field of pediatric radiation oncology and pediatric oncology as a whole. Recent estimates suggest that approximately 75% of children diagnosed with a brain tumor can expect a long-term DFS following modern treatment.[116] Advances in both radiation and imaging techniques and a better understanding of CNS malignancies allow for fewer long-term side effects and a greater optimism that patients will survive to live relatively healthy lives. Molecular patterns of many tumors are being discovered and we are likely seeing just the tip of the iceberg for the use of distinct genetic patterns to provide prognostic information and guide therapies. Although current treatment recommendations are still based on a tumor's location and its appearance under the microscope, future therapies will likely be dictated by genomic analyses that define the molecular characteristics of a specific tumor. This information will also reveal molecular mutations critical for the viability of tumor cells that can either be directly targeted or perhaps made more sensitive to radiation or chemotherapy. Advanced forms of radiation, such as proton radiation, are becoming increasingly available allowing more children to receive targeted treatments. However, we must be cautious, as often the technology is not as important as the as the users experience and care in its delivery. In the future, we may see a decreased role for radiation as some CNS malignancies become curable with less radiation, whereas our role for others may increase as a broadly curative modality rather than a specifically or primarily palliative measure.

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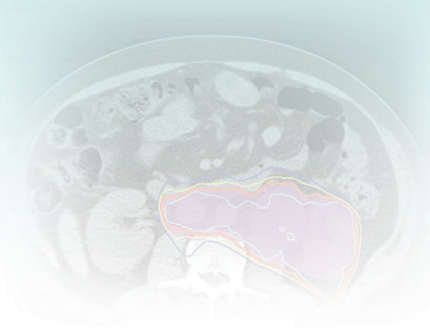
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CHAPTER

68 Pediatric Soft-Tissue Sarcomas



Michael W. Bishop and Matthew J. Krasin

INCIDENCE

There are 350 cases annually in the United States of rhabdomyosarcoma (RMS).
- Of those, embryonal rhabdomyosarcoma (ERMS) comprises 75% (260 cases), botryoid subtype (35 cases), and alveolar rhabdomyosarcoma (ARMS) comprises 25% (90 cases).

There are 500 cases annually of non-rhabdomyosarcoma soft-tissue sarcoma (NR-STS) in the United States. These are divided into high grade (Pediatric Oncology Group [POG] grade III), 67% (335 cases), and low and intermediate grade (POG grade I/II), 33% (165 cases).

BIOLOGIC CHARACTERISTICS

RMS
- With EMRS, there is a loss of heterozygosity chromosome 11p and RAS/NF1 pathway mutations.
- In alveolar rhabdomyosarcoma, t(2;13) or t(1;13) translocations result in *PAX-FKHR* fusion protein (80%)

There are diverse histologies in NR-STS with mixture of distinct genetic events. Examples include:
- Synovial cell sarcoma: t(X;18) and resulting fusion product *SYT-SSX*
- Alveolar soft-part sarcoma: der(17)t(X;17) and resulting fusion *TFE3-ASPL*
- Diverse genetic signatures (e.g., malignant fibrous histiocytoma)

STAGING EVALUATION

RMS
- There is the Intergroup Rhabdomyosarcoma Study Group (IRSG) clinical grouping system based on the degree of surgery, nodal involvement, and metastatic disease.
- In the TNM pretreatment staging classification, stages are based on location of primary tumor, size, invasiveness, nodal involvement, and metastatic disease.

NR-STS uses the American Joint Committee on Cancer staging system, which is based on grade, size, invasiveness, nodal involvement, and metastatic disease.

PRIMARY THERAPY

For RMS, nonmorbid "upfront" surgery is the first line of therapy.
- Radiation therapy (RT) is used for primary and metastatic sites of disease. The following are recommended doses:
  - microscopic disease: 36 Gy; microscopic nodal disease: 41.4 Gy; and gross disease: 50.4 Gy
- Local failure rates are 10% for Group I/II and 13% for Group III.

For NR-STS, the recommended course is surgical resection with or without adjuvant RT (55.8 Gy to 63 Gy) or brachytherapy (34 Gy at 3.4 Gy twice daily, high-dose rate).
- In some cases, preoperative chemoradiation (conventionally fractionated external beam RT, 45 Gy to 50.4 Gy) followed by surgery is needed.
- Local failure rates are 4% for resected and range from 40% to 80% for unresected disease.

ADJUVANT THERAPY

For RMS, vincristine, dactinomycin (Actinomycin D), cyclophosphamide (VAC)–based chemotherapy is the standard. For high-risk disease, vincristine, irinotecan, dactinomycin, cyclophosphamide, doxorubicin, ifosfamide, etoposide, or experimental agent(s) is used. With these treatments, there is a 5-year event-free survival:
- low risk (group I/II embryonal RMS): 90%;
- intermediate risk (alveolar RMS groups I-III, embryonal RMS group III): 70% to 73%; and high risk (metastatic embryonal or alveolar RMS): <30%.

In NR-STS,
- neoadjuvant chemoradiation or adjuvant chemotherapy (ifosfamide/doxorubicin) is used. There is a 5-year event-free survival:
  - Localized, resected: 75%; localized, unresectable: 45%; and metastatic: 10%.

EPIDEMIOLOGY

Soft-tissue sarcomas (STS) account for approximately 7% of all pediatric cancers. RMS comprises 40% of STS, and the other NR-STS comprise 60%.[1,2] This results in 350 patients with RMS and 500 with NR-STS (divided about 2:1 between high and low grade) available for participation in clinical trials in the United States annually. Based on prior clinical trials, 75% of children with RMS have required RT, and based on the presence of high-grade disease only, approximately two thirds of children with NR-STS receive irradiation. This yields 600 sarcoma cases annually for the study of radiation-specific clinical trial questions, training of young radiation oncologists, and study of radiation-specific long-term sequelae.

Patients with RMS have benefited from the Children's Oncology Group (COG) sarcoma studies (formerly the IRSG). The trials conducted by these groups have defined the combined modality management of children with RMS in North America and allowed the randomized comparisons of new chemotherapeutics as well as RT strategies that would not be possible without the cooperative group structure. These approaches, as well as the specifics of modern RT, are discussed in this chapter.

Treatment of children with NR-STS is less well defined. Local therapy approaches have evolved from adult paradigms, incorporating limb salvage over amputation, adjuvant irradiation, and subsequently, preoperative RT approaches.[3-6] Despite an adult parallel to draw from, little prospective

research has been conducted in the pediatric NR-STS population. A recently closed trial through COG (ARST0332) sought to address some of these deficiencies delivering both preoperative and postoperative RT in conjunction with surgery and chemotherapy to define the role of local and systemic approaches in a comprehensive clinical trial; preliminary data from this recently closed study suggests that a risk-based approach may be used with lower dose RT or RT avoidance in select patients.[7]

BIOLOGIC CHARACTERISTICS AND PATHOLOGY

Rhabdomyosarcoma

RMS is broadly classified as one of the small, round, blue cell malignancies of childhood.[8] The histologic subtypes, in order by worsening prognosis, include ERMS, the most common form (with spindle cell and botryoid comprising two favorable variants); ARMS; and undifferentiated sarcoma. Patients with undifferentiated sarcoma were previously enrolled in IRSG clinical trials in a fashion similar to ARMS. More recently, these patients have received systemic therapy similar to patients with Ewing's sarcoma and have also been included in the COG ARST0332 trial. Light microscopy often describes ERMS with spindle-shaped cells and ARMS with small, round, blue cells forming alveolar-like spaces, although tumor biopsy specimens may also look like collections of poorly differentiated cells complicating definitive diagnosis by hematoxylin and eosin staining alone. Immunohistochemical staining can include positivity for MyoD1.[9] Cytogenetic events occur in ERMS with a loss of heterozygosity on chromosome 11p and frequent mutations of the RAS/NF1 pathway,[10,11] and in 80% of ARMS with translocations between chromosomes 2 and 13 or 1 and 13. These represent loci of *PAX3* and *PAX7* (chromosomes 2 and 1) and their fusion with *FKHR* on chromosome 13. These fusion proteins act as transcription factors and are diagnostic of ARMS.[8] Other genetic abnormalities and syndromes associated with RMS include neurofibromatosis type 1 (with a prevalence of 1:200 noted on IRSG-IV), Li-Fraumeni syndrome, and Beckwith-Wiedemann syndrome.[12-14]

Nonrhabdomyosarcoma Soft-Tissue Sarcoma

The pediatric NR-STS comprise a heterogeneous group of tumors managed homogeneously largely because of the limitations in patient numbers and effective chemotherapy. The most common histologies include synovial cell sarcoma and malignant peripheral nerve sheath tumor (MPNST), although several rarer variants including rhabdoid tumor and infantile fibrosarcoma are almost exclusive to the pediatric age group.[15,16] Although many NR-STSs have no genetic signature, several histologic variants do have specific translocations or deletions[15,17] (Table 68-1).

CLINICAL MANIFESTATIONS

Rhabdomyosarcoma

The presentation of children with RMS is diverse, characterized by the site of involvement and extent of disease. The median age for children presenting with RMS is younger than 5, although a second incidence peak occurs in the mid-teens. The head and neck region is the most frequent site of involvement and is divided into favorable and unfavorable (parameningeal) sites.[18,19] This site comprised 42% of localized presentations in patients enrolled in IRSG III and IRSG IV and serves as an example of the important nature of primary tumor location.[20] Metastatic disease occurs 20% of the time at presentation, and nodal involvement is rare (<5%) except for paratesticular (25%) and extremity (24%) sites of disease, which warrant computed tomography ([CT] including paratesticular sites at <10 years of age), nodal sampling (paratesticular sites for ≥10 years of age), or sentinel node biopsy (extremity sites).[21-25]

Nonrhabdomyosarcoma Soft-Tissue Sarcoma

The presentation of NR-STS is often as a painless mass, whereas other symptoms are site specific. Approximately half of the cases arise in the extremity, and the incidence increases throughout the adolescent years and into adulthood.[26,27] Although the vast majority of soft-tissue "masses" are either not real or benign, consideration should be given to malignancy because an ill-chosen surgical approach may compromise future local therapy (Figure 68-1).

Fifteen to 22 percent of patients present with metastatic disease at diagnosis, with the lungs being the predominant

TABLE 68-1 Genetic Abnormalities: Nonrhabdomyosarcoma Soft-Tissue Sarcomas

Histology	Genetic Abnormality
Synovial cell sarcoma	t(X;18); fusion *SYT-SSX*
Clear cell sarcoma	t(12;22); fusion *EWS-ATF1*
Desmoplastic small round cell tumor	t(11;22); fusion *EWS-WT1*
Infantile fibrosarcoma	t(12;15); fusion *ETV6-NTRK3*
Alveolar soft-part sarcoma	der(17)t(X;17); fusion *TFE3-ASPL*
Low-grade fibromyxoid sarcoma	t(7;16); fusion *FUS-CREB3L2*
Myxoid and round cell liposarcoma	t(12;16); fusion *FUS-DDIT3*



Figure 68-1 Rhabdomyosarcoma of the pinna of the ear presenting as a painless soft-tissue mass.

site of metastatic involvement.[16,28] Clear cell sarcoma and epithelioid sarcoma carry a risk of regional nodal involvement and warrant evaluation of the draining nodal bed(s) with sentinel node sampling.[29]

STAGING

Rhabdomyosarcoma

Staging workup is similar for most patients with RMS (Table 68-2). A site-specific history and physical examination should be performed by the treating radiation oncologist at the time of presentation to define the site of primary disease, its extent, and symptoms possibly related to potential metastatic sites of involvement. Attention to cranial nerve involvement for head and neck primary sites as well as attending the examination under anesthesia for genitourinary sites (vaginal, cervix, uterus, bladder, and prostate) will assist in the multidisciplinary discussions regarding staging and local therapy approaches.

Laboratory studies include a complete blood cell count and chemistry panel, which may be suggestive of bone marrow disease (anemia) or other organ-specific dysfunction related to metastatic involvement.

Review of the pretreatment imaging is critical to ensure adequate imaging of the primary tumor as well as understanding the extent of disease. Often, standard diagnostic imaging protocols (particularly magnetic resonance imaging [MRI]) will not encompass the entire tumor, because the studies were designed for evaluation of joint or intracranial disease. Repeating these studies will facilitate better local therapy decisions and delivery. Standard diagnostic imaging should include MRI of the primary site of disease, CT of the chest (and abdomen for infradiaphragmatic presentations), bone scintigraphy, and site-specific imaging related to potential metastatic disease.[19] F-Fluorodeoxyglucose–labeled positron emission tomography (FDG-PET) may be useful in the evaluation of distal metastases, especially lymph nodes, and may eventually replace bone scintigraphy.

Bone marrow aspiration and biopsy should be performed for all patients, as well as cerebrospinal fluid cytology for patients with parameningeal, orbital, and paraspinal primary sites of disease. Lymph node sampling should be performed for patients 10 years of age or older with paratesticular primary tumors, and sentinel node mapping and sampling should be done for patients with disease of an extremity.

After staging evaluation, a clinical stage should be assigned (outlined in Table 68-3). If surgery has been performed (or

TABLE 68-2 Staging Workup and Follow-Up Evaluations for Patients with Rhabdomyosarcoma and Nonrhabdomyosarcoma Soft-Tissue Sarcomas

	Rhabdomyosarcoma	Nonrhabdomyosarcoma Soft-Tissue Sarcomas
Staging		
Clinical	Site-directed history and physical examination	Site-directed history and physical examination
Imaging	MRI of primary tumor CT of chest CT of abdomen (infradiaphragmatic tumors) Bone scintigraphy	MRI of primary tumor CT of chest
Procedures	Biopsy: primary tumor/metastasis Extremity: sentinel lymph node biopsy Paratesticular (>10 years): ipsilateral retroperitoneal lymph node dissection Head and neck: cerebrospinal fluid cytology Genitourinary: examination under anesthesia	Biopsy: primary tumor/metastasis Histology: specific sentinel lymph node biopsy
Follow-up		
Year 1	History and physical examination every 3 months, laboratory studies, MRI of primary tumor area CT of chest and other metastatic imaging every 3 months	History and physical examination, laboratory studies every 3 months, MRI of primary tumor area CT of chest every 6 months
Years 2 to 3	Every 4 months: history and physical examination, laboratory studies, MRI of primary area Every 4 months: CT of chest and other metastatic imaging	Every 6 months: history and physical, laboratory studies, MRI of primary tumor region, CT of chest
Years 4 to 5	Every 6 months: history and physical, MRI of primary area, chest radiograph	Annual history and physical laboratory studies, MRI of primary area, CT of chest

CT, *Computed tomography;* MRI, *magnetic resonance imaging.*

TABLE 68-3 Clinical Staging System for Rhabdomyosarcoma

Stage	Sites	Tumor	Size	Node	Metastasis
1	Favorable site: Orbit, head and neck (excluding parameningeal), genitourinary (excluding bladder/prostate), biliary tract	T1 or T2	a or b	N0 or N1 or Nx	M0
2	Unfavorable site: Bladder/prostate, extremity, cranial parameningeal, other (includes trunk, retroperitoneum, etc.)	T1 or T2	a	N0 or Nx	M0
3	Unfavorable site: Bladder/prostate, extremity, cranial parameningeal, other (includes trunk, retroperitoneum, etc.)	T1 or T2	a b	N1 N0 or N1 or Nx	M0
4	All	T1 or T2	a or b	N0 or N1	M1

TABLE 68-4 Clinical Grouping System for Rhabdomyosarcoma

I	Completely resected localized disease
Ia	Confined to muscle of origin
Ib	Involvement outside of muscle of origin (contiguously)
II	Microscopic residual disease and regional nodal involvement
IIa	Microscopic residual disease (after gross resection, N0)
IIb	Regional nodal involvement (without microscopic residual disease)
IIc	Regional nodal involvement (with microscopic residual disease)
III	Gross residual disease
IIIa	After biopsy
IIIb	After gross major resection (>50% of disease)
IV	Distant metastasis

after a planned surgical resection or biopsy), a grouping should be defined (Table 68-4). These two factors plus the patient's histology are combined into a risk classification to assign patients to protocol therapy.

Nonrhabdomyosarcoma Soft-Tissue Sarcoma

The workup for patients with NR-STS is similar to that for RMS (see Table 68-2). A site-specific history and physical examination should be performed by the treating radiation oncologist at the time of presentation to define the site of primary disease, its extent, as well as symptoms related to potential metastatic sites of involvement.

Laboratory studies include a complete blood cell count and chemistry panel, the findings from which may be suggestive of organ-specific dysfunction related to metastatic involvement.

Diagnostic imaging studies include MRI of the primary site, CT of the chest, and other metastatic imaging, including bone scintigraphy, as indicated by symptoms and laboratory studies. FDG-PET may be useful in the workup of patients

EVALUATION AND DEFINITION OF RISK CLASSIFICATION

Rhabdomyosarcoma

Favorable and unfavorable sites of disease are defined as part of the staging system and are noted in Table 68-3. In addition, histology affects outcome and is related to site of disease; favorable sites of disease in the orbit and genitourinary region are four and five times as likely to be of an embryonal histology as opposed to alveolar or undifferentiated histology. This yields higher disease control rates for localized ERMS compared with ARMS (failure-free survival [FFS], 82% versus 65%).[20] Clinical group (see Table 68-4) is also prognostic of FFS in both ERMS and ARMS. Because of the strong interaction of site, histology, group, and stage, a risk classification system was devised to stratify patients for therapeutic decisions. This resulted in three strata[20,30,31]:

1. Patients with low-risk disease (ERMS, stage 1, groups I to III and ERMS, stage 2 to 3, groups I to II) whose tumor is treated by upfront with or without nodal resection at any site as well as patients with group III orbital site of disease. Patients with nonorbital group III ERMS are also considered low risk in the context of current research protocols. The FFS for this group is approximately 90%.
2. Patients with intermediate-risk disease (ERMS, stage 3, group II to III and ARMS stage 1 to 3, group I to III) are the remaining localized tumors and have variable outcomes, ranging from 30% to 85% FFS.
3. Patients with high-risk disease are those with metastatic disease and have FFS rates of 26% to 40%.

Future classification systems may adjust certain subsets of patients with low-risk disease into the intermediate group where treatment reduction yielded poorer outcomes.[32,33] The presence or absence of PAX/FKHR fusion protein has been shown to be more closely associated with outcome than histologic classification and will likely be included in future risk stratifications.[34]

Nonrhabdomyosarcoma Soft-Tissue Sarcoma

Stratification for patients with NR-STS is based on retrospective data being tested in a prospective clinical trial.[23,24] Patients with low-risk disease are those with low-grade tumors (POG grade I or II) as well as high-grade tumors (POG grade III) that are less than or equal to 5 cm in maximal diameter, with an expected overall survival (OS) above 90%. Patients with intermediate-risk disease with large (>5 cm) high-grade tumors have a 5-year OS of 56%, and patients with high-risk disease with metastatic disease fare poorly, with a 5-year OS of 15%.[26,27]

PRIMARY THERAPY

Rhabdomyosarcoma

All patients with RMS are managed in a combined modality fashion. Participation by a pediatric oncologist, pediatric surgeon, radiation oncologist, and orthopedic or otolaryngologic oncologist (if indicated) at the outset ensures optimal planning for the many therapeutic decisions necessary for this diverse and complicated disease. This multimodal approach has been the hallmark of the studies of the IRSG performed in North America. Since 1972, these trials have enrolled thousands of patients, unified the therapeutic approach across the United States, and improved OS for this disease.

IRSG I (1972-1978) and IRSG II (1978-1984) answered several important questions. Patients in group I (without RT) and group II (with RT at doses of 40 Gy to 45 Gy) were noted to fare well with a regimen of vincristine and dactinomycin [Actinomycin], VA (and omitting cyclophosphamide).[18,35] Patients in group III did not benefit from the addition of doxorubicin, whereas patients treated in the CT era (IRS-II) with parameningeal disease and specific meningeal RT guidelines fared significantly better (OS, 67% versus 45%).[18] Unfortunately, 75% of patients in group IV continued to experience progressive disease.

IRSG III (1984-1991) went on to confirm that the VA regimen is equivalent to therapy with VAC for patients in group I and resulted in a progression-free survival of 83% without RT. The addition of doxorubicin to VA did not improve outcome for group II disease, and patients with groups III/IV disease did not benefit from the addition of cisplatin or etoposide, with progression-free survival for the latter group remaining at 27%.[36]

IRSG IV (1991-1997) was the first trial to employ presurgical staging in addition to the grouping system. A randomized question was asked about systemic therapy (now standard VAC versus VAI [ifosfamide] versus VIE [ifosfamide/etoposide]) for patients with stages 1 to 3 disease. Despite the hope for improvement in overall outcomes, no benefit was seen, and VAC remains the standard of care.[37] Patients with group III disease also underwent a randomization between

standard RT (50.4 Gy/1.8 Gy daily fraction) and hyperfractionated RT (59.4 Gy/1.1 Gy twice daily fractions). Hyperfractionated RT yielded the same FFS (73%) as conventional RT, and local failure was equivalent (15% versus 12%).[38] IRSG IV, in a retrospective fashion compared with IRSG III, also clarified the management of patients with group I paratesticular disease. Patients younger than age 10 years could be evaluated by CT for retroperitoneal lymphatic involvement (without retroperitoneal lymph node dissection [RPLND]), maintaining a 90% FFS. Those 10 years old or older benefited from RPLND (100% FFS with RPLND compared with 63% with CT alone) to define nodal involvement and the need for subsequent lymphatic RT.[22,37]

IRSG V is the last of the intergroup named trials, now named with the COG nomenclature ARST. Patients with group II disease had a reduction in RT dose from 41.4 Gy to 36 Gy for positive microscopic surgical margins. Orbital primary tumors were also irradiated using a reduced dose of 45 Gy. Outcome on this low-risk trial appears equivalent to previous studies, suggesting this is a safe and effective approach, particularly when cyclophosphamide is included in chemotherapy regimens.[39,40] Another randomized question was tested for patients with intermediate-risk disease comparing VAC against VAC alternated with VTC (substituting topotecan). This did not improve outcome, with a 4-year FFS of 73% and 68%, respectively.[41] Patients with high-risk disease during this era underwent several Phase II window therapy trials incorporating new agents. The combination of vincristine and irinotecan demonstrated a 70% response rate. Although FFS remained poor (26% at 2 years), its activity was sufficient to incorporate VI into further trials for patients with intermediate- and high-risk disease.[30]

The most recent round of trials in low-risk RMS (ARST0331) further tailored and reduced therapy for patients with ERMS resected upfront (groups I/II), stage 1 to 3, and unresected (group III), stage 1 disease. The RT dose remained 36 Gy for microscopic disease and 41.4 Gy for nodal disease. Group III vaginal tumors were treated with intent to avoid or delay radiation therapy, but a 2 year FFS of 42% in this subset demonstrated the importance of RT for local control.[33] Patients with intermediate-risk disease (ERMS stages 2/3, group III and alveolar RMS stage 1 to 3, groups I to III) were randomized between VAC and VAC/VI (ARST0531), incorporating irinotecan from the prior high-risk pilot trials. Patients with high-risk disease received multiple-agent systemic therapy (ARST0431) that was later used as a backbone to incorporate new agents such as an insulin-like growth factor-1 receptor inhibitor or temozolomide (ARST08P1), seeking improvement in FFS in this poor prognosis population.

A general algorithm for the integration of chemotherapy, surgery, and RT is shown in Figure 68-2. As a first principle in nearly all North American RMS trials, only a nonmorbid surgical resection should be performed. Amputation, exenteration, or other extensive procedures are discouraged because RT will offer equivalent rates of local control with organ preservation. The timing of RT has varied across studies and disease stage. RT may be integrated after multiple weeks of chemotherapy, facilitating the time necessary to plan with modern radiotherapeutic techniques, allowing some reduction in tumor bulk, as well as potentially integrating a second-look surgical procedure. One exception to this variance is the consistent early introduction of RT in patients with parameningeal disease and intracranial extension.[42]

Nonrhabdomyosarcoma Soft-Tissue Sarcoma

The management of children with NR-STS, particularly the local therapy component, has paralleled that of adult

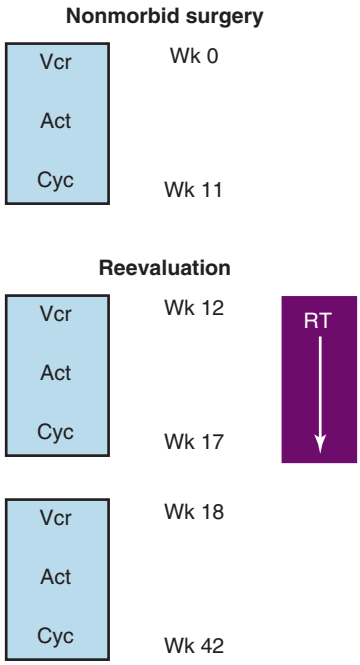


Figure 68-2 General algorithm for the delivery of multimodal therapy for rhabdomyosarcoma. *RT*, Radiation therapy; *Wk*, week; *Vcr*, vincristine; *Act*, actinomycin; *Cyc*, cyclophosphamide.

paradigms, including the move to wide local surgical excision (WLE) from amputation, the role of adjuvant RT, and most recently, the shift to preoperative chemoradiation. Compared with RMS, clinical trials in North America for children with NR-STS have been smaller, fewer, and have not resulted in well-defined prognostic groups from either a local disease control or overall outcome perspective.

The mainstay for management of children with NR-STS is surgery. Absent this modality, the outcome for patients is poor, with a fourfold higher risk of death.[43] The presence of metastatic disease predicts for subsequent disease recurrence in the majority of patients (10% EFS).[44] All patients, but particularly those with resectable primary site disease, benefit from multidisciplinary discussion before initiation of therapy. Planning the appropriate surgery in the context of tumor grade, size, location, probable surgical margin status, and the patient's age is the first critical step in the local management of patients with NR-STS. No prospective, completed clinical trials exist in the pediatric population to assist clinicians in selecting patients for specific aspects of local or systemic chemotherapy. The recent COG trial (ARST0332), stratified by risk group and local therapy approach, accrued more than 550 patients with the goal to determine the relative benefit of specific local and systemic therapeutic approaches. This multimodal approach to therapy incorporated standard-of-care approaches for NR-STS adapted for children and is outlined in Figure 68-3. More importantly, this trial provided a uniform, prospectively treated population of patients on which to evaluate prognostic factors, both clinical and biologic. The analysis of this study could lead to improved risk stratification of patients with NR-STS on future trials.

RADIATION THERAPY

Indications and Outcomes of Local Therapy

Rhabdomyosarcoma

The role of RT is to eradicate microscopic disease present after resection, treat gross disease, and consolidate visible sites of

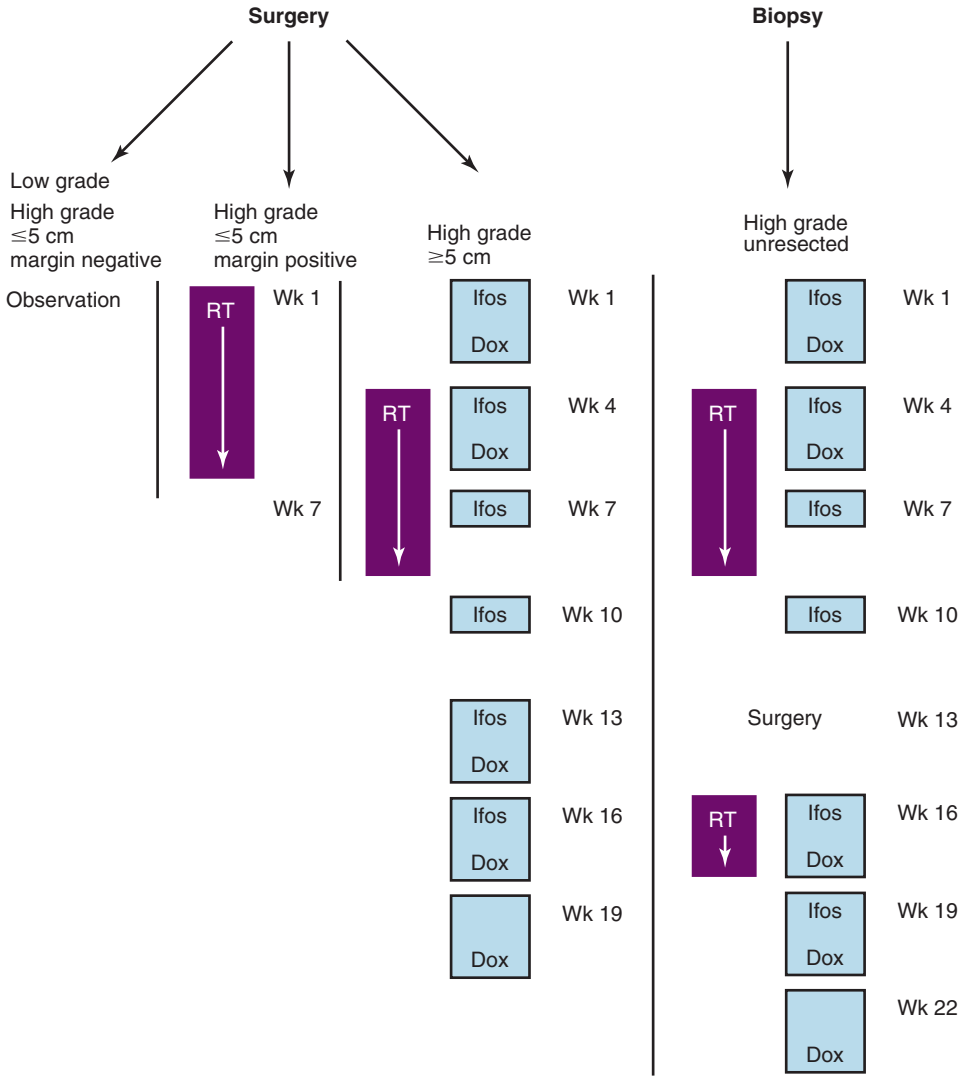


Figure 68-3 General algorithm for the delivery of multimodal therapy for nonrhabdomyosarcoma soft-tissue sarcomas. *RT*, Radiation therapy; *Wk*, week; *Ifos*, ifosfamide; *Dox*, doxorubicin.

TABLE 68-5 Indication for Radiation Therapy and Prescribed Doses for Patients with Rhabdomyosarcoma

Disease Status	Embryonal Histology	Alveolar Histology
Margin negative	No radiation	36.0 Gy
Margin positive	36.0 Gy	36.0 Gy
Node positive	41.4 Gy	41.4 Gy
Gross disease	50.4 Gy	50.4 Gy

metastatic involvement. The indications and doses, although complicated by site, can be generalized (Table 68-5). Doses are delivered at 1.8 Gy per fraction daily.

Data for the treatment of completely resected disease (group I) come from review of prior IRSG trials I to III demonstrating improvement in FFS and OS for patients with ARMS when RT is delivered (73% versus 44% and 82% versus 52%, respectively).[45] Patients with group II disease received adjuvant radiation, resulting in local failure rates of less than 10%.[46] Patients with group III disease have local failure rates of 11% to 16.5%, depending on site, size, and era of treatment.[38,41,47,48]

The parameningeal sites (middle ear, nasopharynx, paranasal sinuses, infratemporal and pterygopalatine fossae, and parapharyngeal region) require special attention to the skull base for adequate coverage of possible intracranial extension. If intracranial extension is present (Figure 68-4), then RT should be initiated within the first few weeks of the start of chemotherapy.

The orbit is a favorable site of disease involvement. Local management for this site with RT calls for delivery of 45 Gy at 1.8 Gy daily and yields excellent local control.[39,40] Despite the extremely thin and fragile nature of the bony orbit and the adjacent globe, these two structures are essentially never breached by orbital primary tumors and should be constrained out of the clinical target volume. If tumor does extend through these structures, consideration should be given that this may be parameningeal instead.

Female genitourinary tract (vulvar, vaginal, cervix, and uterus) tumors of ERMS (particularly the botryoid subtype) require adequate local therapy despite the often young age of the patients (frequently <2 years of age [Figure 68-5]). These patients should either undergo complete resection (group I) at



Figure 68-4 Coronal T1 contrast-enhanced magnetic resonance image obtained at presentation in a child with intracranial extension from a pterygopalatine fossa rhabdomyosarcoma.

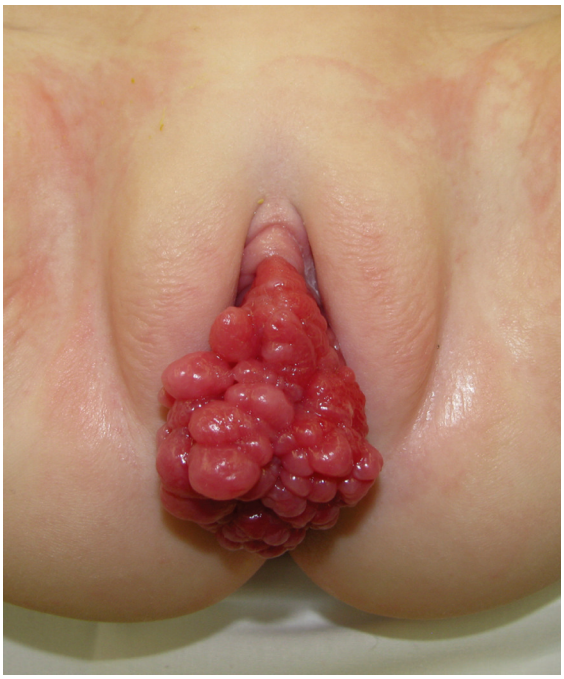


Figure 68-5 Botryoid embryonal rhabdomyosarcoma of the female urogenital tract in an infant.

diagnosis or receive adjuvant RT with either external beam or interstitial and intracavitary techniques. Absent adequate local control, high failure rates have been noted in the most recent low-risk clinical trials, prompting the call for improved local control.[33]

Paratesticular RMS is initially managed with radical inguinal orchiectomy with high ligation of the spermatic cord. RPLND, following a surgical template based on laterality, is conducted for all children 10 years of age or older.[22] Younger patients may still be managed with CT evaluation of their retroperitoneal lymphatics. Treatment of the lymphatic region is based on the discovery of microscopically or grossly involved lymph nodes.

Nonrhabdomyosarcoma Soft-Tissue Sarcoma

The best local tumor control rates are achieved in the context of microscopic disease and, as such, surgical resection—WLE or marginal—should be the goal for every patient presenting with NR-STS, including with metastatic disease. Clear surgical margins, defined as 5 mm or more of normal tissue beyond the tumor, are beneficial in cases in which RT may be avoided. Conversely, the operating surgeon should not proceed with a morbid or disfiguring resection to obtain clear surgical margins because there does not appear to be a significant reduction in local control when adjuvant radiation is delivered.[14] Preoperative RT may be employed in the context of larger (>5 cm) tumors or those deemed difficult to initially resect. This is most commonly combined with neoadjuvant doxorubicin and ifosfamide chemotherapy and given concurrently with ifosfamide chemotherapy to a cumulative dose of 45 Gy to 50.4 Gy at 1.8 Gy daily. Postoperative RT either in the form of external beam irradiation or interstitial brachytherapy may be delivered to the tumor bed after margin negative WLE (for high-grade tumors > 5 cm) or smaller high-grade tumors with involved surgical margins to doses of 55.8 Gy to 63 Gy at 1.8 Gy daily. Outcomes for either of these approaches have yielded excellent local control, with local failure occurring less than 5% of the time.[16]

Techniques

All treatment for pediatric patients with STS should be volumetric imaging based, require target volume and normal tissue delineation, and allow plan evaluation with dose-volume histograms. Conformal, intensity-modulated, and proton beam RT are all acceptable methods of radiation delivery backed by published outcome data from both cooperative group and institutional clinical trials. Patients treated on the D9803 trial with either three-dimensional conformal radiation therapy (3D-CRT) or intensity-modulated radiated therapy (IMRT) demonstrated similar rates of FFS despite superior target coverage by IMRT, and no differences in dose to critical adjacent structures.[49] Initial and postchemotherapy imaging studies are used to define the extent of disease. MRI is essential because CT provides poor soft-tissue definition for evaluating tumor extent. The definitions for gross tumor volume (GTV) and clinical target volume (CTV) are described in Table 68-6 for both RMS and NR-STS. It is important for the radiation oncologists to understand the point of origin or attachment of gross disease, which is often facilitated by examination of the patient and review of imaging at diagnosis. In tumors with an exophytic component such as bladder and prostate or female genitourinary rhabdomyosarcoma, this baseline evaluation will be valuable in helping define the GTV once significant response to chemotherapy occurs. Target volume delineation is anatomically constrained, meaning that the radiation oncologist determines the presumed infiltration of the gross tumor toward adjacent normal tissues when designing the shape of the clinical target volume. Planning volumes are institution, site, and treatment specific (e.g., photons compared to protons), but are typically 3 mm to 5 mm with some form of daily localization (cone-beam CT or fiducials) using photon techniques. Motion may be defined and managed through respiratory gating as necessary.

Treatment planners should consider adjacent normal tissues and weigh the relative risks of site-specific late effects

TABLE 68-6 Target Volume Delineation for Rhabdomyosarcoma and Nonrhabdomyosarcoma Soft-Tissue Sarcomas

	Rhabdomyosarcoma	Nonrhabdomyosarcoma Soft-Tissue Sarcomas
Gross Tumor Volume (GTV)		
Postoperative irradiation	The GTV (more appropriately defined as a CTV) will include the soft-tissue tumor bed and soft tissue contiguous with the tumor prior to surgical resection as defined by physical examination, imaging studies, operative notes, and pathology reports. The tumor bed may have "collapsed" in regions and may no longer have the same shape or extent as the presurgical, prechemotherapy volume. If bone was involved, the GTV includes the margin of bone initially involved with tumor.	Same as defined for rhabdomyosarcoma
Definitive irradiation/ preoperative irradiation	The GTV is defined as the initial tissues in contact with the tumor before therapy and the preirradiation extent of the visible mass, defined by examination and imaging studies before and after chemotherapy and physical examination. Bone involvement warrants targeting the pretherapy extent in bone. Gross residual disease (after an incomplete resection) will be targeted as a definitive irradiation case. Unresected, involved lymph nodes will be included as part of the GTV but may not form one contiguous gross tumor volume depending on tumor and nodal geometry.	Same as defined for rhabdomyosarcoma
Clinical Target Volume (CTV)	The CTV is the GTV with a 1.0-cm anatomically constrained margin of normal tissue accounting for probable pathways of microscopic disease spread. This margin may be reduced (constrained) at fascial planes, bony interfaces, or body cavities based on tumor biology. Nodal involvement is encompassed in the CTV, ideally in a contiguous volume with the GTV.	The CTV is the GTV with a 1.5-cm anatomically constrained margin of normal tissue accounting for probable pathways of microscopic disease spread. This margin may be reduced (constrained) at fascial planes, bony interfaces, or body cavities based on tumor biology. Nodal involvement is encompassed in the CTV, ideally in a contiguous volume with the GTV.

relative to one another. Every effort should be made to deliver the recommended prescribed dose of radiation because doses used in many pediatric malignancies have already been lessened significantly because of concerns of late effects. Parallel-opposed fields should be avoided in nearly all cases to reduce normal tissue exposure to high radiation doses. Even in extremity sites, treatment with circumferential irradiation using an IMRT technique (resulting in low doses to the entire circumference of the extremity as opposed to sparing a strip of skin [Figure 68-6]) has not resulted in clinically documented lymphedema with moderate follow-up.[16]

Interstitial brachytherapy may be used for NR-STS and RMS (less frequently) at the time of surgical resection. Catheters are usually placed into the operative bed transcutaneously while the resection cavity is exposed after removal of the primary tumor. Catheters are spaced at 1-cm intervals and extend 1 cm to 2 cm beyond the known tumor bed. The tumor bed may be marked with surgical clips or other radiopaque markers to define the region to be treated at the time of planning. High-dose-rate brachytherapy is delivered to a dose of 34 Gy at 3.4 Gy twice daily for NR-STS and 21 Gy at 3 Gy twice daily for RMS.

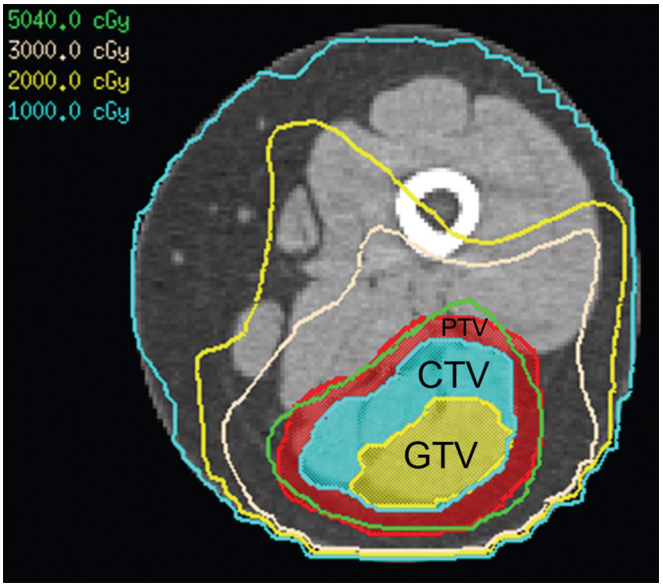


Figure 68-6 Cross-sectional image of an intensity-modulated radiation therapy plan for alveolar rhabdomyosarcoma of an extremity. *CTV,* Clinical target volume; *GTV,* gross target volume; *PTV,* planning target volume.

Timing

Rhabdomyosarcoma

The timing of delivery of radiation to the primary site of disease in patients with localized rhabdomyosarcoma has varied across the IRSG and COG clinical trials over time. Currently, for patients with low-risk disease, RT is performed after 12 weeks of every 3-weeks of chemotherapy. Patients with intermediate-risk disease also receive RT at week 12. Those with parameningeal tumors and evidence of intracranial extension receive RT near the start of treatment, primarily based on evidence of improved outcome for patients with parameningeal sites of disease irradiated earlier in the course of therapy.[42] Cranial nerve palsy and cranial base bony erosion are no longer considered high-risk features mandating early

RT.[50,51] Patients with high-risk disease (metastatic) require aggressive chemotherapy. Local control of the primary sites of disease is conducted at week 20, and metastatic sites of disease are irradiated with similar doses at the end of systemic therapy, unless symptomatic. Vincristine, cyclophosphamide, and irinotecan are given concurrently with RT whereas dactinomycin is held, owing to increased skin and mucosal toxicities.

Nonrhabdomyosarcoma Soft-Tissue Sarcoma

Postoperative RT is delivered 2 weeks or more after resection, allowing for the initiation of wound healing and stabilization of the tumor bed. Adjuvant brachytherapy should be initiated on postoperative day 5 or later to allow for adequate healing. Preoperative chemoradiation on ARST0332 (the most recent COG NR-STS trial) is initiated at week 4 immediately after the second cycle of ifosfamide/doxorubicin chemotherapy.

FUTURE DIRECTIONS

The treatment of children with STS is now well centered in the modern conformal era. All of the benefits of focal, highly conformal, modern RT can be realized in this population when the treating radiation oncologist uses available means to ensure adequate tumor dose delivery and sparing of adjacent normal tissues. The increasing use of proton therapy in the treatment of pediatric cancers will yield further opportunities for research. Cooperative group trials will continue to select patients with low-risk disease for whom radiation can be decreased or eliminated, whereas RT remains a critical component of treatment for intermediate- and high-risk disease. Less favorable populations of patients will be managed with the incorporation of new therapeutic agents to improve overall outcome.

Pediatric radiation oncologists should focus on selection of patients for RT, better delineation of target volumes, including incorporation of functional imaging into the treatment paradigm, and leading the way in understanding radiation-related treatment effects that affect how we deliver RT.

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A full list of cited references is published online at www.expertconsult.com.

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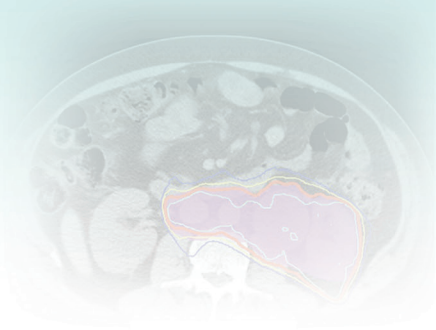
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CHAPTER

69 Pediatric Sarcomas of Bone



Nadia Issa Laack

INCIDENCE
The pediatric sarcomas of bone are osteosarcoma (5.6 cases per million children per year) and Ewing's sarcoma (2.8 cases per million children per year).

BIOLOGIC CHARACTERISTICS
Osteosarcoma is associated with inactivation of the retinoblastoma gene. Ewing's sarcoma is characterized by a reciprocal translocation involving breakpoints on the *EWSR1* gene on chromosome 22q12A. The most common chromosomal translocation, t11:22 (q24;q12), is present in 85% to 90% of Ewing's sarcoma.

STAGING EVALUATION
Staging involves determining whether disease is localized or metastatic.

PRIMARY THERAPY
The primary therapy for osteosarcoma is surgical resection and multiagent chemotherapy. The 5-year survival rate is 60% to 70%. Ewing's sarcoma is treated with surgery or radiation therapy, or both, and neoadjuvant and adjuvant multiagent chemotherapy. The 5-year survival rate is 70%.

ADJUVANT THERAPY
For both osteosarcoma and Ewing's sarcoma, neoadjuvant and adjuvant multiagent chemotherapy are used.

ADVANCED DISEASE
Advanced osteosarcoma requires multiagent neoadjuvant and adjuvant chemotherapy, as well as surgical resection of the primary tumor and limited metastatic disease. The 5-year overall survival (OS) rate is 20% to 30%.

Ewing's sarcoma requires multiagent neoadjuvant and adjuvant chemotherapy, radiation therapy, or surgery, or a combination of these treatments for the primary tumor. Metastatic sites require definitive local therapy, most often with radiotherapy. The 5-year OS rate is 10% to 30%.

PALLIATION
Chemotherapy, surgery, or radiation therapy is used for palliation.

Osteosarcoma and Ewing's sarcoma are the two most-common malignant bone tumors in the pediatric and adolescent age-groups. Although osteosarcoma is more common than Ewing's sarcoma, radiotherapy is only used in rare situations. This section, therefore, is devoted largely to the discussion of Ewing's sarcoma. As with all other pediatric malignant diseases, patients should be treated on protocols and in institutions familiar with, and experienced in, the treatment of childhood tumors.

ETIOLOGY AND EPIDEMIOLOGY

In the United States, 650 to 700 children and adolescents younger than 20 years old are diagnosed with bone tumors every year. Ewing sarcoma family of tumors (ESFT) is the rarer of the two with approximately only 200 cases diagnosed each year. The incidence of Ewing's sarcoma is approximately 2.8 cases per million in children younger than 15 years of age.[1] Generally, the disease occurs in the teenage years during the adolescent growth spurt (ages 10 years to 15 years). However, approximately 30% of cases occur in the first decade of life and 30% occur in the third decade. There is a slight male predominance (1.6:1). Genome wide analysis suggests ethnic variations in susceptibility genes associated with Ewing's sarcoma but the strong Caucasian predominance is not completely understood.[2]

The cause of Ewing's sarcoma is unknown, and it does not appear to be induced by any known agents.

Osteosarcoma also is primarily a disease of adolescents and young adults; a different type of osteosarcoma linked to Paget's disease occurs in older adults. This section focuses on osteosarcoma in the younger age-group. Similar to Ewing's sarcoma, the peak incidence coincides with a period of rapid bone growth. Osteosarcoma is known to be associated with retinoblastoma gene mutations as well prior radiation therapy, particularly in children with retinoblastoma or other genetic abnormalities.[3]

PREVENTION AND EARLY DETECTION

The rate of secondary osteosarcomas has decreased with the declining use of radiotherapy in retinoblastoma patients. Some evidence suggests that limiting dose to <60 Gy can reduce risk of secondary osteosarcoma in patients receiving radiotherapy for Ewing's sarcoma. Early detection is possible with careful evaluation of persistent swelling or pain.

BIOLOGIC CHARACTERISTICS AND MOLECULAR BIOLOGY

The histogenesis of Ewing sarcoma is controversial. The tumor was first described as an endothelioma of bone. Another hypothesis suggests Ewing is a primitive cell of neural origin, specifically from postganglionic, parasympathetic, and primordial cells.[4] Most recently, an alternative hypothesis suggests Ewing cells arise from mesenchymal progenitor or mesenchymal stem cells (MSC), which are found in bone marrow.[5] Previously, extraosseous Ewing's sarcoma and malignant peripheral neuroectodermal tumor (PNET) were considered separate entities from Ewing's sarcoma of bone and were treated differently; genetic studies now confirm they

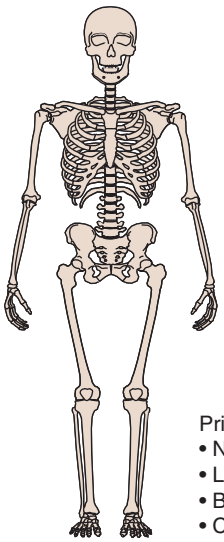


Figure 69-1 Distribution of primary sites and sites of metastases in Ewing's sarcoma.

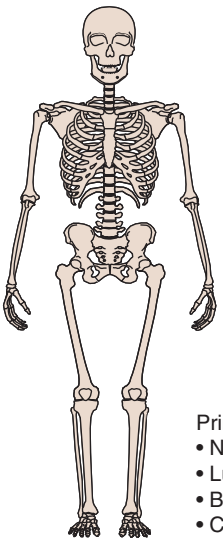


Figure 69-2 Distribution of primary sites and sites of metastases in osteosarcoma.

are from the same family of tumors, and together are termed *Ewing sarcoma family of tumors* (ESFT).[4] All exhibit identical chromosomal translocations, t11:22 (q24;q12), and more than 85% of patients share a common surface antigen, MIC2.[6-8] Ewing's sarcoma, atypical Ewing's sarcoma, and PNET of bone exist in the spectrum within this family, from the most undifferentiated tumors to those with neural differentiation. PNET can be differentiated from Ewing's sarcoma by the presence of a globular growth pattern, neuron-specific enolase (NSE) positivity, and Homer Wright rosettes.

Osteosarcoma is associated with inactivation of the retinoblastoma tumor suppressor gene (13q14), which occurs in approximately one third of cases.[9] Other genetic abnormalities include translocations, gene amplification, and abnormal *TP53* function.[10,11]

PATHOLOGY AND PATHWAY OF SPREAD

Ewing's sarcoma is an undifferentiated blue round cell tumor usually of the bone. Its pathologic appearance is a monomorphic pattern of densely packed, small, round, malignant cells with hyperchromatic nuclei and varying amounts of cytoplasm.[12] Immunohistochemical studies reveal cell-surface glycoprotein p30/32 MIC2 (CD 99) and vimentin, HBA-71, and β_2-microglobulin positivity. Occasionally, cytokeratin and NSE are positive. These studies can help differentiate ESFT from other small round cell malignant tumors of childhood. Approximately 87% of cases within the ESFT are Ewing's sarcoma of bone.[13] The remainder is PNETs or extraosseous Ewing's sarcoma.

About 75 % percent of patients with Ewing's sarcoma present with localized disease at diagnosis (Figure 69-1). Approximately 80% of children experience distant metastases if treated with only local therapy. This suggests that in the majority of cases, there are unidentifiable micrometastases present at diagnosis. The most common site of metastasis is the lung, followed by bone. Other distant sites include bone marrow, soft tissues, and rarely, the liver or central nervous system (Figure 69-1).

Osteosarcoma is derived from bone-forming mesenchyme and is described as a malignant sarcomatous stroma associated with the production of osteoid bone, its defining histopathologic feature.[12] The most common types in the pediatric population are the conventional osteosarcomas, including osteoblastic, chondroblastic, and fibroblastic types. Each type has varying amounts of osteoid formation and a different predominant component. There is no difference in outcome or treatment recommendations among these different types. Other types of less common osteosarcomas include telangiectatic, small cell, juxtacortical, periosteal, and high-grade surface sarcomas.

Approximately 90% of children with osteosarcoma present with localized disease at diagnosis (Figure 69-2). However, if only the primary tumor is treated, about 90% will experience metastatic disease.[12]

CLINICAL MANIFESTATIONS, PATIENT EVALUATION, AND STAGING

Patients with Ewing's sarcoma present in general with localized pain, swelling, and a palpable mass. The most common primary tumor sites are illustrated in Figure 69-1. In Ewing's sarcoma, plain radiographs show a lytic, destructive lesion, most typically of the diaphysis, with or without a soft-tissue mass. Codman's triangle may form from the elevated periosteal reaction. An "onion skin" effect, derived from the development of parallel, multilaminar, periosteal reactions, is typically seen.

Patients with osteosarcoma present with similar signs and symptoms, in general, localized pain, swelling, and a palpable mass. The frequency with which osteosarcoma occurs within the different regions of the body is illustrated in Figure 69-2. Plain radiographs of patients with osteosarcoma typically show sclerotic or lytic lesions of the metaphysis. The elevated periosteal reaction may cause Codman's triangle to form. In osteosarcoma, periosteal new bone formation may be present, with the blastic component showing a bony sunburst pattern.

The evaluation for patients with Ewing's sarcoma and osteosarcoma is similar. A complete history and physical examination are performed, with particular attention to the duration of symptoms, the presence of pain, difficulty of function, neurologic symptoms, and the location and size of the mass. Studies commonly obtained to evaluate the extent of disease include routine blood work, urine analysis, bone scanning, plain radiographs, and computed tomography (CT) scanning or magnetic

TABLE 69-1 Staging Investigations at Diagnosis in Osteosarcoma and Ewing's Sarcoma

Investigation	Diagnosis	Follow-up
Radiograph in two planes, whole bone with adjacent joints	+	+
MRI or CT, affected bone(s) and adjacent joints	+	+
Biopsy: material for histologic and molecular biologic testing	+	
Thoracic CT (lung window)	+	+
Bone marrow biopsy and aspirates (in Ewing's sarcoma): microscopy (molecular biology still investigational)	+	
Whole-body technetium-99 m bone scan	+	+
FDG-PET scan	++	++

CT, *Computed tomography;* FDG-PET, *fluorine-18 fluorodeoxyglucose-positron emission tomography;* MRI, *magnetic resonance imaging; +, mandatory; ++, indicated, if available.*

resonance imaging (MRI) of the primary region. A chest CT scan should be obtained to rule out lung metastases. If the chest radiograph is negative and the CT scan is positive for subtle anomalies, an excision may be needed for accurate staging and treatment recommendations. Single-institution and small multiinstitutional studies suggest fluorodeoxyglucose-positron emission tomography (FDG-PET) has improved sensitivity to bone and lymph node metastases compared to bone scan and CT.[14] An electrocardiogram and echocardiogram are included in the evaluation before chemotherapy is initiated. In the case of Ewing's sarcoma, a bone marrow biopsy is obtained. A summary of staging and follow up investigations is given in Table 69-1.

A biopsy of the primary lesion should be obtained after complete evaluation, ideally by the surgeon who will perform the definitive resection. The biopsy should be placed carefully to avoid contamination of uninvolved areas, vital structures, and hematoma development. It must not increase the extent of surgery or preclude a limb-sparing procedure or sparing of a strip of skin outside the radiation port.

Currently, there is no staging system for Ewing's sarcoma. Patients are classified as having either localized disease or metastatic disease and are treated accordingly.

In osteosarcoma, available staging systems are those of the Musculoskeletal Tumor Society and, lately, of the International Union Against Cancer and American Joint Committee on Cancer (UICC/AJCC).[15,16]

The prognosis for patients with Ewing's sarcoma is dependent on a number of factors, the most important of which is the presence or absence of metastatic disease. Data from European studies suggest histologic response to chemotherapy is the primary predictor of outcome in patients undergoing surgery.[17] This has yet to be confirmed in North American regimens although single-institution reports suggest response correlates with improved survival (Ahmed). Historically, other prognostic factors include the site of the lesion and its size and age and gender of the patient. In more recent studies, data is conflicting with no association of outcome with site or size reported in INT-154, a Children's Oncology Group (COG) study evaluating dose-intense multiagent chemotherapy.[18] However, on the recently reported COG AEWS0031 evaluating interval-compressed multiagent chemotherapy, pelvic site was associated with inferior event-free survival (EFS) and OS.[19] The French study EW93 reported poorer outcomes in axial and pelvic tumor as well as large tumor volumes, however, prognostic factors varied by type of local therapy. For surgical patients, location and histologic response correlated with survival. For radiotherapy patients, tumor volume remained significant but site did not.[17] Historically, older patients and male gender was also associated with poor survival. When accounting for histologic response in more recent studies, age and gender have not remained significant.[17] Age older than 18 was associated with poorer survival in the most recent COG study reported (AEWS0031) but histologic response was not assessed in this study.[19] Multiple retrospective studies suggest molecular biomarkers such as *p53* and *p16* may correlate with outcomes, however, prospective validation has not confirmed these findings.[20]

The prognostic features of osteosarcoma are similar, namely, the presence or absence of metastatic disease, the tumor location and size, whether complete resection of the primary tumor was possible, and the response to adjuvant chemotherapy.[21] No molecular markers have been validated in osteosarcoma.

TREATMENT OF EWING'S SARCOMA

Primary Therapy

Historically, patients with Ewing's sarcoma received treatment to the primary lesion only; cure rates were less than 20%. In the early 1960s, single-institution studies began to show an improved outcome with the addition of adjuvant chemotherapy.[22-24] Today, the standard treatment consists of local therapy and neoadjuvant and adjuvant polychemotherapy. Local therapy consists of surgery or radiotherapy or a combination of both. Concerning systemic therapy, a number of randomized trials have been performed to assess the value of different drug combinations.

The first Intergroup Ewing Sarcoma Study (IESS) investigated the use of polychemotherapy from 1973 until 1978. Patients received radiation therapy to the primary lesion and were randomized among three adjuvant chemotherapy treatment arms: vincristine, actinomycin D, and cyclophosphamide (VAC); VAC plus doxorubicin (trade name Adriamycin, so the regimen is known as VACA); or VAC plus bilateral pulmonary radiation therapy.[25] This study showed a significant improvement in all parameters with the addition of doxorubicin. Furthermore, VAC plus bilateral lung irradiation, although less effective than VACA, showed superior results to VAC alone. As a consequence of these results, doxorubicin was considered to be an essential drug in further trials.[26]

The third large intergoup study, INT-0091, investigated the addition of etoposide and ifosfamide to VACA; at 5 years, data showed a statistically significant benefit from the addition of these two drugs. In addition, local control was also significantly improved in patients on the experimental arm.[27] In the European Cooperative Intergroup Ewing Sarcoma Study EICESS-92, the value of the single agents was evaluated. In standard-risk patients (localized disease and tumor volume of <100 mL), VACA was randomized against VAIA (ifosfamide instead of cyclophosphamide). There was no significant difference in EFS rates between the groups. In high-risk patients (larger tumors or metastatic disease), VAIA was randomized

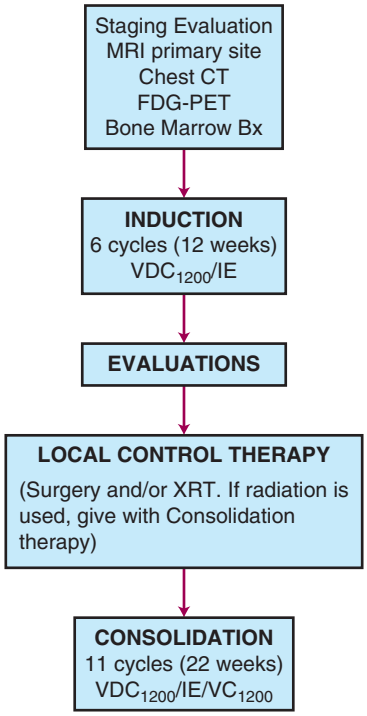


Figure 69-3 Treatment schema. *CT*, Computed tomography; *FDG-PET*, fluorodeoxyglucose-positron emission tomography; *IE*, ifosfamide-etoposide; *MRI*, magnetic resonance imaging; VC1200, vincristine-cyclophosphamide 1200 mg; VDC1200, vincristine-doxorubicin-cyclophosphamide 1200 mg; *XRT*, radiation therapy.

against VAIA plus etoposide; again, no significant difference in EFS rates was observed, but a marginal benefit was demonstrated for patients with large localized disease with the use of etoposide.[28] The most recently reported COG trial, AEWS0031, comparing vincristine, doxorubicin, cyclophosphamide, ifosfamide-etoposide (VDC-IE) dosed every 3 weeks versus every 2 weeks showed an 8% 5-year EFS benefit for interval compressed chemotherapy. This regimen remains the current standard in the United States.[19] Figure 69-3 depicts the most common treatment schema in North America. An alternative for treatment intensification used more commonly in European studies has been high-dose chemotherapy with stem cell rescue.[29] Because of its toxicity, this treatment is mainly used for very high-risk patients. In the Euro-EWING 99 trial, patients with poor pathologic response were randomized to either high-dose chemotherapy with busulfan or conventional therapy with vincristine, ifosfamide, doxorubicin, and etoposide (VIDE) give every 3 weeks. For patients with lung metastases only, high-dose chemotherapy with busulfan was compared to conventional chemotherapy and whole-lung irradiation with 15 Gy or 18 Gy, depending on the age of the patient. Results of this trial are still pending for localized patients. The results for patients with metastatic disease are discussed in this chapter.

A summary of results of different Phase III trials is given in Table 69-2.

Advanced Disease and Palliation

Children with metastatic Ewing's sarcoma at diagnosis continue to have a poor outcome despite the use of aggressive multiagent chemotherapy. The European approach in these patients is to intensify adjuvant and neoadjuvant chemotherapy using high-dose chemotherapy with busulfan or etoposide or treosulfan, and melphalan with autologous stem-cell rescue for patients with bone metastases. EuroEwing99 results using six cycles of VIDE followed by one cycle VID then local therapy. Patients then went onto high-dose busulfan and melphalan followed by stem cell rescue. Overall 3-year EFS and OS were 27% and 34%, respectively.[29] Patients with lung metastases only appear to be a more favorable subset of metastatic patients. European studies have used risk adapted strategies that are intermediate intensity compared to localized and bone metastases patients. Standard chemotherapy with whole-lung radiation has shown favorable results in the Cooperative Ewing Sarcoma Studies (CESS) and European Intergroup Cooperative Ewing Sarcoma Studies (EICESS) trials in comparison to patient with lung metastases only who did not receive whole lung radiation (5-year EFS 40% and 19%, respectively).[30] The EuroEwing99 pulmonary metastases arm evaluated the use of standard chemotherapy with whole-lung irradiation compared to high-dose chemotherapy with stem-cell rescue. The results are still pending. In the United States, metastatic patients were included on the intergroup study INT-0091 evaluating the addition of Ifosphamide/Etoposide (IE). The addition of IE did not result in and improvement in survival (5-year EFS 22%) for metastatic patients.[27] Interval compression was not evaluated in metastatic Ewing's sarcoma, however, because of the favorable results in localized patients it has been adopted for use in metastatic disease as well. In the upcoming COG study, AEWS1221, which will include all metastatic sites, interval compressed VDC-IE chemotherapy with whole lung radiation for lung metastasis patients will be the standard arm reflecting current clinical practice in the United States. Definitive treatment of metastatic sites appears to improve outcomes in metastatic Ewing's sarcoma. Definitive local treatment with surgery or radiotherapy is recommended on the upcoming COG AEWS1221 trial that is also evaluating the role of stereotactic body radiotherapy (SBRT) for bone lesions to improve feasibility of treatment. Even in patients in whom definitive local treatment of all metastatic sites is not feasible, radiation therapy can be used as a palliative local measure.

Local Therapy

Local therapy is an essential modality in the treatment of Ewing's sarcoma. With systemic therapy alone, cure cannot be obtained. Local control on modern COG studies is close to 90%. The modality of local therapy with best local control rates and functional outcome has been a matter of debate for some time. Retrospective analyses of cooperative group studies suggest that local control is improved when surgery is performed although a selection bias for more favorable tumor likely exists confounding these analyses.[31-34] Regardless of differences in efficacy, because of the risk of secondary malignancy associated with radiation, surgery is generally the recommended treatment when an oncologic resection can be obtained with acceptable morbidity. However, because Ewing's sarcoma is radiosensitive and radiotherapy is curative, radiotherapy is recommended for tumors that cannot be resected without significant morbidity. In United States, 60% to 65% of patients are treated with surgery alone, 20% to 25% are treated with radiation alone, and the remainder receives a combination of both. European studies report slightly higher rates of radiation and surgery and lower rates of surgery alone reflective of the risk-adapted approach used for higher risk tumors.[35-38] Patients on EuroEwing99 received preoperative radiation when margins were expected to be close with surgical resection and received postoperative radiation for poor histologic response.

TABLE 69-2 Treatment Results in Selected Clinical Studies of Localized Ewing's Sarcoma Family Tumors

Study	Reference	Schedule	No. Patients	5-year Event-Free Survival
COG				
IESS-I (1973-1978)	Nesbit, J Clin Oncol 8:1664, 1990	VAC VAC + WLI VACD	342	24% 44% 60%
IESS-II (1978-1982)	Burgert, J Clin Oncol 8:1514, 1990	VACD-HD VACD-MD	214	68% 48%
First POG-CCG (INT-0091) (1988-1993)	Grier, N Engl J Med 348:694, 2003	VACD VACD + IE VACD ± IE (metastatic)	200 198 120	54% 69% ($p = 0.005$) 22% ($p = 0.81$)
Second POG-CCG (1995-1998)	Granowetter, J Clin Oncol 27:2536, 2009	VCD + IE 48 wk VCD + IE 30 wk	247 231	70% 72% ($p = 0.57$)
AEWS 0031	Womer, J Clin Oncol 30:4148, 2012	VDC + IE 3/wk VDC + IE 3/wk	284 284	65% 73% ($p = 0.048$)
MEMORIAL SLOAN-KETTERING CANCER CENTER				
T2 (1970-1978)	Rosen, Cancer 41:888, 1978	VACD (adjuvant)	20	75%
P6 (1990-1995)	Kushner, J Clin Oncol 13:2796, 1995	HD-CVD + IE	36	77% (2 year)
P6 (1991-2001)	Kolb, J Clin Oncol 21:3423, 2003	HD-CVD + IE	68	Localized: 81% (4 year) Metastatic: 12% (4 year)
ST. JUDE CHILDREN'S RESEARCH HOSPITAL				
ES-79 (1978-1986)	Hayes, J Clin Oncol 7:208, 1989	VACD	52	82% < 8 cm (3 year) 64% ≥ 8 cm (3 year)
ES-87 (1987-1991)	Meyer, J Clin Oncol 10:1737, 1992	Therapeutic window with IE	26	Clinical responses in 96%
EW-92 (1992-1996)	Marina, J Clin Oncol 17:180, 1999	VCD-IE × 3	34	78% (3 year)
UKCCSG/MRC				
ET-1 (1978-1986)	Craft, Eur J Cancer 33:1061, 1997	VACD	120	41%
ET-2 (1987-1993)	Craft, J Clin Oncol 16:3628, 1998	VAID	201	62%
CESS				
CESS-81 (1981-1985)	Jürgens, Cancer 61:23, 1988	VACD	93	<100 mL 80% ≥100 mL 31% (both 3 year) Viable tumor < 10%: 79% >10%: 31% (both 3 year)
CESS-86 (1986-1991)	Paulussen, J Clin Oncol 19:1818, 2001	<100 mL (SR): VACD ≥100 mL (HR): VAID	301	52% (10 year) 51% (10 year)
EICESS (CESS PLUS UKCCSG)				
EICESS-92 (1992-1999)	Paulussen, J Clin Oncol 6:4385, 2008	SR: VAID/VACD HR: VAID/EVAID	155 492	68%/67% ($p = 0.72$) 44%/52% ($p = 0.12$)
ROI/BOLOGNA, ITALY				
REN-3 (1991-1997)	Bacci, Eur J Cancer 38:2243, 2002	VDC + VIA + IE	157	71%
SFOP/FRANCE				
EW-88 (1988-1991)	Oberlin, Br J Cancer 85:1646, 2001	VD + VD/VA	141	58%
EW-93 (1993-1999)	Gaspar, Eur J Cancer 48:1376, 2012	<100 mL >95% response (SR): VD + VD/VA >100 mL, 70-95% response, <50% size response (IR): VD + VD/VA + IE >100 mL, <70% response, <50% size response (HR): VD + VD/VA + IE + HD	116 46 48	70% 54% 48%
SSG/SCANDINAVIA				
SSG IX (1990-1999)	Elomaa, Eur J Cancer 36:875, 2000	VID + PID	88	58% (metastases-free survival)
EUROEWING (EICESS + SFOP)				
EuroEwing99 (1999-2005)	Ladenstein, J Clin Onc 28:3284 2010	R3 (multiple metastases): VIDE + VAI + HD	281	27% (3 year)

A, *Actinomycin D;* C, *cyclophosphamide;* D, *doxorubicin;* E, *etoposide;* HD, *high dose;* HR, *high risk;* I, *ifosfamide;* MD, *moderate dose;* P, *cisplatin;* SR, *standard risk;* V, *vincristine;* WLI, *whole-lung irradiation.*

Definitive Radiotherapy

Patients who receive radiotherapy as the only local therapy modality usually represent an unfavorably selected group of patients. They frequently present with large tumors or tumors in unfavorable locations (e.g., vertebral or pelvic tumors). In an analysis of 1058 patients with localized Ewing's sarcoma treated in the EICESS trials, 266 patients received radiotherapy alone for local treatment. Local or combined local and systemic failures in this subgroup occurred in 26% of patients, a recurrence rate that was worse than the rate following surgery with or without radiotherapy (4% to 10%).[33,34]

Bacci et al[39] performed a single-institution analysis of 512 patients treated in four consecutive trials. Treatment results in patients who received radiotherapy alone were worse than in patients who underwent surgery (local failure rates of 19% with radiotherapy alone, 11% with surgery and radiotherapy, and 9% with surgery alone). When analyzed by tumor site, radiotherapy alone was unfavorable in extremity sites but not in central tumor sites suggesting central tumor sites are problematic for surgical local control as well. Similar results were seen in a retrospective analysis of COG INT-0091 evaluating local control for pelvic tumors only. Overall local failure was 22% with no difference between surgery and radiation. Although not statistically significant, outcomes were improved in patients who received combination of surgery and radiotherapy as opposed to either surgery or radiotherapy alone (25% versus 10%, $p = 0.45$). Patients on the experimental arm (receiving IE chemotherapy) had improved local control with only 11% local failure rate for all patients.[38a]

Definitive radiotherapy is indicated is surgery is expected to leave gross disease (R2 resection). Debulking procedures do not improve local control rates and are associated with unnecessary morbidity. In the CESS and EICESS trials[33,34] and in the Bologna experience by Bacci et al,[39] patients who had intralesional resection followed by radiotherapy had the same local control rate as patients who had radiotherapy alone.

Postoperative Radiotherapy

Postoperative radiotherapy is always indicated following intralesional resections. These debulking procedures are not sufficient to obtain local control and should be avoided. Oncologic resection in Ewing's sarcoma has historically been defined by the Enneking classification.[15] Enneking et al reporting on outcomes in soft-tissue sarcoma described local failure rates of 50% for marginal resections (tumor was shelled out within the surrounding reactive zone), 25% after wide resection (resection passed through normal tissue outside the reactive zone but within the anatomical compartment), and 4% after radical excision (entire compartment resected). Although wide excisions are generally felt to ideal if possible with reasonable morbidity, with improvements in systemic chemotherapy modern surgeries are more accurately described as wide excisions. Historically COG trials recommend postoperative radiotherapy after close margins defined as margins <1 cm bone, <5 mm in muscle, and <2 mm along a fascial plane. Local control after surgery alone is approximately 90% on these studies.[18,19] In the CESS and EICESS trials, local control with surgery alone was excellent in all patients who had a wide resection according to the Enneking classification and showed a good response on histologic testing following initial chemotherapy (defined as <10% viable tumor cells in the resected specimen).[40] Only one local failure in 101 patients occurred in this subgroup. Patients with wide resection and a poor histologic testing response were at higher risk of local failure (12%). This local failure rate was improved with the use of postoperative radiotherapy (6%).[33] There was also a trend toward benefit with the use of postoperative irradiation in patients who had a marginal resection. Bacci et al[39] observed no improvement with postoperative radiotherapy following wide or marginal resection (local failure rate of 7% without postoperative radiotherapy and 6% with postoperative radiotherapy). Based on the importance of histologic response in local control reported in European studies, the current COG trial (AEWS1031) is evaluating the possibility of limiting postoperative radiotherapy after close margins (less than Enneking but still negative or R0 resections) to patients with poor histologic responses. Postoperative radiotherapy is still required for microscopic positive (R1 resection) margins.

Preoperative Radiotherapy

The systematic use of preoperative radiotherapy was incorporated into the EICESS-92 trial. The governing objective was to sterilize the tumor compartment before surgery and thereby potentially reduce the rate of dissemination during surgery. With growing experience with the use of preoperative radiotherapy, it was used in this trial when narrow resection margins were expected. More than 40% of the EICESS patients were treated with preoperative radiotherapy. In an analysis of the data from these 246 patients, however, a reduction in systemic failure could not be demonstrated.[33] On the other hand, the local control rate following preoperative radiotherapy was excellent, with only 5% of the patients experiencing local or combined local and systemic failures. However, preoperative irradiation may increase the infection rate postoperatively and may also interfere with bony union. In North America, preoperative radiotherapy remains fairly uncommon in Ewing's sarcoma for this reason.

Irradiation Techniques and Tolerance

Radiation Dose and Fractionation

The first Intergroup Ewing Sarcoma Study (IESS-I) evaluated the effect of dose on local control and showed no dose response between 30 Gy and 65 Gy. Single-institution report of the St. Jude experience showed higher rates of local recurrence in children treated with doses <40 Gy with no local failures using >40 Gy.[37] Although a clear dose-response correlation at doses above 40 Gy has not been established for definitive radiotherapy, doses between 55 Gy and 60 Gy are usually given. When surgery precedes or follows radiotherapy, the doses range between 45 Gy and 55 Gy, depending on the individual risk factors (e.g., resection margins and response). The current COG study (AEWS1031) recommends 45 Gy to prechemotherapy target volume, 55.8 Gy to postchemotherapy residual disease, and 50.4 Gy for microscopic positive margins postoperatively.

Usually, conventional fractionation with daily fractions of 1.8 Gy to 2 Gy is given. In the CESS-86 and EICESS-92 trials, hyperfractionated radiotherapy with a twice-daily dose of 1.6 Gy was also applied; after a total of 22.4 Gy had been given, a 10-day break was scheduled to permit the administration of chemotherapy. There has been no difference in local control rates between the two different fractionation groups.[40]

Target Volume

In terms of volume, previous treatment recommendations were to include the entire bone. The Pediatric Oncology Group (POG) series and other series confirmed that local failures occur generally within the high-dose irradiation volume.[38] In a randomized trial, the treatment of the whole tumor-bearing compartment showed no better results than irradiation to the tumor and an additional safety margin.[41] With reliance on MRI for target volume delineation, margins have been reduced successfully on the most recent COG studies without increase in local failure.[18] Current COG recommendations include all

T1-gadolinium enhancing tumor, all T2 signal abnormality, and all bone abnormalities to be included in the prechemotherapy gross target volume (GTV). Prechemotherapy clinical target volume (CTV) is a 1-cm expansion of this volume. Prechemotherapy GTV and CTV can be modified for pushing, noninfiltrative, borders such as paraspinal tumors pushing into the abdominal cavity or lungs that have receded after induction chemotherapy and can be modified to be restricted to fascial planes if there is no evidence of infiltration. Postchemotherapy GTV includes residual soft-tissue mass after induction chemotherapy as well as all bone abnormality present prechemotherapy. Postchemotherapy CTV is a 1-cm expansion of GTV modified for anatomic pushing borders and limited to fascial planes if there is no evidence of infiltration. Planning target volumes (PTVs) are a 0.5-cm to 1-cm expansion on CTV depending on tumor location and daily image-guidance available at the institution. Surgically contaminated areas, scars, and drainage sites must be included in the radiation fields. Circumferential irradiation of extremities should be avoided to reduce the risk of lymphedema. In growing children, growth plates must be considered. They should either be fully included in the radiation field up to 30 Gy, or they should not be included at all. A dose gradient through the epiphysis results in asymmetric growth and may lead to functional deficits. Similarly, vertebral bodies should either be fully included or spared from the radiation field. Three-dimensional conformal radiotherapy should be given in patients with Ewing's sarcoma. In selected cases (i.e., in vertebral tumors), intensity-modulated radiotherapy (IMRT) or proton therapy may be beneficial. Figures 69-4 to 69-6 show an example of treatment planning.

Irradiation of Lung Metastases

The benefit of lung irradiation in Ewing's sarcoma tumors has been shown in the randomized IESS-I trial.[25] In patients without radiologic evidence of metastases (in the era before CT became available), the best results were observed with

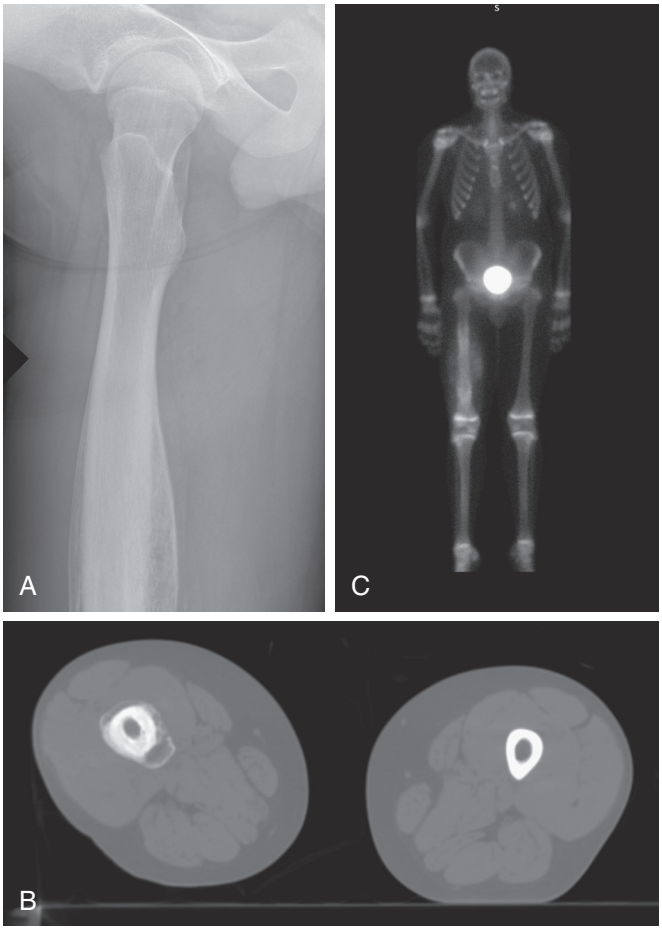


Figure 69-4 **A,** Plain radiograph; **B,** axial CT; and **C,** 99mTc bone scan of Ewing's sarcoma of right femur.

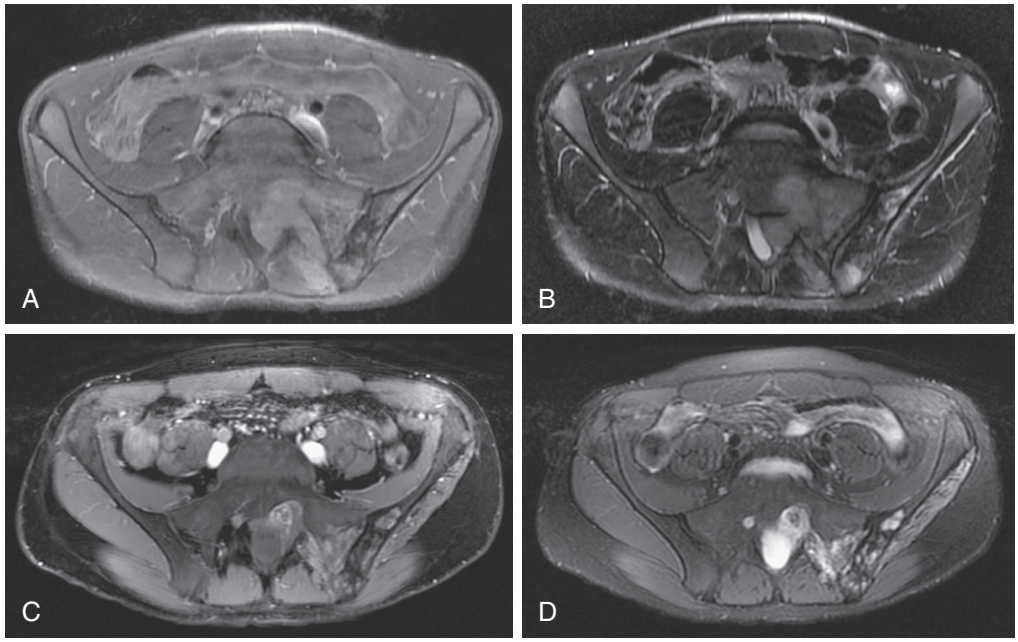


Figure 69-5 **A,** Pretreatment axial contrast-enhanced T1 MRI of a Ewing sarcoma located in the pelvis. **B,** Pretreatment axial T2 MRI of a Ewing's sarcoma located in the pelvis. **C,** Postinduction axial contrast-enhanced T1 MRI of a Ewing's sarcoma located in the pelvis. **D,** Postinduction axial T2 magnetic resonance imaging of a Ewing's sarcoma located in the pelvis.

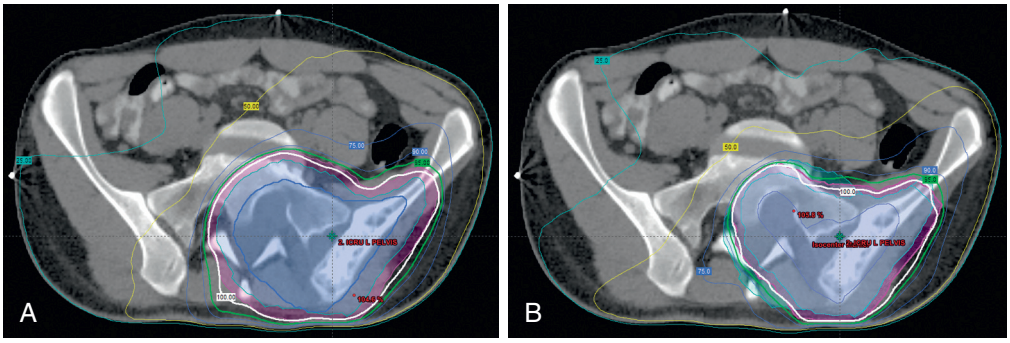


Figure 69-6 **A,** Dose distribution resulting from computed tomography (CT)-based intensity modulated radiotherapy treatment following induction chemotherapy for prechemotherapy planning target volume (PTV) receiving 45 Gy. **B,** Dose distribution resulting from CT-based intensity-modulated radiotherapy treatment following induction chemotherapy for postchemotherapy PTV receiving 10.8 Gy boost.

VACA, although VAC plus lung irradiation was significantly better than VAC alone. In an analysis of the EICESS-92 trial, patients with lung metastases alone showed a trend toward a better outcome with the use of radiotherapy.[42] The recommended dose is 15 Gy to 20 Gy in 1.5-Gy daily fractions. Opposing radiation portals should include both lungs down to the diaphragmatic recess. When possible, breath-hold treatment (treatment in deep inspiration) should be used to help to reduce the volume of irradiated liver, stomach, and upper kidneys. The inferior extent of the lung recesses is not well-seen on conventional or four-dimensional CT. If treatment cannot be performed with breath-hold technique, fluoroscopic evaluation or deep inspiration lateral chest x-ray should be used to define the inferior lung border. Doxorubicin and actinomycin D must not be given during whole-lung radiotherapy because of the increased risk of pneumonitis, and actinomycin D should also be avoided after lung irradiation because of the risk of recall pneumonitis. Lung radiotherapy is therefore best given after completion of conventional chemotherapy. Lung irradiation is not given in the context of a busulfan-containing regimen as a result of risk of significant lung toxicity.

Radiation Therapy of Bone Metastases

Radiotherapy is indicated in patients presenting with bone metastases. In an analysis of metastatic patients treated in the EURO-EWING 99 trial, there was a significant improvement in the 3-year EFS rate in patients who received local therapy to the primary tumor and to all metastatic sites compared with patients who received local therapy to the primary tumor only or no local therapy at all (39% versus 17% versus 14%).[43] In a multivariate analysis that considered patient age, volume of the primary tumor, number of bone metastases, type of therapy (i.e., high-dose chemotherapy and local therapy to the primary tumor or to extrapulmonary metastases), significant factors associated with a poor prognosis were no local therapy to the primary tumor or extrapulmonary metastases and no high-dose chemotherapy. When bone metastases are few, definitive radiotherapy can be given to all initially involved sites. Irradiation of more than 50% of the estimated bone marrow volume can result in significant myelosuppression may interfere with ability to administer the remaining chemotherapy. Therefore, in patients presenting with multiple bone metastases that preclude irradiation of all sites at the time of local therapy, radiotherapy can be either be administered at the end of therapy or may need to be selectively administered to bulky regions, lesions showing slow response to initial therapy (PET residual at the time of local therapy), or lesions with residual PET avidity at the end of therapy. Following high-dose busulfan therapy, two cases of myelopathy have been reported with the application of 50 Gy in conventional fractionation to vertebral sites. In this context, a dose reduction is necessary.

TREATMENT OF OSTEOSARCOMA

Primary Therapy

The overall current recommended approach to treatment of osteosarcoma is surgical resection of the primary tumor either by amputation or a limb-sparing procedure. Local treatment is preceded by neoadjuvant chemotherapy and followed by postoperative chemotherapy. Single-institution studies showed an improvement in OS rates among patients receiving adjuvant chemotherapy compared with historic controls.[20,44,45] Two prospective, randomized studies confirmed this, one at the University of California Los Angeles and one national multiinstitution study.[46,47] Currently, the initial chemotherapeutic agents used include methotrexate, cisplatin, doxorubicin, and ifosfamide. Pathologic response (tumor necrosis greater than 90%) is associated with improved survival in osteosarcoma.[19,20] If the primary tumor shows only minimal response to neoadjuvant chemotherapy, many believe the chemotherapy agents should be altered for the postoperative therapy, but this has not been proven. Currently, between 60% and 70% of patients with localized osteosarcoma are cured.

Because of the radioresistant nature of these tumors, radiotherapy has a limited role in osteosarcoma. Definitive irradiation is used in patients in whom complete surgical resection cannot be obtained as adjuvant therapy for close or positive margins and for palliation in patients with inoperable metastases.

Local Therapy

Surgery is the mainstay of local treatment of osteosarcoma. Surgical resection is performed either by amputation or a limb-sparing approach and has a 5% local failure rate. Although not well studied and rarely used, the addition of radiation therapy in limb-sparing approaches is a possibility and can be considered in special circumstances. Osteosarcoma is usually considered to be a radioresistant tumor. In vitro studies, however, show that it has a radiosensitivity similar to that of other human tumor cell lines.[48] Also, there have been case reports of patients with inoperable or residual tumor treated with radiation doses ranging between 50 Gy and 70 Gy who remained in continuous remission.[49] In an analysis of patients with osteosarcoma refusing surgery but receiving systemic therapy and local irradiation, the local progression-free survival rate at 5 years was 56%.[50] The survival rate was about

90% at 5 years in the subgroup of irradiated patients responding to chemotherapy. DeLaney et al reported on 41 patients with osteosarcoma who received radiotherapy with no surgery or close or positive resection margins. The respective local control rates at 5 years were 40%, 78%, and 78%, respectively.[51] Median dose was 66 Gy although doses as high as 80 Gy were used for gross disease. Because of the often unfavorable site of these tumors, 56% of patients received some or all of their treatment with proton radiotherapy. Recent reports suggest a benefit for heavier particle therapy in unresectable osteosarcoma. In a retrospective review of 78 patients with unresectable axial osteosarcoma treated with carbon ion radiotherapy, local control was 62% at 5 years and 88% for smaller tumors (<500 mL). Treatment was hypofractionated and patients received a median of 70.4 CGE in 16 fractions over 4 weeks. Although surgery is the local treatment of choice, cure can also be achieved with irradiation in inoperable tumors or patients refusing surgery.[52]

Advanced Disease and Palliation

The overall approach to metastatic disease with osteosarcoma is with multiagent chemotherapy. The overall prognosis depends on the location and number of metastases, whether complete surgical resection of all tumor tissue was possible, and the response to chemotherapy.[53,54] Patients with metastasis only in the lung or a limited number of metastases who can undergo complete surgical resection fare better; the 3-year survival rate is approximately 50%, compared with 20% to 30% for more advanced disease.

Radiation therapy to the lungs for metastases, when appropriate, can be given to a dose of 15 Gy to 20 Gy to the whole lung. The use of whole-lung radiation therapy in the setting of metastatic disease is controversial. Whole-lung radiation therapy as prophylaxis against metastatic disease is also controversial and is usually not recommended. Randomized trials of the European Organization for Research and Treatment of Cancer (EORTC) showed that prophylactic whole-lung radiation therapy compared well with chemotherapy.[55] However, no benefit was shown in the U.S. studies.[56]

Radiation therapy may be incorporated into the treatment of osseous metastatic sites not amenable to surgical resection. In an analysis of the prognosis of relapsing patients treated in the Cooperative Osteosarcoma Study Group (COSS) trials, results were best when metastases could be surgically removed. Radiotherapy of inoperable sites, though, was associated with an improved survival rate compared with that of patients who received no local therapy.[57]

The use of samarium-153 (^{153}Sm) ethylenediaminetetramethylene phosphonic acid (^{153}Sm-EDTMP) therapy has been investigated in unresectable osteosarcoma (for the primary tumor and metastases). This therapeutic beta-emitting isotope, which also emits a gamma photon to permit imaging and dosimetry, localizes to osteoblastic lesions with very high tumor to nontumor ratios.[58] Although it is not yet possible to make any definitive statements about the long-term efficacy of this treatment modality, a multimodal concept of high-activity ^{153}Sm-EDTMP in combination with external beam radiation therapy, polychemotherapy, and autologous hematopoietic progenitor cell support for unresectable osteosarcoma seems to be promising.[59,60]

It is therefore reasonable to offer radiation therapy in the treatment of osteosarcoma for (1) unresectable primary tumors or following incomplete resection, (2) patients who refuse surgery, and (3) unresectable metastatic tumors. The recommendation is to treat the tumor to the highest tolerable dose based on the surrounding structures, using a shrinking-field technique.

Treatment Planning Techniques

The treatment planning techniques used for osteosarcoma of the extremities and other sites are similar to those described for the treatment of Ewing's sarcoma.

FUTURE POSSIBILITIES AND CHALLENGES

Future challenges include maintaining a good outcome in patients with localized disease while decreasing treatment toxicity and increasing organ functionality. For patients with metastatic disease and for poor responders, the challenge is to improve the outcome. Pathologic response for patients who undergo surgery appears to be associated with survival outcomes but a reliable prognostic factor for nonsurgical patients is not available as yet. FDG^{18} PET-CT as a predictor of response is being evaluated on the currently open COG AEWS1031. Risk-adapted treatment based primarily on baseline characteristics and pathologic response when available is being evaluated in European studies but because of perceived lack of effective alternative treatment for poor responders has not been adopted in North America. Future possibilities include identifying new active agents based on molecular profiling of tumors and a better understanding of mechanism of oncogenesis.

New radiation therapy approaches to the treatment of pediatric bone sarcomas include the use of smaller margins and more conformal techniques such as intensity-modulation therapy and proton or heavy ion therapy.[51,52] Risk-adapted dose and volume constraints are being evaluated in the currently open COG AEWS1031 study for postoperative patients based on pathologic response. Risk-adapted dose and volume strategies for definitive radiotherapy patients also await validated results with noninvasive imaging such as FDG^{18}-PET.

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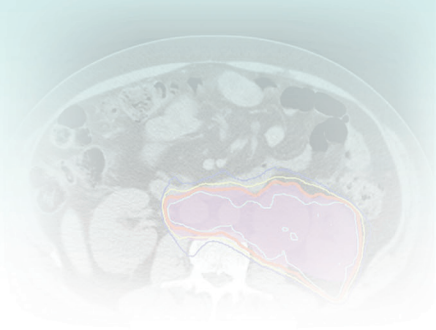
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CHAPTER

70 Wilms' Tumor



John A. Kalapurakal and Jeffrey S. Dome

INCIDENCE

Renal tumors are the fifth-most common cancer in children younger than 15 years of age. It is estimated that 7.1 per million children are affected, and 500 new cases are reported each year in the United States. The median age at presentation is 3.5 years.

HISTOLOGY OF PEDIATRIC RENAL TUMORS

Favorable histology Wilms' tumor: 80% to 85%
Anaplastic Wilms' tumor: 5% to 8%
Renal cell carcinoma: 5% to 8%
Clear cell sarcoma of the kidney: 2% to 3%
Rhabdoid tumor of the kidney: 1% to 2%
Mesoblastic nephroma: 1% to 2%

BIOLOGIC CHARACTERISTICS

WT1 (11p13), *WT2* (11p15), and genes in the WNT signaling pathway (WTX and β-catenin) are implicated in the development of Wilms' tumor. Loss of heterozygosity (LOH) at 1p and 16q and gain of chromosome 1q are associated with higher relapse rates. Children's Oncology Group (COG) protocols include LOH results in addition to tumor stage and histology for risk stratification.

STAGING EVALUATION

Staging requires a patient history, physical examination, complete blood cell count, hepatic and renal serum chemistries, urinalysis, chest computed tomography (CT), abdominal and pelvic CT or magnetic resonance imaging (MRI), and abdominal ultrasonography if the renal vein and inferior vena cava are not well visualized by cross sectional imaging.

PRIMARY THERAPY

Surgical resection (nephrectomy, tumor resection, and staging) is the primary therapy for this tumor in the United States. Preoperative chemotherapy is routinely used in Europe.

ADJUVANT THERAPY

National Wilms Tumor Study Group (NWTS) studies show vincristine and dactinomycin result in excellent cure rates for patients with localized (stages I and II) Wilms' tumor of favorable histology. Radiation therapy (RT) and doxorubicin are added for advanced local or metastatic disease (stages III and IV).

The recently completed COG protocol augmented chemotherapy for patients with LOH at 1p and 16q.

Chemotherapy is also intensified for focal and diffuse anaplastic Wilms' tumor, clear cell sarcoma of the kidney (CCSK), and rhabdoid tumor of the kidney (RTK).

The flank or abdominal radiation dose is 10.8 Gy. Higher doses are recommended in patients with gross residual tissue or for stage III anaplastic tumors and RTK (19.8).

RETRIEVAL THERAPY

Retrieval therapy is based on original stage, prior treatment, and sites of relapse and includes surgery, RT, and intensive multiple-agent chemotherapy with or without stem-cell transplantation.

Wilms' tumor, or nephroblastoma, is the most common childhood renal tumor, accounting for about 6% of pediatric malignant diseases.[1] It was first described in 1814, but Max Wilms first identified the true nature of the condition as a neoplasm with mixed cellular elements in 1899.[2] His name has become synonymous with nephroblastoma. The early advances in managing these small patients with huge tumors were made by surgeons, who reduced the operative mortality from 25% to the current rate of less than 1%. The survival of children with Wilms' tumor gradually increased from less than 10% to about 50% by the 1940s and 1950s. Postoperative RT became routine after results from Boston Children's Hospital documented an increased cure rate. The advent of effective chemotherapy (dactinomycin and vincristine) also had an impact on the survival of these children.[3] The systematic development of multidisciplinary management for Wilms' tumor resulted in a striking improvement in survival. Thus, the grim outlook at the beginning of the 20th century (90% mortality rate) has effectively inversed to a survival rate of 90% in the early 21st century. Randomized clinical trials in North America under the aegis of the NWTS and those in Europe, largely by the International Society of Pediatric Oncology (SIOP), have resulted in Wilms' tumor therapy becoming a paradigm for successful multidisciplinary integration in the treatment of cancer. Successive NWTS clinical trials have been based on postoperative therapies, whereas preoperative strategies have been the focus of SIOP investigators.[4]

Clinical risk factors such as tumor stage and histology were identified so that treatment could be modulated in intensity according to risk groups, the objective being to achieve cure with minimum complications. As a result, children with low-risk tumors now receive minimal therapy whereas those at high risk benefit from more intensive therapy. The modern survivors of Wilms' tumor enjoy a better quality of life owing to sequential reductions in the intensity of therapy.[5] Current Wilms' tumor studies in the United States and Canada are conducted by the COG.

ETIOLOGY AND EPIDEMIOLOGY

The cause of Wilms' tumor is unknown. The peak incidence is between 3 and 4 years of age. Wilms' tumor may arise as sporadic or hereditary tumors or in the setting of specific genetic disorders. The overall annual incidence of Wilms'

tumor is 7.1 per million children, and approximately 500 new cases can be expected each year in North America. Wilms' tumor is found more often in black than in white children, with a ratio of 1.25:1. Girls are affected more than boys in the same ratio.[1]

PREVENTION AND EARLY DETECTION

Prevention awaits an identified cause. Uncommon congenital anomalies (aniridia, genitourinary malformations, hemihypertrophy, or signs of overgrowth) may be seen in 13% to 28% of children with unilateral or bilateral disease, respectively.[6] Syndromes associated with a higher risk for developing Wilms' tumor include the "WAGR" syndrome (aniridia, genitourinary malformation, mental retardation), the Beckwith-Wiedemann syndrome, and the Denys-Drash syndrome (see section on molecular biology). Children with such syndromes should be screened for the development of Wilms' tumor using ultrasonographic examinations of both kidneys every 3 months until age 5 years (WAGR) or 7 years (Beckwith-Wiedemann syndrome).[6,7]

BIOLOGIC CHARACTERISTICS AND MOLECULAR BIOLOGY

The biologic characterization of Wilms' tumor has provided the foundation for our understanding of key concepts in cancer genetics, including the roles of tumor suppressor genes and loss of genomic imprinting in tumorigenesis. Although Wilms' tumor was one of the original examples in Knudson's two-hit model of cancer development, subsequent research has shown that multiple genes and several genetic events contribute to the formation of this malignant disorder.[8] The molecular changes that have been described in Wilms' tumor can be classified as primary events predisposing to the development of tumor or secondary events associated with tumor progression.

WT1

Initial insights into the molecular biology of Wilms' tumor were derived from the observation that in patients with WAGR syndrome the risk for developing the tumor is more than 30%. Cytogenetic analysis of individuals with this syndrome showed deletions at chromosome 11p13, which was later found to be the locus of a contiguous set of genes including *PAX6,* the gene causing aniridia, and *WT1,* one of the Wilms' tumor genes. The *WT1* gene encodes a transcription factor that is crucial to normal kidney and gonadal development.[7] The Denys-Drash syndrome, which is characterized by pseudohermaphroditism, glomerulopathy, renal failure, and a 95% chance of Wilms' tumor development, is caused by point mutations in the zinc-finger DNA-binding region of the *WT1* gene.[7] Although *WT1* has a clear role in tumorigenesis of Wilms' tumor in patients with the WAGR and Denys-Drash syndromes, only a minority of patients with sporadic Wilms' tumor carries *WT1* mutations in the germline (<5%) or in tumor tissue (6% to 18%).[7]

IGF2/H19

The Beckwith-Wiedemann syndrome is an overgrowth disorder manifested by large birth weight, macroglossia, organomegaly, hemihypertrophy, neonatal hypoglycemia, abdominal wall defects, ear abnormalities, and predisposition to Wilms' tumor and other malignant disorders. Approximately 5% of individuals with this syndrome develop Wilms' tumor. Beckwith-Wiedemann syndrome maps to chromosome 11p15, a locus sometimes called "WT2" because it was the second locus shown to be associated with Wilms tumor.[9]

The 11p15 locus consists of several genetically imprinted genes that are in two clusters or imprinting centers. Several combinations of genetic and epigenetic alterations can give rise to Beckwith-Wiedemann syndrome, with increasing recognition of genotype-phenotype relationships.[10,11] Imprinting Center 1, which contains the *IGF2* and *H19* genes, has been most implicated in Wilms' tumor predisposition. Alterations in Imprinting Center 2, which contains the genes *CDKN1C, KCNQ1,* and *KCNQ1OT1,* are not strongly linked to Wilms' tumor development. Approximately 70% of Wilms' tumors have LOH or loss of imprinting (LOI) at the 11p15 locus.[12]

Wnt Signaling Pathway Genes (WTX and β-Catenin)

Alterations of the Wnt signaling pathway have been implicated in several human malignancies. Central to the pathway is the activator, β-catenin, which is degraded in the absence of Wnt signaling. Activating mutations in the gene encoding β-catenin *(CTNNB1)* occur in approximately 15% of Wilms' tumors.[13] Interestingly, mutations in *CTNNB1* occur mostly in tumors in which *WT1* is also mutated, suggesting that these two events cooperate in the formation of Wilms tumor. *WTX,* a recently discovered novel Wilms' tumor suppressor gene on the *X* chromosome, is inactivated in one third of sporadic Wilms' tumor cases. In contrast to the two-hit model of inactivation of *WT1, WTX* is inactivated by a monoallelic "single-hit" event that targets the *X* chromosome in tumors in males and the active *X* chromosome in tumors in females.[14] *WTX* has been shown to be a negative regulator of Wnt/β-catenin signaling.[15]

Familial Wilms' Tumor Genes

Familial predisposition to Wilms' tumor is rare, identified in only 1.5% of patients. A few families were shown to carry constitutional mutations of the *WT1* gene, but genetic linkage analysis has excluded *WT1* in most familial Wilms' tumor pedigrees. Rare pedigrees of familial Wilms' tumor recently have been associated with *BRCA2* mutations.[16] Linkage analysis has uncovered two familial Wilms' tumor loci, FWT1 (17q) and FWT2 (19q), but the causative genes remain to be identified.[8]

TP53 Mutation

Germline mutations of the *TP53* tumor suppressor gene are responsible for the Li-Fraumeni cancer predisposition syndrome (LFS).[17] Several LFS families with Wilms tumor have been identified.[18] Approximately 75% of anaplastic Wilms' tumors have detectable *TP53* mutations, whereas *TP53* mutations are uncommon in favorable histology tumors.[19] Studies are under way to evaluate whether *TP53* mutations carry prognostic significance in anaplastic Wilms' tumor.

Loss of Heterozygosity at 1p and 16q

One of the major goals of the NWTS-5 trial was to prospectively analyze the prognostic significance of LOH at chromosomes 1p and 16q. Analysis of these data revealed that the relative risks for relapse for patients with stages I to IV favorable histology tumors with LOH stratified by stage are 1.77 for LOH 1p ($p < 0.01$) and 1.39 for LOH 16q ($p = 0.05$). When the effects of LOH for both 1p and 16q were considered jointly, the relative risk for relapse in stage I and II favorable histology

disease was 2.88 ($p = 0.001$) and that for stages III and IV favorable histology disease was 2.41 ($p = 0.01$). The relative risk for death for patients with stages I and II favorable histology disease with LOH for both regions is 4.25 ($p = 0.01$), and for stages III and IV it is 2.66 ($p = 0.04$).[20]

Chromosome 1q Gain

Gain of chromosome 1q, observed in almost 30% of Wilms' tumor samples, is one of the most common cytogenetic findings in Wilms' tumor.[21] Several small studies of heterogeneously treated patients suggested an association between 1q gain and recurrence.[22,23] The association between 1q gain and adverse outcome was recently validated in an analysis of 212 patients treated on NWTS-4.[24] In this study, the 8-year event-free survival estimate was 76% (95% confidence interval [CI], 63% to 85%) for patients with 1q gain and 93% (95% CI, 87% to 96%) for those lacking 1q gain ($p = 0.0024$). The 8-year overall survival estimate was 89% (95% CI, 78% to 95%) for those with 1q gain and 98% (95% CI, 94% to 99%) for those lacking 1q gain ($p = 5.0075$). Interestingly, there was a strong association between chromosome 1q gain and LOH at 1p and 16q because some of the tumors with 1q gain had translocations between chromosomes 1 and 16.[24] Future COG studies will likely use 1q gain as one of the biological factors in the risk stratification schema.

PATHOLOGY AND PATHWAYS OF SPREAD

Initially, most pediatric renal tumors were classified as Wilms' tumor, with either favorable or unfavorable histology. After careful histopathologic examination of all unfavorable histology tumors registered in the first two NWTS studies, pathologists from the study group recognized that certain tumors represented separate disease entities. Therefore from NWTS-3 onward, CCSK and RTK were treated with distinct treatment regimens and analyzed separately from true Wilms' tumors.

Most Wilms' tumors are solitary lesions, although 6% involve both kidneys and 12% show multifocal involvement within a single kidney. The classic triphasic "favorable histology" Wilms' tumor consists of varying proportions of three cell types—blastemal, stromal, and epithelial—recapitulating various stages of normal renal development (Figure 70-1, *A, B*). Less commonly, heterologous epithelial or stromal components are identified, including mucinous or squamous epithelium, skeletal muscle, cartilage, osteoid, or fat. Not all specimens are triphasic; biphasic and monophasic patterns are frequently encountered. Favorable histologic features characterize 87% of Wilms' tumors.[25]

The histologic feature of greatest clinical significance is anaplasia, defined by the presence of greatly enlarged polyploid nuclei (see Figure 70-1, *C, D*). Anaplasia is present in approximately 8% of Wilms' tumors; it is rare in the first 2 years of life and increases in frequency to approximately 13% in children older than age 5 years. Anaplasia is far more frequent in black patients than in white patients and, as noted previously, has been strongly linked to the presence of *TP53* mutations.[19,26] The distinction between focal and diffuse anaplasia is prognostically significant.[27]

Further correlations between histologic characteristics and clinical behavior vary according to whether the tumor specimen is taken before or after chemotherapy. In patients undergoing immediate nephrectomy, blastemal-rich tumors are typically invasive and present at an advanced stage; there is not a strong correlation with outcome when correcting for stage.[28] In patients undergoing preoperative chemotherapy, blastemal subtype has a clear correlation with adverse outcome, suggesting that residual blastemal cells that persist after chemotherapy represent a treatment-resistant population.[29] Tumors that contain predominantly well-differentiated cells, either epithelial or stromal (rhabdomyomatous), are more likely to present at a low stage and not exhibit much size reduction with chemotherapy, though the prognosis is favorable.[29] Analysis of the cohort of young children with small stage I intrarenal tumors assigned no adjuvant chemotherapy provides further support for the excellent prognosis of epithelial-differentiated Wilms' tumors.[30] Although much of the past success of the NWTS has relied on accurate histologic subclassification of Wilms' tumors to define high-risk and low-risk subtypes, further risk classification is likely to depend on molecular genetic features.

The existence of precursor lesions (nephrogenic rests) is rather common. These lesions consist of abnormally persistent intrarenal embryonal nephroblastic tissue with small clusters of blastemal cells, tubules, or stromal cells. Nephrogenic rests can be subclassified by their positions within the kidney and histologic appearance: perilobar nephrogenic rests are limited to the periphery of the renal cortex, and intralobar nephrogenic rests occur randomly throughout the renal lobe. Nephroblastomatosis refers to the presence of multiple nephrogenic rests typically throughout the kidney. There are several possible fates for nephrogenic rests: most become dormant or involute spontaneously; only a small number develop clonal transformation into Wilms' tumor. The presence of nephrogenic rests within a kidney resected for Wilms' tumor indicates the need for monitoring the contralateral kidney for tumor development, particularly in young infants.[31]

The other major cellular types of kidney tumors are outlined in Table 70-1, including:

1. Mesoblastic nephroma (1% to 2% of pediatric renal tumors). This is the most common renal tumor encountered in the first month of life; the median age at presentation is 3 months. Hypercalcemia may be present. Local recurrence is rare after surgery alone; distant metastases are similarly uncommon. Survival rates are excellent after surgery alone.[32]
2. Clear cell sarcoma (2% to 3%). Once considered a Wilms' tumor variant, this tumor is now recognized as a separate entity. The tumor cells have poorly stained cytoplasm with cytoplasmic vacuolations (see Figure 70-1, *E*). Bone and brain metastases, rare in the other tumor types, are common in CCSK.[25,33]
3. RTK or malignant rhabdoid tumor (2%). This rare but extremely aggressive neoplasm predominantly affects

TABLE 70-1 Relapse Patterns in Patients without Metastases at Diagnosis*

Site†	FH	Ana	CCSK	RTK	MN	RCC
Lung	66	40	19	54	—	50
Liver	10	20	4	12	—	—
Bone	1	4	50	4	—	33
Brain	—	—	19	12	—	—
Flank/abdomen	18	48	8	50	4	—
Kidney	10	—	—	—	—	—
Other	11	12	15	15	—	33

Adapted from D'Angio GJ, Rosenberg H, Sharples, K, et al: Imaging methods for primary renal tumors at childhood. Costs versus benefits. Med Pediatr Oncol 21:205–212, 1993.

Ana, *Anaplasia;* CCSK, *clear cell sarcoma of the kidney;* FH, *favorable histology;* MN, *mesoblastic nephroma;* RCC, *renal cell carcinoma;* RTK, *rhabdoid tumor of the kidney.*

**Percentage of all patients with relapse in column.*

†More than one site might have been involved.

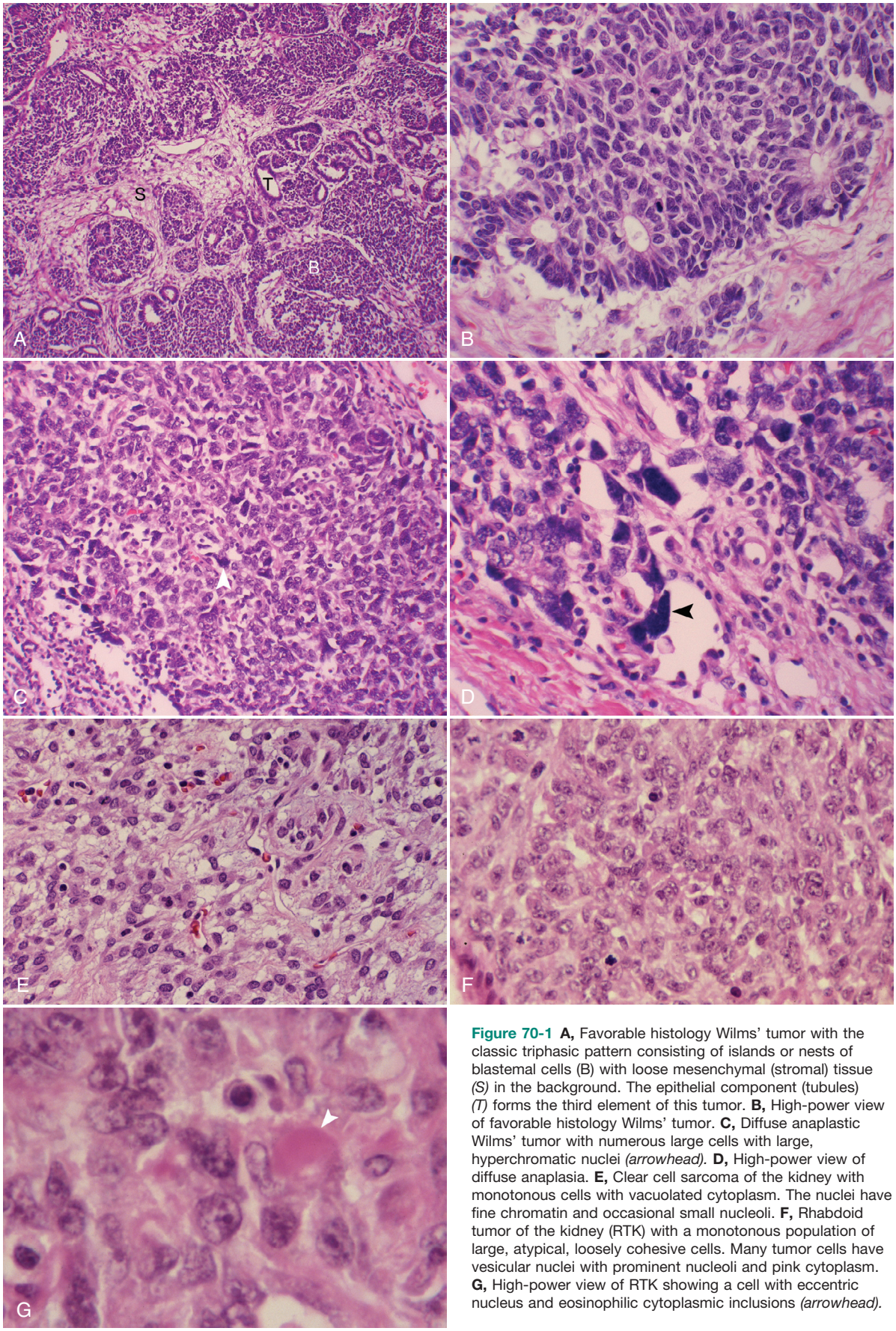


Figure 70-1 **A,** Favorable histology Wilms' tumor with the classic triphasic pattern consisting of islands or nests of blastemal cells (B) with loose mesenchymal (stromal) tissue *(S)* in the background. The epithelial component (tubules) *(T)* forms the third element of this tumor. **B,** High-power view of favorable histology Wilms' tumor. **C,** Diffuse anaplastic Wilms' tumor with numerous large cells with large, hyperchromatic nuclei *(arrowhead).* **D,** High-power view of diffuse anaplasia. **E,** Clear cell sarcoma of the kidney with monotonous cells with vacuolated cytoplasm. The nuclei have fine chromatin and occasional small nucleoli. **F,** Rhabdoid tumor of the kidney (RTK) with a monotonous population of large, atypical, loosely cohesive cells. Many tumor cells have vesicular nuclei with prominent nucleoli and pink cytoplasm. **G,** High-power view of RTK showing a cell with eccentric nucleus and eosinophilic cytoplasmic inclusions *(arrowhead).*

infants, in whom hypercalcemia may be present. Rhabdoid cells are characterized by eosinophilic cytoplasm that contains hyaline globular inclusions (see Figure 70-1, *F, G*). Metastases to the lung and intraabdominal relapses are frequent.[25]

4. Renal cell carcinoma (RCC) (5% to 8%). This type of carcinoma was not traditionally studied by the NWTS but is included in current COG studies. Pediatric RCCs are typically identified as the translocation subtypes (papillary, renal medullary, and oncocytic renal cell histiotypes), which are characterized by translocations typically involving the *TFE3* or *TFEB* genes. It is not clear that these subtypes respond to the same therapies (immunotherapies, tyrosine kinase/antiangiogenesis inhibitors, and mTOR pathway inhibitors) that have efficacy in the more classic clear cell subtype seen in the adult population. Its patterns of spread do mimic the adult counterpart (i.e., the lungs, lymph nodes, and bone).

CLINICAL MANIFESTATIONS, PATIENT EVALUATIONS, AND STAGING

Children with Wilms' tumor typically show no tumor-specific symptoms. The most common presentation is with an asymptomatic abdominal mass, although about 33% of patients present with abdominal pain, anorexia, vomiting, malaise, or a combination of these symptoms. Physical examination reveals hypertension in about 25% of patients and congenital anomalies (aniridia, genitourinary malformations, hemihypertrophy, or signs of overgrowth) in 13% to 28% of children, higher in those with bilateral disease. Up to 30% of patients have hematuria; fewer than 10% have coagulopathy.

Laboratory evaluation after physical examination should include a complete blood cell count, routine hepatic and renal chemistries, and urinalysis, noting the presence or absence of urinary protein and white or red blood cells. Imaging studies before surgery are designed to evaluate the extent of the renal mass and differentiate primary intrarenal tumors from neuroblastoma (most often arising from the adjacent suprarenal gland or retroperitoneal structures), the presence of a normally functioning, morphologically normal contralateral kidney, the presence of a patent renal vein and inferior vena cava (i.e., free from thrombosis, most often tumor thrombosis when seen), and the presence or absence of metastases in the lungs. Diagnostic imaging studies include abdominal ultrasonography (particularly useful in the detection of tumor thrombosis) and CT or MRI of the abdomen (Figure 70-2). A chest CT scan should be used to detect lung metastasis. The clinical significance of metastatic tumors detected by chest CT but not on chest radiographs remains unclear, although evidence is increasing that some of these patients do not fare well with chemotherapy with vincristine and dactinomycin alone.[34,35] MRI of the abdomen can help to distinguish between nephrogenic rests and Wilms' tumor.[36] Postoperatively, when the histology is established, a bone scan and brain MRI should be obtained for all patients with CCSK, RTK, and patients with RCC if they have symptoms to suggest bone or brain involvement.

Staging

Wilms' tumors are staged on the basis of anatomic tumor extent; therapy is currently based on stage and histology.[31] Classifications based on tumor extent have evolved over the years. After analysis of the prognostic significance of several clinicopathologic factors in NWTS-1 and NWTS-2, an NWTS staging system has been in use from NWTS-3 onward. Patients

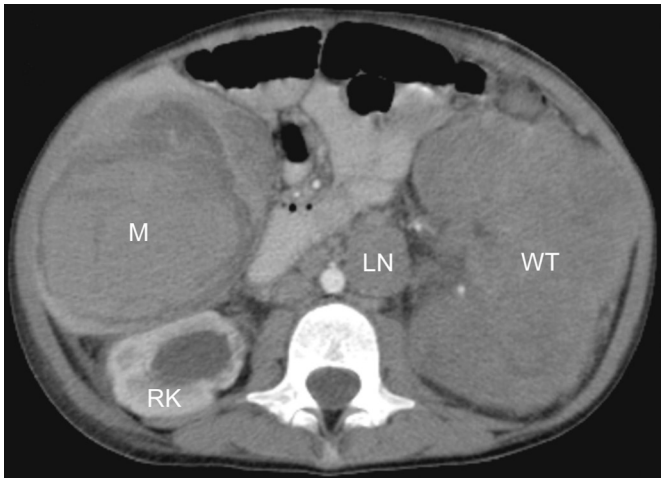


Figure 70-2 Abdominal computed tomography scan of a 4-year-old girl with a large left-sided Wilms' tumor *(WT)* measuring 10.5 × 11 × 17 cm. The right kidney *(RK)* did not show any lesions. There were multiple enlarged paraaortic lymph nodes *(LN)* and liver metastases *(M)*.

with lymph node involvement, previously included with stage II disease, are now classified as having stage III disease, and those with local tumor spill were moved from stage III to stage II disease.[37] Refinements to the inclusion criteria for stages I and II disease were introduced in the NWTS-5 study. Criteria for stage I were refined to accommodate an important subset of Wilms' tumor currently managed by nephrectomy alone. Before NWTS-5, the distinction between stages I and II in the renal sinus was established by the hilar plane, which was an imaginary plane connecting the most medial aspects of the upper and lower poles of the kidney. This criterion was difficult to apply because of tumor distortion, and thus the hilar plane criterion has been replaced with renal sinus vascular or lymphatic invasion. The latter definition includes not only the involvement of vessels within the hilar soft tissue but also vessels located in the radial extensions of the renal sinus into the renal parenchyma.[38]

The current COG staging guidelines for Wilms' tumor are shown in Table 70-2. These guidelines are essentially similar to those for NWTS-5 except for the fact that children with tumor spillage are upstaged from stage II to stage III because of the higher risk for relapse in these patients when treated with two-drug chemotherapy without RT.[39]

PRIMARY THERAPY

Primary surgical resection of Wilms' tumor remains the standard initial therapy undertaken in North America. A transabdominal transperitoneal approach is recommended to provide adequate exposure for complete locoregional staging.[40] This procedure includes biopsy of hilar and regional nodes (even if normal appearing), which remains a crucial factors in staging. Although suspicious lymph nodes are excised irrespective of location, a formal lymph node dissection is neither beneficial nor recommended.

Most Wilms' tumors that appear to involve contiguous structures actually only compress or adhere to the adjacent organs without invasion. Therefore, radical en bloc resection in these tumors, which is associated with increased surgical complications, can be avoided. However, wedge resection of infiltrated structures such as the diaphragm, liver, or psoas muscle can be undertaken if all disease can be completely removed with little operative morbidity. This procedure is advantageous because the tumor can be downstaged to stage

TABLE 70-2 Children's Oncology Group Staging of Wilms' Tumor (2010)

Stage	Description
I	Tumor limited to kidney, completely resected. The renal capsule is intact. The tumor was not ruptured or sampled before removal. The vessels of the renal sinus are not involved. There is no evidence of tumor at or beyond the margins of resection.*
II	The tumor is completely resected and there is no evidence of tumor at or beyond the margins of resection. The tumor extends beyond kidney, as is evidenced by any one of the following criteria†: • There is regional extension of the tumor (i.e., penetration of the renal capsule or extensive invasion of the soft tissue of the renal sinus). • Blood vessels within the nephrectomy specimen outside the renal parenchyma, including those of the renal sinus, contain tumor.
III	Residual nonhematogenous tumor present after surgery and confined to abdomen. Any one of the following may occur: • Lymph nodes within the abdomen or pelvis are involved by tumor.‡ • The tumor has penetrated through the peritoneal surface. • Tumor implants are found on the peritoneal surface. • Gross or microscopic tumor remains postoperatively (e.g., tumor cells are found at the margin of surgical resection on microscopic examination). • The tumor is not completely resectable because of local infiltration into vital structures. • Tumor spillage occurred either before or during surgery. • The tumor was sampled (whether Tru-Cut, open, or fine needle aspiration) before removal. • Tumor is removed in more than one piece (e.g., tumor cells are found in a separately excised adrenal gland; a tumor thrombus within the renal vein is removed separately from the nephrectomy specimen).
IV	Hematogenous metastases (e.g., lung, liver, bone, brain), or lymph node metastases outside the abdominopelvic region are present. (The presence of tumor within the adrenal gland is not interpreted as metastasis and staging depends on all other staging parameters present.)
V	Bilateral renal involvement by tumor is present at diagnosis. An attempt should be made to stage each side according to the above criteria on the basis of the extent of disease.

**For a tumor to qualify for certain therapeutic protocols as stage I, regional lymph nodes must be examined microscopically.*
†Rupture or spillage confined to the flank, including biopsy of the tumor, is no longer included in stage II and is now included in stage III.
‡Lymph node involvement in the thorax or other extraabdominal sites is a criterion for stage IV.

II and subsequent therapy reduced. Tumor extension into the renal vein and proximate inferior vena cava can, in most cases, be removed en bloc with the kidney. However, primary resection of extension into the inferior vena cava to the hepatic level or into the atrium is associated with higher operative morbidity. In these circumstances, preoperative chemotherapy decreases the size and extent of the tumor thrombus, facilitating subsequent excision.

Tumor spillage remains an important concept in the surgery of Wilms' tumor. Surgeons must be aware of any tumor-capsule violation with contamination of the peritoneal cavity during resection. The accurate assessment of a local spill from diffuse contamination is difficult; peritoneal contamination definitely increases the risk for local and abdominal recurrence, and both localized and diffuse peritoneal spill (or preoperative tumor rupture) are now considered stage III disease.[40]

Some tumors are initially judged to be unresectable or to pose too great a surgical risk because of massive size. In these cases, preoperative chemotherapy results in reduction of the tumor mass and generally renders it resectable.

RADIATION THERAPY

Flank and Abdominal Irradiation

RT continues to play an important role in the management of Wilms' tumor. Successive NWTS trials have refined the indications for RT. In NWTS-1 and NWTS-2, an age-adjusted dose schedule was used for flank irradiation, ranging from 18 Gy to 24 Gy for children younger than 18 months to 35 Gy to 40 Gy for children older than 40 months. The abdominal relapse rate was 3% to 5% for groups II and III tumors, and there was no dose-response relationship observed across these dose ranges.[41,42] NWTS-3 proved that RT could be avoided in children with stage II tumors if vincristine and dactinomycin were both given. This study also showed that children with stage III favorable histology tumors who received 10.8 Gy and vincristine, dactinomycin, and doxorubicin had tumor control similar to that of those who received 20 Gy with vincristine and dactinomycin. This was an important finding because it eliminated the need for an age-adjusted dose schedule and significantly reduced the recommended radiation dose.[43]

NWTS-1, NWTS-2, and NWTS-3 showed that delay in initiating RT beyond 10 days was correlated with poor outcome primarily in cases with unfavorable histology.[41-43] A study of the impact of RT delay on patients with favorable histology in NWTS-3 and NWTS-4 showed that a delay of more than 10 days did not significantly influence flank or abdominal tumor recurrence rates. It is currently recommended for children requiring RT that it be initiated without undue delay (within 14 days of nephrectomy) to eliminate abdominal recurrence as a variable in the analyses of outcomes in future Wilms' tumor trials.[44]

The NWTS evaluated the frequency with which tumor spill of favorable histology produced intraabdominal recurrence in NWTS-3 and NWTS-4. Flank irradiation but not doxorubicin reduced abdominal relapse rates. The odds ratio for the risk of recurrence was 0.35 for 10 Gy and 0.08 for 20 Gy when compared with those with no radiation therapy. Tumor spillage resulted in higher relapse and significantly lower survival among patients with stage II disease in NWTS-4 (i.e., those without RT). The 8-year relapse-free survival with and without spillage were 79% and 87% ($p = 0.07$), and overall survival rates were 90% and 95% ($p = 0.04$), respectively.[39]

Although diffuse anaplastic tumors are relatively resistant to chemotherapy, and presumably relatively resistant to RT, these tumors have not shown a radiation dose response between 10.8 Gy and 40 Gy.[45] The optimum radiation dose for anaplastic Wilms' tumor and other unfavorable histology tumors remains unknown. In NWTS-5, children with stage I focal and diffuse anaplasia were treated with two-drug chemotherapy (vincristine and dactinomycin) alone without flank irradiation; the approach resulted in a poor survival rate.[46] The current COG study recommends flank irradiation (10.8 Gy) with three-drug chemotherapy for these tumors. The survival

rates for children with stage III diffuse anaplastic tumors and rhabdoid tumors continue to be poor (Table 70-3). The COG study will test the value of a higher dose of irradiation (19.8 Gy) together with intensified chemotherapy (Tables 70-4 and 70-5). The COG protocol will also prospectively study whether flank irradiation could be avoided in children with stage I CCSK who have undergone lymph node sampling and central pathology review (see Tables 70-4 and 70-5).

Whole-Lung Irradiation

In children with lung metastases detected on chest radiographs, whole-lung irradiation (WLI) results in high cure rates. In NWTS-3, the 4-year relapse-free survival and overall survival were 72% and 78%, respectively, in children with favorable histology Wilms' tumor and lung metastases.[47] These results are superior to the survival rates reported by investigators from the United Kingdom Children's Cancer Study Group (UKCCSG) study in which all patients did not receive WLI.[48] In children with pulmonary metastases visible on CT but not chest radiographs, the role of WLI is unclear. In such patients treated on NWTS-3 and NWTS-4, the 4-year, event-free survival with WLI was 89% compared with 80% with chemotherapy alone, a difference that was not statistically significant.[49] The current COG protocol recommends WLI based on the response of pulmonary metastatic lesions to one course of chemotherapy with vincristine, dactinomycin, and doxorubicin. Central radiology review of chest CT will be performed before and at week 6 after chemotherapy. WLI will be omitted only in patients with favorable histology tumors with no LOH at 1p and 16q and those who have achieved a complete response to chemotherapy on chest CT central radiology review at week 6. All other children will receive WLI (12 Gy).

The current RT recommendations of the COG Renal Tumors Committee are shown in Table 70-4. There are several differences in the current COG recommendations compared with those from NWTS-5: (1) patients with local tumor spillage are upstaged to stage III and will receive flank RT; (2) patients with stage I focal and diffuse anaplastic tumors will receive flank RT; (3) the radiation dose for children with stage III diffuse anaplasia and stage I to III RTK will be increased to 19.8 Gy; and (4), in an effort to study if irradiation could be omitted in stage I CCSK, patients who have undergone nodal sampling and central pathology review will not receive flank RT.

TABLE 70-3 Long-Term Results of National Wilms' Tumor Studies 3 and 4

Stage/Histology	No. Patients	10-Year Relapse-Free Survival (%)	10-Year Overall Survival (%)
Stage I FH	1582	91.4	96.6
Stage II FH	1006	85.5	93.4
Stage III FH	1038	84.2	89.5
Stage IV FH	592	75.2	80.7
Stage V FH	344	65.1	77.9
All FH	4562	84.4	90.8
Clear cell sarcoma	170	67.1	77.1
Stages II-III anaplasia	128	43.0	49.2
Stage IV anaplasia	55	18.2	18.2
Rhabdoid tumor	88	27.3	28.4

FH, *Favorable histology.*

Intensity-Modulated Radiation Therapy for Wilms Tumor

Like in other pediatric tumors, RT techniques used in Wilms' tumor continue to be critically examined. Lung and mediastinal irradiation with or without doxorubicin have resulted in a higher incidence of cardiac complications such as congestive heart failure (CHF), myocardial infarction, pericardial disease, and valvular heart disease in childhood cancer survivors.[50-52] The demonstration of a threshold dose (>5 Gy) for cardiac mortality highlights the importance of delivering a lower dose to the heart.[52] Dosimetry studies have shown several advantages for the use of whole-lung IMRT over standard anteroposterior/posterior-anterior (AP/PA) techniques. They

TABLE 70-4 Radiation Therapy Recommendations for the Children's Oncology Group Renal Tumor Protocols

Tumor Stage/Histology	RT Dose and Fields
Stages I and II FH	No RT
Stage III FH, stages I-III focal anaplasia, stages I-II diffuse anaplasia, stages I-III CCSK‡	10.8 Gy flank* RT†
Stage III diffuse anaplasia, stages I-III RTK	19.8 Gy (infants 10.8 Gy) flank* RT†
Stage IV (lung metastases, FH)	12 Gy (whole-lung irradiation in children who are not in complete remission at week 6 after induction chemotherapy)
Stage IV (lung metastases, UH)	12 Gy whole-lung irradiation regardless of chemotherapy response
Stage IV (liver metastases)	No RT if resected before chemotherapy, all others 19.8 Gy
Stage IV (brain metastases)	21.6 Gy (whole brain) + 10.6 Gy (local boost) or whole brain 30.6 Gy
Stage IV (bone metastases)	25.2 Gy (tumor + 3-cm margin)
Lymph node metastases not surgically resected	19.8 Gy
Relapsed Wilms' tumor (flank/abdomen)	12.6 Gy to 18 Gy (<age 12 mo) and 21.6 Gy in older children if previous radiation dose is ≤10.8 Gy 9-Gy boost to gross residual tumor after surgery

CCSK, *Clear-cell sarcomas of the kidney;* FH, *favorable histology;* RTK, *rhabdoid tumors of the kidney;* UH, *unfavorable histology.*

**Whole-abdomen irradiation is indicated when there is diffuse tumor spillage, intraperitoneal tumor rupture, peritoneal tumor seeding, and cytology-positive ascites. When dose is >10.8 Gy, renal shielding is required to limit the dose to the remaining kidney to <15 Gy.*

†*A boost of 10.8 Gy is to be administered to areas of gross residual tumor after surgery.*

‡*Patients with stage I CCSK will not receive flank irradiation if lymph node sampling and central pathologic review were performed.*

TABLE 70-5 Children's Oncology Group Renal Tumor Protocol Schema

Tumor Risk Classification	Multimodality Treatment
Very low-risk favorable histology Wilms' tumor: <2 years, stage I FH, tumor weight <550 g	Nephrectomy without adjuvant therapy, only if central pathology review and lymph node sampling has been performed
Low-risk favorable histology Wilms' tumor: ≥2 years, stage I FH, tumor weight ≥550 g, stage II FH without LOH of 1p and 16q	Nephrectomy, no RT, regimen EE4A
Stages I and II FH with LOH of 1p and 16q	Nephrectomy, regimen DD4A
Stage III FH without LOH of 1p and 16q	Nephrectomy, RT, regimen DD4A
Stages III and IV FH with LOH of 1p and 16q, stage IV FH slow/incomplete responders	Nephrectomy, RT, regimen M, whole-lung irradiation
Stage IV FH: complete resolution of lung metastases at week 6 with regimen DD4A (rapid early responders)	Nephrectomy, RT, regimen DD4A. No whole-lung irradiation
Stages I-III focal anaplasia Stages I diffuse anaplasia	Nephrectomy, RT, regimen DD4A
Stage IV focal anaplasia Stages II-IV diffuse anaplasia Stage IV CCSK Stages I-IV RTK	Nephrectomy, RT, regimen UH1
Stages I-III CCSK	Nephrectomy, RT, regimen I (RT omitted for stage I)

CCSK, *Clear cell sarcoma of kidney;* FH, *favorable histology;* LOH, *loss of heterozygosity;* RT, *radiation therapy;* RTK, *rhabdoid tumor of kidney.*
Regimens: DD4A: vincristine/dactinomycin/doxorubicin; EE4A: vincristine/dactinomycin; I: vincristine/doxorubicin/cyclophosphamide, cyclophosphamide/etoposide; M: vincristine/dactinomycin/doxorubicin, cyclophosphamide/etoposide; UH1: cyclophosphamide/carboplatin/etoposide, vincristine/doxorubicin/cyclophosphamide.

include superior cardiac protection, superior four-dimensional (4D) lung planning target volume (PTV) dose coverage, and superior dose-uniformity in the lungs with fewer hot spots.[53] Another report has shown that compared to standard AP-PA techniques, the use of whole liver IMRT was associated with superior 4D liver dose coverage and delivered a lower dose to the remaining solitary kidney.[54] Another important finding of these reports is the importance of using 4D simulation to accurately determine the internal target volume (ITV) of the lung and liver after consideration for maximal organ movement during respiration. A National Institutes of Health (NIH)–funded multicenter feasibility study of whole-lung IMRT has recently been completed. If feasible, whole-lung IMRT with 4D planning may replace standard techniques as the new standard of care.

CHEMOTHERAPY

Chemotherapy and Combined-Modality Treatment

Single-agent chemotherapy has been used for Wilms' tumor since the 1950s, when both dactinomycin and vincristine were found to be active. The interplay between relatively more aggressive chemotherapy and locoregional irradiation was tested in the initial NWTS studies. NWTS-1 showed that RT conferred no advantage in children younger than age 24 months with group I tumors who also received 15 months of dactinomycin.[55] NWTS-2 showed that RT could be avoided in all children with group I Wilms' tumor if they received both vincristine and dactinomycin.[56] The results of NWTS-3 showed that stage II tumors required only vincristine and dactinomycin without any RT. NWTS-3 also demonstrated an interaction between chemotherapy and RT: 10.8 Gy with three drugs (vincristine, dactinomycin, doxorubicin) was equivalent to 20 Gy with two drugs (vincristine, dactinomycin).[47] In NWTS-4, two questions were posed concerning duration of chemotherapy (6 months versus 15 months) and the delivery of dactinomycin and doxorubicin (pulse-intensive, single-dose versus 5-day course of dactinomycin or 3-day course of doxorubicin). Results showed no advantage to prolonged therapy or divided doses, which actually proved to be more toxic; the consolidated 2-year, relapse-free rate and survival results were 90% and 97%, respectively, for the patients with low- and high-risk disease (see Table 70-3). Thus, the shorter courses of the pulse-intensive regimens are now considered standard, reducing both clinic time and cost for both parents and staff.[57] NWTS-5 asked whether young patients younger than 24 months old with stage I favorable histology Wilms' tumor weighing less than 550 grams could be treated with nephrectomy only without adjuvant chemotherapy. The study was stopped early because the number of relapses observed exceeded the predefined stopping rule. However, nearly all patients with relapse were successfully treated, leading to 5-year event-free and overall survival rates of 84% and 98%, respectively.[58,59] Based on the outstanding overall survival, the question of omitting adjuvant therapy was readdressed in the recent COG studies.

Anaplastic Histology

The first NWTS trial to stratify patients with anaplastic Wilms' tumor into a distinct treatment group was NWTS-3. Both NWTS-3 and NWTS-4 called for 15 months of vincristine, dactinomycin, and doxorubicin, with randomization to receive cyclophosphamide or not. Patients with stages II to IV diffuse anaplastic tumors who were treated with cyclophosphamide had significant improvement in 4-year relapse-free survival (27% versus 55%)[45] (see Table 70-3). Patients with all stages of focal anaplastic histology or stage-I diffuse anaplastic histology had excellent outcomes, regardless of treatment regimen. Based on these results, patients with anaplastic histology were treated in prospective single-arm studies in NWTS-5. Patients with stage-I anaplastic tumors were treated with vincristine and dactinomycin for 18 weeks without RT. Patients with stages II to IV diffuse anaplastic histology were treated with vincristine, doxorubicin, cyclophosphamide, and etoposide for 24 weeks plus flank and abdominal RT. Among 2596 patients with Wilms' tumor enrolled in NWTS-5, 281 (10.8%) had anaplastic histology. The 4-year event-free and overall survival rates for stage-I anaplastic histology tumors were 70% and 83%, respectively. These results were less satisfactory

than expected and clearly inferior to results with stage-I favorable histology tumors. Therefore, the recent COG study augmented therapy for this group of patients to include doxorubicin and flank radiation. The 4-year event-free and overall survival in stages II, III, and IV diffuse anaplastic tumors after immediate operative chemotherapy and RT were 83% and 82%, 65% and 67%, and 33% and 33%, respectively.[46] These results were improved compared to historical standards and form the basis for the most COG study that recommended further augmentation of therapy for stages II to IV diffuse anaplastic tumors using a treatment regimen containing cyclophosphamide, carboplatin, and etoposide alternating with vincristine, doxorubicin, and cyclophosphamide (see Table 70-5). The study recently closed and the results have not yet been reported.

Clear Cell Sarcoma of the Kidney

Data from NWTS-1 to NWTS-4 suggested that the addition of doxorubicin to vincristine and dactinomycin improved relapse-free survival rates of patients with CCSK.[60,61] NWTS-3 demonstrated no improvement in outcomes of patients with CCSK with the addition of cyclophosphamide, though the cyclophosphamide was administered at a lower dose-intensity than is commonly employed in more recent treatment regimens.[47] NWTS-4 included a double-randomization that evaluated the effect of "pulse-intensive" dactinomycin and doxorubicin given over 1 day instead of 3 to 5 days (first randomization) and of total duration of therapy (second randomization). In patients with CCSK there was no significant difference in outcome between the standard and pulse-intensive chemotherapy regimens. However, there was a trend toward improved relapse-free survival with long duration therapy (additional 9 months) compared to standard chemotherapy with 8-year relapse free survival estimates of 88% and 61%, respectively ($p = 0.08$). However, there was no difference in overall survival, with 8-year overall survival estimates of 88% and 86% for the long- and short-duration therapy.[62] A group of patients with CCSK that fares particularly well are those with stage-I disease. A recent analysis of patients enrolled on NWTS 1-5 with stage I CCSK based on the updated NWTS-5 definition of stage I disease showed that regardless of treatment regimen, the event-free and overall survival rates were 100%.[63]

Preliminary analysis of NWTS-5 has shown promising results with the new chemotherapy regimen (vincristine, doxorubicin, cyclophosphamide, and etoposide) and RT except for patients with stage IV disease (NWTS, unpublished data). Based on these results, the recent COG study used the same regimen as in NWTS-5 for stages I-III disease, except that RT was omitted for patients with stage I disease. Patients with stage IV CCSK were treated with cyclophosphamide, carboplatin, and etoposide alternating with vincristine, doxorubicin, and cyclophosphamide, similar to patients with diffuse anaplastic Wilms' tumor (see Table 70-5).

Rhabdoid Tumor of the Kidney

Patients with RTK have been treated on NWTS trials with agents such as vincristine, dactinomycin, and doxorubicin with or without cyclophosphamide. The outcomes attained with these agents have been consistently very poor[47,64,65] (see Table 70-3). To try to improve on these results, NWTS-5 adopted a different treatment strategy consisting of carboplatin and etoposide alternating with cyclophosphamide. Preliminary analysis of patients treated with this regimen revealed an overall survival of 26%, not an improvement compared with previous studies, and thus the treatment arm was closed.[65]

The recent COG protocol evaluated whether a treatment regimen containing cyclophosphamide, carboplatin, and etoposide alternating with vincristine, doxorubicin, and cyclophosphamide improves the event-free and overall survival in these patients. The results have not yet been reported.

TREATMENT RESULTS

Treatment results are outlined in Table 70-3.

IRRADIATION TECHNIQUES

Parallel-opposed (AP/PA) treatment portals using 4-MV or 6-MV photons are recommended for flank, whole-abdomen, and whole-lung irradiation. The details regarding the planning techniques and setup for conventional RT are shown and described in Figures 70-3 to 70-5. If the lungs and either flank or abdomen have to be treated simultaneously, it is preferred that they be included as one radiation volume. However, if these two sites have to be treated sequentially, appropriate field gap calculations should be used for field matching, to avoid overlap, particularly over critical structures such as the liver and kidney.

CURRENT CLINICAL RECOMMENDATIONS

Based on the results of NWTS-5, the new COG renal tumor protocol will use LOH at both 1p and 16q in addition to tumor stage and pathologic classification for defining tumor-risk groups and assigning risk-adapted therapy (see Table 70-5). The goals of therapy in the COG study are to reduce the incidence of treatment-related morbidity in low-risk groups who have good survival rates and increase treatment intensity in high-risk tumors to improve cure rates.

OTHER STUDIES

In addition to the NWTSG, there have been randomized studies in SIOP, typically built on preoperative therapy (chemotherapy and, in defined instances, RT),[4,66-68] and the UKCCSG.[48,69]

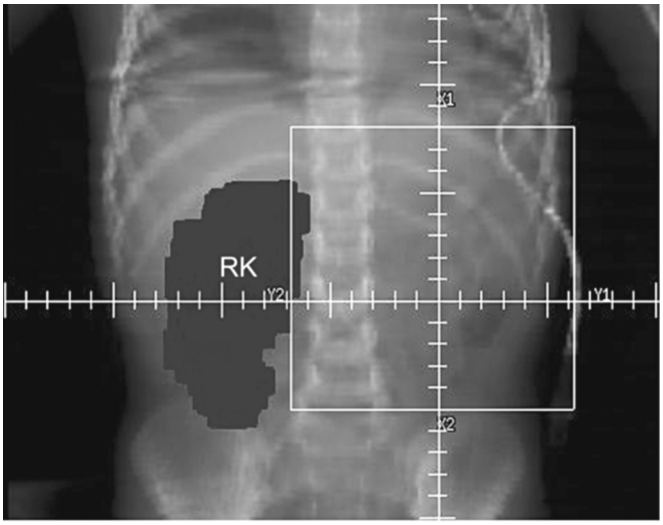


Figure 70-3 Anteroposterior left flank irradiation portal in a child with a stage-III favorable histology Wilms' tumor. The superior and inferior field margins are placed approximately 1 cm from the preoperative renal tumor volume. The medial field margin should include the entire width of the vertebral body to irradiate the lymph nodes and avoid scoliosis. The outline of the normal right kidney (RK) is shown.

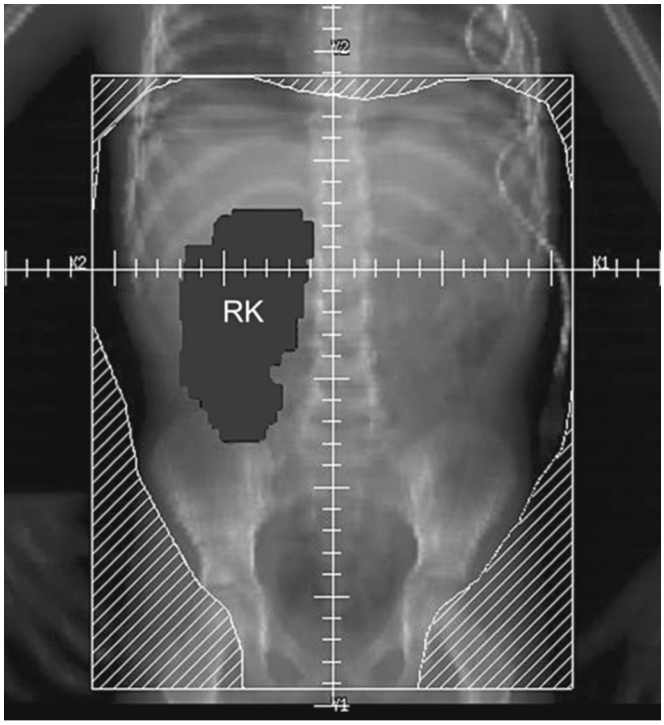


Figure 70-4 Anteroposterior whole-abdomen irradiation portal. The upper margin of the abdominal field must include the diaphragm. The acetabulum and femoral head should be excluded from the irradiated volume to decrease the probability of slipped femoral epiphysis. The outline of the normal right kidney (RK) is shown.

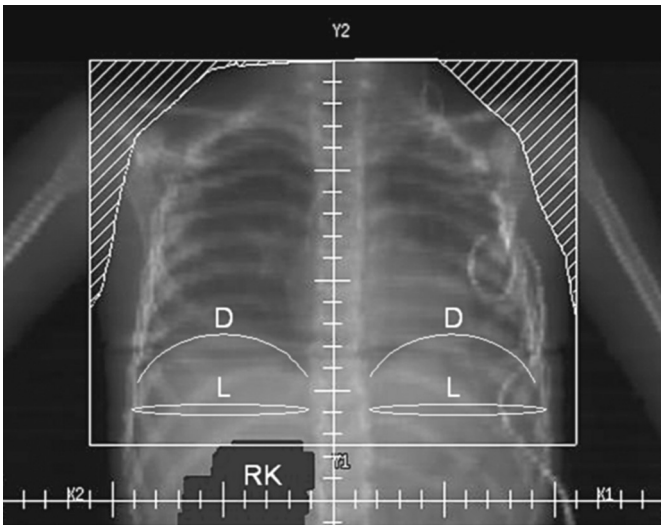


Figure 70-5 Anteroposterior whole-lung irradiation portal. The dome of the diaphragm *(D)* and the lower extent *(L)* of the costophrenic angles at the lung bases are shown. A lateral radiograph of the chest at the time of simulation or review of the sagittal and coronal images during computed tomography simulation is required to ascertain inclusion of the anterior and posterior costophrenic angles with a 1-cm margin at the inferior edge of the treatment volume. The outline of the normal right kidney *(RK)* is shown.

RETRIEVAL THERAPY

Children with relapsed favorable histology Wilms' tumor have a variable prognosis, depending on the site of relapse, the time from initial diagnosis to relapse, and previous therapy. Favorable prognostic factors include no previous treatment with doxorubicin, relapse more than 12 months after diagnosis, and intraabdominal relapse in a patient not previously treated with abdominal irradiation.[70-72] Patients with relapsed or progressive disease after initial chemotherapy with vincristine and dactinomycin and no RT were treated on a specific stratum in NWTS-5, consisting of alternating courses of vincristine, doxorubicin, cyclophosphamide, and etoposide and cyclophosphamide, plus surgery and RT. The 4-year event-free and overall survival was 71% and 81% for all patients, 68% and 81% for those who experienced relapse in the lung only, and 78% and 83% for those who had relapse in the operative bed with or without lung metastasis.[71] Patients who had experienced relapse or whose disease progressed after initial chemotherapy that included vincristine, dactinomycin, and doxorubicin plus RT were treated with alternating courses of drug pairs (cyclophosphamide and etoposide and carboplatin and etoposide), surgery, and RT. The 4-year event-free and overall survival was 42% and 48% for all patients and 49% and 53% for those who had relapse in the lung only.[72] In children who previously had not received RT, the recommended flank radiation dose is 12.6 Gy to 18 Gy (birth to 12 months) and 21.6 Gy (≥13 months). Supplemental boost fields could be added for gross residual disease (see Table 70-4). The COG protocol recommends postoperative irradiation for all children with abdominal relapse because these tumors are generally large and infiltrative and surgical resection with negative margins is unlikely.

LATE EFFECTS

As the follow-up of successfully treated children increases, data are increasingly emerging on the late consequences of treatment. The types of late sequelae and their severity depend on the age and sex of the child, extent of surgery, chemotherapy drugs, and irradiation-related factors. The most common cause for renal failure in patients with Wilms' tumors is bilateral nephrectomy, whereas the second leading cause is irradiation-induced damage or surgical complications affecting the remaining kidney. The frequency of renal failure in bilateral Wilms' tumor was 16.4% for NWTS-1 and NWTS-2, 9.9% for NWTS-3, and 3.8% for NWTS-4.[73] The incidence of scoliosis ranges from 40% to 60% with radiation doses of 25 Gy to 40 Gy. However, the rate of scoliosis should be low with the current doses of 10.8 Gy.[74,75] The cumulative frequency of CHF among patients on NWTS-1 to NWTS-4 was 4.4% at 20 years among patients treated initially with doxorubicin and 17.4% among patients treated with doxorubicin for first or subsequent relapse. Factors significantly associated with heart failure were female sex, cumulative doxorubicin dose, lung irradiation, and left-sided abdominal irradiation.[50] Women who are Wilms' tumor survivors have significantly higher rates of adverse pregnancy outcomes, such as malposition of the fetus and premature labor, with the incidence greatest after flank irradiation to doses higher than 25 Gy. Their offspring more often are premature and of low birth weight compared with control cohorts; a trend toward an increased number of congenital malformations has been noted after flank irradiation.[76,77] The cumulative 15-year risk of second malignant neoplasms was 1.6% among patients enrolled on the NWTS, after a mean follow-up of 7.5 years per patient. Higher doses of abdominal irradiation and doxorubicin increased the risk of another neoplasm.[78]

The standardized mortality ratio in an NWTS review was 24.3 within 5 years of diagnosis, 12.6 for the next 5 years, and more than 3.0 thereafter. The main cause of mortality within the first 5 years related to the original disease (91%). Beyond 5 years the mortality was equally related to the original disease (40%) and late effects of treatment (39%). The three most-common treatment-related effects contributing to mortality were second malignant neoplasms, CHF, and end-stage renal disease. The risk of death particularly from treatment-related late effects remained elevated even 20 years after diagnosis.[79]

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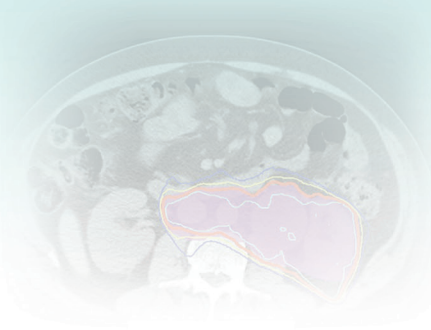
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CHAPTER

71 Retinoblastoma

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INCIDENCE

Retinoblastoma accounts for 2.5% to 4% of all pediatric malignancies. Its incidence is two to five cases per million children per year, and there are 300 new cases per year in the United States.

BIOLOGY

There are two forms of retinoblastoma:

1. Unilateral (75%), *RB1* somatic mutations
   sporadic (90%)
   inherited (familial) (10%)
2. Bilateral (25%), RB1 germline mutations
   sporadic (in utero new mutations) (75%)
   inherited (familial) (25%)

STAGING

The staging for retinoblastomas is based on intraocular grouping, which is based on intraocular tumor burden, site and size of lesions, and presence of vitrous seeding

Retinoblastoma also can be based on systemic staging:
Locoregional: Orbit, preauricular nodes
Central nervous system (CNS) dissemination
Extra CNS metastases

The treatment principles that need to be considered for retinoblastoma include tumor burden (group and stage), laterality (unilateral or bilateral), and visual potential.

The priorities in retinoblastoma are to save patient's life, eye salvage, and vision preservation.

It is important to offer patients multidisciplinary care at state-of-the-art treatment center, which includes ophthalmologic care, pediatric oncologic, care radiation oncologic care, cccupational therapy, and psychosocial therapy.

TREATMENT MODALITIES

Treatment modalities include various forms of chemotherapy, including focal treatments (cryotherapy, thermotherapy, photocoagulation, brachytherapy), external beam radiation therapy (EBRT), and enucleation.

INTRODUCTION

Retinoblastoma is the most-frequent neoplasm of the eye in childhood, representing 2.5% to 4% of all pediatric cancers. The average age-adjusted incidence rate of retinoblastoma in the United States and Europe is 2 to 5 per million children or approximately one in 14,000 to 18,000 live births.[1,2] Retinoblastoma is a cancer of the young; two thirds of all cases are diagnosed before 2 years of age, and 95% of cases are diagnosed before 5 years of age.[1]

Retinoblastoma presents in two distinct clinical/genetic forms: (1) a bilateral or multifocal form in 25% of presenting children, characterized by the presence of germline mutations of the *RB1* gene with documented familial history in 25% of cases or the result of a new (sporadic) germline mutation in 75%; or (2) a unilateral or unifocal form in 65% to 80% of presenting children, 90% of whom do not have a family history of retinoblastoma.

ETIOLOGY AND EPIDEMIOLOGY

The incidence of retinoblastoma is higher (6 to 10 cases per million children) in Africa, India, and among children of American Indian descent in North America. The increased incidence occurs primarily in unilateral cases. In industrialized countries, an increased incidence of retinoblastoma is associated with poverty and low levels of maternal education, suggesting a role for the environment.[3,4] Human papilloma viruses (HPV) have been implicated in the pathogenesis of retinoblastoma. The viral oncoprotein E7 of high-risk HPV types has been shown to bind to and inactivate the *RB1* gene product (pRB), acting functionally to create biallelic loss of *RB1*.[5,6] High-risk HPV sequences have been detected in 28% to 36% of tumors.[6]

BIOLOGY

In 1971, based on mathematical analysis of the age at presentation of bilateral (hereditary) and unilateral (mostly nonhereditary) cases of retinoblastoma, Knudson proposed the "two-hit hypothesis," in which two mutational events in a developing retinal cell lead to the development of retinoblastoma.[7] This hypothesis was subsequently extended to suggest that the two events could be mutations of both alleles of the *RB1* gene, located in chromosome 13q14 and identified in 1986.[8,9] Its product, pRb, is a key substrate for G1 cyclin-CDK complexes, which phosphorylate target gene products required for the transition of the cell through the G1 phase of the cell cycle. The active pRb functions as a tumor suppressor and is the major gatekeeper controlling this critical point in growth regulation. The lack of pRb or its inactivation will remove the pRb constraint on cell cycle control, with the consequence of deregulated cell proliferation. Biallelic loss of *RB1* function is required for tumor development; this loss is germline and somatic for patients with bilateral disease, and somatic in a single cell in patients with unilateral disease. The *RB1* gene is a large gene, containing 27 exons over about 200 kilobases of DNA, and in patients with familial disease, mutations have been described in almost every exon.[10] New germline mutations have an overwhelming preference for the paternal allele.[5] Penetrance of the trait is greater than 90%.[11] In both hereditary and nonhereditary retinoblastoma, the second tumorigenic event is usually chromosomal in nature, often as a result of mitotic recombination errors.[12] This second hit occurs at a

much higher frequency than the first hit and is more sensitive to environmental factors such as ionizing radiation, perhaps explaining the increased risk of radiation-induced malignancies in survivors of retinoblastoma.

Additional events are required for tumor progression. Approximately two thirds of tumors have *MDM4/MDM2* amplification leading to inactivation of the *p53* pathway.[13] Next-generation sequencing studies have shown up-regulation of the proto-oncogene *SYK* in a large proportion of cases.[14] Other genes and pathways are probably also involved; studies using comparative genomic hybridization have consistently shown chromosomal gains and amplifications at 6p and 1q, and losses at 16q1. Finally, a small proportion of tumors appear to develop in the context of normal *RB1;* amplification of *N-MYC* has been described in those cases.[15]

PREVENTION, EARLY DETECTION, AND GENETIC COUNSELING

The successful management of retinoblastoma depends on the ability to detect the disease while it is still intraocular. Disease stage correlates with delay in diagnosis.[16] In developing countries, late diagnosis is associated with orbital and metastatic disease.[17] Eye assessment is encouraged in all newborns and at subsequent health visits. The consensus guidelines by the American Academy of Pediatrics and Bright Futures for Pediatric Preventive Care include health supervision visits at birth and at 3 weeks to 5 weeks of life; at 1 months, 2 months, 4 months, 6 months, 9 months, and 12 months during the first year; at 15 months, 18 months, and 24 months during the second year; and at 30 months and 3 years, 4 years, and 5 years of life. Importantly, evaluation of vision and ocular health, including red reflex examination, is a component of each visit. Mass screening is being considered, especially where the tumor is common such as in parts of South America and Asia.

Retinoblastoma is a unique neoplasm in that the genetic form imparts a predisposition to developing tumor in an autosomal dominant fashion with almost complete penetrance (85% to 95%).[18] The majority of such children acquire the first mutation as a new germline mutation, with only 15% to 25% having a positive family history. However, some families display an inheritance pattern characterized by reduced penetrance and expressivity. Also, the *RB1* gene mutation can occur at a late stage of embryogenesis, resulting in a variable expression depending on the tissue, causing mosaicisms in 10% to 15% of the patients or their progenitors.[19] Recognizing the inheritance pattern and the existence of mosaicisms, the following familial risk estimates can be made[18]:

1. *Risk for offspring of survivors of retinoblastoma:*
    1. The risk of retinoblastoma arising in the offspring of survivors of bilateral disease is 45%.
    2. In patients with unilateral disease, the risk of retinoblastoma in offspring is 2.5%. (The estimate includes offspring of the 10% of patients with unilateral retinoblastoma with a positive family history in whom the risk is similar to that of bilateral cases, 45%.)
2. *Risk for siblings of patients with retinoblastoma:* In siblings of bilaterally affected children whose parents are also affected, the risk of retinoblastoma is 45%; if the sibling is unilaterally affected, the risk is 30%. Without a family history, the risk is 2% for siblings of bilateral cases and 1% for siblings of unilateral cases.

Genetic counseling is of the utmost importance to assist parents in understanding the genetic consequences of each form of retinoblastoma and to estimate the risk in relatives. With the refinement in methods of mutational analysis over the last decade, detection rates have increased to greater than 90%.[10]

PATHOLOGY AND PATHWAYS OF SPREAD

Macroscopically, retinoblastoma is soft and friable, tending to outgrow its blood supply with resultant necrosis and calcification. Dissemination within the vitreous and retina in the form of small, white nodules (seeds) is common, sometimes making it difficult to distinguish a multicentric primary from a disseminated tumor.[20] The microscopic appearance depends on the degree of differentiation. Undifferentiated retinoblastoma is composed of small, round, densely packed cells with hypochromatic nuclei and scant cytoplasm. Several degrees of photoreceptor differentiation have been described, characterized by distinctive cellular arrangements. Flexner-Wintersteiner rosettes (clusters of low columnar cells arranged around central lumens bounded by eosinophilic membranes analogous to the external membrane of the normal retina) seen in 70% of tumors are specific for retinoblastoma. Fleurettes (composed of larger cells with abundant eosinophilic cytoplasm arranged in a distinctive *fleur de lys* pattern) are less frequent; cells exhibit ultrastructural characteristics of photoreceptor differentiation. Well-differentiated tumors composed almost entirely of fleurettes have been called *retinomas or retinocytomas.* Ultrastructurally, retinoblastoma cells demonstrate photoreceptor differentiation with the presence of the 9-0 microtubule doublet pattern, abundant cytoplasmic microtubules, synaptic ribbons, and neurosecretory granules. In cases of disseminated disease, positive cone-rod homeobox-containing gene (CRX) staining may help differentiate retinoblastoma from other common small blue round cell malignancies of childhood.[21] Guidelines for processing and evaluation of the enucleated eye have been published.[22]

CLINICAL MANIFESTATIONS, PATIENT EVALUATION, AND STAGING

Retinoblastoma is a tumor of young children. Bilateral retinoblastoma presents at a younger age (usually before 1 year of age) than patients with unilateral disease (typically 1 year to 3 years).[18,23] Half of the cases of retinoblastoma diagnosed during the first year are bilateral, compared with fewer than 10% of those diagnosed after 1 year of age.

In more than 50% of cases, the presenting sign is leukocoria, sometimes first noticed after a flash photograph. Strabismus is the second-most common presenting sign, usually correlated with macular involvement. The differential diagnosis includes other childhood diseases that can present with leukocoria: persistent hyperplastic primary vitreous, retrolental fibrodysplasia, Coat's disease, congenital cataracts, toxocariasis, and toxoplasmosis.

Although most patients with bilateral retinoblastoma carry a germline mutation of the *RB1* gene, only 5% carry a deletion involving the 13q14 locus large enough to be detected by karyotype analysis. In those cases, retinoblastoma is part of a more complex syndrome resulting from the loss of additional genetic material. Patients with the 13q-syndrome are characterized by typical facial dysmorphic features, subtle skeletal abnormalities, and varying degrees of mental retardation and motor impairment.[24] The severity of deficits correlates with the size of the deletion; normal psychomotor development may be seen in patients in whom the deletion is restricted to the 13q14 band.

Trilateral retinoblastoma refers to the association of bilateral retinoblastoma with a typically asynchronous brain tumor.[25] The majority of tumors are pineal region primitive

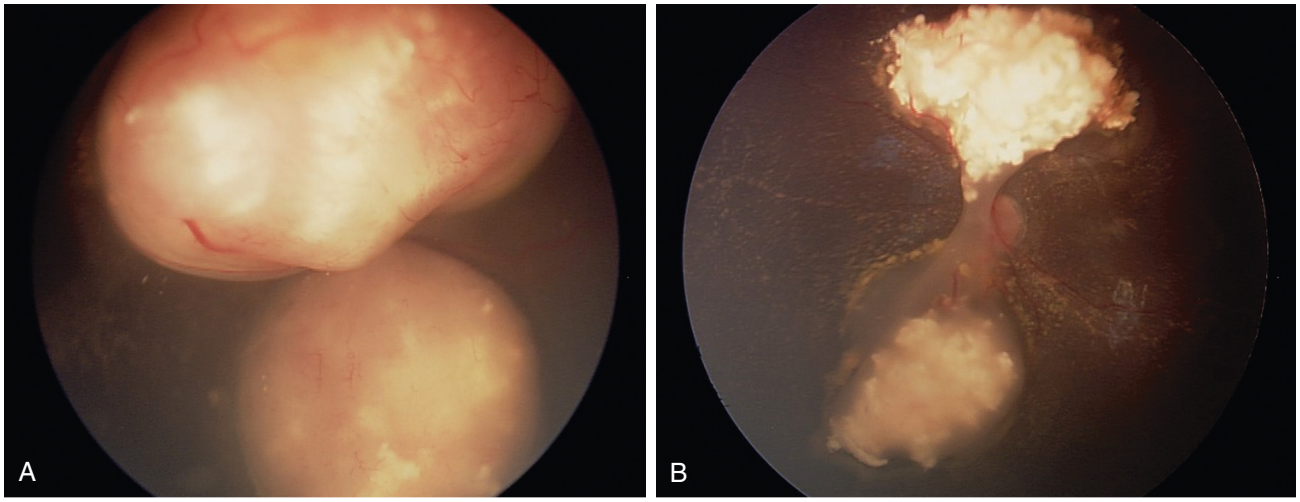


Figure 71-1 **A,** Advanced intraocular retinoblastoma in a patient with bilateral disease. **B,** Same eye after four cycles of chemotherapy.

neuroectodermal tumors PNETs (pineoblastomas); 20% to 25% of the tumors are suprasellar or parasellar. They exhibit varying degrees of neuronal or photoreceptor differentiation, suggesting an origin from the germinal layer of primitive cells. Trilateral disease occurs in 3% to 9% of patients with the genetic form of retinoblastoma and appears to be more common in familial cases. The prognosis until recently has been almost uniformly fatal. The median age at diagnosis of trilateral retinoblastoma is 23 months to 48 months; the interval between initial diagnosis of bilateral retinoblastoma and the diagnosis of the brain tumor is usually more than 20 months.[26] In recent years, with the more widespread use of chemotherapy for patients with bilateral retinoblastoma, the incidence of trilateral retinoblastoma appears to have decreased.[27] Approximately 5% of patients with bilateral disease develop pineal cysts; these appear to be a *forme fruste* of trilateral retinoblastoma.[28]

The diagnosis of intraocular retinoblastoma is usually made without pathologic confirmation. An examination under anesthesia with a maximally dilated pupil and scleral indentation is required to examine the entire retina (Figure 71-1). Endophytic tumors are those that grow inward to the vitreous cavity and may seed the vitreous cavity. Exophytic retinoblastoma grows into the subretinal space, causing progressive retinal detachment and subretinal seeding. A detailed documentation of the number, location and size of tumors, the presence of retinal detachment and subretinal fluid, and the presence of vitreous and subretinal seeds must be performed. Wide-angle real-time retinal imaging systems such as RetCam provide a 130-degree field of view and digital recording, facilitating diagnosis and follow-up.

Imaging studies that aid in diagnosis include bidimensional ultrasound, computerized tomography (CT), and magnetic resonance imaging (MRI); however, it is important to know that neuroimaging findings do not always correlate with pathology in terms of microscopic scleral or optic nerve involvement.[29] Imaging is particularly important to evaluate extraocular extension and to differentiate retinoblastoma from other causes of leukocoria. Evaluation for the presence of metastatic disease also needs to be considered in a subgroup of patients. Metastatic disease occurs in approximately 10% to 15% of patients, usually in association with advanced intraocular features, such as deep choroidal and scleral invasion, or involvement of the iris or ciliary body or the optic nerve beyond the lamina cribrosa.[30,31] In such cases, additional staging should include bone scintigraphy, bone marrow aspirate and biopsy, and lumbar puncture for cerebrospinal fluid (CSF) cytology.

TABLE 71-1 Reese-Ellsworth Grouping for Suitability for Treatment of Retinoblastoma by Radiation Therapy[32]

GROUP I. VERY FAVORABLE	
Ia	Solitary tumor smaller than 4 dd at or behind the equator
Ib	Multiple tumors, none larger than 4 dd, all at or behind equator
GROUP II. FAVORABLE	
IIa	Solitary tumor 4-10 dd, at or behind equator
IIb	Multiple tumors 4-10 dd, at or behind equator
GROUP III. DOUBTFUL	
IIIa	Any lesion anterior to equator
IIIb	Solitary tumor larger than 10 dd behind equator
GROUP IV. UNFAVORABLE	
IVa	Multiple tumors, some larger than 10 dd
IVb	Any lesion extending anteriorly to the ora serrata
GROUP V. VERY UNFAVORABLE	
Va	Massive tumors involving more than half the retina
Vb	Vitreous seeding

dd, *Disk diameter (1.5 mm).*

The Reese-Ellsworth (R-E) grouping system has been the standard for intraocular disease. The R-E system was designed to predict the outcome after EBRT. It divides eyes into five groups on the basis of the size, location and number of lesions, and presence of vitreous seeding (Table 71-1).[32] The changed paradigm for "conservative" chemoreduction (CRD) strategies for intraocular retinoblastoma has made the R-E system less predictive of ocular preservation. A new staging system (International Classification of Retinoblastoma) has been developed to provide a simpler, more user-friendly classification applicable to current therapies. The new system is based on extent of tumor seeding within the vitreous cavity and subretinal space and seems to be a better predictor of treatment success[33] (Box 71-1).

For patients undergoing enucleation, pathologic staging incorporates features known to influence outcome, guiding the therapeutic approach; such factors include choroidal and scleral involvement, optic nerve extension, and presence of

BOX 71-1 International Classification for Intraocular Retinoblastoma

GROUP A

Small tumors away from foveola and disc

- Tumors ≤3 mm in greatest dimension confined to the retina, *and*
- Located at least 3 mm from the foveola and 1.5 mm from the optic disc

GROUP B

All remaining tumors confined to the retina

- All other tumors confined to the retina not in Group A
- Subretinal fluid (without subretinal seeding) ≤3 mm from the base of the tumor

GROUP C

Local subretinal fluid or seeding

- Local subretinal fluid alone >3 to ≤6 mm from the tumor
- Vitreous seeding or subretinal seeding ≤3 mm from the tumor

GROUP D

Diffuse subretinal fluid or seeding

- Subretinal fluid alone >6 mm from the tumor
- Vitreous seeding or subretinal seeding >3 mm from tumor

GROUP E

Presence of any or more of these poor prognosis features

- More than two thirds globe filled with tumor
- Tumor in anterior segment
- Tumor in or on the ciliary body
- Iris neovascularization
- Neovascular glaucoma
- Opaque media from hemorrhage
- Tumor necrosis with aseptic orbital cellulitis
- Phthisis bulbi

Modified from Shields CL, Mashayekhi A, Au AK, et al: The international classification of retinoblastoma predicts chemoreduction success. Ophthalmology 113:2276–2280, 2006.

BOX 71-2 International Retinoblastoma Staging System, Proposed (Treatment-Based System, Chantada)[33]

Stage 0. Patients treated conservatively
Stage I. Eye enucleated, completely resected histologically
Stage II. Eye enucleated, microscopic residual tumor
Stage III. Regional extension
1. Overt orbital disease
2. Preauricular or cervical lymph node extension

Stage IV. Metastatic disease
1. **Hematogenous metastasis** (without central nervous system involvement)
   1. Single lesion
   2. Multiple lesions
2. **Central nervous system extension** (with or without any other site of regional or metastatic disease)
   1. Prechiasmatic lesion
   2. Central nervous systems mass
   3. Leptomeningeal and cerebrospinal fluid disease

metastatic disease. A third proposed staging system developed by an international consortium of ophthalmologists and pediatric oncologists incorporates the most important elements of the older systems[34] (Box 71-2).

Growth and invasion occur as a sequence of events, and extraretinal extension occurs only after the tumor has reached large intraocular dimensions. As part of this process, retinoblastoma extends into the ocular coats (choroids and sclera), the optic nerve, and the anterior segment. Extraocular disease is the next step in this progression. Locoregional dissemination occurs by direct extension through the sclera into the orbital contents and preauricular lymph nodes. Extraorbital disease manifests as intracranial tumor, leptomeningeal dissemination, or hematogenous metastasis.

PRIMARY THERAPY: PRINCIPLES OF TREATMENT

Treatment of retinoblastoma aims to save life and preserve useful vision, with attention to the risk of late functional and carcinogenic effects, and contemporary care requires coordination between the ophthalmologist, pediatric oncologist, and radiation oncologist.[35]

Surgery

Enucleation is indicated for large tumors filling the vitreous when there is little or no likelihood of restoring vision, and when tumor is present in the anterior chamber or associated with neovascular glaucoma. The eye must be removed intact, without seeding tumor cells into the orbit.[36] For optimal staging, a long segment (10 mm to 15 mm) of the optic nerve is removed with the globe. An orbital implant is usually fitted during the same procedure, and the extraocular muscles are attached to it. A ceramic false eye is later fitted in the orbital socket. Orbital exenteration is seldom indicated. For patients presenting with orbital (extraocular) disease, judicious use of chemotherapy, surgery, and radiation therapy often provides tumor control so that orbital exenteration is now usually reserved for cases of recurrent disease after radiation therapy.

Focal Surgical Therapies

Focal treatment is used for small tumors (less than 3 mm to 6 mm), classically in patients with bilateral disease and in combination with chemotherapy. Focal therapies are central to conservative therapy (chemotherapy and focal treatment) to avoid enucleation and EBRT in unilateral intraocular disease. Photocoagulation with argon laser is used for the treatment of tumors situated at or posterior to the equator of the eye and for the treatment of retinal neovascularization occasionally seen after radiation therapy.[37] This technique is limited to tumors measuring no greater than 4.5 mm in base and no greater than 2.5 mm in height. The treatment aims to obliterate blood supply to the tumor. Two- or three-monthly sessions are usually required, achieving local tumor control in approximately 70% of cases. Cryotherapy is used for the treatment of small equatorial and peripheral lesions, measuring no more than 3.5 mm in base and no more than 2 mm in height.[38] One- or two-monthly sessions of triple freeze and thaw are performed; the resultant tumor control is usually excellent. A more recently introduced focal therapy is transpupillary thermotherapy, which applies focused heat at subphotocoagulation levels, usually with diode laser.[39] In thermotherapy, the goal is to deliver a temperature of 42°C to 60°C for 5 minutes to 20 minutes to the tumor, relatively sparing retinal vessels from photocoagulation. The use of focal treatments is especially important in conjunction with chemotherapy, where both treatment modalities appear to have synergistic effects. Sequential thermotherapy and carboplatin enhances

antitumor effect by increasing the platinum-DNA adducts; thermochemotherapy is becoming an important component of therapy for intraocular retinoblastoma.[40] In general, local control rates of 70% to 80% can be achieved. Complications of focal treatments include transient serous retinal detachment, retinal traction and tears, and localized fibrosis.

Chemotherapy

Chemotherapy is indicated in patients with extraocular disease, in patients with intraocular disease undergoing enucleation and found to have high-risk pathology, and in patients with intraocular disease in whom it is given either systemically or intraarterially in conjunction with aggressive focal therapies for ocular preservation. Agents effective in the treatment of retinoblastoma include platinum compounds, etoposide, cyclophosphamide, doxorubicin, vincristine, and ifosfamide.[35,41] Melphalan, carboplatin, and topotecan are the agents most commonly used in intraarterial administration.[42,43]

Intravitreal and Intraarterial Chemotherapy for Intraocular Retinoblastoma

Japanese investigators have pioneered the use of intravitreal and intraarterial melphalan for patients with advanced or recurrent intraocular retinoblastoma.[44] Good clinical responses in patients with progressive retinoblastoma were obtained using intravitreal melphalan followed by hyperthermia.[44] Kaneko et al initially reported the feasibility of injecting melphalan into the ipsilateral carotid artery, with documented efficacy.[44] The technique was later perfected by Mohri using a balloon catheter inflated in the distal internal carotid artery, which allowed for selective flow into the ophthalmic artery.[45] More recently, Abramson et al reported a variation of this technique that includes a direct cannulation of the ophthalmic artery using a microcatheter.[46] Using this approach, high ocular salvage rates can be achieved after the administration of 3 mg to 5 mg of intraarterial melphalan, although other agents such as topotecan and carboplatin are also used.[42,43,47] The use of this new treatment modality is being progressively incorporated into the frontline of ocular salvage for intraocular retinoblastoma. Direct administration of melphalan into the vitreous is also a promising approach for cases with vitreous disease.[48,49]

Radiation Therapy

Radiation therapy was historically the primary treatment for patients with bilateral disease. Through the early 1990s, debate focused on optimizing irradiation for localized and locally advanced intraocular disease, extraocular extension, and CNS disease (primarily trilateral, but also leptomeningeal extension). Although disease control in most local-regional presentations was excellent, the documentation of a high incidence, particularly in bilateral or hereditary retinoblastoma, of secondary malignancies continuing three to five decades after irradiation prompted a paradigm shift. Neoadjuvant chemotherapy combined with focal therapy for consolidation or focally "resistant" disease is now the standard of care for early-stage disease, unilateral or bilateral. Focal therapies as discussed, as well as radioactive plaques, are used in advanced intraocular disease requiring postchemotherapy consolidation or salvage. For cases with more advanced intraocular disease, extraocular extension, or distant metastasis, consolidative EBRT is used for local tumor control. Low-dose consolidative radiation therapy at a point when advanced intraocular or CNS disease is minimal yet "responsive" to, rather than resistant to, chemotherapy is under investigation.[50]

PRIMARY THERAPY: INTRAOCULAR RETINOBLASTOMA

Unilateral Retinoblastoma

Enucleation is curative for 85% to 90% of children who present with unilateral intraocular disease. Outcome is excellent, with good functional results and minimal long-term effects.[51] In view of the success in treating bilateral intraocular disease with chemotherapy and focal therapy, a similar "conservative" approach may be appropriate in unilateral intraocular disease, especially in young children who may later evidence contralateral disease. With the use of intraarterial chemotherapy, ocular salvage rates above 70% to 80% can be achieved for patients with intraocular unilateral disease.[43]

For patients undergoing enucleation, adjuvant treatment is indicated in patients with scleral invasion and those with tumor at the cut end of the optic nerve. Adjuvant treatment for other patients with intraocular disease is debatable. In the absence of randomized studies, available information would suggest that the use of adjuvant chemotherapy is beneficial for selected patients at higher risk of extraocular dissemination such as those with retro-laminar and choroidal involvement, and possibly those with massive choroidal involvement. Adjuvant chemotherapy is not indicated for patients with prelaminar involvement or isolated focal choroidal involvement.[35] Different chemotherapy regimens have been proposed. A 6-month treatment with vincristine, cyclophosphamide, and doxorubicin (VDC), vincristine, carboplatin, and etoposide (VCE), or a hybrid, with alternating courses of both regimens, appears to be effective. Radiation therapy is indicated only when there is transscleral disease or involvement of the cut end of the optic nerve.

Bilateral Retinoblastoma

Bilateral disease typically presents with advanced disease in one eye and relatively more localized disease contralaterally. In the past, treatment typically consisted of enucleation of the eye with more advanced disease (when little or no visual potential is apparent) and EBRT for the remaining eye. However, although associated with good tumor control, such treatment is associated with important long-term sequelae. Irradiation of the orbit during a period of rapid growth in young children results in significant reduction in orbital and zygomatic facial growth, whether symmetric (following opposed lateral radiation techniques) or asymmetric (with unilateral orbital irradiation), with dysmorphic changes apparent before puberty. As well, patients are at significant risk for secondary cancers; the standard incidence ratio (SIR) for sarcomas exceeds 100 times the expected rate and for carcinomas (e.g., breast, thyroid, lung, head and neck), at or above 10 times the expected rate.[52] This risk may be age-related and less in older children.[53]

The treatment of patients with bilateral retinoblastoma now incorporates upfront chemotherapy, either by systemic or intraarterial administration, intended to achieve maximum chemoreduction of the intraocular tumor burden, followed by aggressive focal therapies (Figure 71-2). The use of carboplatin-based multiagent chemotherapy or melphalan-based intraarterial therapy, along with consolidative local therapies, has resulted in avoidance of both enucleation and EBRT in more than 75% of patients.

For systemic therapy, the best results have been obtained with combinations of VCE.[35] When using intraarterial therapy, best responses are achieved with melphalan, alone or in combination with carboplatin and topotecan.[42,43]

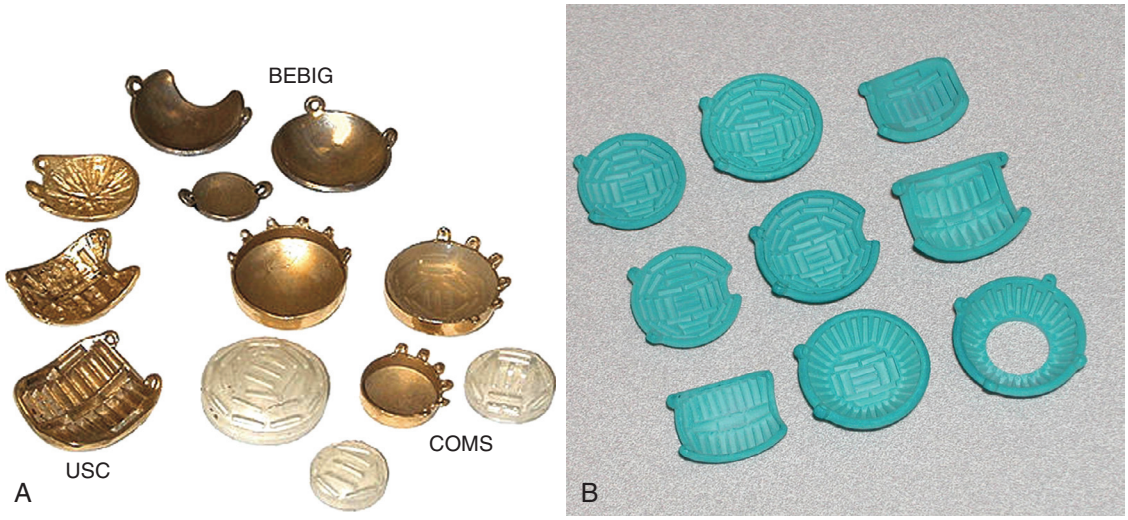


Figure 71-2 **A,** A mixture of some of the current plaques that are available today from various vendors. **B,** Prototypes showing the shapes that are possible in modern plaques.
From Astrahan M: Plaque Simulator X computer program and electronic manual [screen capture of the program written by Dr. Melvin Astrahan called Plaque Simulator X]. Image used with permission, 2010.

For systemic administration, although the three-drug regimen is the standard of care, for patients with early intraocular disease (R-E Groups I to III, International Group B), a nonintense two-drug regimen of vincristine and carboplatin has also been shown to be effective when aggressive focal consolidation is added.[35,54] With more advanced tumors, a major proportion of failures represent tumor growth as vitreous seeding or subretinal implants. Carboplatin diffuses well into the vitreous, and periocular (subconjunctival or episcleral) administration has been explored in conjunction with systemic carboplatin delivery to maximize intraocular exposure of retinoblastoma cells. However, this approach has not shown a significant impact in ocular survival.[55]

New agents with better intraocular penetration are being investigated. Topotecan is of interest with excellent intraocular penetration and preclinical and clinical efficacy.[56,57] The recent description of *MDM4* amplification as the mechanism of inactivation of the *p53* pathway in retinoblastoma has opened the door to the use of specific targeted molecular therapies. Nutlin-3 is a small-molecule inhibitor of the *MDM2-p53* interaction.[58] *MDM4* and *MDM2* bind *p53* with similar affinities, and studies have shown that nutlin-3 prevents the *MDM4-p53* interaction in retinoblastoma cells, inducing *p53*-mediated apoptosis in vitro and in vivo. Subconjunctival injection of nutlin-3 to mice with intraocular retinoblastoma resulted in significant tumor responses. The combination of nutlin-3 with a DNA damaging agent such as topotecan resulted in a synergistic effect.[13,59] Finally, targeting the SYK proto-oncogene may also offer a new therapeutic approach.[14]

TREATMENT OF EXTRAOCULAR RETINOBLASTOMA

Extraocular dissemination of retinoblastoma usually reflects delayed diagnosis and treatment. In Europe and the United States, fewer than 5% of patients present with extraocular disease, in contrast to more than 20% to 40% in less-developed countries.[60,61] Four patterns of extraocular disease have been recognized: (1) locoregional, including orbital infiltration, tumor extending into the optic nerve or to the cut end of the nerve, and lymphatic spread to preauricular lymph nodes; (2) CNS dissemination; (3) trilateral retinoblastoma; and (4) metastatic retinoblastoma.

Orbital and Locoregional Retinoblastoma

Orbital retinoblastoma occurs as a result of progression of the tumor through the emissary vessels and sclera; transscleral disease is considered to be extraocular and is treated as such. Orbital retinoblastoma is isolated in 60% to 70% of cases; lymphatic, hematogenous, and CNS metastases occur in 30% to 40% of patients with metastasis.[62] Treatment includes systemic chemotherapy and radiation therapy; with this approach, 60% to 85% of patients are cured. Failures occur predominantly in the CNS, highlighting the importance of drugs with CNS penetration. Different chemotherapy regimens have proven effective, including vincristine, cyclophosphamide, and doxorubicin, platinum- and epipodophyllotoxin-based regimens, or combinations thereof.[35] For patients with macroscopic orbital disease, upfront chemotherapy is followed by surgery, usually obviating the need for orbital exenteration. Postoperative chemotherapy and orbital irradiation (40 Gy to 45 Gy) consolidate therapy.[63] Similar management is appropriate for patients with scleral disease although good outcomes without irradiation have also been reported.[60] Patients with involvement of the optic nerve at the cut end should also receive similar systemic treatment with irradiation to the entire orbit, typically to a dose of 36 Gy with a 9-Gy to 10-Gy boost to the remainder of the optic nerve and chiasm (total 45 Gy to 46 Gy). Recent data from Argentina show disease control in 70% of cases with the use of induction chemotherapy, enucleation, and adjuvant chemotherapy together with radiotherapy (45 Gy) for patients ($N = 26$) with tumor at the optic nerve resection margin.[64] Excellent results have been described by the Children's Hospital Los Angeles group using a similar approach in nine patients with proximal optic nerve enhancement on MRI, but with more selective use of radiation. All were disease-free at 22 months of follow-up, only two of them having been given orbital radiation.[65]

The preauricular and cervical lymph nodes should be imaged carefully because 20% of patients with orbital extension have lymphatic metastases.[62] Lymphatic dissemination may not carry a worse prognosis, provided that the involved lymph nodes are also irradiated.

Central Nervous System Involvement

Intracranial dissemination occurs by direct extension along the optic nerve. Prognosis is dismal.[60,63] Treatment includes platinum-based intensive systemic chemotherapy and CNS-directed therapy. Although intrathecal chemotherapy has been traditionally used, there is no preclinical or clinical evidence to support its use. Although controversial, standard therapy includes radiotherapy consisting of craniospinal irradiation to a dose of 23.4 Gy to 36 Gy followed by a boost to 45 Gy to sites of overt or nodular disease. Therapeutic intensification with high-dose, marrow ablative chemotherapy and autologous hematopoietic progenitor cell rescue has been explored, but its role is not yet clear.[66,67] Despite such treatment, survivors are anecdotal.

Trilateral Retinoblastoma

The prognosis for patients with trilateral retinoblastoma is poor; most patients die of disseminated neuraxis disease in less than nine months.[26] The rare survivors are usually those diagnosed by screening imaging while asymptomatic and treated with intensive chemotherapy with or without craniospinal irradiation. Given the short interval between the diagnosis of retinoblastoma and the occurrence of trilateral retinoblastoma, routine screening might detect the majority of cases within 2 years. Typical treatment now consists of intensive chemotherapy followed by consolidation with myeloablative chemotherapy and autologous hematopoietic progenitor cell rescue without radiation therapy, an approach similar to that used in the treatment of brain tumors in infants.[68,69]

(Extracranial) Metastatic Retinoblastoma

Hematogenous metastases are most commonly seen in bone and bone marrow, and, less frequently, the liver. Long-term survival after conventional chemotherapy is anecdotal. However, recent reports suggest that metastatic retinoblastoma can be cured using short and intensive induction regimens usually containing alkylating agents, anthracyclines, etoposide, and platinum compounds consolidated with marrow-ablative chemotherapy and autologous hematopoietic cell rescue.[67] In the latter series, patients with hematogenous bone metastases who responded to induction chemotherapy did not always require radiation therapy.

TECHNIQUES OF IRRADIATION

In contemporary management of retinoblastoma, radiotherapy is most often used as consolidative or "salvage" therapy for disease resistant to or recurrent following chemotherapy, or as part of initial treatment for patients with extraocular spread. Consequently the target volume for radiation therapy ranges from focal to whole orbit, optic nerve and chiasm, and the technique to be used therefore is the most appropriate of several options including plaque brachytherapy, three-dimensional conformal radiation therapy (3D-CRT), intensity-modulated radiation therapy (IMRT), stereotactic radiation therapy (SRT), and proton therapy.

Plaque Brachytherapy

Radioactive plaques have been used for the treatment of ocular tumors since the 1920s, at that time using radon seeds.[70,71] Other radioactive sources have since become available including cobalt-60 in the 1950s, and more recently iodine-125 (^{125}I), iridium-192 (^{192}Ir), and ruthenium-106 (^{106}Ru).[72-76]

Plaque radiotherapy is an option for localized retinoblastoma limited to one or two lesions not involving the optic disc or macula. It can also be used in conjunction with chemoreductive therapy.

Planning for plaque placement involves identification of tumor size and location as evaluated by the ophthalmologist, together with direct visualization with the RetCam and ocular ultrasound, and sometimes MRI. The target volume includes the tumor base as projected through the sclera plus a 1-mm to 2-mm margin. Tumor height is a direct measurement from the imaging data with 1 mm added for the thickness of the sclera. The plan provides proper positioning based on the plaque's center and suture eyelets and the distance from the limbus. The surgeon provides access to the sclera underlying the typically posterior tumor, marking the center and edges of the tumor based on projection. A dummy plaque of identical configuration is used to verify positioning and the loaded episcleral plaque is sutured onto the sclera by the ophthalmologist. A lead eye shield is used to reduce exposure of personnel when ^{125}I is used. Inpatient or outpatient status depends on radiation exposure and local requirements.

The dose is prescribed at the tumor apex or extended to include overlying vitreous seeds if present. The target dose is typically 40 Gy to 45 Gy at the apex for ^{125}I at a dose rate of 40 cGy/hr to 80 cGy/hr.[72,74,75] Most of the experience with ^{106}Ru reports apical doses of 50 Gy, or sometimes 70 Gy.[73,76] The dose at the tumor base (scleral dose) approximates 120 Gy for ^{125}I and 150-200 Gy with ^{106}Ru.

Most plaques today use ^{125}I, a low-energy γ-ray emitter (27 keV to 35 keV; half-life, 60 days) that is readily available in encapsulated form, allowing custom fabrication of gold plaques of varying sizes and configured either as round or notched templates, the latter to allow placement adjacent to the optic nerve. The ^{125}I seeds can be differentially loaded within the wells of the plaque to achieve a dose distribution appropriate for the tumor. ^{125}I plaques are typically used for tumor height up to 10 mm and basal diameter ≤ 16 mm. Figure 71-3 shows some current and prototype plaques. Figure 71-4 demonstrates a case using a collimating plaque. ^{192}Ir is an alternative radioisotope (295 keV to 612 keV; half-life, 74 days), also available as sealed sources with somewhat less desirable dosimetric characteristics. Experience with ^{106}Ru has primarily been reported from Europe.[73,76] The pure β emitter provides a spectrum of β particles with energies up to 3.5 MeV; the half-life is longer than ^{125}I and ^{192}Ir at 374 days. The dosimetric profile of ^{106}Ru limits utilization to tumors with height ≤6 mm; the uniformly round plaques are typically not applied within 2 mm of the optic nerve.[73] Both ^{125}I and ^{106}Ru limit radiation exposure to patient and medical personnel while allowing one to diminish dose to the underlying orbital bones and the optic lens.

At the Wills Eye Hospital, Philadelphia, 208 tumors (141 children) were treated with plaque radiotherapy between 1976 and 1999, 71% of which had received prior treatment.[72] Tumor control was 83% at 1 year, and 79% at 5 years. For tumors treated with plaque RT as their primary treatment, recurrence at 1 year was 12%, compared to 20% for those treated for salvage after failure of prior treatment. Factors predicting for tumor recurrence were presence of tumor seeds in the vitreous, presence of subretinal tumor seeds, and increasing patient age. At 5 years, radiation-induced complications included cataract (31%), nonproliferative retinopathy (27%), papillopathy (26%), maculopathy (25%), proliferative retinopathy (15%), and glaucoma (11%). No cases of scleral necrosis were observed. In 2006, the same group published their experience using ^{125}I plaque RT for tumors recurring after chemoreduction (1994 to 2005).[74] Eighty-four tumors were treated in 71 eyes (64 patients). At 5 years, tumor control was documented in 95% of patients. Failures occurred at a median of 4 months postimplant.

A similar 5-year tumor control rate of 94.4% was reported in a retrospective analysis of 175 tumors (134 patients) treated

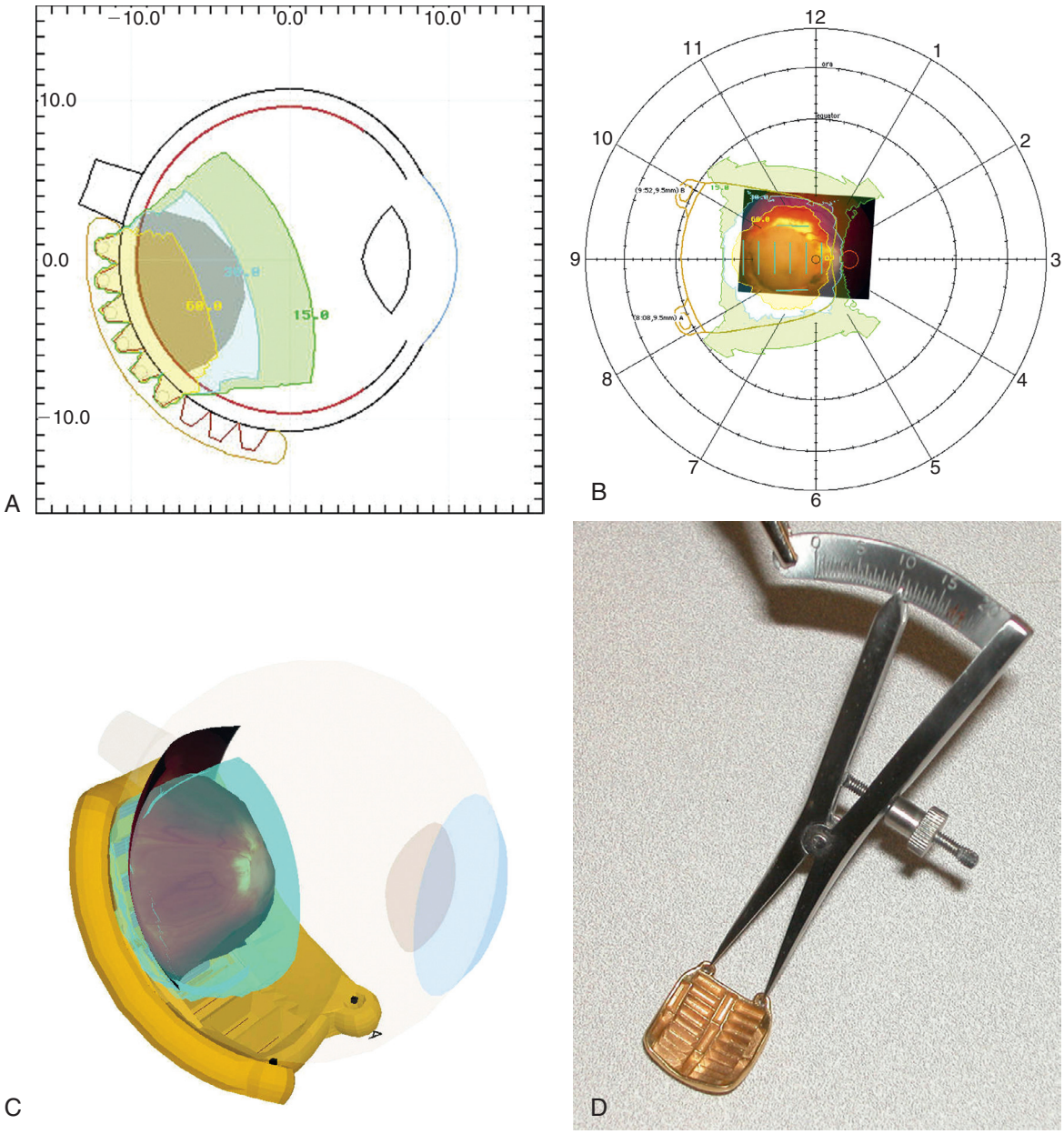


Figure 71-3 This 8-month-old child's eye had a diameter of 22 mm and required a plaque with an 11-mm radius of curvature; the dose prescribed was 30 Gy in 71 hours to the apex of the 6.7-mm high tumor. Only the seeds at the posterior end of this semielliptical, mildly notched plaque that lie under the tumor are loaded. This allows the sutures to be placed anteriorly. The perfect fit of the plaque to the eye ensures that the plaque will not lift up at the posterior end when sutured anteriorly. **A,** Retinoblastoma with a grooved plaque in which the grooves help collimate the radiation dose as shown by the isodose levels. **B,** Diagram of the retina in the same plan with suture marks in the model to help guide the team in the operating room. **C,** Three-dimensional conformal isodose map of the same plan. **D,** Measuring the actual plaque's eyelets from the same plan using Castroviejo calipers.
From Astrahan M: Plaque Simulator X computer program and electronic manual [screen capture of the program written by Dr. Melvin Astrahan called Plaque Simulator X]. Image used with permission, 2010.

with ^{106}Ru plaque at the University Hospital in Essen, Germany.[73] Their estimate for eye preservation at 5 years was 86.5%. Most of the cases (119 tumors in 95 eyes) had received plaque radiotherapy as a secondary treatment.

More recently, Francis et al from the Memorial Sloan Kettering Cancer Center described their experience with plaque radiotherapy in 15 eyes after intraarterial chemotherapy (OAC).[77] Thirteen patients were treated with plaque radiotherapy as salvage therapy, of whom 12 had localized vitreous seeding. The estimate for ocular survival at 18 months was 79.4%. Of note, patients with ocular complications had a significantly shorter interval (mean, 2.5 months) between their last OAC and plaque than patients without ocular complications (mean, 6.5 months).

Stereotactic Radiotherapy

Stereotactic radiotherapy (SRT)[78-81] is an alternative to plaque radiotherapy for the treatment of locally progressive disease or as focal consolidative therapy. Compared with plaque radiotherapy, SRT is a noninvasive treatment that does not require special technical skills and that can be delivered using

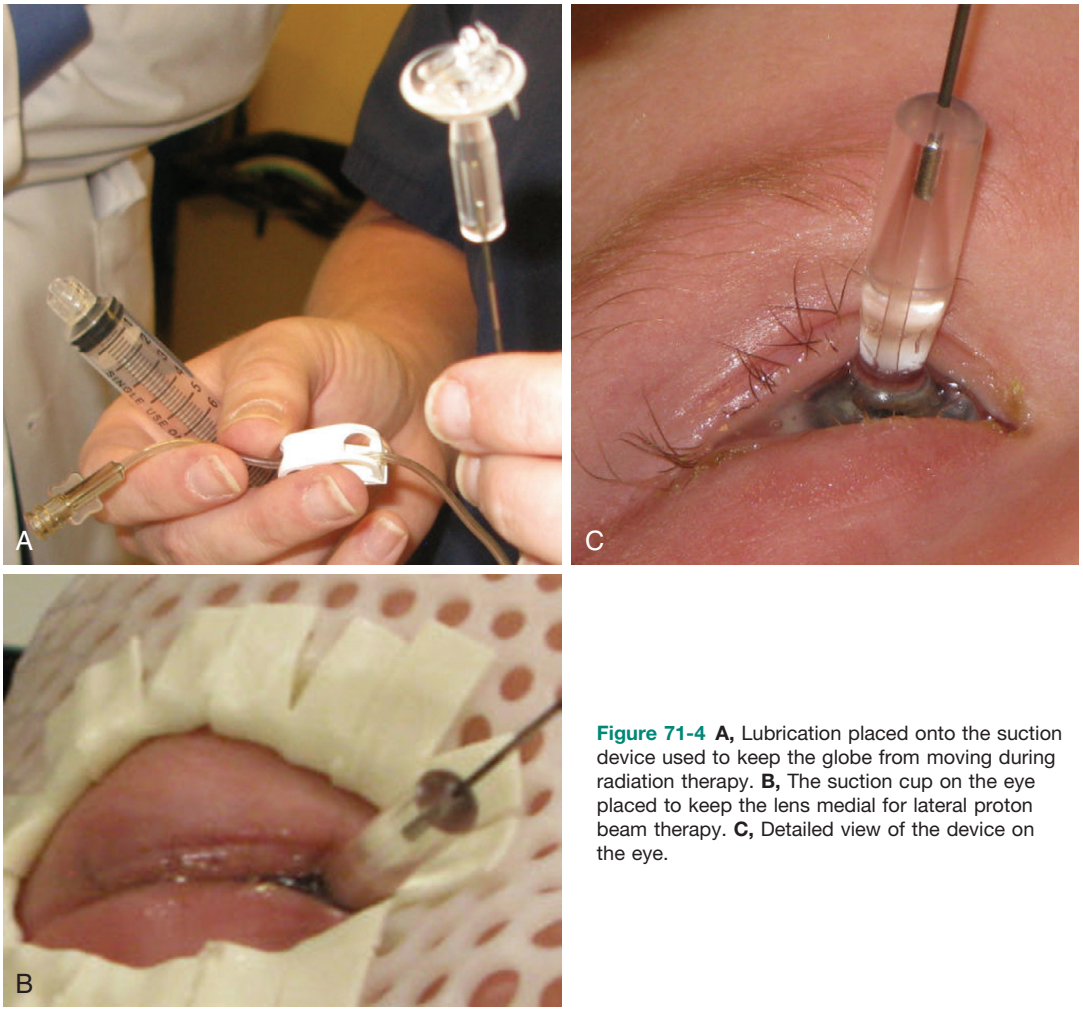


Figure 71-4 **A,** Lubrication placed onto the suction device used to keep the globe from moving during radiation therapy. **B,** The suction cup on the eye placed to keep the lens medial for lateral proton beam therapy. **C,** Detailed view of the device on the eye.

conventional fractionation. The dose within the target volume is more homogeneous and the dose to the external sclera lower, thus reducing the risk of optic nerve damage for tumors close to the optic nerve.[80]

Clinical experience in 11 children (15 eyes) treated in Switzerland with SRT with a dose of 50.4 Gy in 28 fractions showed a high local control rate of 87%, at a median follow-up of 20 months.[81] In this series, patients selected for SRT were those with recurrent retinoblastoma involving the optic nerve or macula after chemotherapy or other local treatment and potentially active residual papillary tumor not suitable for other focal therapy. Patients with diffuse subretinal or vitreous seeds, retrobulbar optic nerve invasion and other extraocular involvement were considered not suitable for SRT. Long-term side effects were observed in only four children: two cases of focal microangiopathy, one case of transient recurrence of retinal detachment and one case of bilateral cataracts. No optic neuropathy was seen.

The target volume for SRT is the GTV as seen on the planning CT (with or without MRI) to which a margin of 2 mm to 3 mm is added to obtain the planning target volume (PTV). Immobilization of the eye using a suction device (see discussion) at CT simulation and on each treatment day is critical.

External Beam Radiation Therapy

Classically, full orbital irradiation was used in children with bilateral disease; the eye with more advanced disease was enucleated and irradiation was given for the contralateral eye. Less commonly, irradiation was administered to both eyes when reasonable likelihood of disease control and visual preservation was present bilaterally. Now, however, EBRT is more typically used as consolidative therapy in conjunction with chemoreductive therapy for intraocular disease, for treatment of locoregionally extensive tumor, or as salvage therapy for disease progressing on chemotherapy.

Historically, irradiation of the retina was delivered using a single lateral field when treating one eye or parallel-opposed fields for both eyes. However, such "D-shaped" fields, by attempting to spare the lens, underdose the anterior retina from the equator to the ora serrata. Other techniques, such as a direct anterior electron or photon field technique, a two field-technique using a lateral field and an anterior field with a lens block, modified lateral field technique using oblique angles, noncoplanar arcs, IMRT, and many other techniques can also be used, each one having its advantages and disadvantages. In a dosimetry study comparing 13 techniques, Reisner et al found that IMRT best spared the orbit and lacrimal gland while ensuring a therapeutic dose to the ora serrata and vitreous.[82] Similarly, Krasin et al showed that IMRT reduced the dose to the bony orbit by more than one third in comparison to anterior-lateral photon and electron techniques, and by 23% compared with conformal techniques.[83] Doses to the temporal lobe and contralateral orbit were also reduced.

The prescription dose for retinoblastoma is classically 45 Gy at 1.8 Gy to 2.0 Gy per fraction. Foote reviewed the

Mayo Clinic experience, documenting a lack of dose-response relationship above 45 Gy, except perhaps for tumors larger than 10 DD that had a lower control rate (67%) in this series.[84] The use of lower doses of 32 Gy to 38 Gy (median, 36 Gy), was reported by Merchant et al.[85] In a series of 38 children (49 eyes) treated at St. Jude Children's Research Hospital, therapy was individualized based on presentation, with use of several treatment modalities in addition to EBRT for certain cases (laser, plaque radiotherapy, chemotherapy, etc.). Additional treatment was required after EBRT for 19 of 49 eyes, at a median time of 13.7 months. The ocular preservation rate was estimated to be 82% at 10 years for the whole cohort, but lower for patients with R-E groups III-V disease, with 7 of the 20 advanced-disease eyes requiring enucleation.

In the setting of chemoreductive therapy for group E eyes, consolidative EBRT has been tested at a reduced "prophylactic" dose of 26 Gy when initially advanced disease is yet responsive to induction chemotherapy.[50] The use of EBRT resulted in a globe salvage rate of 80% at 5 years, compared to 48% with eyes treated with chemoreductive therapy alone.

Children with retinoblastoma requiring EBRT are generally planned and treated under anesthesia, typically immobilized with a thermoplastic mask. The use of an ocular suction system integrated to a stereotactic mask enables immobilization of the eye during anesthesia and enhances precision in localization and treatment delivery. A planning CT scan should be obtained, with slices 1-mm to 2-mm thick. Coregistration with MRI is helpful, especially for SRT for focal irradiation. When treating the whole eye, the clinical target volume (CTV) encompasses the globe and the proximal 0.5 cm of the optic nerve. If the optic nerve is involved, the CTV will extend posteriorly to include the remaining optic nerve and optic chiasm. If there is extraorbital extension, the CTV will extend to the walls of the orbit. The PTV depends on the immobilization used and the availability of in-room image guidance and will therefore vary between 2 mm and 5 mm. Organs at risk (OAR) include the ipsilateral and contralateral bony orbits, the temporal lobe and whole brain, the contralateral eye and lens, the lacrimal glands, the optic nerves and chiasm, and the pituitary gland. The PTV should be adequately covered by the 95% prescription isodose. Homogeneity within the target and minimization of doses to OARs should be considered during the optimization process. The volume of the ipsilateral bony orbit receiving a dose of ≥20 Gy should be minimized because it is the suggested threshold for bone growth.

Proton Therapy

Proton therapy may be an interesting option for patients with retinoblastoma, whether for focal or whole eye treatment (Figures 71-5 and 71-6). In a retrospective dosimetric study of three cases from the M. D. Anderson Cancer Center, proton therapy was found to provide the best target coverage combined with the greatest orbital bone sparing in patients treated to a dose of 36 Gy in 18 fractions to the entire retina and vitreous cavity.[86] While providing 100% target coverage, protons were able to limit the mean orbital bone volume irradiated at ≥5 Gy to 10%, a dose low enough to potentially decrease the likelihood of orbital bone growth defects postirradiation. Krengli et al similarly described homogeneous target coverage for different intraocular tumor locations, with lens sparing and reduction of doses to bony structures.[87]

In 2011, Chang et al reported their clinical experience with three children who received proton therapy for retinoblastoma treated with chemoreductive therapy and focal therapy that were either not responding or progressing.[88] All patients responded to proton therapy but two eventually needed enucleation for recurrence. Clinical use of proton therapy for retinoblastoma has also been described by investigators from the Paul Scherrer Institute,[79] as well as the group from Boston that compared outcomes in patients treated with proton radiotherapy ($N = 55$) and photon radiotherapy ($N = 31$) between 1986 and 2011.[89] With the caveat that follow-up was shorter in the cohort treated with protons (median, 6.9 years versus 13.1 years), the 10-year cumulative incidence of radiotherapy-induced or in-field second malignancies was significantly lower with proton RT (0% versus 14%).

LONG-TERM EFFECTS OF RETINOBLASTOMA AND ITS TREATMENT

Children treated for retinoblastoma are at risk of functionally and cosmetically significant bony abnormalities that become evident by early adolescence when orbital growth is largely complete. Both enucleation, which causes orbital contraction, and radiation therapy, which induces arrest of bone growth, adversely affect orbital growth. In children treated for bilateral retinoblastoma, the impact of enucleation in orbital development is not different from that of irradiation. Patients with retinoblastoma are also at risk of chemotherapy-related complications. Carboplatin-induced ototoxicity has been rarely reported[90]; however, infants younger than 6 months of age appear to be at a higher risk of hearing loss.[91]

However, the principal concern, and the one that has motivated practice change over the past decade, is the risk of secondary malignancies, particularly in children with germline mutations of the *RB1* gene identified in long-term survivor cohorts as those with hereditary retinoblastoma who are at especially high risk. Patients with nonhereditary retinoblastoma are not inherently at increased risk. In the largest cohort study that combined data from major pediatric centers in Boston and New York City, the cumulative incidence of secondary cancers in 1601 patients treated between 1914 and 1984 and surviving more than 1 year postdiagnosis was 36% for the hereditary form and 5.7% for the sporadic/nonhereditary cohort at 50 years postdiagnosis. Exposure to radiation therapy increased the risk of second malignant neoplasms in the hereditary population 3.1-fold. At 50 years post diagnosis, the cumulative incidence of second malignant neoplasms was 38.2% following irradiation and 21% without radiation therapy.[52,92] In the sporadic cohort, the risk of second malignant neoplasms exceeded the general population only for breast cancer (2.8 times), especially among those with radiation exposure (10 times).

In a subsequent report that now included at total of 1854 patients treated between 1914 and 1996, cumulative mortality from second malignant neoplasms at 50 years postdiagnosis was 25.5% for hereditary retinoblastoma survivors and 1% for the nonhereditary cohort.[93] Among hereditary retinoblastoma survivors, the most-common secondary malignant neoplasms were sarcomas of bone and soft tissue, melanoma, and cancers of brain and other parts of the CNS. Cancers of bone and soft tissue accounted for 76.5% of all deaths from secondary cancers before an attained age of 25 years. In hereditary retinoblastoma survivors older than age 25, cancers of bone and soft tissue accounted for a smaller percentage (35.7%) of all deaths from secondary cancers and excess mortality from secondary cancers at other sites began to emerge including lung and corpus uteri. With the exception of lung cancer, the mortality rates were consistently higher among hereditary retinoblastoma survivors who were irradiated. In a Dutch population-based series standardized mortality rates (SMR) were higher for hereditary retinoblastoma survivors treated with chemotherapy in addition to radiotherapy (SMR = 60.9 as compared with 18.1 for radiotherapy alone) and lower for

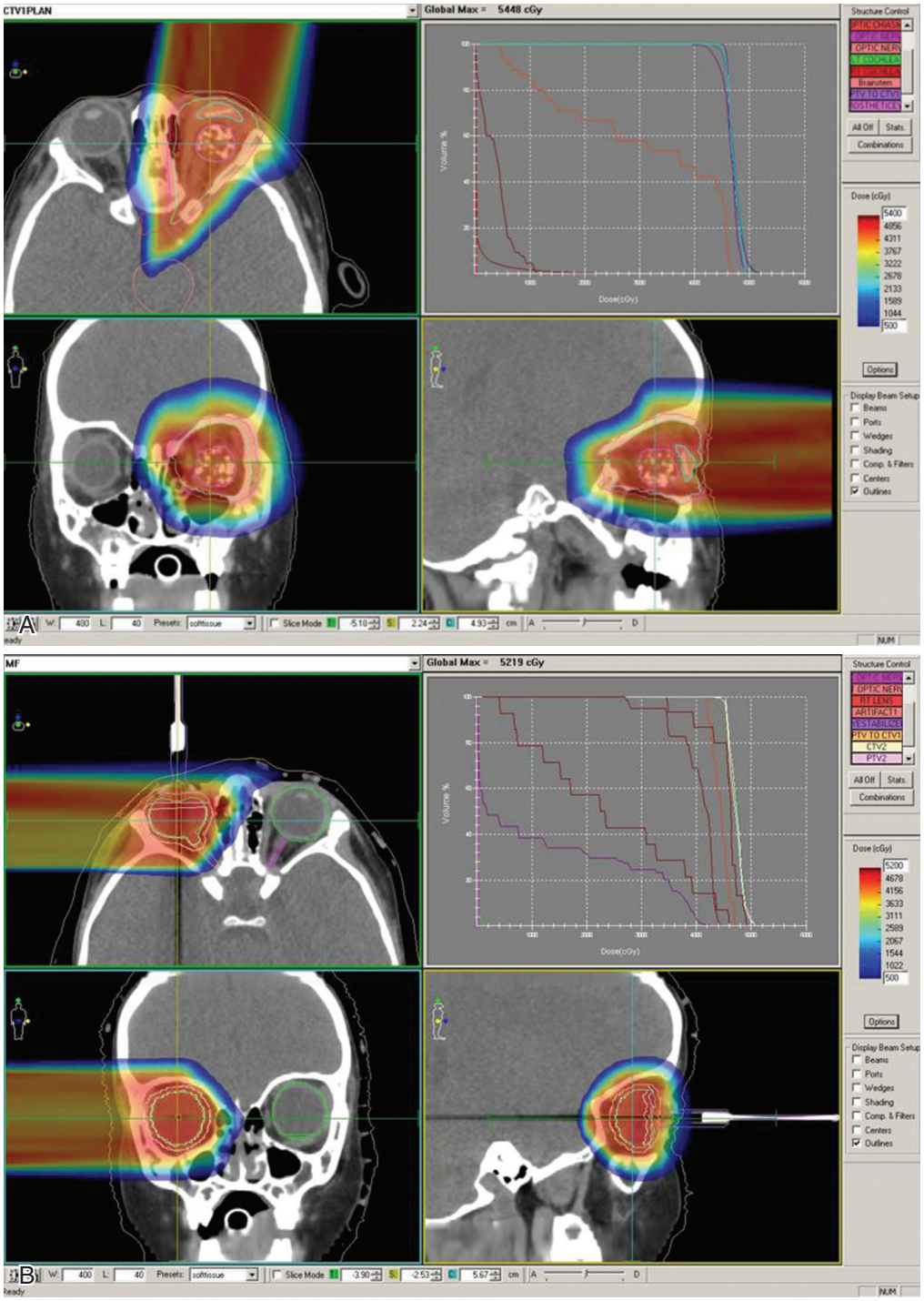


Figure 71-5 **A,** Single proton field anterior dosimetry using active scanning. **B,** Single proton field lateral dosimetry using active scanning. *From Simmons J: Active Scanning Proton Beam Plans from the Midwest Proton Radiotherapy Institute. Bloomington, IN, 2010.*

those treated with surgery alone (7.95).[94] Although bone and soft tissue tumors arising in the radiation field may be difficult to treat, good treatment options exist for many other secondary malignancies and all patients need good follow up with appropriate screening to ensure early intervention.

Current treatment approaches are likely to result in a reduced risk of late sequelae as compared to those used in the past. Decreased use of EBRT is expected to result in a decreased incidence of secondary malignant neoplasms.[95] When radiation therapy is necessary, delay to treatment (on average, using chemoreductive therapy, for at least 6 or 7 months to median age 21 months) is likely to result in reduced frequency and severity of the most prevalent postirradiation side effects because effects on bone development and susceptibility to carcinogenesis appear to be greatest following radiation exposure during the first year of life.[96] Finally, newer radiotherapy techniques that allow greater sparing of orbital bone, the use of conventional fractionation schedules and lower total doses, as well as newer modalities such as protons are also likely to reduce the risk of late sequelae.[89]

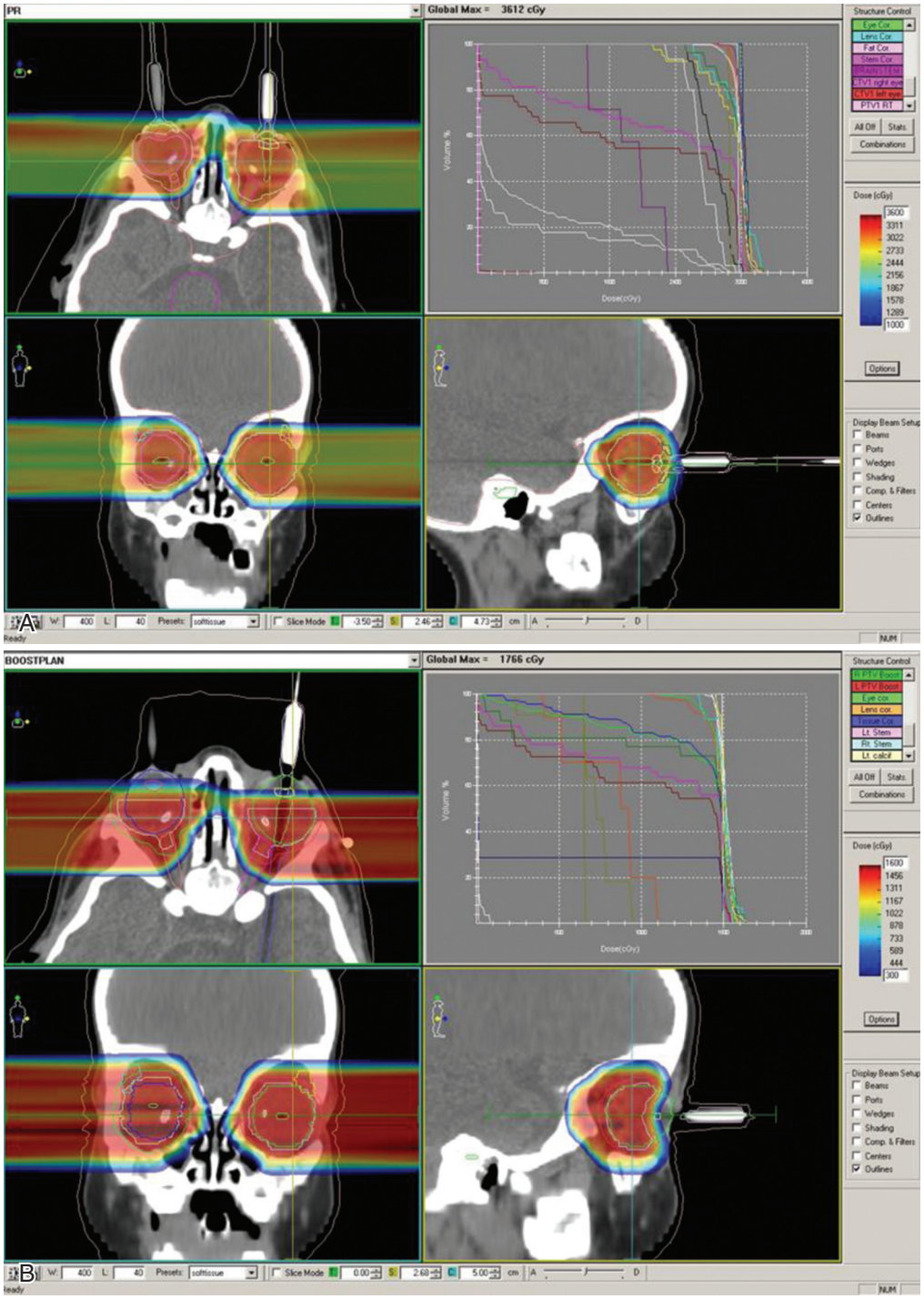


Figure 71-6 **A,** Initial bilateral proton plan using active scanning. **B,** Boost bilateral proton plan using active scanning.
From Simmons J: Active Scanning Proton Beam Plans from the Midwest Proton Radiotherapy Institute. Bloomington, IN, 2010.

TREATMENT ALGORITHMS, CONTROVERSIES, PROBLEMS, AND FUTURE DIRECTIONS

One of the challenges of retinoblastoma management is the process of accurate staging. This requires a multidisciplinary team of experienced ophthalmologists, radiologists, and pathologists. The description of the retina by the ophthalmologist during the examination under anesthesia is critical. Technology that allows panoramic imaging of the eye has proven its worth, but not to the point where detailed surgical notes are no longer needed. The experience of the pathologist is critical because the handling and evaluation of the eye globe is challenging. For this reason, it has been necessary for research protocols to include explicitly tissue-handling

guidelines meant to optimize the quality of pathological collection of retinoblastoma tissue.[22]

Once properly staged, it is important to review the most appropriate treatment approach, which may range from upfront enucleation to an eye-preserving approach with systemic or intraarterial chemotherapy and aggressive focal consolidation or radiation therapy. The use of intraarterial and intravitreal chemotherapy is becoming more common, but those approaches should only be undertaken in specialized centers. Decisions must be made in the context of a multidisciplinary team with expertise in the disease; ideally, patients should be managed at a state of the art retinoblastoma treatment center. The newer techniques of potential value in retinoblastoma make a simple chart of what to do relatively inadequate to the task. Figure 71-7 outlines current therapeutic algorithms.

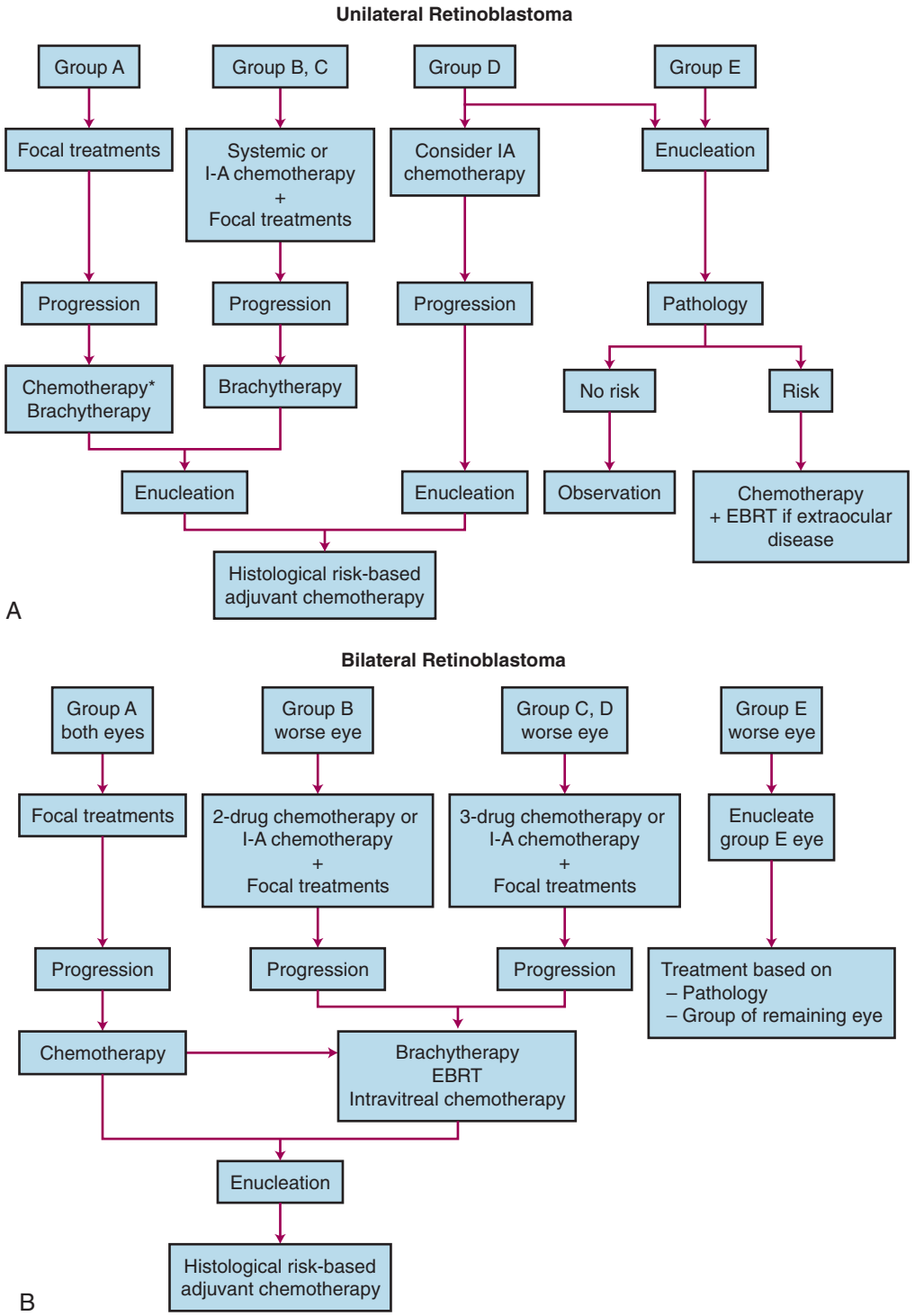


Figure 71-7 Algorithms for the management of retinoblastoma. **A,** Unilateral retinoblastoma. **B,** Bilateral retinoblastoma. *EBRT,* External beam radiation therapy.

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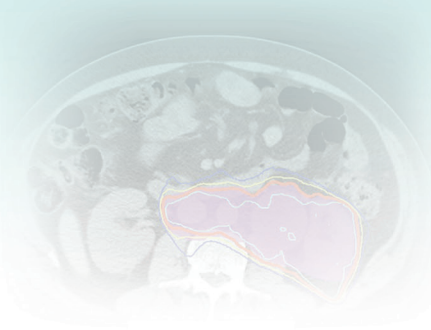
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CHAPTER

72 Neuroblastoma



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EPIDEMIOLOGY

Neuroblastoma comprises 8% to 10% of childhood cancers, with 650 cases reported annually in the United States. It is the most common extracranial solid tumor in children and the most common malignancy in infants. The tumor primarily occurs in neural crest–derived tissues, and the adrenal gland is its most common location.

EARLY DETECTION

Screening has not impacted on survival or detection of high-risk neuroblastoma. Neuroblastoma-like cells are found in normal development.

BIOLOGY, CLASSIFICATION, AND STAGING

Segmental chromosomal abnormalities including deletions of 1p36 and 11q and unbalanced gain of chromosome 17q and *MYCN* amplification are associated with a worse prognosis. Neuroblastoma contains small, round, blue cells that stain for neural features. Lymphatic spread is common, as is spread to the bones of the skull, whereas lung metastases are rare. Brain metastases are seen in 5% to 10% of cases at relapse. Children younger than 18 months of age generally have localized disease, whereas older children generally have disseminated tumors.

The International Neuroblastoma Pathology Committee (INPC) classification system is the most widely used and validated. The International Neuroblastoma Response Group (INRG) staging system is replacing the previous staging systems. Staging studies include bone marrow aspirates and biopsies, computed tomography (CT), magnetic resonance imaging (MRI), and bone scintigraphy with iodine-123–labeled metaiodobenzylguanidine (^{123}I-MIBG) (or ^{18}F-fluorodeoxyglucose–labeled positron emission tomography [FDG-PET]). Urinary catecholamines should be measured.

THERAPY

Treatment is based on risk stratification. Survival varies from 95% for patients with low-risk disease to 30% to 40% for patients with high-risk disease:

- Low-risk disease: generally treated with surgery alone with chemotherapy for progressive disease
- Intermediate-risk disease: 4 months to 8 months of chemotherapy followed by surgery and radiation therapy (21 Gy) for residual disease
- High-risk disease: surgery, induction chemotherapy with or without autologous stem-cell transplant, anti-GD2 immunotherapy, irradiation to primary site with or without metastases

Neuroblastoma comprises a range of tumors (neuroblastoma, ganglioneuroblastoma, and ganglioneuroma) that arise from primitive adrenergic neuroblasts of neural crest tissue, typically in young children. The clinical behavior, and therefore, therapy for neuroblastoma varies tremendously, depending on an array of clinical and biologic characteristics. Although some tumors regress spontaneously, others are highly malignant and often fatal.[1,2]

Significant progress in therapy has been made during the past several decades owing to an increased understanding of tumor behavior and effective risk-group stratification. Patients with low- and intermediate-risk tumors now have high survival rates with minimal intervention, and those with high-risk disease have improving survival as a result of intensive multimodality therapy.

Neuroblastoma is a fascinating and multifaceted disease. The investigation of biologic features of neuroblastoma and subsequent translation of these findings into effective therapy may serve as a model for other diseases.

ETIOLOGY AND EPIDEMIOLOGY

Neuroblastoma accounts for 8% to 10% of all childhood cancers, with approximately 650 cases diagnosed annually in the United States. It is the most-common extracranial solid tumor in children and the most common malignancy of infants. The median age at diagnosis is 17 months, and the male-to-female ratio is 1.1:1. Forty percent of patients are diagnosed when younger than 1 year of age, 89% are younger than 5 years of age, and 98% are younger than 10 years of age.[1-3]

Most primary neuroblastoma tumors occur in an anatomic distribution that is consistent with the location of neural crest tissue because the tumor arises from primitive adrenergic neuroblasts. The adrenal gland is the most common primary tumor site, accounting for 35% of cases overall. However, children younger than 1 year of age have a tumor arising from the adrenal gland in only 25% of cases. Other common sites include the low thoracic and abdominal paraspinal ganglia (30%) and posterior mediastinum (19%). Ganglia in the pelvic and cervical regions account for 2% to 3% of tumors, and in 1% the primary site is unknown.[1,4]

PREVENTION AND EARLY DETECTION

Because neuroblastomas frequently produce high levels of catecholamines, which can be detected in the urine, mass screening for the disease in infants has been performed. Extensive trials in numerous countries have shown that tumors detected by screening tend to be extremely favorable. Unfortunately, screening has not had an impact on survival or early detection of high-risk neuroblastoma.[5,6]

Microscopic neuroblastoma-like nodules frequently can be found at autopsy in infants who die of unrelated causes.[7] Furthermore, clusters of cells consistent with neuroblastoma occur uniformly in the adrenal glands of all fetuses, peaking

at between 17 weeks and 20 weeks of gestation, and then spontaneously regress by birth or in early infancy.[8] Thus, the development and subsequent regression of clusters of cells histologically identical to neuroblastoma appears to be a normal embryologic event, whereas the development of clinically detectable neuroblastoma appears to be a consequence of disruption of this normal developmental process.

The cause of neuroblastoma is not known in most cases. Prenatal or postnatal exposure to drugs, chemicals, or radiation has never been proven to be associated with an increased incidence of the disease.[1] A small fraction of neuroblastomas are familial and are usually associated with a germline mutation in the anaplastic lymphoma kinase *(ALK)* or *PHOX2b* genes. At least 20% of patients with familial neuroblastoma have bilateral or multifocal disease, which tends to present at an earlier age.[9-12]

BIOLOGIC CHARACTERISTICS AND MOLECULAR BIOLOGY

Neuroblastoma is a model disease where improved genetic understanding of the tumor has allowed biology-based risk stratification and treatment. Numerous recurrent genetic changes have been identified in neuroblastoma and are correlated with disease outcome. Recent discoveries of germline mutations in the *ALK* and *PHOX2B* genes in a rare subset of patients with neuroblastoma (less than 1%) has been linked to hereditary neuroblastoma.[12-14] However, somatic *ALK* mutations are also found in 8% to 10% of neuroblastomas and may suggest biologically unfavorable disease. Most aggressive neuroblastomas contain genomic level instability, resulting in chromosomal rearrangement and unbalanced translocation. In contrast, less aggressive tumors tend to show whole chromosome losses and gains.[2,15,16] Those tumors that have loss or gain of whole chromosomes and few or no segmental chromosome abnormalities generally have an excellent prognosis, with many undergoing spontaneous differentiation or regression. In contrast, high-risk neuroblastoma is characterized by recurrent segmental chromosome abnormalities with nonrandom alterations of numerous chromosomes, particularly deletions of 1p36 and 11q and unbalanced gain of chromosome 17q.[17] The most critical genomic alteration is amplification of the MYCN oncogene, occurring in approximately 20 percent of neuroblastomas, and is associated with advanced disease, older age (>18 months), and a significantly poorer outcome.[18-21]

PATHOLOGY AND PATHWAYS OF SPREAD

Neuroblastoma is the most common of the small round, blue cell tumors of childhood. Other malignancies that can appear similar with standard pathology staining include non-Hodgkin lymphomas, Ewing's sarcoma, primitive neuroectodermal tumors, and soft-tissue sarcomas. Neuroblastoma can be distinguished from these other tumors by immunohistochemical staining for various markers including neuron-specific enolase, synaptophysin, and neurofilament. The characteristic histologic appearance is that of small, uniform cells containing dense, hyperchromatic nuclei and scant cytoplasm with neuropil. Homer-Wright pseudorosettes representing neuroblasts surrounding areas of eosinophilic neuropil are seen in up to 50% of cases.

Histologic subtypes represent different points along the maturation pathway and include (in order of increasing differentiation) neuroblastoma, ganglioneuroblastoma, and ganglioneuroma. Ganglioneuromas are considered benign and consist of mature ganglion cells, neuropil, and Schwann cells. Ganglioneuroblastomas have pathologic characteristics of both neuroblastoma and ganglioneuroma and can have an intermediate behavior as well.[22]

A variety of different pathology classification systems have been used for risk stratification. The International Neuroblastoma Pathology Committee (INPC) system is the most widely used and validated. Characteristics of this system are listed in Table 72-1. This represents a modification of the Shimada system that classifies tumors by patient age, the degree of

TABLE 72-1 Prognostic Evaluation of Neuroblastic Tumors According to the International Neuroblastoma Pathology Classification (Shimada System)

International Neuroblastoma Pathology Classification		Original Shimada Classification	Prognostic Group
Neuroblastoma			
Favorable	(Schwannian stroma-poor)	Stroma-poor (favorable)	Favorable
<1.5 year	Poorly differentiated or differentiating and low or intermediate MKI tumor		
1.5-5 years	Differentiating and low MKI tumor		
Unfavorable		Unfavorable	Unfavorable
<1.5 year	(a) Undifferentiated tumor*		
	(b) High MKI tumor		
1.5-5 years	(a) Undifferentiated or poorly differentiated tumor		
	(b) Intermediate or high MKI tumor		
>5 year	All tumors		
Ganglioneuroblastoma, intermixed	(Schwannian stroma-rich)	Stroma-rich intermixed (favorable)	Favorable†
Ganglioneuroma	(Schwannian stroma-dominant)		
Maturing		Well differentiated (favorable)	Favorable†
Mature		Ganglioneuroma	
Ganglioneuroblastoma, nodular	Composite schwannian stroma-rich/stroma-dominant and stroma-poor (schwannian stroma-rich)	Stroma-rich nodular (unfavorable)	Unfavorable†

Data from Shimada H, Ambros IM, Dehner LP, et al: The International Neuroblastoma Pathology Classification (the Shimada system). Cancer 86:364–372, 1999.
MKI, *Mitosis-karyorrhexis index.*
**Rare subtype, especially diagnosed in this age group; further investigation and analysis are required.*
†Prognostic grouping for these tumor categories is not related to patient age.

differentiation toward ganglion cells, amount of Schwann cell stroma present, whether the tumor is nodular, degree of calcification, and the mitosis-karyorrhexis index.[23]

Neuroblastoma commonly spreads via lymphatics to regional lymph nodes, often in the paraaortic chain, and less commonly to the next echelon of lymphatics, such as the left supraclavicular fossa (Virchow node) in patients with abdominal tumors. Hematogenous spread often occurs to bone marrow, bone, and less commonly, to liver. Neuroblastoma appears to have a proclivity for the bones of the skull and especially the posterior orbit, which can cause the clinical presentation of "raccoon eyes" from periorbital ecchymosis. Lung and brain metastases are rare at presentation. However, with improvements in systemic therapy, isolated parenchymal brain metastases are now occurring in about 5% to 10% patients with high-risk disease at relapse. These central nervous system relapses require craniospinal radiation therapy (RT) because of a high risk of leptomeningeal dissemination.[24]

CLINICAL MANIFESTATIONS, PATIENT EVALUATION, AND STAGING

The clinical presentation for neuroblastoma is highly variable because of the wide variety of disease sites. Primary tumor location and extent of disease vary with age. Most children (57%) younger than 1 year of age have locoregional disease at the time of diagnosis, whereas most children (81%) older than 1 year of age have disseminated disease. Children with abdominal tumors may present with abdominal pain, distention, or gastrointestinal disturbances but more commonly it is asymptomatic and discovered incidentally by a caregiver. Many with disseminated disease will present with fever, pain, limp, and significant irritability, especially younger children. Paraneoplastic syndromes, such as opsoclonus-myoclonus syndrome (myoclonic jerking and random eye movements) or vasoactive intestinal peptide (VIP) syndrome (intractable secretory diarrhea, with hypokalemia and dehydration caused by tumor secretion of VIP) are rare, occurring in less than 4% of patients.[25-27] The catecholamines secreted from most neuroblastomas are not likely to cause hypertension, flushing, or tachycardia.

A plain radiograph of the chest or abdomen may show a soft-tissue mass representing the primary tumor, and calcifications are present in 85% of tumors. Staging of neuroblastoma requires numerous imaging modalities. The primary tumor and regional lymph nodes should be imaged with CT or MRI. These studies should also be used to assess for metastases in the liver as well as spinal extension and resectability of the primary tumor. They also may be used to clarify the extent of bone metastases in specific locations, such as the skull.

At least 90% of neuroblastomas exhibit uptake of MIBG; thus bone metastases are primarily imaged using ^{123}I-MIBG scintigraphy. Technetium-99m (^{99m}Tc)–labeled bone scintigraphy is rarely used as a primary modality because MIBG imaging is more sensitive and specific. ^{18}F-fluorodeoxyglucose–labeled positron emission tomography (FDG-PET) can be useful in delineation of metastatic lesions in patients whose tumor is MIBG non-avid as well as in patients with low-risk disease.[28-30] Complete staging also includes two bilateral posterior iliac crest bone marrow aspirates and biopsies. A single positive result is sufficient for the documentation of bone marrow involvement.[31,32]

Because excess catecholamines are produced in most cases, urine catecholamines and their metabolites, specifically vanillylmandelic acid (VMA), and homovanillic acid (HVA) are typically measured. Urinary levels of catecholamines are often given as ratios to the urinary creatinine value.[33]

TABLE 72-2 International Neuroblastoma Staging System

Stage	Description
1	Localized tumor with complete gross excision, with or without microscopic residual disease; representative ipsilateral lymph nodes negative for tumor (nodes adherent to and removed with the primary tumor may be positive).
2A	Localized tumor with incomplete gross excision; representative nonadherent lymph nodes negative for tumor microscopically.
2B	Localized tumor with or without complete gross excision, with ipsilateral, nonadherent lymph nodes positive for tumor. Enlarged contralateral lymph nodes must be negative microscopically.
3	Unresectable unilateral tumor infiltrating across the midline,* with or without regional lymph node involvement; or localized unilateral tumor with contralateral regional lymph node involvement; or midline tumor with bilateral extension by infiltration (unresectable) or by lymph node involvement.
4	Any primary tumor with dissemination to distant lymph nodes, bone, bone marrow, liver, skin, or other organs (except as defined in stage 4S).
4S	Localized primary tumor (as defined for stage 1, 2A, or 2B), with dissemination limited to skin, liver, or bone marrow† (limited to infants <1 year of age).

Data from Brodeur GM, Seeger RC, Barrett A, et al: International criteria for diagnosis, staging and response to treatment in patients with neuroblastoma. J Clin Oncol 6:1874–1881, 1988; Brodeur GM, Pritchard J, Berthold F, et al: Revisions in the international criteria neuroblastoma diagnosis, staging and response to treatment. J Clin Oncol 11:1466–1477, 1993.

**The midline is defined as the vertebral column. Tumors originating on one side and crossing the midline must infiltrate to or beyond the opposite side of the vertebral column.*

†Marrow involvement in stage 4S should be minimal, that is, less than 10% of total nucleated cells identified as malignant on bone marrow biopsy or on marrow aspirate. More extensive marrow involvement would be considered to be stage 4. The MIBG scan (if performed) should be negative in the marrow.

Neuroblastoma staging has undergone several revisions over the past years. Older staging systems, including the Evans and D'Angio classification, were replaced by the International Neuroblastoma Staging System (INSS) (Table 72-2).[31] This staging system is now being replaced by the INRG staging system (Table 72-3).[32]

In 2009, the INRG Task Force introduced a new stratification schema named the INRG classification system, which is emerging as the international standard.[21] This system includes INRG stage (Table 72-3), age, histologic category, grade of tumor differentiation, *MYCN* status, presence/absence of 11q aberrations, and tumor cell ploidy (Table 72-4). Based on this classification, patients are stratified into four different risk groups: very low, low, intermediate, and high risk. Treatment strategies are based on this classification.[32] Survival varies from greater than 90% for patients with low-risk disease to about 40% for patients with high-risk disease.

PRIMARY THERAPY

The therapeutic approach for neuroblastoma varies tremendously, depending on risk group stratification. The available treatment modalities include surgery, chemotherapy, RT, biologic therapy, or immunotherapy. The following is a discussion of therapy for low-, intermediate-, and high-risk disease,

with an emphasis on the role of RT. A basic treatment algorithm for each risk group is shown in Figure 72-1.

Very-Low-Risk Neuroblastoma

Patients with very-low-risk disease have small tumors (or asymptomatic stage 4S, now called MS disease) that will generally undergo spontaneous regression or differentiation into benign ganglioneuromas. These tumors have been successfully managed with close observation without therapeutic intervention. A recently published report by the Children's Oncology Group (COG) study of observation of perinatal neuroblastoma showed event-free and overall survival rates of 97.7 and 100%, respectively.[34]

Ms disease (formerly called stage 4s disease, where "s" represents "special") is an entity unique to neuroblastoma. This stage is defined by patients up to 18 months of age at diagnosis with metastatic disease sites limited to the liver, skin, and less than 10% involvement of bone marrow.[35] Despite it being metastatic, the overall prognosis for patients with Ms disease is good, with a recent reports showing an overall survival rate of 92%.[36] Very young infants (usually less than 3 months of age at time of diagnosis), however, may have rapid tumor progression leading to massive hepatomegaly and subsequent cardiorespiratory failure, requiring immediate intervention. Chemotherapy (per the intermediate-risk group protocols) can sometimes be successful at reversing the rapid tumor progression.[37] However, in infants with rapidly progressive disease or who have failed to respond adequately to chemotherapy, low-dose irradiation to the liver should be considered. Treatment can be given efficiently because simulation and anesthesia are not necessary; the liver generally fills the entire abdomen and can be seen on a port film, and the patients are young enough to be immobilized in a papoose. The typical fractionation schedule in this setting is 1.5 Gy for three fractions, which usually leads to rapid relief of symptoms. The risk of long-term harm to the child from radiation exposure is small because of the low dose. MYCN amplification in this cohort is rare; when present these patients should be treated with intensive therapy as per a high-risk protocol.[20]

TABLE 72-3 International Neuroblastoma Risk Group Staging System*

Stage	Description
L1	Localized tumor not involving vital structures as defined by the list of image-defined risk factors† and combined to one body compartment
L2	Locoregional tumor with presence of one or more image-defined risk factors
M	Distant metastatic disease (except stage MS)
MS	Metastatic disease in children younger than 18 months with metastases confined to skin, liver, or bone marrow

Table modified from The International Neuroblastoma Risk Group (INRG) Staging System: An INRG Task Force Report. J Clin Oncol 27:298–303, 2009.
†Image-defined risk factors are surgical risks factors detected by imaging that make complete resection of the tumor unsafe at the time of diagnosis. See the primary reference for a full listing and description of these risk factors.

Low-Risk Neuroblastoma

Patients with low-risk neuroblastoma (see Table 72-3) can often be cured with surgery alone, even when only a partial resection is obtained.[38,39] Adjuvant RT was used in the past for incompletely resected tumors but has been shown to be unnecessary. Chemotherapy and RT are now reserved for progressive or recurrent disease.

Intermediate-Risk Neuroblastoma

The current treatment approach for intermediate-risk disease (see Table 72-3) consists of surgery for the primary tumor as well as standard-dose, multiple-agent chemotherapy for 4 months to 8 months. Definitive surgery may be delayed until after chemotherapy, which often makes the tumor more easily resectable.

Previously, RT was used in intermediate-risk disease; however, various studies have now shown that RT is not required as part of their initial therapy.[40]

TABLE 72-4 International Neuroblastoma Risk Group Classification System*

INRG Stage	Age (months)	Histologic Category	Grade of Tumor Differentiation	MYCN	11q Aberration	Ploidy	Pretreatment Risk Group
L1/L2		GN maturing; GNB intermixed					Very low
L1		Any, except GN maturing or GNB intermixed		NA			Very low
				AMP			High
L2	<18	Any, except GN maturing or GNB intermixed		NA	NO		Low
					Yes		Intermediate
	≥18	GNB nodular; neuroblastoma	Differentiating	NA	No		Low
					Yes		Intermediate
			Poorly differentiated or undifferentiated	NA			
				AMP			High
	<18			NA		Hyperdiploid	Low
	<12			NA		Diploid	Intermediate
M	12 to <18			NA		Diploid	Intermediate
	<18			AMP			High
	≥18						High
MS	<18			NA	No		Very low
					Yes		High
				AMP			High

Table modified from The International Neuroblastoma Risk Group (INRG) Staging System: An INRG Task Force Report. J Clin Oncol 27:298–303, 2009.

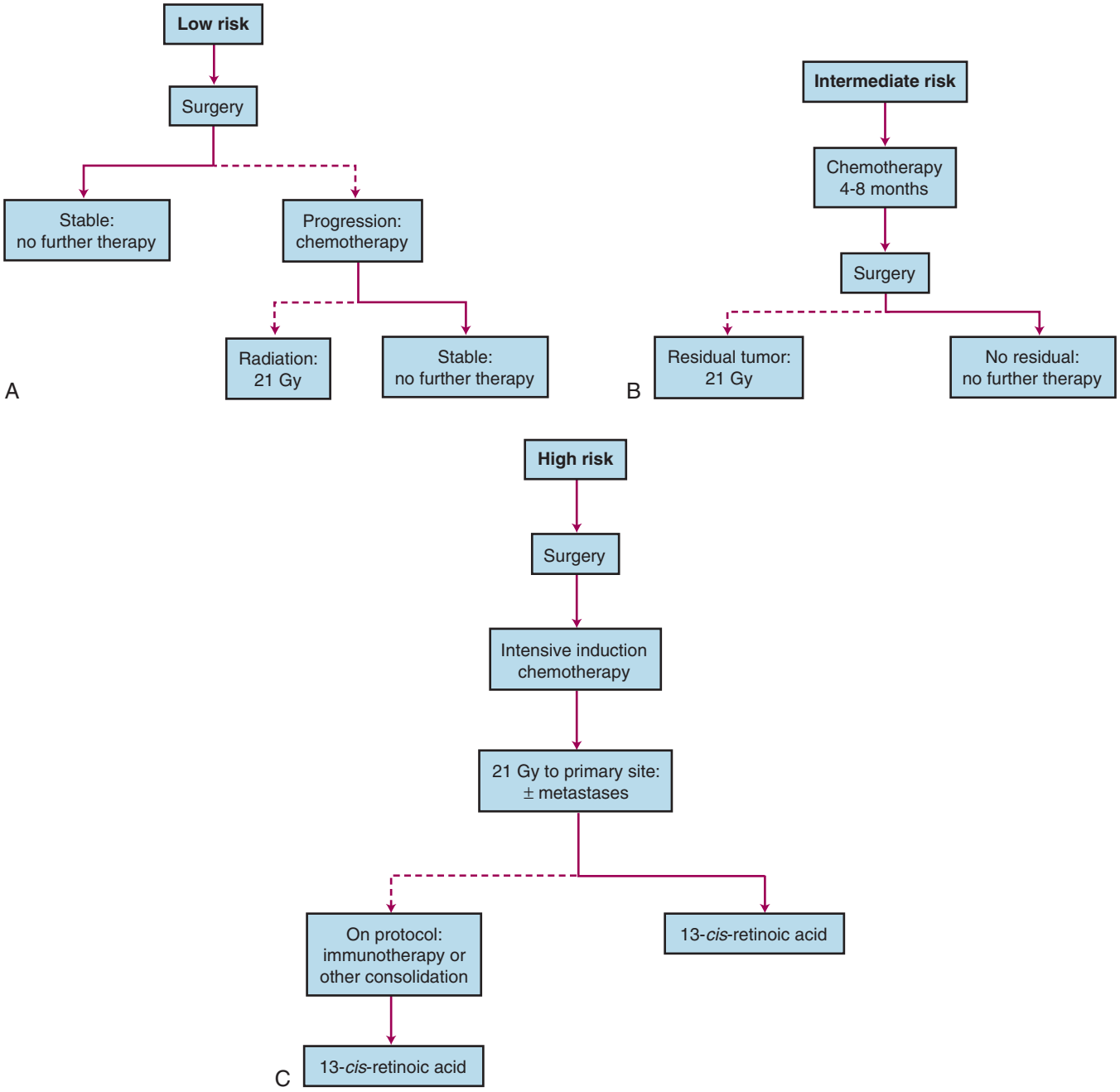


Figure 72-1 Treatment algorithm for low-risk **(A),** intermediate-risk **(B),** and high-risk **(C)** neuroblastoma.

In the COG study A3961, patients with intermediate-risk disease underwent surgery as well as chemotherapy (with cyclophosphamide, doxorubicin, carboplatin, and etoposide). The duration of chemotherapy was based on biologic risk factors for individual patients. The results of that study, published in 2010, demonstrated a 3-year overall survival of 96% among all patients, with 98% overall survival within the favorable biology group, and 93% overall survival among the patients with unfavorable biological features.[37] Importantly, these studies have shown that aggressive surgery and RT are not required to achieve excellent results. RT thus is indicated only for those with disease progression or persistent tumor after chemotherapy and second-look surgery.

High-Risk Neuroblastoma

The current therapeutic approach for high-risk disease includes intensive induction chemotherapy, surgical resection of the primary tumor, and possible myeloablative consolidation therapy with stem-cell rescue, followed by RT and biologic therapy using 13-cis retinoic acid and anti-GD2 immunotherapy to target minimal residual disease. Patients who have a complete or good partial response to induction chemotherapy have a better prognosis.[29] The induction regimens currently in use are all based on similar backbones of alkylating agents (cyclophosphamide and so on), anthracyclines (doxorubicin), and platinum compounds (cisplatin and

carboplatin). Dose and timing varies among the regimens, but published reports have shown that high-dose platinum and alkylator-based regimens have overall induction response rates (CR + VGPR + PR) of 70% to 80%.[41-46]

Consolidation therapy targets potentially resistant neuroblastoma cells using additional high-dose or myeloablative chemotherapy,[47] followed by RT. Maintenance therapy is biological and immunotherapy targeting minimal residual disease (MRD). 13-*cis*-retinoic acid is given as a monthly14-day cycles for 6 months.[47] Additionally, the COG recently reported that the addition of immunotherapy using the chimeric antibody ch14.18 directed at the neuroblastoma tumor antigen GD2, combined with the cytokines granulocyte-macrophage colony stimulating factor (GMCSF) and interleukin-2 (IL-2) significantly improved survival; 2-year event-free survival was 66% with immunotherapy compared with 46% in the control group.[48] Memorial Sloan Kettering (MSK) has also recently reported significantly improved long-term outcomes using the anti-GD2 mouse monoclonal antibody 3F8.[49,50]

The most recent COG protocol for high-risk disease, ANBL0532, included RT to the primary tumor site, regardless of the extent of surgical resection. The dose was 21.6 Gy in 1.8 Gy fractions in the case of complete resection and a boost of 14.4 Gy for a total of 36.0 Gy in the case of incomplete resection. RT was also indicated to sites of metastatic disease that demonstrated persistent MIBG avidity on the pretransplant scan. For patients with greater than five MIBG positive metastatic sites on pretransplant scan, another MIBG scan was performed 4 weeks posttransplant. RT was then limited to avid sites on that scan.

Evidence for the benefit of primary site RT comes from cooperative group trials as well as single institution series.[47] Haas-Kogan et al examined the role of RT on local control in the Children's Cancer Group study 3891. It appears that both 10 Gy to the primary site as well as 10 Gy of total-body irradiation decreased the local recurrence rate. The largest benefit was seen when patients received both local RT and total-body irradiation, for a total dose of 20 Gy. Further supporting the role of postoperative radiation therapy is a series from MSK where a total dose of 21 Gy was given in twice-daily 1.5-Gy fractions. Among 99 patients treated with irradiation to the primary site, the local failure rate was 10%.[51] Only 7 of these patients had residual disease at the primary site at the time of irradiation, and 3 of these had local recurrence, suggesting that 21 Gy is not an adequate dose for gross residual disease. Although final results are not available for the boost dose of 36 Gy in ANBL0532, this strategy may not be effective for most patients. Achieving a gross total resection of the primary tumor before RT seems to be necessary for optimal local control.

Targeted radiopharmaceuticals are also under investigation as an alternative means of delivering specific RT to metastatic tumor sites, either for refractory disease or as part of a myeloablative regimen. Targeted radioisotope therapy using MIBG for delivery of radiation in the form of iodine-131 has been tested extensively in clinical trials in patients with relapsed neuroblastoma. Efforts are currently under way by the COG to include high dose (12 mCi/kg to 18 mCi/kg) I^{131}-MIBG therapy with stem-cell rescue as primary therapy for patients with high risk disease; however, this remains somewhat controversial and the feasibility and tolerability of this approach is still under investigation.

RECURRENT DISEASE AND PALLIATION

Current approaches for treating recurrent or refractory neuroblastoma include novel cytotoxic agents and targeted delivery of radionuclides, retinoids, and other investigational agents. Cyclophosphamide and topotecan, and irinotecan and temozolomide are frequently used cytotoxic regimens.[52-55] RT plays an important role in palliation for neuroblastoma. Patients with incurable disease often live for an extended period of time. However, they often suffer severe pain and functional impairment from metastases, most commonly to bone. External beam radiation therapy (EBRT) is the most effective tool for managing painful metastases. Fractionation schemes depend on the site, field size, marrow reserves, and anticipated life span of the patient. A high-functioning child may benefit from 2-Gy fractions to 30 Gy, whereas a patient with end-stage disease may be better served by a single fraction of 7 Gy to 8 Gy.

IRRADIATION TECHNIQUES

Irradiation techniques depend on the site being treated. Most commonly, patients with high-risk disease have a primary tumor arising from the adrenal gland or abdominal paravertebral region. Radiation volume for localized neuroblastoma is determined by the surgeon's operative findings and presurgical imaging studies. Margins and normal tissue-sparing parameters vary from protocol to protocol. Based on patterns of failure data, it is important to include the paraaortic lymph nodes in the radiation field.[56] CT planning is imperative to delineate the target region as well as normal tissues, including the kidneys, liver, and in some cases, ovaries. Attention should be paid to treatment of vertebral bodies to reduce the risk of scoliosis. Simple anterior and posterior beams, as demonstrated in Figure 72-2, may be a good solution, but intensity-modulated radiation therapy (IMRT) may be better for controlling dose to adjacent organs. Proton therapy may also be considered but may lead to unacceptable kidney doses when posterior beams are used. Bone metastases are often best treated with simple opposed beams. However, more

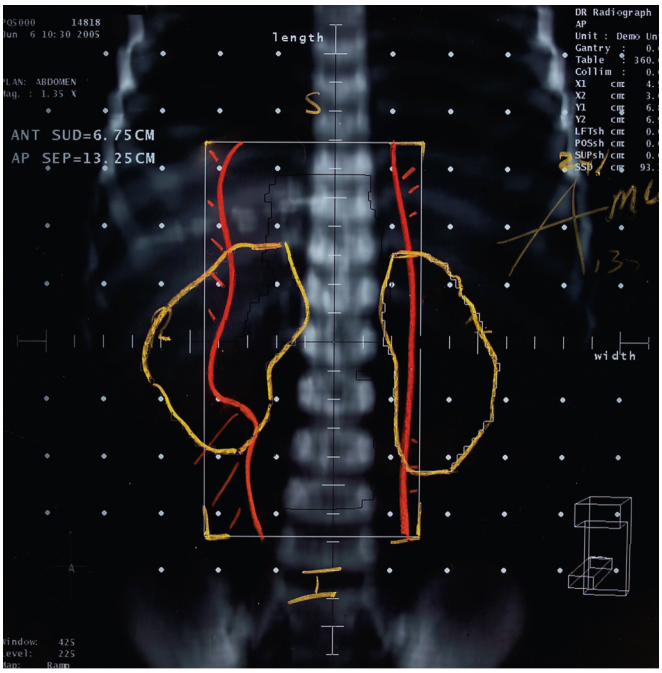


Figure 72-2 Typical anterior and posterior radiation therapy field for adrenal neuroblastoma. Generous coverage of paraaortic lymph nodes is recommended. Adequate kidney sparing is accomplished by treating postchemotherapy tumor volume.

sophisticated approaches may be needed when treating sites in the head and neck because of the complex anatomy and critical structures. Neuroblastoma is common in young children, necessitating the frequent use of anesthesia for RT. In this case, propofol is safe and well tolerated, even for twice-daily treatments.

Intraoperative radiation therapy (IORT) is not an acceptable alternative to EBRT in the context of initial therapy. A report from the University of California–San Francisco showed reasonable local control after complete resection but not after subtotal resection and a high rate of severe aortic complications in patients receiving IORT.[57] In the setting of local relapse following prior EBRT, MSK reported a relatively favorable 50% rate of local control and low rate of complications for 44 patients who underwent subsequent surgery and reirradiation with IORT for locally relapsed neuroblastoma.[58]

LATE EFFECTS

Consideration for long-term complications is critical when treating neuroblastoma. Patients treated years ago with higher doses of radiation frequently suffered from spinal deformities secondary to surgery and RT. Orthopedic problems from RT are less severe with a dose of 21 Gy but should still be considered when designing treatment fields. As a general rule, it is desirable to limit as much of each kidney as possible to doses less than 15 Gy to 18 Gy to prevent major impairment in renal function. One must also inform parents about the low risk of diabetes mellitus and second malignancies. A prospective trial is currently under way at MSK testing a stepwise reduction in radiation dose from 21 Gy to 18 Gy to 15 Gy. It is likely that even small dose reductions in this range will result in lower risks of spinal growth abnormalities and diabetes mellitus. A recent study of long-term survivors of high-risk neuroblastoma shows that the majority have late complications of therapy, including hearing loss, hypothyroidism, ovarian failure, musculoskeletal abnormalities, and pulmonary dysfunction. However, most complications were considered to be of mild-to-moderate severity.[59] All members of multimodality teams that care for patients with neuroblastoma patients must be mindful of late effects and strive to minimize complications while ensuring the best chance for cure.

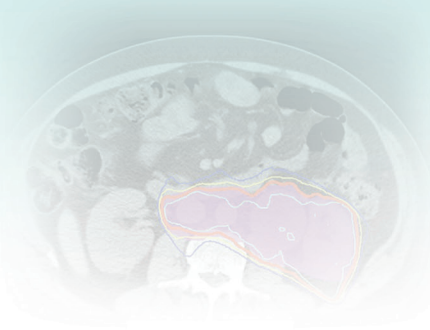
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CHAPTER

73 Pediatric Leukemias and Lymphomas



Karen Jean Marcus and John Torsten Sandlund, Jr.

EPIDEMIOLOGY

Acute leukemias (acute lymphoblastic leukemia [ALL] and acute myelogenous leukemia [AML]) and lymphomas (Hodgkin's and non-Hodgkin's [NHL]) together represent approximately 40% of malignancies in children.

The annual incidence of new cases in the United States in children younger than age 15 years for ALL is 2500 to 3500; AML, 500; and NHL, 500.

BIOLOGY, CLASSIFICATION, AND STAGING

ALL is classified by:

- Immunophenotype: B-cell progenitor, T-cell progenitor, non-B cell, and non-T cell
- Morphology and immunologic markers
- Cellular DNA content (ploidy)
- Cytogenetics (presence of specific translocations, trisomies, and other chromosomal or genetic aberrations)

Staging involves evaluation of bone marrow, cerebrospinal fluid, and evaluation of extramedullary sites.

AML is classified according to the French-American- British (FAB) morphology. Staging is as for ALL.

NHL is classified by the World Health Organization (WHO) Classification of Tumors of the Haematopoietic and Lymphoid Tissues. The major subtypes are lymphoblastic lymphoma, Burkitt's lymphoma, and large cell lymphoma. Large cell lymphomas can be of B-cell origin or T-cell origin.

Staging involves examination of bone marrow and cerebrospinal fluid as well as radiographic and nuclear imaging for nodal and extranodal sites.

THERAPY

The primary treatment of leukemias and lymphomas includes systemic chemotherapy. The intensity of therapy for leukemia and the duration of therapy for lymphoma are determined by risk stratification according to biologic and clinical features.

Therapy for ALL involves induction chemotherapy, intensification or consolidation, central nervous system (CNS) therapy, and maintenance therapy.

Therapy for AML includes induction chemotherapy based on the FAB classification. Intensification or consolidation may be with bone marrow transplant.

Therapy for NHL involves chemotherapy based on the biologic and clinical features of histologic subtype and clinical stage.

INDICATIONS FOR RADIATION THERAPY

ALL:

- Cranial irradiation for CNS prophylaxis in selected patients with high-risk disease
- Cranial irradiation for treatment of children with CNS involvement at diagnosis or relapse
- Testicular irradiation for relapse in the testes
- Total-body irradiation as part of the myeloablative regimen in stem-cell transplantation

AML:

- Primary use is total-body irradiation for stem-cell transplantation.

NHL:

- Total-body irradiation for some patients is part of the myeloablative regimen in stem-cell transplantation in patients with lymphoblastic lymphoma.

LATE SEQUELAE

Late sequelae include neurocognitive disorders, endocrinologic problems, growth delay, and induction of secondary malignancies.

TREATMENT OF RELAPSE AND PALLIATION

Local radiation therapy (RT) can be used to palliate symptomatic recurrences in leukemias and lymphomas. Relapses in the testes and CNS are treated by intensive systemic chemotherapy with RT. Treatment of relapse often includes bone marrow transplantation with total-body irradiation as part of the myeloablative regimen.

ACUTE LYMPHOBLASTIC LEUKEMIA

ALL is the most-common malignancy in children, accounting for one fourth of all childhood cancers. The advances in the treatment of ALL since the 1940s represent one of the most tremendous success stories in modern medicine. The early successes resulted from the identification of single-agent chemotherapy and then the development of combination chemotherapy, recognition of the need for CNS preventative therapy, and maintenance chemotherapy. Concurrent with these developments, new understanding of immunophenotyping, molecular characterization, and treatment responses allowed for the definition of risk groups to tailor therapy.

Epidemiology

ALL accounts for 75% of childhood leukemia and is diagnosed in 2500 to 3000 children in the United States annually[1,2] with a peak age incidence between 2 years and 5 years. The incidence of ALL is higher among boys than girls. This difference is more pronounced in pubertal children[3] and particularly evident in cases of T-cell ALL. In the United States, ALL occurs more commonly among white children than among black children.[4]

Etiology

A single etiology of ALL has not been identified; however, predisposing risk factors include genetics, environmental factors, viral infection, and immunodeficiency. Genetics appears to play a role in the cause of ALL in some children as evidenced by the association between specific chromosomal abnormalities and childhood ALL. The most-common constitutional chromosomal abnormality associated with childhood leukemia is trisomy 21 or Down syndrome[5]; less-common chromosomal abnormalities include Kleinfelter's syndrome and trisomy G syndrome.[6] The majority of cases of leukemia in children cannot be attributed to any known factor.

ALL is believed to develop from the malignant transformation of a single abnormal progenitor cell that then expands indefinitely. In pediatric ALL, evidence suggests that it occurs in committed lymphoid precursors. In contrast, in Philadelphia chromosome–positive ALL and in pediatric AML this event may occur earlier because mutations are observed in multiple cell lineages.[7,8] The sequence of events resulting in malignant transformation is likely to be multifactorial. Leukemia can develop along any point in the normal stages of lymphoid development, which reflects the fact that ALL is a biologically heterogeneous disorder.

Classification and Immunophenotyping

ALL is divided into two distinct subtypes based on the expression of cell surface markers. B-ALL, representing approximately 85% of cases and T-ALL, making up approximately 15% of cases. B-ALL is characterized by the expression of CD79a, CD19, HLA-DR, and other B cell-associated antigens. Ninety percent of precursor B-cell ALL cases express the CD10 surface antigen. Patients with B-cell precursor ALL whose lymphoblasts express CD10 on their cell surfaces have a more favorable prognosis than those who do not, primarily owing to the strong association of CD10 negativity with rearrangements of the *MLL* gene on chromosome 11.[9,10] In approximately 1% to 2% of cases of ALL, the cells express surface immunoglobulin.

Ten to 15 percent of children will have ALL that is of T-cell origin. T-ALL is characterized by the expression of cytoplasmic CD3 and surface expression of T-cell antigens including CD2, CD5, and CD7. In contrast to B-cell precursor ALL, T-cell ALL is more frequently associated with older age at diagnosis, a higher presenting leukocyte count, and bulky extramedullary disease. Extramedullary involvement can include an anterior mediastinal mass, lymphadenopathy, hepatosplenomegaly, and overt CNS involvement.[11]

Cytogenetics

Advances in cytogenetics have led to an increasing understanding of the biology of ALL.[12] Cytogenetic abnormalities identified in ALL include abnormalities in chromosomal number (ploidy) as well as those in chromosomal structure. Ploidy is determined either by counting the modal number of chromosomes in a preparation of a metaphase karyotype or by measuring DNA content by flow cytometry. Hyperdiploidy exists when there are more than 46 chromosomes. Most cases of ALL are diploid or hyperdiploid. Ploidy in childhood B-lineage leukemia has prognostic significance.[13-15] Children with higher ploidy, greater than 50 chromosomes, have a better prognosis than other children with ALL, including those with 47 to 50 chromosomes; those with 51 to 65 chromosomes (higher hyperdiploid) with specific trisomies (including chromosomes 4, 10, and 17) appear to have an especially favorable prognosis.[16-18] Those patients who have hyperdiploid leukemia with favorable trisomies also tend to have other favorable prognostic features (see discussion in this chapter). Hypodiploidy (modal chromosomal number less than 44) is associated with inferior outcomes, especially among those with near-haploid ALL, with 24 to 28 chromosomes.[19-21]

Structural chromosomal abnormalities occur in ALL leukemia cells. The most common of these abnormalities are translocations. Translocations lead to alterations in the regulation of oncogenes. The activation of oncogenes and the loss of tumor suppressor genes are examples of the altered regulation believed to be involved in the evolution of leukemia. The most frequently identified translocation in ALL is t(12;21) and leads to the TEL-AML1 fusion protein. This occurs in approximately 20% of cases (nearly exclusively in those with B-lineage phenotype) and is associated with a favorable prognosis.[22,23] In contrast, t(9;22) and t(4;11) translocations are associated with early treatment failure.[15,24]

The t(9;22)(q34;q11) translocation results in the formation of the Philadelphia (Ph) chromosome and is found in 5% of childhood ALL. Children with Ph chromosome–positive ALL have a poor response to standard therapy but may fare better with intensive regimens that include the use of a tyrosine kinase inhibitor such as imatinib.[25-29]

Other unique chromosomal translocations have been observed in childhood ALL. The role of these and all translocations in the development of leukemia remains speculative. Some translocations that result in altered gene expression appear to confer a proliferative advantage for the leukemic cells. When patients with ALL are in remission, the cytogenetic abnormalities just described are not detectable. When relapse occurs, reappearance of the original cytogenetic abnormality confirms that there is a recurrence of the original leukemia.

Presentation and Evaluation

The presenting signs and symptoms of ALL are related to the degree of bone marrow infiltration as well as the extent of extramedullary involvement. These can include fever, petechiae, lymphadenopathy, and bone pain. Hepatosplenomegaly is found in two thirds of patients. Children with T-cell ALL have some distinctive features. T-cell ALL more frequently occurs in older boys, presents as high initial white blood cell (WBC) counts, and often has a mediastinal mass at diagnosis. The definitive diagnosis is made by bone marrow aspiration, although a bone marrow biopsy may be required in some cases and allows for morphologic assessment, immunophenotyping, karyotyping, and molecular evaluations such as reverse transcriptase/polymerase chain reaction and fluorescent in-situ hybridization for chromosomal characterization.

At the time of initial diagnosis the evaluation of patients includes cerebrospinal fluid examination, evaluation of uric acid levels, liver function tests, renal function tests, coagulation screening, chest radiography, evaluation for infection, and echocardiography (Box 73-1). Manifestations of CNS involvement such as headache, lethargy, papilledema, and cranial neuropathies (most often the third, fourth, sixth, and seventh) are infrequently present at diagnosis. CNS involvement is divided into three categories based on the number of white blood cells (WBCs) and the presence of lymphoblasts on the Cytospin. CNS-1 is defined as no evidence of lymphoblasts in the cerebrospinal fluid. CNS-2 is defined as fewer than five WBCs per microliter with blasts present in the Cytospin, and CNS-3 is defined as five or more WBCs per microliter with blasts in the Cytospin or the presence of cranial nerve palsy. CNS-3 involvement of the CNS at diagnosis is found in less than 5% of children with ALL.[30]

BOX 73-1 Initial Evaluation

History and physical examination
Laboratory studies
Bone marrow aspirate and biopsy*
Complete blood cell count and differential
Coagulation profile
Lactate dehydrogenase
Uric acid
Electrolytes
Liver and renal function tests
Chest radiograph
Serum immunoglobulin
Varicella zoster titer
Human immunodeficiency virus test
Purified protein derivative skin test
Urinalysis
Cultures
Echocardiogram
Cerebrospinal fluid examination†

**Bone marrow studies: morphology, cytogenetics, immunophenotype, and cytochemistry.*
†Therapeutic lumbar puncture performed for diagnosis concurrent with administration of intrathecal chemotherapy.

BOX 73-2 Prognostic Factors in Acute Lymphoblastic Leukemia

Initial white blood cell count
Age at diagnosis
Sex
Race
Presence of mediastinal mass
Organomegaly and lymphadenopathy
Hemoglobin level
Platelet count
Cytogenetics and ploidy
Immunophenotype
French-American-British morphology
Expression of myeloid antigens on leukemic cells
Serum immunoglobulins
Nutritional status
Rapidity of response

Prognostic Factors

Several clinical and biologic factors determined at diagnosis have been identified and shown to have prognostic significance (Box 73-2). These prognostic factors are used to assign patients to risk strata that tailor the treatment. These factors have been integral in the development of all modern therapeutic trials. Although many of these factors have shown prognostic importance, not all are currently used to determine risk stratification.

The presenting leukocyte counts and age at diagnosis are uniformly accepted as prognostic features. Children with the highest initial WBC count have a poorer prognosis.[31,32] Infants younger than 1 year of age have the worst prognosis, and adolescents also have a poorer event-free survival than younger children, except those younger than age 1 year.[33,34] Children older than 10 often have other poor risk features including T-cell phenotype.[34] Infants with ALL have shown the worst outcome, with an event-free survival of 10% to 20%.[33] Infants also have other poor-risk features, including high presenting WBC count, presence of CNS leukemia, massive organomegaly, and a poor day 14 response to induction chemotherapy.[33] Infant ALL has unique biologic features, including chromosomal abnormalities that are associated with a worse prognosis. Structural abnormalities of chromosome 11, such as rearrangement of band q23, within the *MLL/ALL1* gene are often present.[35,36] The t(4;11) translocation is commonly seen, and many have leukemia cells that coexpress myeloid markers (CD15).[33,35,37] This finding suggests that infant ALL arises in a multipotent precursor cell. Chromosomal abnormalities in the leukemia cells also have prognostic significance. The presence of the Ph chromosome and of *MLL* rearrangements (even in noninfant patients) is associated with a higher risk of relapse.

Recent studies using genomic profiling have identified a biologically distinct subset of patients with a high risk of relapse. These patients have a gene expression signature similar to patients with BCR-ABL-positive ALL but lack the BCR-ABL translocation.[38]

T-cell immunophenotype and the presence of CNS disease at diagnosis are also considered high-risk features. Early responses to initial therapy are also prognostic. These include the time to achieve remission and the decrease in peripheral blast count after administration of corticosteroids, when longer time to remission or poor response to initial corticosteroid therapy is associated with worse outcomes. Rapid morphologic clearance of blasts in the marrow 7 days to 14 days after the initiation of multiple-agent chemotherapy has been associated with more favorable outcomes.

Nearly all current leukemia protocols include measurements of minimal residual disease at the end of induction chemotherapy. Multiple-parameter flow cytometry and polymerase chain reaction assays of leukemia-specific gene arrangements have been used to assess submicroscopic levels of minimal residual disease soon after the initiation of therapy.[39-42] High levels of minimal residual disease at the end of the first month of therapy and other early time points has been associated with a high risk of subsequent relapse.[43-47]

On most protocols, children with high levels of minimal residual disease at the end of remission induction are now considered to be high or very high risk (regardless of other presenting features) and receive intensified therapy.

As therapy for ALL has become more intensive and the outcomes have improved, many of these factors have lost statistical significance as prognostic factors. In addition, the definitions of high leukocyte counts and age varied among cooperative groups. To allow comparisons of results, the National Cancer Institute held a workshop to develop a uniform set of prognostic factors.[48] The age and WBC count criteria for childhood ALL agreed on at the Cancer Treatment and Evaluation Program/National Cancer Institute Workshop are shown in Table 73-1.

Treatment

The foregoing prognostic indicators are used to stratify children with ALL into risk groups. The stratification is dependent on prompt, accurate evaluation and sophisticated techniques. To accomplish this, as well as to treat patients with the increased intensity of current therapy, evaluation and treatment is most appropriately carried out in recognized pediatric oncology centers. The treatments for the different risk groups vary in intensity and by institution. However, the framework for all risk groups includes four key elements: remission induction, CNS preventative therapy, consolidation, and maintenance (Figure 73-1).

Induction treatment is designed to achieve complete remission, defined as no evidence of leukemia. Peripheral blood cell

counts must be within the normal range, and the bone marrow must be of normal cellularity and contain less than 5% lymphoblasts. There should be no evidence of CNS disease on examination of the cerebrospinal fluid, and there must be no extramedullary disease. Remission can be achieved in 85% of children with ALL using vincristine and a glucocorticoid; however, the addition of l-asparaginase or the addition of an anthracycline will improve the remission induction rate to 95%.[49] In general, most current regimens use a three- or four-drug induction phase, including vincristine, a corticosteroid, and L-asparaginase plus or minus an anthracycline.

TABLE 73-1 Uniform Age and White Blood Cell Count Criteria for B-Precursor Acute Lymphoblastic Leukemia Standard and High-Risk Cohorts*

Risk	Definition	4-Year Event-Free Survival (%)	B-Precursor Patients (%)
Standard	WBC count <50,000/μL Age 1.00-9.99 year	80.3	68
High	WBC count ≥50,000/μL *or* Age ≥10.00 year	63.9	32

From Smith M, Arthur D, Camitta B, et al: Uniform approach to risk classification and treatment assignment for children with acute lymphoblastic leukemia. J Clin Oncol 14:20, 1996. Reprinted from the Am Soc Clinl Oncol.
**Adopted at the Cancer Treatment and Evaluation Program/National Cancer Institute Workshop.*

The prevention of CNS disease is one of the major elements of successful ALL treatment. The approach to CNS prophylaxis has evolved over the decades since it was first incorporated into ALL therapy in the 1970s. Craniospinal irradiation and cranial irradiation plus intrathecal methotrexate reduced the relapse rate in the CNS from 50% to less than 10%.[50] To avoid the myelosuppression and the effects on spinal growth, intrathecal methotrexate was substituted for spinal irradiation as part of the standard CNS preventative therapy. Intrathecal therapy has been shown to successfully prevent CNS relapse in patients with standard-risk disease and avoids the neurocognitive sequelae and secondary tumors that can result from cranial irradiation. Intrathecal chemotherapy in conjunction with intensive systemic therapy has also provided adequate CNS prevention for some children with high-risk features.

Children with an increased risk of CNS relapse include those with other high-risk features such as high initial WBC count, T-cell phenotype, very young age, t(4;11), the presence of the Ph chromosome, and lymphomatous presentation. For patients with these features, cranial irradiation (see discussion in this chapter) is generally incorporated into the treatment protocol, although many current protocols are intensifying intrathecal therapy and omitting cranial irradiation for some patients. Children with infant ALL are treated with intensive chemotherapy to avoid the late sequelae of cranial irradiation in this age group. The CNS-directed therapy for patients with CNS-3 is not preventative but therapeutic.

Once complete remission has been achieved, consolidation and maintenance therapy are used to provide continued

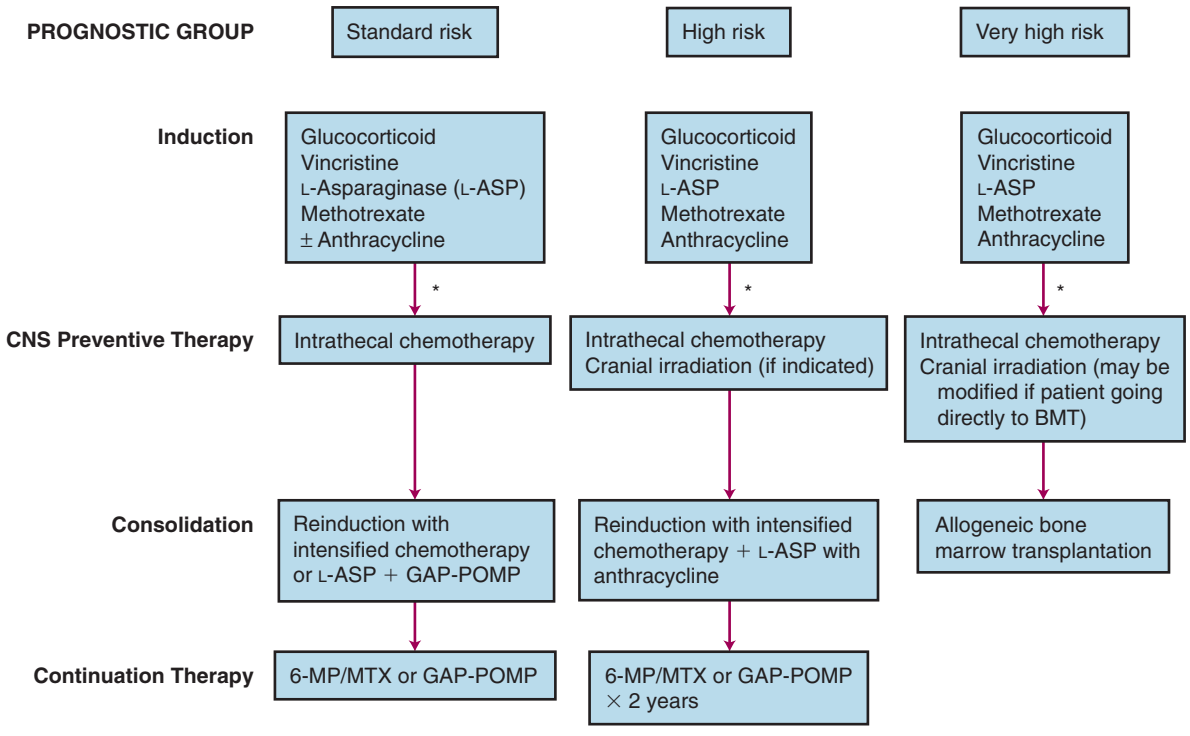


Figure 73-1 **Treatment algorithm for acute lymphoblastic leukemia.** *6-MP,* 6-mercaptopurine; *BMT,* bone marrow transplant; *CNS,* central nervous system; *MTX*, methotrexate. *GAP-POMP* (GAP refers to the schedule of mercaptopurine administration given on 14 days of each 21-day cycle, thus a 7-day GAP) repeats a 3-week cycle until 2 years of continuous complete remission: vincristine, prednisone, mercaptopurine, methotrexate; high-dose cycle; vincristine, mercaptopurine, high-dose intravenous and intrathecal methotrexate.

cytoreduction of the leukemic cell burden without permitting the emergence of drug-resistant clones. Components of the consolidation phase vary according to risk group, with more intensive treatments used for patients classified as high or very-high risk. The continuation phase consists of less-intensive, low-dose chemotherapy. Nearly all regimens include weekly methotrexate and daily 6-mercaptopurine during this phase. Some protocols also use intermittent pulses of vincristine and corticosteroid in addition to methotrexate and 6-mercaptopurine.[51] Total duration of therapy is typically 2 years to 3 years. On some regimens, boys receive a longer maintenance phase than girls.

Indications for Radiation Therapy

The role of RT in the treatment of childhood ALL has diminished in recent years. Improvements in the efficacy of chemotherapy administration and a clearer understanding of the prognostic factors have been responsible for this changing role. However, RT remains an important modality in ALL in specific situations. These include prophylactic cranial irradiation in select groups of patients with high-risk disease, therapeutic CNS treatment for patients with meningeal leukemia, treatment of testicular disease, and total-body irradiation for some patients for whom stem-cell transplant is recommended.

In most regimens, CNS prophylaxis for patients at lower risk is achieved with systemic and intrathecal chemotherapy without cranial irradiation. Children with high-risk features are at an increased risk of CNS relapse and, historically, have received prophylactic cranial irradiation. These features include a presenting WBC count of 50,000/μL or greater; those with WBC counts over 100,000/μL are at particularly high risk of CNS relapse. Additional high-risk features that are indications on some treatment protocols for cranial irradiation are T-cell phenotype, Ph chromosome–positive ALL, and the presence of t(4;11). Infants younger than age 12 months with 11q23 abnormalities are at high risk of CNS relapse but because of their young age are usually treated without cranial irradiation, using intensified systemic and intrathecal chemotherapy to treat the CNS. Historically, the standard dose for high-risk ALL cranial prophylaxis had been 1800 cGy; however, published trials from the Berlin-Frankfurt-Munster group used 1200 cGy in patients with CNS-1 disease with good results.[52] The standard dose for prophylactic cranial irradiation in those patients with high-risk disease still treated with irradiation is now 1200 cGy.

Currently, fewer than 20% of children with ALL are treated with prophylactic cranial irradiation. Investigators are continuing to evaluate whether cranial irradiation can be eliminated in a greater proportion of patients, especially in young children in whom the toxicities from irradiation are the most significant. Some protocols have omitted cranial irradiation entirely, using strategies that intensify the use of intrathecal chemotherapy and CNS-penetrant systemic chemotherapy, such as high-dose methotrexate.[53,54] In one such study from St. Jude Children's Research Hospital, the 5-year cumulative risk of isolated CNS relapse was 2.7% and that of any CNS relapse (isolated or combined with bone marrow) was 3.9%, although the risk of relapse was higher in some patients with high-risk disease subsets.[54]

Children who present with CNS-3 disease at diagnosis, regardless of the other features of their disease, are deemed at high risk and are considered to have meningeal leukemia. The treatment of these patients varies, and some protocols continue to employ craniospinal irradiation or cranial irradiation in addition to intrathecal chemotherapy. Irradiation is not administered until the patient is in remission, including clearance of the cerebrospinal fluid. After achievement of complete remission, 1800-cGy cranial irradiation has been administered early in the therapy.[52]

Isolated CNS relapse is rare with the current approach to ALL treatment. The treatment depends on the time from first remission as well as the extent of prior CNS therapy. Patients with an isolated CNS relapse occurring 18 months or more after initial diagnosis have an event-free survival of approximately 80% when treated with intensive systemic chemotherapy and cranial or craniospinal irradiation. A dose of 1800 cGy to the cranial field has been shown to be effective in such patients.[55] Patients with earlier CNS relapses, or those with T-cell phenotype or a history of cranial irradiation prior to CNS relapse, may be considered for stem-cell transplant once a second remission is achieved. In that situation the total dose of craniospinal irradiation may need to be modified depending on timing of the transplant.

Cranial nerve palsies can be seen in patients with meningeal leukemia. Urgent RT to the base of the skull initially to reverse the palsy is often given, with full cranial irradiation given at the scheduled time for CNS treatment. Doses between 1000 cGy and 1200 cGy are used. Although the use of higher doses has been reported, no dose response was observed for higher doses.[56]

The technique for cranial irradiation must ensure coverage of the cranial meninges as well as other areas of potential access to the CNS such as the cribriform plate, the posterior retina and posterior globe of the eye, the exit regions of cranial nerves III, IV, V, and VI, and the inferior extent of the temporal meninges. The cribriform plate should be identified by following the anterior clinoids anteriorly and locating the superior orbital plate. The field extends to the C1-C2 interspace unless a clinical field arrangement is used, in which case the field would be brought to the C2-C3 interspace. To ensure adequate dose to the meninges, the entire calvaria is covered and the energy should be 4 MV or 6 MV photons. Custom blocks are used to shield normal tissues. Parallel opposed lateral fields are used. Immobilization is critical to ensure precise treatment and reproducibility and use of immobilization devices is recommended when possible. Sedation may be required for younger patients who are unable to fully cooperate.

Testicular Leukemia

Testicular involvement that is clinically apparent at diagnosis is infrequent; however, occult disease is found in 25% of boys.[57] Overt involvement is manifest as painless testicular enlargement, which may be unilateral or bilateral. Testicular biopsies during maintenance or at the conclusion of all therapy have been abandoned because the biopsy results did not accurately predict eventual relapse.[13,58,59] Some protocols have used prophylactic bilateral testicular irradiation, although this approach has not been widely used because the current systemic therapy protocols have lessened the rate of testicular relapse and testicular irradiation causes permanent sterility.[60,61]

Testicular relapse occurs in less than 5% of cases in the current era of intensive therapy.[62,63] Both systemic therapy as well as local RT directed at the testes are used to treat testicular relapse. Reinduction therapy is needed as well as CNS-directed treatment. Bilateral testicular irradiation is used to doses of 2400 cGy to 2600 cGy in 200-cGy fractions.[64] The treatment is delivered with the child supine in the frog-leg position with the soles of the feet touching. The penis is taped or secured out of the RT field. A bolus dose may be needed to ensure adequate dose to the testes or electron boost therapy can be used. Radiation is delivered to the entire scrotal contents.

Late Sequelae

With dramatic improvement in the outcome of children with ALL, the late effects of therapy on the survivors have become increasingly apparent. The late effects are multifactorial and are related to both chemotherapy and RT and vary with each child, based on underlying clinical factors. A multidisciplinary approach is needed because the late sequelae involve many organ systems and vary in severity. The following discussion focuses on those late effects chiefly related to RT.

The CNS sequelae are of particular concern. Neurocognitive functional impairment has been observed in ALL survivors. Lower doses of cranial irradiation, for example, 1200 cGy rather than 1800 cGy in patients with high-risk disease, and the elimination of cranial irradiation from patients with standard-risk disease should help lessen the late sequelae. However, in a prospective randomized trial comparing 1800 cGy with no cranial irradiation, all patients received intrathecal and intravenous methotrexate and the patients who underwent irradiation had no worse neurocognitive effects.[65] Children irradiated when younger than 8 years of age and particularly when younger than 5 years of age appear to experience the most severe neurocognitive sequelae. Leukoencephalopathy is a devastating and fortunately uncommon event in the current era. It is characterized by multifocal demyelination. Although this occurs most commonly in patients who have received higher cumulative doses of RT as well as higher cumulative doses of intrathecal and systemic methotrexate (e.g., those with recurrent meningeal leukemia), this severe form of neurotoxicity has been observed in children who received no cranial irradiation.[66,67]

Neuroendocrine sequelae involving the hypothalamic-pituitary axis have been observed in ALL survivors treated with cranial irradiation. Most commonly seen is growth hormone deficiency, which appears to be dose related in that children treated with 1800 cGy have reduced growth hormone levels compared with healthy controls but not as low levels as those treated with 2400 cGy.[68] However, growth delay and short stature have also been seen in unirradiated ALL survivors, suggesting that the cause is likely to be multifactorial.

The risk of second tumors in ALL survivors is estimated to be between 3% and 12% at 5 years to 24 years after the initial diagnosis.[69,70] Second solid tumors have most commonly occurred in patients treated with cranial irradiation and are within or near the RT field. However, there are reports of ALL patients not irradiated who developed secondary CNS tumors.[71] The most common hematopoietic tumors are AML and myelodysplastic syndrome.[69,70]

Testicular irradiation results in sterility. Some studies have shown elevated follicle-stimulating hormone and luteinizing hormone levels, decreased testosterone levels, and delays in sexual maturation, suggesting that the endocrine function of the testes may be adversely affected at doses of 2400 cGy and higher.[72,73] Supplemental or replacement androgens may be required.

ACUTE MYELOGENOUS LEUKEMIA

AML comprises a group of hematologic malignancies that arise from the precursors of the myeloid, monocytoid, erythroid, and megakaryocytic cell lineages. AML represents 15% to 25% of childhood leukemia but accounts for over 30% of deaths from leukemia. The classification used in AML is the FAB schema, which defines seven subtypes of AML (M1 to M7), characterized by morphologic, histochemical, immunophenotypic, and cytogenetic features (Table 73-2). An M0 subtype has been used for an acute undifferentiated leukemia.[74]

TABLE 73-2 Morphology of Acute Myelogenous Leukemia: French-American-British (FAB) Classification System

FAB Type	Name
M1	Acute myeloblastic: no maturation
M2	Acute myeloblastic with maturation
M3	Acute promyelocytic: hypergranular type
M3v	Acute promyelocytic: microgranular variant
M4	Acute myelomonocytic
M4Eo	Acute myelomonocytic with eosinophilia
M5a	Acute monocytic
M5b	Acute monocytic with differentiation
M6	Acute erythroleukemia
M7	Acute megakaryoblastic

In 2002 the WHO proposed a new classification system incorporating cytogenetic information correlated with outcome. This was expanded in 2008 with additional cytogenetic abnormalities linked to AML classification. This cytogenetically based classification provides biologic and prognostic information that informs treatment of patients. Children with t(8;21), inv(16), t(15;17), and those with translocations of the MLL gene make up almost half of the cases of AML and are classified as "AML with recurrent cytogenetic abnormalities."[75]

Children with AML present with a broad range of signs and symptoms. Fever is present in one third of patients, owing to the release of pyrogens from leukemic cells or from macrophages and lymphocytes reacting to the proliferating leukemic blasts or from secondary bacterial infections from neutropenia. Pallor, headache, tinnitus, fatigue, and congestive heart failure can be present if anemia is severe. Bleeding from thrombocytopenia or from disseminated intravascular coagulation can occur. Bone pain is a frequent complaint. Hepatosplenomegaly as a result of organ infiltration is present in approximately half of children at diagnosis.

Treatment of AML involves first stabilization of the patient at diagnosis, aggressive supportive care to treat potential complications such disseminated intravascular coagulation, infectious complications, tumor lysis syndrome, and hyperleukostasis. Induction of remission involves multiagent chemotherapy. Induction is followed by postremission consolidation and intensification and CNS prophylaxis. The postremission consolidation consists of varying number of courses of intensified chemotherapy with or without allogeneic stem-cell transplantation. Maintenance is not part of AML therapy with the exception of acute promyelocytic leukemia for which maintenance therapy does improve event-free and overall survival. Induction therapy for AML most commonly includes cytarabine coupled with an anthracycline plus or minus additional agents such as etoposide, thioguanine, or dexamethasone.[76,77] Treatment of M3 AML, a disease characterized by promyelocytic morphology and the presence of t(15;17), includes all-trans-retinoic acid in addition to cytotoxic chemotherapy.

Postremission therapy, particularly with increased dose intensity of cytarabine, resulted in lower relapse rates and longer remission duration.[78,79] CNS chemoprophylaxis is used for all patients. Children with the highest risk of a CNS relapse are those with M4 or M5 AML or with high presenting peripheral blast counts. CNS relapse is generally followed by bone marrow relapse. With the use of prophylaxis in all patients with AML, the incidence of CNS relapse is 5%.[78,80]

TABLE 73-3 Non-Hodgkin's Lymphomas in Children

Subtype	Proportion of Cases (%)*	Phenotype	Common Site of Primary Tumor	Translocation
Burkitt's	39	B cell	Abdomen or head/neck	t(8;14)(q24;q32) t(2;8)(p11;q24) t(8;22)(q24;q11)
Lymphoblastic	28	T cell	Mediastinum or head/neck	t(1;14)(p32;q11) t(11;14)(p13;q11) t(11;14)(p15;q11) t(10;14)(p24;q11) t(7;19)(q35;p13) t(8;14)(q24;q11) t(1;7)(p34;q34)
Large cell	26	B cell, T cell, indeterminate	Mediastinum, abdomen, head/neck, or skin	t(2;5)(p23;q35)†

**Other histologies account for approximately 7%.*[93]
†Anaplastic large cell lymphoma (ALCL) histologic subtype.

Extramedullary disease outside the CNS can also occur, such as the development of chloromas, most commonly in M4 and M5 subtypes. There was no benefit to the use of local RT to treat chloromas, in addition to systemic therapy in children.[81] If a chloroma is causing significant morbidity, such as vision loss or spinal cord compression, RT is indicated.

Because the use of intensified chemotherapy has improved the event-free survival in children with AML, this raised the question as to whether even greater dose intensification, such as with myeloablative therapy and stem-cell rescue, could improve the event-free survival even more. Randomized trials have shown that children with AML who undergo allogeneic stem-cell transplants from human leukocyte antigen–matched siblings have an improved relapse-free survival.[82-88] Postremission consolidation therapy with allogeneic bone marrow transplantation has become the standard of care for children with high-risk AML based on the presence of certain molecular features or a poor response to initial therapy. Total-body irradiation is sometimes used as a part of the myeloablative regimen for bone marrow transplantation.

NON-HODGKIN'S LYMPHOMA

Lymphomas in children comprise the third-most common malignancy of childhood, superseded only by ALL and brain tumors. In children younger than age 15 years, 60% of cases are NHL. If one includes children through age 18, Hodgkin's disease is slightly more frequent.[89] NHL is diagnosed annually in the United States in approximately 500 children. The median age at diagnosis is 10 years; NHL is less frequent in children younger than age 3 years. There is no bimodal age distribution; the frequency increases with increasing age. For unknown reasons, NHL is more common in the white population than in blacks and two to three times more frequent in males than in females.[1] Specific populations at increased risk of developing NHL include children with congenital immunodeficiency disorders such as Wiskott-Aldrich syndrome, ataxia-telangiectasia, and X-linked lymphoproliferative syndrome.[90]

In contrast to NHL in adults, NHL in children is primarily aggressive, with diffuse tumors and frequently extranodal presentation. There are three main subtypes: Burkitt's, lymphoblastic, and large cell (diffuse large B-cell lymphoma and anaplastic large cell lymphoma)[91] (Table 73-3). The staging system used in childhood NHL is the Murphy/St. Jude's Children's Research Hospital staging system, which incorporates extent of disease and clinical patterns[92] (Table 73-4). Treatment of childhood NHL is based on the stage, immunophenotype, and histology.

TABLE 73-4 Staging of Non-Hodgkin's Lymphoma in Children

Stage	Description
I	Involvement of a single extranodal site or single anatomic nodal site, excluding the mediastinum or abdomen
II	Involvement of a single extranodal site with regional nodal involvement Two or more nodal areas on the same side of the diaphragm Two extranodal sites with or without regional nodal involvement on the same side of the diaphragm A primary gastrointestinal tract tumor, usually ileocecal, with or without mesenteric node involvement that is completely resected
III	Two single extranodal sites on opposite sides of the diaphragm Two or more nodal groups above and below the diaphragm All primary intrathoracic tumors All extensive (unresectable) intraabdominal primary tumors All paraspinal or epidural tumors
IV	Any of the preceding stages with initial involvement of the bone marrow, central nervous system, or both

Burkitt's lymphoma makes up 39% of childhood NHL and is of mature B-cell immunophenotype. These lymphomas present in the abdomen or in the head and neck. The epidemiology of Burkitt's lymphoma is of great interest because of its major differences in incidence and clinical features based on geography. For example, it is the most-common childhood malignancy in equatorial Africa, yet is rare in Japan.[94] In Africa, the endemic subtype occurs and is characterized by younger age at diagnosis and frequent involvement of the jaw, abdomen, orbit, and paraspinal area.[94] The sporadic subtype, which occurs in the United States and Western Europe, is characterized by older median age at diagnosis and frequent involvement of the abdomen, nasopharynx, and bone marrow. These tumors are characterized by translocations that result in the juxtaposition of the *CMYC* gene and an immunoglobulin gene; there are breakpoint differences within these translocations that have also been reported to vary with geography.[94] The association of Epstein-Barr virus with Burkitt's lymphoma varies with geography; Epstein-Barr virus is highly associated with the endemic (African) subtype.[94]

The treatment of Burkitt's lymphoma uses cyclophosphamide-based chemotherapy, with the addition of agents including vincristine (Oncovin), prednisone, doxorubicin (Adriamycin), and methotrexate. Children with advanced-stage Burkitt's lymphoma have an improved outcome with the addition of cytarabine or high-dose methotrexate. Children with bone marrow or CNS involvement have an improved outcome, with more intensive regimens resulting in an 80% to 90% event-free survival even for patients with advanced-stage disease.[93,95-98] Current trials are examining the benefits of incorporating an anti-CD20 monoclonal antibody (rituximab) into a conventional multiagent chemotherapy regimen.[99]

Lymphoblastic lymphomas make up approximately 29% of childhood NHL. Children with lymphoblastic lymphoma typically present with advanced-stage disease (i.e., mediastinal mass which in some cases is associated with bone marrow involvement); however, some children do present with limited-stage disease. These lymphomas share morphologic, immunophenotypic, and cytogenetic features with ALL. The majority (~90%) are characterized by a T-cell immunophenotype and are designated as precursor T-lymphoblastic leukemia/lymphoma in the WHO classification system; the remainder have a precursor B-cell immunophenotype.[91] The distinction between ALL and lymphoblastic lymphoma is made arbitrarily on the basis of degree of bone marrow involvement. Those with greater than 25% replacement of the marrow by lymphoblasts are considered to have ALL, whereas those with a lesser degree of involvement are considered to have advanced stage (IV) lymphoblastic lymphoma. Whether there is a biologic distinction between lymphoblastic leukemia and lymphoblastic lymphoma is somewhat controversial; however, there appear to be subtle differences in the molecular biology, cytogenetics, and immunophenotypic markers between these two entities.[92,100,101] The treatment of lymphoblastic lymphoma in children uses multiple-agent chemotherapy comprising drugs similar to those used for T-cell ALL, which include vincristine, prednisone, L-asparaginase, doxorubicin, cytarabine, cyclophosphamide, and high-dose methotrexate. Recent studies have indicated that high-dose methotrexate may not be necessary in some patients if sufficient intrathecal chemotherapy is given.[102,103] The total duration of therapy generally ranges from 2 years to 3 years, although shorter durations have been attempted. With contemporary treatment protocols, between 80% and 85% of patients are long-term event-free survivors.[104-106] Current trials are incorporating minimal residual disease technology into treatment stratification and planning based on results from a recent COG trial.[107]

Large cell lymphomas represent approximately 27% of childhood lymphomas. Forty to 50 percent are T-cell anaplastic large cell lymphomas (ALCL), CD30+ and often associated with t(2;5)[108]; 30% to 40% are diffuse large B-cell lymphomas (DLBCL), which include the mediastinal large B-cell lymphomas (MLBCL); and the remainder are nonanaplastic mature T-cell lymphomas.[109] Historically, the treatment of childhood NHL in the United States has been based on histology. However, there has been a shift toward using an immunophenotype-directed approach, which has been the standard practice in Europe for many years. With this approach, children with DLBCL are treated with regimens for children with Burkitt's lymphoma and achieve a comparable outcome.[96] The MLBCLs have a slightly poorer prognosis than the DLBCLs.

Those patients with ALCL are treated with either cyclophosphamide, hydroxydaunomycin (doxorubicin), vincristine (Oncovin), and prednisone (CHOP)-based regimens or regimens derived from Burkitt's lymphoma regimens.[110-113] A randomized comparison of ACOP versus APO (doxorubicin [Adriamycin], vincristine [Oncovin], prednisone with or without cyclophosphamide) showed no significant difference in outcome.[113,114] The optimal approach for treatment of ALCL in children has not been established. Approximately 70% of children are long-term event-free survivors regardless of approach.[111,112] Single-agent vinblastine has been shown to be active in children with recurrent ALCL.[115] However, when it has been incorporated into frontline multiagent regimens, there has been no improvement in long-term event-free survival.[116] Targeted therapeutic approaches are currently being studied.[117,118]

The role of local RT in the management of NHL in children has been more limited because of the improved outcomes with more effective chemotherapy. In a prospective randomized trial evaluating the need for local RT in early-stage NHL,[119] no benefit was found for the addition of local RT. A second trial,[120] built on the results of the first, confirmed this. Although children with primary lymphoma of bone were not randomized in the first trial and all received local RT, in the second trial RT was not given and there were no local relapses. Based on these results, the current management of localized NHL of bone includes chemotherapy but does not use consolidative local RT. Children with advanced-stage lymphoma do not benefit from involved-field RT.[121]

Cranial irradiation has been eliminated as a component of CNS prophylaxis in the management of children with NHL.[97,105,106] RT is used for some cases of relapse or refractory disease and as a palliative modality. Children with persistent disease after chemotherapy or who experience relapse are often considered for high-dose chemotherapy protocols with stem-cell rescue if they have chemosensitive disease.[122] Consolidative RT can be considered either before or after transplant in some cases. There are no prospective randomized trials in pediatrics to confirm the benefit of this approach.

Urgent RT is rare, but there are occasions when it is considered. Mediastinal masses in children can cause significant airway compromise or superior vena cava compression. If a tissue diagnosis cannot be established to allow administration of systemic therapy, urgent RT may be considered. It should be noted that if one treats empirically with systemic therapy for the most likely diagnosis, the correct treatment is given in the vast majority of cases.[123] Radiation oncologists are often called to be aware of children with newly diagnosed mediastinal masses. If RT is given, only a few fractions are needed to achieve stabilization and allow appropriate systemic therapy to be initiated once a histologic diagnosis is made.

Encouraging progress has been made in the treatment of childhood leukemias and lymphomas. However, many children continue to succumb to disease despite aggressive therapy and many children experience significant treatment-related short- and long-term sequelae. Oncologists and radiation oncologists need to strive for improvements in treatment while minimizing the late effects of therapy. Continued research in the biology of these malignancies coupled with a search for new biologic and clinical prognostic factors will help to achieve this goal.

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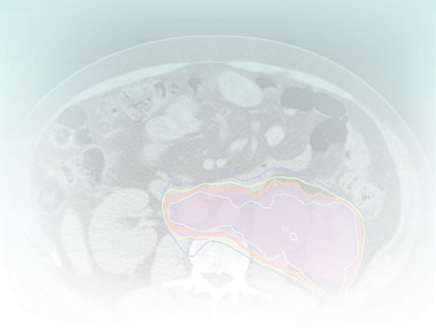
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CHAPTER

74 Pediatric Hodgkin's Lymphoma



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EPIDEMIOLOGY AND BIOLOGIC CHARACTERISTICS

Relative to adult Hodgkin's lymphoma (HL), pediatric Hodgkin's lymphoma has:

- Distinct features in relation to geographic distribution, gender, association with Epstein-Barr virus (EBV), and histological subtype;
- Relatively higher incidence in developing countries and in males;
- Nodular lymphocyte predominant subtype is more frequent.

STAGING EVALUATION

- All patients: history and physical examination; complete blood count; blood chemistries; upright posteroanterior and lateral thoracic radiographs; computed tomography (CT) of the neck, chest, abdomen, and pelvis; functional nuclear imaging studies with ^{18}fluoro-2-deoxyglucose [FDG] positron emission tomography [PET]);
- Bone marrow biopsies in selected patients with clinical stages III and IV disease or B symptoms;
- Staging laparotomy is rarely appropriate, but biopsy of specific sites with equivocal findings by clinical staging should be considered where results will alter therapy;
- Two thirds of children are stage I or II, and one third have B symptoms.

PRIMARY THERAPY

- Risk-adapted therapy based on some of the following presenting features at diagnosis:
  - B symptoms, mediastinal and peripheral lymph-node bulk, extranodal extension of disease to contiguous tissues, number of involved nodal regions, Ann Arbor stage, and gender;
- Response to chemotherapy:
  - Profound prognostic factor;
  - Reduction in therapy may be based on rapidity and the degree of response to chemotherapy;
  - Augmentation of therapy may be based on lack of or insufficient response to chemotherapy;
- Toxicity
  - Children have a relatively increased risk, compared with adults, for long-term cardiopulmonary compromise, musculoskeletal growth impairment, and subsequent malignant neoplasms;
  - Late effects experience (e.g., second cancers, cardiopulmonary effects) from the legacy of archaic extended field high-dose radiotherapy technique have limited bearing on modern clinical practice;
- Chemotherapy:
  - Common regimens:
    - doxorubicin, bleomycin, vinblastine, dacarbazine (ABVD)
    - vincristine, doxorubicin, methotrexate, prednisone (VAMP)
    - vincristine, etoposide in boys, procarbazine in girls, predinsone, doxorubicin (OEPA/OPPA)
    - mechlorethamine, vincristine, procarbazine, prednisone (MOPP)
    - MOPP substituting cyclophosphamide for mechlorethamine (COPP)
    - bleomycin, etoposide, doxorubicin added to COPP (BEACOPP)
    - mechlorethamine, doxorubicin, vinblastine, vincristine, bleomycin, etoposide, prednisone (Stanford V)
    - doxorubicin, bleomycin, vincristine, etoposide, prednisone, cyclophosphamide (ABVE-PC)
  - Early stage favorable disease most commonly uses ABVD or derivative chemotherapy; VAMP and OEPA/OPPA are alternatives
  - Intermediate- or high-risk disease use dose dense combinations derived from both ABVD and MOPP (nitrogen mustard, vincristine, procarbazine, and prednisone) along with the addition of etoposide; ABVE-PC, OEPA/OPPA with COPP are examples of this.
- Radiotherapy:
  - Use of low-dose radiation therapy (RT) following chemotherapy is response based. RT used for slowly responding, bulk, residual, or recurrent disease is the emerging standard across all stages;
  - Ongoing concerns about the incremental toxicity of RT, particular secondary cancers, remain a stimulus for investigations of chemotherapy alone;
  - Shift to involved-node or involved-site RT from traditional involved field volumes
- Results
  - Chemotherapy alone: long-term event-free survival (EFS) ranges from 85% to 100% in patients with localized favorable disease and 70% to 90% in those with advanced or unfavorable disease;
  - Incremental improvements in EFS with addition of involved field RT are in range of 5% to 10%. Rapid response to chemotherapy predicts for negligible benefit from RT.
  - The subset of patients who relapse after initial therapy have a high chance for long-term disease remission with second-line therapies.

INTRODUCTION

Given the high cure rates in treating children with HL, the ongoing challenge has been the development of less toxic therapy. In this regard, the progress in HL management in children has often presaged that in adult patients. Although many similarities between pediatric and adult HL exist, there are a number of distinctions that suggest different biologic processes, though this remains controversial. Differences associated with age include gender ratio, the proportion of patients with the most common histologic subtypes, the underlying biology (e.g., the role of EBV), and the potential for cure.[1] Pediatric HL has an excellent prognosis with high survival rates.[1,2] Given the high cure rates, HL, particularly in children, has provided much of the knowledge base we have about late toxicities of RT and cytotoxic chemotherapy. Because of the increased vulnerability of children to the adverse effects of therapy, the management of pediatric HL has led the way in the evolution of treatment strategies that consider both the toxicity and efficacy of therapy.

Historically, the desire to avoid the musculoskeletal hypoplasia that occurred following high-dose extended field RT, and leukemogenesis and infertility associated with certain alkylating agents led to a more rational combined modality therapy. Subsequent observations of cardiovascular dysfunction and increased risk of secondary cancers have played additional roles in modifying therapeutic approaches. The first generation of combined-modality therapy regimens used cycles of chemotherapy to replace a portion of the RT in children staged with laparotomy.[3-8] Second-generation regimens used doxorubicin-containing combinations to replace or reduce offending alklylating agents. Concurrent with advances in diagnostic imaging, investigators eventually abandoned surgical staging after demonstrating efficacy of the combined-modality treatment approach.

In time, risk-adapted trials evolved that prescribed fewer cycles of multiagent chemotherapy and lower radiation doses and treatment volumes for patients with favorable clinical presentations.[9,10] The definition of risk groups for disease stratification can vary in different trials and has changed with therapeutic advances. In some trials, gender-related predispositions also influence the treatment algorithm. For example, following cumulative doses of alkylating agent chemotherapy used in primary treatment regimens, boys exhibit a greater sensitivity to gonadal toxicity compared to girls, who generally maintain ovarian function unless chemotherapy is combined with abdomino-pelvic radiotherapy.[11] Conversely, young women treated with thoracic RT have a markedly increased risk of a breast cancer that is not observed in their male counterparts; however, current approaches with more restricted RT volumes are decreasing this risk.[12-14]

Because of the spectrum of prognostic factors in pediatric HL, and the unique developmental and gender-related predispositions to therapy effects, no single treatment method is ideal for all patients. Contemporary treatment for children and adolescents with HL uses a risk-adapted approach that considers presenting risk features at diagnosis. Therapy duration and intensity are selected to maintain long-term remission with minimal treatment-related morbidity. Moreover, the response to initial chemotherapy is itself an important prognostic factor and now a trigger to reduce or augment therapy.[7,15,16] The Children's Oncology Group (COG) intermediate-risk group Phase III trial AHOD0031 was the first HL trial to demonstrate that a rapid interim response to chemotherapy would allow for the elimination of involved field RT.[17]

Consequently, the evolution of therapy for pediatric HL has served as a model for other cancers. Pediatric HL management has also been early to adopt improved risk stratification and more recently response-based strategies that titrate the aggressiveness of therapy to improve the therapeutic ratio. Ongoing investigations aim to identify subgroups of HL that may be treated with reduced volume and dose of irradiation or with chemotherapy alone. The concerns about RT are to a certain extent the legacy of the significant late complications (second malignancies, cardiopulmonary dysfunction, and musculoskeletal hypoplasia) observed following archaic extended field high-dose RT techniques that have limited bearing on modern clinical practice. Nevertheless, children are more susceptible to late effects of therapy, and the trends in clinical trials have been to strive to reduce adjuvant RT despite many individual trials showing a small improvement in disease-free survival (DFS) from involved field RT and even a meta-analysis showing a small survival advantage in patients who are in early-stage disease.[18] With better risk- and response-adapted therapies, there is a general decline in RT for the upfront management of pediatric HL. RT remains important, however, to (1) complement chemotherapy when there is slowly responding, residual, or possibly initial bulky disease; (2) reduce chemotherapy intensity in selected patients where the predicted late toxicity risk for RT is small; and (3) help manage relapsed disease.

ETIOLOGY AND EPIDEMIOLOGY

Pediatric HL, accounts for 5% to 6% of childhood cancers and exhibits distinctive epidemiologic features. The childhood form, which presents in patients younger than 15 years of age, is associated with a marked male predominance, increasing family size, and decreasing socioeconomic status.[19-21] In developed countries, HL is rarely diagnosed in children younger than 5 years of age. The young adult form, which presents in patients ages 15 years to 34 years, is associated with a higher socioeconomic status in industrialized countries. Overall, the incidence is highest in developed countries (North America and Europe) and rare in Asian populations; in childhood, however, some developing regions have relatively higher incidences.[22] In adolescents, the incidence between males and females is roughly equal, and most older adolescent patients are white.[21] The risk for young adult HL decreases significantly with increased sibship size and birth order.[23,24] Specifically, the risk of HL in young adults is lower in individuals with multiple older, but not younger, siblings. Histologic subtypes also vary by age at presentation. Mixed cellularity subtype (more commonly associated with EBV) is more common in HL of childhood and the elderly, whereas nodular sclerosing subtype is more frequently observed in adolescents and young adults.

Although underappreciated because of the rarity of HL, there is a genetic predisposition that may be important to better advise families as well to help elucidate the underlying etiology of this disease. First-degree siblings of HL patients younger than 40 years of age have a 3-fold increased risk for HL.[25] Other studies report that siblings have as high as a increased incidence that may be a 9-fold increased risk in same-sex siblings.[26] Parent-child dyads have been observed. Moreover, a 99-fold increase risk in identical twins, but not in dizygotic twins has been reported.[27] More recent genetic correlative studies and exon sequencing has linked the genetic susceptibility for HL with various chromosomal loci, human leukocyte antigen (HLA) subtypes, and single nucleotide polymorphisms.[28-31] In this regard, there may be interactions with specific HLA loci and viral pathogenesis. The nodular lymphocyte predominant variant—thought to be more akin to a low-grade B cell non-HL with a lengthy time to diagnosis and time to relapse—also has a familial pattern of inheritance in some instances, linked to mutation in the ataxia

telangiectasia gene.[32,33] Increased risk for nodular lymphocyte predominant HL has also been observed in individuals with autoimmune lymphoproliferative syndrome (ALPS), a disorder associated with defects in fas-mediated apoptosis.[34]

Pediatric HL exhibits epidemiologic features similar to that seen with paralytic poliomyelitis. Delayed exposure to an infectious agent might increase the risk of the young adult form of HL, whereas early and intense exposure to an infectious agent might increase the risk for the childhood form of HL.[23] Data also indicate an association between nursery school or daycare attendance and reduced risk of HL among young adults, supporting a model in which childhood exposure to common infections promotes maturation of cellular immunity.[35] The presence of high-antibody titers to EBV, in situ hybridization evidence of EBV genomes in Reed-Sternberg cells, and EBV early RNA1 and RNA2 (EBER1 and EBER2-Epstein-Barr Early Ribonucleoprotein 1) sequences provide evidence that enhanced activation of EBV may play a role in the development of HL.[36,37] The incidence of EBV-associated HL varies by age, sex, ethnicity, histologic subtype, regional economic level, and underlying immune function.[38,39] Approximately 30% to 40% of patients with HL have associated EBV.[38] In one series of childhood HL, EBV early RNA1 was expressed in the malignant Reed-Sternberg cells in 58% of cases.[40] More specifically, an association with EBV is greater in populations of lower socioeconomic status, cases of mixed cellularity HL, and cases occurring in both young children and in the elderly.[36] Finally, there is an increased incidence of EBV-associated HL in patients with primary immunodeficiency disorders such as common variable immunodeficiency as well as with secondary immunodeficiency (e.g., HIV infection and immunosuppression for solid organ transplantation).[41]

PATHOLOGY AND PATHWAYS OF SPREAD

The pathologic features of HL are similar in adults and children; however, the distribution of the histological subtypes defined by the World Health Organization may vary by age at presentation.[42,43] Nodular lymphocyte-predominant Hodgkin's lymphoma (nLPHL) makes up almost 10% of pediatric cases. This histological subtype usually presents as clinically localized disease and is more common among male and younger patients. In contrast to classical HL, which is CD-15 and CD-30 positive, nLPHL is an indolent B cell neoplasm with histopathology notable for lacunar or Reed-Sternberg–like giant cells that are CD-20 positive and usually CD-15 and CD-30 negative.

Nodular sclerosing HL represents the most common histologic subtype in pediatric cases under the rubric of classical HL, affecting approximately 70% of adolescents and children.[44] Nodular sclerosing HL most commonly involves the lower cervical, supraclavicular, and mediastinal lymph nodes. The bulky growth of some involved nodal regions (particularly in the mediastinum) may be associated with persistent radiographic abnormalities even when the patient has fully responded to therapy. The other classical form, mixed-cellularity HL is observed in approximately 15% of patients, is more common in children aged 10 years or younger, and more frequently presents as advanced disease with extranodal involvement.[44] Lymphocyte-depleted HL is rare in children but relatively more common in patients infected with human immunodeficiency virus (HIV).[45] Lymphocyte-depleted disease in patients who are HIV-positive is often associated with EBV. Lymphocyte-rich classical Hodgkin lymphoma (LRHL) makes up approximately 5% of all HL and closely overlaps with the nodular lymphocyte-predominant subtype in presenting clinical features and prognosis.[46] The median age at presentation for LRHL (32 years) is, however, higher than for NLPHL, and there is a slightly higher incidence of mediastinal involvement and stage III disease at presentation.[47]

STAGING, CLINICAL MANIFESTATIONS, PATIENT EVALUATION, AND PROGNOSTIC FACTORS

Staging

Physical examination and diagnostic imaging evaluations are used in pediatric patients to designate a clinical stage according to the Ann Arbor staging system.[48] This historical staging system is based on anatomical groups of regional lymph nodes as delineated at the 1970 Ann Arbor symposium. It was subsequently revised at the Cotswolds meeting in 1989, although not all recommendations are in current usage.[49] This staging system persists to date with stage I identifying disease confined to one nodal region. Stage II signifies disease confined to two or more regions, but on one side of the diaphragm. Stage III indicates nodal disease that is on both sides of the diaphragm, whereas stage IV is diffuse or disseminated disease that includes extranodal sites. A special subset of stages I and II disease may be designated as extralymphatic or extranodal with the "E" suffix, which historically had been interpreted to be a disease distribution that could be encompassed within a reasonable radiation treatment portal; this operational definition has current difficulties because the role of RT is being curtailed but still is needed for prognostic purposes to designate early stage. Largely ignored from the Cotswold recommendations in current practice is the suffix "X" to designate bulky disease (greater than 10 cm maximum dimension) and a category of response to therapy, unconfirmed/uncertain complete remission (CR[u]), introduced to accommodate the difficulty of persistent radiological abnormalities of uncertain significance before the current use of metabolic imaging.

Lymphoma staging continues to be unique with the inclusion of prognostically significant constitutional symptoms. The absence of symptoms is labeled with the suffix "A," whereas "B" symptoms included in the staging assignment are unexplained fever with temperatures taken orally that are higher than 38°C, unexplained weight loss of 10% within 6 months preceding diagnosis, and drenching night sweats. At one time pruritus had been included as a B symptom but was dropped many decades ago.

In the past, pathologic staging, based on the findings of a staging laparotomy, including splenectomy, was routinely used to assess infradiaphragmatic disease. The increasing use of systemic therapy in children and the development of more accurate diagnostic imaging modalities led to the routine use of clinical staging and abandonment of surgical staging except to assess equivocal findings. Currently, surgical staging—most typically nodal sampling without splenectomy—is pursued only if the anticipated findings will significantly alter the treatment plan.

Clinical Manifestations

Pediatric patients most commonly present with painless cervical or supraclavicular lymphadenopathy. Mediastinal lymphadenopathy occurs in up to 66% of patients and may be associated with a nonproductive cough or other symptoms of tracheal or bronchial compression. Axillary or inguinal lymphadenopathy is less frequently seen as the first presenting sign. Primary infradiaphragmatic disease is rare in pediatric patients and occurs in fewer than 5% of cases. Splenic involvement occurs in 30% to 40% of pediatric patients with HL, whereas hepatic involvement is exceedingly rare. The pulmonary parenchyma, chest wall, pleura, and pericardium are the most

TABLE 74-1 Pediatric Hodgkin's Lymphoma: Demographic and Clinical Characteristics at Presentation

	Children*,† (%) *N* = 1985	Children‡ (%) *N* = 2836	Adults‡ (%) *N* = 18,898	Adults† (%) *N* = 1912
TOTAL PATIENTS				
<10 y	360 (18)	312 (11)		
≥10 y	1625 (82)	2524 (89)	18,898 (100)	1912 (100)
GENDER				
Male	1100 (55)	1455 (51)	10,330 (55)	1147 (60)
Female	885 (45)	1381 (49)	8568 (45)	765 (40)
HISTOLOGY				
Lymphocyte predominant	192 (10)	177 (6.3)	1224 (6.5)	96 (5.0)
Lymphocyte depleted	—	8 (0.3)	321 (1.7)	115 (6.0)
Mixed cellularity	307 (16)	284 (10)	3176 (17)	325 (17)
Nodular sclerosing	1431 (72)	2142 (76)	11,583 (61)	1377 (72)
Not classified	55 (2.8)	225 (7.9)	2594 (14)	
B SYMPTOMS				
Present	564 (28)	863 (39)	6477 (48)	612 (32)
Absent	1421 (72)	1337 (61)	7012 (52)	1300 (68)
STAGE§				
I	229 (12)	522 (19)	4208 (23)	210 (11)
II	1078 (54)	1337 (49)	7021 (39)	899 (47)
III	391 (20)	518 (19)	3569 (20)	593 (31)
IV	287 (15)	366 (13)	3156 (18)	210 (11)

y, *Year.*

**Data taken from Ruhl U, Albrecht M, Dieckmann K, et al: Response-adapted radiotherapy in the treatment of pediatric Hodgkin's disease: An interim report at 5 years of the German GPOH-HD 95 trial. Int J Radiat Oncol Biol Phys 51(5):1209–1218, 2001[50] and Nachman JB, Sposto R, Herzog P, et al: Randomized comparison of low-dose involved-field radiotherapy and no radiotherapy for children with Hodgkin's disease who achieve a complete response to chemotherapy. J Clin Oncol 20(18):3765–3771, 2002.[51]*

†*Data taken from Cleary SF, Link MP, Donaldson SS: Hodgkin's disease in the very young. Int J Radiat Oncol Biol Phys 28(1):77–83, 1994.*

‡*Data taken from Bazzeh F, Rihani R, Howard S, et al: Comparing adult and pediatric Hodgkin lymphoma in the Surveillance, Epidemiology and End Results Program, 1988-2005: An analysis of 21 734 cases. Leuk Lymphoma 51(12):2198–2207, 2010[52]; breakdown by age <10 versus ≥10 years estimated from chart.*

§*Data derived from both pathologically and clinically staged patients.*

commonly involved extranodal sites of disease. Bone marrow involvement at the time of initial presentation of HL is also uncommon in children. Approximately 65% of children have stages I and II disease and 35% have stages III and IV disease (Table 74-1).

Nonspecific systemic symptoms are often associated with lymphadenopathy and may include fatigue, anorexia, mild weight loss, and pruritus. The prognostically significant B symptoms have already been defined and occur in approximately 33% of patients (see Table 74-1). Laboratory changes observed at presentation are nonspecific but may provide clues about the extent of disease. Hematological abnormalities may include anemia, neutrophilic leukocytosis, lymphopenia, eosinophilia, and monocytosis. Anemia may be associated with the presence of advanced disease and may result from impaired mobilization of iron stores or less commonly from hemolysis. Several autoimmune disorders have been reported in patients with HL including nephrotic syndrome, autoimmune hemolytic anemia, autoimmune neutropenia, immune thrombocytopenia, and autoimmune lymphoproliferative disorder.[53] These conditions typically remit as the lymphoma is responding to therapy. Several acute phase reactants including erythrocyte sedimentation rate, serum copper, ferritin, and C-reactive protein levels may be elevated at diagnosis and useful in follow-up evaluations.

Patient Evaluation

Posteroanterior and lateral thoracic radiographs should be performed as soon as HL becomes part of the differential diagnosis to assess mediastinal involvement, airway patency, and other intrathoracic structures. This is particularly important if sedation is planned for diagnostic procedures. An excisional lymph node biopsy is the preferred diagnostic procedure because it permits evaluation of the malignant Hodgkin Reed-Sternberg cells within the background of characteristic architectural changes of the specific histological subtypes. All nodal regions, including Waldeyer's ring, should be assessed by careful physical examination. Historically, an upright chest radiograph was also important to assess mediastinal bulk that is defined by mediastinal lymphadenopathy measuring 33% or more of the maximum intrathoracic cavity. Whether or not this definition for bulk mediastinal adenopathy may be replaced by CT-based mass dimensions or volumes is currently under debate. CT is most frequently used to evaluate the nodal regions in the neck, axilla, thoracic and abdominal cavities, and pelvis. Administration of both oral and intravenous contrast agents is required for CT to accurately distinguish lymphadenopathy from other infradiaphragmatic structures. Organ size is an unreliable indicator of lymphomatous involvement in the liver or spleen because tumor deposits may be less than 1 cm in diameter and not visualized by diagnostic imaging modalities. Increased size of either organ can, of course, be caused by nonmalignant causes. The presence of hypodense lesions by CT or abnormal functional avidity PET scanning provides stronger evidence of tumor infiltration in these organs.

Functional nuclear-imaging studies are appropriately used in patients with HL as a diagnostic and monitoring modality. FDG-PET scanning has become a standard part of the staging

TABLE 74-2 Risk Stratification in Pediatric Hodgkin's Lymphoma Cooperative Group Clinical Trials

Trial	Low Risk	Intermediate Risk	High Risk
Children's Oncology Group			
AHOD0431 (low risk); AHOD0031 (intermediate risk); AHOD0831 (high risk)[17,65]	IA, IIA with no bulk	IA bulk or E; IB; IIA bulk or E; IIB; IIIA, IVA	IIIB, IVB
C5942[51,66]	IA, IB, IIA with no bulk, no hilar nodes and <4 sites	IA, IB, IIA with bulk, hilar nodes or ≥4 sites; III	IV
C59704 (high risk)[67]			IIB/IIIB with bulk, IV
P9425/P9426[68]	IA, IIA with no bulk	IB, IIA, $IIIA_1$ with bulk; $IIIA_2$	IIB, IIIB, IV
German Multicenter/Euronet			
GPOH-HD 95; GPOH-HD 2002; PHL-C1*[,69-71]	1A/B, IIA	I_EA/B; II_EA; IIB; IIIA	II_EB; III_EA/B; IIIB; IV
Stanford/St. Jude/Dana-Farber Cancer Institute Consortium			
HOD08† (low risk); HOD05‡ (intermediate risk); HOD99§ (high risk)	IA, IIA with no bulk, E and <3 sites	IB, IIIA, IA/IIA with E, ≥3 sites or bulk	IIB, IIIB, IV

Adapted from Kelly KM: Management of children with high-risk Hodgkin lymphoma. Br J Haematol 157(1): 3–13, 2012.[72]
E, *Extralymphatic stage;* $IIIA_1$, *minimal splenic, splenic hilar, or celiac involvement stage;* $IIIA_2$, *massive splenic or lower abdominal node involvement.*
**ClinicalTrials.gov identifier: NCT00433459.*
†*ClinicalTrials.gov identifier: NCT00846742.*
‡*ClinicalTrials.gov identifier: NCT00352027.*
§*ClinicalTrials.gov identifier: NCT00846742.*

work-up and assessment of response to therapy. Fused positron emission tomography/computed tomography (PET-CT) offers the advantage of integrating functional and anatomic tumor characteristics. Residual or persistent FDG avidity appears to be useful in predicting prognosis and the need for additional therapy in posttreatment evaluation.[54-58] Moreover, PET may be useful in evaluating abnormalities that become clinically manifest or appear on imaging to assess recurrence.[59] The utility of PET for follow-up is being studied because other reports suggest low rates of diagnosing relapsed disease and problems with a high degree of false-positive findings.[60-62] Because extranodal disease involving the bones and bone marrow is relatively uncommon in children, these staging evaluations can be omitted in patients presenting with localized and asymptomatic disease. Bone pain should be evaluated with plain radiographs; magnetic resonance (MR) may also be necessary in this situation for questions about focal bone involvement. PET scanning is supplanting technetium-99 bone scans for skeletal evaluation, which historically have also been performed when there was an elevated serum alkaline-phosphatase concentration beyond that expected for age, or extranodal disease identified by other staging evaluations. A bone marrow biopsy should be performed in any patient with clinical stage III or IV disease or B symptoms, although this standard recommendation is being reconsidered when PET imaging shows no bone or bone marrow involvement.[63] Because the pattern of infiltration in the bone marrow may be diffuse or focal and is often accompanied by reversible marrow fibrosis, a bone marrow aspirate alone is inadequate to assess the marrow for disease.

Prognostic Factors

The identification of prognostic factors has taken on importance as a determinant of risk- and response-adapted treatment algorithms. Many prognostic factors have been identified from adult trials. Regardless, this effort is complicated by several concepts. First, prognostic factors are in flux as more effective or higher intensity therapy may negate adverse risk factors previously demonstrated.[64] Second, various risk-stratification schemes have been used by different institutions and cooperative groups to allocate patients to various treatments regimens making comparisons of patient populations challenging. Most data are based on reports that primarily include adults. Although there is overlap in the biology and response to therapy of pediatric and adult forms of HL, there is divergence in prognostic groupings just as there are differences in treatment regimens. Even among pediatric protocols and cooperative groups there is a lack of standardization in prognostic factors. See Table 74-2. Third, there is an evolving understanding that early response to systemic therapy may be an important prognostic factor that may be used to guide further treatment decisions.[57] While this concept is under investigation in adults with HL, response-based therapy has recently developed firm roots in pediatric HL treatment paradigms.[17] Thus, there is much variability in classifications of patients with HL into favorable, intermediate, and unfavorable/advanced strata.

Dating from the time that early-stage HL was treated with subtotal or total nodal irradiation including splenic irradiation—often termed extended field radiotherapy (EFRT)—numerous adverse prognostic factors in stages I to II disease have identified those patients who benefit from combined-modality therapy.[73-76] In pediatric management, EFRT was abandoned in favor of primary chemotherapy and reduced dose involved field RT in the 1970s and 1980s to reduce late effects of full dose EFRT. This switch in adult management of early-stage disease did not occur until the mid-1990s. Regardless, the concept of risk-adapted therapy was first developed in which the presence of poor prognostic factors drive more intensive therapy; at the same time, favorable factors identify a population appropriately treated with less intensive therapy designed to maintain high cure rates with fewer acute and late side effects. Prognostic factors identified in these analyses include the number of involved lymphoid regions, the size of individual nodes, the extent of mediastinal disease, patient gender and age, the presence of B symptoms or pruritus, histology, erythrocyte sedimentation rate (ESR), and overall tumor burden as measured by number of sites and disease bulk.

Even for pediatric management, it is relevant to note that the adult cooperative groups have refined favorable versus unfavorable groupings. For instance, the European Organization for Research and Treatment of Cancer (EORTC) and

Groupe d'Etudes des Lymphomes de l'Adulte (GELA) specify the following as unfavorable factors: age >50 years, ESR ≥ 50 in the absence of B symptoms, ESR ≥ 30 with B symptoms, ≥4 sites of involvement or bulky mediastinal involvement.[77] For the German Hodgkin Lymphoma Study Group (GHSG), the following are considered unfavorable factors: ESR ≥50 in the absence of B symptoms, ESR ≥ 30 with B symptoms, ≥3 sites of involvement, extranodal involvement, or bulky mediastinal mass.[78]

For pediatric practice, adverse prognostic features have included advanced stage, B symptoms, extranodal extension, peripheral or mediastinal bulky disease, hilar adenopathy, and three or more involved nodal regions. Based on the most recent intermediate risk COG protocol AHOD0031, a preliminary prognostic scoring system has been proposed, with the acronym CHIPS for Childhood Hodgkin International Prognostic Score. Based on a multivariate analysis, four predictors—stage IV, large mediastinal adenopathy, albumin <3.5, and fever—were identified as predictive of adverse EFS.[79] This simple scoring system needs further validation, particularly as treatment algorithms change, prognostic factors may change and become more difficult to identify. But for the present, several prognostic factors continue to influence the success and choice of therapy for pediatric practice:

1. *Stage of disease:* Stage persists as the most important prognostic variable. Patients with advanced stage disease, especially stage IV, have a poorer outcome than patients with early-stage disease.[80]
2. *B symptoms:* These constitutional symptoms likely result from cytokine secretion, and correlate with biologic aggressiveness. Thus, unexplained fevers, drenching night sweats, or significant weight loss with definitions noted in the Ann Arbor staging classification system[48] continue to have prognostic importance and in turn influence management decisions. The presence of B symptoms has correlated with a higher likelihood of systemic disease, including occult subdiaphragmatic disease when staging laparotomies were once performed. Evidence suggests that fevers and weight loss have more prognostic significance than night sweats alone.[81]
3. *Bulk:* The bulk of disease combines the number of disease sites and the volume of involvement at each site. Patients with several sites of involvement, defined variably as either three or four or more sites of disease, fare less well.[82] This prognostic factor may also influence treatment selection as to the reduction or elimination of RT after primary chemotherapy for patients with early-stage HL.[83,84] Moreover, the presence of large mediastinal adenopathy or bulky disease in nonmediastinal sites has been another consistent risk factor. A variety of definitions of large mediastinal adenopathy have been reported in the literature.[85] The most commonly used definition is based on a measurement of the maximum width of the mediastinal mass on standing posteroanterior (PA) chest radiograph, compared with the maximum intrathoracic diameter. A ratio greater than one third is defined as "bulky." Other reports have used a ratio with the intrathoracic width at T5-6 as the denominator,[86] whereas still others use absolute measurements,[87] surface area calculations, or volume measurements. In the absence of a chest x-ray, CT-based measurements of mediastinal masses have not reached a consensus recommendation, but some commentators have suggested that 10-cm maximal diameter may be reasonable. Bulky disease in nonmediastinal sites has similarly been classified with varying definitions. Some protocols define bulky as ≥10 cm, while others use ≥5 cm[88] or ≥6 cm.[17,89,90] In Europe, the EuroNet Pediatric Hodgkin Lymphoma Group uses a volumetric definition of bulk. This was initially assessed by a definition of 50 mL,[64] but subsequent experience has found a 200-mL volume definition to be more prognostically discriminatory and is now used in their EuroNet PHL C2 trial to stratify patients.[91] Moreover, volume of a given site of disease is estimated by a simple formula estimating an ellipsoid where $V = (xyz)/2$ where x, y, and z are the diameters of the mass in three dimensions. This becomes much more complex when measuring mediastinal masses where adding multiple ellipsoids of disease to avoid counting normal structures is the procedure.
4. *Laboratory studies*, including the ESR, hemoglobin level, and serum albumin, have been reported to predict worse outcomes.[76] This could reflect disease biology or bulk. In adult cooperative group trials, ESR has been an important stratification factor in treatment protocols. Low hemoglobin and albumin levels have been found to be important factors in an International Prognostic Score.[92]
5. *Histologic subtype* has importance. As already noted, patients with NLPHL are biologically different and generally have improved DFS and overall survival (OS) relative to classical HL; separate protocols with minimal therapy are under way for patients with early-stage NLPHL. Patients with lymphocyte depleted Hodgkin's lymphoma (LDHL) fare poorly. Mixed reports suggest better or poorer outcome of other histologies that may be related to other prognostic factors as well. Some reports suggest that the mixed cellularity subtype of classical HL may have better prognosis than nodular sclerosis subtype in the pediatric age group.[93]
6. *Age* is a significant factor with survival rates for children with HL approaching 85% to 95%, and higher than adults stage for stage. In a report from Stanford, the 5-year and 10-year survival rates for children with HL ≤ 10 years of age was 94% and 92%, respectively, compared with 93% and 86% for adolescents (aged 11-years to 16-years old) and 84% and 73% for adults.[21]
7. *Rapidity of response to initial chemotherapy* is an important prognostic variable. Early-response to therapy was initially observed in patients with advanced stage HL treated on Pediatric Oncology Group (POG) 8725, where 93% of patients who attained a complete response (CR) after three cycles of chemotherapy remained disease free.[7] This was also confirmed for lower stage patients[16] and afterward incorporated in the latest COG front-line trials. Early CR to therapy has also been successfully incorporated into the German trials with low-risk patients who achieve CR after two cycles of oncovin, etoposide, prednisone, and Adriamycin (OPEA)) not requiring further RT.[69,94] Response-based therapy is currently the paradigm on which modern pediatric trials are based.

PRIMARY THERAPY

Risk-Adapted Treatment Approach

Contemporary treatment for children and adolescents with HL involves a risk-adapted and now a response-adapted approach based on the patient's presenting features at diagnosis[50,51,70,71,95-98] and re-evaluation after one or two cycles of chemotherapy. Factors included in the risk assessment may vary across studies; but they most often include the presence of B symptoms, mediastinal and peripheral lymph node bulk, extranodal extension of disease to contiguous structures, number of involved nodal regions, Ann Arbor stage, and gender. A favorable clinical presentation is typically characterized as localized (stages I and II) nodal involvement in the absence of B symptoms and bulky disease. Although the historical definition of mediastinal bulk has been based on the ratio greater than one third between the transverse dimension

of the mediastinal mass to the intrathoracic cavity on an upright chest radiograph, some trials have moved to use a simple size criteria on cross-sectional imaging as used for peripheral lymph node bulk. That definition, however, is highly variable across studies ranging from 4 cm to 10 cm as a minimal threshold. Moreover, there is additional subjectivity in the definition of bulk when there are multiple matted or adjacent nodes, contributing to confusion on such risk stratification in practice. Fewer than three or four involved nodal regions are considered favorable. In some risk-adapted treatment protocols, patients with localized disease presenting with unfavorable features are designated intermediate in risk and treated similarly to those with advanced-stage disease; whereas in others a therapy intermediate in intensity is prescribed. The criteria for unfavorable clinical presentations has also differed among studies, but most often it is comprised of the presence of B symptoms, bulky lymphadenopathy, hilar lymphadenopathy, more than three to four involved nodal regions, extranodal extension to contiguous structures, or advanced-stage (IIIB-IV) disease. The results of contemporary trials indicate that children and adolescents with early-stage or favorable presentations of HL are excellent candidates for reduced therapy.[50,51,96,98] Ongoing trials are evaluating whether intensification of therapy improves outcomes in patients with intermediate- and high-risk presentations.

Although not widely used to guide therapy assignment in pediatric trials, other factors such as gender, age at diagnosis, and histology are most definitely considered in individual patients. The trials organized by the German-Austrian Pediatric Oncology Group (GPOH) and one trial by the Children's Cancer Group (now integrated in the Children's Oncology Group [COG]) have been unique in their aims to prospectively evaluate gender-based therapy.[50,99] Long-term follow-up of the GPOH 90 and 95 studies demonstrate that the substitution of etoposide for procarbazine in the OPPA regimen does not compromise DFS and provides less potential risk for gonadal toxicity.[50,70] Although age at presentation has not been used as a criterion to assign therapy in prospective trials, reports describing outcomes after treatment with chemotherapy alone stress the benefits of this approach in younger children at higher risk of radiation-related toxicity.[51,97]

Prognostic groupings now dictate the intensity of therapy with the goal of matching up just enough cytotoxic therapy to yield a high chance for cure while minimizing those exposures responsible for late complications. Within the last cycle of COG trials, patients were allocated into a favorable group if they had stage IA or IIA disease without bulk. Unfavorable patients were those with stage IIIB or IVB disease. The heterogeneous group of patients in between were deemed intermediate risk. See Table 74-2. The upcoming cycle of COG trials beginning in 2014 will categorize patients either into low- or high-risk strata; high risk will include those patients with stage IIB disease with bulk, IIIB, IVA, and IVB disease. In Europe, the GPOH has merged into a geographically broader EuroNet cooperative group in which patients will be categorized as follows[91]:

1. TG-1: patients of stages I A/B and II A without bulk ≥200 mL and without ESR ≥ 30 mm/hr
2. TG-2: patients of stages IEA/B, IIEA, II B, or III A and patients of stages I A/B and II A with bulk ≥200 mL or ESR ≥ 30 mm/hr
3. TG-3: patients of stages IIEB, IIIEA/B, III B, or IV A/B

Finally, a collaborative group of investigators from St Jude's, Stanford, and Harvard have defined a favorable early-stage cohort that may be treated with minimal therapy; patients with stages I to IIA disease without mediastinal bulk, no extranodal disease, and less than three sites of disease.[83]

A summary of trials in children with early- and intermediate- and advanced-stage HL is provided in Tables 74-3 and 74-4.

Response-Based Therapy

The response to chemotherapy, either early in its course or at its completion, is known to be an important prognostic factor in HL.[15] This has led to a hypothesis that modifications in therapy may be based on the initial response to chemotherapy in a similar fashion to the management of acute lymphoblastic leukemia. Based on rapidity of a complete response to chemotherapy, a reduction or augmentation of therapy may be possible, a concept under cautious investigation in clinical trials. Response-based approaches titrate the overall duration of chemotherapy or the need for RT by assessing the early response to chemotherapy. Two Pediatric Oncology Group trials from the USA (POG 8725 and 8625) comparing chemotherapy alone versus chemo-radiotherapy supported this idea that a rapid early response (RER) to chemotherapy reflects the chemosensitivity of a patient's HL and is a predictor of good long-term control.[7,16] The implication is that treatment can be reduced in intensity or duration for those with RER to mitigate toxicity or increased for those with a slow early response (SER) to improve disease control.

The augmentation in therapy for SER can be either an increased RT dose, additional chemotherapy, or both. The French Society of Pediatric Oncology MDH90 treated 202 children with stage I or II HL with four cycles of vinblastine, bleomycin, etoposide, and prednisone (VBVP). Good responders received 20 Gy IFRT alone, whereas poor responders were given an additional one to two cycles of OPPA and then either 20 Gy IFRT (good responders at second evaluation) or 40 Gy IFRT (poor responders). The 5-year OS and EFS were 97.5% and 91.1%, respectively.[98] In the German trial, GPOH HD-95, patients with early-stage disease who had a complete response to chemotherapy (two cycles OPPA for girls or two cycles OEPA for boys) did not receive adjuvant RT. OPPA/OEPA chemotherapy alone produced a 5-year DFS of 88%, which was not significantly different from that observed in patients who received RT (92%).[70] In this German trial, higher-risk patients who received RT were prescribed radiation doses of up to 35 Gy if complete response was not achieved. The use of higher-dose RT with simple anterior-posterior beams is certainly known to cause undesirable musculoskeletal toxicities and the potential for increased cardiopulmonary injury and secondary cancers, such that augmentation of chemotherapy or more conformal RT may be better approaches for nonresponders. POG 9425 administered three versus five cycles of doxorubicin, bleomycin, vincristine, etoposide, prednisone, and cyclophosphamide (ABVE-PC) chemotherapy and 21-Gy regional RT for rapid and slow responders, respectively.[68] Two-year EFS was 88.2%, with no statistical difference between early and slow responders. These studies suggest that interim or early response-adapted therapy may be useful in identifying patients with favorable disease, who can be treated with lower RT doses or abbreviated chemotherapy.

The recent COG intermediate-risk HL study AHOD0031 was a response-based paradigm in which chemotherapy was intensified enough to safely eliminate RT for some patients. Although the results are detailed, children with stages IA and IIA with bulky disease, IB, IIB, IIIA, or IVA disease received two cycles of ABVE-PC prior to response evaluation with CT imaging. Those with RER defined as at least a 60% reduction in the sum of the product of the perpendicular diameters of up to six target lesions, and who proceed to a complete response with at least an 80% reduction in disease

TABLE 74-3 Published Treatment Results for Low-Risk Pediatric Hodgkin Lymphoma

Reference	Group or Institution	Patients (*N*)	Stage	Chemotherapy	Radiation (Gy), Field	Survival: DFS, EFS, or RFS (%)	Overall Survival (%)	Follow-up Interval (y)
COMBINED MODALITY TRIALS								
Gehan, 1990[5]	Intergroup Hodgkin (SWOG/POG)	97	PS I-II	6 MOPP	35, IF	97	93	5
Schellong, 1992[100]	GPOH-HD 82	100	IA/IB-IIA	2 OPPA	35, IF	98	100	9
		53	IIB-IIIA	2 OPPA/2 COPP	30, IF	94	96	9
	GPOH-HD 85	53	IA/IB-IIA	2 OPA	35, IF	85	95	6
		21	IIB-IIIA	2 OPA/2 COMP	30, IF	55	95	6
Schellong, 1999[10,71,101]	GPOH-HD 90	275	IA/IB-IIA	2 OEPA/OPPA	25, IF	94/95	99	5
		124	IIB-IIIA	2 OEPA/OPPA + 2 COPP	25, IF	90/96	97	5
Dörffel, 2003, 2010[69,70]	GPOH-HD 95	328	I-IIA	2 OPPA/OEPA	20-35, IF for PR; no rt if CR	93.2	98.8	10
		256	II_EA, IIB, IIIA	2 OPPA/OEPA + 2 COPP		86.7	97.3	10
Shankar, 1997[102]	Royal Marsden	125	II	6-10 ChlVPP	35, IF	85.0	92.0	10.0
Shankar, 1998[103]	Royal Marsden	46	I-III	8 VEEP	30-35, IF	82.0	93.0	5.0
Cramer, 1985[104]	Hôpital St. Louis, Paris	72	CS IA-II2A	3 MOPP	35-40, IF	87.6	91.6	6.8
			CS II3A-IIB	6 MOPP or 3 MOPP + 3 CVPP	35-40, IF for pathologic residual dz			
Oberlin, 1992[105]	SFOP MDH-82	79	CS I-IIA	4 ABVD	20-40, IF	90		6
		67	CS I-IIA	2 MOPP/2 ABVD	20-40, IF	87		6
		31	CS IB-IIB	3 MOPP/3 ABVD	20-40, IF		92	6
Landman-Parker, 2000[98]	SFOP MDH-90	171	I-II	4 VBVP, good responders	20, IF	91.0	97.5	5.0
		27	I-II	4 VBVP + 1-2 OPPA, poor responders	20, IF	78.0		5.0
Hudson, 1993[106]	St. Jude	58	CS II/III	4-5 COP(P)/3-4 ABVD	20, IF	96.0/97.0	96.0/100.0	5.0
Hunger, 1997[107]	Stanford	44	CS/PSI-III	3 MOPP/3 ABVD	15-25.5, IF	100.0	100.0	10.0
Donaldson, 2007[96,108]	Stanford/St. Jude/Dana Farber Consortium	110	CS I/II†	4 VAMP	15-25.5, IF	92.7	99.1	5.0
						89.4	96.1	10.0
Hudson, 2004[109]	Stanford/St. Jude/Dana Farber Consortium	77	I	3 VAMP/3 COP (2 cycles/RT/2 cycles/RT/2 cycles/RT)	15, IF for CR; 25.5, IF for PR	100.0	92.7 (all)	5.8
			II			78.4		
Vecchi, 1993[110]	AEIOP MH-83	58	IA-IIA nonbulk	3 ABVD	20-25 IF	94.6	85.7	7
		56	IIA bulk - IIIA	3 MOPP/3 ABVD	20-25 EF	81.4		7

Continued

TABLE 74-3 Published Treatment Results for Low-Risk Pediatric Hodgkin Lymphoma—cont'd

Reference	Group or Institution	Patients (*N*)	Stage	Chemotherapy	Radiation (Gy), Field	Survival: DFS, EFS, or RFS (%)	Overall Survival (%)	Follow-up Interval (y)
Nachman, 2002; Wolden, 2012[51,66]	USA-CCG 5942	94	CS IA/B, HA*	4 COPP/ABV	21, IF	97.0 100	100.0	3 10
Kung, 2006[16]	USA POG 8625	81	PS IA-IIIA1	2 MOPP/2 ABVD	25.5 Gy, IF	91.1	96.8	8
Tebbi, 2006[111]	USA POG 9426	46	CS IA-IIIA1	4 DBVE	25.5 Gy, IF	91	98	6
Metzger, 2012[83]	Stanford/St. Jude/Dana Farber Consortium	41	CSIA-IIA, no extranodal, no mediastinal bulk, <3 sites	4 VAMP, partial response	25.5 Gy, IF	92.5	100	2
CHEMOTHERAPY ALONE TRIALS								
Lobo-Sanahuja, 1994[112]	Costa Rica	52	CS IA-IIIA	6 CVPP	None	90.0	100.0	5.0
Sackmann-Muriel, 1997[113]	GATLA	10 16	CS IA, IIA CS IB, IIB	3 CVPP 6 CVPP	None None	86.0 87.0		6.7 6.7
Behrendt, 1987[114]	Netherlands	21 16	CS I-II nonbulk CS I-II bulk	6 MOPP 6 MOPP	None None	87.5 86	100	5 5
Behrendt, 1996[115]	Netherlands	17	CS I-II (12 pts) CS III-IV (5 pts)	6 ABVD	None	71 (5 relapses, but only 2 with early stage)	92	8
Nachman, 2002; Wolden, 2012[51,66]	USA-CCG 5942	106	CS IA/B, HA†	4 COPP/ABV	None	91.0 82.9	100.0	3.0 10.0
Baez, 1997[116]	Nicaragua	14	CS IA-IIA	6 COPP	None	100	100	3
Sripada, 1995[117]	Madras, India	10	CS IA-IIA	6 COPP/ABV	None	89		5
Olweny, 1978[118]	Uganda	18	CS IA-IIIA	6 MOPP	None	75	75	5
Kung, 2006[16]	POG 8625	78	PS IA-IIIA1	4 MOPP/4 ABVD	None	82.6	93.6	8
Ekert, 1993[119]	Australia/New Zealand	25	CS IA-IVA	2-3 EVAP + 0-4 EVAP/ABV	None	60	100	3
Metzger, 2012[83]	Stanford/St. Jude/Dana Farber Consortium	47	CSIA-IIA, no extranodal, no mediastinal bulk, <3 sites	4 VAMP, complete response	None	89.4	100	2

ABVD, *Adriamycin (doxorubicin), bleomycin, vinblastine, and dacarbazine;* CCG, *Children's Cancer Group;* ChlVPP, *chlorambucil, vinblastine, procarbazine, and prednisolone;* COP, *cyclophosphamide, Oncovin (vincristine), and procarbazine;* COPP, *cyclophosphamide, Oncovin (vincristine), prednisone, and procarbazine;* COPP/ABV, *cyclophosphamide, Oncovin (vincristine), procarbazine, prednisone/Adriamycin (doxorubicin), bleomycin, and vinblastine;* CR, *complete response;* CS, *clinical stage;* DFS, *disease-free survival;* EFS, *event-free survival;* IF, *involved field;* GATLA, *Grupo Argentino de Tratamiento de Leucemia Aguda;* GPOH-HD, *German-Austrian Pediatric Oncology Group-Hodgkin's disease;* MOPP, *mechlorethamine, vincristine, procarbazine, and prednisone;* OEPA, *Oncovin (vincristine), etoposide, prednisone, and Adriamycin (doxorubicin);* OPPA, *Oncovin (vincristine), procarbazine, prednisolone, and Adriamycin (doxorubicin);* PR, *partial response;* PS, *pathologic stage;* R, *regional;* RFS, *relapse-free survival;* RT, *radiation therapy;* SFOP, *French Society of Pediatric Oncology;* VAMP, *vinblastine, doxorubicin, methotrexate, and prednisone;* VBVP, *vinblastine, bleomycin, etoposide, and prednisone;* VEEP, *vincristine, etoposide, epirubicin, and prednisolone;* y, *year.*

**Without adverse features.*

†With adverse features.

(Adverse disease features comprise one or more of the following: hilar adenopathy; involvement of >4 nodal regions; mediastinal tumor with diameter more than one third of the chest diameter; node or nodal aggregate with a diameter >10 cm.)

TABLE 74-4 Published Treatment Results for Intermediate- and High-Risk Pediatric Hodgkin Lymphoma

Reference	Group or Institution	Patients (*N*)	Stage	Chemotherapy	Radiation (Gy), Field	Survival: DFS, EFS, or RFS (%)	Overall Survival (%)	Follow-up Interval (y)
COMBINED MODALITY TRIALS								
Schellong, 1992[100]	GPOH-HD 82	50	II_EB, III_EA/B, IIIB, IVA/B	2 OPPA/4 COPP	25, IF	86	85	9
Schellong, 1996[100]	GPOH-HD 65	24	II_EB, III_EA/B, IIIB, IVA/B	2 OPA/4 COMP	25, IF	49	100	6
Schellong, 1999[10,71,101]	GPOH-HD 90	179	II_EB, III_EA/B, IIIB, IVA/B	2 OPPA/OEPA + 4 COPP	20-35, IF	86	94	5
Dörffel, 2003, 2013[69,70]	GPOH-HD 95	341	II_EB, III_EA/B, IIIB, IVA/B	2 OPPA/OEPA + 4 COPP	20-35, IF for PR; no RT if CR	84.5	93.2	10
Oberlin, 1992[105]	SFOP MDH-82	40 21	CS III CS IV	3 MOPP/3 ABVD 3 MOPP/3 ABVD	20-40, EF 20-40, EF	82 62		6 6
Vecchi, 1993[110]	AEIOP-83	49	IIIB-IV	5 MOPP/5 ABVD	20-40, EF		60	7
Sackmann-Muriel et al, 1997[113]	GATLA	43 21 24	Intermediate risk High risk	6 CVPP 6 AOPE CCOPP/CAPTe	30-40, IF	87 67 83		5 5 5
Mauch, 1983[120]	Joint Center/Harvard	83	IA-IIIB	6 MOPP	25-40	77	95	11
Shankar, 1997[102]	Royal Marsden	80 27	III IV	6-10 ChlVPP 6-10 ChlVPP	35, IF 35, IF	73 38	84 71	10 10
Hudson, 1993[106]	St. Jude	27	CS IV	4-5 COP(P)/3-4 ABVD	20 Gy, IF	85	86	5
Donaldson, 1987[3]	Stanford	28	III-IV	6 MOPP	15-25.5, IF	84	78	7.5
Hunger, 1997[107]	Stanford	13	III-IV	3 MOPP/3 ABVD	15-25.5, IF	69	85	10
Friedmann, 2002[97]	Stanford/St. Jude/Dana Farber Consortium	56	CS I/II bulky (n = 26), CS III/IV (n = 30)	6 VEPA	15-25.5, IF	67.8	81.9	5
Jenkin, 1990[121]	Toronto	57	CS IIA-IV	6 MOPP	25-30, EF	80	85	10
Hudson, 2004[109]	Stanford/St. Jude/Dana Farber Consortium	82	III IV	3 VAMP/3 COP (followed by consolidative RT)	15, IF for CR; 25.5, IF for PR/NR	68.9 68.5	92.7 (all)	5.8
Fryer, 1990[4]	USA-CCG	64	PS III-IV	12 ABVD	21, R	87	89	3
Hutchinson, 1993[122]	USA-CCG 521	54	PS III-IV	6 ABVD	21, EF	87	90	4
Weiner, 1991[8,56]	USA-POG 8426	62	CS/PS IIB, $IIIA_2$, IIIB, IV	4 MOPP/4 ABVD	21, TLI	77	91	3
Weiner, 1997[7]	USA-POG 8725	80	CS/PS IIB, $IIIA_2$, IIIB, IV	4 MOPP/4 ABVD	21, EF	80	87	5
Nachman, 2002; Wolden, 2012[51,66]	USA-CCG 5942	103 36	CS I/II*, CS IIB, CS III CS IV	6 COPP/ABV COPP/ABV + CHOP + Ara-C/VP-16	21, IF 21, IF	87 84 90 88.5	95 100	3 10 3 10

Continued

TABLE 74-4 Published Treatment Results for Intermediate- and High-Risk Pediatric Hodgkin Lymphoma—cont'd

Reference	Group or Institution	Patients (*N*)	Stage	Chemotherapy	Radiation (Gy), Field	Survival: DFS, EFS, or RFS (%)	Overall Survival (%)	Follow-up Interval (y)
Kelly, 2002, 2011[67,99]	USA-CCG 59704	99	CS IIB/IIIB, bulky; IV	4 BEACOPP then if RR: 4 COPP/ABV (girls) or 4 ABVD (boys); if NRR: 4 BEACOPP	Female RR: no RT; Male RR: 21-35 Gy, IF NRR: 21, EF + boost to residual to 35 Gy	94	97	5
Schwartz, 2009[68]	USA-POG 9425	216	IB bulky-IV	RER: 3 ABVE-PC SER: 5 ABVE-PC	21 Gy, IF 21 Gy, IF	86 83	95 95	5 5
CHEMOTHERAPY ALONE TRIALS								
Atra, 2002[95]	UKCCSG	67	CS IV	6-8 ChlVPP	None	55.2	80.8	5
Ekert, 1988[123]	Australia/New Zealand	53	CS IV	6-8 MOPP or 6 ChlVPP	None	92	94	4
Ekert, 1999[124]	Australia/New Zealand	53	CS I-IV	5-6 VEEP	None	78	92	5
Olweny, 1978[118]	Uganda	10	CS IIIB-IV	6 MOPP	None	60		5
Baez, 1997[116]	Nicaragua	23	CS IIIB-IV	8-10 COPP/ABV	None	75		3
Lobo-Sanahuja, 1994[112]	Costa Rica	24	CS IIIB-IV	6 CVPP/6 EBO	None	60	81	5
Sripada, 1995[117]	Madras, India	43	CS IIB-IVB	6 COPP/ABV	None	90	5	
Van den Berg, 1997[125]	Netherlands	21 17 21	CS I-IV (<4 cm node) CS I-IV	6 MOPP 6 ABVD 3 MOPP/3 ABVD	None None None	91 70 91	100 94 91	5 5 5
Hutchinson, 1998[6]	USA-CCG	57	PS III/IV	6 MOPP/6 ABVD	None	77	84	4
Nachman, 2002; Wolden, 2012[51,66]	USA-CCG 5942	122 30	CS I/II*, CSIIB, CS III CS IV	6 COPP/ABV COPP/ABV + CHOP + Ara-C/VP-16	None None	83 78 81 79.9	100 94	3 10 3 10
Weiner, 1997[7]	USA-POG	81	CS IIB, III_2A, IIIB, IV	4 MOPP/4 ABVD	None	79	96	5

ABVD, *Adriamycin (doxorubicin), bleomycin, vinblastine, and dacarbazine;* ABVE-PC, *Adriamycin (doxorubicin), bleomycin, vincristine, etoposide, prednisone, and cyclophosphamide;* ara-C, *Arabinosylcytosine;* BEACOPP, *bleomycin, etoposide, Adriamycin (doxorubicin), cyclophosphamide, vincristine, procarbazine, and prednisone;* CCG, *Children's Cancer Group;* ChlVPP, *chlorambucil, vinblastine, procarbazine, and prednisolone;* CHOP, *cyclophosphamide, Adriamycin (doxorubicin), Oncovin (vincristine), and prednisone;* COP, *cyclophosphamide, Oncovin (vincristine), and prednisone;* COP(P), *cyclophosphamide, Oncovin (vincristine), prednisone, and procarbazine;* COPP/ABV, *cyclophosphamide, Oncovin (vincristine), procarbazine, prednisone/Adriamycin (doxorubicin), bleomycin, and vinblastine;* CR, *complete response;* CS, *clinical stage;* CVPP, *cyclophosphamide, vinblastine, procarbazine, and prednisone;* DFS, *disease-free survival;* EF, *extended field;* EFS, *event-free survival;* GPOH-HD, *German-Austrian Pediatric Oncology Group-Hodgkin's disease;* IF, *involved field;* MOPP, *mechlorethamine, vincristine, procarbazine, and prednisone;* NR, *no response;* OEPA, *Oncovin (vincristine), etoposide, prednisone, and Adriamycin (doxorubicin);* OPPA, *Oncovin (vincristine), procarbazine, prednisolone and Adriamycin (doxorubicin);* POG, *Pediatric Oncology Group;* PR, *partial response;* PS, *pathologic stage;* R, *regional;* RFS, *relapse-free survival;* RT, *radiation therapy;* UKCCSG, *United Kingdom Children Cancer Study Group;* VEEP, *vincristine, etoposide, epirubicin, and prednisolone;* VEPA, *vinblastine, etoposide, prednisone, and Adriamycin (doxorubicin);* y, *year.*

**With adverse features.*

(Adverse disease features comprise one or more of the following: hilar adenopathy; involvement of >4 nodal regions; mediastinal tumor with diameter ≥one-third of the chest diameter; node or nodal aggregate with a diameter >10 cm.)

cross-sectional area and normalization of metabolic abnormalities on gallium or FDG-PET after an additional two cycles of the same chemotherapy, were randomized to 21-Gy IFRT or no additional treatment. On the other hand, patients with SER to two cycles of chemotherapy are randomized to either standard therapy (an additional two cycles of ABVE-PC + 21 Gy IFRT) or intensified therapy (standard therapy plus two additional cycles of chemotherapy—dexamethasone, etoposide, cytarabine, and cis-platinum [DECA]—prior to IFRT). This trial showed that an excellent response to chemotherapy allowed for selection of patients who may avoid RT, but chemotherapy intensification among those with SER was not helpful in this instance. However, analysis is still under way to be confident that select subgroups, such as those who present with bulk mediastinal disease and hematologic abnormalities (e.g., anemia, elevated ESR), do not retain a benefit in EFS from IFRT. Two other pediatric trials have sorted out situations when favorable prognosis patients may have RT withheld after a good response to initial chemotherapy[69,83]; however, another COG trial, AHOD0431 (for the most favorable patients) found that AV-PC chemotherapy for three cycles was not sufficiently intensive to allow for RT to not be given when response was adjudicated by CT scan criteria only.[126]

Although most completed trials have used CT, with or without gallium or PET to determine response, it is becoming increasingly clear that PET scanning after the initial (one or two) chemotherapy cycles will better identify good-prognosis patients and facilitate treatment intensification.[15,57,127,128] When RT can be omitted among patients with a good response to chemotherapy, PET assessment appears to be important. The corollary problem is how to define a response by PET criteria as low levels of residual FDG activity after therapy are common. Another unresolved problem is the interpretation of splenic or hepatic involvement by HL given the physiologic uptake of FDG in these organs. A consensus panel has promulgated PET-based response criteria known as the International Harmonization Project, using mediastinal blood pool as a reference visual threshold to determine residual FDG uptake.[129,130] However, more recently a visual five-point score known as the Deauville criteria has been shown to improve prediction of outcome that is reproducible enough in adult advanced-stage HL to serve as a standard reporting criterion in clinical trials and practice.[131,132] Moreover, a preliminary analysis of this Deauville criteria in a pediatric cohort has suggested that more sensitive response criteria uses liver uptake rather than blood pool as a threshold indicator of interim response to chemotherapy.[133]

Chemotherapy Regimens and Radiation Therapy

MOPP and Derivative Chemotherapy

The prototype alkylator combination that provided the first effective systemic therapy for HL was MOPP.[134] Follow-up studies of MOPP-treated survivors confirmed that secondary acute myeloid leukemia (s-AML) and infertility resulted from the alkylating agents in the regimen and exhibited a dose-dependent relationship.[135] Subsequently, investigators developed a variety of MOPP-derivative regimens in an effort to reduce the risk of secondary leukemogenesis and gonadal toxicity.

The risk of secondary leukemia following alkylating agent chemotherapy peaks in frequency in the first 5 years to 10 years after treatment and plateaus to less than 2% after 10 years from diagnosis.[136] Older age at treatment, history of splenectomy, presentation with advanced disease, treatment with high cumulative doses of alkylating agents, and history of relapse have been reported to predispose to this complication.[136-141] Some alkylating agents are more potent leukemogens than others; the 15-year cumulative incidence of s-AML is 4% to 8% after MOPP-based therapy compared to less than 1% with cyclophosphamide, Oncovin (vincristine), procarbazine, prednisone (COPP)-based therapy that substitutes cyclophosphamide for nitrogen mustard.[142] Pediatric protocols that limit the total dose of alkylating agents or substitute other less-leukemogenic drugs, such as cyclophosphamide, for mechlorethamine, have been associated with low incidence rates of s-AML.[142]

Gonadal injury is common in pediatric patients treated with MOPP and its derivative combinations. Azoospermia is typically irreversible in men treated with six or more cycles of MOPP-like therapy.[135,143] However, germ cell function may be preserved if treatment is limited to no more than three cycles of alkylator therapy.[144] In contrast, most young women will maintain or resume menses after a temporary period of amenorrhea following treatment including alkylating agents.[143] Ovarian transposition and shielding reduces the incidence of gonadal injury in young women requiring pelvic radiation, but these patients will experience a higher risk of premature menopause.[145] The radiation oncologist should also be aware of the age dependency in risk for ovarian failure.[146] Younger females tolerate a modestly higher radiation dose related to the gradual decline in oocyte numbers associated with aging.

ABVD and Derivative Chemotherapy

The ABVD combination provided a systemic therapy that produced superior DFS compared to MOPP and was not associated with an excess risk of secondary leukemia or infertility.[4,147] However, follow-up of patients treated with the ABVD regimen established its association with cardiopulmonary toxicity that was enhanced with the addition of thoracic radiation.[4] Many ABVD derivatives soon followed, aiming to reduce the risk of these sequelae.

Anthracycline agents are an important component of chemotherapy regimens for children with HL because of their significant lympholytic effects. In adults the cumulative incidence of cardiomyopathy increases significantly after anthracycline dose exceeds 550 mg/m^2; children are at increased risk of cardiac dysfunction at lower cumulative doses.[148-151] Other risk factors for anthracycline toxicity identified in studies of childhood leukemia survivors include younger age at treatment (especially younger than 5 years old) and female gender. Combination treatment with chest radiation or other cardiotoxic agents such as amsacrine or cyclophosphamide may also enhance risk of cardiac dysfunction.[150,152-155] Because treatment protocols for pediatric HL frequently include chest radiation or other chemotherapeutic agents with potential cardiotoxicity, most regimens limit cumulative doses of anthracycline agents to below 250 mg/m^2, particularly for patients with favorable-risk disease presentations.

Bleomycin in the ABVD regimen increases the risk of pulmonary toxicity that is most commonly manifested as pulmonary fibrosis and chronic pneumonitis.[156] Thoracic radiation may augment this risk. Patients at highest risk of pulmonary complications are those treated with cumulative bleomycin doses exceeding 400 U/m^2, that far exceed doses used in pediatric regimens for HL. Contemporary protocols use bleomycin doses in the range of 60 U/m^2 to 100 U/m^2; these cumulative exposures are usually associated with asymptomatic pulmonary restriction and diffusion deficits in long-term survivors, some of which will improve over time.[157,158] Serial monitoring of pulmonary function during therapy and withholding bleomycin doses in patients exhibiting significant declines in pulmonary function (20% or more from baseline) may reduce the risk of further pulmonary injury and does not appear to compromise disease control.[106]

Chemotherapy Combinations Including Etoposide

Etoposide has been increasingly incorporated into treatment regimens for pediatric HL over the last few decades. This agent is used in risk-adapted regimens for favorable patients as an effective alternative to alkylating agents in an effort to reduce gonadal toxicity.[68,71,97,98,103,113] Etoposide has been added to alkylating and anthracycline chemotherapy in regimens for advanced and unfavorable patients to enhance treatment response. For example, the previously mentioned dose-intensive ABVE-PC regimen used in recent U.S. cooperative groups yields excellent survival outcomes in intermediate- to high risk patients.[68] Balanced with this survival advantage is an excess risk of s-AML seen with topoisomerase-II inhibitors like etoposide and doxorubicin that differs in epidemiology and biology from alkylator-related s-AML.[159] Secondary AML that occurs in association with topoisomerase-II inhibitors is characterized by a brief time of onset from primary diagnosis, absence of a preceding myelodysplastic phase, monoblastic and myelomonoblastic histology, and translocations involving the *MLL* gene at chromosome band 11q23. Studies of childhood patients with leukemia suggest that intermittent weekly or twice weekly dosing schedules may result in transforming mutations of myeloid progenitor cells by epipodophyllotoxins.[160] A relationship between leukemogenic activity and cumulative epipodophyllotoxin dose could not be established in an evaluation of s-AML cases developing in patients treated with multiagent chemotherapy regimens including epipodophyllotoxins, alkylating agents, doxorubicin, and dactinomycin for pediatric solid tumors.[159] However, the risk of s-AML following treatment with regimens that restricted etoposide doses to 5.0 g/m^2 or less did not exceed that associated with other agents used in solid tumor regimens.[159] Pertinent to this discussion is the report of an increased incidence of second malignancies observed in children treated with ABVE or dose-intensified ABVE with prednisone and cyclophosphamide and the cardiopulmonary protectant dexrazoxane.[161] In these Pediatric Oncology Group trials, patients were randomly assigned to receive dexrazoxane to evaluate its potential to decrease cardiopulmonary toxicity. Unexpectedly, 10 patients developed SMN with AML/myelodysplastic syndrome (MDS) accounting for 8 of the 10 cases. Six of the 8 cases of AML/MDS and two solid tumors occurred in children randomized to receive dexrazoxane. The authors speculated that the use of multiple topoisomerase II inhibitors (dexrazoxane, etoposide, and doxorubicin) may have potentiated carcinogenesis. Collectively, most data support the relative safety of using limited doses of etoposide, but reports of s-AML in patients receiving etoposide for treatment of favorable pediatric HL raise concerns about whether this agent should be avoided in favorable disease presentations.[98]

Gender-Based Therapy

The German Paediatric Oncology and Haematology Society (GPOH) has explored the use of not only risk-adapted, but also gender-adapted therapy featuring the OEPA regimen for boys to limit the amount of alkylators, whereas girls received OPPA, substituting procarbazine for etoposide. Procarbazine is especially problematic in boys as a cause of infertility.[11,162] Although this has not caught on in North America as a strategy to limit late effects, the CCG 59704 high-risk study did include a successful gender-based consolidation phase. All patients received the escalated BEACOPP regimen pioneered by the GHSG as a backbone, having documented efficacy in adult trials with unfavorable features. All patients with a slow response received four additional cycles of BEACOPP and IFRT. But for rapidly responding males, two cycles of ABVD with IFRT were given while females received four cycles of COPP/ABV without radiotherapy particularly to avoid the risks for breast cancer and infertility with mantle and pelvic fields respectively. The concept of gender-based use of RT has been abandoned for now, though it remains quite reasonable as females seem to be particularly predisposed to secondary radiation-related cancers.[163-165]

Radiotherapy Considerations

The curability of pediatric HL and the vulnerability of the developing child to both RT and chemotherapy are critical issues in appropriately integrating radiation into the complex treatment algorithms currently used. Most newly diagnosed children will be treated with risk-adapted chemotherapy alone or combined-modality therapy including low-dose, involved-field RT. Full-dose, extended-field RT using techniques that were once standard for adults and even children has been long abandoned because of concerns primarily relating to growth inhibition, cardiovascular toxicity, and second malignant neoplasms. Historically, the results of treatment with RT alone for early-stage disease were superior at institutions that treated many patients with HL. Although different institutions and radiation oncologists may use slightly different treatment techniques, underlying principles, and in fact, most of the technical details remained constant.[166] However, currently in the United States, most adults with HL are treated in the community setting. Because most children are treated at academic or tertiary care hospitals often on institutional (or multiinstitutional) studies, the radiation oncologist should confirm all aspects of the diagnostic workup and staging; they must also understand study requirements to deliver appropriate RT. Supportive of this premise, up-front centralized review of patients entered into the GPOH-HD 90 study altered the treatment approach in a large number of children.[167] Similarly, prior Pediatric Oncology Group trials observed inferior outcomes related to major deviations in radiation protocol compliance.[168] These data support the need for prospective central review of RT in current COG HL protocols.

In contemporary trials, there is a considerable impetus to minimize RT when possible in children with HL to remove the associated late risks of therapy that include secondary malignancy, cardiovascular complications, and hypothyroidism among others. Secondary malignancy is the most compelling concern as children are more susceptible than adults for this problem despite the reduction in RT dose and volume relative to the historical use of extended field RT.[165] Moreover, young females getting low dose involved field RT to the chest are particularly at risk for breast cancer.[164,165] The risk for subsequent coronary artery disease, valvular heart disease, and heart failure after treatment for HL is multifactorial with both anthracycline and radiations exposures playing a role.[169] However, risk related to RT is radiation dose and volume dependent, and the risk is decreased with doses in the 20-Gy to 25-Gy range.[170] In turn, efforts within the Radiation Oncology community to make the use of low-dose RT safer include more conformal dose distributions with three-dimensional conformal techniques including intensity-modulated radiotherapy (IMRT) and proton RT, deep inspiration breath-hold techniques to improve radiation targeting, and a reduction in the volume of RT with involved-node radiotherapy (INRT) or involved-site radiotherapy (ISRT).

It is hoped that response-adapted therapy may identify patients with favorable-risk pediatric HL who can be treated with chemotherapy alone without significantly reducing DFS. In the past, chemotherapy-alone regimens for advanced-stage disease used higher cumulative doses, predisposing survivors to greater risks of acute and late toxicity associated with alkylating agents, anthracyclines, and bleomycin. These protocols

were designed with the hopes of avoiding toxicities because of RT. However, RT remains an effective agent in HL, and a danger continues to be engendered when systemic therapies are overemphasized and their own set of complications are underappreciated. Current protocols strive to carefully balance chemotherapy exposures along with RT details of dose and volume to limit long-term risks. Importantly, response-based paradigms now allow patients with a rapid response to systemic therapy to minimize the use of RT. The data suggest that children with HL may require RT for both early and advanced disease when the chosen chemotherapy program is insufficiently intensive, when there is a slow response to chemotherapy, when there is residual disease at completion of therapy, possibly when there is bulky disease at presentation, and selectively for relapsed lymphoma. Identification of prognostic features including response features that dictate integration of RT to optimize disease control is a focus of many ongoing pediatric trials.

There is considerable impetus to minimize RT exposures in HL because of late effects, particularly secondary malignancies. Some of the concern results from the historic use of extended field, high-dose radiotherapeutic practices that are no longer representative of modern RT. For example, the Late Effects Study Group analyzed patients treated from 1955 to 1986, before the widespread use of customized lung shielding, megavoltage linear accelerators, or CT-based image guided RT planning.[138] Both the RT doses and volumes are now significantly reduced in managing pediatric HL. As a result, the risk of late effects may be overestimated when analysis are based on past, antiquated techniques. As an example, several studies reveal a marked decrease in the risk for secondary breast cancer when RT volumes and doses are reduced.[14,163,171] But, an important confounding factor leading to reduction in breast cancer risk related to RT occurs from akylating agent chemotherapy or pelvic radiotherapy obstensibly because of ovarian failure and the consequential loss of hormonal influence on the neoplastic process. Nevertheless, the transition from extended-field RT to IFRT significantly reduces the dose to breast and lung tissue,[172] and has been predicted to result in a substantial reduction in secondary cancer risk.[13] Thyroid cancer may be one exception to the general concept that higher radiation doses correlate with higher risk for secondary cancers.[173] In this case, an update to the Late Effects Study Group has shown a nonlinear relationship of dose and cancer incidence with a maximum risk associated with radiation doses in the range of 15 Gy to 25 Gy and decreasing risk with higher doses greater than 29 Gy. Yet despite the use of lower radiation doses, children with HL still continue to harbor an increased risk for secondary solid-type malignancies relative to the general population risk from the use of RT, especially breast cancer in females.[164,165]

Volume

Treatment volumes are continuing to evolve with a current transition in progress from involved field to involved nodal or involved site RT.[174] When RT is indicated, meticulously and judiciously designed fields are necessary for maximum success in terms of both disease control and minimal tissue damage. Until recently, an anatomic region was targeted, designed in terms of lymph node distribution, patterns of disease extension into regional areas, and consideration for match-line problems should disease recur. An understanding of involved field principles remains important to understand the historical results of combined-modality therapy and potential side effects for follow-up purposes. Involved fields typically included not just the identifiably abnormal lymph nodes, but the entire lymph node region containing the involved nodes (Table 74-5). These traditional definitions of lymph node regions have operational details that date to a time when treatment planning technology required the use of simple parallel opposed fields with boundaries that dated to the use of lymphangiography rather than modern cross-sectional imaging. Successful outcomes had cemented field design concepts that have only recently been changed in response to the understanding of late effects.

TABLE 74-5 Historical Involved Field Radiation Guidelines

Involved Node(s)	Radiation Field
Cervical	Neck and infraclavicular/supraclavicular†
Supraclavicular	Neck and infraclavicular/supraclavicular with or without axilla
Axilla	Axilla with or without infraclavicular/supraclavicular
Mediastinum	Mediastinum, hila, infraclavicular/supraclavicular*†
Hila	Hila, mediastinum
Spleen	Spleen with or without para-aortics
Para-aortics	Para-aortics with or without spleen
Iliac	Iliacs, inguinal, femoral
Inguinal	External iliac, inguinal, femoral
Femoral	External iliac, inguinal, femoral

**Prechemotherapy volume is treated except for lateral borders of the mediastinal field, which is postchemotherapy.*
†Upper cervical region not treated if supraclavicular involvement is extension of the mediastinal disease.

However as past is prologue, a discussion of involved field RT remains relevant despite the current move toward more restricted fields (See Table 74-5). For example, the cervical and supraclavicular lymph nodes have generally been treated when abnormal nodes are located anywhere within this area; this is consistent with the anatomic definition of lymph node regions used for staging purposes. However, the hila have usually been irradiated when the mediastinum is involved, despite the fact that the hila and mediastinum are separate lymph node regions. Similarly, the supraclavicular fossa (SCV) has typically been treated when the axilla or the mediastinum is involved, and the ipsilateral external iliac nodes have often been treated when the inguinal nodes are involved. However, in both situations care would have been taken to shield relevant normal tissues to the degree possible, such as the breast in the former situation and ovaries in the latter. Moreover, the decision to treat the axilla or mediastinum without the SCV, and the inguinal nodes without the iliacs, might have been appropriate depending on the size and distribution of involved nodes at presentation. In a young child (younger than age 5 years), consideration would be given to treating bilateral areas (e.g., both sides of the neck) to avoid growth asymmetry. However, this is less of a concern with low radiation doses, and unilateral fields are usually appropriate if the disease is unilateral. Efforts to exclude unnecessary normal tissues are always important, such as breast tissue in a child with isolated mediastinal disease and no axillary involvement.

Treatment of involved supradiaphragmatic fields or a mantle field has required precision because of the distribution of lymph nodes and the critical adjacent normal tissues. These fields could be simulated with the arms up over the head or down with hands on the hips. The former pulls the axillary lymph nodes away from the lungs, allowing greater lung shielding. However, the axillary lymph nodes then

move into the vicinity of the humeral heads, which should be blocked in growing children. Thus, the position chosen involves weighing concerns regarding lymph nodes, lung, and humeral heads. Attempts are consistently made to exclude or position breast tissue under the lung and axillary blocking.

When the decision is made to include some or all of a critical organ in the RT field, such as liver, kidney, or heart, normal tissue constraints, depending on the chemotherapy used and patient age, are critical. Thus, the width of a mediastinal field is generally based on the postchemotherapy residual disease, whereas the cephalad-caudad dimension respects the original disease extent. Humeral head blocks are appropriate unless bulky axillary adenopathy is thereby shielded. Laryngeal and occipital blocks have also been used unless disease is located in the vicinity of these structures; these blocks can be placed at the beginning of treatment or after some portion of it. Depending on the response of the disease to chemotherapy and the dose administered, field reductions might be considered. The entire heart or lungs are rarely treated above doses of 10 Gy to 16 Gy, depending on the distribution of disease and chemotherapy used.

When the subdiaphragmatic region has been treated, a treatment-planning CT is essential to devise the shielding. When treating the pelvis, special attention must be given to the ovaries and testes. The ovaries may be relocated or transposed and marked with surgical clips, laterally along the iliac wings or centrally behind the uterus. In this manner appropriate shielding may be used. The testes might still receive 5% to 10% of the administered pelvic dose, which is sufficient to cause transient or permanent azoospermia, depending on the total pelvic dose. The greatest shielding can be afforded to the testes if the patient is placed in a frog-legged position with an individually constructed testes shield. If multileaf collimation is available, the multileaf can be placed over the testes, additionally decreasing the transmitted dose.

Even though IFRT has been a standard treatment volume in recent studies, there is a clear shift to what is alternatively termed either INRT or ISRT. The rationale for this volume reduction derives from reconsideration of the anatomic definitions of lymph node regions and the patterns of recurrence in HL. Clinical definitions of lymph node regions are historic and based on anatomic or bony landmarks without the benefit of CT scanning to identify the location of nodes. The EORTC-GELA has introduced the concept of INRT.[175,176] This uses all available clinical information including pre- and postchemotherapy imaging with CT and FDG/PET scans to define the treatment field according to the prechemotherapy extent of disease. The concept is based on evidence that recurrence occurs most often in initially involved lymph nodes[177,178] suggesting that chemotherapy is adequate to treat disease contained within radiologically normal lymph nodes, while RT is needed only to treat sites of macroscopic enlargement. In a study of patients with early-stage HL, PET identified presumptively involved lymph nodes that were radiographically occult on CT scan. Therefore, evaluation with FDG/PET scan before chemotherapy may help to delineate the complete extent of clinical disease.[175] Initial clinical data with the use of INRT is only just emerging. Campbell et al reviewed clinical outcomes of patients with limited stage HL treated with EFRT, IFRT, and INRT ≤ 5 cm. No marginal recurrences or locoregional failures occurred with INRT.[179]

Various European trials are actively incorporating and testing INRT along with reported guidelines.[180] In the EORTC/GELA H11 trial for early-stage, unfavorable-prognosis HL, INRT was adopted in both the standard and experimental arms. Meanwhile, the German Hodgkin's Study Group (GHSG) is enrolling patients in a randomized trial with unfavorable-prognosis, early-stage disease (HD17) comparing IFRT versus INRT.

Recently, a new set of field designs, the involved site (ISRT), have been developed, published, and endorsed by the steering committee of the International Lymphoma Radiation Oncology Group (ILROG).[181] This represents the first effort by an expert group of radiation oncologists, having experience with lymphoma management, recognizing a need to promulgate a "modernized" version of IFRT. These new field designs take into account modern technology, including the use of staging PET/CT scans, three-dimensional and four-dimensional treatment planning with CT scanners, conformal treatment techniques, and the use of image guidance. These fields are expected to be somewhat smaller than the traditional IFRT, but larger than INRT especially recognizing the difficulty of staging PET-CT scans not being performed in the patient position used during eventual treatment planning and RT delivery. Regardless, in the years to come it is expected that these ISRT concepts will be applied to pediatric protocols and become more standardized in practice. Finally, as previously noted, RT for unfavorable and advanced HL is variable and protocol dependent. Although IFRT has been a standard when patients are treated with combined-modality therapy, restricting RT to areas of initial bulk disease (generally defined as 5 cm to 6 cm or more at the time of disease presentation), slowly responding sites, or postchemotherapy residual disease (generally defined as 2 cm to 2.5 cm or more, or residual PET avidity) is under investigation.

Dose

In the setting of combined therapy, certainly the intensity of the chemotherapy is important to consider in the choice of the RT dose and volume. In general, doses of 15 Gy to 25 Gy are typical with shrinking fields and boosts individualized. In the tables summarizing recent clinical trials (see Tables 74-3 and 74-4), the RT doses selected to complement the chemotherapy regimen are provided. Doses of more than 25 Gy are uncommon in the pediatric setting. Of interest are the results of the GPOH HD-90 trial, in which doses of 20 Gy to 25 Gy were administered in combination with OPPA or OEPA, with or without COPP. The radiation doses administered were 20 Gy to 25 Gy, with a local boost of 5 Gy to 10 Gy for insufficient remission following chemotherapy. Tumor burden, indicated by bulky disease or number of involved nodes, proved not to be prognostically significant because of the relatively high doses used for bulk disease.[64] In the GPOH-95 trial, the safety of lowering the standard radiation dose to 20 Gy was demonstrated, although boosts to residual large masses were still allowed.[69] Most current treatment approaches for children include radiation doses at the lower end of the 20-Gy to 25-Gy range. Indeed within the COG, radiation dose has been standardized to 21 Gy in 14 fractions.

Treatment Approaches

Chemotherapy Alone Versus Combined with Radiation Therapy

Noncross-resistant combination chemotherapy alone is well established as an effective modality for the treatment of pediatric HL.[7,8,95,112,113,115,116,123,125,182] This treatment approach eliminates the risk of radiation-induced growth complications, thyroid and cardiopulmonary dysfunction, and solid tumor carcinogenesis. However, the higher-cumulative doses of anthracyclines, alkylating agents, and bleomycin chemotherapy increase the risk of cardiopulmonary, toxicity infertility, and leukemogenesis and may be less effective as combined-modality therapy for treatment of bulky nodal disease. Chemotherapy alone trials have been limited by their small

numbers of patients, nonrandom treatment assignments, lack of long-term follow-up related to disease control, and late-treatment sequelae. Despite these deficiencies, identification of clinical factors predicting an optimal outcome following treatment with chemotherapy alone remains an important objective of many ongoing trials because of the desire to avoid late RT sequelae. As already noted, the early response to chemotherapy of sufficient intensity appears to be the one factor allowing for the elimination of RT.[17,83]

Investigators from North American pediatric cooperative groups have undertaken three longitudinal controlled trials to evaluate chemotherapy alone versus combined-modality therapy in pediatric HL.[6,7,51,66] The first two trials failed to show a statistically significant advantage in EFS or OS with the addition of RT to noncross-resistant chemotherapy. The Children's Cancer Group compared 12 cycles of alternating MOPP/ABVD to 6 cycles of ABVD plus low-dose (21 Gy) radiation.[6] EFS and OS suggested a survival advantage for the combined-modality group (90% 4-year EFS) over the chemotherapy-alone group (84% 4-year EFS), but this difference was statistically insignificant. In a Pediatric Oncology Group trial, adding low-dose radiation to four cycles of alternating MOPP and ABVD chemotherapy did not improve DFS or OS.[7] However, statistical and quality-assurance issues produced problems with interpretation of these data. Moreover, the findings of both studies are irrelevant to present-day practice because the treatments evaluated included the more leukemogenic MOPP-based therapy and an excessive number of treatment cycles.

Using an antiquated hybrid regimen, the Children's Cancer Group compared chemotherapy alone with COPP/ABV to combined-modality therapy including low-dose IFRT.[51,66] Clinical risk features including the presence of B symptoms, hilar lymphadenopathy, mediastinal and peripheral lymph node bulk, and the number of involved nodal regions determined treatment assignment. Patients who achieved a complete response to chemotherapy were eligible to be randomized to receive low-dose, IFRT or no further therapy. The trial was prematurely terminated because patients treated with chemotherapy alone had a significantly higher number of relapses. As updated with a median follow-up of 7.7 years, those patients receiving IFRT had a statistically improved EFS of 92.5% at 10 years compared to 83.5% for chemotherapy alone ($p = 0.004$).[66] OS was the same the result of effective retrieval therapies that often included high-dose chemotherapy with an autologous stem cell transplant. Risk factors for relapse included nodular sclerosis subtype, B symptoms, and bulk disease. Ten-year EFS was 83.5% for patients with nodular sclerosing histology compared with 96% for patients with other histologies. Patients with B symptoms at diagnosis had a 10-year EFS of 71.7% compared with 87.5% for patients without B symptoms ($p < 0.001$). And finally, patients with bulk disease had a 10-year EFS of 75.6% compared with 87.2% for patients with no bulk ($p < 0.001$).

European experience in pediatric HL with end of treatment assessment using CT or MRI scan criteria also suggests that elimination of RT may be detrimental in certain patient subsets. In a nonrandomized trial that omitted radiation for patients achieving a CR with chemotherapy, German-Austrian investigators reported a similar advantage for patients treated with radiation consolidation following combination chemotherapy in the GPOH-HD 95 trial.[69] In this study patients treated with RT after partial response to combination chemotherapy defined as more than 75% volume reduction received 20 Gy using a "reduced involved-field" along with an additional 10-Gy or 15-Gy boost to larger residual masses. In the early stage (TG1) patients, there was no detriment to omitting RT for those patients not in CR; the progression-free survival (PFS) at 10 years was 97% for CR patients not receiving RT compared to 92% for those receiving RT ($p = 0.21$). PFS was unsatisfactory for nonirradiated intermediate risk patients (TG2) at 68.5% compared to those who received RT who had a PFS of 91.4% ($p < 0.0001$). The TG3 advanced risk group patients had a nonsignificant trend favoring the receipt of RT with a 10 year PFS of 88.7% versus 82.6% without RT.

Contemporary practice now allows for interim assessment of response to chemotherapy incorporating both PET and anatomical criteria. RT may be reduced or eliminated after sufficiently intensive chemotherapy producing a rapid early response, even with initially bulky masses. The landmark COG AHOD0031 trial of intermediate-risk patients has already been mentioned. Final published results are eagerly awaited. Thus, the standard of care is shifting and no longer is involved field RT given across all stages of pediatric HL.

The results of chemotherapy-alone regimens in carefully selected patients document excellent efficacy of this treatment approach particularly in children with early-stage favorable HL and those with a rapid-early response to chemotherapy with intermediate-risk disease. Circumstances where RT may have particular toxicity, such as in young children, may warrant chemotherapy alone. The incremental value of adjuvant RT is small, but its importance lies in the avoidance of relapse therapy that often includes high-dose chemotherapy with an autologous stem-cell transplant. At the same time, there is an appreciation that safe radiation volume reductions using ISRT[181] are appropriate to reduce side effects and normal tissue exposures. As noted previously, European studies of adult HL are evaluating INRT as a shift away from targeting anatomic compartments.[175-178] PET imaging is proving particularly useful not only for response assessment but also RT planning.[183] By the same token conformal techniques such as IMRT or proton radiotherapy are also under investigation in HL.[175,184-190] Figures 74-1 and 74-2 are examples of the use of IMRT to ensure coverage of involved regions. In the first case, the mediastinal disease has extensive anterior chest wall extension, whereas the second case depicts splenic IMRT with AP-PA mantle fields. In these examples, radiation exposure to normal tissues (lung, heart, and kidney) was minimized to reduce toxicity, not readily accomplished by standard AP-PA beam arrangements.

Risk-Adapted Therapy: Favorable Risk Disease

Favorable risk has variable definitions across various studies as already noted, but generally includes patients with stages I and II disease without adverse prognostic features. These unfavorable features may be B symptoms, extranodal extension, peripheral or mediastinal bulky disease, hilar adenopathy, and three or more nodal regions involved. Treatment typically involves two to four cycles of chemotherapy and low-dose, IFRT. But in some instances, RT has been reduced or eliminated based on a favorable response to chemotherapy.[51]

The GPOH HD-95 trial used OEPA in boys and OPPA in girls, with RT successfully omitted in patients achieving a CR to chemotherapy, as already noted. The criteria for CR did not entail metabolic imaging, but rather volume reduction of ≥95% with ≤2 mL of the initial volume remaining. An unconfirmed CR that triggered low-dose RT occurred if volume reduction was ≥75% or <b2 mL, occurring in less than 30% of the favorable cohort. One caveat to note is that patients with nLPHL were included in this trial.[69,70] These results were confirmed in the GPOH-HD 2002 study that excluded nLPHL patients.[94] In the GPOH-HD2002 study, all patients received

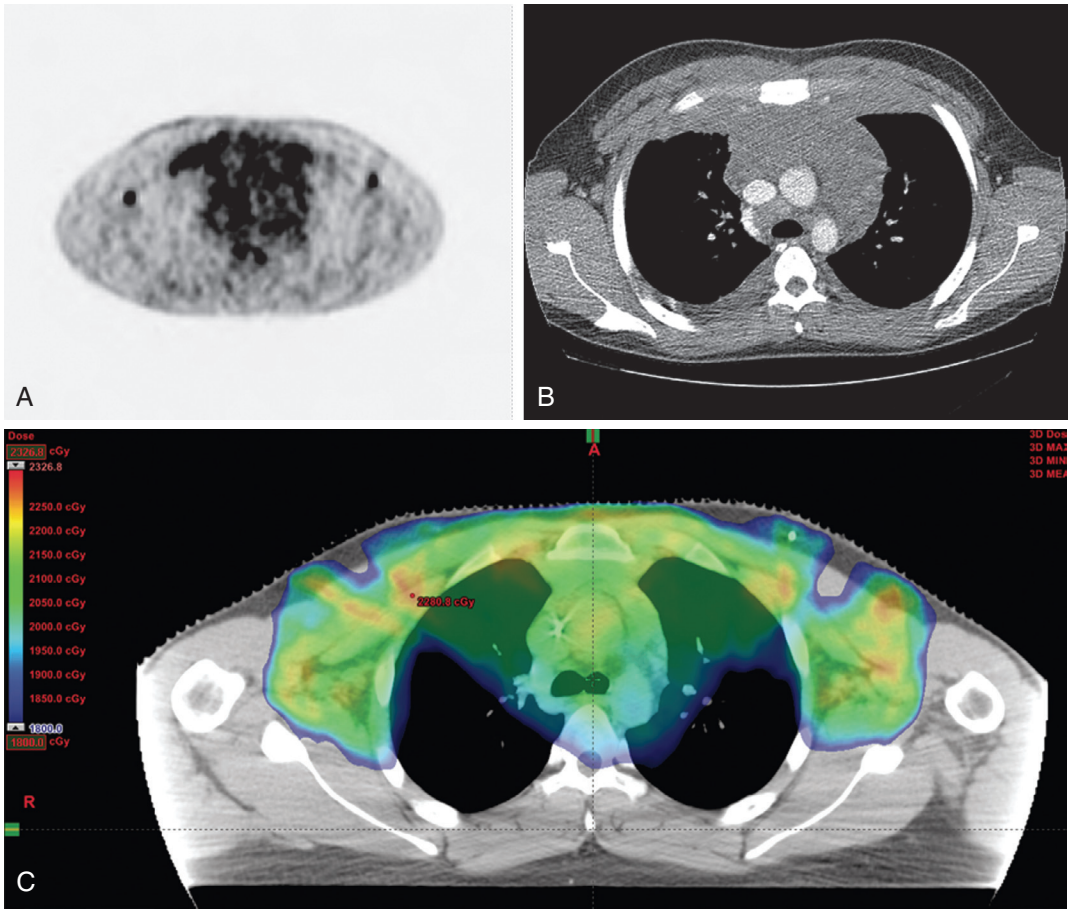


Figure 74-1 Use of intensity-modulated radiation therapy (IMRT) is not standard in Hodgkin's lymphoma but may be preferred in special circumstances. In this case, IMRT was used to treat extensive anterior chest wall involvement at diagnosis. This 18-year-old male with stage IVB nodular sclerosing Hodgkin's lymphoma presented with fevers, sweats, chest pain, purities, and right supraclavicular adenopathy. Staging showed neck, bilateral axillary, and bulky mediastinal adenopathy. Panel A and B shows extensive anterior chest wall involvement on positron emission tomography (PET) and computed tomography (CT) imaging, respectively. After a complete response to ABVE-PC chemotherapy for four cycles, the patient underwent involved field radiotherapy to 21 Gy in 14 fractions. Standard anteroposterior and posteroanterior (AP-PA) fields would have included too much lung. Instead, an IMRT plan yielded a better dose distribution with lower risk for pulmonary toxicity while insuring good coverage of initial sites of involvement. Panel C shows the IMRT dose distribution in a color wash superimposed on an axial CT scan postchemotherapy at the level of the carina. Two years following therapy, patient remains free of lymphoma and is a competitive swimmer in college.

IFRT to 19.8 Gy except patients in the early stage (IA/B and IIA without extranodal involvement) disease category who achieved a CR after induction therapy as defined in GPOH-HD 95. In contrast to North American practice, regions defined as a partial response by anatomic criteria (<75% volume reduction) received a boost to 30 Gy while residual masses greater than 100 mL were boosted even higher to 35 Gy.

Several North American investigators have observed excellent treatment results in combined modality trials for favorable risk HL. Investigators from St. Jude's, Stanford, and Harvard reported treatment results using a nonalkylator regimen, VAMP for children with clinical I/II, non-bulky HL.[108] Patients received four cycles of VAMP chemotherapy and response-based IFRT after two cycles of chemotherapy in which the radiation dose varied from 15 Gy to 25 Gy. At a median follow-up of 9.6 years, 5-year and 10-year EFS rates were 92.7% and 89.4%, respectively.[108] In a follow-up trial, the same investigators limited VAMP chemotherapy alone to a favorable group with less than three nodal sites of disease and no extranodal sites with a CR after one cycle of chemotherapy.[83] The 2-year EFS for patients who did not require RT was 89.4% compared with 92.5% for those who were not deemed in CR and received low-dose IFRT ($p = 0.61$). These results need to be contrasted with more mature adult experience with another minimal therapy approach that includes ABVD for two cycles and 20-Gy IFRT for similar favorable risk patients in which the PFS was 95.1% at 5 years and 86.5% at 8 years.[84]

In contrast to adult trials, there has been remarkably little study of ABVD in pediatric HL. The Pediatric Oncology Group (POG)[111] evaluated the feasibility of combined-modality therapy using four courses of DBVE followed by IFRT to 25.5 Gy to treat stages IA, IIA, and IIIA HL. At a median follow-up of 8.4 years, remarkably good 6-year OS and EFS rates were 98% and 91%, respectively, with almost (98%) all patients achieving remission after completion of therapy. This regimen (DBVE) was used by the POG/COG to support reduction of chemotherapy via an early-response–based treatment algorithm. Patients received only two courses of ABVE if they achieved an early CR, which occurred in 45% patients, whereas

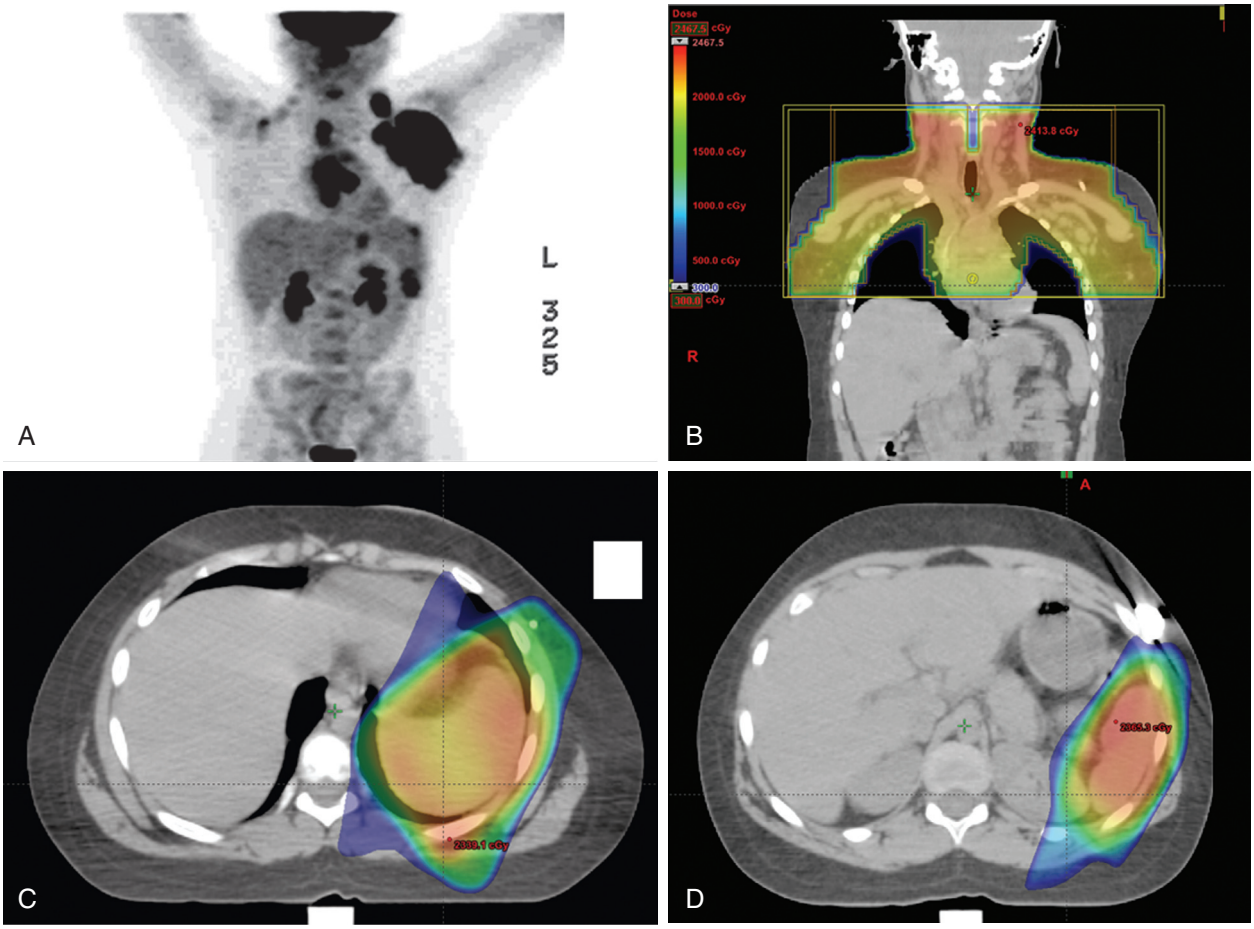


Figure 74-2 Use of non-standard IMRT to treat spleen along with anteroposterior and posteroanterior (AP-PA) mantle field. A 12-year old presented with stage IIIAS lymphocyte predominant Hodgkin's lymphoma with bulky right axillary adenopathy. On staging evaluation, PET scanning shown in Panel A showed bilateral neck and axillary adenopathy, bulky mediastinal disease, as well as multiple splenic nodules. After a complete response to ABVE-PC chemotherapy for four cycles, involved field radiotherapy to 21 Gy in 14 fractions was initiated. The supradiaphragmatic disease was well covered by standard APPA fields as shown in Panel B. APPA or oblique fields to the spleen would have treated too large a volume of the heart or kidney. Instead, a four-field IMRT field along with shallow breathing and appropriate margin for respiratory motion was devised. Panel C and D show superior and inferior aspects of the spleen treatment with the dose distribution shown with a color wash superimposed on the treatment planning CT scan. IMRT technique successfully minimized dose to the heart and left kidney.

four courses of ABVE were given to slow responders. All patients received 25.5 Gy IFRT, resulting in 5-year OS and EFS of 98% and 88%, respectively. With the desire to minimize the use of any RT, the COG AHOD0431 single-arm study already mentioned, stages IA and IIA patients who achieved a CR after three cycles of AVPC received no further therapy. Those with a partial response (PR) received 21-Gy IFRT. The 2-year EFS rate was 80% for those who did not receive RT versus 88% for patients achieving PR (and receiving IFRT) (p = 0.11). The 2-year OS rate was 100%. Of the evaluable patients with FDG-PET results after one cycle of chemotherapy (PET1), the 2-year EFS rates for CR patients who had a positive/equivocal PET1 versus a negative PET 1 were 65% versus 87%, respectively (p = 0.005). The 2-year EFS rates for PR patients who had a positive/equivocal PET1 versus a negative PET1 were 82% versus 96%, respectively (p = 0.047).[126,191] These preliminary results suggest that CT response alone is not adequate to identify patients who can be treated without RT after minimal therapy such as AVPC chemotherapy for three cycles.

Risk-Adapted Therapy: Intermediate-Risk Disease

In risk-adapted treatment regimens, localized disease presenting with unfavorable features are often grouped into an intermediate-risk category and includes those with localized (stages IA, IIA) disease with unfavorable features and those with stage IIIA disease. The GPOH-HD84 study was the first study to match this group of patients with chemotherapy whose intensity was midway between that of favorable and unfavorable/advanced patient cohorts. Building on this concept, the GPOH-HD 2002 study reported a 5-year EFS rate of 88% with two cycles of OEPA for boys and OPPA for girls. This was followed by two cycles of COPP for girls and cyclophosphamide, vincristine, prednisone, and dacarbazine (COPDAC) for boys to spare fertility by reducing alkylator exposure. Deletion of RT appears to have been detrimental with reduced EFS for this group as already discussed.

The COG has developed an approach of using dose-dense chemotherapy to support response-adapted therapy.

An intensive regimen of doxorubicin, bleomycin, vincristine, etoposide, prednisone and cyclophosphamide (ABVE-PC) chemotherapy was used for patients with both intermediate- and high-risk disease in the POG9425 study. Patients with a RER to three cycles of ABVE-PC received 21 Gy of regional field RT (mantle, para-aortic, or pelvis). Slow early responders (SER) received an additional two cycles of ABVE-PC and then received IFRT to 21 Gy. The 5-year EFS rates were 86% for RER patients and 83% for SER patients ($p = 0.85$) and the 5-year OS rate was 95%.[68]

In the recently completed COG AHOD 0031 study, patients received two cycles of ABVE-PC followed by response assessment. Patients with RER received two additional cycles of ABVE-PC followed by a second response assessment. Those with a CR as defined by an 80% reduction in cross-sectional area of disease and resolution of metabolic uptake on gallium or FDG-PET were randomized to 21-Gy IFRT or no further therapy. Patients who did not have a CR constituted a third of the RER cohort and all received IFRT—a subtlety in the results of this trial that may be underrecognized. All SER patients were randomized to either two additional cycles of ABVE-PC or dexamethasone, etoposide, cisplatin, and cytarabine (DECA) followed by an additional two cycles of ABVE-PC. All SER patients received 21-Gy IFRT after chemotherapy. Three-year EFS rates were 87.1% for RER patients versus 77.8% for SER patients ($p = 0.0001$). The 3-year OS rate for RER patients was 98.7% versus 96.9% for SER patients ($p = 0.02$). The 3-year EFS rate was 87.9% for RER/CR patients randomized to receive IFRT versus 85.4% for those randomized to no IFRT ($p = 0.07$). These results suggest that early response to chemotherapy defined by early reduction (60%) in tumor size—based on CT after two cycles can be a powerful predictor of outcome and help optimize subsequent treatment Moreover, the inclusion of a PET analysis after two cycles of ABVE-PC chemotherapy might more definitively help define a cohort of patients who do not benefit from IFRT, even in the presence of initial bulky disease.[192]

Risk-Adapted Therapy: Unfavorable Risk Disease

The criteria for the unfavorable prognostic group is also quite variable from one clinical trial to another, but typically include the presence of B symptoms, bulky lymphadenopathy, hilar lymphadenopathy, involvement of three or more nodal regions, extranodal extension to contiguous structures, or advanced stage (IIIB-IV). RT for unfavorable and advanced HL is also variable and protocol dependent. Suffice it to say, IFRT remains the standard in patients with advanced pediatric HL in good part because of the CCG 5942 results,[66] but restriction of RT volumes to regions of initial bulky disease or post-chemotherapy residual disease is under investigation.[51,94]

For patients with unfavorable or advanced disease, two primary treatment approaches have been used. First, a conventional treatment approach involves outpatient chemotherapy on a twice-monthly schedule for 6 months to 8 months. In adults the use of ABVD therapy for early unfavorable or high-stage HL has reported PFS in the range of 65% to 75% (which is low by pediatric standards).[193-195] In a limited Children's Cancer Study Group pilot trial, CCSG 521-P, ABVD for six cycles produced an 87% EFS and the same OS rate at 3 years. The principal problem, however, was a high serious pulmonary toxicity rate of 9%, predominantly occurring before RT was given.

An alternative strategy used dose-dense chemotherapy to reduce the theoretic risk of developing resistant disease but may also increase the risk for acute and late side effects. The C59704 trial, employing BEACOPP followed by gender-based consolidation, has some of the best disease control results for this high-risk group. A high 5-year EFS rate of 94% was achieved while the 5-year OS rate was 97%.[196] The GPOH, building up on their original experience with the OPPA/COPP regimen, showed that six cycles OEPA/COPDAC together with 20-Gy to 30-Gy IFRT also produced reasonably good results with a 5-year EFS rate of approximately 87%.[94]

Results of the COG AHOD0831 trial will be of interest, but none have yet been reported. This trial treated patients with stages IIIB and IVB disease with ABVE-PC for five cycles with higher doses of cyclophosphamide than the intermediate risk 0031 trial along with response assessment after cycles 1 and 2 with PET-CT imaging. Patients with SER received augmented chemotherapy of ifosfamide and vinorelbine for an additional two cycles. Radiation prescription rules were novel in which the goal was an incremental reduction in the volume of RT over past trials while the dose used was 21 Gy in 14 fractions. Regions of disease targeted were confined to initial sites of bulky disease that included any gross splenic involvement, slow responding sites, and residual masses at least 2.5 cm in diameter. Whole lung RT was discouraged.

Nodular Lymphocyte Predominant Hodgkin Lymphoma

In contrast to classical HL, nLPHL is considered a different disease that is more akin to a low-grade B-cell non-HL, having an indolent pattern of spread and growth with relapses that may occur after many years of follow-up.[197] Patients with nLPHL are characterized by early-stage disease, limited peripheral lymph node (cervical, axillary, or inguinal) presentations with rare involvement of the mediastinum, a male predominance, and an overall good prognosis.[198] Late complications of treatment such as secondary malignancies or cardiopulmonary toxicity,[199] or transformation to aggressive B-cell lymphoma[200] account for the majority of adverse fatal events. Historically, patients with nLPHL were treated like classical HL but more recent experience suggests that minimal therapy is often sufficient in both adults and children. In adults, IFRT alone is now favored with reports of good outcomes using 30 Gy to 36 Gy.[201,202] Because of concerns of growth abnormalities and secondary cancers from these radiation doses, this approach is not appropriate in most children. Because this is still an uncommon disease in children, much data derive from small retrospective series with a variety of treatment approaches that generally have acceptable short-term outcomes.[199,203,204] However, unique for lymphoma management is the excellent outcomes for excisional surgery alone with nLPHL.[205,206] Roughly half of such patients undergoing surgery only had good long-term disease control in one European trial of 58 children.[206] Relapses tend to be localized and limited, quite amenable to additional therapy with curative potential.

At the same time, early-stage nLPHD responds well to chemotherapy alone or combined modality therapy. One example of the former approach is a report entailing 55 pediatric patients with low-stage nLPHL treated with cyclophosphamide/vinblastine/prednisone (CVP), with 11 cases treated after initial surgical relapse. The 40-month freedom from treatment failure and OS for the entire cohort were 75.4% and 100%, respectively. On the other hand, excellent results with combined-modality therapy were reported with the VAMP combination plus LDRT in a series of 33 patients having a 100% 10-year survival and EFS.[108] The COG has validated this watchful waiting approach after surgery with its AHOD03P1 study. A total of 52 patients with stage IA disease underwent surgery only if disease was confined to a single lymph node. Twelve relapses have been localized and all were successfully salvaged with three cycles of AV-PC (Adriamycin, vincristine, prednisone, and cyclophosphamide) and no radiotherapy. The current 2-year EFS estimate among

these patients treated without chemotherapy is 81.6%.[207] A separate cohort of 127 patients with stage II or stage I with multiple nodes were treated upfront with AV-PC for three cycles. The vast majority of patients had a CR and were observed, whereas 12 patients with residual disease received low-dose IFRT. Nine additional patients with local relapse after surgery were also included in this scheme in which the 4-year EFS is estimated at 86.8%.[207]

TREATMENT OF RELAPSED AND REFRACTORY DISEASE

The generally excellent outcome in pediatric HL has limited opportunities to evaluate salvage therapy programs. Most relapses in patients with HL occur within the first 3 years, but some patients may relapse as long as 10 years after initial diagnosis.[208] Treatment and prognosis after relapse depends on the primary therapy, initial stage, and duration of remission (time of relapse). Harker-Murray et al have reviewed the literature on retrieval therapy for HL and have suggested a favorable to intermediate risk cohort of patients with early-stage disease without initial B symptoms and at least a 1 year remission duration to define a group for whom conventional chemotherapy with selective use of RT may be reasonable.[209] Indeed, such an approach may salvage 40% to 50% of children relapsing after a sustained remission (1 year or longer); however, adverse effects of treatment, including second malignancies, may reduce ultimate survival.[210-212] Patients who demonstrate refractory disease, or recurrence within 1 year after completing therapy, respond poorly to conventional salvage therapy, as do patients with multiple relapses. These high-risk patients have a better chance of achieving a durable remission if they are consolidated with myeloablative therapy followed by hematopoietic cell transplantation (HCT).

For higher risk relapses, a combination of ifosfamide/vinorelbine for pediatric patients in first relapse was studied by the COG (AHOD00P1 trial). This regimen showed a good overall complete or partial response rate of 78% and achieved good stem-cell mobilization for future autologous stem-cell transplant.[213] For patients who relapse after transplant or are upfront refractory to chemotherapy, a combination of a gemcitabine/vinorelbine has also studied by the COG, documenting a response rate of 76%.[214]

OS rates in children and adolescents with relapsed HL treated with high-dose chemotherapy and hematopoietic transplant range from 30% to 60%. Because of the higher transplant-related mortality associated with allogeneic transplantation, autologous HCT is preferred for patients with relapsed HL. However, recent investigations of reduced-intensity allogeneic transplantation have demonstrated acceptable rates of transplant-related mortality.[215-217] Nonmyeloablative conditioning regimens most often use fludarabine or low-dose total-body irradiation to provide a nontoxic immunosuppression and establish a graft-versus-lymphoma effect.

IFRT to sites of recurrent disease should be considered in the setting of HCT. In a Stanford report, patients with stages I to III disease at relapse who received autologous bone marrow transplantation and IFRT had a 3-year freedom from relapse of 100% and OS of 85%, compared with 67% and 60%, respectively, for patients not receiving IFRT.[218] For patients not previously irradiated, IFRT was associated with an improved freedom from relapse of 85% and OS of 93%, in contrast to 57% and 55%, respectively, for those previously irradiated. Morbidity was similar to those not irradiated, although RT may have contributed to the peritransplant death of two patients. Other reports on the use of consolidative RT suggest a benefit and low to moderate morbidity, although these are mostly adult data which suffer from inherent selection and publication biases.[219-224] Central issues relating to the use of IFRT are the dose, target volume, and timing with respect to the transplant. RT doses are generally 15 Gy to 25 Gy, in 1.5-Gy to 2.0-Gy fractions. This variation relates to potential normal tissue toxicity as well as the consideration for higher radiation doses in patients with an identifiable tumor that demonstrates radiation responsiveness. RT volume can vary and include treatment to all sites of initial disease, recurrent disease, persistent disease following salvage chemotherapy, persistent disease following the preparative regimen for transplant, or all nodal sites. Unless protocol-specific therapy is directed, individual considerations for such decision making are necessary at this time. IFRT can be administered before the high-dose chemotherapy program to place patients in a minimal disease state. Alternatively, RT can also be administered after the high-dose chemotherapy program to decrease the overall potential for disease progression and avoid RT-related peritransplant morbidity such as esophagitis, pneumonitis, cardiomyopathy, and veno-occlusive disease. Possible disadvantages of this approach include the loss of the pretransplant cytoreductive effect and the theoretical carcinogenic effect of RT on the newly proliferating hematopoietic system.

New agents for HL are being evaluated in the relapse setting. In particular there is great excitement with the anti-CD30-drug conjugate, Brentuximab Vedotin, that has shown excellent activity in early clinical trials.[225] This type of targeted therapy hold promise for greater efficacy with less toxicity as it is carefully combined with other agents. Clinical trials incorporating this agent in upfront therapy for both adults and children with HL are under way or being planned.

Treatment Algorithms

Table 74-6 summarizes recommendations for risk-adapted treatment approaches. Because patients with localized favorable disease presentations can achieve long-term disease-free survival using regimens that minimize alkylators, doxorubicin-based chemotherapy such as ABVD or ABVE is preferred for this group.[96,98,105,110] However, alkylating agents or etoposide can be added to the regimen without compromising disease outcome if the clinician prefers to restrict anthracycline chemotherapy exposure to preserve cardiac function.[50,51,101] Combined-modality treatment approaches including low-dose IFRT have historically produced excellent results in children with favorable localized disease and reduce cumulative chemotherapy doses. However, there is an increasing trend to try to use response-based programs to reduce or eliminate the use of radiotherapy in patients with a rapid early response with a goal of lessening the burden of late effects of therapy.

Combinations such as ABVE-PC or older ABVD/MOPP-type hybrid regimens with the addition of etoposide still provide the most effective chemotherapy strategies for children and adolescents with intermediate- or high-risk disease presentations.[50,51] In older regimens reporting good long-term outcomes, low-dose RT is administered following chemotherapy to areas of bulk disease, or nodes (usually the regions harboring the involved nodes) present at diagnosis. However, the use of dose-intensive regimens such as ABVE-PC allows rapid responders to significantly decrease their exposure to RT. This is rapidly evolving into a new standard for pediatric HL. At the same time this type of abbreviated, dose-dense regimen that induce rapid tumor response may permit reduction of cumulative chemotherapy doses below threshold levels associated with significant long-term toxicity.[68]

TABLE 74-6 Recommendations for Treatment Approach in Pediatric Hodgkin Lymphoma

Clinical Presentation	Stage	Recommended Treatment Approach
EARLY (low risk)		**RECOMMENDED THERAPY**
<3-4 nodal regions; no B symptoms, bulk, or extranodal extension from contiguous nodal disease	IA, IIA	2-4 cycles noncross-resistant chemotherapy without alkylators plus low-dose IFRT (15 Gy-21 Gy); in highly favorable patients with no extranodal disease and less then 3 sites, abbreviated chemotherapy with a CR on interim assessment or at completion of therapy may allow for deletion of RT **IN CLINICAL TRIAL SETTING ONLY** 2-4 cycles of chemotherapy alone if there is negative PET2; or such chemotherapy followed by ISRT or RT limited to initial bulky sites or residual disease sites (15 Gy-21 Gy)
INTERMEDIATE		**RECOMMENDED THERAPY**
≥3-4 nodal regions; bulky lymphadenopathy (mediastinal ratio ≥33%; peripheral lymph node mass ≥6-10 cm)	IA, IIA, IIB* IIIA, some IIIB	4-6 cycles (3-5 compacted, dose-intensive cycles) noncross-resistant chemotherapy. Low-dose RT (15 Gy -21 Gy) is reserved for patients with slow response, incomplete response, or residual disease or masses. **IN CLINICAL TRIAL SETTING ONLY** 4-6 cycles (3-5 compacted, dose-intensive cycles) noncross-resistant chemotherapy alone if there is negative PET2; or such chemotherapy followed by ISRT or RT limited to initial bulky sites or residual sites of disease (15 Gy-21 Gy)
ADVANCED (HIGH risk)		**RECOMMENDED THERAPY**
Stage II patients with fever or weight loss and/or bulk*; any patient with advanced stage (not all stage III would be high risk)	IIB* IIIB IV	6 cycles (4-6 compacted, dose-intensive cycles) of noncross-resistant chemotherapy plus low-dose IFRT (15 Gy-21 Gy) **IN CLINICAL TRIAL SETTING ONLY** 6 cycles (4-6 compacted, dose-intensive cycles) of noncross-resistant chemotherapy plus low-dose IFRT (15 Gy-25 Gy) restricted to (1) sites of initial bulky disease, (2) PET2 positive disease, or (3) residual masses

IFRT, *Involved-field radiotherapy;* INRT, *involved-nodal radiotherapy;* PET2, *PET scan after second cycle of chemotherapy used as indicator of rapid early response.*
**Patients with stage IIB disease have been variably treated as intermediate or unfavorable risk. Some studies use associated factors, e.g., weight loss, bulk disease, extranodal extension, for further risk stratification.*

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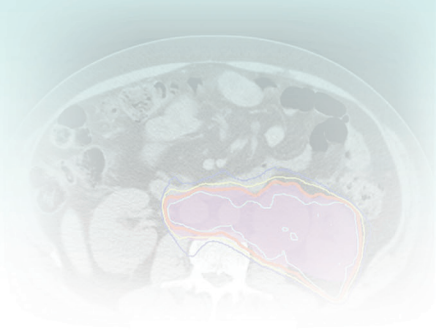
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CHAPTER

75 Rare Pediatric Tumors



Luke E. Pater and John Breneman

INCIDENCE

Hepatic tumors: 1.6 per million; male predominance.

Germ cell tumors: 3% of childhood malignancies; female predominance.

Juvenile nasopharyngeal angiofibroma: 0.05% of head and neck tumors.

Pleuropulmonary blastoma: Extremely rare.

Hemangioma and lymphangioma: Hemangiomas: 1% of infants; lymphangiomas: 0.01% of infants.

Diffuse, small, round cell tumor: Extremely rare; primarily affects young males.

Langerhans cell histiocytosis: 1 million to 5 per million; slight male predominance.

Nasopharyngeal cancer: 1% of pediatric cancers; 2:1 male predominance.

BIOLOGIC CHARACTERISTICS

Hepatic tumors: Fetal-type hepatoblasts with sinusoidal hematopoiesis; typically alpha-fetoprotein positive.

Germ cell tumors: Vary widely from undifferentiated germinomas to benign well-differentiated teratomas.

Juvenile nasopharyngeal angiofibroma: Mixed endothelial-lined vessels and fibrous stroma; β-catenin mutations seen in 75%.

Pleuropulmonary blastoma: Mixed blastemal and sarcomatous elements with cystic and solid morphologies. Solid variants behave more aggressively.

Hemangioma and lymphangioma: Abnormal dilated blood or lymph vessels.

Diffuse, small, round cell tumor: Small, round blue cells with collagen dense stroma.

Langerhans cell histiocytosis: Dendritic histiocytes; CD207, S-100, and CD1a positive.

Nasopharyngeal cancer: Mostly lymphoepithelioma; Epstein-Barr virus related.

STAGING

Hepatic tumors: Right upper quadrant ultrasonography, magnetic resonance imaging/computed tomography (MRI/CT) of liver, CT of chest, alpha-fetoprotein level.

Germ cell tumors: Ultrasonography of primary tumor, CT of chest, abdomen, and pelvis; alpha-fetoprotein, β-human chorionic gonadotropin, and lactate dehydrogenase levels.

Juvenile nasopharyngeal angiofibroma: Angiography and CT or MRI of the head.

Pleuropulmonary blastoma: CT of the chest, abdomen, and pelvis; MRI of the brain.

Hemangioma and lymphangioma: CT or MRI of affected site; angiography in selected cases.

Diffuse, small, round cell tumor: CT with intravenous and oral contrast enhancement.

Langerhans cell histiocytosis: Skeletal survey, chest radiography, CT, bone scintigraphy.

Nasopharyngeal cancer: Nasopharyngoscopy, positron emission tomography (PET)/CT, MRI, blood chemistries, and dental and endocrine evaluation.

PRIMARY THERAPY

Hepatic tumors: Neoadjuvant chemotherapy and surgery; overall survival (OS) is about 65% for hepatoblastoma and 25% for hepatocellular carcinoma.

Germ cell tumors: Surgery alone for teratomas or stage I tumors; others get surgery plus chemotherapy. Cure rate is more than 90%.

Juvenile nasopharyngeal angiofibroma: Surgical resection controls approximately 70% of tumors.

Pleuropulmonary blastoma: Surgical resection; cure obtained in 80% of type I tumors and 45% of types II and III tumors.

Hemangioma and lymphangioma: Surgical resection; local control achieved in most patients.

Diffuse, small, round cell tumor: Surgical resection; cure is uncommon.

Langerhans cell histiocytosis: Varies by extent of disease.

Nasopharyngeal cancer: Radiotherapy (RT) with OS of 51% to 95% and relapse-free survival of 36% to 91%

ADJUVANT THERAPY

Hepatic tumors: Cisplatin-based chemotherapy.

Germ cell tumors: Cisplatin/etoposide/bleomycin (PEB) chemotherapy for three to four cycles.

Juvenile nasopharyngeal angiofibroma: Consider RT with 36 Gy to 40 Gy.

Pleuropulmonary blastoma: Chemotherapy with ifosfamide/vincristine/dactinomycin (Actinomycin-D)/doxorubicin (IVADo) or similar regimen.

Hemangioma and lymphangioma: None.

Diffuse, small, round cell tumor: Chemotherapy with alkylating regimen and whole-abdomen irradiation.

Langerhans cell histiocytosis: Surgery, chemotherapy, RT, or corticosteroids.

Nasopharyngeal cancer: Neoadjuvant or adjuvant chemotherapy.

THERAPY FOR LOCALLY ADVANCED DISEASE

Hepatic tumors: Neoadjuvant chemotherapy, surgery, possible liver transplantation; consider RT if unresectable.

Germ cell tumors: Neoadjuvant chemotherapy plus surgery.

Juvenile nasopharyngeal angiofibroma: RT with 36 Gy to 40 Gy controls approximately 80% of tumors.

Pleuropulmonary blastoma: Neoadjuvant chemotherapy with delayed resection. Consider RT with 44 Gy.

Hemangioma and lymphangioma: Surgery, embolization, corticosteroids.

Diffuse, small, round cell tumor: Neoadjuvant chemotherapy, surgical debulking.

Langerhans cell histiocytosis: Low-dose RT or chemotherapy.

Nasopharyngeal cancer: Most disease is locally advanced and treated with chemoradiation.

PALLIATION

Hepatic tumors: Chemotherapy or RT.

Germ cell tumors: Consider RT or additional chemotherapy.

Juvenile nasopharyngeal angiofibroma: Consider diethylstilbestrol or flutamide. Cytotoxic chemotherapy may be effective.

Pleuropulmonary blastoma: RT for brain metastases and symptomatic bone metastases.

Hemangioma and lymphangioma: Consider RT with 10 Gy to 25 Gy for life-threatening conditions.

Diffuse, small, round cell tumor: RT for symptomatic disease.

Langerhans cell histiocytosis: Low-dose RT or chemotherapy.

PRIMARY LIVER TUMORS OF CHILDHOOD

Etiology and Epidemiology

Primary malignant liver tumors (PMLT) in children are rare malignancies representing ~1% of pediatric cancers. They are comprised almost entirely of hepatoblastoma (HBL) and hepatocellular carcinoma (HCC). In people younger than 20 years old, 67% of PMLTs are HBL and 31% are HCC.[1] Age-adjusted rates show a slight male-to-female predisposition for both HBL and HCC.[1,2] HBL has been associated with prematurity, low birth weight, fetal alcohol syndrome, use of maternal oral contraceptives, Beckwith–Wiedemann syndrome, hemihypertrophy, and familial adenomatous polyposis.[3-8] HCC is strongly associated with hepatitis B virus (HBV) as well as α_1-antitrypsin deficiency, hereditary tyrosinemia, extrahepatic biliary a tresia, Fanconi anemia, ataxia-telangiectasia, Sotos syndrome, glucose-6-phosphatase deficiency, congenital hepatic fibrosis, Byler disease, and Wilson disease.[3,9]

Biologic Characteristics and Molecular Biology

There is no familial clustering of HBL, though genetic syndromes are associated with approximately 15% of cases.[10] Familial adenomatous polyposis coli (FAP) with the heritable mutation of the adenomatous polyposis coli (APC) gene has been associated with risk of HBL[11,12] as have been Beckwith–Wiedemann, Sotos syndrome, and Simpson–Golabi–Behmel syndrome. Trisomy 18 has been observed in HBL, particularly in females and patients with multifocal tumors. Other cytogenetic findings in HBL include gains of chromosomes 2, 8, or 20 and loss of 18.[13-16] Mutations of β-catenin and phosphatidylinositol-3-kinase have been reported in sporadic cases,[17,18] as well as differential expression of imprinted genes and altered methylation of gene promoters.[19-21]

HBV is associated with nearly all cases of HCC in areas endemic for HBV.[22] Molecular hybridization reveals incorporation of viral DNA into both malignant and adjacent benign liver cells. The time to development of HCC in children after HBV infection is known to be shorter in children than in adults.

Pathology and Pathways of Spread

HBL is an embryonal tumor thought to arise from a hepatocyte precursor cell, and accounts for 60% to 75% of PMLTs of childhood.[23,24] Two subtypes are recognized; epithelial and mixed, with epithelial type further divided into fetal, embryonal, macrotrabecular, small-cell undifferentiated (SCU), and cholangioblastic variants. The SCU variant has a particularly poor prognosis and is often viewed distinctly for treatment decisions. Within the mixed type, stromal and teratoid variants are identified.[25]

There is a strong relationship between HCC and preexistent hepatic disease or cirrhosis. Fibrolamellar HCC is a variant found in approximately one third of pediatric HCC and typically in cases without preexisting liver disease.[25] This variant has sometimes been reported to have a higher rate of resectability and improved clinical outcome, though this was not supported by the Pediatric Intergroup Hepatoma INT-0098 results.[26]

Clinical Manifestations, Patient Evaluation, and Staging

The majority of children with PMLTs present with a painless right upper quadrant abdominal mass. Additional findings may include abdominal enlargement, pain, anorexia with associated weight loss, nausea, emesis, fever, and jaundice.

Initial evaluation consists of abdominal ultrasound with characteristic findings of a solid intrahepatic mass. Subsequent evaluation should include dual-phase CT of the abdomen and pelvis or axial and coronal MRI with gadolinium at arterial, portal venous, and equilibrium phases. CT of the chest is also required because lung metastases are present in approximately 20% of HBL cases and 30% of HCC cases. Bone scan is reserved for symptomatic patients.[27-29] Laboratory evaluation includes: complete blood count (CBC), differential, platelets, urinalysis, electrolytes including calcium, phosphate, magnesium, creatinine, ALT/AST, bilirubin and total protein/albumin. Alpha-fetoprotein (AFP) is elevated in approximately 90% of patients with HBL and between 60% and 80% of patients with HCC.[28,30] AFP levels less than 100 ng/mL have been associated with poor prognosis.

PMLTs of childhood are typically staged using the Children's Oncology Group Staging system (Table 75-1) and the PRETEXT surgical staging system (Figure 75-1). The PRETEXT staging is based on the number and relative locations of involved liver segments on preoperative imaging. The left lobe of the liver consists of a lateral sector (segments 2 and 3) and a medial sector (segment 4), whereas the right lobe is divided in an anterior sector (segments 5 and 8) and a posterior sector (segments 6 and 7). The number of affected liver

TABLE 75-1 Children's Oncology Group Staging System for Hepatoblastoma

Stage	Description
I	Completely resected localized tumors
II	Grossly resected tumors with microscopic residual tumor
III	Unresectable tumors (measurable residual tumor or abdominal lymph node involvement)
IV	Distant metastases

From Schnater JM, Kohler SE, Lamers WH, et al: Where do we stand with hepatoblastoma? A review. Cancer 98:668–678, 2003.

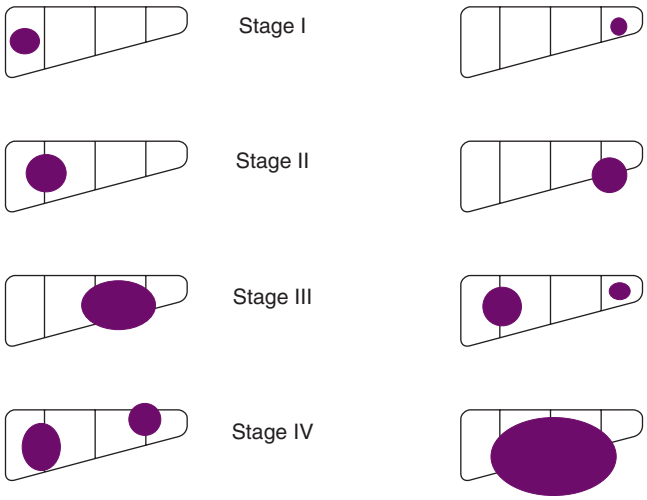


Figure 75-1 PRETEXT surgical staging system for hepatoblastoma. *Adapted from Schnater JM, Aronson DC, Plaschkes J, et al: Surgical view of the treatment of patients with hepatoblastoma. Results from the first prospective trial of the International Society of Pediatric Oncology Liver Tumor Study Group. Cancer 94:1111–1120, 2001.*

sectors determines the PRETEXT category.[27] Staging using the same criteria applied after two to four cycles of chemotherapy is referred to as POST-TEXT. Additional staging notations can be made for involvement of the vena cava or all three hepatic veins (+V), involvement of the portal vein bifurcation or both right and left portal veins (+P), involvement of the caudate lobe (+C), extrahepatic contiguous tumor (+E), and distant metastatic disease (+M).

Primary and Adjuvant Therapy and Results

Surgical resection is the primary treatment modality for PMLTs of childhood and provides the only potential for cure. Approximately half of patients with HBL are able to undergo complete resection at the time of diagnosis. Because HBL is highly chemosensitive, many patients are treated with neoadjuvant chemotherapy, which increases resectability to approximately 75%. Patients with HBL undergoing complete resection have an event-free survival (EFS) of approximately 90%.

The SIOPEL-1 trial reported by the International Society of Paediatric Oncology (SIOP) evaluated the use of four to six courses of preoperative cisplatin and doxorubicin. Eighty-two percent of patients showed at least a partial response and 77% achieved complete resection. The 5-year EFS and OS were 66% and 75%, respectively.[29] The third study of the International Society of Paediatric Oncology Epithelial Liver Tumor Group (SIOPEL-3) randomized patients to cisplatin alone versus cisplatin plus doxorubicin for three cycles preoperatively, followed by two postoperative cycles in children with HBL involving three or fewer liver segments and an alpha-fetoprotein level greater than 100 ng/mL. Outcomes at 3 years were identical: 95% and 93% underwent complete resection in the respective chemotherapy arms, and OS was 95% and 93%, respectively. Grade-3 and grade-4 toxicities were significantly more common in the combination arm.[31]

An analysis of stage I pure fetal histology (PFH) HBL treated with complete surgical resection only on Children's Oncology Group Study P9645 showed all patients free of disease at a median follow-up of 4.9 years.[26]

Children with HCC on the SIOPEL-1 trial presented with more advanced disease and fared significantly worse than patients with HBL. Partial response to neoadjuvant chemotherapy was seen in 49%, and complete resection was achieved in only 36%; 5-year OS and EFS were 28% and 17%, respectively.[28] The Pediatric Intergroup Hepatoma Protocol INT-0098 randomized patients with HCC to postoperative cisplatin/vincristine/5-fluorouracil versus cisplatin and doxorubicin. There was no difference in outcome between the treatment regimens, and the overall 5-year EFS was 17% (75% for stage I, 8% for stage II, and 0% for stage IV).[28] Subsequent SIOPEL studies evaluated a regimen of cisplatin and carboplatin, with no substantial improvement in outcome.[28]

The current COG study reduces chemotherapy for patients with low-risk disease with stage I non-pure fetal histology, non-SCU HBL or stage II non-SCU HBL to two adjuvant cycles of cisplatin, 5-flouorouracil and vincristine (C5V). Intermediate-risk cases with stage I SCU, stage II SCU, or any stage III are given six cycles of C5V + doxorubicin (C5VD).

Locally Advanced Disease and Palliation

Patients with high-risk HBL include those with stage IV disease as well as patients with any stage of HBL or initial AFP under 100 ng/mL. The Pediatric Oncology Group study 9345 treated children with unresectable or metastatic HBL with neoadjuvant carboplatin and C5VD, followed by surgery when feasible, or with high-dose cisplatin and etoposide. Thirty-six percent of patients with stage IV disease were able to undergo subsequent resection. For patients able to undergo resection, 5-years EFS was 79%.[32] The recent SIOPEL-4 trial was a single-arm prospective study for high-risk HBL using neoadjuvant dose-dense cisplatin plus doxorubicin. This approach yielded good outcomes with 74% of children able to undergo complete resection and an 83% 3-year OS.[33] Other approaches include orthotopic liver transplantation when disease is unresectable, with documented long-term survival in a limited number of patients.[27,32]

The approach for patients with metastatic disease uses neoadjuvant chemotherapy followed by surgery, if possible, and consideration of metastectomy if local control is achievable. For patients considered for orthotopic liver transplantation, radiographic clearance of metastatic disease must be confirmed before transplant.

Irradiation Techniques

RT is infrequently used in the treatment of PMLTs. Habrand et al used doses of 25 Gy to 45 Gy in conjunction with chemotherapy in a heterogeneous group of 15 patients; 11 with documented HBL, 2 with HCC, and 2 with unknown pathology. Those with inoperable HBL or minimal (<2 cm) disease postoperatively showed a possible benefit of radiotherapy. No benefit was seen for patients with HCC.[34] There are few current indications for hepatic irradiation or treatment beyond palliation to metastatic sites with HBL or HCC. The current Children's Oncology Group HBL study specifically excludes use of RT. It is clear that the RT dose ranges noted previously are less than those now known to be necessary in adults with HCC. Modern techniques of respiratory gating and stereotactic techniques may provide for additional options for RT of pediatric liver tumors in select cases.

Treatment Algorithms, Controversies, Challenges, and Future Possibilities

The cornerstone of treatment for PMLTs is surgical resection. Most children are treated with neoadjuvant and adjuvant platinum-based chemotherapy because of bulky disease. Orthotopic liver transplantation can provide cures for selected patients in whom resection is not possible. Investigational treatments for HBL include chemoembolization, stereotactic

radiosurgery to focal liver lesions, angiogenesis inhibitors, and biologic agents.

PEDIATRIC EXTRACRANIAL GERM CELL TUMORS

Etiology and Epidemiology

Germ cell tumors (GCTs) can be either malignant or benign and are thought to arise from primitive germ cells that fail to undergo complete differentiation. These tumors are found within the ovary and testis, but also among midline structures such as the sacrococcygeal region, retroperitoneum, mediastinum, and the pineal gland. The rationale for their distribution is attributed to embryologic development as cells migrate from the allantoic stock to the genital ridge, coming to rest as the genitalia.[35]

GCTs account for approximately 3% of all pediatric malignancies[35] and are the most common malignancy in neonates.[36] The overall incidence of GCTs is higher in females, but males are more at risk for malignant GCTs.[37] A bimodal age distribution is noted with peaks at 2 and 20 years of age.

Prevention and Early Detection

Several risk factors have been identified for these rare tumors. Intersex disorders of pseudohermaphroditism, androgen insensitivity, and 5α-reductase deficiency are associated with risk of gonadoblastoma, which can transform into GCT.[38] Undescended testis increases the incidence of testicular GCT to 30 to 50 times the incidence in the general population. This risk is even higher for intraabdominal testis.[39-41]

Biologic Characteristics and Molecular Biology

Pediatric GCTs are genetically distinct from adult GCTs. More than 80% of adult GCTs have isochromosome 12p and many of the remaining display amplification of 12p. These are infrequently observed abnormalities in pediatric GCTs,[42-44] where aberrations on chromosome 1 and 6 are more commonly identified.[43,44]

Pathology and Pathways of Spread

GCTs comprise a spectrum of entities from benign to malignant, with elements of multiple histologic types present in 25% of cases.[45] The most common pediatric GCT is the teratoma, which is composed of tissue from more than one embryonic layer. Teratomas can be either mature, consisting of well-differentiated tissues, or immature, consisting of immature elements (most commonly neuroepithelial tissue).

Yolk sac or endodermal sinus tumors are highly malignant, occur most commonly in the ovary, testis, and sacrococcygeal region and secrete alpha-fetoprotein. Histologically they show classic perivascular formations called Schiller-Duval bodies. Embryonal carcinomas are composed of large, pleomorphic undifferentiated cells. They often occur in combination with endodermal sinus tumors. Choriocarcinomas are rare tumors composed of malignant cytotrophoblasts and syncytiotrophoblasts. They typically secrete β-human chorionic gonadotropin. All three of these GCT types are highly undifferentiated tumors with the propensity to metastasize to lung, liver, bone, and lymph nodes. In a series of 95 patients with sacrococcygeal endodermal sinus tumors,[45] 15% had positive lymph nodes at diagnosis and 35% had distant metastases.

Tumors of undifferentiated germ epithelium are named according to the site of origin: seminomas originate in the testis, dysgerminomas in the ovary, and germinomas in the brain. Seminoma and dysgerminoma are infrequent in childhood.

Clinical Manifestations, Patient Evaluations, and Staging

Clinical manifestations of GCTs are largely dependent on the location of the tumor. The most common location for pediatric extracranial GCTs is the sacrococcygeal region, and because of their early presentation, they may sometimes be identified by fetal ultrasound. Older children more commonly present with large pelvic masses, with malignant degeneration often seen in children over 6 months to 12 months of age. The ovaries, testes, and mediastinum are also common sites, but GCTs can occur in the retroperitoneum, neck, stomach, and vagina as well. Laboratory evaluation includes complete blood count with differential, urinalysis, tumor markers (AFP, β-human chorionic gonadotropin, lactic dehydrogenase, CA-125), electrolytes, creatinine, bilirubin, ALT, alkaline phosphatase, total protein, albumin, phosphorus, magnesium, and calcium. Diagnostic imaging should include chest/abdomen/pelvis CT or MRI and often bone scan. Tumor marker profiles are indicative of different histologies as noted in Table 75-2.

Sacrococcygeal tumors are staged according to the Altman classification. Type I tumors are predominantly external projecting from the sacrococcygeal region and presenting with distortion of the buttocks. Type II tumors are predominantly external but also have a large intrapelvic component. Type III tumors are predominantly intrapelvic with a small external component, and Type IV tumors are entirely internal with no external or buttock component.[46]

Other GCTs are staged according to their site of origin as defined by the Children's Cancer Group and Pediatric Oncology Group staging system outlined in Table 75-3.

Primary Therapy, Adjuvant Therapy, and Results

Primary therapy is dictated by the resectability of the presenting lesion as well as the histology and thus anticipated response to adjuvant therapy options. For most malignant tumors a multidisciplinary approach combining surgery and

TABLE 75-2 Profiles of Germ Cell Tumor Histologies

	AFP	β-HCG	Chemosensitivity	Radiosensitivity
Teratoma				
Mature	—	—	—	—
Immature	–/+	—	—	—
Endodermal sinus tumor	+++	—	+++	—
Choriocarcinoma	—	+++	+++	—
Embryonal carcinoma	—	—	—	—
Seminoma/germinoma	—	+	+++	+++

TABLE 75-3 Children's Cancer Group and Pediatric Oncology Group Staging System for Pediatric Germ Cell Tumors

Stage	Description
OVARIAN	
I	Limited to ovary (ovaries), peritoneal washings negative, tumor markers normal after appropriate half-life
II	Microscopic residual or positive lymph nodes (<2 cm), peritoneal washing negative, tumor markers positive or negative
III	Lymph node involvement >2 cm, gross residual disease, biopsy only, contiguous visceral involvement, peritoneal washings positive, tumor markers positive or negative
IV	Distant metastases
TESTICULAR	
I	Limited to testis, tumor marker normal after appropriate half-life, completely resected with high inguinal orchiectomy
II	Transscrotal orchiectomy, microscopic disease in scrotum or high in spermatic cord, retroperitoneal lymph node <2 cm, increased tumor marker after appropriate half-life
III	Retroperitoneal lymph node >2 cm, no visceral of extraabdominal involvement
IV	Distant metastases
EXTRAGONADAL	
I	Complete resection at any site, negative margins, coccygectomy for sacrococcygeal sites
II	Microscopic residual, lymph nodes negative
III	Gross residual or biopsy only, regional lymph nodes positive or negative
IV	Distant metastases

cisplatin-based chemotherapy (often similar to the adult PEB regimen of cisplatin, etoposide, and bleomycin) is standard.

Sacrococcygeal teratomas are approached with the goal to preserve the levator ani musculature and external sphincter using an inverted-V incision. Inadequate surgery has proven deleterious with a 37% local recurrence rate if the coccyx is spared inappropriately.[47]

Ovarian GCTs are chemosensitive and a conservative surgical approach is usually indicated. Resection of the primary tumor sparing the fallopian tumor if possible is combined with collection of ascites and examination and palpation of the peritoneal surfaces, retroperitoneal lymph nodes, omentum, and the contralateral ovary.[48] These fertility-sparring approaches have cure rates of approximately 95% with 80% of patients preserving reproductive function.[49]

Testicular tumors are removed via a high inguinal incision with high inguinal orchiectomy performed for malignant lesions and a more conservative tumor enucleation for teratoma.

Adjuvant therapy for extracranial GCTs is based on the stage, degree of resection, and histologic subtype (Table 75-4). Observation is recommended following resection of mature and immature teratomas with reported survivals of 82% to 100%.[47]

Resection of sacrococcygeal tumors with negative margins provides cure rates in excess of 90%, though this falls to 75% to 85% in the setting of microscopically involved margins, and 40% for macroscopic residual tumor.[50] There is minimal guidance for the use of RT in the adjuvant setting. A dose of ≥45 Gy

TABLE 75-4 General Treatment Guidelines for Extracranial Germ Cell Tumors

LOW-RISK DISEASE	
All teratomas Stage I gonadal Stage I extragonadal	Surgery and observation
INTERMEDIATE-RISK DISK	
Stages II-IV gonadal Stage II extragonadal	Surgery with adjuvant chemotherapy
HIGH-RISK DISEASE	
Stages III-IV extragonadal	Surgery with adjuvant chemotherapy
INITIAL UNRESECTABLE OR BIOPSY ONLY	Neoadjuvant chemotherapy followed by second surgery, followed by adjuvant chemotherapy for residual pathologic disease

appears reasonable based on a report by Schneider et al.[51] Platinum-based chemotherapy has been advocated for patients with recurrent immature teratomas based on the POG 9048/CCG 8891 trial. Four of five patients with recurrence were rendered disease-free using this salvage approach.[52]

Locally Advanced Disease and Palliation

With a primary goal of resection, bulky and locally invasive disease is treated with neoadjuvant chemotherapy followed by surgery or second-look surgery as appropriate.

The POG 9049/CCG 8882 trial[53] randomized patients with stages III and IV gonadal and stages I to IV extragonadal GCTs to high-dose PEB versus standard-dose PEB with a 6-year EFS of 89.6% versus 80.5% but no benefit in OS. Progressive and metastatic GCTs often respond to cisplatin, paclitaxel, and ifosfamide regimens.[53] The COG AGCT0521 study used the regimen with carboplatin substituted for cisplatin with the goal to improve the toxicity profile. The addition of hyperthermia to resection for relapsed disease is being explored.[54]

Irradiation Techniques

The role of RT for GCTs has diminished significantly owing to the effectiveness of current chemotherapy regimens. RT is now used only in the setting of unresectable disease that is unresponsive to chemotherapy or in the setting of relapse. Radiation doses of ≥40 Gy are typically used.[51]

Treatment Algorithms, Controversies, Challenges, and Future Possibilities

Surgical resection is the first line of treatment with chemotherapy given neoadjuvantly to achieve this goal when possible and in cases of recurrent or metastatic disease. PEB chemotherapy is the currently recommended regimen for patients presenting as locally advanced or metastatic tumor with OS approaching 75%. Because of the high curability of these tumors, current protocols are seeking to decrease toxicity of therapy using algorithms based on histology, site, stage, and genetic aberrations to provide risk-adapted therapy.

JUVENILE NASOPHARYNGEAL ANGIOFIBROMA

Etiology and Epidemiology

Juvenile nasopharyngeal angiofibroma (JNA) is a highly vascular tumor that is histologically benign but locally invasive.

JNA occurs almost exclusively in adolescent boys and young adult men, suggesting a prominent hormonal role in the tumor's etiology; the average age at diagnosis is 17 years.[55,56] The incidence of this tumor is approximately 3.7 per million in the population at risk.[57] There is an increased incidence of JNA in patients with familial adenomatous polyposis, suggesting a connection to the β-catenin pathway.[58]

Biologic Characteristics and Molecular Biology

Both androgen and estrogen receptors have been demonstrated in JNAs.[59,60] Recently, estrogen beta-adrenergic receptors have been found in a high percentage of JNAs. Schlauder et al[60] have postulated that the presence of aromatase in tumor cells converts endogenous androgens to estrogens, causing tumor growth via an autocrine-like mechanism.[61] Most tumors stain for vascular endothelial growth factor, and approximately 40% have a GSTM1 mutation.[62]

Pathology and Pathways of Spread

JNA is a benign tumor, although its exact nature is controversial. Some have suggested that it is a vascular hamartoma and similar to a hemangioma,[63] but others believe it is neoplastic.[64] Histologically, tumors are composed of fibrous connective tissue with abundant endothelium-lined vascular spaces.[63] Localization of β-catenin to tumor stromal cells suggests these may be the neoplastic component rather than the endothelial cells.[65] Tumors typically arise from the superior margin of the sphenopalatine foramen and invade laterally through the pterygomaxillary fissure toward the infratemporal fossa.[55] Intracranial extension is seen in up to a third of cases, although actual dural invasion is uncommon.[66,67] Tumors can be locally invasive of bone and extend into the parapharyngeal spaces, paranasal sinuses, orbit, and base of skull. This pattern of spread predicts for a high risk of local recurrence.[67] Blood supply is primarily from the internal maxillary arteries of the external carotid system.

Clinical Manifestations, Patient Evaluation, and Staging

Presenting symptoms include recurrent painless spontaneous epistaxis, nasal obstruction, nasal discharge, a reduced sense of smell, snoring, headache, cranial nerve palsies, and facial swelling.[56] Angiography is essential to define the tumor's blood supply for planning surgery and, typically, for preoperative embolization to decrease surgical blood loss. There are usually multiple tortuous feeding vessels with a dense, homogeneous blush in the capillary phase.[68] CT and MRI help define the anatomic extent of the enhancing tumor. Distant metastases do not occur, so systemic evaluation is not required. Biopsy can be hazardous owing to the tumor's vascularity; not all authors require biopsy confirmation before treatment if clinical and radiographic data are consistent with the diagnosis.[69]

Several staging systems have been proposed (Table 75-5). Most are designed to guide decisions regarding the resectability and optimal surgical approach to the tumor rather than to predict prognosis.[69-73]

TABLE 75-5 Staging Systems for Juvenile Nasopharyngeal Angiofibroma

ANDREWS STAGING SYSTEM[36]	
Stage I	Tumor limited to the nasal cavity and nasopharynx
Stage II	Tumor extension into the pterygopalatine fossa, or maxillary, sphenoidal, or ethmoidal sinuses
Stage IIIa	Extension into the orbit or infratemporal fossa without intracranial extension
Stage IIIb	Stage IIIa with minimal extradural intracranial extension
Stage IVa	Extensive extradural intracranial or intradural extension
Stage IVb	Extension into cavernous sinus, pituitary, or optic chiasm
CARRILLO STAGING SYSTEM[34]	
Stage I	Tumor limited to nasopharynx, nasal fossae, maxillary antrum, anterior ethmoid cells, and sphenoidal sinus
Stage IIa	Invasion to pterygomaxillary fossae or infratemporal fossae anterior to pterygoid plates, with major diameter <6 cm
Stage IIb	Invasion to pterygomaxillary fossae or infratemporal fossae anterior to pterygoid plates, with major diameter ≥6 cm
Stage III	Invasion to infratemporal fossae posterior to pterygoid plates or posterior ethmoid cells
Stage IV	Extensive skull base invasion >2 cm or intracranial invasion
CHANDLER STAGING SYSTEM[37]	
Stage I	Tumor confined to the nasopharynx
Stage II	Tumor extending into the nasal cavity or sphenoidal sinus
Stage III	Tumor involvement of one or more of the maxillary or ethmoidal sinuses, pterygomaxillary and infratemporal fossae, and orbit or cheek
Stage IV	Tumor extending into the cranial cavity
FISCH STAGING SYSTEM[35]	
Type I	Tumor limited to the nasopharynx and nasal cavity with no bone destruction
Type II	Tumors invading the pterygomaxillary fossa and the maxillary, ethmoidal, and sphenoidal sinuses with bone destruction
Type III	Tumors invading the infratemporal fossa, orbit, and parasellar region remaining lateral to the cavernous sinus
Type IV	Tumors with massive invasion of the cavernous sinus, optic chiasmal region, or pituitary fossa

Primary and Adjuvant Therapy and Results

Surgical removal, often preceded by tumor embolization, is the primary treatment for JNA. A craniofacial approach is used for locally advanced tumors. Endoscopic techniques have less morbidity and are effective for earlier-stage lesions.[55] Gross total removal is usually curative.[66] A number of cases prove not to be amenable to complete resection; depending on case selection, there is a rate of local recurrence after surgery that approximates 20% to 40%, with most recurrences occurring in large, incompletely resected lesions.[55,56] Moderate doses of RT may be indicated for postoperative residual tumor, although observation is more often considered because spontaneous involution of tumor is a well-recognized phenomenon.[74,75] Most recurrences present within a year of surgery. The risk of recurrence is greatest in patients with large tumors that erode the skull base, young age at presentation, and irradiated tumors that are slow to regress.[68,76] There are

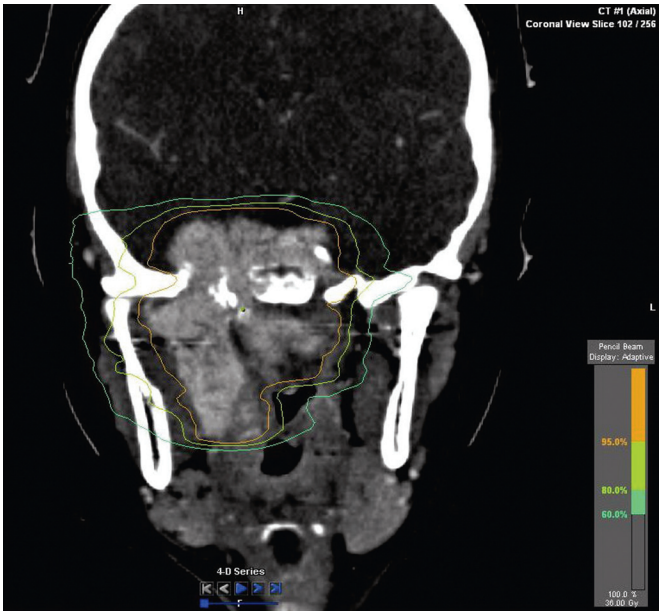


Figure 75-2 Intensity-modulated radiation therapy (IMRT) isodose plan for a patient with juvenile nasopharyngeal angiofibroma.

currently no indications for adjuvant chemotherapy after initial resection.

Locally Advanced Disease and Palliation

RT can provide effective control for recurrent or large, unresectable tumors. Objective tumor response after RT is typically slow, but ultimate control rates range from 75% to 92%[77]; 90% of responders have no residual tumor 3 years after treatment.[78] Given the strong association of JNA with hormonal receptors, there has been interest in hormonal manipulation for patients with advanced disease. Diethylstilbestrol and flutamide have been used, but results have been inconsistent.[68,79,80] A recent trial supports the use of flutamide in postpubertal patients with 13 of 15 patients showing a partial radiographic response to this agent.[81] Case reports of chemotherapy for recurrent tumor show efficacy for doxorubicin, dactinomycin, vincristine, cyclophosphamide, and cisplatin in selected patients.[82-84]

Techniques of Irradiation

No radiation dose-response curve has been reported for JNA. Local control rates greater than 80% are seen with doses ranging from 30 Gy to 50 Gy,[69,85-89] and a dose of 36 Gy is commonly used. Intensity-modulated RT (IMRT) techniques provide high conformality for sparing of normal structures (Figure 75-2). Stereotactic radiosurgery using single doses of 17 Gy to 20 Gy and hypofractionated RT using 45 Gy in three fractions have been reported effective in small series of patients.[90]

Treatment Algorithms, Controversies, Challenges, and Future Possibilities

Preoperative embolization is followed by maximal surgical resection. Postoperative residual tumor can be observed or treated with RT. Recurrent tumor can be managed with RT. Hormonal manipulation and cytotoxic chemotherapy may be tried for recurrent, refractory disease. The elevated levels of vascular endothelial growth factors in these tumors suggest a potential role for inhibitors of angiogenesis.[91]

PLEUROPULMONARY BLASTOMA

Etiology and Epidemiology

Pleuropulmonary blastoma (PPB) is a dysontogenetic neoplasm of childhood that originates in the lung or pleura.[92] Although rare, it is the most common primary lung tumor in children.[93] It is analogous to other dysontogenetic tumors such as Wilms' tumor, neuroblastoma, and hepatoblastoma.[94]

PPB is thought to progress through a distinct sequence of clinical and pathologic changes beginning as a relatively nonaggressive cystic lesion and subsequently developing into the more malignant mixed cystic/solid and purely solid morphologies.[95] Median age at presentation is 3 years.[96] Younger children typically present with predominantly cystic tumors, whereas older children are more likely to have significant solid components.[97] Boys and girls are equally affected.[97] Siblings of patients with PPB have a higher incidence of PPB than the general population, and mutations of in *DICER1* have been found in many of these families.[98] There is also an increased incidence of other types of dysplasia and neoplasia in relatives of children with PPB.[99]

Prevention and Early Detection

The incidence of PPB in apparently benign lung lesions such as congenital cystic adenomatoid malformations is approximately 4%.[100] However, cystic PPB is clinically indistinguishable from benign cysts, and some authors recommend excision of all such lesions.[101] Further supporting this approach is evidence that PPB can arise de novo from lung cysts, so that resection of these "precancerous" lesions is indicated.[102,103] Others advocate a policy of watchful waiting for purely cystic lesions, only intervening if radiographic changes suggest progression.

Biologic Characteristics and Molecular Biology

Germline mutations of *DICER1*, a gene coding for an endoribonuclease involved in regulation of mesenchymal proliferation, have been identified in families affected by PPB.[98] *TP53* mutations have been described in PPB and may portend a worse prognosis.[104] Polysomy of chromosome 8 has also been noted.[105]

Pathology and Pathways of Spread

Histologically, PPB has small, primitive blastemal cells separated by an uncommitted sarcomatous stroma.[94,97,106] Tumor cells stain with vimentin and may show myogenic differentiation.[93] Rhabdomyoblasts and cartilage nodules are reported in 40% to 50% of patients.[101]

Tumors usually arise in the lung parenchyma. Spread to contiguous structures such as the mediastinum and pleura is associated with a poorer prognosis. Invasion into the chest wall is uncommon.[107] Hematogenous metastases occur, most often to the brain. In one series,[92] the incidence of brain metastases was 11% in mixed cystic/solid tumors and 54% in purely solid tumors.

Clinical Manifestations, Patient Evaluation, and Staging

Presenting symptoms of PPB include cough, dyspnea, wheezing, symptoms of respiratory infection, and occasionally, spontaneous pneumothorax. Chest CT usually reveals a heterogeneous low-attenuation mass with pleural effusion and

mediastinal shift.[107] Differential diagnosis includes rhabdomyosarcoma, Askin tumor, and nonrhabdoid sarcomas; examination of the cystic fluid or solid tumor is required to make a diagnosis. Bone scintigraphy and MRI of the brain should be performed for staging, especially for tumors with a significant solid component.

PPB has no anatomic staging system but is classified into three morphologic types that have prognostic significance. Type I consists of purely cystic tumors, type III lesions are solid tumors, and type II have mixed cystic and solid components.[108] Both type II and type III tumors have significantly poorer prognosis than type I, with an incidence of distant metastases at diagnosis approximating 30%.[96] A fourth type, type Ir (type I, regressed), has been described for cystic lesions without a neoplastic component, hypothesized to have "regressed" from an earlier type I PPB, or alternatively, represent a genetically determined lung cyst that has not yet evolved along a dysplastic path.[109]

Primary and Adjuvant Therapy and Results

Surgery is the cornerstone of management, although most patients cannot undergo gross total resections owing to involvement of critical structures.[96,106] Neoadjuvant chemotherapy can be used in large tumors to render the tumor resectable; adjuvant chemotherapy is often given postoperatively to patients with types II and III tumors. Chemotherapy may improve survival in type I tumors,[95,109] although it is not generally recommended if the tumor is completely resected.[96] Drug regimens parallel those used for other pediatric sarcomas and include ifosfamide/carboplatin/etoposide (ICE regimen), and ifosfamide/vincristine/dactinomycin (Actinomycin-D)/doxorubicin (IVADo regimen). Other active drugs include irinotecan[110] and cisplatin.[97] RT may be indicated in unresectable tumors, although large treatment volumes and young patient age often hinder the use of this modality.[111] Five-year survival rates are approximately 80% for patients with type I tumors and 45% for patients with types II and III.[96,97,106]

Locally Advanced Disease and Palliation

In patients who experience a recurrence, local relapse is somewhat more common than distant failure.[96] When type I tumors recur, they usually recur as types II or III.[95,101] Re-resection should be performed when possible, but second-line chemotherapy is often the primary treatment owing to the extent of disease. RT may be useful for brain metastases and palliation of painful bone lesions.

Irradiation Techniques

Fractionated external beam RT using a dose of 44 Gy has been recommended for incompletely resected tumors, although its role in local control is difficult to assess.[96,106] Normal tissue tolerances may preclude this amount of irradiation; use of a lesser dose may be required in circumstances in which volume and dose exceed organ tolerance. Microscopic margins were controlled in one case report using 36 Gy,[97] but local recurrence was reported after 30 Gy in 10 fractions in a patient with gross tumor.[112] Intracavitary phosphorus-32 has also been used and may contribute to local control in selected patients.[106]

Treatment Algorithms, Controversies, Challenges, and Future Possibilities

Initial resection is performed if possible. Neoadjuvant chemotherapy is used when initially unresectable, followed by delayed surgery. Adjuvant chemotherapy is indicated for most patients. RT should be considered for microscopic or gross residual tumor after surgery. Children should be followed with chest CT at 3-month to 6-month intervals for 2 to 3 years.

HEMANGIOMAS AND LYMPHANGIOMAS

Etiology and Epidemiology

Although often considered together, hemangiomas and lymphangiomas are clinically and histologically distinct entities. Many semidescriptive terms have been applied to these lesions (especially the cutaneous hemangiomas), contributing to confusion regarding their study and management. Synonyms for cutaneous hemangioma include "neonatal stain," "stork bite," "salmon patch," "spider angioma," and "strawberry angioma."

Hemangiomas occur in about 1% of infants, most often during the first few months of life, with about a third of these presenting in the head and neck.[113] Lymphangiomas are much less common, with an incidence between 1 in 6,000 and 1 in 16,000 live births.[114] Half are congenital; 90% are evident before the age of 2 years. Three fourths of lymphangiomas occur in the neck or head areas.

Pathology and Pathways of Spread

Hemangiomas consist of thin-walled vessels lined by endothelial cells and a discontinuous layer of pericytes and reticular fibers.[115] They have been reported to occur in a wide variety of locations, including the skin, liver, bone, central nervous system (CNS), bladder, trachea, and other soft tissues.[116] Lymphangiomas are dilated endothelial-lined lymph channels with thick walls containing smooth muscle.[117] Lymphangiomas can involve the skin, skeletal tissue, spleen, liver, mediastinum, or lung.[118] Hemangiomas and lymphangiomas classically are malformations or low-grade and benign neoplasms with no capacity for metastasis.

Clinical Manifestations, Patient Evaluation, and Staging

Hemangiomas are classified as capillary, cavernous, or mixed, depending on the size of the vessels involved. When they involve the skin, capillary hemangiomas are often raised, circumscribed red lesions. They usually present early in the first year of life, and the great majority undergo spontaneous involution over the subsequent years. They are distinct from vascular malformations such as port-wine stains, which do not regress.[113] Clinical manifestations of hemangiomas are largely dependent on the location of the lesion and can include cosmetic deformity, functional impairment, airway obstruction, bleeding, infection, and high-output cardiac failure. Kasabach–Merritt syndrome describes a giant hemangioma causing thrombocytopenia due to consumption coagulopathy.

Lymphangiomas are also categorized according to the size of the abnormal lymph vessels. Lymphangioma circumscriptum contains relatively small-caliber lymph channels and is usually superficial in location. Cystic hygroma or cavernous lymphangioma consists of large, cystic areas of lymph fluid arising in deeper tissues. Unlike hemangiomas, lymphangiomas do not tend to regress spontaneously and may enlarge during adolescence.[119] Symptoms of lymphangiomas can include disfigurement, pain, infection, and complications of chronic lymph secretion. Lymphangiomas occurring in the mediastinum may cause chylothorax, which can be life threatening.

Classification schemes have been proposed for these lesions, but there is no widely accepted staging system.[115,120]

Primary and Adjuvant Therapy and Results

RT was the mainstay of therapy for both hemangiomas and lymphangiomas through the early 1950s and, in some centers, into the 1970s. Subsequently, the use of RT has been all but abandoned as the natural history of spontaneous involution of hemangiomas was recognized and the late morbidities of RT were reported.[121]

Spontaneous involution will occur in 95% of capillary hemangiomas over the course of several years; most require no treatment.[122] Cavernous hemangiomas do not usually regress spontaneously and require treatment if symptomatic.[115] For symptomatic hemangiomas, topical or intralesional corticosteroids are often the first line of treatment.[123] Systemic corticosteroids are also effective.[113] Surgical resection is an effective treatment in appropriate circumstances. Other treatments include interferon, laser ablation, cryotherapy, compression, electrocautery, and embolization. Other pharmacologic interventions include antiangiogenic and antifibrinolytic agents. Irradiation for hemangiomas with life-threatening complications can be performed and is often effective, with improvement or resolution occurring in more than 80% of patients.[116,124]

Surgical removal of lymphangiomas is curative, although can be cosmetically or functionally morbid in many anatomic sites. Sclerotherapy using agents such as OK-432 or bleomycin is a common nonsurgical treatment, with complete responses seen in about 40% of patients and partial responses in another 40% to 45%.[114] Other nonsurgical therapies include diathermy, cryotherapy, and interferon alfa-2b.[118] RT has also been used with some efficacy in selected patients.[119,125-127]

Locally Advanced Disease and Palliation

Mortality from Kasabach–Merritt syndrome can exceed 10%. Large hemangiomas causing coagulopathy or cardiac failure require aggressive treatment.[128] RT may be useful when other modalities fail.[129] Fractionated RT to doses of 10 Gy to 20 Gy has been effective in these life-threatening situations.[116,124,128,129] Tumors such as lymphangiosarcoma and malignant hemangioendothelioma are highly aggressive neoplasms and require multimodality treatment (Figure 75-3).[130,131]

Irradiation Techniques

Although the efficacy of RT for these conditions is well established, the availability of other effective treatments and the concern for late effects of irradiation in this young patient population appropriately limit RT to a seldom-used option today.[122,132] No definite dose-response relationship has been established for the treatment of hemangiomas, and fractionated radiation doses ranging from 3 Gy to 40 Gy have been recommended.[116,128] Braun-Falco et al[122] reported a large series of patients with hemangiomas; most were treated with fractionated radiation doses between 12 Gy and 25 Gy. Responses were seen in 73% of patients, with complete responses in 50%. Some have reported good results, with lower doses of 3 Gy to 11 Gy,[133] although others recommend a dose of at least 25 Gy.[134] Partial improvement after RT can often be noted within a few weeks, but maximum response can take several months to years.

Lymphangioma has been successfully treated with 10 Gy to 20 Gy of fractionated RT.[119,126,127] Responses can be seen much more quickly in lymphangiomas than in hemangiomas.

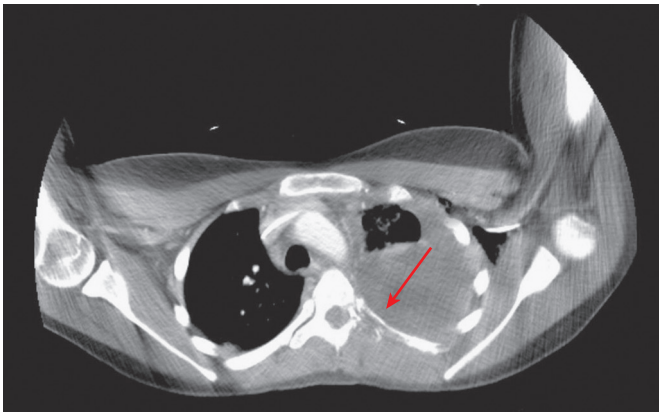


Figure 75-3 Lymphangiosarcoma in a 16-year-old girl arising from a preexisting lymphangioma. The patient's pain and chylous effusion were effectively palliated using 30-Gy radiotherapy. *Arrow* references primary site evident by bony erosion.

Treatment Algorithms, Controversies, Challenges, and Future Possibilities

Observation is usually indicated for hemangiomas. When treatment is required, corticosteroids or locally ablative treatment such as surgery or embolization can be used, as well as systemic agents. RT may be indicated for life-threatening situations. Lymphangioma is usually treated with surgical resection or sclerosing agents such as OK-432. RT, again, is reserved for life-threatening circumstances.

DESMOPLASTIC SMALL ROUND CELL TUMOR

Etiology and Epidemiology

Desmoplastic small round cell tumor (DSCRT) is a rare disease diagnosed in children and young adults at a median age of 22 years (range, 6 years to 49 years). DSCRT was first described by Gerald et al and Park et al in 1991.[135,136] There is a strong male to female predilection ranging from 5:1 to 20:1.[137] Approximately 200 cases have been reported in the literature.[135,138]

Biologic Characteristics and Molecular Biology

A t(11;22)(p13;q12) translocation is the predominant cytogenetic abnormality in DSRCT and breakpoint mapping has demonstrated that all chromosome 11 translocation breakpoints involve intron 7 of the Wilms' tumor gene *WT1*. The *EWS/WT1* fusion gene is used as a specific marker for the diagnosis of DSRCT.[139,140]

Pathology and Pathways of Spread

DSRCT arises from the serosal lining of the body cavities and visceral organs. It is histologically described as nests of small round blue cells separated by desmoplastic stroma. Tumor cells are typically small to medium-sized with round to oval hyperchromatic nuclei and scant to moderate cytoplasm with indistinct cell borders. Larger cells are less commonly present.

There is often significant heterogeneity in differentiation with immunohistochemical reactivity for epithelium (epithelial membrane antigen), mesenchyme (vimentin), myogen (desmin), and neurons (neuron-specific enolase, CD56).[141]

Clinical Manifestations, Patient Evaluation, and Staging

DSRCT usually presents with diffuse abdominal metastatic disease (Figure 75-4). Extensive peritoneal surface involvement results in poor absorption of intraperitoneal fluid and

the build-up of ascites results in symptoms of abdominal fullness and distension, with constipation, weight loss, loose stool, and jaundice. Other primary sites include bone,[142] paratestes,[143] CNS,[144] kidney,[145] and pleura.[146] Common sites of metastases are the intrathoracic cavity, mediastinum, pleura, paratesticular region, and soft tissues.[138]

Initial work-up includes CT or MRI of the chest, abdomen and pelvis with consideration for PET/CT. Extensive disease at presentation often precludes complete resection leading to open biopsy as the usual diagnostic procedure. Though a staging system has been proposed,[147] none has been widely accepted, and essentially all cases are considered "stage 4" with dissemination at the time of diagnosis.

Primary and Adjuvant Therapy and Results

Although no universally accepted treatment recommendation exists for DSRCT, treatment usually begins with an alkylator-based chemotherapy regimen such as cyclophosphamide, doxorubicin, and vincristine alternating with ifosfamide and etoposide. This is followed by aggressive surgical debulking, whole-abdomen RT and targeted RT to high-risk sites, and autologous stem-cell transplantation. Median survival with this approach is 19 months.[148] Lal et al reported 3-year survival of 58% in patients who underwent aggressive tumor debulking versus 0% for those who did not, illustrating the importance of surgery in the management of DSRCT.[149] Hyperthermic intraperitoneal chemotherapy perfusion, typically with cisplatin, has also been used with reports suggesting a survival benefit with this approach.[138] Liver metastases have been treated using yttrium-90 with radiographic response.[150] Although radiographic and clinical response is frequent with aggressive therapy, long-term prognosis remains poor with 5-year survival of approximately 15%[149,151] (Figure 75-5).



Figure 75-4 Desmoplastic small round cell tumor in a 12-year-old boy. There is extensive caking of the omentum as well as metastases to the liver and spleen.

Irradiation Techniques

RT plays an important role in the trimodality treatment of DSRCT. In a series of patients from Memorial Sloan Kettering Cancer Center, 3-year survival was 55% for those receiving chemotherapy, surgery, and RT versus 27% when fewer than three modalities were used.[149] Because of typical presentation with extensive abdominal disease and serosal spread, whole-abdomen radiotherapy is the most commonly applied approach. Whole-abdomen dose is typically 30 Gy guided primarily by normal tissue tolerance. With IMRT or conformal techniques, boost of gross disease to 45 Gy should be considered. Kidney dose of approximately 15 Gy whole organ and 20 Gy to 50% volume as well as liver dose of 24 Gy whole organ and 30 Gy to 50% volume are typical dose constraints.

Treatment Algorithms, Controversies, Challenges, and Future Possibilities

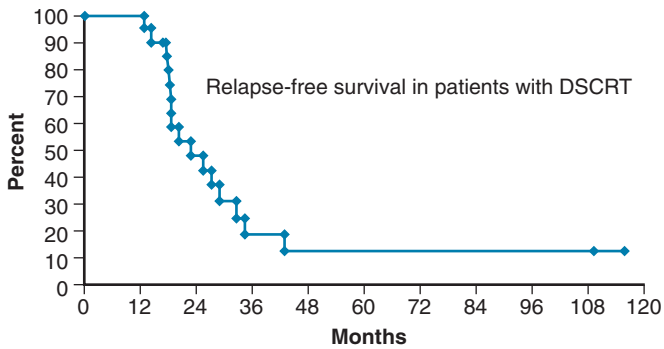
The current treatment algorithm for DSRCT consists of biopsy followed by neoadjuvant chemotherapy, second-look debulking surgery, and whole-abdominal RT with boost to bulk disease. Hyperthemic intraperitoneal chemotherapy is being investigated in Phase II trials and autologous bone marrow transplant has also been used.[147,148,152]

Targeted biologic therapies either upfront or at time of relapse are being considered for immunohistochemically positive for markers such as placental alkaline phosphatase, *ERBB2*, androgen receptor, and c-KIT.[153] Additionally, there are case reports of antitumor activity for bevacizumab[151] and trastuzumab.[153]

LANGERHANS CELL HISTIOCYTOSIS

Etiology and Epidemiology

Langerhans cell histiocytosis (LCH) refers to the spectrum of diseases arising from clonal proliferation of the CD1a and



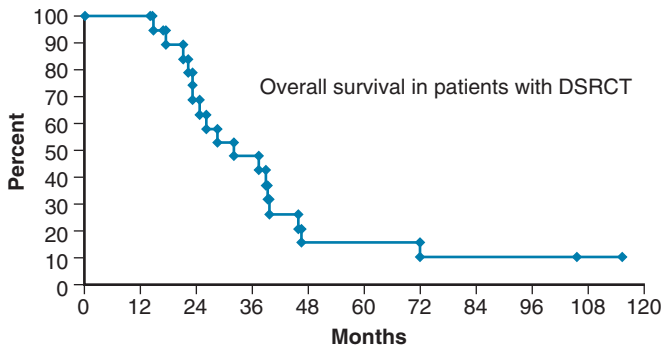


Figure 75-5 Disease-free survival and overall survival for desmoplastic small round cell tumor (DSRCT).
Data from Goodman KA, Wolden SL, La Quaglia MP, et al: Whole abdominopelvic radiotherapy for desmoplastic small round-cell tumor. Int J Radiat Oncolog Biol Phys 54:170–176, 2002.

CD207 positive reticuloendothelial Langerhans cell. The historical name "histiocytosis X" was coined in the 1950s to indicate the histiocytic origin of the disease, with the "X" reflecting the mysterious clinical spectrum of disease presentation.[154] This designation was replaced by the term LCH in 1987.[155] LCH has an incidence of between 1 and 5 cases per million in the United States with approximately 1200 cases diagnosed each year.[156] Most children are under 15 years old at the time of diagnosis with a peak incidence between 1 and 4 years of age. There is a 2:1 male predominance with a slightly higher incidence in Caucasians. The precise etiology of LCH is unknown.[156,157] Some have posited it may be caused by a viral infection, possibly human herpes virus 6 (HHV-6), although this has been disputed. Additionally, abnormalities in the intracellular communication between T cells and macrophages as well as irregularities in cytokine regulations have been proposed as etiologic mechanisms.[158-162]

Biologic Characteristics and Molecular Biology

The origin of LCH is believed to be the epidermal Langerhans cell. A clonal disorder, it is known to spontaneously regress in some patients and prove fatal in others. Most cases arise spontaneously, although there are rare genetic forms of the disease associated with specific cytokine gene variants that tend to occur early with multifocal disease.[163-165]

Pathology and Pathways of Spread

Histiocytic disorders have been classified into three groups by the Histiocyte Society: dendritic cell histiocytosis, macrophage-related disorders, and malignant histiocytosis with LCH falling into the first group.

Although the clinical manifestations of LCH can be quite varied, the pathology has more consistent characteristics. The presence of Langerhans cells is the hallmark of LCH. They are usually accompanied by macrophages, eosinophils, multinucleated giant cells, and T-cells.[166,167] The pathognomonic Langerhans cell is a large ovoid cell with a folded nucleus and a slightly eosinophilic cytoplasm. Birbeck granules can be visualized with electron microscopy. Expression of langerin (CD207) is the most specific marker. Additionally, cytoplasmic S-100 protein positivity and positivity of major histocompatibility (MHC) class II and CD1a are usually present.[168]

Clinical Manifestations, Patient Evaluation, and Staging

LCH is often grouped into three distinct entities that have different clinical presentations and prognoses. These distinctions are somewhat artificial, however, because there is a continuous spectrum of protean disease presentations. Approximately 30% of patients present with unifocal lytic lesions of bone known as eosinophilic granuloma.[169] These lesions occur in older children and commonly involve the skull. They can be painful and cause swelling and fractures, though they may also be incidentally identified.[170] This form of LCH is usually indolent and easily treated. Hand–Schüller–Christian disease is intermediate in severity. It presents as a triad of exophthalmos, skull lesions, and diabetes insipidus and occurs at a somewhat younger age.[171] Letterer–Siwe disease is the most aggressive form of LCH. It is typically seen in children younger than 3 years of age and involves multiple organ systems. Common presentations include splenomegaly, lymphadenopathy, anemia, and blood dyscrasias with diffuse skeletal involvement. These children may have fever, popular rash, and cachexia. The prognosis of this presentation is poor.

There is no uniform staging system for LCH. Children are generally grouped by burden of disease such as number of lesions involved, single or multiple organ involvement, and "non-risk sites" (skin, bone, lymph nodes) versus "risk sites" (liver, spleen, lung, bone marrow). Those with "risk sites" involved are now often considered as having "high-risk" LCH versus others considered to have "low-risk" disease.[169,172] A Turkish study of 217 patients reported 41.5% of patients with single-system disease, 34.1% with multiple-system disease, and 24.4% with multiple-system disease with organ dysfunction.[170]

Workup should include skeletal survey as lesions are typically lytic and bone scintigraphy, although recommended, may not detect some lesions. Visceral disease status is evaluated by CT or MRI of the chest and abdomen, and brain MRI to rule out CNS involvement. PET/CT can be used to assess lymphatic involvement and may be more specific for bony lesions.[173] Bone marrow biopsy is recommended in cases with cytopenias. Diabetes insipidus evaluation via urine specific gravity and osmolality should also be performed. Liver biopsy may be indicated in cases with elevated liver function tests (LFTs). Pulmonary function tests and high-resolution CT are indicated when pulmonary involvement is suspected.

Primary and Adjuvant Therapy and Results

LCH involving a solitary bone may be appropriate for observation as spontaneous regression is possible. More frequently local therapy with surgical curettage or corticosteroid injection is used. RT is effective as well, though less frequently used. These local therapy modalities have an excellent outcome for unifocal disease with a cure rate of 94% reported by Titgemeyer et al.[174] Limited skin involvement can be treated with topical steroids or photodynamic therapy.

Locally Advanced Disease and Palliation

Multifocal disease is treated with systemic therapy. Risk-adapted regimens using combinations of vinblastine, etoposide, and prednisone are usually prescribed.[175] Risk is based on age, extent of multifocal disease, and critical organ involvement. Early response to chemotherapy has been identified as a prognostic indicator with multisite patients responding to therapy at 6 weeks having a 92% OS and non-responders 11% OS.[175] In non-responders and refractory disease, stem-cell transplantation has been used.[176,177]

Irradiation Techniques

The use of radiotherapy in the treatment of LCH has steadily declined because of the effectiveness of alternative treatments and concerns for late RT effects in this young patient population. Current considerations for the use of RT include lesions where surgical intervention would have potential morbidity or in cases of lesions refractory to other treatments. Low-dose RT for bone lesions has been consistently effective with 88% to 96% local control reported for doses of 6 Gy to 15 Gy (median, 9 Gy).[178,179] RT has also been used for diabetes insipidus secondary to LCH. Doses of 15 Gy to 20 Gy to the sellar/hypothalamic area have been used, and when given within 1 to 2 weeks of onset, 25% to 35% of patients show biochemical improvement.[180-182]

Treatment Algorithms, Controversies, Challenges, and Future Possibilities

Overall, most patients enjoy a favorable prognosis. Unfortunately, there are a minority of children (up to 20% to 30%) with

extensive organ involvement who succumb to LCH within 5 years. Targeted therapy and immune modulators have been evaluated in small studies including anti-CD1a antibodies, cytokine inhibitors, alemtuzumab, low-dose oral cyclophosphamide, and all-trans retinoic acid.[183-185] Imatinib and B-raf inhibitors have also been studied.[186-188] The Histiocyte Society and its website is a frequently updated resource for ongoing clinical trials and emerging information on LCH.[189]

NASOPHARYNGEAL CARCINOMA

Etiology and Epidemiology

Pediatric nasopharyngeal carcinoma (PNC) is a rare tumor with an incidence and histologic subtype that varies significantly based on geographic location.[190]

In children, the median age at diagnosis is 13 years and there is a 2:1 male predominance.[191,192] Comparisons are often made between the adult and juvenile variants of nasopharyngeal carcinoma (NPC), and indeed much of the treatment regimens for PNC have been extrapolated from adult data owing to the rarity of the pediatric tumors. The diseases are similar in their relationship to EBV infection, to diets containing nitrites and salted fish, and to the male predominance. Additionally, certain human leukocyte antigen (HLA) subtypes are associated with an increased risk of NPC.[193,194] However, in children, the greatest incidence occurs in the Mediterranean and North America regions rather than China, Southeast Asia, and Alaska; undifferentiated histology is the most common type; and patients present with significantly more advanced disease at diagnosis. In one retrospective series, 92% of pediatric patients had stages III to IV disease versus 67% of adults. However, data show that despite higher stage disease, children have a better overall prognosis in both OS and locoregional disease control.[195-197]

Biologic Characteristics and Molecular Biology

EBV has been a long established etiologic factor for the development of NPC and is associated with 90% of PNCs, particularly the undifferentiated and nonkeratinizing types. The relationship between EBV and NPC was confirmed when EBV DNA was found in neoplastic epithelial cells but was absent in the surrounding lymphocytes.[198] The EBV genome is a double-stranded DNA virus encoding 100 genes, only 10 of which are expressed in latently infected cells in vitro. Of these, six are nuclear proteins (EBNAs), two are latent membrane proteins (LMPs), and two are nontranslated RNA molecules (EBER) that likely aid in cell growth. In NPC, latent membrane protein 1 (LMP1) acts as an oncogene, changing growth patterns and upregulating proteins that inhibit apoptosis, including BCL2.[190] Although BCL-2 is highly expressed in ~80% of adults with NPC, it is likely not associated with pediatric NPC.[199,200] LMP1 also binds to various proteins associated with tumor necrosis factor receptors and is involved in activation of transcription factors, cellular adhesion molecules, and cytokines. *LMP2* is also expressed in NPC and acts by preventing reactivation of the virus by blocking phosphorylation of tyrosine kinases.[190]

NPC development is thought to represent a multistep process initiated most frequently by EBV infection resulting in the expression of *LMP1* and overexpression of *TP53* in the epithelial tumor cells. Additionally, rearrangement of the retinoblastoma tumor suppressor genes, and polymorphism of *CYP2E1* may contribute to tumorigenesis. Genetic gains on chromosome 12 as well as losses on 11q, 13q, and 16q have been associated with invasiveness, whereas *TP53* mutation and altered expression of cadherins are associated with metastasis.[193,201-203] A small proportion of PNC exhibit t(15;19) with the BRD4-NUT oncogene, which perturbs BRD4 functions thus blocking cellular differentiation and contributing to the oncogenic progression in the highly aggressive NUT midline NPC.[204]

Pathology and Pathways of Spread

NPC is grouped into three histiotypes by the World Health Organization (WHO): type I, keratinizing squamous cell carcinoma; type II, nonkeratinizing squamous cell carcinoma; and type III, undifferentiated carcinoma, previously referred to as lymphoepithelioma. Type I shows significant keratin production, is usually seen in adults, and is not usually associated with EBV. Type II is characterized by groups of cells with oval or fusiform nuclei and scant cytoplasm. Type III is an undifferentiated tumor with prominent nonmalignant lymphocytic infiltration. The Cologne modification of the WHO classification further subdivides types II and III; type IIa has pleomorphism without lymphoid infiltration, type IIb has significant lymphoid infiltrate. Type IIIa is characterized by larger, eosinophilic nuclei, and type IIIb has smaller basophilic nuclei. Virtually all PNCs are type III undifferentiated carcinomas.[190,205]

PNC typically originates in the fossa of Rosenmüller, a pharyngeal recess posterolateral to the eustachian tube orifice. Routes of direct spread include the oropharynx or perineural spread along cranial nerves extending to the skull base. The cervical lymph nodes are typically involved early, and less commonly, the spinal accessory chain and retropharyngeal nodes. Most patients present with locoregionally advanced disease; distant metastases at presentation is infrequent. The most frequently affected metastatic sites are the bones, lungs, liver, bone marrow, and mediastinum.[206]

Clinical Manifestations, Patient Evaluation, and Staging

The most common presenting symptom of PNC, occurring in up to 90% of patients, is a painless cervical mass representing lymphadenopathy. Bilateral lymph nodes are often present because of the midline location of the nasopharynx with regional drainage to the internal jugular nodes, the spinal accessory nodes, and the retropharyngeal nodes. Local extension of tumor can cause epistaxis, nasal obstruction, hearing loss, or otitis media from obstruction of the eustachian tubes, which can also lead to ear pain and tinnitus. Base-of-skull invasion can result in headache, facial pain, neck pain, and cranial neuropathies.[190,193,194,207] Uncommonly, the syndrome of inappropriate antidiuretic hormone secretion (SIADH) has been reported and can cause severe hyponatremia.[208] The duration of symptoms before diagnosis ranges from 1 month to 24 months, with an average of 5 months.[190]

Work-up includes history and physical examination with nasopharyngoscopy. Laboratory evaluation consists of CBC, kidney and liver function tests, serum EBV titers, a baseline audiogram, and CT or MRI of the head and neck. CT of the chest and abdomen or, alternatively, PET/CT, is done to screen for distant metastases.[209] Dental and endocrine evaluations should be obtained in preparation for RT and to establish baseline function.

Staging is based on the American Joint Committee on Cancer staging system for NPC in adults (Table 75-6). The nodal staging for nasopharyngeal tumors takes into account the anatomic level of nodal involvement, an important prognostic factor. Retropharyngeal lymph nodes, regardless of their laterality, are considered N1.[210,211]

TABLE 75-6 Nasopharyngeal Carcinoma Staging: American Joint Committee on Cancer

PRIMARY TUMOR	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Primary tumor confined to nasopharynx, extending to oropharynx, or nasal cavity without parapharyngeal space extension
T2	Tumor extends to soft tissues
T2a	Tumor extends to oropharynx and/or nasal cavity (no parapharyngeal extension)
T2b	Tumor within parapharyngeal space*
T3	Invasion of bone of skull base or paranasal sinuses
T4	Tumor with intracranial extension or cranial nerve involvement, extension to hypopharynx, orbit, or infratemporal fossa/masticator space
REGIONAL LYMPH NODES	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node involvement
N1	Unilateral metastasis ≤6 cm above the supraclavicular fossa and/or unilateral or bilateral retropharyngeal lymph nodes ≤n6 cm
N2	Bilateral lymph node metastasis, ≤6 cm, above the supraclavicular fossa
N3	Metastasis in a lymph node >6 cm or extension to supraclavicular fossa
N3a	>6 cm
N3b	Extension to supraclavicular fossa
DISTANT METASTASES	
M0	No distant metastasis
M1	Distant metastasis
AJCC STAGE	
Stage 0	TisN0M0
Stage I	T1N0M0
Stage IIA	T2aN0M0
Stage IIB	T1-2aN1M0 T2bN0-1M0
Stage III	T1-2a-2bN2M0 T3N0-1-2M0
Stage IVA	T4N0-1-2M0
Stage IVB	T1-4N3M0
Stage IVC	M1

From Edge SB, Byrd DR, Compton CC, et al, editors: AJCC Cancer Staging Handbook, ed 7, New York, 2010, Springer.
**Parapharyngeal extension denotes posterolateral spread of tumor.*

Primary and Adjuvant Therapy and Results

Surgery for PNC is limited by anatomic location and involvement of critical structures, which would usually result in a morbid and incomplete resection. Therefore, RT is the mainstay of therapy for every stage of PNC. PNC is radiosensitive. However, outcome with RT alone has been unsatisfactory, with local recurrence rates of 20% to 60% and rates of distant metastases ranging from 20% to 55%.[212-216] Therefore, combined-modality therapy is most often used.

Treatment of PNC was initially extrapolated from recommendations in the adult literature and cisplatin has been the agent most frequently used in conjunction with RT. This was based primarily on the Intergroup 0099 trial, which compared chemoradiation with RT alone in adults with NPC, delivering 70 Gy with or without cisplatin, followed by three cycles of adjuvant cisplatin and 5-fluorouracil.[217] Three-year progression-free survival was 69% with chemoradiation versus 24% with RT alone, and 3-year OS was 78% versus 47%, respectively. The use of cisplatin was further supported by a meta-analysis of adult patients that reported a 20% survival benefit for concurrent cisplatin with RT versus RT alone.[218]

Historically, PNC was treated with RT alone. OS ranged from 50% to 55% with relapse-free survival of 36% to 75%. RT doses varied significantly from 35 Gy to 86 Gy.[219-221] More recently, combined-modality regimens and advanced RT techniques such as intensity-modulated RT (IMRT) and image-guided RT (IGRT) have improved outcomes for PNC. Ayan et al[222] and Wolden et al[223] reported improved survival after chemoradiation, particularly using neoadjuvant chemotherapy, with OS as high as 76%. Data from these studies also suggested a benefit when radiation doses exceeded 60 Gy. However, the 10-year actuarial rate of severe complications using these radiation doses was 24% including a significant risk of sensorineural hearing loss when the cochlear dose exceeded 48 Gy.[224]

Ozyar et al[195] reported a large, multiinstitutional international review of PNC treated over a 25-year interval which demonstrated the benefit of cisplatin as well as higher RT dose. Overall 5-year survival was 77.4% with DFS of 68.8% after combined irradiation and chemotherapy; the only significant negative prognostic factor for OS and DFS was N3 disease. RT doses less than 66 Gy adversely affected locoregional control, and RT without chemotherapy decreased locoregional control and DFS.

Kupeli et al published their experience treating PNC using RT with concurrent cyclophosphamide versus concurrent vincristine, cyclophosphamide, epirubicin, and dactinomycin (AVAC) versus neoadjuvant cisplatin. OS with neoadjuvant cisplatin was 80% versus 63% with AVAC and 31% with cyclophosphamide.[225]

The Pediatric Oncology Group 9486 study used neoadjuvant chemotherapy (cisplatin, 5-fluorouracil, methotrexate, and leucovorin) followed by RT (50.4 Gy to the upper neck, 45 Gy to the lower neck, and a boost to the primary tumor to a total dose of 61.2 Gy).[226] Four-year EFS and OS was 77% and 75%, respectively.

A prospective German trial tested three cycles of cisplatin, 5-fluorouracil, methotrexate, and leucovorin followed by RT (59.4 Gy) for stages III IV PNC; patients were then maintained on interferon-beta for 6 months. After a median follow-up of 30 months (range, 6 months to 95 months), EFS rate was 92.4%, and OS was 97.1%. Acute toxicity was mainly leucopenia, mucositis, and nausea; late toxicity consisted of hearing loss and hypothyroidism. The excellent outcomes were hypothesized as due, in part, to the administration of interferon-beta during a period of relative immune suppression in EBV-positive NPC.[227]

Factors that correlate with DFS include age, nodal stage, TNM stage, node size, node fixation, radiation dose, and response to neoadjuvant chemotherapy.[228]

Response-adapted RT has been investigated to reduce RT toxicity. Habrand et al[229] used sequential cisplatin-based regimens and response-adapted RT doses of 50 Gy after marked response and 65 Gy to 70 Gy after poor response to chemotherapy. Five-year EFS and OS were 64% and 68%, respectively; locoregional failures were similar between the groups, but the low RT dose group actually had superior OS and EFS, with apparent reduction in late toxicities. Orbach et al[230] reported results of risk-adapted RT following one of three chemotherapy protocols (both neoadjuvant and adjuvant

chemotherapy). Objective response to preirradiation chemotherapy was seen in 78% of cases; those with complete response or good partial response received a reduced dose RT regimen (median dose 47 Gy) to the clinically negative cervical nodes and 59.4 Gy to the primary tumor. Patients not meeting response criteria were given 60 Gy median dose to all involved sites. The 5-year OS was not compromised in the reduced-dose cohort, with OS of 73% at 5 years, local failure rate of 10%, and regional failure rate of 3%.

Irradiation Techniques

Because of the high-risk of lymph node involvement at presentation, RT for PNC targets the primary tumor, clinically involved nodes, and nodal areas at risk. Prophylactic RT includes lymph nodes in the bilateral upper deep jugular, submandibular, subdigastric, midjugular, low jugular and supraclavicular, posterior cervical, and retropharyngeal chains.

The optimal doses to maximize tumor control and minimize toxicity continue to evolve with current recommendation for 60 Gy to 70 Gy to the primary tumor and gross disease and 45 Gy to 50 Gy for at-risk nodal areas. The recent COG protocol ARAR0331 specifies RT alone for stages I and IIa disease to 61.2 Gy and 66.6 Gy, respectively. For advanced disease, patients are given neoadjuvant cisplatin and 5-flourouracil, with responding patients treated to 61.2 Gy versus 70.2 Gy for non-responders.

IMRT allows for sparing of normal tissues with reduced toxicity and superior target coverage. Both acute and long-term toxicity with IMRT are likely improved as compared to other techniques. However, this comes at the expense of increased integral dose and the possibility of increased risk of radiation-induced tumors.[231] Proton therapy has been used for PNC and its use will likely grow because of the inherent decrease in normal tissue exposure with particle therapy.[232]

Simulation should be CT based, with appropriate immobilization and localization techniques. The Children's Oncology Group currently recommends delineation of the gross tumor volume (GTV) based on MRI; lymph nodes larger than 1.5 cm or of any size with a necrotic center are included in the GTV. The clinical target volume (CTV) includes the GTV plus a 1-cm margin, the entire nasopharynx, retropharyngeal nodes, skull base, pterygoid fossa, parapharyngeal space, inferior sphenoidal sinus, and posterior third of the nasal cavity, and maxillary sinuses as well as the bilateral cervical lymphatic levels I to V. The lower halves of levels IV and V can be excluded in patients with early-stage disease. A boost, or second CTV, may include the nasopharynx and residual enhancing disease that remains after neoadjuvant chemotherapy.

Critical normal structures include the spinal cord and brainstem, mandible/temporomandibular joint, temporal lobes, and optic apparatus. Other structures at risk are the parotid gland, oral cavity, larynx, eyes, lens, cochlea, and pituitary. Xerostomia, neck fibrosis, dental caries, chronic sinusitis, chronic serous otitis, trismus, hypopituitarism, hypothyroidism, hypoplasia of facial bones or clavicles, and second malignancies have been well documented[190,223,225] (Table 75-7).

TABLE 75-7 Incidence of Treatment-Related Toxicity in Nasopharyngeal Cancer

Complication	Percentage
Xerostomia	3.5-84
Soft-tissue fibrosis	23-61
Dental caries	7-33
Chronic otitis	18
Hypothyroidism	9.5-12
Trismus	7.1-9
Chronic sinusitis	7
Second malignancy	2-6
Osteoradionecrosis	3
Optic neuritis	3

Treatment Algorithms, Controversies, Challenges, and Future Possibilities

Standard treatment for most PNC is defined as three to four cycles of platinum-based neoadjuvant chemotherapy followed by RT to the primary tumor and regional lymphatics with concurrent cisplatin. This may be followed by additional chemotherapy. Early-stage disease may be considered for RT alone. Dose recommendations will likely continue to evolve with ongoing studies reviewing response-based dosing. IMRT techniques are recommended with the use of proton RT being reported on as well. Future challenges will likely be related to optimal dose definition and using improved RT techniques to minimize toxicity, integration of EBV-directed therapy, and immunomodulation.

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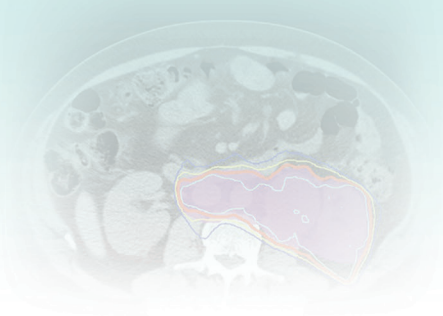
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Overview



Andrea K. Ng

BASIC ISSUES IN LYMPHOMA

Significant progress had been made in recent years in the understanding of the molecular basis of lymphomagenesis, and in the diagnosis, staging, treatment, and follow-up of patients with lymphoid malignancies. The current pathological classification incorporates molecular characteristics, in addition to morphologic and clinical features in identifying distinctive subtypes of disease entities.[1] Advances in DNA microarray techniques allow improved prognostic classification of patients and provide the opportunity to develop molecularly targeted therapy for specific disease types.[2-11] More accurate staging is now available through modern medical imaging techniques and the increasing experience with functional imaging.[12]

The treatment of lymphoid malignancies had also evolved over the years. For diseases in which a high cure rate has already been achieved, the emphasis is now on treatment reduction to reduce late effects. Meanwhile, more dose-dense and dose-intense treatment, and incorporation of targeted therapy including novel agents against molecular targets or pathways, immunotherapy, and radioimmunotherapy are being used in diseases in which the cure rate is still suboptimal.

PATHOLOGICAL CLASSIFICATION

The classification of lymphoid malignancies has evolved over the past century. Previous lymphoma classification relied mainly on subtleties of morphology, cell lineage and differentiation, or clinical survival data. In 1994, the International Lymphoma Study Group published the Revised European-American Lymphoma (REAL) classification of tumors of hematopoietic and lymphatic tissues, which was later modified and updated in the World Health Organization (WHO) project.[13-15] The WHO classification combined information on morphology, immunophenotype, genetic features, and clinical features to define individual disease entity. The 2008 update provided new criteria for the recognition of some previously described neoplasms and clarified the defining criteria for others. Furthermore, it added new entities that were defined by recently discovered genetic features.[16] Despite its seeming complexity, its clinical practicality is supported by the fact that the majority of cases could be classified into one of the disease categories, that an excellent interobserver reproducibility has been demonstrated, and that the disease entities in the classification were indeed clinically distinctive, both at initial presentation and in treatment outcome.

Modern pathological classification allows researchers, pathologists, and clinicians to have a common language in diagnosing and treating different disease types and in comparing treatment results. It is anticipated that with continued progress in the field of genetic analysis, continued updating and revisions of any current classification will be necessary. Advances in the field may provide additional markers for classification, and identify new categories of disease that are not currently recognized.

MOLECULAR BASIS OF LYMPHOID MALIGNANCIES

Emerging data are now available on the origin of the malignant cells of Hodgkin's disease, the Hodgkin's Reed-Sternberg cells, and the molecular events that lead to the malignant transformation.[17-19] The nuclear factor-kappa-B (NF-κB) pathway has been implicated to play an important role in the pathogenesis of Hodgkin's disease,[20,21] and continued research in this area may provide new therapeutic targets for the disease.

Researchers have used cDNA microarray techniques to identify molecular prognostic factors for lymphoma.[2-4,6] For diffuse large B-cell lymphoma (DLBCL), using transcriptional profiling, subtypes of disease with distinct clinical outcome have been identified.[2-4,7] Genes that have been implicated in predicting treatment outcome, independent of that of the international prognostic index (IPI), include ones that regulate molecular signaling pathways and apoptotic response to treatment.[3,4] Using similar techniques, it has also been shown that the tumor microenvironment and host inflammatory response may play a key role in identifying subgroups of patients with differing prognoses in both follicular lymphoma and DLBCL.[6,22-24] Molecular prognostic factors promise to further improve risk stratification, and more importantly, provide insights into molecular pathogenesis of different subtypes of lymphoma and guide the development of novel, targeted therapy.[25]

STAGING

Improvement in imaging techniques had led to the modification of the original Ann Arbor staging classification for lymphoma, allowing incorporation of computed tomography (CT) scan results in assessing disease extent.[26] Currently, functional imaging is routinely included as part of initial lymphoma staging. The superior accuracy of fludeoxyglucose

(18F)-positron emission tomography (FDG-PET) has been shown to result in a change in the stage of 18% to 45%, and a change in management in 18% to 31% of the patients.[12] Furthermore, it has been demonstrated that incorporation of FDG-PET in radiotherapy planning resulted in modification of target volume and fields in a considerable proportion of patients.[27-30]

TREATMENT

The following is a summary of the overall treatment approaches, with a focus on the role of radiation therapy, for the three types of hematological malignancies: Hodgkin's lymphoma, non-Hodgkin's lymphoma, and plasma cell neoplasms.

Hodgkin's Lymphoma

Stages I to II Hodgkin's Lymphoma

Combined modality therapy for early-stage Hodgkin's lymphoma is associated with a cure rate of more than 90%. Currently, one of the main challenges in the management of patients with early-stage Hodgkin's lymphoma is to minimize treatment-related late complications while preserving excellent disease control. Strategies to reduce treatment, from the radiation therapy standpoint, include the use of smaller treatment fields, lower radiation doses, or elimination of radiation therapy.

Over the last several decades, radiation treatment fields for Hodgkin's lymphoma have evolved from extended-field to involved-field,[31-33] and mostly recently to involved-site/involved node radiotherapy (ISRT/INRT).[34,35] Retrospective studies have shown that ISRT/INRT as part of combined-modality therapy for early-stage Hodgkin's lymphoma did not result in any marginal misses, and yielded progression-free survival rates of more than 90%.[36,37] In the EORTC/Lymphoma Study Association (LYSA)/the Italian Lymphoma Foundation (FIL) H10 and H11 trials, INRT was adopted in both the standard and experimental arms, the results of which are pending at this time. In the ongoing German Hodgkin's Study Group (GHSG) HD17 trial for patients with early-stage disease with risk factors, the standard arm consisted of chemotherapy and involved-field radiotherapy, and the experimental arm used INRT for patients with PET-positive disease after chemotherapy.

Radiation dose deescalation from 30 Gy to 20 Gy was explored in the GHSG HD10 and HD11 trials for patients with early-stage, low-risk disease (no bulky mediastinal mass or extranodal disease, less than three nodal sites, low sedimentation rate) and high-risk disease, respectively.[38,39] In the HD10 trial, at a median follow-up of 7.5 years, there were no differences in 8-year freedom-from-treatment-failure and overall survival between 20 Gy versus 30 Gy after two to four cycles Adriamycin, bleomycin, vinblastine, and dacarbazine (ABVD) chemotherapy.[38] This suggests that in patients with low-risk disease as per the GHSG criteria, two cycles followed by 20 Gy of radiotherapy is adequate. In the HD11 trial,[39] at a median follow-up of 82 months, there was no significant difference in 5-year freedom-from-treatment-failure rates between baseline bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone (BEACOPP) and ABVD when followed by 30 Gy of involved-field radiotherapy; however, inferiority of 20 Gy cannot be excluded after four cycles of ABVD, leading to the authors' conclusion that 30 Gy as optimal radiotherapy dose after ABVD for early-stage, unfavorable Hodgkin's lymphoma.

Randomized trials have been performed examining whether radiation therapy can be safely omitted.[40-47] The Cochrane Haematological Malignancies Group conducted a meta-analysis that included five randomized controlled trials comparing chemotherapy alone with identical chemotherapy combined with radiotherapy for patients with stages I to II Hodgkin's lymphoma.[48] The results showed that, in addition to a significant disease-control benefit favoring the combined-modality therapy approach, there was a highly significant overall survival benefit with the addition of radiation therapy (hazard ratio [HR], 0.4; $p < 0.00001$).

The elimination of radiotherapy based on PET-response or early PET-response to chemotherapy is being explored by a number of randomized trials. In the EORTC/LYSA/FIL H10 and H11 trials, the experimental arms consisted of omission of radiation therapy for patients with complete PET response after two cycles of ABVD, compared against the standard arms of combined-modality therapy. Interim analysis results showed that in both studies, the objective of noninferiority of chemotherapy alone as compared with combined-modality therapy has not been met, and at the recommendation of an independent data monitoring committee, the experimental arms of no radiotherapy in both groups of patients were closed.[49] The United Kingdom RAPID trial compared combined-modality therapy with chemotherapy alone in early-stage patients with complete PET-response after three cycles of ABVD.[50] At a median follow up time of 48.6 months, by intent-to-treat analysis, there was no difference between the radiotherapy versus no radiotherapy. However, by per-treatment analysis, there is a significant benefit in the radiotherapy arm (3-year progression-free survival 97% versus 90.7%, $p = 0.03$). Based on these preliminary result, there appears to be a modest, approximately 7% gain in progression-free survival with the addition of radiotherapy on patients who achieved a complete PET response after chemotherapy. This slightly lower cure rate and toxicity of salvage therapy in the small proportion of patients with relapse disease needs to be weighed against the limited toxicity of modern radiotherapy. Two ongoing trials conducted by the GHSG are exploring omission of radiotherapy by PET-response, including the HD16 trial for patients with low-risk early-stage disease, and the HD17 trial for patients with early-stage disease with adverse risk factors. Results from the ongoing trials as well as mature results of completed trials are needed to confirm the safety of elimination of radiotherapy in patients with early-stage disease with complete PET response to chemotherapy.

Stages III to IV

The role of radiation therapy in patients with advanced-stage Hodgkin disease is controversial. Most of the randomized trials do not show a significant benefit with the addition of radiation therapy to chemotherapy.[51-58] However, there are subgroups of patients who may benefit from consolidative radiation therapy, namely, patients who failed to achieve a complete response to chemotherapy and those with bulky disease at presentation.[52,56,59,60] In a study from the United Kingdom, comparing irradiated versus patients who were nonirradiated with advanced-stage disease recruited on several clinical trials,[60] at a median follow-up of 6.9 years, a significantly higher progression-free survival (71% versus 86%, $p < 0.0001$) and overall survival rates (87% versus 93%, $p = 0.014$) were found in patients who received radiation therapy, despite the fact that there were significantly more patients with bulky disease and patients with partial response in the irradiated cohort.

The GHSG HD12 trial is a four-arm study for patients with bulky stage IIB and stages III to IV disease comparing two different BEACOPP variants with or without radiation therapy.[58] At a median follow-up of 69 months, there was no significant difference in 5-year FFTF between the radiotherapy or no-radiotherapy arms (90.4% versus 87%, $p = 0.08$). However,

on subgroup analysis, among patients with residual disease of >1.5 cm, there was a significantly higher (5.8%; 95% confidence interval [CI], 1.0% to 10.7%) 5-year freedom-from-treatment failure in the radiotherapy arm. However, among patients with <1.5-cm residual disease after chemotherapy, there was no significant benefit with the addition of radiotherapy even among patients with initial disease of 5 cm or greater.

In the GHSG HD15 trial,[61] patients with advanced-stage disease with complete response or with residual disease <2.5 cm after chemotherapy received no further treatment, whereas patients with residual disease of 2.5 cm or greater underwent PET scanning. Radiotherapy was administered only in patients with residual PET-avid disease, and as such only 11% of patients on this trial received radiotherapy. The planning target volume in this trial included the PET-positive residual disease with a 1.5-cm expansion. The 4-year progression-free survival of patients who achieved a complete response to chemotherapy and did not receive radiation therapy was 92.1%. It is noteworthy, however, that this excellent outcome was based on patients treated with variants of BEACOPP regimens and may not be applicable to patients treated with ABVD. In the response-adapted trials conducted by the GITIL and FIL (HD0607 and HD0801) for patients with advanced-stage Hodgkin's lymphoma, patients with complete PET-response after ABVD chemotherapy, patients were randomized to radiotherapy versus no-radiotherapy. The results of these two trials will clarify the role of consolidative radiotherapy in patients with advanced-stage Hodgkin's lymphoma with complete PET-response after ABVD chemotherapy.

Nodular Lymphocyte Predominant Hodgkin's Disease

Nodular lymphocyte predominant Hodgkin's disease (NLPHD) is a disease entity distinct from classical Hodgkin's disease based on its morphologic, immunophenotypic, and clinical characteristics.[14,62] The majority of cases of NLPHD present with stages I to II disease. Different management options exist[63-67]; however, radiation therapy alone remains the mainstay treatment for patients with localized disease. Studies have shown that as treatment fields evolved from extended- to involved-field radiation therapy, there was no significant compromise of disease control. The current recommendation is further field reduction to ISRT to 30 Gy to 36 Gy. In the setting of radiotherapy as the only treatment modality, the clinical target volume (CTV) should encompass gross disease as well as suspected subclinical disease.[34]

Patients with additional relapses tend to remain responsive to further therapy. These patients are more likely to die from treatment-related causes than from the lymphoma, which argues for limiting treatment upfront because of the indolent nature of the disease.

Non-Hodgkin's Lymphoma

Non-Hodgkin's lymphoma is a heterogeneous disease. The two most common histologic subtypes are DLBCL and follicular lymphoma, accounting for three quarters of all cases of non-Hodgkin's lymphoma. The role of radiation therapy in both of these subtypes is mostly limited to patients with early-stage disease. Marginal zone lymphoma or mucosa-associated lymphoid tumor (MALT) is another subtype of non-Hodgkin's lymphoma, which is highly responsive to radiation therapy, and in patients who present with localized, early-stage disease, radiation therapy alone may be curative.

Diffuse Large B-Cell Lymphoma

Randomized trials have compared chemotherapy alone versus combined modality therapy in early-stage aggressive non-Hodgkin's lymphoma with mixed results, likely as a result of patient selection and differences in chemotherapy regimens used in the comparison arms in two of the trials. However, the most significant limitation of these trials was that they were conducted in the pre-Rituximab era.[68-71]

The current standard systemic therapy for DLBCL, which accounts for the majority of cases of aggressive non-Hodgkin's lymphoma, is rituximab, cyclophosphamide, vincristine and prednisone (R-CHOP).[72-75] Several studies have retrospectively compared irradiated versus nonirradiated patients after modern R-CHOP chemotherapy, all showing a significantly superior disease-free survival in patients who received radiotherapy compared to patients treated with chemotherapy alone.[76-79] In the largest study, from M. D. Anderson on 469 patients with DLBCL, not only a significantly higher progression-free (59% versus 82%, $p < 0.001$), but also overall survival (68% versus 91%, $p = 0.03$) rates were observed in irradiated patients. The significant benefit of radiation therapy in this study persisted on multivariable analysis, as well as on matched-pair analyses on patients with stages I to II disease and patients with stages III to IV disease, respectively, after a complete response to six to eight cycles of R-CHOP.

The German High-Grade Non-Hodgkin's lymphoma Study Group (DSHNHL) recently published their experience on the role of radiotherapy in selected patients with DLBCL on their clinical trials.[80,81] The first report took patients with skeletal involvement and complete response to chemo from the MabThera International Trial (MInT) and RICOVER-60 trials, and found that those who received consolidative radiotherapy had a significantly improved 3-year event-free survival rate (75% versus 36%, $p < 0.001$).[81] On multivariable analysis, the addition of radiotherapy reduced the risk of an event by 70% ($p < 0.001$). In the second report, patients with bulky disease (≥7.5 cm) from the R-CHOP-14 for six arms of the RICOVER-60 trial formed the study population. It was found that compared to patients who did not receive radiotherapy, those who received radiotherapy had significantly improved event-free survival (80% versus 54%, $p = 0.001$), progression-free survival (88% versus 62%, $p < 0.001$), as well as overall survival (90% versus 65%, $p = 0.001$).[80] However, both of these studies were retrospective subgroup analyses and may be prone to selection bias. The UNFOLDER trial, also conducted by the DSHNHL randomized patients with DLBCL to R-CHOP14 versus R-CHOP 21, Patients with initial bulky disease (>7.5 cm) or extranodal involvement and complete response to chemotherapy were further randomized to receive radiotherapy versus no radiotherapy. In the most recent interim analysis, the no-radiotherapy arm was closed because of significantly inferior event-free survival results. The formal results of this trial, however, are still pending at this time.

Radiation doses used in previous trials ranged from 30 Gy to as high as 55 Gy.[82] In a prospective trial conducted by Lowry et al,[83] 640 sites of aggressive non-Hodgkin's lymphoma (81% treated with combined-modality therapy) were randomized to 30 Gy in 15 fractions versus 40 Gy to 45 Gy in 20 to 23 fractions. At a median follow-up of 5.6 years, there was no significant difference in freedom-from-local progression and overall survival rates between the two arms, suggesting the 30 Gy may be adequate in these patients after chemotherapy. However, the study did not describe the types of chemotherapy used and data on response to chemotherapy were not available.

There have been attempts to limit radiation fields in patients receiving consolidative radiotherapy for aggressive non-Hodgkin's lymphoma. Campbell et al reported on the British Columbia experience of using INRT ≤5 cm and found no difference in patterns of failure compared with a previous cohort of patients who received involved-field radiation therapy.[84] Verhappen et al recently reported on results of 67 patients

with stages I to II aggressive non-Hodgkin's lymphoma treated with INRT (64 of 67 patients received combined-modality therapy) as per the EORTC guidelines,[85] and there was only one relapse that was outside the INRT field but in the involved-field radiation therapy volume, supporting the use of more limited fields after chemotherapy in early-stage aggressive non-Hodgkin's lymphoma.

Follicular Lymphoma

About 20% to 25% of patients with follicular lymphoma present with stages I to II disease. There have been a number of retrospective series showing that radiation therapy alone is curative in 35% to 40% of cases.[86-95] Median doses of 36 Gy to 40 Gy resulted in control rates of 90% to 95%. Relapses beyond 10 years are uncommon, accounting for less than 5% of cases. In most series the radiation fields varied over time, with larger fields employed in the earlier years, and more limited fields in patients treated in the modern era. Campbell et al reported on the British Columbia experience of 95 with localized follicular lymphoma treated with INRT <5 cm alone, and found that only 1% of patients had regional-only recurrence.[96] Because more than half the patients with stages I to II disease will eventually relapse, the use of more limited radiation fields preserves the ability to effectively treat patients with recurrent disease or those who transform to a higher grade histology.

In most of the earlier retrospective series of radiotherapy alone for stages I to II follicular lymphoma, doses of 35 Gy to 40 Gy were employed. Lowry et al from the United Kingdom conducted a randomized trial on 361 sites of indolent lymphoma comparing 24 Gy in 12 fractions versus 40 Gy to 45 Gy in 20 to 30 fractions,[83] and found no differences in rates of local progression, progression-free survival, and overall survival between the two arms, suggesting that 24 Gy may be an adequate definitive dose for indolent lymphoma.

For patients with advanced-stage follicular lymphoma, several small series, which included patients with stage III disease, have reported results on the use of "central" or "comprehensive" lymphoid irradiation, with 10-year to 15-year disease-free survival of 30% to 40%.[97-99] Molecular complete responses, assessed by polymerase chain reaction techniques, have also been demonstrated after the treatment.[100] This approach of wide-field radiation therapy, however, is not widely accepted because of concerns with long-term toxicity for the treatment for an indolent disease and the ability to deliver effective salvage therapy at the time of relapse. Emerging data are available on the effectiveness of low-dose IFRT for palliation in patients with indolent lymphoma, with response rates of 80% to more than 90%.[101-107] The advantages of this approach, in addition to the high response rate, include minimal treatment toxicity, patient convenience, potential delay in need of starting systemic therapy, and the option of reirradiation if needed. However, results of the recently published FoRT trial showed that 4 Gy in 2 fractions was significantly inferior to 24 Gy in 12 fractions in patients with either follicular or marginal zone lymphoma in terms of response rates (81% versus 74.1%, $p = 0.006$), and 2-year progression-free survival rates (93.7% versus 80.4%, $p < 0.001$) in the 4 Gy-arm.[108] These findings led to the conclusion that although 4 Gy in 2 fractions remains a useful regimen in the palliative setting, 24 Gy is the standard dose for patients treated with radical intent.

MALT Lymphoma

Marginal zone B-cell lymphoma (MALT) accounts for about 8% to 10% of non-Hodgkin's lymphoma. The majority of cases are localized at presentation and tend to remain localized for long periods of time. This subtype of lymphoma is highly responsive to radiation therapy. Doses of around 30 Gy to involved nodal regions or extranodal sites will yield local control rate of close to 100%, with a chance of long-term cure in about three quarters of the patients,[109-114] although results from the United Kingdom randomized trial suggested that 24 Gy may be adequate.[83] Relapses tend to occur at other extranodal sites in which MALT lymphomas tend to occur or in a nonirradiated contralateral paired organ.[115] The likelihood of achieving a second remission in patients with limited relapses remains excellent with further local radiation therapy.

Multiple Myeloma and Plasma Cell Malignancies

Multiple myeloma at this time remains an incurable disease. However, novel agents including bortezomib and lenalidomide have been shown to be effective in the relapsed setting, and they are increasingly being adopted as first-line therapy.[116,117] Additional novel agents, including pomalidomide, a new immunomodulatory agent, and carfilzomib, an irreversible proteasome inhibitor, have shown promising antimyeloma activity in patients with refractory disease.[118,119] Finally, monoclonal antibodies are emerging as an important modality in the treatment of the disease.[120,121]

The current role of radiation therapy in the management of multiple myeloma is therefore largely limited to palliation, in patients with painful bony lesions, nerve root or cord compression, or lytic lesions in a weight-bearing bone at risk for pathological fractures. Kyphoplasty in conjunction with radiation therapy for patients with compression fracture of the vertebral bodies may provide more immediate and effective palliation.[122-124] Fractionation schemes of 30 Gy in 10 fractions or other biological equivalent doses are recommended because lower doses are associated with less durable palliation, and retreatment is often less effective.[125-129]

Solitary plasmacytoma accounts for 5% to 10% of all plasma cell dyscrasias. In patients with solitary plasmacytoma of the bone, local radiation therapy to doses of 45 Gy to 50 Gy can provide effective local control of more than 80%.[130-136] However, about half of the patients will progress to multiple myeloma at 10 years, and by 15 years, most will develop multiple myeloma. Unlike solitary plasmacytoma of the bone, extraosseous solitary plasmacytoma is associated with a lower risk of progression to multiple myeloma and has a more favorable disease-free survival.[133,135,137-139] Most series employed doses of 45 Gy to 50 Gy, which yielded local control rates of 85% to 90%.

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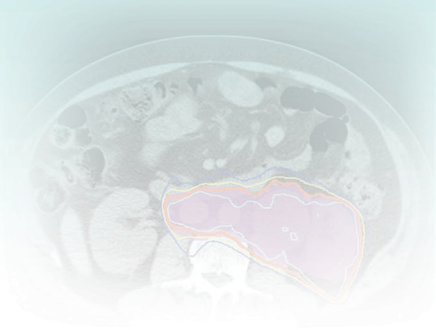
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CHAPTER

76 Hodgkin's Lymphoma



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INCIDENCE

There are approximately 8,500 new cases in the United States each year.

BIOLOGIC CHARACTERISTICS

Hodgkin's/Reed-Sternberg (HRS) cells are the malignant cells in Hodgkin's lymphoma.

Increasing epidemiologic and molecular evidence support that a combination of genetic susceptibility, immune response impairment, and exposure to specific infectious agents may play a central role in the pathogenesis of the disease.

PATHOLOGY

Classical Hodgkin's lymphoma (HL; CD15+, CD30+, CD45–), four subtypes: nodular sclerosis, lymphocyte rich, mixed cellularity and lymphocyte depleted.

Nodular lymphocyte predominant HL (CD45+, CD20+, CD 15–, CD 30–).

STAGING EVALUATION

History and physical examination, focusing on constitutional symptoms, nodal involvement, and organomegaly.

Complete blood count, erythrocyte sedimentation rate (ESR), and serum albumin.

Computed tomography (CT) of chest, abdomen, and pelvis; positron emission tomography (PET).

Bone marrow biopsy if constitutional symptoms present or advanced-stage disease is.

THERAPY IN EARLY-STAGE DISEASE

Standard therapy is combined-modality therapy with two to four cycles of Adriamycin, bleomycin, vinblastine, and dacarbazine (ABVD) followed by involved-site radiation therapy in favorable patients and four to six cycles of ABVD followed by involved-site radiation therapy in patients with unfavorable disease, with 5-year disease-free survival (DFS) of about 90%.

Abbreviated regimens in patients with unfavorable prognostic features (bulky disease, four or more sites of disease, presence of constitutional symptoms) should be avoided.

Clinical trials are evaluating the role of PET response to chemotherapy in guiding the use of adjuvant radiotherapy.

THERAPY IN ADVANCED-STAGE DISEASE

Standard therapy is chemotherapy alone with ABVD, with 5-year DFS of 70% to 80%.

Dose-escalated bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone (BEACOPP) and its variants may yield superior freedom-from-treatment failure but is associated with increased toxicity.

There is no difference between Stanford V and ABVD as shown in the ECOG 2496 randomized trial on advanced HL.

There may be a role for consolidative radiation therapy in selected cases, including initial bulky disease or lack of complete response to chemotherapy.

SALVAGE THERAPY

High-dose therapy with autologous bone marrow or stem-cell transplantation is the salvage therapy of choice in patients who are refractory to, or relapsed after, a short initial remission to chemotherapy.

Selected patients may be candidates for conventional dose salvage therapy, namely, patients with limited nodal relapse, absence of constitutional symptoms, and long remission duration.

INTRODUCTION

HL was first described by the British physician Thomas Hodgkin in 1832, when he reported six patients with pathologic enlargement of lymph nodes and spleen at Guy's Hospital.[1] Attempts to treat the disease using various chemical or surgical means were unsuccessful until around the turn of the century, when the effectiveness of x-ray in shrinking the disease was first demonstrated. Only crude, low energy x-ray equipment was available at the time, which merely allowed the temporary reduction of the enlarged lymph nodes. The development of kilovoltage equipment in the 1920s and the subsequent pioneering work of Gilbert, a Swiss radiotherapist, paved the way for the definitive treatment of patients with HL.[2] Vera Peters at Ontario Institute of Radiotherapy first reported the curability of early-stage HL in 1950 using high doses of fractionated radiation therapy.[3] The availability of modern, high-energy radiation therapy equipment in the late 1950s and early 1960s allowed the delivery of higher doses of radiation to deep-seated tumor with less limitations by reactions in the superficial tissues. The introduction of effective combination chemotherapy further improved the treatment outcome of HL, especially in patients with unfavorable prognostic features or advanced-stage disease.[4] Over the last three decades, continued improvements in radiation therapy techniques allowing more uniform and better targeted dose delivery, development of more effective and less toxic multiagent chemotherapy regimens, advances in radiographic imaging technology, and the refinement of prognostic factors that allow better tailoring of treatments, HL, a previously fatal illness, has now become one of the most curable forms of malignancy.

ETIOLOGY AND EPIDEMIOLOGY

HL is a relatively uncommon neoplasm, with approximately 8,500 new cases in the United States each year, representing less than 1% of all cancer diagnosis.[5] The incidence, age, and gender distribution of HL vary depending on the geographic

location. The age-incidence curve in developed countries is characterized by a bimodal distribution.[6,7] There is an initial peak in young adults at around age 25, and a second peak occurring at ages 60 to 70, in which a male predominance is observed. The majority of the cases seen in young adulthood are of nodular sclerosis (NS) histology, and many of the factors that have been associated with the development of HL in these patients appear to be a reflection of delayed exposure to infectious agents or higher socioeconomic status. These include early birth order, small sibship size, growing up in single-family houses, few playmates, and high parental education.[8-10] In contrast, in economically disadvantaged parts of the world, HL is relatively rare among young adults.[7] Mixed cellularity (MC) is the predominant histologic subtype in developing countries, with an initial peak in childhood for boys and a late peak in older patients.

The etiology of HL is an unresolved issue but is likely complex and may vary depending on the different subtypes. A combination of genetic susceptibility, immune response impairment, and environmental exposures, especially specific infectious agents, are likely to play a central role in the pathogenesis of the disease.

Several of the epidemiological and clinical features of the disease are suggestive of infectious causes, and there have been increasing evidence that Epstein Barr Virus (EBV) may be involved in the pathogenesis of HL in at least a subset of cases. Patients with history of infectious mononucleosis, in which EBV is the causative agent, are at an approximately threefold increased risk for HL, and particularly EBV-associated HL.[7,11,12] Elevated levels of the IgG and IgA immunoglobulins against the EBV capsid antigen have been demonstrated months to years before clinical HL development.[13,14] In about one third to one half of cases of classical HL occurring in Western populations, monoclonal EBV genome can be detected in the Reed-Sternberg cells.[15,16] EBV positivity is predominantly associated with the MC subtype,[17] which is more common among young children and older adults, and is less frequently associated with NS cases seen mostly in the young adults in the developed world.

The observation of familial aggregation of cases of HL suggests that genetic susceptibility as well as environmental exposure may contribute to the development of HL. A 5-fold increased risk has been demonstrated in first-degree relatives, and siblings of young adults with HL have a 7-fold increased risk.[18] The excess risk appears to be more pronounced in same-sex siblings, which may be related to more shared environmental exposure.[19] In a twin study of young adults with HL, monozygotic twins of patients had an almost 100-fold increased risk,[20] whereas no increased risk for dizygotic twins was observed, supporting the contribution of heritable factors to the development of the disease. In particular, follow-up twin studies have suggested that persons with genetically determined lower IL-6 levels may be less susceptible to young adult HL.[21] In addition, a genome screen of families at high risk for HL has provided evidence for a susceptibility gene on several chromosomes, particularly chromosome 4.[22] Finally, a number of specific human leukocyte antigen (HLA) haplotypes, as well as specific polymorphisms within chromosome 6p21.32 (an area which includes genes involved in immune function, including *HLA-DRB$_1$ and HLA-DOB$_1$*) have been identified to be associated with an increased risk of HL.[22-25] Because immune response is genetically determined by the HLA type, patients with these HLA haplotypes may have increased susceptibility to certain infections, which in turn may lead to the increased HL risk as well as increased susceptibility to autoimmune conditions. In fact, an elevated risk of HL has been found in patients with personal histories of several autoimmune conditions.

BIOLOGIC CHARACTERISTICS AND MOLECULAR BIOLOGY

The malignant cells in classical HL, the HRS cells, are large, uni- or multinucleated cells, which usually comprise only 1% of the cells present in the tissue sample, with the majority of the tumor consisting of a variety of nonneoplastic inflammatory cells and fibrosis. Results of molecular single-cell studies have shown that in more than 90% of cases, HRS cells have monoclonal immunoglobulin gene rearrangements that are characteristic of mature B lymphocytes, and somatically mutated VH genes that are specific markers for germinal center B cells and their descendants, supporting a germinal center or postgerminal center B-cell origin.[26,27] However, unlike normal B cells that have undergone successful maturation through the germinal cells, HRS cells characteristically show absence of immunoglobulin gene expression. This has been attributed to mutations in the coding or regulatory regions,[28] lack of expression of transcription factors that are responsible for activation of the promoters and enhancers,[28] epigenetic silencing of the immunoglobulin heavy-chain transcription,[29] and constitutive expression of master regulators such as Notch1, ID2, activated B-cell factor 1, and STAT5.[29] Despite their inability to express immunoglobulin receptors, HRS cells are resistant to apoptosis, which normally removes immunoglobulin negative B cells that have traversed the germinal center.

There is increasing evidence connecting the prevention of apoptosis and survival of HRS cells to the activation of the nuclear factor kappa B (NF-κB) transcription factor-signaling pathway. Constitutive NF-κB is required for proliferation and survival of HL tumor cells.[30] The cause of the constitutive activation of NF-κB is probably multifactorial and may include amplification of the REL gene,[31] mutations in NF-κB inhibitors, and somatic mutations in the novel tumor suppressor gene *TNFAIP3*.[32] There is an inverse relationship between EBV infection and inactivation of A20, the protein encoded by the *TNFAIP3* gene, suggesting that they may represent alternative pathways of pathogenesis.[29]

Molecular profiling experiments using HL-derived cell lines with suppressed and unsuppressed NF-κB activity have been performed to better understand the NF-κB signaling pathway and to identify its target genes. One of the regulators of apoptosis that is expressed in dependence of NF-κB is cIAP2, a direct inhibitor of caspase 3, suggesting that HRS cells are protected from caspase 3–induced apoptosis by cIAP2.[33] Another NF-κB dependent regulator of apoptosis is CD95, which has been shown to be upregulated in HRS cells. However, unlike the other NF-κB-dependent regulators, CD95 is known to trigger apoptosis rather than prevent it. The resistance of HRS cells to CD95-mediated apoptotic cell death may be because of functional inhibition of death receptor pathways by cellular FADD-like IL1B-converting enzyme inhibitory proteins (c-FLIP), which is one of the most strongly NF-κB-regulated genes.[34] The contribution of NF-κB signaling to the development of HL is further supported by epidemiological data showing that regular aspirin use is associated with a reduced risk of developing HL, presumably through inhibition of NF-κB transcription.[35] Continued efforts in the elucidation of the NF-κB pathway in the pathogenesis of HL may have important therapeutic implications through pharmacological downregulation of NF-κB activity and its target genes, and increasing the susceptibility of HRS to apoptosis. However, bortezomib, a proteasome inhibitor that inhibits NF-κB activity, does not appear to be clinically active against HL.

The JAK/STAT pathway may also be important in the pathogenesis of HL with chromosomal gains in JAK2 found in about 20% of cases and, in rare cases, a translocation

involving JAK2 may be found.[36] JAK2 may be an activator of STAT signaling. Other signaling pathways possibly deregulated in HL include the PI3K/AKT, MAPK/ERK, and various receptor tyrosine kinase pathways.

Finally, translocations involving the MHC class II transactivator gene CIITA have been found in a subset of classical HL cases, and may contribute to the pathogenesis of HL by inhibiting MHC class II expression.[37]

PATHOLOGY

Since the 1930s, a number of pathological classification systems for HL have been developed. The Rye classification system, introduced at a conference in Rye, New York, in 1966, divided cases of HL into lymphocyte predominance (LP), nodular sclerosis (NS), mixed cellularity (MC), and lymphocyte depletion (LD).[38] This system was widely adopted in the next 25 years and was subsequently modified in the revised European-American classification of malignant lymphomas (REAL) and later in the World Health Organization (WHO) classification (Table 76-1).[39,40] In the current classification system, HL is specifically recognized as a lymphoma. Based on morphological, immunophenotypic, and clinical characteristics, it is divided into two distinct entities: classical HL and nodular lymphocyte predominant Hodgkin's lymphoma (NLPHD). Table 76-2 compares the morphological and immunophenotypic features of the malignant cells of these two entities. The diagnosis of HL is based on morphological assessment with identification of HRS cells or their variants, along with immunohistochemical studies.

Classical Hodgkin Lymphoma

In the majority of cases of the HRS of classical HL, most markers for B cells or T cells, as well as leukocyte common antigen (CD45) are absent, whereas a number of antigens including CD30 and CD15, which are not usually expressed by normal B cells or T cells, can be detected. The immunophenotypic and genetic features of the malignant cells of the four histological subtypes of classical HL are similar. However, the four subtypes vary in the morphology of the HRS cells, nature of the surrounding reactive cells, association with EBV, and clinical characteristics.

TABLE 76-1 The WHO Histological Classification of Hodgkin Lymphoma[40]

Nodular lymphocyte predominant Hodgkin's lymphoma (NLPHL)
Classical Hodgkin's lymphoma (CHL):
Nodular sclerosis classical Hodgkin's lymphoma (NSHL)
Mixed cellularity classical Hodgkin's lymphoma (MCHL)
Lymphocyte rich classical Hodgkin's lymphoma (LRCHL)
Lymphocyte-depleted classical Hodgkin's lymphoma (LDHL)

TABLE 76-2 Comparison of Morphological and Immunophenotypical Characteristics of the Malignant Cells of Classical HD and NLPHD

	Classical HD (HRS cells)	NLPHD (L&H cells)
Nuclei	Mono- and multinucleated, mono- and multilobulated	Mononucleated, multilobulated
Nucleoli	Large	Multiple, small
CD30	+	—
CD15	+ in majority of cases	—
CD45	—	+
CD20	— in majority of cases	+
CD79a	— in majority of cases	+

HD, *Hodgkin's disease;* HRS, *Hodgkin and Reed/Sternberg;* L&H, *lymphocytic and histiocytic;* NLPHD, *nodular lymphocyte predominant Hodgkin's disease.*

The NS subtype accounts for approximately 70% of classical HL, affecting predominantly young adults. Morphologically, it is characterized by the presence of one or more sclerotic bands radiating from a thickened lymph node capsule. The British National Lymphomas Investigation subclassified NS HL into two grades based on the percentage of nodules showing lymphocyte depletion or increased number of anaplastic-appearing HRS cells.[41,42] However, the prognostic value of this grading system with modern therapy is unclear.

The MC subtype is more frequently seen in developing countries, accounting for more than half of the cases, whereas in the more developed parts of the world, it comprises approximately 25% of classical HL. Morphologically, HRS cells are seen scattered in a diffuse inflammatory background with the absence of nodular sclerosing fibrosis. In contrast to the NS and lymphocyte rich classical Hodgkin's lymphoma (LRCHD), EBV positivity is much more frequent in the MC subtype.[43]

LRCHD accounts for approximately 5% of classical HL, has a male predominance and older median age at presentation.[44] It is characterized by a background infiltrate of small, mature, predominantly B-lymphocytes with rare HRS and variants. It can resemble NLPHD morphologically, and immunohistochemical studies of the malignant cells are essential to make the distinction. The prognosis may be slightly better than other subtypes of classical HD.[44]

The LD subtype has increased number of HRS and is depleted in lymphocytes. Many cases that were previously classified as LD HL are now determined to be anaplastic or large-cell non-Hodgkin's lymphoma based on immunohistochemical studies.[45] Reliable clinical data on this subtype is limited given its rarity and uncertainty concerning its diagnosis.

Adverse pathologic prognostic factors include macrophage gene expression signature and higher numbers of CD163+ or CD68+ macrophages; expression of BCL2, the T-cell antigens CD2 and CD4, galectin-1, ABCC1 by HRS cells; a characteristic mRNA signature; and a characteristic miRNA signature.[46]

Nodular Lymphocyte Predominant Hodgkin's Lymphoma

NLPHD comprises 5% of HL. The malignant cells of NLPHD are the LP cells, which are also known as popcorn cells because of their characteristic appearance. The pathogenesis of LP cells is probably distinct from that of HRS but probably shares constitutive NF-κB activity; recurrent translocations involving BCL6 are present in about one half of cases. Unlike classical HL, the neoplastic cells of NLPHD typically lack the expression of CD15 and CD30 markers but are consistently CD20 and CD45 positive.[47] A nodular pattern is seen usually completely or partially replacing the lymph node. The nodules tend to be large and closely packed, and the LP cells are typically seen within or around the nodules. There are usually large numbers of CD57 positive small lymphocytes in the nodules, often with ringing around the lymphocytic and histiocytic (L&H) cells. In about 3% to 5% of cases, transformation to diffuse large B-cell lymphoma may occur.

CLINICAL MANIFESTATIONS, PATIENT EVALUATION, AND STAGING

Clinical Presentation

The most common clinical presentation of HL is nontender lymphadenopathy, mostly in the cervical nodal chain,

occurring in about 70% of cases. Axillary or inguinal adenopathy are less frequently reported, found in about 15% and 10% of patients, respectively. Another common presentation is mediastinal adenopathy detected on radiographic imaging. In cases of large mediastinal adenopathy, patients may occasionally present with local symptoms including shortness of breath, chest pain, cough, or superior vena cava syndrome. Rarely, patients may present with an enlarging anterior chest wall mass because of local extension.

Patients may also present exclusively with constitutional symptoms in the absence of any physical findings. These symptoms, also known as B symptoms, include fever, unexplained weight loss, and drenching night sweats. Severe, generalized pruritus, not classified as a B symptom, is noted in about 10% to 15% of patients, and has been associated with a poorer prognosis.[48] Alcohol-induced pain, typically at the site of lymphadenopathy or bony involvement, can be a presenting symptom in some patients.[49]

Staging System

The Ann Arbor staging classification (Table 76-3), developed in 1971, is a four-stage system formulated to provide prognostic information and to guide therapeutic decisions. However, it does not reflect other important prognostic factors such as bulky disease or multiple sites of involvement.[50] The availability of improved imaging techniques has also changed its applicability. In 1988, revisions to the Ann Arbor staging system were made based on a meeting in Coltswolds, England (Table 76-4).[51] Main changes include the following: (1) Allowed the use of CT scanning to assess disease involvement below the diaphragm. (2) For stage II disease, the number of anatomic nodal sites were indicated by a subscript (e.g., stage II_3). (3) For stage III disease, upper and lower abdominal involvement were subdivided as III_1 and III_2, respectively. (4) Bulky disease was denoted by *X*, defined as more than one third widening of the mediastinum at T5-6 level or >10 cm maximum dimension of the nodal mass. (5) Unconfirmed/uncertain complete remission (CRu) was introduced to denote presence of residual imaging abnormality but absence of pathologically confirmed residual disease.

TABLE 76-3 Ann Arbor Staging Classification

Stage	Definitions
Stage I	Involvement of single lymph node region (I) or of single extralymphatic organ or site (I_E)
Stage II	Involvement of two or more lymph node regions on the same side of the diaphragm alone (II) or with involvement of limited, contiguous extralymphatic organ or tissue (II_E)
Stage III	Involvement of lymph node regions on both sides of the diaphragm (III), which may include the spleen (III_S), or limited, contiguous extralymphatic organ or site (III_E) or both (III_{SE})
Stage IV	Diffuse or disseminated foci of involvement of one or more extralymphatic organs or tissues, with or without associated lymphatic involvement

The absence or presence of fever, night sweats or unexplained weight loss of 10% or more of body weight in the 6 months preceding admission are to be denoted in all cases by the suffix letters A or B, respectively. The clinical stage (CS) denotes the stage as determined by all diagnostic examinations and a single biopsy only. If a second biopsy of any kind has been obtained, whether negative or positive, the term pathologic stage (PS) is used.

Patient Evaluation and Staging Workup

An adequate surgical biopsy for pathological assessment by an experienced hematopathologist is essential in the initial diagnosis of HL. All patients need to undergo a careful history and physical examination. Particular attention should be placed on the presence and duration of constitutional symptoms, as well as other symptoms that may be indicative of extent and bulkiness of local disease. On physical examination, all nodal groups should be thoroughly palpated with clear documentation of the extent of disease involvement. Baseline blood work, some of which have been shown to be of prognostic value in patients with HL, should be obtained. These include complete blood count with differential, sedimentation rate, and serum albumin.[52] Fluorine-18-fluorodeoxyglucose positron emission tomographic (FDG-PET) scan, which has been shown to be more sensitive then CT scanning, and results in upstaging of 15% to 25% of patients, is now considered part of standard staging work-up for HL.[53-59] A separate diagnostic CT is not necessary if it was done as part of an integrated PET-CT scan. The performance of bone

TABLE 76-4 The Coltswolds Staging Classification for Hodgkin's Lymphoma

Stage	Definitions
Stage I	Involvement of a single lymph node region or lymphoid structure (e.g., spleen, thymus, Waldeyer's ring) or involvement of a single extralymphatic site (IE)
Stage II	Involvement of two or more lymph node regions on the same side of the diaphragm (hilar nodes, when involved on both sides, constitute stage II disease); localized contiguous involvement of only one extranodal organ or site and lymph node region(s) on the same side of the diaphragm (IIE). The number of anatomic regions involved should be indicated by a suffix (e.g., II_3)
Stage III	Involvement of lymph node regions on both sides of the diaphragm (III), which may also be accompanied by involvement of the spleen (III_S) or by localized contiguous involvement of only one extranodal organ site (IIIE) or both III SE) III_1: With or without involvement of splenic, hilar, celiac or portal nodes III_2: With involvement of paraaortic, iliac, and mesenteric nodes
Stage IV	Diffuse or disseminated involvement of one or more extranodal organs or tissues, with or without associated lymph node involvement
DESIGNATIONS APPLICABLE TO ANY DISEASE STAGE	
A	No symptoms
B	Fever (temperature >38°C), drenching night sweats, unexplained weight loss >10% of body weight within the prior 6 months
X	Bulky disease (a widening of the mediastinum by more than one third of the presence of a nodal mass with a maximal dimension greater than 10 cm)
E	Involvement of a single extranodal site that is contiguous or proximal to the known nodal site
CS	Clinical stage
PS	Pathological stage (as determined by staging laparotomy)

TABLE 76-5 Patient Evaluation and Staging

HISTORY
Constitutional symptoms
Symptoms that may be indicative of extent and bulk of local disease (e.g., pulmonary symptoms, swelling, pain)
PHYSICAL EXAMINATION
Careful palpation of all nodal groups
Palpate for organomegaly
RADIOGRAPHIC STAGING
PET/CT scan
PATHOLOGICAL EVALUATION
Excisional biopsy depending on location of disease
Bone marrow biopsy only in patients with advanced stage disease or constitutional symptoms
BLOOD WORK
CBC with differential
ESR
Serum albumin
PRETREATMENT BASELINE EVALUATION
Patients to be receiving Adriamycin: baseline MUGA scan
Patients to be receiving bleomycin: baseline pulmonary function tests

CBC, *Complete blood count;* ESR, *erythrocyte sedimentation rate;* MUGA, *multigated acquisition scan;* PET/CT, *positron emission tomography/computed tomography.*

marrow biopsy should be limited to patients with advanced-stage disease or in those with constitutional symptoms given the low yield in patients with early-stage, favorable-prognosis disease of less than 1%.[60,61] The recommended patient evaluation and staging studies for newly diagnosed HL are listed in Table 76-5.

Prognostic Factors

For patients with early-stage HL, several prognostic factors, largely based on patients treated with radiation therapy alone, have been identified. These include B symptoms, sedimentation rates, disease bulk, number of sites of disease, age, and histology. Cooperative groups have used varying combination of these factors to stratify patients into favorable versus unfavorable disease in clinical trials. Examples of various prognostic classification systems used by cooperative groups are shown in Table 76-6.

For patients with advanced-stage disease, Hasenclever et al developed the International Prognostic Score (IPS), using data from more than 5000 patients with advanced-stage HL, mostly treated with doxorubicin-based combination chemotherapy.[52] Seven factors were found to have similar independent prognostic value in predicting freedom-from progression (FFP) and overall survival (OS). These included hypoalbuminemia (<4 g per deciliter), anemia (<10.5 g per deciliter), male sex, age 45 years or older, stage IV disease, leukocytosis (>15,000 per cubic millimeter), and lymphocytopenia (<600 per cubic millimeter, <8 percent of the white-cell count, or both). The 5-year FFP ranged from 42% in patients with an IPS score of ≥5% to 84% in patients with a score of 0 (Table 76-7). However, patients with five or more of the adverse factors account for only 7% of the study population. The IPS has been used in trials for patient selection and patient stratification, and it may also have a role in guiding tailored therapy based on relapse risk in advanced-stage patients.

An early response to PET has been identified as a powerful prognostic tool in HL.[62] In a joint Italian-Danish study,[53] PET response after two cycles of chemotherapy overshadowed the prognostic value of IPS and emerged as the single most important prognostic factor in advanced-stage HL. Several PET-adaptive clinical trials are testing the hypothesis that interim PET results can guide decisions regarding treatment escalation or deescalation.

TABLE 76-6 The Prognostic Classification Systems for CS I-II Hodgkin's Lymphoma

Institution	Prognostic Classification
EORTC	***Unfavorable Prognosis***: Presence of *any* one of the following: Age >50 years No B symptoms with ESR ≥50 B symptoms with ESR ≥30 ≥4 sites of involvement Bulky mediastinal involvement ***Favorable Prognosis***: Absence of *all* of the factors in the unfavorable prognosis group
GHSG	***Unfavorable Prognosis***: Presence of *any* one of the following: Elevated erythrocyte sedimentation rate (≥50 mm without or ≥30 mm with B symptoms) ≥3 sites of involvement Extranodal involvement Large mediastinal mass ***Favorable Prognosis***: Absence of *all* of the factors in the unfavorable prognosis group
NCI-C (excluded patients with bulky disease)	***Low risk***: Presence of *all* of the following: LP/ NS Age <40 ESR <50 <3 sites of involvement ***High risk***: All other patients

CS, *Clinical stage;* EORTC, *European Organisation for Research and Treatment of Cancer;* ESR, *erythrocyte sedimentation rate;* GHSG, *German Hodgkin Study Group;* LP, *lymphocyte predominant;* NCI-C, *National Cancer Institute-Canada;* NS, *nodular sclerosis.*

TABLE 76-7 The International Prognostic Scoring System for Advanced-Stage Hodgkin's Lymphoma

Prognostic Score	5-Year Freedom-From-Progression (%)	5-Year Overall Survival (%)
0	84	89
1	77	90
2	67	81
3	60	78
4	51	61
>5	42	56

Note: Each of the following factors carries a score of one: hypoalbuminemia, anemia, male sex, age ≥45, stage IV disease, leukocytosis, and lymphocytopenia.

PRIMARY THERAPY FOR EARLY-STAGE HODGKIN'S LYMPHOMA

Early-stage HL comprises about 60% of all cases of HL. Historically, the primary therapy for early-stage HL had been

extended-field radiation therapy alone, with addition of chemotherapy in the presence of unfavorable prognostic factors. Since the introduction of Adriamycin, bleomycin, vinblastine, dacarbazine (ABVD), a more effective and less toxic combination chemotherapy regimen than mechlorethamine, vincristine, procarbazine, prednisone (MOPP), there has been a shift to the use of combined-modality therapy in patients with early-stage disease, which yields long-term cure rates of approximately 90% or higher. Randomized studies have shown a significantly higher FFTF with combined-modality therapy than with radiation therapy alone.[63-65]

Because of the excellent survival in this relatively young group of patients, late effects of therapy have been increasingly recognized.[66-73] Most of the current trials on early-stage HL focus on treatment reduction and modification. The key questions addressed by the trials on the use of combined-modality therapy for early-stage HL include the following: (1) What is the optimal combination chemotherapy regimen? (2) How many cycles of chemotherapy are needed? (3) What are the appropriate radiation field size and dose? (4) Can radiation therapy be eliminated?

Optimal Combination Chemotherapy Regimen

Investigators have explored alternatives or modification of the ABVD regimen to limit toxicity in favorable patients or to improve efficacy in unfavorable patients. Examples include vinblastine, bleomycin, and methotrexate (VBM)[74-77]; methotrexate, vinblastine, and prednisone (MVP)[75]; doxorubicin, cyclophosphamide, etoposide, vincristine, bleomycin, prednisolone (VAPEC-B)[78]; doxorubicin, vinblastine (AV)[63]; mitoxantrone, vincristine, vinblastine, and prednisone (NOVP)[79]; and epirubicin, bleomycin, vinblastine, and prednisone (EBVP II, administered monthly).[80] Most of these regimens showed promising results at least in patients with favorable-prognosis disease, with relapse-free survival (RFS) rates of about 90%. The Stanford V regimen (nitrogen mustard, Adriamycin, vincristine, vinblastine, etoposide, bleomycin, and prednisone, followed by radiation therapy to initial nodal involvement in selected cases), a short but intensive 12-week regimen, was originally developed for patients with advanced-stage disease or bulky, early-stage disease.[81,82] The Stanford group reported the results on 87 patients with nonbulky, stages I to IIA disease treated with an abbreviated, 8-week course of Stanford V followed by involved-field radiotherapy (IFRT) to 30 Gy.[83] At a median follow-up of 10 years, the FFP, DFS, and OS were 94%, 99%, and 94%, respectively. The German Hodgkin's Study Group (GHSG) HD13 trial compared two cycles of ABVD, AVD, ABV, and AV, all followed by 30 Gy of involved-field irradiation in clinical stage (CS) I to CS II patients without risk factors. The two arms without dacarbazine (AV and ABV) were closed early because of higher than expected relapse rates. In the most recent update, the AVD arm was significantly inferior to the ABVD arm mainly as a result of late relapses.

Attempts to deescalate chemotherapy in patients with unfavorable-prognosis disease have been disappointing.[84] To improve the treatment outcome in patients with unfavorable features, trials had been conducted to determine whether these patients may benefit from the regimen BEACOPP, originally developed for patients with advanced-stage disease. Both the European Organization for Research and Treatment of Cancer (EORTC) H9U and the GHSG HD11 studies compared four to six cycles of ABVD with four cycles of BEACOPP-baseline, followed by involved-field irradiation to 20 Gy to 30 Gy. No significant differences in 4-year EFS or OS were observed between BEACOPP and ABVD in the EORTC H9U trial. In the GHSG HD11, at a median follow-up of 82 months, a significantly higher 5-year freedom-from-treatment failure (FFTF) in the four cycles of baseline BEACOPP arm over the four cycles ABVD arm, if followed by 20 Gy of involved-field radiation therapy (86.8% versus 81.1%; 95% confidence interval [CI] of difference, 0.1% to 11.3%). However, there was no significant difference between BEACOPP and ABVD if followed by 30 Gy of involved-field radiation therapy.[85] Patients treated with baseline BEACOPP had a higher rate of severe toxicity than patients treated with ABVD (73.8% versus 51.5%, $p < 0.001$). The GHSG HD 14 trial tested increasing dose intensity using dose-escalated BEACOPP in patients with unfavorable CSs I-II disease, randomizing patients to four cycles of ABVD versus two cycles of dose-escalated BEACOPP and two cycles of ABVD (two-plus-two regimen), followed by involved field irradiation to 30 Gy. At a median follow up of 43 months, the two-plus-two regimen had a significantly improved 5-year FFTF by 7.2% (hazard ratio [HR], 0.44, $p < 0.001$), though it was associated with more acute toxicity. There was no difference in overall survival between the two arms.[86]

Optimal Duration of Chemotherapy

Whether the number of cycles of chemotherapy can be shortened in patients with favorable-prognosis disease was by addressed by the GHSG HD10 trial, in which CSs I-II patients without risk factors were randomized to four cycles or two cycles of ABVD, followed by 30 Gy or 20 Gy involved-field irradiation. At a median follow-up of 7.5 years, there were no significant differences between four versus two cycles of chemotherapy in 8-year FFTF (88.4% versus 85.7%), 8-year OS (94.6% versus 94.4%).[87] In patients with unfavorable-prognosis disease, the optimal number of cycles of chemotherapy was one of the study questions in two successive EORTC trials using different chemotherapy regimens. In the EORTC-H8U trial, patients were randomized to six cycles of MOPP/ABV followed by involved-field irradiation, four cycles of MOPP/ABV followed by involved-field irradiation or four cycles of MOPP/ABV followed by extended-field irradiation.[88] At a median follow-up of 92 months, there was no significant difference in 5-year EFS rates among the three treatment groups (84%, 88%, and 87%). The OS rates at 10 years were also not significantly different (88%, 85%, and 84%).[64] In the previously described EORTC-H9U trial, randomizing patients to six cycles of ABVD, four cycles of ABVD, or four cycles of BEACOPP, all followed by involved-field irradiation, at a median follow up of 57 months, there was no difference in 4-year EFS among the three arms (91%, 87%, and 90%, $p = 0.38$).[89]

Optimal Radiation Field Size

Historical Radiation Fields

Historically, extended field radiation therapy (EFRT) alone was standard treatment for early-stage HL, and later administered as part of combined-modality therapy. However, mature results from several randomized trials have since become available, showing no difference in FFTF and OS between EFRT versus IFRT after chemotherapy for early-stage HL.[64,90,91] As expected, more second malignancy cases were seen in the EFRT arm than the IFRT arm.

In most clinical trials conducted in the past decade, IFRT was employed. An involved field encompasses not only the involved nodes but also the other lymph nodes within the same lymph node region, as denoted by the Rye classification for staging. It was developed in the two-dimensional treatment planning era, in which the field design is largely based on bony landmark, with inclusion of a considerable volume of normal tissue in the irradiated field.[92] However, there are data suggesting that relapse sites in HL after chemotherapy

alone are largely limited to the initially involved node.[93] This has led to the concept of involved-node radiotherapy (INRT), first described by the European Organization for Research and Treatment of Cancer/Groupe d'Etudes des Lymphomes de l'Adulte (EORTC/GELA) and later the GHSG.[94,95]

Modern Radiation Fields: ISRT and INRT

Availability of cross-sectional imaging for radiation planning, accurate dosimetry using modern algorithms that adjust for tissue inhomogeneities, complex beam shaping with multileaf collimation, and intensity-modulated beam delivery in selected cases have made it possible to better define and further decrease radiation fields. Guidelines for INRT and involved-site radiation therapy (ISRT), based on best available evidence and consensus of expert opinion, were recently published by the International Lymphoma Radiation Oncology Group (ILROG).[96] The key difference between INRT and ISRT is whether an optimal prechemotherapy PET-CT scan is available to guide the treatment planning. For INRT, ideally, the prechemotherapy PET/CT is acquired in the treatment position, using the same breathing instructions and immobilization device. However, prechemotherapy PET/CT scan with patient in an approximate position suitable for later radiation treatment is also considered sufficient. ISRT accommodates cases in which optimal prechemotherapy imaging is not available. In such cases, allowance should be made in the clinical target volume (CTV) for uncertainties resulting from differences in positioning of the prechemotherapy scan and planning CT.

For volume definitions, the guidelines recommend that the CTV be determined by fusion of planning CT with with prechemotherapy PET-CT. The original disease volume is first contoured, and then uninvolved normal structures (e.g., lungs, muscles, major vessels) are excluded. Figure 76-1 illustrates case examples of CTV determination based on prechemotherapy PET-CT results. The determination of the CTV is the most important and challenging step because it heavily relies on the availability of optimal prechemotherapy imaging.

In selected sites, there may also be a need to determine an internal target volume (ITV), with expansion of the CTV to account for uncertainties in size, shape, and position of the CTV because of motion. Margins for extension from CTV to ITV may be obtained from four-dimensional CT or fluoroscopy. This may be most relevant where target motion is expected, including chest and upper abdominal sites, and where breath-hold techniques are not available. The EORTC/GELA group defines the planning target volume (PTV) as 1-cm isotropic expansion of the CTV to allow for organ motion and set-up variations.[94] The GHSG defines the PTV as 2-cm axial and 3-cm cranial caudal expansion of the CTV (if necessary, can be reduced to 1 cm to 1.5 cm if close proximity to critical structures) and for mediastinal disease, 1-cm axial and 2-cm cranial caudal expansion.[95] Unlike the European guidelines, the ILROG guidelines do not specify the extent of the PTV expansion. Instead, the recommendation is to use standard margins per institution, depending on immobilization device, body site, and patient cooperation.

Several studies have addressed the safety of radiation field reduction from IFRT. Investigators from the British Columbia reported results of their experience on INRT for patients with early-stage HL. At a median follow up of 50 months, no local recurrences were observed. However, the INRT employed in this study encompassed the initially involved lymph nodes with a margin ranging from 1.5 cm to 5 cm to the field edge and therefore included a larger volume than that of the INRT as defined by the European groups.[97] In addition, two-dimensional planning was performed in some of the patients. In a study from the Institut Gustave Roussy, results of 50 patients with early-stage HL treated with ABVD followed by INRT as per the EORTC/GELA definition was reported. With a median follow-up time of 53 months, the 5-year progression-free survival (PFS) rate was 92%. A total of four relapses were observed, including two distant and two infield relapses. Maraldo et al reported on treatment outcome of 97 patients with early-stage HL treated with ABVD followed by INRT according to the EORTC/GELA guidelines. A 4-year FFP rate of 96% was reported at a median follow up of 50 months. There were three relapses, two of which were infield and one was in the contralateral neck. Results thus far therefore suggest that the use of a much more limited field than the traditional IFRT does not appear to be associated with marginal misses and may indeed be safe in the presence of effective chemotherapy.

In the EORTC/Lymphoma Study Association (LYSA)/the Italian Lymphoma Foundation (FIL) H10 trial (which will be discussed later) for early-stage favorable and unfavorable HL, INRT was adopted in both the standard and experimental arms. In the ongoing GHSG HD17 trial for early-stage HL with risk factors (which will be discussed later), addressing the use of PET response to guide radiotherapy use, INRT is used in the experimental arm in patients with PET-positive disease after chemotherapy.

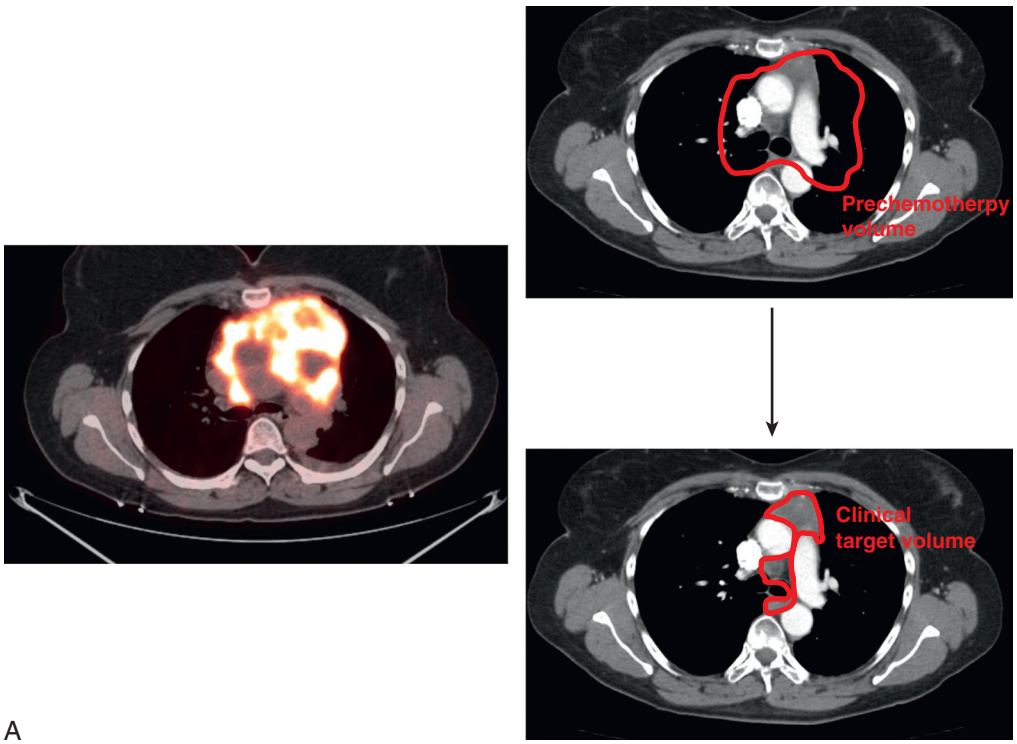
Optimal Radiation Dose

The appropriate radiation dose after chemotherapy in early-stage HL has been explored by three trials.[80,85,87,98,99] The EORTC H9F trial is a three-arm trial in which all patients receive six cycles of EBVP II.[80] After a complete response, patients were randomized to receive no further treatment, 36 Gy, or 20 Gy of IFRT. Patients with a partial response all received 36 Gy of IFRT with or without a 4-Gy boost. A complete response or complete response unconfirmed was achieved in 619 patients. At a median follow-up of 33 months, the 4-year EFS in the three arms of 36 Gy, 20 Gy, and no radiotherapy were 87%, 84%, and 70%, respectively. The difference in treatment results between the two doses of radiotherapy was not significant. However, the no-radiotherapy arm was closed early because stopping rules were met (>20% of events, which will be discussed).

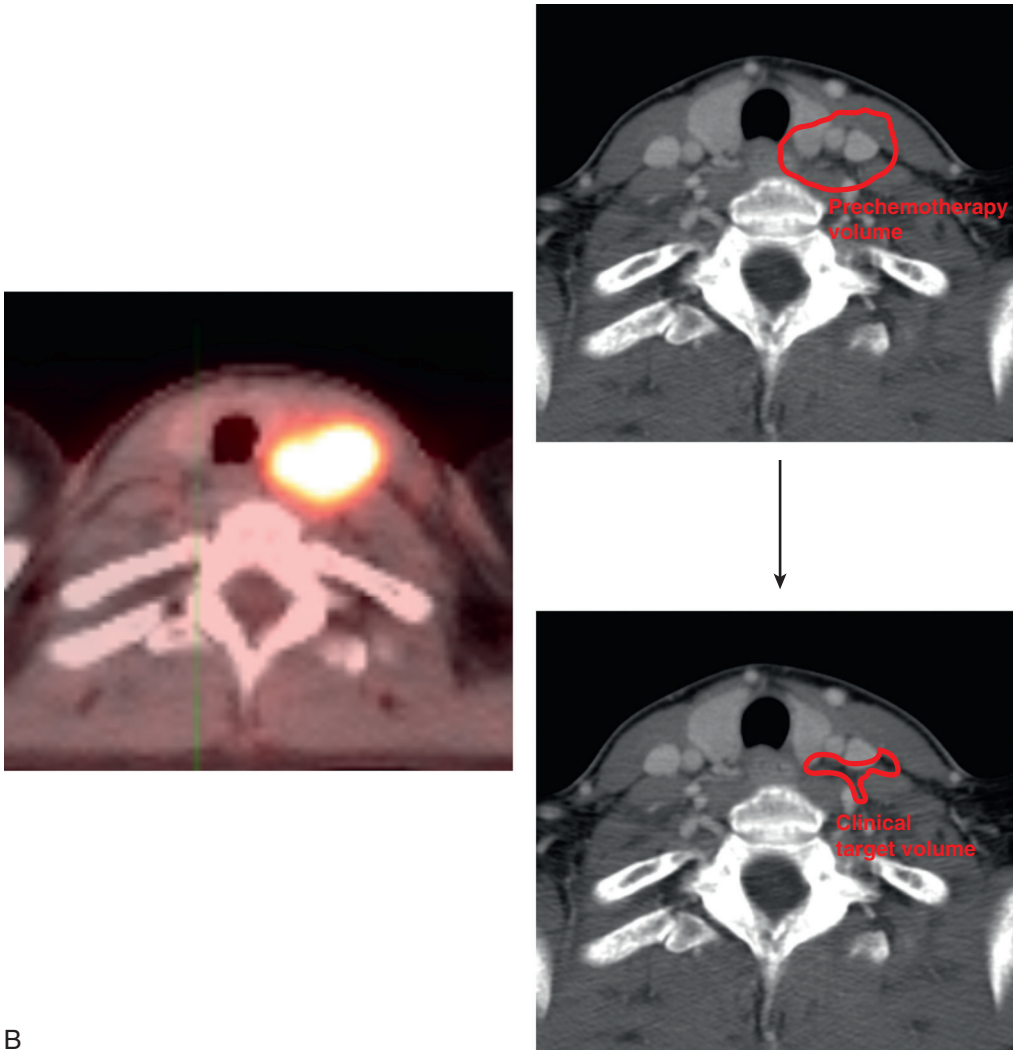
The GHSG HD10 trial is a four-arm trial for low risk (no bulky mediastinal mass or extranodal disease, 3 or less nodal sites, low sedimentation rate) patients at CSs I to II, in which involved-field radiotherapy to 30 Gy versus 20 Gy after four or two cycles of ABVD were compared.[87] At a median follow-up of 7.5 years, there were no significant differences between 30 Gy versus 20 Gy of involved-field radiotherapy in 8-year OS (94.9% versus 95.6%), 8-year FFTF (87.8% versus 88.6%) and 8-year PFS (88.1% versus 88.9%). The question of optimal radiation dose in unfavorable patients was addressed by the GHSG HD11 trial,[85] a four-arm trial comparing 20 Gy versus 30 Gy after four cycles of ABVD or baseline BEACOPP. At a median follow-up of 82 months, the 5-year FFTF rates were 81.1%, 85.3%, 86.8%, and 87.0%, respectively. Baseline BEACOPP was more effective than ABVD when followed by 20 Gy of IFRT, but the two regimens yielded similar outcome when followed by 30 Gy of IFRT. There was no significant difference in 5-year FFTF rate between baseline BEACOPP and ABVD when followed by 30 Gy of IFRT; however, inferiority of 20 Gy cannot be excluded after four cycles of ABVD, leading to the authors' conclusion of four cycles of ABVD followed by 30 Gy of IFRT as optimal therapy for early-stage, unfavorable HL.

Chemotherapy Alone

There are well-documented late effects of radiotherapy for HL, based largely on patients treated with radiation therapy



A



B

Figure 76-1 Determination of clinical target volume (CTV) based on prechemotherapy volume with disease involvement of the mediastinum **(A),** neck **(B),** and axilla **(C).**

Continued

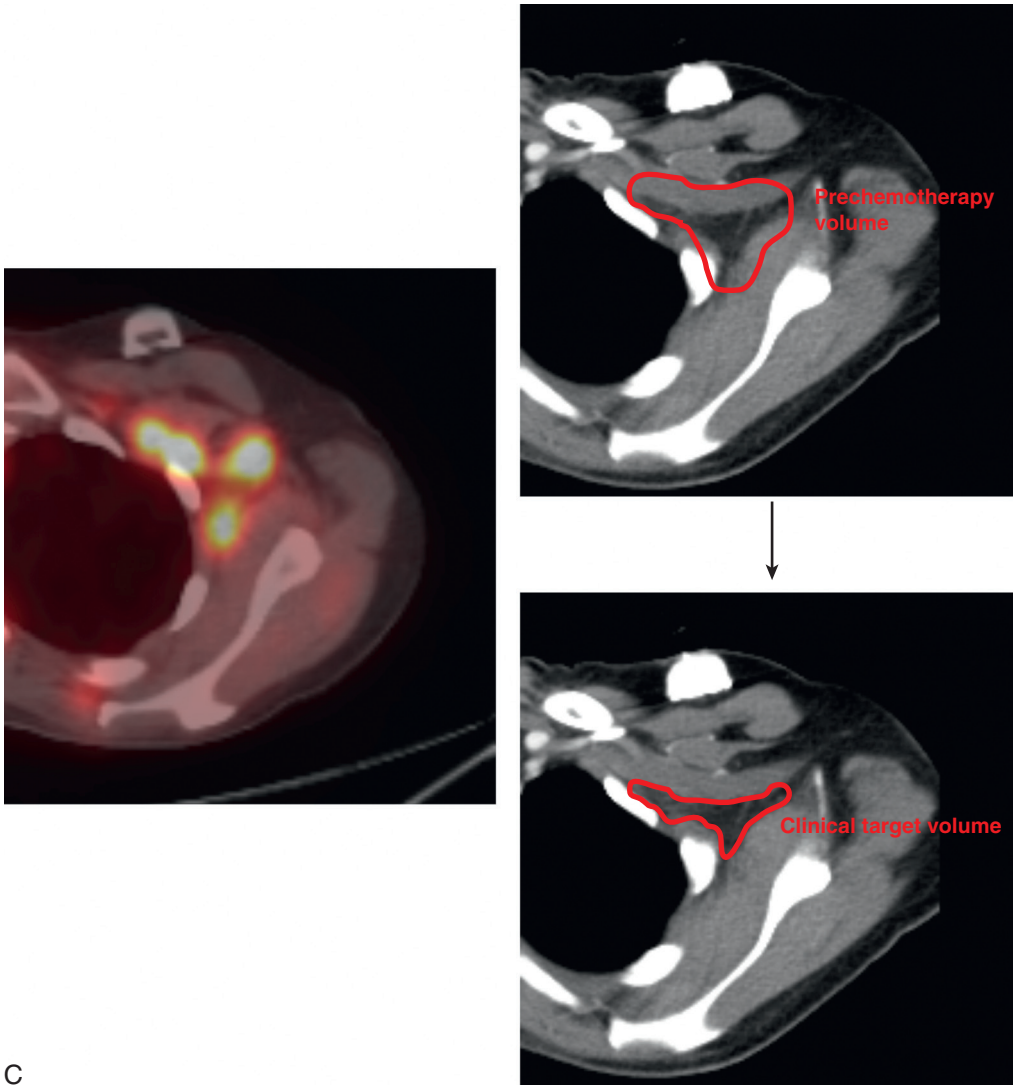


Figure 76-1, cont'd

alone with larger treatment fields and higher doses of radiation than currently employed. These include risks of second malignancies,[100-103] in particular, the risk of breast cancer in women irradiated at a young age,[104,105] and lung cancer among smokers,[106-108] and risks of cardiovascular disease.[109] Because of these concerns, investigators have explored the option of eliminating radiation therapy and treating patients with early-stage disease with chemotherapy alone. Table 76-8 summarizes randomized trials that had compared combined modality therapy with chemotherapy alone.[110-117] These trials varied in the study design, patient population, types of chemotherapy, and radiation fields employed. All but one trial showed a significant DFS, EFS, or freedom-from-progression benefit with the addition of radiation therapy.[110-114] This included the recently reported National Cancer Institute Canadian (NCIC) HD6 trial,[117] which showed that the radiotherapy-containing arms were associated with an improved 10-year failure-free survival rate (92% versus 87%, $p = 0.05$). This is despite the fact that extended-field radiation therapy alone, an approach that has been shown to significantly inferior to combined-modality therapy, was used in patients with low-risk disease. In the same trial, however, despite the improved failure-free survival, the radiotherapy-containing arm was associated with a significantly reduced 10-year OS (87% versus 92%, $p = 0.04$). Ten of the 24 deaths on the radiotherapy-containing arm were from second malignancy, which is likely related to the use of extended-field radiation therapy in patients with both low- and high-risk disease in this trial.

The Cochrane Haematological Malignancies Group recently conducted a meta-analysis,[118] in which five randomized controlled trials that compared chemotherapy alone with identical chemotherapy combined with radiotherapy for patients with stages I to II HL were included. The results showed that, in addition to a significant disease-control benefit favoring the combined-modality therapy approach, there was a highly significant overall survival benefit with the addition of radiation therapy (HR, 0.4; $p < 0.00001$). However, one main criticism of this analysis was the inclusion of trials that used inadequate chemotherapy. It therefore appears that less effective or abbreviated chemotherapy, or alternatives to ABVD designed to limit chemotherapy-related toxicity, is not acceptable when radiation therapy is omitted, and the addition of radiation therapy may allow the use of lower cumulative doses of doxorubicin or less toxic regimens. Toxicities associated with full course ABVD can be nontrivial, and these include myelosuppression, peripheral neuropathy, bleomycin lung toxicity, and cardiac toxicity.[119-121] A significantly increased excess cardiac

TABLE 76-8 Randomized Trials Comparing Combined Modality Therapy and Chemotherapy Alone in Early-Stage Hodgkin's Lymphoma

Institution	No.	Patient Population	Treatment Arms		MED F/U	Results	
						CMT	Chemo Alone
GATLA[114]	277	CS I-II (Included patients with unfavorable factors: age >45, >2 sites or bulky disease) 45% <16 years	CVPP × 6	30 Gy IFRT No RT	84 months	DFS: 71% OS: 89% *Favorable group:* DFS: 77% OS: 92% *Unfavorable group:* DFS: 75% OS: 84%	62% (p = 0.01) 82% 70% 91% 34% (p = 0.001) 66%
CCG[116]	829	Group 1: CS I-II without adverse factors* and without B Sx in CS II Group 2: CS I-II with adverse factors and CS III Group 3: CS IV	Group 1: COPP/ABV × 4 Group 2: COPP/ABV × 6 Group 3: intensive multidrug chemotherapy with GCSF support If CR If PR	 21 Gy IFRT No RT 21 Gy IFRT	92 months	*As-treated:* 10-yr EFS: 91.2% 3-yr OS: 97.1%	82.9% (p = 0.004) 95.9% (p = 0.5) ARM CLOSED
Tata Memorial Hospital[110]	251	CS I-IV (55% CS I-II 46% age <15 years 71% MC histology 15% bulky disease)	ABVD × 6 If CR	 RT† No RT	63 months	8-yr EFS: 88% 8-yr OS: 100%	76% (p = 0.01) 89% (p = 0.002)
MSKCC[115]	152	CS IA-IIB, CS IIIA (bulky disease excluded)	ABVD × 6	RT‡ No RT	60 months	5-yr FFP: 86% 5-yr OS: 97%	81% (p = 0.61) 90% (p = 0.08)
NCIC/ECOG[117]	405	CS I-IIA (bulky disease excluded) Low risk: LP/NS, age <40, ESR <50 and <3 sites High risk: all other	Low risk: High risk:	STNI ABVD × 4-6 ABVD × 2 + STNI ABVD × 4-6	11.3 years	(*Low risk:* STNI; *High risk:* CMT) 10-yr FFS: 92% 10-yr OS: 87%	 87% (p = 0.05) 92% (p = 0.04)
EORTC H9F[80]	771	CS I-II, favorable-prognosis	EBVP II × 6 If CR If PR	 36 Gy IFRT 20 Gy IFRT No RT 36 Gy IFRT ± 4 Gy	33 months	(36 Gy) 4-yr EFS: 87% (20 Gy) 4-yr EFS: 84%	(0 Gy) 70% ARM CLOSED

CCG, *Childhood Cancer Group;* CMT, *combined modality therapy;* CR, *complete response;* CS, *clinical stage;* CVPP, *cyclophosphamide, vinblastine, procarbazine, and prednisone;* DFS, *disease-free survival;* EBVP, *epiribicin, bleomycin, inblastine, prednisone;* EFS, *event-free survival;* EORTC, *European Organisation for Research and Treatment of Cancer;* ESR, *erthryocyte sedimentation rate;* GATLA, *El grupo argentino de tratamiento de la leucemia aguda;* Gy, *gray;* FFP, *freedom-from-prorgression;* IFRT, *involved-field radiation therapy;* LP/NS, *lymphocyte predominant/nodular sclerosis;* MC, *mixed cellularity;* MSKCC, *Memorial Sloan Kettering Cancer Center;* NCIC/ECOG, *National Cancer Institute-Canada/East Coast Oncology Group;* OS, *overall survival;* PR, *partial response;* STNI, *subtotal nodal irradiation;* yr, *year.*

**Adverse factors: hilar disease, >4 sites, LMA or bulky disease >10 cm.*

†IFRT 30 + 10 Gy boost for early-stage and EFRT 25 + 10 Gy boost for advanced-stage.

‡Modified extended-field RT in 83% of patients (91% received 36 Gy).

mortality has been demonstrated after ABVD without mediastinal irradiation.[120,121]

Elimination of Radiation Therapy Based on PET-Response

Convincing data on the high prognostic value of response to chemotherapy based on PET findings, especially for patients with advanced-stage disease,[53,122] has led to an increasing interest in the use of PET response (either early in the course of chemotherapy or at the end of chemotherapy) to identify patients in whom radiation therapy can be eliminated. Picardi et al conducted a randomized trial designed to evaluate whether radiation therapy can be safely eliminated if a complete response by PET scan is achieved after chemotherapy.[123] A total of 260 patients with stages I to IV HL with tumor mass greater than 5 cm were included in the study. One hundred and sixty patients became PET negative and had a more than 75% reduction in the tumor mass at the completion of six cycles of etoposide, epirubicin, bleomycin, cyclophosphamide, and prednisolone (VEBEP). These patients were randomized to 32 Gy of IFRT versus no further treatment. At a median follow-up of 40 months, there was a significant DFS benefit with the addition of consolidative radiation therapy (96% versus 86%, $p = 0.03$), suggesting that even in carefully selected patients based on optimal functional imaging response to chemotherapy, the omission of radiation therapy is associated with a higher relapse rate. However, this study is limited by the use of suboptimal chemotherapy.

In recent years, several randomized trials were designed to specifically address the elimination of radiation therapy in patients with early-stage HL based on PET response to modern chemotherapy.[87,124] In the EORTC/LYSA/FIL H10 trial, patients with favorable early-stage disease were randomized to the standard arm of three cycles of ABVD followed by INRT, versus the experimental arm of two cycles of ABVD followed by PET scan. If the scan was negative, patients received two additional cycles of ABVD and then no further treatment. If the PET scan was positive, patients received two cycles of dose-escalated BEACOPP, followed by INRT. For patients with unfavorable early-stage disease, the standard arm consisted of four cycles of ABVD followed by INRT, whereas patients on the experimental arm received two cycles of ABVD followed by PET scan. If the scan was negative, patients received four additional cycles of ABVD and then no further treatment. If the PET scan was positive, patients received two cycles of dose-escalated BEACOPP, followed by INRT. In the most recent interim analysis, for patients with PET-negative disease after ABVD, there were 9 events in the no radiotherapy arm versus 1 event in the radiotherapy arm (HR, 9.36) in the favorable group, and 16 events in the no radiotherapy arm versus 7 events in the radiotherapy arm (HR, 2.42) in the unfavorable groups. This led to the conclusion that the objective of non-inferiority of chemotherapy alone as compared with combined-modality therapy has not been met, and at the recommendation of an independent data monitoring committee, the experimental arms of no radiotherapy in both groups of patients were closed.

In United Kingdom RAPID trial,[125] patients with CS IA and IIA non-bulky HL underwent PET scan after three cycles of ABVD. If the scan was negative, patients were randomized to IFRT versus no further treatment. In the most recent update of this trial,[124] 571 patients had a PET scan following three cycles of ABVD. The Deauville Criteria was used to determine PET response: A score of 1 or 2 was considered negative (uptake less than or equal to mediastinal blood pool). A total of 426 patients (74%) were scored as PET-negative, and the remaining were scored as PET-positive and went on to receive IFRT. Among the 420 patients who were PET-negative randomized, 209 were randomized to the radiotherapy arm, though 26 of the patients did not receive radiotherapy. At a median follow-up time of 48.6 months, by intent-to-treat analysis, there was no difference between the radiotherapy versus no radiotherapy arm (3-year PFS 94.5% versus 90.8%, $p = 0.23$). By per-treatment analysis, however, there is a significant benefit in the radiotherapy arm (3-year PFS 97% versus 90.7%, $p = 0.03$). There was a nonsignificant trend toward lower survival in the radiotherapy arm (97.1% versus 99.5%, $p = 0.07$). However, among the seven deaths in patients randomized to the radiotherapy arm, five occurred prior to initiation of the radiotherapy.

Two ongoing trials conducted by the GHSG are exploring omission of radiotherapy by PET-response. The HD16 trial randomizes patients with low-risk early-stage disease to two cycles ABVD followed by 30 Gy IFRT irrespective of PET results after chemotherapy, versus two cycles ABVD followed by 30 Gy IFRT for only patients with positive PET after chemotherapy and no further therapy if PET is negative after chemotherapy. The HD17 trial randomizes patients with high-risk early-stage disease to two cycles of dose-escalated BEACOPP followed by two cycles ABVD (two-by-two regimen), followed by 30 Gy IFRT irrespective of PET results after chemotherapy, versus the same two-by-two regimen, followed by 30 Gy INRT only for patients with positive PET after chemotherapy and no further therapy if PET is negative.

Recommendation on Treatment for Early-Stage Hodgkin's Lymphoma

The optimal treatment for early-stage HL is in evolution. At this time, in patients with early-stage disease with favorable prognosis based on GHSH criteria (no bulky mediastinal mass or extranodal disease, 3 or fewer nodal sites, low sedimentation rate), two cycles of ABVD chemotherapy followed by ISRT to 20 Gy may be adequate.[87] In patients with unfavorable early-stage disease, four cycles of ABVD may be adequate, but 30 Gy of ISRT is needed after ABVD.[85]

Based on early results, there appears to be an approximately 7% gain in PFS with the addition of radiotherapy in patients who achieved PET-negative disease (less than or equal to mediastinal blood pool uptake) after chemotherapy. Preliminarily, the lower cure rate and toxicity of salvage therapy in the small proportion of patients with relapse disease needs to be weighed against the toxicity of INRT (which will be discussed later). However, longer follow-up of these recently completed or ongoing trials will be needed to account for late relapses in both arms.

PRIMARY TREATMENT FOR ADVANCED-STAGE HODGKIN'S LYMPHOMA

The introduction of the combination chemotherapy regimen, MOPP, in the mid-1960s substantially improved the curability of patients with advanced-stage HL.[4] The ABVD regimen was initially introduced as a second-line therapy in patients who had a poor response to, or relapse after MOPP chemotherapy.[126] Its role as primary treatment in newly diagnosed patients was subsequently substantiated by several randomized trials in patients with advanced-stage disease, showing that ABVD-containing regimens are associated with a higher failure-free survival than MOPP.[127-130] Results of an intergroup randomized trial comparing MOPP/ABV hybrid versus ABVD in advanced-stage HL showed that the addition of MOPP to ABVD did not confer any therapeutic benefit but did add to treatment-related toxicity.[131] ABVD is significantly less myelosuppressive, and it also does not carry the risk of

gonadal dysfunction and leukemogenesis. Currently, in the United States, ABVD is accepted by most as the standard systemic therapy for advanced-stage HL, which yields long-term failure-free survival of 60% to 65% and OS of 70% to 75%. To further improve treatment results, dose-escalated or dose-dense regimens for advanced-stage HL have been developed. The two major regimens, BEACOPP and its variants, and Stanford V, are discussed here.

Alternatives to ABVD

BEACOPP

The dose-escalated BEACOPP regimen (eTable 76-1), developed by the GHSG, yielded significantly higher survival outcome compared with conventional-dose regimens in the GHSG HD9 study.[132] In this three-armed trial, patients with stages IIB, IIIA, IIIB, and IV were randomized to eight cycles of COPP-ABVD, baseline-dose BEACOPP, or dose-escalated BEACOPP. In the most recent update of the study on 1196 evaluable patients, at a median follow-up of 111 months, the 10-year freedom-from-relapse rate was significantly higher in the dose-escalated BEACOPP arm than the baseline BEACOPP and COPP-ABVD arms (82%, 70%, and 64%, respectively, $p < 0.0001$).[133] The corresponding 10-year OS rates were 86%, 80%, and 75%, respectively ($p = 0.0005$). However, in the standard arm of this trial, COPP-ABVD, rather than modern ABVD, was used. Also, it was noted that patients on the dose-escalated BEACOPP arm had significantly higher 10-year cumulative incidence of acute myelogenous leukemia and myelodysplasia (3.2%, 2.2%, and 0.4%, respectively, $p = 0.03$).

In an attempt to reduce treatment-related toxicity, the GHSG explored the efficacy of modified versions of the BEACOPP regimen. The GHSG HD12 trial is a four-arm study for patients with bulky stage IIB and stages III to IV disease comparing eight cycles of dose-escalated BEACOPP with or without radiation therapy, versus four cycles of escalated and four cycles of baseline BEACOPP with or without radiation therapy. In the most recent update that included 1571 eligible patients, at a median follow-up of 69 months,[134] the 5-year FFTF, PFS, and OS of the entire cohort were 85.5%, 86.2%, and 91%, respectively. There were no significant differences in outcome between the two chemotherapy regimens, but less hematologic toxicities were observed in the arm that contained baseline BEACOPP.

The GHSG HD 15 trial compared right cycles of dose-escalated BEACOPP ($8B_{esc}$), six cycles of dose-escalated BEACOPP ($6B_{esc}$), or eight cycles of $BEACOPP_{14}$ ($8B_{14}$) a time-intensified variant of baseline BEACOPP baseline.[135] This study also evaluated the use of PET to select patients for chemotherapy alone (which will be discussed). At a median follow up of 48 months, the 5-year FFTF rates were 84.4%, 89.3%, and 85.4% in the $8B_{esc}$ $6B_{esc}$ $8B_{14}$ arms, respectively, and the 5-year OS rates were 91.9%, 95.3%, and 94.5%, respectively. There were more deaths from acute toxicity and more second malignancies in the $8B_{esc}$ arm. This led to the authors' conclusion that six cycles of dose-escalated BEACOPP is more effective and less toxic than eight cycles of the chemotherapy.

Variations of the BEACOPP regimen have also been investigated by other groups. The Gruppo Italiano per lo Studio dei Linfomi conducted a randomized trial comparing four cycles of dose-escalated BEACOPP followed by two cycles of baseline BEACOPP, ABVD, and the CEC hybrid regimen (cyclophosphamide, lomustine, vindesine, melphalan, prednisone, epidoxorubicin, vincristine, procarbazine, vinblastine, and bleomycin) for patients with stages IIB to IV HL.[136] Radiotherapy was administered to sites of bulky disease to 25.2 Gy, or to slowly or partially responding sites to 30.6 Gy. Among 295 evaluated patients, at a median follow-up of 41 months, those assigned to the BEACOPP arm had a significantly higher 5-year FFS and PFS compared with patients on the ABVD arm (65% versus 78%, $p = 0.036$ and 68% versus 81%, $p = 0.038$). Unlike the GHSG HD9 trial, however, a significant difference in OS was not observed, and this may be related to the relatively small size of the study, the limited follow-up time, and the different chemotherapy used in the standard arms of the two trials. It was noted, however, that the 5-year FFS of 65% in patients treated with ABVD on this trial was inferior to the outcome of a previous trial that included similar patients receiving ABVD, where a 5-year FFS of 78% was observed.[136] The Michelangelo, Gruppo Italiano Terapie Innovative nei Linfomi (GITIL) and Intergruppo Italiano Linfomi (IIL) cooperative groups conducted a randomized trial comparing six to eight cycles of ABVD versus four cycles of dose-escalated followed by four cycles of baseline BEACOPP as first-line therapy, with preplanned high-dose therapy as salvage.[137] At a median follow up of 61 months, BEACOPP was associated with a significantly higher 7-year FFP (85 versus 73%, $p = 0.004$) than ABVD, though differences in EFS (78% versus 71%, $p = 0.15$) and OS (89% versus 84%, $p = 0.39$) were not observed. Finally, the EORTC 20012 trial, an international multicenter study, compares four cycles of dose-escalated followed by four cycles of baseline-dose BEACOPP versus right cycles of ABVD in patients with stages III to IV disease. At a median follow up of 3.8 years, there was a significantly higher PFS rate in the BEACOPP versus the ABVD arms (83.4% versus 72.8%, $p = .005$). However, there were no EFS (69.3% versus63.7%, $p = 0.03$) or OS (90.3% versus 86.7%, $p = 0.2$) differences between the two arms.[138]

A number of ongoing or recently completed trials are addressing treatment deescalation in patients who achieved negative interim PET results.[139] For patients with early PET complete response, the GHSG HD18 is comparing six cycles versus four cycles escalated BEACOPP, the RATHL study compares ABVD with AVD, and the GELA AHL trials compares BEACOPP with standard ABVD. The HD0607 and HD0801 trials conducted by the GITIL and FIL are investigating radiation therapy versus no radiation therapy after six cycles of ABVD in patients with interim and final PET-negative results.

Stanford V

The Stanford V regimen is a 12-week, seven-drug regimen that is administered on a weekly basis (eTable 76-2).[140] It contains lower cumulative doses of mechlorethamine, Adriamycin, and bleomycin than MOPP and ABVD, respectively, to limit leukemogenesis, sterility, cardiac, and pulmonary toxicity. Patients with initial disease of 5 cm or larger or macroscopic splenic disease, which account for about 90% of the patients, receive 36 Gy of involved-field radiation therapy 2 weeks after the chemotherapy. In a report on 142 patients with stage III or IV or locally extensive mediastinal stage I or II HL, a 5-year FFP and overall survival of 89% and 96%, respectively, were achieved.[140] No secondary leukemia was observed at a median follow-up of 5.4 years, although one case of acute leukemia was reported in an earlier Eastern Cooperative Oncology Group (ECOG) pilot study using the same regimen on 45 patients.[82]

The importance of radiation therapy as part of Stanford V was highlighted by a multiinstitutional randomized trial from Italy.[141] In this study, 355 patients with bulky stage II or advanced-stage HL were randomized to receive ABVD, MEC hybrid, and Stanford V. In this study, radiation therapy was limited to patients with initially bulky disease (>6 cm) or with partial response to chemotherapy, and those with only two or more sites of disease. In the most recent update, at a median follow up time of 86 months, the 10-year failure-free survival

eTABLE 76-1 Schedule for the Dose-Escalated BEACOPP

		Days													
Drug	**Dose (mg/m²)**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**
Bleomycin	10	—	—	—	—	—	—	—	X	—	—	—	—	—	—
Etoposide	100	X	X	X	—	—	—	—	—	—	—	—	—	—	—
Doxorubicin	35	X	—	—	—	—	—	—	—	—	—	—	—	—	—
Cyclophosphamide	1200	X	—	—	—	—	—	—	—	—	—	—	—	—	—
Vincristine	1.4	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Procarbazine	100	X	X	X	X	X	X	X	—	—	—	—	—	—	—
Prednisone	40	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Note: The regimen repeated on day 22 for a total of eight cycles; filgrastim from day 8 of each cycle until the leukocyte count returned to normal; radiation therapy given for bulky disease of >5 cm.

eTABLE 76-2 Schedule of the Stanford V regimen

		Week											
Drug	**Dose (mg/m²)**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
Mechlorethamine	6	X	—	—	—	X	—	—	—	X	—	—	—
Doxorubicin	25	X	—	X	—	X	—	X	—	X	—	X	—
Vinblastine	6	X	—	X	—	X	—	X	—	X	—	X	—
Vincristine	1.4	—	X	—	X	—	X	—	X	—	X	—	X
Bleomycin	5	—	X	—	X	—	X	—	X	—	X	—	X
Etoposide	60	—	—	XX	—	—	—	XX	—	—	—	XX	—
Prednisone qod	40	X	X	X	X	X	X	X	X	X	X	X	X

Note: Patients with initial bulky disease (≥5 cm) received involved-field radiation therapy to 36 Gy.

in the ABVD, MEC hybrid, and Stanford V arms were 75%, 74%, and 49%, respectively ($p < 0.001$). Among patients randomized to receive Stanford V, the 10-year DFS rates were significantly higher in patients who received radiation therapy versus those who did not (76% versus 33%, $p = 0.004$).

Another multicenter trial, conducted by the United Kingdom National Cancer Research Institute, randomized 520 patients with poor risk early-stage and advanced-stage HL to six to eight cycles of ABVD versus Stanford V.[142] In this trial, specified indications for radiotherapy in the Stanford V arm was the same as the original regimen, although the decision on whether to irradiate was left up to teams in the individual centers. Overall, 73% of patients in the Stanford V arm received radiotherapy, which is lower than that in the original Stanford study (91%). The proportion of patients not receiving radiotherapy as specified was not reported. At a median follow-up of 52 months, there were no significant differences in 5-year PFS (76% versus 74%) and OS (90% versus 92%) between ABVD versus Stanford V.

Results of the ECOG 2496 comparing ABVD and Stanford V in patients with locally extensive and advanced-stage HL were recently reported by Gordon et al.[143] At a median follow up of 6.2 years, there was no difference in 5-year FFS between the ABVD versus Stanford V arms (74% versus 71%, $p = 0.32$) and no OS differences (88% versus 88%, $p = 0.86$). In this study, 75% of patients received radiotherapy in the Stanford V arm for disease >5 cm, whereas in the ABVD arm, 41% received radiation therapy for bulky mediastinal disease.

The Role of Radiation Therapy in Advanced-Stage Hodgkin's Lymphoma

The rationale for the addition of radiation therapy to combination chemotherapy in advanced-stage HL is based on the patterns of failure after chemotherapy, in which the majority of relapses are at the site of initial disease.[144,145] A number of randomized trials have been performed addressing the role of consolidative radiation therapy after chemotherapy in advanced-stage HL.[88,146-150] Summarized in Table 76-9 are some of the more recent randomized studies comparing combined-modality therapy versus chemotherapy alone, using the same chemotherapy regimens in both arms, for advanced-stage HL.[134,146,149-151] The results of these trials were largely negative for significant benefit with the addition of radiation therapy. The previously described study from Tata Memorial Hospital, which included patients of all stages, is the only study that showed a significant survival benefit of combined-modality therapy over chemotherapy alone.[110] On subgroup analysis, the survival benefit was limited to patients with advanced-stage disease. The 8-year overall survival for patients with stages III to IV disease was 80% in the chemotherapy alone arm versus 100% in the combined modality arm ($p = 0.006$). Other subgroups that appeared to especially benefit from radiation therapy in this trial included patients with B symptoms and younger age patients.

In the EORTC trial, patients with stages III to IV disease with a complete response to MOPP-ABV were randomized to receive either radiation therapy or no further treatment.[150] At a median follow-up of 79 months, there were no differences in 5-year EFS or OS. The 5-year cumulative risk of second malignancy was significantly higher in the 172 patients randomized to radiation therapy than the 161 patients randomized to no radiation therapy (7.8% and 4.0%, $p = 0.05$). However, among the patients with a partial response who received radiation therapy to a higher dose, the 5-year cumulative risk of second malignancy was only 3.2%, but the reason for the discrepancy is not entirely clear. The authors also separately reported results of the 227 patients with a partial response who went on to receive 30 Gy of consolidative radiation therapy with or without additional boost.[152] The 8-year EFS and OS rates were 76% and 84%, respectively, which were comparable to the treatment results of patients who had a complete response, leading to the conclusion that patients with a partial response after chemotherapy may benefit from radiation therapy.

One study analyzed the outcomes of nonrandomized consolidative involved-field radiotherapy given after an objective response to chemotherapy in 702 patients with advanced-stage or early-stage unfavorable HL.[153] Consolidative radiation therapy of at least 30 Gy was recommended for patients with incomplete response to chemotherapy or bulky disease at presentation, and was received by 300 of the 702 patients. With a median follow-up of 6.9 years, a significantly higher PFS (71% versus 86%, $p < 0.0001$) and OS rates (87% versus 93%, $p = 0.014$) were found in patients who received radiation therapy, despite the fact that there were significantly more

TABLE 76-9 Randomized Trials Comparing Combined Modality Therapy and Chemotherapy Alone in Advanced-Stage Hodgkin's Lymphoma

Institution	No.	Patient Population	Treatment Arms		MED F/U	Results	
						CMT	Chemo Alone
SWOG[146]	278	Stages III-IV	MOP-BAP × 6		8 years	5 yr-RFS: 74% 5 yr OS: 86%	66% ($p > 0.2$) 79% ($p > 0.2$)
			If CR →	20 Gy RT No RT			
GATLA[149]	151	Stages III-IV	CVPP × 3 →	CVPP × 3 (total 6) 30 Gy RT CVPP × 3	7 years	7-yr FFS: 45% 7-yr OS: 71%	21% ($p = 0.0016$) 58 ($p = 0.15$)
EORTC[150]	421 (333 randomized)	Stages III-IV (excluded stage IIIAs)	MOPP-ABV × 6-8		79 months	5-yr EFS: 84% 5-yr OS: 79% If PR: 5-yr EFS: 79% 5-yr OS: 87%	91% ($p = 0.35$) 85% ($p = 0.07$)
			If CR →	24 Gy RT No RT			
			If PR →	30 Gy RT			
GHSG (Borchmann 2011, JCO)	1670	Bulky Stage II, Stage III-IV	bulky sites esc. BEA × 8 →	RT to No RT	69 months	5-yr FFTF: 90.4%	5-yr FFTF: 87%
			bulky sites esc. BEA × 4/ BE × 4 →	RT to No RT			

bulky patients and patients with partial response in the radiation therapy cohort.

As previously described, one of the study questions of the GHSG HD12 study is the role of radiation therapy in advanced-stage HL.[134] At a median follow-up of 69 months, there was no significant difference in 5-year FFTF between the radiotherapy or no-radiotherapy arms (90.4% versus 87%, $p = 0.08$) after either eight cycles of dose-escalated BEACOPP or four cycles escalated and four cycles of baseline BEACOPP. On subgroup analysis, among patients with residual CT abnormality of >1.5 cm, there was a significant 5.8% (95% CI 1.0% to 10.7%) higher 5-FFTF in the radiotherapy arm. However, among patients with <1.5-cm residual disease after chemotherapy, there was no significant benefit with the addition of radiotherapy even among patients with initial disease of 5 cm or greater.

In the GHSH HD15 trial comparing eight cycles of dose-escalated BEACOPP, six cycles of dose-escalated BEACOPP, versus eight cycles of BEACOPP-14, radiation therapy was limited to patients with residual disease of 2.5 cm and with residual PET avidity. Kobe et al reported results of 311 patients from this trial who had residual disease of 2.5 cm and underwent postchemotherapy PET scanning.[154] Sixty-six patients (21%) were found to have residual PET avidity, 63 of whom received 30-Gy radiation therapy to the residual mass as per protocol. Among patients with at least 12 months of follow-up, the 1-year PFS for PET-negative patients and PET-positive patients were 96% and 85%, respectively ($p = 0.011$). Although the treatment outcome of patients with residual PET avidity who received radiation therapy was inferior to those with negative PET in this study, the results are far superior to those reported in other series for patients with PET residual disease after chemotherapy, with PFS rates ranging from 0% to 33%.[122,155] In the most recent update, the 4-year PFS in patients with complete response or those with PET-negative disease and partial response after chemotherapy and did not receive radiation therapy were 92.6% and 92.1%, respectively.[135] As previously described, the HD0607 and HD0801 trials conducted by the Gruppo Italiano Terapie Innovative nei Linfomi (GITIL) Fondazione Italiana Linfomi (FIL) randomized patients with interim and final PET-negative results to radiation therapy versus no radiation therapy, although final results are not yet available.

Optimal Radiation Dose and Field Size

There are limited data on the optimal dose and appropriate radiation treatment field after chemotherapy in advanced-stage HL. Randomized data are not available comparing radiation doses or fields as part of combined-modality therapy in advanced-stage HL. An earlier GHSG study combined data from two of the randomized trials on patients with stages I to III disease, with or without bulk, and found no differences in FFTF and OS between 20 Gy, 30 Gy, and 40 Gy of consolidative radiation therapy.[148] The radiation dose employed in several more recent trials on advanced-stage HL varied. In general, initially nonbulky sites, if treated, received to 20 Gy to 30 Gy, initially bulky sites received 30 Gy to 36 Gy and sites with partial response were treated to 30 Gy to 40 Gy.[132,136,142,150,153-155]

The treatment fields that have been used in trials are also variable. For instance, in the EORTC trial, the protocol mandated irradiating all initially involved areas (except for bone marrow) and that both the spleen and the paraaortic nodes be included in the treatment field even if only one of the sites were involved.[150] Patients also received low-dose whole lung or whole-liver irradiation if disease was initially present at these sites. Although referred to as "involved-field," patients can be treated to a large volume because of their disease extent. Other groups have restricted the radiation treatment field to initially bulky sites. In both the Stanford V and the original BEACOPP regimens in the GHSG HD9 trial, only sites that were initially 5 cm or greater were included in the radiation field.[132,140] With more effective systemic therapy, availability of functional imaging to assess response to systemic therapy, and concerns with toxicity associated with large field radiation therapy, there are further efforts to limit the field size if radiation therapy is to be given. In the HD15 trial, for patients receiving radiation therapy, the treatment field was limited to postchemotherapy residual masses. Patterns of failure were recently reported by Eich et al. Among the 175 patients who received radiotherapy to 30 Gy to the PET-positive site(s), 28 patients relapsed. Twelve (42%) patients had an "infield" relapse, 8 (29%) patients had a relapse outside of the irradiated site, and a further 8 (29%) patients had "in- and outfield" relapse.[156]

Recommendation on Treatment of Advanced-Stage Hodgkin's Lymphoma

In the United States, six to eight cycles of ABVD is still considered by most as the standard systemic therapy for advanced-stage HL. Dose-escalated BEACOPP has been shown to result in a significant survival advantage over conventional-dose regimens (although standard ABVD was not used in the GHSG HD9), but it is also associated with substantial toxicity. Dose-reduced variants of BEACOPP have been developed and tested against ABVD, showing an improved freedom-from-progression, but at the expense of increased toxicity and no difference in OS. Results of ECOG 2496 showed no difference between Stanford V and ABVD.[143] The use of early PET response in identifying patients for treatment escalation or deescalation in patients with advanced-stage disease is addressed by a number of ongoing trials.

Routine addition of radiation therapy after chemotherapy in patients with advanced-stage disease is not supported by available data. However, in selected cases, including initially bulky disease or lack of complete response to chemotherapy, there may be a role for consolidative radiation therapy. In the context of more effective, modern systemic therapy and the availability of functional imaging to assess response, if the decision is to proceed with radiation therapy, it is reasonable to limit the radiation treatment field to initially bulky sites and postchemotherapy residual disease. With the more restricted fields to high-risk areas, doses of 30 Gy to 36 Gy should be considered.

PRIMARY TREATMENT FOR NLPHD

In the REAL and WHO classification systems, NLPHD is classified as a distinct entity based on morphologic and immunophenotypic features.[39,40] Clinically, it is characterized by a male predominance, older age at diagnosis of 30 years to 50 years, peripheral nodal presentation with seldom mediastinal, liver, spleen, or bone marrow involvement, predominantly early-stage disease, an indolent clinical course, and late, multiple relapses.[47,157-161] Because of its rarity, comprising only about 5% of all cases of HL, there is a lack of randomized data in guiding its management, which range from watch and wait,[158] surgery alone,[162] radiation therapy with or without chemotherapy,[157-160,163-165] or immunotherapy.[166-168] Observations have been made that ABVD may not be as effective in patients with NLPHD, and alkylating-agent containing regimens may be a better choice when chemotherapy is indicated,[157,169] although data from British Columbia suggested that ABVD may be associated with a better outcome. Because NLPHD is rarely fatal, and the main cause of death in these patients is

treatment-related rather than disease-related,[157,158,161,168] it is sensible to choose a modality with well-established effectiveness while limiting the treatment exposure of these patients. Several series have reported on results of radiation therapy for early-stage NHLPD, with relapses occurring in 20% to 25% of patients, typically at sites outside of the irradiated field.[157,160,164,165,170] However, patients tend to remain responsive to further therapy despite multiple relapses.[158] The use of more limited treatment fields such as involved-field or regional-field radiation therapy to 30 Gy to 36 Gy did not appear to compromise treatment outcome compared with the use of more extensive fields.[160,165] In patients with neck or axillary involvement, the mediastinum, which is rarely involved, can be blocked, thereby avoiding exposure of the lungs and heart to radiation. For limited-stage NLPHD where radiation therapy is often the sole modality, the GTV should be readily visualized during simulation. The ILROG ISRT guidelines recommend that in this situation, the CTV should be more generous because microscopic or subclinical disease is more likely to be present without chemotherapy.[96]

REFRACTORY AND RECURRENT DISEASE

The standard salvage therapy for patients who are refractory, or relapsed, after a short initial remission to chemotherapy is high-dose therapy with autologous bone marrow or stem-cell transplantation. Two randomized trials compared high-dose therapy with bone marrow or hematopoietic stem cell rescue versus conventional-dose chemotherapy as salvage for patients with refractory to or relapsed HL after chemotherapy.[171,172] The British National Lymphoma Investigation group prospectively randomized 40 patients to either high-dose carmustine (BCNU), etoposide, cytarabine, melphalan (BEAM) followed by autologous bone marrow transplantation or mini-BEAM.[172] The inclusion criteria were lack of complete response after MOPP or similar regimen, or relapsed disease either within 1 year, or disease failure after two or more chemotherapy regimens. At a median follow-up of 34 months, 3-year actuarial eventful survival of the two arms were 53% and 10%, respectively ($p = 0.025$) and PFS were 88% and 35%, respectively ($p = 0.005$), favoring the high-dose therapy arm. The GHSG conducted a similar study comparing high-dose BEAM followed by autologous stem-cell transplantation and dexamethasone with conventional dose BEAM.[171] Only patients with chemosensitive disease were included in the trial. At a median follow-up of 39 months, the FFTF of the two arms were 55% and 34%, respectively ($p = 0.019$). Significant survival differences were not detected in either of the two trials, however.

One of key factors that influences outcome is chemosensitivity to second-line cytoreductive chemotherapy prior to the high-dose therapy and transplantation. Other factors that have been shown to be of prognostic significance include duration of complete response to initial treatment,[173] extranodal disease,[173,174] constitutional symptoms[74,173,175] or bulky disease[176] at the time of relapse, and Hasenclever index.[177]

In recent years, CD30, a cell surface protein expressed on the RS Hodgkin cells, has emerged as a therapeutic target for patients with relapsed or refractory HL. Brentuximab vedotin, an antibody-drug conjugate (ADC) that selectively delivers monomethyl auristatin E, an antimicrotubule agent, into CD30-expressing cells, was shown in a Phase I study to induce durable objective responses and result in tumor regression for most patients with relapsed or refractory CD30-positive lymphomas.[178] In a subsequent Phase II study,[179] the efficacy and safety of brentuximab vedotin were evaluated in patients with relapsed or refractory HL after autologous stem-cell transplantation. A total of 102 patients were treated with brentuximab vedotin 1.8 mg/kg by intravenous infusion every 3 weeks to a maximum of 16 cycles. The overall response rate was 75% with a complete remission rate of 34%. Based on these results, brentuximab vedotin was approved by the Food and Drug Administration for patients who have relapsed after autologous stem cell transplantation (ASCT) or experiencing refractory or relapse disease after at least two prior multiagent chemotherapy regimens in patients who are deemed not to be ASCT candidates. Trials are also currently ongoing exploring brentuximab vedotin combined with second-line chemotherapeutic agents for salvage, as part of consolidation post-ASCT, and as part of frontline therapy in newly diagnosed patients.

Role of Radiation Therapy Before or After High-Dose Therapy

Further relapses after high-dose therapy tend to occur at sites of initial relapsed disease.[180] The role of involved-field radiation therapy given either before or after high-dose therapy have not been addressed prospectively by randomized trials, but retrospective studies have indicated that the addition of radiation therapy may contribute to improved outcome. In one study from Stanford, subgroups of patients who significantly benefited from involved-field radiation therapy given either before or after the transplantation included patients with relapsed stages I to III disease and patients who did not receive prior radiation therapy.[81] In a study from University of Chicago, the use of involved-field radiation therapy in conjunction with high-dose therapy significantly improved local control of all sites of disease.[181] Patients with persistent disease following high-dose therapy had significantly improved PFS (40% versus 12.1%, $p = 0.04$). Wendland et al reviewed 65 patients with refractory or relapsed HL who underwent high-dose therapy and transplant.[182] Twenty-one patients received IFRT, whereas 44 patients did not receive radiation therapy. Half of the patients in the no IFRT group (22 of 44) died compared with 23.8% (5 of 21) of patients in the IFRT group, which was of borderline significance ($p = 0.06$). Kahn et al, in a study examining the role of IFRT in patients with HL and non-HL receiving transplant, found that patients who did not receive IFRT had a 2.09 relative risk of death, which was of borderline statistical significance on multivariable analysis ($p = 0.066$).[182] A study from the University of Rochester on 62 patients who underwent ASCT for relapsed or refractory HL found improved 3-year OS (69.6% versus 40%, $p = 0.05$), disease-specific survival (82.1% versus 57.6%, $p = 0.08$), and local control (94% versus 69%, $p = 0.03$) among patients who received IFRT posttransplant.[183] Results of these retrospective series, however, need to be interpreted with caution because of differences in characteristics of patients who did and did not receive radiation therapy. For example, patients who were offered radiation therapy tend to have bulkier disease or chemotherapy refractory disease, whereas patients who did not receive radiation therapy may have more disseminated disease.

The optimal temporal relationship between radiation therapy and high-dose therapy is unclear. In patients with persistent disease after cytoreductive chemotherapy, radiation therapy given before transplantation can allow further disease debulking. Furthermore, irradiation pretransplantation avoids exposure of newly engrafted stem cell to radiation, which may increase the risk of myelodysplasia and leukemia. This is especially relevant in patients with pelvic disease requiring radiation therapy to a large volume of bone marrow. In these patients, stem-cell mobilization or bone marrow harvest should be performed before initiation of pelvic irradiation. Delivery of radiation therapy before transplantation, however, can increase peritransplant morbidity such as pneumonitis and veno-occlusive disease. Also, there is a risk of systemic

disease progression during the time of the radiation therapy with the delay of the high-dose therapy.

Limited Relapse After Chemotherapy

A small proportion of patients who relapsed after chemotherapy can be successfully salvaged with conventional-dose salvage chemotherapy or radiation therapy. A number of series showed that in selected patients with favorable features, salvage rates as high as 80% can be achieved without exposing patients to high-dose therapy.[97,184-188] Potential candidates for conventional dose-salvage therapy include patients with initial remission duration of 1 year or longer, limited nodal relapse without extranodal disease, and absence of constitutional symptoms at relapse. In one series of 28 patients with limited nodal relapse after chemotherapy, the combination of salvage chemotherapy and radiation therapy yielded significantly superior outcome than radiation therapy alone.[186] In patients who received combined modality salvage therapy, the 7-year freedom from further relapse was 93% and the OS was 85%, whereas the corresponding actuarial estimates in patients treated with radiation therapy alone were significantly lower at 36% ($p = 0.002$) and 36% ($p = 0.03$), respectively. These data suggest that in carefully selected patients with favorable criteria at relapse, salvage with conventional-dose therapy can be considered, thereby sparing patients the toxicity of high-dose therapy.

TECHNIQUES OF RADIATION THERAPY

Radiation therapy is one of the most effective modality for the treatment of HL. Radiation therapy for HL has evolved from two-dimensional treatment planning, with field set-up mostly based on bony landmark to extensive treatment fields, to conformal therapy with improved image guidance to restricted treatment volumes.

Modern Conformal Therapy

Although three-dimensional conformal therapy is currently the most widely adopted radiation technique, there are emerging data on the use of newer, more sophisticated techniques, including IMRT and proton beam therapy for HL.

IMRT uses multiple beams over the targeted volume to provide a highly conformal radiation dose distribution. Dosimetric studies have shown IMRT plans to produce the most conformal high-dose distribution, significantly better PTV coverage and greater protection of the heart, coronary arteries, esophagus, and spinal cord, though at the expense of a greater volume of normal tissue receiving low radiation doses.[189-192] In a dosimetric study reported by Fiandra et al,[191] five different treatment techniques in a cohort of young women with HL were compared: three-dimensional conformal radiation therapy (3D-CRT), and four different IMRT solutions, including single-arc volumetric-modulated arc therapy (VMAT, single-arc), B-VMAT ("butterfly", multiple arcs), helical tomotherapy (HT) and Tomodirect (TD), a rapid, low-modulation solution of the tomotherapy. The B-VMAT technique, developed to reduce low doses radiation exposure to lungs and breasts, and consists of two coplanar arcs of 60 degrees (gantry starting angles 150 degrees and 330 degrees) and one non-coplanar arc of 60 degrees, was found to be associated with the lowest mean doses to the lungs and breasts. When INRT rather than IFRT was employed, there was no difference in cardiac structures sparing between three-dimensional conformal therapy and IMRT approaches. Paumier et al reported on outcome of 32 patients with early-stage HL treated with INRT with IMRT technique to a median dose of 40 Gy. Despite the high prescribed dose, the median heart V30 and lung V20 were 15.5% and 28.6%, respectively, and the median mean heart and lung doses were 4.8 Gy and 15.1 Gy, respectively. There was one in-field relapse and two out-of-field relapses at a median follow up of 60 months. One patient developed grade-3 radiation pneumonitis and there were no cardiac events at the time of last follow-up.

IMRT can play an especially important role in selected cases, including extensive chest wall involvement where conventional techniques would result in exposing large volumes of lungs in the irradiated field, or in the retreatment setting where there is significant dose limitation to vital structures such as the spinal cord. Goodman et al reported on their experience using IMRT for extremely large mediastinal masses or in patients with prior radiation therapy to the mediastinum.[193] In these special case scenarios, the use of IMRT resulted in not only improved PTV coverage, but also lower mean doses to the lungs.

Another modern conformal technique is proton therapy, in which charged particles deposit most of their energy at a proportional depth, resulting in a characteristic dose distribution known as the Bragg peak. With the addition of multiple energies, a spread-out Bragg peak can be created such that the target can be covered by a limited number of fields. Investigators from the University of Florida reported on dosimetric outcome of 10 patients with stages I to IIIB HL treated with INRT with proton beam technique.[194] Compared with 3D-CRT, proton therapy led to a median reduction of body V4 (total body exposed to 4 Gy or higher) by 51% ($p = 0.0098$), and compared with IMRT, a median reduction by 59% ($p = 0.002$). Proton therapy also provided the lowest mean doses to the heart, lungs, and breasts. Early results of 16 patients treated with involved-node proton therapy from the same institution were recently reported. At a median follow-up of 32 months, one patient with initial stage IIB disease relapsed both in and out-of-field, and one patient developed primary mediastinal large B-cell lymphoma. Proton beam therapy therefore appears to be associated with favorable dosimetric outcome and preliminary clinical outcome data are promising. However, major limitations of proton therapy at this time include the complexity and uncertainty of the treatment planning, costs, and access to photon facilities.

The Role of PET in Guiding Radiation Planning

Data from PET-CT are increasingly incorporated into radiation therapy decision making and in the radiation planning process. A number of studies have investigated the impact of PET-CT data in target volume definition for HL radiation therapy planning. Hutchings et al identified 30 patients with HL treated with involved field.[195] All patients had prechemotherapy PET-CT scan, although only the CT component was used for planning purposes. When the PET data was incorporated retrospectively in the planning, the involved field was increased in 7 patients (23%) and decreased in 2 patients (7%). Girinsky et al fused the prechemotherapy PET scan with the post-chemotherapy CT planning scan in 30 patients with HL treated with INRT.[196] In 11 of the 30 patients (36%), the PET scan identified involved nodal disease that was missed by the CT, resulting in changes of the radiation treatment field. It was also noted that on average only 25% of the lymphoma volume on CT showed FDG avidity on PET, leading to the conclusion that the target must include both CT-positive and PET-positive disease. Similarly, Terazakis et al found that the incorporation of PET data in the treatment planning of 29 patients with hematologic malignancies to 32 sites resulted in increase in PTV in 47% and reduced PTV in 40% of the planned sites.[197] These data suggest that PET/CT is the most accurate imaging

TABLE 76-10 Treatment Algorithm for Patients with Early-Stage Hodgkin's Lymphoma

CLASSICAL HODGKIN'S LYMPHOMA, FAVORABLE-PROGNOSIS
Two to four cycles of ABVD (restaging PET/CT scan after two to three cycles and at the end of chemotherapy)*
Involved-node or involved-site radiation therapy 3 to 4 weeks postchemotherapy to 20 Gy to 30 Gy*
CLASSICAL HODGKIN'S LYMPHOMA, UNFAVORABLE-PROGNOSIS
Four to six cycles of ABVD (restaging PET/CT after two to three cycles and at the end of chemotherapy)
Involved-node or involved-site radiation therapy 3 to 4 weeks postchemotherapy to 20 Gy to 30 Gy
NODULAR LYMPHOCYTE PREDOMINANT HODGKIN'S LYMPHOMA
Involved-node or involved-site radiation therapy alone to 30 Gy to 36 Gy

**The use of two cycles of ABVD and 20-Gy IFRT limited to patients with early-stage disease without risk factors as per GHSG criteria.*

TABLE 76-11 Treatment Algorithm for Patients with Advanced-Stage Hodgkin's Lymphoma

CLASSICAL HODGKIN'S LYMPHOMA
Six to eight cycles of ABVD (restaging PET/CT after two to three cycles and at the end of chemotherapy)
Other regimens, depending on institutional experience, include Stanford V and dose-escalated BEACOPP and its variants
Consolidative radiation therapy to 30 Gy to 36 Gy to sites of initial bulky disease (>5 cm) or without complete response to chemotherapy
NODULAR LYMPHOCYTE PREDOMINENT HODGKIN'S LYMPHOMA
Alkylating-agent based chemotherapy regimen (e.g., chlorambucil, vinblastine, procarbazine and prednisolone [ChlVPP] or rituximab, cyclophosphamide, vincristine, prednisone [R-CVP])

method for determining disease extent in HL, Thus, up-front PET/CT is considered mandatory for INRT design.[96]

Respiratory Motion Adaptation Techniques

As radiation treatment fields become more conformal, it is important to take into account respiratory motion, especially when treating sites that are subject to the effect of diaphragmatic motion, such as the mediastinum, lungs, pericardial nodes, or spleen. Breathing adaptation techniques, in the simplest form, involves covering the entire span of respiratory motion of the target on a four-dimensional CT scan. With respiratory gating, the radiation beam is turned on only during a prespecified period of the respiratory cycle, such that organ motion within the radiation field is limited to the motion taking place during the prespecified beam on time. Results of deep inspiration breath-hold (DIBH) techniques have been reported in patients with HL,[198-200] all demonstrating reduced doses to the heart and lungs. The ILROG ISRT/INRT guidelines encourage the use of four-dimensional imaging or DIBH technique for disease sites that are significantly affected by respiratory motion. In addition, when highly conformal techniques such as IMRT are used, adoption of strategies that account for respiratory motion is deemed especially important.

TREATMENT ALGORITHM, CHALLENGES, AND FUTURE DIRECTIONS

The treatment algorithm for patients with early-stage and advanced-stage HL are outlined in Tables 76-10 and 76-11, respectively. In patients with favorable, early-stage disease, cure rates of more than 90% have been achieved. The key challenge in the management of these patients is to identify ways to limit late effects of HL therapy because multiple studies have demonstrated that over time, there is a significantly increased risk of mortality from causes other than HL, with second malignancies and cardiac disease being the two leading problems.[73]

There are increasing data available showing that these late effects are significantly related to radiation dose and volume.[103,105,107,201-204] A significant radiation dose-response relationship has been shown for the development of breast cancer,[104,105,202] lung cancer,[106,107] and gastric cancer[203] in HL survivors. Data are also available showing a significantly reduced risk of breast cancer with more restricted treatment fields.[103,204] These data justify current efforts of reducing radiation dose and field sizes in the treatment of early-stage HL. For patients with unfavorable prognosis disease or advanced-stage disease, the challenge remains further improving the cure of HL. More effective multiagent chemotherapy regimens are being developed and tested in clinical trials. In addition to traditional chemotherapy, new drugs and targeted immunotherapy, including brentuximab vedotin may benefit not only patients with chemotherapy refractory disease but also may serve as adjuncts to chemotherapy with curative intent.[205]

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CHAPTER

77 Non-Hodgkin's Lymphoma



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EPIDEMIOLOGY AND INCIDENCE

There were an estimated 70,800 new cases and 18,990 deaths in the United States in 2014. The incidence is increasing in many countries, including the United States. Most common types are diffuse large B-cell (~30%) and follicular lymphoma (~25%). The etiology is uncertain, but immunosuppression and infectious agents, including Epstein-Barr virus (EBV), human T-lymphotrophic virus-1 (HTLV-1), and *Helicobacter pylori* contribute.

BIOLOGIC CHARACTERISTICS

Lymphomas are a diverse group of diseases clinically, pathologically and genetically.

Prognosis relates to histologic subtype, age, extent of disease, and treatment.

STAGING EVALUATION

Pathologic diagnosis is performed by experienced hematopathologist. History and physical examination; blood count; lactate dehydrogenase (LDH); bone marrow biopsy; computed tomography (CT) of neck, thorax, abdomen and pelvis; and fludeoxyglucose-positron emission tomography (FDG-PET) scan are taken.

PRIMARY THERAPY

Stages I and II follicular and marginal zone lymphomas are treated with involved-site radiation therapy (RT), expecting a >95% local control rate and 50% long-term disease free survival. Stages III and IV follicular and marginal zone lymphomas are not cured with currently available therapy; however, chemotherapy and RT are effective in controlling the disease.

Stages I and II diffuse large B-cell lymphoma and other aggressive histology are treated with combined-modality therapy, expecting a cure in 70% to 90% of patients depending on age and tumor burden. Stages III and IV diffuse large B-cell lymphoma and other aggressive histology are treated primarily with doxorubicin-based chemotherapy with the addition of adjuvant RT in selected cases.

SALVAGE THERAPY

Diffuse large B-cell lymphoma and other aggressive histology lymphomas refractory to chemotherapy or relapsing after previous complete response is treated with high-dose chemotherapy and autologous stem-cell transplantation (ASCT) when possible. Patients with bulky disease or incomplete response to salvage chemotherapy receive local RT to sites of disease as planned-combined salvage treatment. RT may be delivered before or after ASCT. Patients so treated have a cure rate of 30% to 50%.

PALLIATION

Palliative low dose RT (4 Gy in two fractions) for small cell lymphomas (follicular, mantle cell, and marginal zone lymphomas) provides local control in two thirds of patients and relief of symptoms in almost all. Diffuse large cell lymphomas are also responsive to RT, but results are not as good as in small cell lymphomas particularly if the disease is refractory to chemotherapy and bulky. Doses of >35 Gy may be required to achieve local control but symptom relief is common.

INTRODUCTION

Non-Hodgkin's lymphoma (NHL) encompasses a heterogeneous group of neoplasms of the lymphoid system. The common factor is the malignant cell, a lymphocyte. Beyond that, malignant lymphomas differ in their etiology, pathogenesis, genetics, clinical manifestations, patterns of spread, response to treatment, and survival. Both incidence and mortality of NHL are increasing worldwide. The increase in incidence has been related to environmental factors including occupational exposures and HIV infection. The most prevalent lymphomas in North America are of B-cell origin with follicular lymphomas and diffuse large B-cell lymphomas. Lymphomas presenting in extranodal sites account for 20% to 45% of all cases. Primary extranodal lymphomas with their propensity to present with localized disease are of special interest to radiation oncologists.

The management of NHL is primarily influenced by histology and stage. RT achieves local tumor control and is curative for those with truly localized disease. Chemotherapy is used in generalized disease. Although RT has traditionally been the treatment of choice for localized disease and remains the principal treatment modality for localized indolent lymphomas (follicular lymphoma and mucosa-associated lymphoid tissue [MALT] lymphoma), combined-modality therapy is the current standard approach for patients with localized large cell lymphomas. Chemotherapy has the potential to cure patients with large cell lymphomas and high-grade lymphomas, but currently available agents are not curative for indolent lymphomas. The management of patients with indolent lymphomas presents a challenge, given that many patients present with generalized disease, currently no curative systemic therapy is available, and prolonged survival necessitates careful application of treatment.

ETIOLOGY AND EPIDEMIOLOGY

The American Cancer Society estimates that in 2014, 70,800 new cases of NHL were diagnosed and 18,990 people died of this cancer in the United States.[1] The incidence of NHL has

been increasing in the United States and worldwide.[2-4] In many developed countries, there was a 2% to 4% per year rise in the incidence of NHL from the 1970s to 1990s, but this rate stabilized over the last two decade. In the United States, the annual rise in incidence rate had slowed to 1% to 2% in the 1990s[3,4] and was more notable in older persons. The cause of the increase in NHLs may be the result of an aging population, increase in immunosuppression (HIV infection and iatrogenic), spread of infectious agents such as HTLV-1 and EBV, increased use of chemicals, or improved pathologic diagnosis leading to more defined cases.

The epidemiology of certain histologic subtypes of lymphomas follows distinct patterns related to the epidemiology of the putative causative agent and any environmental cofactors. The classical example is Burkitt lymphoma in Africa, with the endemic role of EBV and the contribution of immunosuppression resulting from malaria infection.[5] Similarly, EBV-related T/natural killer (NK) cell lymphoma of the nasal region is more frequent in oriental populations of south Asia.[6,7] Adult T-cell leukemia/lymphoma caused by HTLV-1 is endemic in the Caribbean and southern Japan.[8] The frequency of HIV-related lymphomas is proportional to the HIV infection rate in the population, explaining the observation of high incidence rates in large urban cities, and a role of Kaposi's sarcoma-associated herpes virus.[9] MALT lymphomas of the stomach are seen more frequently in regions where *H. pylori* infection is endemic.

Despite an increasing body of knowledge on the genetic and phenotypic events underlying the development and progression of NHL, the causative agent has not been identified in the majority of cases. The putative causative agents and associated conditions with a predisposition for the development of NHL are listed in Table 77-1. There are some genetic predispositions to the development of NHL, including specific human leukocyte antigen (HLA) allele associations.[10,11] Changes in the immune state, either immunosuppression or autoimmune disease with immune stimulation can predispose to NHL. The immunosuppression can be primary, that is, inherited (severe combined immunodeficiency syndrome), secondary to retrovirus infection (HIV), or iatrogenic (following solid organ or bone marrow transplantation). The incidence of NHL in individuals who are HIV positive has declined since the late 1990s as a result of highly effective antiretroviral therapy.[12,13] Autoimmune diseases such as Sjögren's syndrome, rheumatoid arthritis, and celiac disease are also associated with an increased risk of NHL.[14]

Infectious agents have been shown to be etiologic factors in NHL (e.g., *H. pylori* in gastric MALT lymphomas and *Chlamydia psittaci* in ocular adnexal lymphomas).[15] There is a large variation in Chlamydia positivity rate in orbital lymphomas depending on geographic location.[16,17] Viruses have been implicated, including EBV,[5] HTLV-1, human herpes virus 8 (HHV-8), and hepatitis C virus (HCV). HTLV-1 carriers have a 2% cumulative risk of developing adult T-cell leukemia/lymphoma, and it is a major public health problem in some parts of the world where the seropositivity rate is high.[8] HHV-8 virus sequences have been implicated in primary effusion lymphomas and multicentric Castleman's disease. Hepatitis C infection is also a predisposing factor for some B-cell lymphomas, often in association with essential mixed cryoglobinemia.[18]

Epidemiologic studies suggest an association with environmental factors including industrial chemicals, rural residence possibly linking to use of pesticides or other agricultural chemicals, hair dyes,[19] diet,[20] and obesity.[21] Small excess risk was also found in atomic bomb survivors for males but not for females,[22] whereas minimal or no risk was found for low dose x-ray exposures (see Table 77-1).

TABLE 77-1 Causative Agents and Associated Conditions with a Predisposition to NHL

IMMUNODEFICIENCY
Congenital: Severe combined immunodeficiencies, ataxia-telangiectasia
Acquired: Organ or hematopoietic stem-cell transplantation, HIV infection
GENETIC PREDISPOSITION
Variants within 6q21 (HLA)
TNF G308A polymorphisms
AUTOIMMUNE DISEASES
Sjögren's syndrome
Hashimoto's thyroiditis
Celiac disease
Rheumatoid arthritis
Systemic lupus erythematosus
VIRAL AGENTS
Epstein-Barr virus
HTLV-1
Human herpes virus type 8
Hepatitis B and C
BACTERIAL
Helicobacter pylori (gastric lymphoma)
Chlamydia psittaci (orbital lymphoma)
Borrelia burgdorferi (cutaneous lymphoma)
Campylobacter jejuni (alpha heavy chain disease)
DRUGS
Alkylating agents
Other immunosuppressive drugs
PESTICIDES
Phenoxy herbicides
Organophosphate insecticides
Fungicides
SOLVENTS AND OTHER CHEMICALS
Benzene
Trichloroethylene
Hair dyes
DIET
N-nitroso compounds
Fat
Overweight/obesity

PREVENTION AND EARLY DETECTION

With a better definition of environmental causative factors for NHL and ongoing studies to delineate risk factor profiles,[23] it is expected that preventive strategies will be developed. For adult T-cell leukemia/lymphoma, initiatives are being implemented to reduce the disease burden in susceptible populations, the most important being the control of breast feeding to prevent maternal-fetal transmission of the HTLV-1 virus. Other promising areas of prevention currently include heightened awareness of potentially toxic agents and the development of improved products (chemicals and hair dyes). Genetic tests that aim to identify persons at higher risk of developing lymphoma are under investigation.[11,24] For viral agents, the development of vaccines is under active study.[25] For organ transplantation, avoidance of transplanting an EBV-positive donor organ into an EBV-negative recipient should reduce the risk of posttransplant NHL. For persons infected with HIV, effective combination antiviral treatments have contributed to a decreased incidence of lymphoma detection and eradication

of *H. pylori* infection in the stomach is an important strategy with potential to control or prevent MALT lymphoma[26,27] and its transformation. As additional microorganisms and viruses other than the ones mentioned here are being discovered to play critical roles in the pathogenesis of some lymphomas,[9,28] prevention and early treatment strategies will become increasingly important in the future.

BIOLOGIC CHARACTERISTICS AND PATHOLOGY

The present classification of NHL emphasizes lineage, function, and distinct clinical-pathologic disease entities, with a liberal use of phenotypic and molecular techniques. The World Health Organization (WHO) classification, fourth edition,[29] is shown in Boxes 77-1 and 77-2. The WHO classification recognized three major categories of lymphoid malignancies: B-cell, T-cell, and Hodgkin lymphoma.

BOX 77-1 WHO Classification (4th Edition, 2008)

MATURE B-CELL NEOPLASMS

CLL/small lymphocytic lymphoma
- B-cell prolymphocytic leukemia
- Lymphoplasmacytic lymphoma
  - Waldenström macroglobinemia
- Splenic B-cell marginal zone lymphoma
- Extranodal marginal zone B-cell lymphoma of MALT (MALT lymphoma)
- Nodal marginal zone lymphoma
  - *Pediatric nodal marginal zone lymphoma*
- Follicular lymphoma
  - *Pediatric follicular lymphoma*
- Primary cutaneous follicular center lymphoma
- Mantle cell lymphoma
- Diffuse large B-cell lymphoma (DLBCL), not otherwise specified
  - T-cell/histiocyte rich large B-cell lymphoma
  - Primary DLBCL of the central nervous system
  - Primary cutaneous DLBCL, leg type
  - *EBV positive DLBCL of the elderly*
- DLBCL associated with chronic inflammation

Lymphomatoid granulomatosis

Primary mediastinal (thymic) large B-cell lymphoma
- Intravascular large B-cell lymphoma
- ALK positive large B-cell lymphoma
- Plasmablastic lymphoma

Large B-cell lymphoma arising in HHV-8-associated multicentric Castleman disease
- Primary effusion lymphoma
- Burkitt lymphoma

B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and Burkitt lymphoma

B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and classical Hodgkin's lymphoma
- Heavy chain diseases
- Alpha heavy chain disease
- Gamma heavy chain disease
- Mu heavy chain disease

Hairy cell leukemia
- Plasma cell myeloma
- Solitary plasmacytoma of bone
- Extraosseous plasmacytoma

Note: The italicized histologic types are provisional entities.

The diagnosis of the individual pathologic and clinical entities continues to be based on morphology but is assisted by immunophenotyping and genotyping. The InterLymph Non-Hodgkin Lymphoma Subtypes Project pooled data from 20 case-controlled studies from North America, Europe, and Australia.[23] The most common lymphoma entities were diffuse large cell lymphoma (DLCL, 26%) and follicular lymphoma (20%). MALT/marginal zone lymphoma constituted 6% of cases, small B-lymphocytic, 13.9%, T-cell lymphomas, 5%, mantle cell. 3%, and Burkitt, <3% of cases. Slight regional variances were noted for incidence of specific disease entities. Because these were the most common entities on three continents, the discussion herein is limited to these diseases. For the rarer entities the reader is referred to the fourth edition of the WHO Classification.[29]

The lineage of B-cell lymphomas is confirmed by pan B-cell markers (CD22, CD19, CD20). T-cell lineage is evident from the presence of T-cell markers (CD3, CD2, CD7), and T-cell subset from CD4 and CD8 analysis. Among indolent lymphomas, the CD5+, CD10–, CD23+ phenotype is characteristic of small lymphocytic lymphoma (chronic lymphocytic leukemia), the CD5–, CD10+, CD23–/+ phenotype of follicular lymphoma and the CD5–, CD10–, CD23– phenotype of MALT lymphoma (Table 77-2). The CD5+, CD10–, CD23– phenotype, in addition to cyclin D1+, is characteristic of mantle cell lymphoma. Among T-cell lymphomas the CD30+ phenotype is characteristic of anaplastic large cell lymphoma (Figure 77-1), whereas CD56+ and EBV+ is associated with extranodal T/NK lymphoma of nasal type. Although surface marker analysis enhances the accuracy of the diagnosis, few surface marker characteristics are totally lineage specific. Ancillary cytologic and histologic techniques used to establish proliferative activity include labeling index, S-phase fraction, and Ki-67 antigen staining[30,31] which has been documented as a strong prognostic factor.

BOX 77-2 WHO Classification

MATURE T-CELL AND NK-CELL NEOPLASMS

T-cell prolymphocytic leukemia

T-cell large granular lymphocytic leukemia

Chronic lymphoproliferative disorder of NK cells

Aggressive NK cell leukemia

Systemic Ebstein-Barr virus positive T-cell lymphoproliferative disease of childhood

Hydroa vacciniforme-like lymphoma

Adult T-cell leukemia/lymphoma

Extranodal NK/T cell lymphoma, nasal type

Enteropathy-associated T-cell lymphoma

Hepatosplenic T-cell lymphoma

Subcutaneous panniculitis-like T-cell lymphoma

Mycosis fungoides

Sézary syndrome

Primary cutaneous CD30 positive T-cell lymphoproliferative disorders
- Lymphomatoid papulosis
- Primary anaplastic large cell lymphoma

Primary cutaneous gamma-delta T-cell lymphoma

Primary cutaneous CD8 positive aggressive epidermotropic cytotoxic T-cell lymphoma

Primary cutaneous CD4 positive small/medium T-cell lymphoma

Peripheral T-cell lymphoma, not otherwise specified

Angioimmunoblastic T-cell lymphoma

Anaplastic large cell lymphoma, ALK positive

Anaplastic large cell lymphoma, ALK negative

Note: The italicized histologic types are provisional entities.

The WHO classification, although aimed to classify distinct disease entities and acknowledges the uniqueness of certain presentations (e.g., the T-cell lymphomas cited previously), does not always consider the presenting site of the lymphoma. Recent evidence strongly suggests that the presenting site is an important factor for primary extranodal lymphomas. Examples include different etiology for MALT lymphoma arising in different sites, which is associated with differences in relapse rate.[32] Similar histology lymphomas may have distinct outcomes—DLBCL involving the brain (poor prognosis)—now clearly identified in the fourth edition of WHO, versus stomach or Waldeyer's ring structures (good prognosis).[33] With further understanding of etiology and pathogenesis of lymphomas, future modifications to classification of these diseases are expected.

The most common types of NHL seen in North America are: DLBCL and the follicular lymphoma and the management of many types of rarer lymphomas is based largely on experience with these two disease entities.

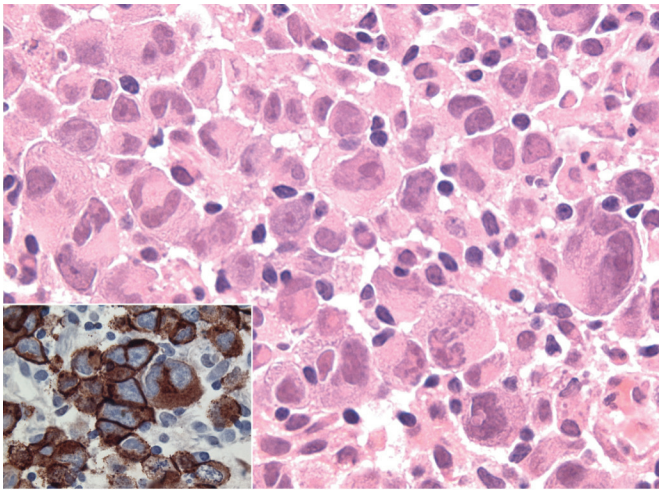


Figure 77-1 Anaplastic large cell lymphoma of lymph node (H & E stained section). The lymphoma cells are intensely CD30 immunoreactive *(inset)*.
Courtesy of Dr. Bruce Patterson, Canada.

TABLE 77-2 Phenotypic Characteristics of NHL

Lymphoma Type	Characteristic CD Antigen Profile
B cell markers	CD19, CD20, CD22
T cell markers	CD2, CD3, CD4, CD7, CD8
Anaplastic large cell lymphoma	CD30+ (Ki-1 antigen)
Small lymphocytic lymphoma (B-CLL)	CD5+, CD10–, CD23+, B-cell markers
Follicular lymphoma	CD5–, CD10+, CD23–/+, CD43–, B-cell markers
Marginal-zone (MALT) lymphoma	CD5–, CD10–, CD23–, B-cell markers
Mantle cell lymphoma	CD5+, CD10–/+, CD23–, CD43+, B-cell markers

Follicular Lymphoma and BCL-2

Follicular lymphoma (FL) is characterized commonly by lymph node involvement in a follicular pattern by follicle center cells (centrocytes) and is graded by the number of centroblasts (large cell) in 10 neoplastic follicles, per 40× high-power field (hpf) under the microscope. Grade 1 has 0 to 5 centroblasts/hpf, grade 2 has 6 to 15 centroblasts/hpf, and grade 3 follicular lymphoma has >15 centroblasts/hpf. Ten high-power fields are counted to get a good representation of the neoplastic follicles. Grade 3 is further divided into grade 3a (centrocytes are present), whereas grade 3b denotes solid sheets of centroblasts. It is generally believed that a higher proportion of centroblasts imply a more aggressive clinical course with worse prognosis, and therefore grade 3b cases are treated as DLBCL. The immunophenotype is distinctive and useful to distinguish FL from other indolent B-cell lymphomas (Table 77-2). The t(14;18)(q32;q21) translocation involving BCL-2 is the most common chromosome translocation found in 80% to 90% of FL (Table 77-3). BCL-2 encodes a 26-kDa membrane protein that controls and prevents cellular apoptosis. The gene is translocated to a J segment of the *IgH* gene on chromosome 14, giving rise to deregulation of BCL-2 with the result being the inhibition of apoptosis of B-cells. FL has a low proliferative potential, but when transformation occurs additional genetic lesions are acquired (*p53* mutation, deletion of chromosome 6q27, c-myc), in parallel with more rapid growth and an aggressive clinical course. Dual translocation (BCL-2 and c-MYC) are of a particularly worse prognosis.

Diffuse Large B-Cell Lymphoma

DLBCL is the most common aggressive lymphoma. Large transformed lymphoid cells replace the normal lymph node

TABLE 77-3 Common Genetic Alterations in Non-Hodgkin's Lymphoma

Oncogene	Translocation	Gene Product	Cellular Activity	Disease
BCL-1	t(11;14)(q13;q32)	Cyclin D1	G1/S progression	Mantle cell (>90%)
BCL-2	t(14;18)(q32;q11)	BCL-2	Suppression of apoptosis	Follicular (~90%) DLBCL (~25%)
BCL-6	3q27	BCL-6	Zinc finger transcription factor	Diffuse large cell (~30%) Follicular (~10%)
c-MYC	8q24	c-MYC	Transcription activation, cell cycle control	Burkitt Transformed DLBCL
p53	17p	p53	Tumor suppressor	Transformed NHL
ALK	t(2;5)(p23;q35) and others	Anaplastic lymphoma kinase	tyrosine kinase	T-anaplastic large cell
LYT-10	10q24	NFκB2	Transcription factor	Cutaneous T-cell lymphoma (~15%)
MALT1	t(11;18)(q21;q21) t(14;18)(q32;q21)	API2-MALT1 fusion transcript	Activates NFκB Deregulation MALT1	MALT (30%, site dependent) MALT (~10%)

DLBCL, *Diffuse large B-cell lymphoma;* NHL, *non-Hodgkin's lymphoma.*

or extranodal organ and tissue, in a diffuse pattern. It typically has a high proliferative fraction, typically Ki-67 staining is seen in 60% to 90% of neoplastic cells. Morphologic variants include the centroblastic (most common), immunoblastic, anaplastic, and T-cell/histiocyte rich subtype, although the treatment approach is similar. The immunophenotype is that of pan-B cell markers positive (CD19, CD20, CD22, CD79a). BCL2 is positive in 30% to 40% of cases. BCL-6 gene (located on 3q27) is translocated in 40% of DLBCL (Table 77-3).[34,35] BCL-6 is thought to mediate the DNA-binding activity of a number of zinc-finger transcription factors, and its presence carries a favorable prognosis, in comparison with those carrying BCL-2 who have a worse outcome, whereas those with neither translocation have an intermediate prognosis.[34,36]

The putative cell of origin can be germinal B cells, or post-germinal center origin. Microarray analysis of cDNA (the "lymphochip", NCI, Bethesda) using hierarchical clustering techniques initially classified DLBCL into two groups.[37] One expressed "germinal center B-cell-like" genes (GCB signature), such as A-myb, LMO2, Jnk3, CD10, BCL-6, c-rel, and bcl-2, whereas the other expressed "activated B-cell-like" genes (ABC signature), such as CyclinD2, IRF-4, Flip, NF-κB, and CD44. For patients treated with anthracycline-based chemotherapy in the prerituximab era, the 5-year survival for GCB group was 60%, compared with the ABC group of 35%, and a type-3 group was 39%.[38] Based on a selection of the most prognostic genes, either a larger series of 17 genes,[38] or condensing further to three immunostains for CD10, BCL-6, and MUM-1,[39] studies have shown that gene expression profiling provide additional prognostic information in addition to the clinical IPI scores.[38,39] Additional studies using oligonucleotide microarrays and a different analysis technique have also successfully identified two categories of patients with different survival rates (70% versus 12%) in DLBCL.[40] Gene profiling of the nonmalignant infiltrating cells in the tumor has also been found to be prognostic in DLBCL, whether treatment included rituximab or not.[41] The "stromal-1" group reflected extracellular matrix deposition and histiocytic infiltration had a better prognosis than the "stromal-2" group that reflected tumor angiogenesis activity.[41] At present, it is still uncertain how microarray assay results can be used to decide the treatment approach, although for cases with morphologic difficulty (e.g., gray zone lymphomas), it may assist in clarifying the diagnosis and hence the treatment required.

B-Cell Lymphoma with c-MYC and BCL-2

The presence of c-myc and bcl-2 translocations in a B-cell lymphoma is recognized as an aggressive subtype of either DLBCL, or B-cell lymphoma, unclassifiable, and carries a poor prognosis. This is also known as "double-hit" lymphoma and conventional treatment with R-CHOP may not induce remission or if a remission is obtained it is commonly not durable.[42,43] Fortunately it is found in less than 10% of patients with DLBCL. Median survival is often less than a year[44] and it is still uncertain if intensified treatment approaches are of any value.

Mantle Cell Lymphoma and BCL-1

Mantle cell lymphoma (MCL) occurs in older adults and commonly presents with generalized disease with spleen, bone marrow, and gastrointestinal (GI) tract involvement. Circulating lymphoma cells are frequently found in the blood. It is associated with a characteristic immunophenotype (CD5+, CD10–/+, and CD23–).[29] The t(11;14)(q13;q32) translocation is found in the majority of MCLs (Table 77-3). BCL-1, also known as PRAD-1, encodes for cyclin D1 that regulates cell cycle progression. This lesion appears to be highly specific for mantle cell lymphoma, with the translocation of BCL-1 on chromosome 11 to *IgH* gene on chromosome 14, making it an extremely useful adjunct to immunophenotyping in distinguishing MCL from other types of lymphomas.

Primary Mediastinal B-Cell Lymphoma

Primary mediastinal B-cell lymphoma (PMBL) is a subtype of DLBCL arising in the mediastinum and the presumed cellular origin is from the thymic B-cells. It presents as localized disease in the mediastinum, often bulky, with invasion into surrounding structures such as lung, pleura, chest wall, and pericardium. Superior vena cava obstruction is common. Females are affected more often than males and usually young adults ages 20 to 45 years. Immunophenotypic finding are similar to DLBCL, but genetic features are distinctive, with gains in chromosome 9p, and amplification of REL gene, and overexpression of *MAL* gene. Deregulated genetic pathways involved are NF-κB and JAK-STAT activation.[45] In general lacking in BLC2, BCL6, and c-MYC rearrangements. Microarray studies indicated genetic similarity of PMBL with Hodgkin's lymphoma, rather than DLBCL, characterized by overactivation of PDL2, a regulator of T cells.[46]

Extranodal Marginal Zone Lymphoma, MALT Type

MALT lymphoma is an indolent lymphoma, with the neoplastic cells being small centrocytes of marginal zone characteristics affecting diverse extranodal organs of MALT type. Most common sites are the GI tract, frequently the stomach, orbital adnexa, salivary gland, other upper aerodigestive tract mucosa sites, lung, skin, thyroid, and breast tissue. Rarely can occur in urinary bladder, liver, and dura. In glandular tissue lymphoepithelial lesions (where lymphoid cell aggregates invade and destroy the epithelium) are characteristic, and sometimes plasmacytic differentiation is also prominent and when present this needs to be distinguished from extramedullary plasmacytoma. The majority of cases (80% to 90%) are localized (stages I and II). Nodal involvement is usually associated with the extranodal site but relatively uncommon. In many cases there is a history of infection or inflammatory condition affecting the extranodal organ in question: for example, *H. pylori* infection in stomach MALT, *C. psittaci* infection in orbital MALT, and Sjögren's syndrome in salivary gland MALT. The immunophenotype is characteristic (Table 77-2). Genetically extranodal MALT lymphoma is found to have a number of mutually exclusive molecular markers: t(11;18)(q21;q21), t(14;18)(q32;q21), t(3;14)(p14.1;q32), t(1;14)(p22;q32), +3, and +18 (Table 77-3). The most important is t(11;18) as its presence in gastric MALT lymphoma is associated with *H. pylori* negative status and hence predicts a lack of response to antibiotic therapy.

Burkitt Lymphoma and c-MYC

Burkitt lymphoma (BL) is an aggressive lymphoma, with a short tumor doubling time and rapid proliferation rate. Several clinical subtypes are recognized: endemic, sporadic, and immunodeficiency-associated. The endemic BL occur in equatorial Africa and is the most common childhood cancer in that area. It affects children typically ages 4 to 7 years, with male predominance, and frequently presents as a jaw tumor. Sporadic BL is seen throughout the world, and accounts for about 1% of NHL in western countries and North America. It usually presents in extranodal organs (e.g., the gastrointestinal tract, gonadal tissue, and breast). Males in the mid-30s predominate. Immunodeficiency-associated BL are usually the result of HIV infection. Morphologically the malignant cells are medium

sized, with diffuse monotonous growth pattern. Mitotic figures are numerous, with high rate of apoptosis as well. Normal macrophages seen to have ingested apoptotic tumor cells give the characteristic "starry sky" pattern. The immunophenotype is CD19/20/22+, CD10+, BCL6+, and surface IgM+. Ki-67 proliferation is seen in 99% to 100% of tumor cells. The majority of BL present as stage IV disease. A staging system proposed by Murphy (or a modification of it) is in common use, largely based on tumor burden.[47,48] The c-MYC oncogene, located on chromosome 8q24, regulates cellular proliferation and differentiation. Its translocation is seen in 100% of BLs typically to chromosome 14q32 (IgH), less commonly to 2p11 (Ig*k*) and 22q11 (Igλ). EBV infection is responsible for and can be documented in almost all cases of endemic BL and about 30% of the sporadic cases.[49,50]

Peripheral T-Cell Lymphoma, Not Otherwise Specified

Peripheral T-cell lymphomas (PTCLs) are a heterogeneous group of T-cell neoplasms, are more common in Asia,[51,52] usually affecting adults, and are commonly generalized at presentation. It is the most-common aggressive T-cell lymphoma in Western countries. An aggressive clinical course is typical, and although potentially curable, many T-cell lymphomas are resistant to current chemotherapy regimens. T-cell immunophenotype is expressed, more frequently CD4+ than CD8+, and CD10–. BCL6—, CD30, and CD56 can be variably expressed. CD20 is negative hence rituximab has no role in therapy. TCR gene is clonally rearranged in the majority but is not mandatory for diagnosis. Males are affected more frequently, and the majority (70%) has stages III and IV disease, with involvement of lymph nodes, bone marrow, spleen, skin, and other extranodal organs. Prognosis is worse than comparably matched DLBCL.[53,54]

Mycosis Fungoides and Sézary Syndrome

Mycosis fungoides (MF) is the most common primary cutaneous T-cell lymphoma. It has indolent behavior, characterized by an evolution of skin patches and plagues, and later progressing to tumorous lesions over a course of many years. Atypical lymphocytes with indented (cerebriform) nuclei infiltrate the epidermis. Collections of these atypical cells form the characteristic "Pautrier microabscesses." The immunophenotype is typically CD2+, CD3+, CD4+, CD5+, CD8–, and TCRβ+. A unique staging system has been used clinically based on the degree of skin involvement and lymph node involvement.[55] Sézary syndrome is characterized by the presence of Sézary cells with cerebriform nuclei in the skin, lymph nodes, and the peripheral blood and is the leukemic manifestation of MF progression. Prognosis is dependent on the burden of disease and is worse for those with diffuse erythroderma, tumorous lesions, Sézary syndrome, and histologic transformation to an aggressive T-cell lymphoma.

Anaplastic Large Cell Lymphoma

Anaplastic large cell lymphoma (ALCL) is an aggressive T-cell lymphoma, separated into anaplastic lymphoma kinase (ALK)-positive, or ALK negative cases. The latter usually presents in older adults and has a worse prognosis. Patients with ALK+ ALCL are younger, and the disease can present in childhood and has a good prognosis.[54] Typically lymph nodes are involved, and where extranodal organs are affected, most common sites are skin, lung, and soft tissues. There is a broad morphologic spectrum, with typically large cells with eccentric nuclei. Variants exist where there maybe histiocytic cell infiltration, or a "Hodgkin-like" pattern. The characteristic immunophenotype of the tumor cell is strongly positivity for CD30, ALK+ for the ALK+ subtype. TCR is clonally rearranged in the majority. For the ALK+ cases, the t(2;5)(p23;q35) translocation is most commonly found (Table 77-3). This translocation involves the fusion of the NPM (nucleophosmin) gene on 5q35 and the ALK (anaplastic lymphoma kinase) gene on 2p23.[29] Others involving ALK-2p23 includes t(1;2)(q25;p23), Inv(2)(p23q35) and many others.[29]

Primary Cutaneous CD30-Positive T-Cell Lymphoproliferative Disorders

This diagnosis encompasses a spectrum of CD30+ diseases ranging from primary cutaneous anaplastic large cell lymphoma (C-ALCL) to lymphomatoid papulosis (LyP), which is a benign skin condition. Histologically the two entities may not be clearly distinguished from the skin biopsy, but the different clinical appearance and course over time is distinctive. There is diffuse infiltration of the skin by sheets of large anaplastic cells that are CD30+. The immunophenotype shows strong CD30 expression, and usually CD4+, with variable loss of CD2, CD5, and CD3. LyP has more variable morphology and some cells can be Reed-Sternberg-like (LyP type A), MF like with cerebriform cells (LyP type B), or monotonous CD30+ cells as in C-ALCL (LyP type C). C-ALCL usually presents as a solitary skin nodule but can be multifocal in 20% of cases. When localized, local RT is the treatment of choice. LyP manifest as papular skin lesions affecting extremities or trunk, with evolving appearance over several weeks, some ulcerating and then self-healing. A small proportion of cases (~5%) may develop into other T-cell lymphoma (e.g., C-ALCL, or MF). Overall the prognosis is excellent.[56]

Extranodal NK/T Cell Lymphoma, Nasal Type

There are many other specific subtypes of T-cell lymphoma but the main one to consider here with special interest to the radiation oncologist is the extranodal NK/T cell lymphoma of nasal type. The entity of NK/T cell lymphoma of nasal type includes disorders previously known as lethal midline granuloma and nasal T-cell lymphoma. It is characterized by an angiocentric and angioinvasive infiltrate[29,57] (Figure 77-2), with CD56+ (T/NK cell) immunophenotype, and are characteristically EBV-positive. Apart from presenting in nasal cavity or surrounding tissues such as the Waldeyer's ring, it may rarely present in skin, lung, testis, and central nervous system (CNS). It is more commonly seen in southeast Asia, in south America, and rarely in Europe. This disease responds poorly to conventional CHOP chemotherapy and usually follows an aggressive course.[58-60] Upfront RT (with or without chemotherapy) is important, with doses of 50 Gy or greater, and is required for disease control.[61]

CLINICAL MANIFESTATIONS, PATIENT EVALUATION, AND STAGING CLASSIFICATION

Clinical Manifestations

NHL may present in any part of the body. Therefore, the presenting signs and symptoms of NHL are highly variable. The most common presentation is with an asymptomatic lymph node enlargement. Peripheral lymph node involvement (cervical, inguinal, etc.) is most common in indolent lymphomas and in generalized presentations. Lack of progressive enlargement of lymph nodes may lead to a delay in diagnosis. The

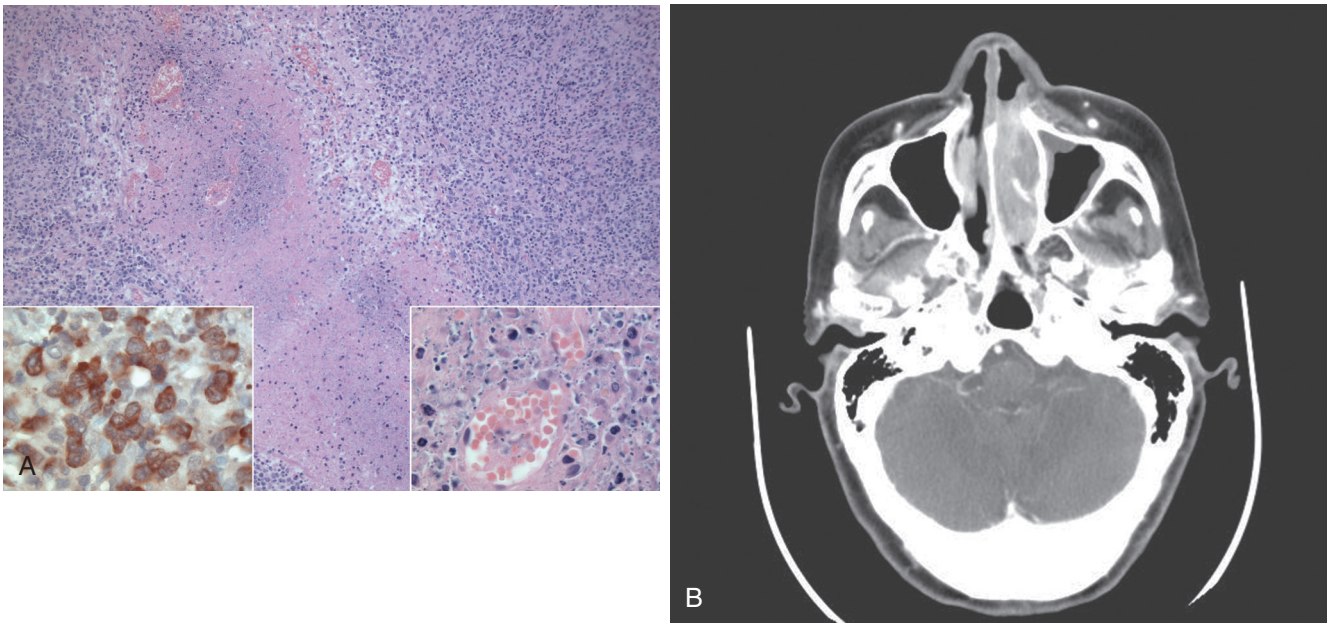


Figure 77-2 **A,** Photomicrograph of an extranodal NK/T-cell lymphoma, nasal type (H & E stained section). There is abundant necrosis, and the lymphoma cells have an angiocentric and angioinvasive growth pattern *(inset right lower corner)*. The lymphoma cells are immunoreactive for Ebstein-Barr virus (EBV) latent membrane protein *(inset left lower corner)*. **B,** Extranodal NK/T-cell lymphoma, nasal type. Axial computed tomography scan showing involvement of the left nasal cavity.
Courtesy of Dr. Bruce Patterson, Canada.

most common presenting sites of nodal lymphomas are cervical, inguinal, and retroperitoneal lymph nodes. Mediastinal lymph node involvement is much less common than in Hodgkin's lymphoma, except for the primary mediastinal large B-cell lymphoma. Patients may also present with systemic symptoms of fever, weight loss, and night sweats, usually heralding the presence of more advanced disease.

As in nodal lymphomas, the presenting symptoms in primary extranodal lymphomas depend on the site of origin and do not differ significantly from symptoms of other malignancies affecting a specific organ. Occasionally the clinical appearance of a lymphomatous lesion may not be characteristic of a malignancy and may mimic benign inflammatory lesions. Careful histopathologic examination, therefore, is extremely important in arriving at an early diagnosis. Characteristically gastric lymphomas present with symptoms of peptic ulcer, bowel lymphomas with intestinal obstruction or diarrhea, whereas primary bone lymphoma presents with pain. Primary lymphomas with diffuse involvement of an organ (e.g., liver, spleen, bone marrow) rather than a distinct tumor is particularly difficult to diagnose and are often a component of advanced disease. Tumor bulk at presentation is also related to primary site. Usually primary lymphomas of skin or orbital structures are visible and therefore diagnosed early; extradural lymphomas develop symptoms early and present with small bulk disease. In contrast, intestinal lymphomas present with nonspecific symptoms, and thyroid lymphomas (especially if associated with preexisting goiter) often present with bulky disease. In the absence of nodal involvement, lymphoma is often not suspected or distinguished clinically from carcinoma; therefore, immunophenotypic and histochemical analysis is particularly important.

Patient Evaluation

After a histopathologic diagnosis has been confirmed, the goal of evaluation is to determine disease extent and bulk, its anatomic distribution, and to ascertain normal organ and immune function relevant to the choice of therapy (Figure 77-3). With the diverse presentation of lymphomas, the investigations may vary, and there may be investigations that vary by institution.[62] Recommendations for initial evaluation and staging were recently updated in the Lugano Classification.[63] The minimum recommended investigations are listed in Box 77-3. Additional tests may be necessary based on the

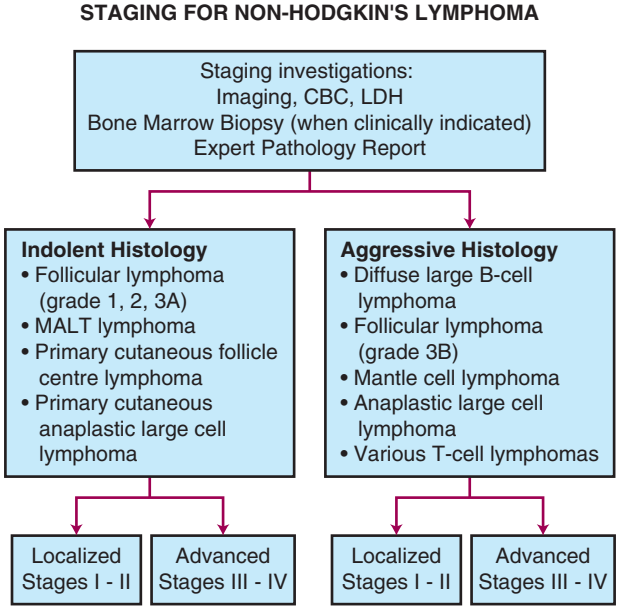


Figure 77-3 Algorithm for staging non-Hodgkin's lymphoma.
CBC, Complete blood count; LDH, lactate dehydrogenase.

BOX 77-3 Diagnostic Workup for Non-Hodgkin's Lymphoma

GENERAL

History, including systemic symptoms (unexplained fever, night sweats, weight loss >10% of body weight), risk factors for HIV infection
Physical examination: special attention to lymphatic sites, organomegaly
For palpable lymph nodes: note and record number, size, location, shape, texture, and mobility
Mirror examination of larynx and pharynx if clinically indicated

IMAGING STUDIES

Standard

Computed tomography scans of neck, thorax, abdomen, and pelvis
Fludeoxyglucose-positron emission tomography (FDG-PET)

SPECIAL TESTS

Standard

Bone marrow biopsy (only if PET negative and clinically relevant)
Review of slides by expert hematopathologist
Cytologic evaluation, if any effusion present
Lumbar puncture to examine cerebrospinal fluid for perimeningeal sites, testes, extradural presentations, or when clinically indicated

Complementary

Upper gastrointestinal or small bowel series when clinically indicated
Computed tomography scan of brain when clinically indicated
Magnetic resonance imaging if clinically indicated

LABORATORY STUDIES

Standard

Complete blood count (including platelet count, reticulocyte count), blood chemistries (including blood urea nitrogen, creatinine, uric acid levels)
Lactate dehydrogenase, bilirubin, transaminases, alkaline phosphatase

Complementary

Erythrocyte sedimentation rate
Serum electrophoresis
HIV serology when clinically indicated
Hepatitis B and C serology

presenting complaint, the subtype of lymphoma, predilection for CNS involvement, and so on.

History and Physical Examination

A complete history with attention to duration of symptoms and rate of lymph node enlargement should be obtained. Constitutional symptoms such as fever, night sweats, and unexplained weight loss as well as performance status should be documented, although presence of B symptoms have not been shown to be prognostic in available prognostic indices, and in the most recently modified Ann Arbor staging for NHL, the recommendation is to eliminate the designation of "B" from the staging.[63] Risk factors for lymphoma particularly immunosuppressive conditions including risk factors for HIV infection, immunosuppressive therapy, and the presence of autoimmune diseases should also be documented. Physical examination should include the lymphoid system, including, where relevant, Waldeyer's ring structures. If not demonstrated on imaging, the location and size of lymph node masses should be documented. This is especially important for the subsequent determination of RT target volume because following chemotherapy, no gross disease may be present at the time of RT treatment planning.

Pathologic Diagnosis

Histologic confirmation of the diagnosis by an experienced hematopathologist is mandatory. Inadequate specimens should prompt the consideration of repeat biopsy with attention to obtaining fresh tissue for immunophenotypic and cytogenetic studies.

Laboratory Tests

Minimum laboratory tests include a complete blood count, LDH, bilirubin, transaminases, and creatinine level. An HIV serology test should be performed when risk factors of HIV infection are present, or in high-grade lymphomas even if there are no obvious risk factors. Screening for hepatitis serology should be done for patients receiving chemotherapy. Because of the high sensitivity of bone marrow involvement by PET-CT, in the most recent recommendation from the Lugano meeting,[63] a PET-CT indicating bone or bone marrow involvement is deemed sufficient to designate advanced disease, and a bone marrow biopsy is not necessary. If the PET-CT is negative, a bone marrow biopsy is indicated in the setting of discordant histology, if relevant for a clinical trial, or patient management. Cerebrospinal fluid (CSF) cytology is performed in patients with risk factors for leptomeningeal spread (i.e., bone marrow, or peripheral blood involvement, Burkitt and lymphoblastic lymphomas, HIV infection, and lymphoma presenting in brain, testes, epidural space, eye, or paranasal sinuses).

Imaging Studies

PET-CT is now a standard staging procedure for all FDG-avid nodal lymphoma, including DLBCL, FL, MCL, Burkitt's lymphoma, nodal marginal zone lymphoma, ALTCL, NK/T-cell lymphoma, and peripheral T-cell lymphoma.[63] The most recent Consensus of the International Conference on Malignant Lymphomas Imaging Working Group[64] recommends staging of FDG-avid lymphomas using visual assessment, with PET-CT images scaled to a fixed SUV display and color table. In addition, the PET-CT can be used to select the best site for a biopsy. Variably FDG-avid histologies should be staged with a CT scan, and intravenous contrast should be included to allow more accurate nodal size measurement as well as to facilitate radiation planning. Other radiographs should be obtained based on the actual or suspected organ involved. Magnetic resonance (MR) imaging is indicated in delineating areas of suspected involvement of bone or CNS (e.g., spinal cord and epidural space, brain stem, base of skull and cavernous sinuses, and leptomeninges). The role of routine MR scans for the thorax, abdomen, and pelvis has not been established.

Staging Classification

The AJCC and UICC have endorsed the use of the Ann Arbor classification for staging of NHL. The Ann Arbor staging classification has been used for more than 40 years.[65,66] In the Ann Arbor system, Waldeyer's ring, thymus, spleen, appendix, and Peyer's patches of the small intestine are considered as lymphatic tissues and involvement of these areas does not constitute an "E" lesion, originally defined as extralymphatic involvement. However, because of the unique pathologic and clinical characteristics of primary lymphoma affecting these

organs, most clinicians consider them as separate clinical entities and report their involvement as extranodal presentation. The Ann Arbor classification differentiates locoregional from widespread lymphoma and documents anatomic extent of disease and B-symptoms, but it is not optimal for describing the extent of local disease, invasion of adjacent organs, tumor bulk, or multiple sites of involvement within one organ (e.g., skin, GI tract). Several modifications to the Ann Arbor classification have been proposed in the past. In gastric lymphoma, substaging of stage I to reflect the depth of the stomach wall penetration has been suggested. In stage II disease, distinction of involvement of the immediate nodal region (II_1) compared to more extensive regional lymph node involvement (II_2) has been found to be of prognostic significance in primary GI lymphomas.[67,68] In the recently published Lugano classification,[63] the designation of "B" symptoms was eliminated from the staging system for NHL because available prognostic scores for various NHL did not find presence of constitutional symptoms to be prognostic.

PROGNOSTIC FACTORS

Although the anatomic extent of disease reflected by Ann Arbor stage is an important prognostic factor, many other factors are known to influence the outcome in patients with NHL. They include histologic type, phenotype (B-cell versus T-cell),[51,52] tumor bulk,[69,70] number of involved nodal regions and extranodal sites, proliferation indices (S-phase fraction, Ki-67 antigen) as well as age, gender, and performance status[71] (Table 77-4). The International Prognostic Index (IPI) was derived from patients with aggressive lymphomas treated with doxorubicin-based chemotherapy in Phase II and Phase III trials. Based on factors identified in multivariate analysis the IPI is based on patient's age, serum LDH, performance status, and number of involved extranodal sites (Table 77-5).[71] Patients are grouped according to the number of adverse factors (i.e., age >60 years, stage III or IV, abnormal LDH level, performance status >1, and more than one involved extranodal site). Patients in the low-risk group (zero to one adverse factors) treated with doxorubicin-based chemotherapy with or without RT had a 73% 5-year survival; in low-intermediate group (two adverse factors), 51%; high-intermediate group (three adverse factors), 46%; and those in high-risk group (four or five adverse factors), 26% 5-year survival.[71] A similar pattern of decreasing survival with an increasing number of adverse factors was observed in younger patients. The validity of the IPI has been confirmed in a population of patients with T-cell lymphomas.[72] The IPI was less useful in indolent lymphomas,[73] and a different index has been proposed, the FLIPI (follicular lymphoma IPI).[74] The FLIPI is based on the following adverse prognostic factors: age >60 years, stage III or IV, abnormal LDH level, 5 or more involved nodal areas, and hemoglobin <120 g/L.[74] A subsequent study (the F2 study) proposed a modification of FLIPI (FLIPI-2) using the following adverse prognostic factors: age >60 years, bone marrow involvement, abnormal beta-2-microglobulin level, maximum tumor diameter >6 cm, and hemoglobin <120 g/L.[75] For MCL in advanced stages, there is a yet another proposed prognostic index known as the mantle IPI (MIPI), based on the following adverse prognostic factors: older age, ECOG performance status, LDH level, and the leukocyte count.[76] Other prognostic factors include the presence of BCL-6 rearrangement, high levels of BCL-2 protein secretion,[77] survivin expression,[78] and *p53* mutation.[79] The prognostic significance of gene profiling with microarray studies has been discussed previously. In addition to the genetic and phenotypic factors, the presenting site of lymphoma has prognostic implications; for example, lymphoma presenting in testis, ovary, eye, CNS, and liver has a particularly adverse prognosis, whereas orbital and skin lymphomas generally have a good prognosis.

PRINCIPLES OF MANAGEMENT

Most cases of localized NHL are treated with curative intent (Figure 77-4). A palliative approach is used when, because of the condition of the patient or the extent or location of the disease, a radical course of treatment carries no potential of cure or would cause significant toxicity. Knowledge of histology, extent, and pattern of disease is essential to select the appropriate therapeutic strategy. Local radiation is routinely used, both for cure and local control. However, the recognition

TABLE 77-4 Prognostic Factors in Non-Hodgkin's Lymphoma

	Favorable	Adverse
Histologic type	Low-grade MALT	Diffuse large-cell Mantle cell
Immunophenotype	B-cell	T-cell, NK-cell
Tumor bulk	<5 cm	>10 cm
Ann Arbor stage	I, II	III, IV
Symptoms	Asymptomatic	B-symptoms
Proliferative indices	S-phase fraction <5% Ki-67 <80%	High % S-phase Ki-67 >80%
Age	<60 years	≥60 years
LDH	Normal level	Abnormal level
β-2 microglobulin	Normal level	High level
HLA-DR expression	Present	Absent
CD-44 expression	Low	High
c-MYC translocation	Absent	Present
BCL-2 protein	High	Low
BCL-6 rearrangement	Present	Absent
Site of extranodal presentation	Orbit, skin, tonsil	Brain, testis

TABLE 77-5 International Prognostic Index (IPI) for Non-Hodgkin's Lymphoma

Risk Factors	Unfavorable Feature	Risk Group Risk factors	Number of Survival	5-Year
Age	>60 years	Low	0 or 1	75%
LDH	>1 × normal	Low-intermediate	2	51%
Performance status*	2-4	High-intermediate	3	43%
Stage (Ann Arbor)	III-IV	High	4 or 5	26%
Extranodal involvement	>1 site			

ECOG, Eastern Co-operative Oncology Group.

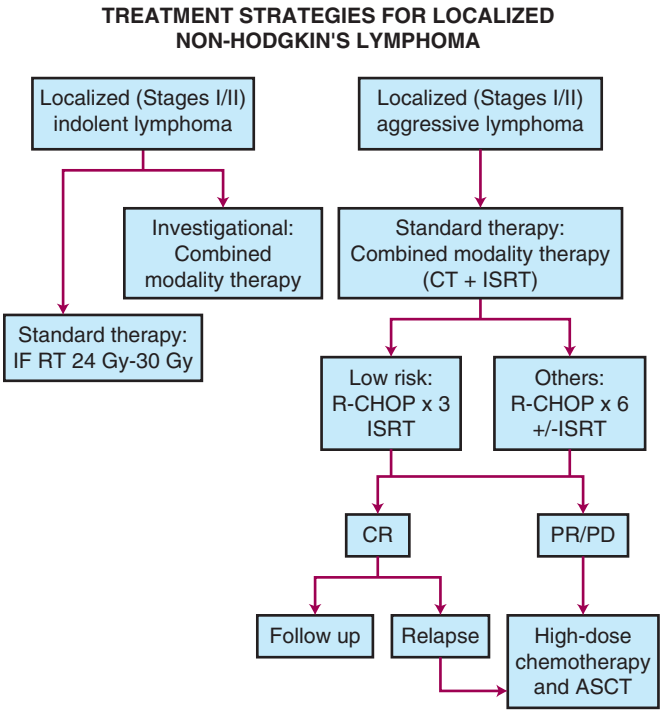


Figure 77-4 Treatment strategies for localized non-Hodgkin's lymphoma.

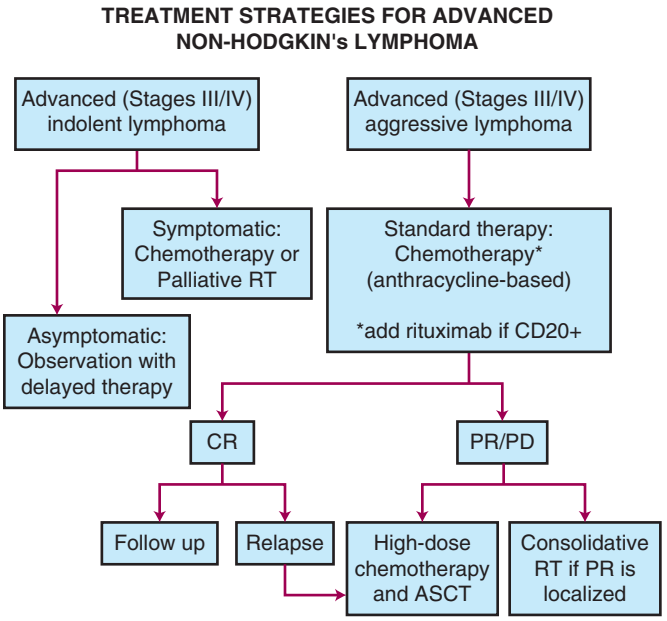


Figure 77-5 Treatment strategies for advanced non-Hodgkin's lymphoma.

of the high risk for occult distant disease mandates the use of chemotherapy in most cases. The primary treatment modalities include chemotherapy and RT, although surgery is used to diagnose and manage selected cases. For localized disease, the curative approach involves combined modality with chemotherapy and RT, chemotherapy alone, or local treatment with definitive RT. The choice is predicated on the inherent risk of occult distant disease, availability of curative chemotherapy, and the potential need for local control. Patients with advance disease (stages III and IV) are usually treated with chemotherapy alone (Figure 77-5).

Radiation Therapy

The aim of RT is to deliver an adequate dose of radiation to the target volume to ensure a high rate of local control. The design for a proper course of RT must take into account the extent of disease, the appropriate margins, routes of lymphatic and possible extranodal spread, and the radiation tolerance of normal tissues and organs. Dose fractionation parameters must assure local control with acceptable acute and long-term toxicity. The technique should guarantee reproducibility of treatment on a daily basis. Custom-designed fields should be used to conform to the target volume while keeping the volume of irradiated normal tissues to a minimum. The use of CT simulation with delineation of target volumes (gross target volume [GTV], clinical target volume [CTV], and planning target volume [PTV]) as well as dosimetric evaluation in three dimensions is standard for most indications.

RT techniques and prescriptions are discussed in detail later in the chapter. It is important to note that when RT follows chemotherapy in combined-modality therapy (CMT) protocols, RT is usually started 4 weeks to 6 weeks following the last course of chemotherapy to allow recovery of blood counts and to minimize the drug-radiation sensitization effect. Concurrent therapy is not indicated because of an increased risk of treatment interruption as a result of both thrombocytopenia and neutropenia with concurrent RT and chemotherapy.[80]

Chemotherapy

Frequently used chemotherapy regimens for NHL are listed in Table 77-6. These include single agents used for indolent lymphoma and anthracycline-containing regimens potentially curative for DLCBL (e.g., CHOP-rituximab) or T-cell lymphomas, and regimens used for patients with recurrent disease. For high-grade lymphoblastic and Burkitt lymphomas, dose-intensive protocols are used with concurrent intrathecal chemotherapy for CNS prophylaxis.[81,82] In a combined-modality approach for localized disease, chemotherapy is given first to promptly address any potential systemic microscopic disease and to reduce the bulk of the known local disease. When a combined course of therapy is planned, the goal of chemotherapy is to facilitate a response but not necessarily obtain a complete response at the local site. Quite often, residual thickening or a minimal mass of tissue remains by palpation or imaging, which should not deter from proceeding with the original radiation therapy plan.

The common acute but reversible toxicity of chemotherapy includes nausea and vomiting, alopecia, mucositis, fatigue, pancytopenia with risk of infection and bleeding, and any organ specific toxicity such as neuropathy for vinca alkaloids, diabetes for glucocorticoids, and pneumonitis for bleomycin. Rituximab may cause infusion related side effects such as fever, chills, and rigors, which can be avoided with a slower infusion rate. Advances in supportive care (e.g., antiemetic drug, and growth factor support) have alleviated many of these acute side effects. Severe long-term toxicity is infrequent, but may include gonadal damage particularly in males, cardiomyopathy (with doxorubicin), pulmonary fibrosis (with bleomycin or methotrexate), neurotoxicity (with vinca alkaloids, cisplatin, or bortezomib), and impairment of hematopoietic reserve (with alkylating drugs).

Surgery

The principal role for surgery is to establish the diagnosis of lymphoma and to obtain sufficient tissue to allow characterization of different disease subtypes. This requires optimal

TABLE 77-6 Common Chemotherapy Regimens for Non-Hodgkin's Lymphoma

Indolent Lymphoma	Histologically Aggressive Lymphoma	Salvage Therapy

• Chlorambucil ± prednisone
• CVP-(R)
  • Cyclophosphamide
  • Vincristine
  • Prednisone
  • (Rituximab)
• CHOP or CHOP-(R) (see next column)
• FCR
  • Ludarabine
  • Cyclophosphamide
  • Rituximab
• FCM-(R)
  • Fludarabine
  • Cyclophosphamide
  • Mitoxantrone
  • (Rituximab)
• Tositumomab and ^{131}Iodine tositumomab (Bexxar)
• ^{90}Yttrium-ibritumomab tiuxetan (Zevalin)
	• CHOP-(R)
	  • Cyclophosphamide
	  • Doxorubicin
	  • Vincristine
	  • Prednisone
	  • (Rituximab)
	• EPOCH
	  • Etoposide
	  • Vincristine
	  • Doxorubicin
	  • Cyclophosphamide
	  • Prednisone
	• MACOP-B
	  • Methotrexate with folinic acid rescue
	  • Doxorubicin
	  • Cyclophosphamide
	  • Vincristine
	  • Bleomycin
	  • Prednisone
	• ProMACE-CytaBOM
	  • Cyclophosphamide
	  • Doxorubicin
	  • Etoposide
	  • Prednisone
	  • Cytarabine
	  • Bleomycin
	  • Vincristine
	  • Methotrexate with folinic acid rescue
		• DHAP
		  • Dexamethasone
		  • Cytarabine
		  • Cisplatin
		• ESHAP
		  • Etoposide
		  • Methylprednisolone
		  • Cytarabine
		  • Cisplatin
		• ICE
		  • Ifosfamide
		  • Mesna
		  • Carboplatin
		  • Etoposide
		• GDP
		  • Gemcitabine
		  • Dexamethasone
		  • Cisplatin

pathologic interpretation, which includes immunophenotypic and molecular studies. Special fixatives and fresh tissue is commonly required, so when possible, it is important to alert the surgeon if a diagnosis of lymphoma is in the differential. The therapeutic role of surgery is not well defined. Case series reports have identified small proportion of patients with stage I nodal or extranodal lymphomas that have been cured with surgery alone. Although surgery can provide excellent local control in select extranodal sites, cure is infrequent because of a high likelihood of microscopic residual disease. Because surgical excision of lymphoma does not diminish the need for chemotherapy or radiation, aggressive surgical procedures that compromise function or cosmesis should be avoided. For example, radical neck dissection is not required for lymphoma presenting in the neck, total parotidectomy with possible risk to the facial nerve is not indicated for parotid lymphoma, mastectomy is not indicated for a breast lymphoma, and cystectomy is not required to cure bladder lymphoma. Situations where surgery is a potentially good treatment option for local control include splenectomy for splenic lymphoma and orchiectomy for testis lymphoma.

MANAGEMENT OF DISTINCT DISEASE ENTITIES

Small Lymphocytic Lymphoma

Small lymphocytic lymphoma (SLL) is a manifestation of chronic lymphocytic leukemia (CLL) and is rarely, if ever, localized. In a situation where the presenting disease appears to be localized, and peripheral lymphocytosis is not obvious, additional investigations with a bone marrow biopsy or flow cytometry of the peripheral blood should be performed and this would likely identify a CD5+ population of abnormal lymphocytes that indicate that the disease is systemic. The management of SLL is the same as for CLL and not further considered here.

Follicular Lymphoma

Localized (Stages I and II) Follicular Lymphoma

Stages I and II presentations of FL account for approximately 30% in the pre-PET era.[75] With the availability of sensitive techniques to detect subclinical disease (e.g., FDG-PET, and BCL-2 by PCR), more patients are diagnosed with stages III and IV disease.[83,84] RT produces excellent local disease control (>95%), and a freedom from relapse rate of 50% at 10 years. Data from multiple institutions[85-92] documented comparable results with more than 90% local control and 10-year relapse-free rates of approximately 50% with the OS rates of 70%. A number of representative single-institution results published in the last two decades are summarized in Table 77-7. At Stanford, the use of extended field, subtotal, or total lymphoid irradiation gave a higher relapse-free rate of 67% at 10 years, compared to 36% for patients treated to only one side of the diaphragm. However, because the OS rate was similar,[85] extended field RT has been abandoned. Prognostic factors predictive of a high risk of relapse included age, extent of disease as reflected by stage, systemic symptoms, and tumor bulk. The addition of chemotherapy (e.g., CVP) tested in several randomized trials in the 1970s did not confer an OS advantage.[93-96] Phase II trials of patients with poor prognostic factors (constitutional symptoms, high LDH, follicular large cell histology) treated with CMT (e.g., CHOP-bleomycin) documented 10-year failure-free rate and OS rates of 73% and 82%, respectively, suggesting benefit for CMT.[97]

With no definitive data showing a survival advantage with CMT, involved-site RT is currently the preferred treatment for

TABLE 77-7 Localized (Stage I-II) Follicular Lymphoma, Treatment Results with Radiation Therapy (RT) ± Chemotherapy (CT)

First Author (year)	Institution	Number of Patients	Treatment	Freedom from Relapse (10 year)	Overall Survival (10 year)
Kelsey, 1994	British National Lymphoma Investigation	148 (RCT)	RT + CT RT	42% 33%	42% 52%
Vaughan Hudson, 1994	British National Lymphoma Investigation	208	RT	47%	64%
MacManus, 1996	Stanford	177	RT	44%	64%
Seymour, 2003	MD Anderson Cancer Center	83	RT + CT	72%	80%
Petersen, 2004	Princess Margaret Hospital, Canada	460	RT	51%	62%
Guadagnolo, 2006	Joint Center, Boston	106	RT ± CT	46%	75%
Clarke, 2010	Princess Margaret Hospital, Canada	672	RT ± CT	45% (at 15 years)	66%
Campbell, 2010	Vancouver	237	RT	49%	66%
Pugh, 2010	SEER	2222	RT ± CT	—	62%

RCT, *randomized controlled trial.*

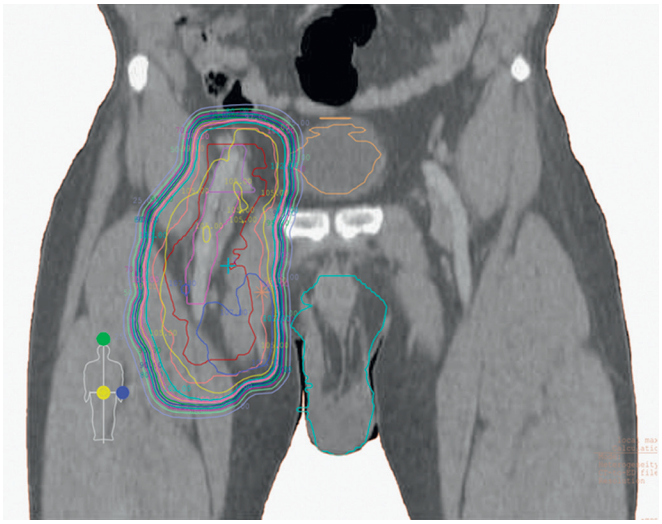


Figure 77-6 Involved site radiation therapy of right femoral lymph node region. Isodose distribution with anteroposterior-posteroanterior opposing fields using 6-MV photons.

most patients with FLs (see Figure 77-6). Patients with grade 3B FL behave similarly to DLBCL and should be treated with CMT. Given the benefits of adding rituximab to either CVP or CHOP in patients with stages III and IV disease, it is logical to incorporate rituximab into these regimens for early-stage disease. A study of selected patients with stages I and II disease who were observed with no initial treatment showed that 38% required therapy after a median of 86 months.[98] Additional studies also showed that selected patients when observed can have similar survival to those subjected to initial RT or chemotherapy.[99,100] However, analysis of SEER database in more than 6500 patients showed that although RT was initially used in only one third of patients, patients treated with RT had consistently higher DFS and OS survival rates compared with other approaches and the benefit was maintained over a follow up period of 20 years.[101] Therefore, a policy of observation is not appropriate for all patients because a plateau in the DFS curve for the radiation-treated patients beyond 15 years has been observed suggesting that a proportion of patients are cured.[85,91,92] There is marked variation in RT practice for localized indolent lymphoma.[62,85,91,102-104] Involved site radiation is currently considered as the standard approach. The International Lymphoma Radiation Oncology Group (ILROG) recently published guidelines for involved-node/involved-site radiation therapy for nodal NHL (discussed in "Technical Aspects of Radiation Therapy"). Involved site RT is defined by three-dimensional CT planning methods with identification of the GTV, CTV, and PTV and with an RT alone approach the CTV should include suspected subclinical disease based on the pretreatment imaging. The CTV should include the GTV and as a minimum nodes adjacent to the GTV.[105] Lymph nodes outside of the involved nodal region do not need to be intentionally treated. Investigators from British Columbia reported on their experience of "involved-node radiation therapy ≤5 cm" for limited-stage FL and found that only 1% of the study cohort had a regional only recurrence.[91]

With moderate doses of radiation (24 Gy to 30 Gy, over a 2-week to 4-week period), the local control rate is more than 95%. A Phase 3 trial examining the optimal dose for indolent lymphomas from the United Kingdom demonstrated no advantage for a higher dose of 40 Gy to 45 Gy in comparison with 24 Gy (in 12 fractions) although this trial did not restrict patients in initial presentation of stages I and II disease, and that the local control rate for either arm was lower than expected—5-year freedom from local progression was slightly lower than 80% for both arms.[106] In patients receiving >30 Gy, relapse occurs almost exclusively in distant unirradiated sites. Treatment at the time of recurrence requires chemotherapy, although RT is also useful in selected cases. High response rates are observed even with a low total dose of 4 Gy (2 × 2 Gy).[107-110] Because of the indolent nature of these lymphomas, long-term follow up is required to test the effects of any new treatment approaches on survival. The variation in the approach to localized disease, the long follow-up required, and competing mortality from unrelated causes form significant barriers to the conduct of clinical trials in this disease.

Advanced (Stages III and IV) Follicular Lymphoma

The advanced stage FLs are not cured with current approaches.[111,112] For asymptomatic patients with slow disease progression, observation is appropriate. Symptomatic patients require chemotherapy and RT is reserved for control of local symptoms. In the classic Stanford report initially observed patients required treatment after a median interval of 3 years. Their OS was 73% at 10 years.[113] Spontaneous regression of disease lasting a median of 13 months was observed in 23% of cases. Patients selected to undergo intensive therapy

(n = 37) in a Phase II study had 10-year survival of 86%.[111] Histologic transformation to a more aggressive histology (usually DLBCL) occurred in 60% at 6 years in one series,[114] and 31% at in 10 years in another.[115] Deferred therapy tested in a randomized study showed no adverse effect on survival (78% versus 70% for early treatment, p = 0.24).[116] Extensive nodal irradiation has been attempted in the past and the available data indicate a high probability of disease control within radiation fields.[84,103,104] However, with the long natural history of this disease and the selection of patients submitted to protocol treatment, it is difficult to ascertain whether extensive lymphatic irradiation improves survival, or results in cure. Other strategies for the treatment of indolent lymphoma include total body irradiation,[117-119] purine analogs,[120,121] rituximab-chemotherapy combinations,[31,122-124] radioimmunotherapy,[125-128] and high-dose chemotherapy with RT and hematopoietic stem-cell transplantation,[111,129,130] autologous or allogeneic. In a Phase III trial comparing 24 Gy in 2 Gy fractions versus 2 Gy × 2 in patients with follicular or MALT lymphoma, 24 Gy was shown to produce higher response rates (91% versus 81%, p = 0.0095), as well as more durable responses (hazard ratio [HR] for time-to-local progression, 3.42, p < 0.0001).[131] Low-dose approach of 2 Gy × 2 should therefore mostly be reserved for patients treated with palliative intent, but not for those treated with curative intent.

The most common chemotherapy regimens are R-CVP, R-CHOP, R-bendamustine, or fludarabine-based regimens. Postchemotherapy maintenance with rituximab has also been shown to improve outcomes.[132,133] Favorable responses have been documented for each of these approaches, but no firm evidence for cure has been evident. A meta-analysis of trials using α-interferon concluded that when used at a dose of ≥5 mU (or ≥36 mU/month) in combination with relatively intensive chemotherapy, improvement in survival and remission duration was seen.[134]

Palliative RT with a low dose regimen of 2 × 2 Gy is useful for symptom relief, with response rates of approximately 80% and usually lasts 12 months to 18 months.[107-109] However, if the goal is to achieve durable local control, for example in a critical site such as spinal cord compression, a higher dose regimen of 20 Gy to 24 Gy is more appropriate given its superior response rates and local control.[131]

Marginal Zone Lymphoma, MALT Type

MALT lymphomas are usually indolent B-cell tumors that present with stages I and II disease in 70% to 90% of cases. They are characterized by infiltration of mucosa, lymphoepithelial lesions, and clonal proliferation of centrocyte-like B cells.[29,135] MALT lymphomas arise most commonly in the stomach, orbit, thyroid, salivary glands, breast, lung, skin, and bladder.[135] The etiology of gastric MALT lymphoma is linked to infection with *H. pylori*. Association of *C. psittaci* with orbital adnexal MALT lymphoma has been documented, with marked geographical variation in different parts of the world.[15,17,28] Cutaneous MALT lymphoma has been associated with *Borrelia burgdorferi* infection in Europe,[136] but not in the United States.[137,138]

Gastric MALT Lymphoma

Patients with gastric MALT lymphoma usually present with gastric symptoms (dyspepsia, pain) typical of gastric ulcer. Some present with significant bleeding. Most cases are associated with *H. pylori* infection, and its eradication improves symptoms and induces remission of the lymphoma. Recommended anti-*Helicobacter* triple-drug therapy includes a proton pump inhibitor (or ranitidine bismuth citrate), clarithromycin, and amoxicillin (or metronidazole).[139,140] The expected rates of eradication of *Helicobacter* are more than 90%.[27,141] Adjuvant use of chlorambucil does not improve the results.[142] However, a response can take many months, and follow-up endoscopies and histologic examination is required to assess response. Residual abnormalities can remain for some time (12 months to 18 months), including persistence of a monoclonal B-cell population by sensitive molecular techniques such as polymerase chain reaction (PCR), and provided that the patient's symptoms are improved, no additional cytotoxic treatment is required. Although the majority of patients with gastric MALT lymphoma respond to antibiotics therapy, the t(11;18)(q21;q21) translocation has been reported to be associated with resistance to *H. pylori* therapy.[143,144] The presence of this marker, or lack of response to antibiotic therapy are two main indications to treat with definitive RT. Patients with asymptomatic minimal residual disease can have an indolent course and not require further treatment,[26,145] particularly if elderly or infirm. Involved site RT with doses of 30 Gy to 35 Gy results in >95% local control and a significant proportion of patients will be cured.[146-150] Relapses are rarely seen.

Orbital MALT Lymphoma

The most common involved site in the orbit is the conjunctiva. This produces redness, swelling, and symptoms of irritation. Clinically it appears as salmon pink infiltration of the conjunctiva, often filling and obliterating the conjunctival sac. Sometimes the disease affects the lacrimal gland, appearing as a soft-tissue swelling, orbital issues, eye lid, or retro-orbital tissue in which case it will give rise to proptosis. Bilateral orbital involvement is seen in 10% of patients but should not be regarded as stage IV disease. Reported association with *C. psittaci* led to the use of antibiotics (specifically doxycycline or clarithromycin) to treat orbital MALT lymphoma, with a variable success rate. The high rate of response reported from the Milan series[28,151] has not been reproduced elsewhere.[17,152] A course of antibiotics therefore can be attempted in patients who tested positive for *C. psittaci* serology. The standard approach in cases not related to infection is orbital radiation therapy with a dose of 25 Gy to 30 Gy. It results in a local control rate of >95% and cure in the majority of patients.[153,154] The relapse rate is 15% to 20%, with patients presenting with lacrimal gland disease[155] at higher risk of relapse than those with conjunctival involvement. The relapse is usually manifest in other systemic nonorbital MALT sites, although some patients may have subsequent involvement of the contralateral orbit, which may either be a new lesion or a true contralateral relapse. Fasola et al recently reported on results of 20 patients with indolent lymphoma of the orbit treated with 2 Gy × 2 to 26 sites, and at a median follow up time of 26 months.[156] The 2-year freedom from regional relapse rate was 96%, with one case of relapse within the ipsilateral orbit (outside of the treatment field). In this study 35% of patients had stage IE disease at diagnosis, and whether 2 Gy × 2 can be used as initial definitive treatment in patients with orbital MALT lymphoma needs to be further investigated.

Other MALT Sites

Less common sites of involvement include the salivary glands, most commonly the parotid gland. This is usually preceded by the presence of Sjögren's syndrome. Patients invariably gave a history of dryness of the mouth and possibly dryness of the eyes. Appropriate serology abnormalities are usually present. Multidisciplinary management with participation of rheumatologist and otolaryngologist is important. Other sites of involvement include the thyroid gland, lung, breast, skin, urinary bladder, liver, the dura, and other organ or structures lined with mucosa. The general approach is to treat with localized therapy—for sites where surgery is possible and a

complete gross disease excision has been achieved (e.g., skin lesion, or a thyroid nodule, or a small lung lesion), no further therapy may be necessary. The more common approach, however is to treat with RT as a standard dose of 30 Gy in 15 fractions to 20 fractions is associated with a high probability of local control for virtually all sites of localized MALT lymphoma. In situations where the morbidity of a full course of therapy is significant, (e.g., lung tissue), the use of a low dose regimen with 4 Gy (2 × 2 Gy) may produce good local control for some time.[157]

Although MALT lymphomas are usually indolent, transformation into aggressive large B-cell lymphomas may occur. The risk factors for future transformation have not been confirmed. Current experience with MALT lymphomas shows a tendency to localized disease and cure with local therapy.[32,158] The nodal counterpart of MALT, also known as monocytoid B-cell lymphoma, occurs in the older age group and is similar morphologically and immunologically to MALT lymphoma,[159] with similar clinical outcomes.[160]

Advanced Stage MALT Lymphoma

Stages III and IV MALT lymphomas have an indolent clinical behavior, similar to FLs. It has a tendency to involve MALT sites and asymptomatic disease may not require cytotoxic treatment. There are case reports that antibiotic therapy can produce responses.[161] Chemotherapy is reserved for symptomatic progression of the disease, with regimens which are active in FL cited previously. Mild therapy with single agent (e.g., rituximab or chlorambucil) may often be useful and cost-effective. The prognostic factors usually relate to burden of disease, a high beta 2 microglobulin, and presence of symptoms.[160,162,163] As in FL, palliative radiation therapy with 4 Gy in two fractions can often be useful for symptom relief.

Mantle Cell Lymphoma

Localized (Stages I and II) Mantle Cell Lymphoma

MCL accounts for 3% to 10% of all newly diagnosed cases of NHL. The disease has a predilection for men and is more common in the elderly (median age 60 to 65). There appear to be two different phenotypes of MCL, the blastic variant which is associated with rapid growth and aggressive behavior, and a more indolent subtype for which a watch and wait policy can be adopted for asymptomatic patients.[164] Because the majority of cases (>90%) present at advanced stage, the evidence for management of localized disease is scarce. However, MCL is radiosensitive, and therefore involved site RT may be appropriate for local disease.

Definitive RT without systemic therapy has been shown to result in long-term remissions in patients with localized MCL[165,166] and may be curative in a subset of cases.[167] In the absence of clinical comorbidities that would preclude the use of chemotherapy, most would favor a course of CMT. Despite the excellent response to systemic agents, several small retrospective studies confirm the important role RT plays an important role in localized disease with improvements in local control and progression-free survival (PFS).[168-170]

Advanced (Stages III and IV) Mantle Cell Lymphoma

The vast majority of MCL will present as advanced disease (stages III and IV) and may involve extranodal sites, including visceral organs, skin, breast, and bone marrow.[171] Expression of a microarray gene profile characterized by high proliferation,[172] or a high Ki-67 growth fraction,[76] confers a worse prognosis. The blastic variant of MCL is also associated with rapid growth and aggressive behavior. Although advance disease is not curable (median survival of 4 years to 6 years), it is responsive to several lines of systemic and local therapies. However, because this is a disease that impacts older adults (median age mid-60s)[168] and treatment is not always with curative intent, care must be taken in deciding when to treat and what agents to use. Observation may be indicated in patients who are asymptomatic and with disease that is behaving more indolently.[164] Once a decision is made to proceed with treatment, there is evidence to support using almost any of the chemotherapy regimens listed in Table 77-6 in MCL.[173] R-CHOP and R-bendamustine are both well-tolerated and effective, with overall response rates of 91% and 97%, respectively.[174] Unfortunately, a complete response is only achieved in a proportion of patients (~30%) leading to the poorer outcomes in patients with MCL than other subtypes of NHL.

Intensive chemotherapy followed by consolidation with high-dose chemotherapy and ASCT is being evaluated as a first-line strategy in younger patients with good performance status.[30,175,176] One study comparing RCHOP compared with R-hyperCVAD followed by ASCT or observation showed no difference in 2-year survival with consolidation, but R-hyperCVAD followed by ASCT was associated with improved PFS.[177] In another study, R-DHAP induced a complete response in 57% of patients versus 12% of patients treated with RCHOP before ASCT.[178] The outcomes were still excellent, with an ORR of 95% and 93%, respectively, and a 5-year OS of 75%, suggesting ASCT may provide improved outcomes for selected patients.

Relapsed and Refractory Mantle Cell Lymphoma

There is no standard approach to relapsed and refractory MCL. ASCT is considered in the setting of relapsed MCL but with the same caveats regarding safety of high-dose therapy in older patients. With improved understanding of the molecular pathogenesis of MCH, several targeted agents have been successfully investigated and are now approved for use in patients with relapsed and refractory MCL.[175] Molecular agents can be used alone or in combination with each other or conventional chemotherapy. These targeted drugs include several classes of agents including proteasome inhibitors (bortezomib), immune modulatory drugs (thalidomide, lenalidomide), the mammalian target of rapamycin (mTOR) inhibitor temsirolimus, and inhibitors of the B-cell receptor pathway (ibrutinib). Based on encouraging results from a Phase I study in patients with relapsed and refractory NHL of a variety of subtypes, the CTLA-4 inhibitor, ipilimumab, is being investigated in several ongoing MCL clinical trials. RT is an effective modality for palliation given the radiosensitivity of MCL. Existing data suggest that doses of 30 Gy or lower provides excellent local control and palliation.[165,179]

Diffuse Large B-Cell Lymphomas

Localized (Stages I and II) Diffuse Large B-Cell Lymphoma

Approximately 30% to 40% of DLBCL presents with stages I and II disease, but factors such as IPI score, the presence of B symptoms, and the size (bulk) of the disease influence the prognosis and therefore affect treatment choices. Immunophenotype, such as the presence or absence of c-myc and BCL-2 or BCL-6, may also influence choice of therapy. RCHOP is a standard chemotherapy regimen, but dose-adjusted EPOCH, CHOEP, and ACVBP used with rituximab also have excellent outcomes, albeit with increased toxicity.[180-183] The number of cycles of chemotherapy is variable; CMT with three to four cycles of chemotherapy followed involved site radiation therapy is standard treatment for limited stage, non-bulky DLBCL (Figure 77-7) An alternative approach is six cycles of

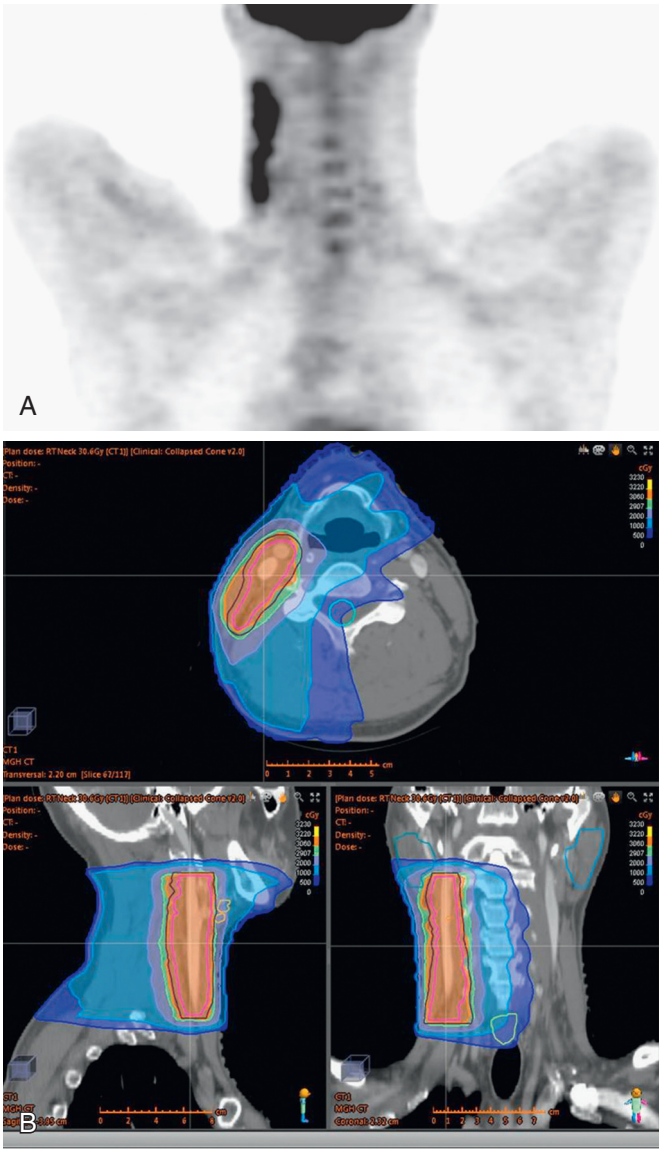


Figure 77-7 Involved site radiation therapy of cervical lymph node region. **A,** Positron emission tomography imaging showing localized disease. **B,** Isodose distribution of intensity-modulated radiation therapy plan to the involved site. Note sparing of parotid glands.

RCHOP with or without consolidative RT. Chemotherapy alone may be selected based on disease extent or location. OS at 5-years for CMT is approximately 90%. Several randomized trials from the prerituximab era showed that CMT is not inferior to longer regimens of chemotherapy alone and the addition of RT improves local control and, in several studies, PFS.[184-187]

In the rituximab-era, several retrospective studies showed an improved DFS and OS rates in patients who received RT compared to those who were treated with chemotherapy alone.[188-191] These studies included both early- and advanced-stage patients. Though the findings were limited by the retrospective study design, the use of RT was associated with improved outcome on multivariable analyses in each of these studies. Improved outcome with the addition of RT is supported by the early closure of the no-RT arms in the German UNFOLDER trial, a Phase III trial that randomized patients with stages I-IV DLBCL with initial bulky disease (defined as ≥7.5 cm) or extranodal involvement to RT versus no-RT after R-CHOP chemotherapy.

A Phase III trial comparing 30 Gy versus 40 Gy to 45 Gy in patients with aggressive NHL (67% with stages I and II) showed no difference in 5-year freedom for local progression between the two arms.[106,192] This trial, however, is limited by the fact that only 73% of patients received RT as consolidation after chemotherapy, and there was no information on response to chemotherapy before the RT. Based on retrospective data and nonrandomized data from clinical trials, radiation doses of 30 Gy to 36 Gy appears to be sufficient in patients who have achieved a complete response to systemic therapy.[185,189,190,193,194] Whether the RT dose can be deescalated to 20 Gy in these patients is currently being addressed by an ongoing Phase II study conducted at Duke University. Higher doses of radiation should be considered when a complete response is not achieved.[195]

The current standard treatment field for aggressive NHL after systemic therapy is involved-node or involved-site RT,[105] depending on the availability of optimal prechemotherapy imaging, detailed in "Technical Aspects of Radiation Therapy." After effective chemotherapy, the CTV should encompass the original lymphoma volume modified for normal tissue boundaries and expanded to accommodate uncertainties in determining the prechemotherapy volume, especially when optimal pretreatment imaging in RT planning position is not available. In a retrospective study comparing patients with early-stage aggressive NHL treated with IFRT versus involved-node RT, there was no difference in 5-year PFS rates between the two groups of patients, and patients treated with involved-node RT had better physical functioning and global quality of life compared to the IFRT group.[196]

Advanced (Stages III and IV) DLBCL

RCHOP is currently considered the standard chemotherapy for advanced (stages III and IV) disease.[191,197-199] Previous studies showed that "adjuvant" RT following a complete response to chemotherapy did not improve the OS in advanced stage NHL.[200,201] As discussed in the previous section, several more recent retrospective studies from the rituximab era that included patients with both early- and advanced-stage disease showed significantly improved outcome in patients who received adjuvant RT.

Early high-dose therapy with stem-cell transplantation had been an attractive approach when tested in patients with adverse prognostic factors, but showed no definite advantage over standard chemotherapy alone.[202-204] A French trial (GELA LNH 93-3) in high-risk and high-intermediate risk patients actually showed a worse outcome for the ASCT arm.[205] The GELA trials did not use RT, despite the inclusion of patients with stages I and II disease (some with bulky disease) that accounted for 30% to 40% of the patients studied.[204,206] In a randomized trial of 253 patients with high-intermediate-risk or high-risk disease comparing early ASCT versus further chemotherapy after CHOP or R-CHOP, an improved 2-year PFS was found in patients in the transplantation arm (69% versus 55%, $p = 0.005$), but no OS difference was detected, likely because of the effectiveness of salvage transplantation.[207] At this time, early stem-cell transplantation as part of initial therapy cannot be considered standard[208-211] but is reserved for patients with refractory or relapsed disease.

Relapsed and Refractory DLBCL

For patients with relapsed or chemotherapy-refractory large cell lymphoma, RT alone is rarely curative. However, in highly selected cases, durable long-term control of disease can be achieved with salvage RT.[212] Conventional salvage chemotherapy also has a low curative potential. Common salvage

regimens include DHAP,[213] mini-BEAM,[214] ESHAP,[215] ICE with or without rituximab,[216,217] and GDP[218] (Table 77-6). For patients with chemotherapy-sensitive disease, high-dose therapy followed by autologous hematopoietic stem-cell transplant is of benefit. A Phase III trial (PARMA) tested the role of high dose therapy in 109 patients. Those demonstrating a response to two cycles of DHAP chemotherapy were randomized to four further courses of DHAP, versus a conditioning regimen of BEAC (carmustine, etoposide, cytarabine, cyclophosphamide) followed by ABMT. The 5-year event-free and OS for the transplant arm were 46% and 53%, versus 12% ($p = 0.001$) and 32% ($p = 0.038$) for the conventional DHAP arm, respectively.[219] RT to a dose of 26 Gy in 20 fractions was given twice daily as a protocol treatment for patients with tumor bulk greater than 5 cm at the time of relapse in the transplant arm and to 35 Gy in 20 fractions in the conventional chemotherapy arm. There was a trend favoring the patients undergoing RT with a lower relapse rate in the transplant group (8 of 22 relapsed versus 18 of 33 relapsed who underwent RT, $p = 0.19$), and no obvious difference in the conventional chemotherapy group (10 of 12 patients who underwent RT relapsed, versus 35 of 42 patients who did not undergo RT relapsed). Although this trial was not designed to examine the role of RT in the salvage setting, it lends support to the use of RT for bulky disease when incorporated into a salvage treatment plan that includes high-dose therapy. The role of RT in bulky disease following partial response to salvage chemotherapy deserves further study in a randomized trial in patients undergoing hematopoietic stem-cell transplant. Until such evidence is available, we recommend routine RT to sites of bulky disease, in sequence with salvage chemotherapy and also RT to sites of incomplete response to chemotherapy.[220-224] Moderate doses of 30 Gy to 35 Gy should be the goal with individualization of the treatment plan in regard to the exact target volume (involved-site RT is preferred), and the timing of RT in relation to chemotherapy and transplant to facilitate the collection and harvesting of stem cells and minimize treatment-related toxicity. For example, if large RT fields are required, RT should be given after stem-cell harvesting and preferably pretransplant. Thoracic RT that will include significant volumes of lung tissue is less risky if given after transplantation.[225,226] In general, the principles of RT should be to treat the most likely site of relapse, or progressive disease. The decision to treat with RT is influenced by the distribution and location of the disease. The spinal cord may be more radiation-sensitive in the posttransplant setting because there are two case reports of radiation myelopathy with conventional fractionated doses of 40 Gy to 45 Gy.[227-229]

Although most cases of DLBCL are treated the same regardless of where they arise in the body, there are a few special presentations that warrant additional consideration.

Primary Mediastinal Large B-Cell Lymphoma

Several clinicopathological features have distinguished PMBL (thymic) from nodal DLBCL lymphoma. The disease typically present in females (female-to-male ratio of 3:1) in fourth or fifth decade of life, as a rapidly growing invasive tumor with contiguous spread into mediastinal tissues. Pleural and pericardial invasion with effusion and B-symptoms are common and 30% to 40% of patients have superior vena caval obstruction at diagnosis. The lesions are frequently bulky (65% being greater than 10 cm diameter), and involve the thymus. Tumors often have moderate to marked sclerosis. The outcome for patients treated with R-CHOP–based chemotherapy or CMT is equivalent to other DLBCL of equivalent stage (i.e., CR rates of 70% to 80% and 5-year survival of 60% to 80%).[230-232] Chemotherapy regimens more intensive than CHOP (e.g., MACOP-B,- or high-dose therapy with stem-cell transplantation) have been reported in retrospective studies to give improved results with 10-year OS ranging from 70% to 77%.[232-236] CMT is the standard approach.[235,236] Occasionally these tumors have demonstrated marked chemo- and radioresistance.[237] Factors determining outcome included bulk (>10 cm), the use of CMT,[233-235] and stage. The use of consolidative RT is being challenged in patients with PMBL; a Phase II trial using six cycles of dose-adjusted EPOCH-R showed that patient achieving a complete response had a 93% event-free survival and an OS of 97%, suggesting this aggressive regimen may obviate the need for RT in this disease entity, even in patients with bulky disease.[238]

Primary Central Nervous System Lymphoma

The most common site of primary central nervous system lymphoma (PCNSL) is the brain.[239] Primary leptomeningeal lymphoma, without parenchymal brain disease, accounts for only 7% of PCNSL. Primary spinal cord lymphoma is even less common.[240] The eye, a direct extension of the CNS, is another site of PCNSL. Aggressive histology B-cell lymphomas are most common; T-cell lymphomas have been reported but are exceedingly rare, with a prognosis similar to the B-cell lymphoma.[241]

Most patients with PCNSL present with symptoms of headache and raised intracranial pressure. Lesions are often multifocal or diffuse and are periventricular with easy access to the cerebrospinal fluid. The incidence of meningeal seeding varies from 7.6% to 69% when a vigorous search is conducted.[242,243] Systemic lymphoma is apparent in only 7% to 8% of autopsied patients. The diagnosis has to be confirmed histologically, but is suspected based on characteristic CT/MRI appearances of the tumor. A diffuse contrast enhancement of tumor on both CT and MRI is typical, but a small proportion of patients have nonenhancing lesions. Historical treatment consisted of whole brain irradiation to 40 Gy to 50 Gy in 1.8-Gy to 2-Gy fractions and corticosteroids producing a rapid symptomatic response. Performance status, age, and solitary tumor are the most important prognostic factors. The median survival has been reported to be 12 months to 18 months with 2-year and 5-year survival rates of 28% and 3% to 4%, respectively.[244-246] In the Princess Margaret Hospital (PMH) experience with RT alone, patients with Karnofsky performance status (KPS) older than 60 had an actuarial 5-year survival of 56% compared with 10% for those with KPS 60 or younger, whereas survival was 42% for those age 60 or younger compared with 9% for those 60 years or older, and for solitary lesions the survival was 30% compared to 15% for multiple lesions.[246] The International Extranodal Lymphoma Study Group (IELSG) study of 378 patients identified five independent poor prognostic factors for OS: age over 60 years, a ECOG performance status 2 or higher, elevated LDH level, elevated cerebrospinal fluid protein level, and involvement of deep brain structures.[247] Patient with none to one of these factors had a 2-year survival of 80%, with two to three factors, 48%, dropping to 15% for those with four to five factors.[247] These factors remain prognostic when the analysis was restricted to patients treated with intravenous methotrexate.

Because of poor results with RT alone and concerns regarding radiation neurotoxicity,[248,249] chemotherapy has become the initial standard treatment.[250-252] In the 1990s several reports have suggested improved median survivals for patients receiving chemotherapy followed by planned RT or RT at progression.[253-258] A policy change from an RT approach to initial chemotherapy consisting of methotrexate did not result in an improvement in survival for an unselected population of 122 patients in the province of British Columbia in Canada, in which up to one third of patients did not receive potentially curative therapy.[259] Despite this, protocols using strategies with high-dose methotrexate, in various combinations with

carmustine, procarbazine, vincristine, and dexamethasone have produced impressive results with or without RT, and with mild to moderate late neurologic toxicity.[250,251,253,255,256,260]

Other chemotherapy approaches included very high-dose of methotrexate (7 g/m^2) alone and deferred RT, and such treatment in 23 patients achieved an overall response rate of 74%, although only 52% had complete response.[257] Adding high-dose cytarabine to methotrexate resulted in a higher response rate in a Phase II study.[261]

In a Phase III trial of methotrexate-based chemotherapy alone versus CMT, the median PFS were 11.9 months and 18.3 months (p = 0.14), respectively, in patients who did not and did receive whole-brain RT.[252] The median OS were 32.4 months and 37.1 months (p = 0.71), respectively, yielding a HR of 1·06 (95% confidence interval [CI] 0.80 to 1.40). In this noninferiority trial, the noninferiority margin was set at 0.9. The results therefore did not support the primary hypothesis that the omission of whole-brain RT is noninferior to CMT. Long-term treatment related neurologic toxicity is a major problem after whole-brain RT for PCNSL, especially in patients older than the age of 60 years.[248,262,263] Investigators from Memorial Sloan Kettering Cancer Center reported their long-term results of a Phase II trial using reduced-dose whole-brain RT of 23.4 Gy in 1.8 Gy fractions in patients in complete response after rituximab, methotrexate, procarbazine, and vincristine.[264] The median age of the study population was 60. Among the 31 patients who achieved a complete response to chemotherapy and received reduced-dose radiation therapy, the 2-year PFS was 77% and 3-year OS was 87%. Prospective neuropsychological evaluation showed no evidence of significant cognitive decline, except for motor speed, and self-reported quality of life remained stable during the follow up period.

For patients with relapsed disease after or refractory disease to high-dose methotrexate-based therapy, salvage whole-brain RT results in response rates of 67% to 79%[265-267]. These reports show that PCNSL that are resistant to chemotherapy remain radiosensitive, but the optimal salvage approach has not yet been clearly defined.

Testicular DLBCL

In contrast to germ cell tumors, primary testis lymphoma affects mostly older men, older than the age of 50. Initial therapy usually involves orchiectomy. Almost all testicular lymphomas are DLBCL. Older series reported 5-year OS rates ranging from 16% to 65% with median survivals of 12 months to 24 months.[162,268-270] Distant failures were commonly observed. In the IELSG study of 373 patients 57% had stage I, and 21% had stage II disease.[162] Median PFS was 4 years. High risk of CNS relapse was observed with an actuarial risk of 34% at 10 years.[162] CNS relapse has been documented despite the use of chemotherapy.[271,272] Other sites of relapse involve extranodal organs including skin, pleura, Waldeyer's ring, lung, liver, spleen, bone, and bone marrow. Failure in the contralateral testis is well documented and occurs in 15% of patients at 3 years, rising to an actuarial risk of 42% at 15 years.[162] Scrotal irradiation with moderate doses (25 Gy to 30 Gy in 10 to 15 daily fractions) reduces this risk to less than 10%.[162] Doxorubicin-based chemotherapy improves survival of patients with localized testicular lymphoma.[162] A clear pattern of failure in the CNS warrants a recommendation for routine CNS prophylaxis with intrathecal chemotherapy,[270] and the IELSG data suggests that a combination of the systemic and intrathecal therapy, with scrotal RT was associated with an improved outcome.[162] In the most recent Phase II study conducted by the IELSG, 53 patients with stage I or II testicular lymphoma were treated with six to eight cycles of R-CHOP and four doses of intrathecal methotrexate (IT-MTX), followed by RT to the contralateral testis to 30 Gy for all patients and to regional lymph nodes for patients with stage II disease. At a median follow-up of 65 months, 5-year PFS and OS rates were 74% and 85%, respectively. With CNS prophylaxis and prophylactic contralateral testicular irradiation, the 5-year cumulative incidence of CNS relapse was 6%, and no contralateral testis relapses were observed.[270]

Breast Lymphoma

Breast lymphoma affecting young women tends to be associated with pregnancy and lactation and is an aggressive histology lymphoma commonly presenting with bilateral disease diffusely involving both breasts. In contrast, the disease affecting older women tends to present with discrete masses, commonly unilateral. Reports in the literature suggest synchronous bilateral involvement in up to 13% of cases and metachronous contralateral involvement in 7% of cases. The most common histologic type is DLBCL.[273] Indolent histology lymphomas are less common and if observed usually consist of secondary involvement from systemic disease.[274,275] MALT lymphoma affecting the breast is rare but has been reported.[274,276] Mastectomy is not recommended and the breast is preserved in the majority of cases. RT results in excellent local control, especially in patients presenting without bulky disease or those with indolent histology. The OS of patients treated with local treatment methods ranges from 40% to 66% at 5 years to 10 years.[273,274,277] The local control rates in patients treated with RT alone range from 75% to 84%.[273,274,278,279] Isolated CNS relapses have been reported.[273] Similarly, late failure in the contralateral breast may occur following therapy of unilateral primary breast lymphoma.[273] CMT is recommended for aggressive lymphomas,[273,280] whereas patients with indolent lymphoma can be successfully treated with RT alone.[274] CNS prophylaxis with intrathecal chemotherapy should be given to all patients with aggressive histology, such as Burkitt lymphoma.

Bone Lymphoma

With RT alone, 5-year and 10-year OS rates of 58% and 53% have been reported for solitary bone lesions. Key issues relating to local control are the intramedullary and soft-tissue extent of disease in relation to RT volume. MRI is particularly important in revealing extension of disease in the bone and soft tissues. Treatment approaches using RT have given high levels of local control (85%), but unacceptable rates of local or marginal failure (20%) probably related to underestimation of tumor extent and bulk, and systemic failure rates approaching 50% were reported. Therefore, patients with localized lymphoma of bone should be treated with CMT comprising initial anthracyline-based chemotherapy and RT.[281] The importance of consolidative RT in patients with bone involvement was highlighted in the retrospective analysis of 161 patients with skeletal involvement and complete response to chemotherapy from the MInT and RICOVER-60 trials. The 3-year event-free survival rates were significantly higher in patients who received RT, compared to those who did not (75% versus 36%, $p < 0.001$). On multivariable analysis adjusting for age, stage, LDH, performance status, E-lesions, IPI, the addition of RT reduced risk of an event by 70% ($p < 0.001$).[282]

T-Cell Lymphomas

Treatment for T-cell lymphoma is just as varied as the distinct clinicopathologic B-cell lymphomas, entities such as peripheral T cell lymphoma (PTCL), anaplastic large cell lymphoma (ALCL), and are currently treated similarly as DLBCL. ALCL has a better prognosis than PTCL. Because standard chemotherapy results in a lower cure rate for PTCL and MCL, new approaches have been advocated, including the incorporation of new drugs,[283-285] and consolidative ASCT.[30,286]

NK/T Cell Lymphoma

In Asia, a destructive, erosive lesion is a characteristic presentation and T/NK-cell tumors predominate and show the characteristic features of angioinvasion, necrosis, and epitheliotropism. Indolent lymphomas are less common. The nasal type of CD56 positive T/NK cell lymphoma is a distinct clinical-pathological entity associated with the EBV.[29,57] T/NK cell tumors with an identical phenotype and genotype can occur rarely in other extranodal sites, usually in the skin, subcutis, GI tract, and testis.[29,287] For DLBCL, the current practice of CMT yields 5-year OS rates of 60% to 75%.[61,288,289] In T/NK-cell disease, the Asian experience with stages I and II presentations are disappointing, with a response rate to doxorubicin-containing chemotherapy of less than 50%, and 5-year survival of 30% to 70%.[287,290-293] Recent Phase I and Phase II studies evaluating the efficacy of SMILE, a multidrug regimen containing dexamethasone, methotrexate, ifosfamide, etoposide, and L-asparaginase, has had more promising results. This regimen includes L-asparaginase, which has been studied in relapsed NK/T cell lymphomas as a single agent.[294,295] In patients with relapsed or refractory NK cell lymphoma, the SMILE regimen resulted in an overall response rate of 74% and complete response of 35% to 50%.[296,297]

The early use of RT to a higher dose of 45 Gy to 50 Gy appears to be important for optimal local control,[287,293,298,299] either by itself or combined with ifosfomide-based chemotherapy.[61,300] IMRT is typically recommended to allow appropriate coverage of the target while sparing normal tissues. In cases where there is skin involvement, bolus is to be applied to ensure adequate dose is delivered to the skin surface (Figure 77-8). Because of the success of single-agent L-asparaginase and the promising results in the relapsed setting, some institutions have adopted the SMILE regimen as part of an upfront combined-modality approach to NK/T cell lymphomas.[301] For patients who responded favorably to initial treatment, the use of consolidation therapy with high-dose chemotherapy and ASCT appears to result in prolonged remissions.[58]

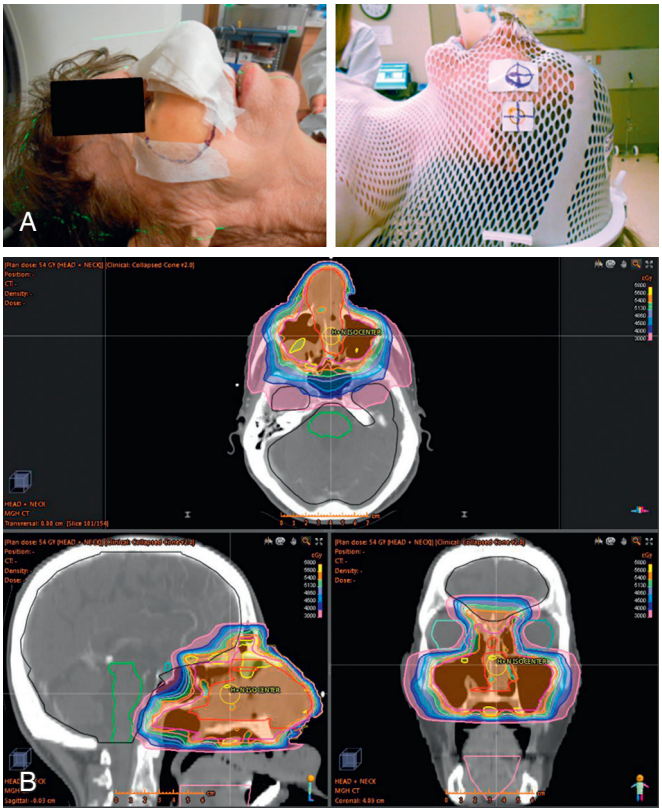


Figure 77-8 Treatment of stage I NK/T cell lymphoma using intensity-modulated radiation therapy (IMRT). **A,** Placement of bolus on areas of skin involvement under immobilizing mask. **B,** Isodose distribution of IMRT plan to the involved site. Neck nodes are not included for this patient with stage I disease.

Assessment of Response and Follow-Up

Cure requires the ability to eradicate disease; therefore, the key is to attain complete remission with the initial treatment plan. In patients treated with RT alone, response is usually assessed 4 weeks to 6 weeks following the completion of therapy. Because the RT dose fractionation schedule is determined before treatment and is usually based on information regarding dose-response relationship and tolerance of tissues within the treatment volume, the presence of residual disease at the end of the treatment course is not an indication for additional RT. The assessment of response includes examination of the organ of presentation and a general examination to rule out disease progression. In the most recent ICML recommendation,[64] PET-CT is considered standard-of-care for remission assessment for patients with FDG-avid lymphoma. However, because of therapy-related inflammation, the recommendation is to wait a minimum of 3 months after RT before obtaining a PET-CT for response assessment.

In patients with FDG-avid lymphoma treated with chemotherapy or CMT, the current recommendation is to use the 5-point scale (Deauville criteria)[302] for both interim and end-of-treatment response assessment, with a score of 1 being no uptake; 2, ≤mediastinal uptake; 3, >mediastinal uptake but <liver uptake; 4, uptake moderately higher than liver; 5, uptake markedly higher than liver or presence of new lesions; X, new areas of uptake unlikely related to lymphoma. Recent data, however, suggest that interim PET-CT may be less predictive of treatment outcome in patients who received immunochemotherapy.[303] Because of the lack of definitive evidence that modifying treatment based on interim PET-CT improves outcome in patients with lymphoma, the ICML recommends against changing treatment solely based on interim PET-CT, except for cases of clear disease progression.[64] However, end-of-treatment PET-CT to assess for remission is standard for FDG-avid lymphoma, and the recommendation is to perform the scan at a minimum of 3 weeks, but preferably 6 weeks to 8 weeks after the last cycle of chemotherapy because of posttreatment inflammatory changes.

Cutaneous Lymphomas

Histopathologic classification for cutaneous lymphomas has been proposed by a joint WHO–European Organization of Research and Treatment of Cancer (EORTC) effort, describing clinical-pathological disease entities unique to the skin.[304] Primary lymphomas of the skin can be divided into three broad categories:

1. Cutaneous B-cell lymphomas (CBCL, 25%), including indolent histologies with follicular center lymphoma and marginal-zone (MALT), and the clinically aggressive: DLBCL, leg type, or other location.
2. Cutaneous T-cell lymphomas of indolent clinical behavior (70%): Mycosis fungoides and its variants, primary cutaneous anaplastic large cell lymphoma (c-ALCL), lymphomatoid papulosis, and other rare types (e.g., subcutaneous panniculitis-like T-cell lymphoma)
3. Cutaneous T-cell lymphoma of aggressive clinical behavior (<10%): Sézary syndrome, peripheral T-cell lymphoma, and

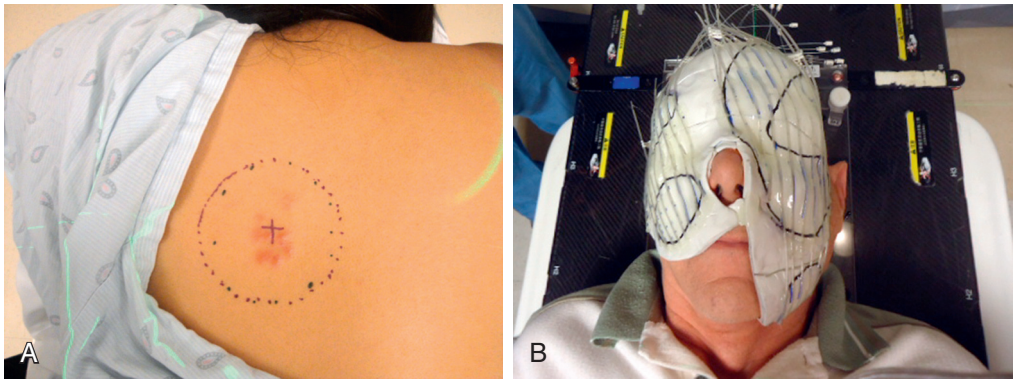


Figure 77-9 Treatment of cutaneous lymphoma. **A,** Treatment planning for electron therapy for a single site of low grade B-cell lymphoma involving the skin of the patient's back. A 2-cm margin is drawn around site of disease. **B,** Custom brachytherapy mold created for treatment of superficial curved surfaces of the face. Catheters are positioned along the surface of the mold. The areas to be treated are outlined in black.

several rare entities such as natural killer (NK) cell lymphoma of nasal type.

Cutaneous diffuse large B-cell lymphomas commonly occur in legs of elderly patients, is clinically aggressive, and has an estimated 5-year disease-specific survival of 55%.[304-309] CMT is the standard as in DLBCL of other sites. In contrast, primary cutaneous follicular center lymphomas are usually confined to the head and neck region or the trunk, with 5-year survival of higher than 95%.[304,305] Unlike nodal follicular lymphoma, BCL-2 protein expression and t(14;18) translocation are infrequent.[304,310] MALT lymphomas are indolent, respond well to local therapy, and have excellent prognosis.[304,311] Infection with *B. burgdorferi* has been implicated in the pathogensis of CBCL[136,312] although a study of 38 cases conducted in United States did not demonstrate such an association,[137] and another study showed no geographic correlation between the incidence of Lyme disease with CBCL.[138] RT is a preferred treatment modality with high local control rates (85% to 100%) and favorable survival.[313,314] Cutaneous lymphomas can be adequately treated with superficial RT techniques, including orthovoltage, electrons, and brachytherapy (Figure 77-9). Following local therapy, the relapse rate is high, frequently with skin lesions in an untreated area, but death from indolent CBCL is uncommon.[304]

Mycosis fungoides is the most common type of cutaneous T-cell lymphoma (CTCL) of indolent clinical behavior and is discussed elsewhere (Chapter 79). The other indolent CTCL is primary c-ALCL, characterized by CD30 positivity but is distinct from the nodal type of ALCL.[57,304] In contrast to nodal ALCL, the vast majority of c-ALCL does not stain for the ALK protein and is also negative for the t(2;5) translocation.[304] In patients with a solitary nodule or localized skin disease, RT is the treatment of choice. These lymphomas can relapse in the skin, but generally have a favorable prognosis,[56] with 5-year survival of 95%.[304] In a Dutch study of 79 patients, only 16% of patients have a systemic relapse of lymphoma 10 years after initial treatment.[56] Lymphomatoid papulosis is a related condition, also CD30+, and has an indolent course with spontaneously remitting disease.[56] Cytotoxic treatment is usually not necessary and life expectancy is not adversely affected, although infrequently the disease can progress to other types of T-cell lymphomas.

Other aggressive types of CTCL represent an extremely heterogeneous group and most are characterized as peripheral T-cell lymphomas—unspecified further in the WHO classification.[57] Some have morphologic and phenotypic characteristics of NK/T-cell lymphoma of nasal type,[315] and other rare entities include the aggressive CD8+ T-cell lymphoma, and gamma-delta T-cell lymphoma. Most are negative for CD30 and have a poor prognosis, with an estimated 5-year survival of 15% to 20%.[304,305]

Radiation Therapy for Palliation

In the context of recurrent lymphomas, patients are encountered where no curative therapy is available. RT is an extremely effective modality in providing symptom relief and local control. Palliative RT has been underused in lymphoma because of a variety of other systemic treatment options. The following are situations where palliative RT should be considered: (1) stages III and IV indolent histology lymphoma, with localized bulky disease; (2) relapsed or primary refractory NHL, any stage, with predominant localized disease, not eligible for intensive therapy because of old age, poor tolerance to chemotherapy or chemotherapy-resistance; (3) relapse of lymphoma postautologous and allogeneic bone marrow transplant; (4) localized lymphoma in patients with comorbidity and poor performance status not suitable for chemotherapy. When palliative RT is considered, it is important to establish the goal of therapy. Distinction should be made between attempts to achieve a prolonged local control of disease, that is, radical RT given for local control in a noncurative situation, or RT given purely for the relief of symptoms. This decision is usually based on the clinical condition of the patient, the location, size, and distribution of disease, and the life expectancy of the patient.

Radical RT for local control is not infrequently required for selected patients with chemotherapy-refractory aggressive histology lymphomas where the disease is predominately localized. In these situations, if normal tissue tolerance allows, it is desirable to deliver full dose RT with 30 Gy to 40 Gy in 10 fractions to 20 fractions over 2 weeks to 4 weeks. For rapidly progressive disease, accelerated fractionation should be considered, to 35 Gy to 40 Gy in 20 fractions to 30 fractions over 2 weeks to 3 weeks, depending on volume and normal tissue tolerance. Accelerated hyperfractionation was reported to be more effective than conventional fractionation in Burkitt's lymphomas,[316] but there are few reports of the use of altered fractionation regimens.[316,317] Concomitant chemotherapy and RT to 40 Gy for chemo-refractory bulky lymphoma was administered in a Phase II study of 21 patients and yielded a response rate of 70%, majority were partial responses.[318] When RT is given for relief of disease-related symptoms, a short course of higher dose-per-fraction therapy can be used as dictated by individual circumstance. Acceptable regimens include 20 Gy in 5 fractions over 1 week, 25 Gy to 30 Gy in 10 fractions

to 12 fractions over 2 weeks, or 12 Gy to 16 Gy in 2 fractions over 1 week.

For indolent lymphomas, excellent palliative responses to low doses of radiation, such as 4 Gy given in two fractions have been observed.[107,108,110,319] This was explained by the predominant mode of tumor cell death largely mediated by apoptosis.[320] Response rates of 90% have been obtained in selected patients with this approach.[107,108,110,319] These results are similar with the historical response rates of 71% to 83% for total body irradiation (TBI) doses of 150 cGy to 220 cGy (10 cGy to 15 cGy per fraction, two to three fractions per week) given over several weeks.[117,119]

Technical Aspects of Radiation Therapy

Because of the wide distribution of lymphoid tissues in the body, the technical aspects for RT planning for lymphomas are highly dependent on the location and extent of the target volume. Guidelines for modern RT on target definition and dose for nodal NHL were recently published by the ILROG. The concept of involved-site RT assumes that systemic therapy eradicates regional microscopic disease, and involved-site RT targets the identifiable prechemotherapy disease extent. Unlike involved-node RT where optimal, high-quality prechemotherapy imaging performed in the RT treatment planning position, ISRT accommodates cases in which optimal prechemotherapy imaging are unavailable. In such cases, the CTV determination relies on clinical judgment in conjunction with the best available imaging, accommodating for the uncertainties in defining the prechemotherapy GTV. In the setting of RT alone, for example for localized FL or marginal zone lymphoma treated with curative intent, the CTV should incorporate GTV and include as a minimum adjacent lymph nodes to encompass suspected subclinical disease.

In general, proper planning involves the appropriate use of immobilization devices, CT assistance and use of prechemotherapy PET-CT for target localization, localization of adjacent normal tissues, custom-designed beam modifying devices, and computerized calculation of isodose distributions. The goals of these steps are to define a GTV and CTV, which is expanded to create the internal target volume (ITV) and PTV. The PTV is then used to define dose coverage to achieve dose uniformity to within ±5% of the prescribed dose as specified by ICRU #83,[321] based on defining while minimizing RT dose to normal tissues. IMRT has gained increasing importance to reduce any morbidity because of the exposure of organs at risk located adjacent to the target volume, particularly in instances of repeat course of RT for relapsed disease.[322] The support of allied healthcare disciplines including dental, nutritional, physiotherapy, and social and psychology services is essential to good patient care.

In the CMT setting where chemotherapy is given before RT, there may be no abnormality or minimal residual disease at the time of RT planning. The CTV should encompass the pretreatment disease, but exclude normal structures such as lungs, kidneys, and muscles that were clearly uninvolved, though previously displaced by the GTV. An example is a bulky mediastinal mass that did not infiltrate lung tissue and has reduced in size following chemotherapy, where the RT plan need only cover the postchemotherapy abnormality. If, however, the disease was infiltrative initially into adjacent normal tissue, regression of the tumor mass still leaves microscopic residual disease in the infiltrated tissue and consideration must be given to adequately cover initial disease extent. An example would be bone lymphoma where the RT volume following a good response to chemotherapy should include the prechemotherapy extent of disease. Other specific examples of additional extranodal sites are outlined in the next section. The expansion from CTV to ITV is most relevant for targets affected by respiratory movement such as mediastinal or upper abdominal disease, where a 1.5-cm to 2-cm superior-inferior expansion may be needed. The determination of PTV depends on the type of immobilization device, body site, internal organ motion, and patient cooperation and may vary from case to case. However, if ISRT alone is used for definitive initial management (e.g., in localized FL or MALT lymphoma) any adjacent lymph nodes or tissues deemed to be at risk of microscopic involvement should be encompassed into the CTV.[105]

The dose of RT required to achieve local control varies depending on histologic type and tumor bulk. FL and MALT lymphoma are more responsive to RT, and a dose of 24 Gy to 30 Gy delivered in 15 fractions to 20 fractions over 3 weeks to 4 weeks results in local control rates in excess of 95%. For small cutaneous or orbital lesions RT doses of 25 Gy are sufficient to achieve 90% to 95% local control. Large cell lymphomas are less sensitive and require doses in the range of 35 Gy to 45 Gy. For low bulk disease treated with full courses of chemotherapy, excellent local control rates are obtained with 30 Gy,[185] whereas for bulky lymphomas treated with CMT, a dose of 35 Gy may be required.

Orbital Lymphomas

Primary orbital lymphomas are highly curable with RT. Doses of 20 G to 25 Gy results in excellent local control rates of >95%.[32,323,324] For anterior orbital lesions in the conjunctiva (Figure 77-10), a direct anterior beam with orthovoltage (250 kv), telecobalt, or 4-MV to 6-MVphotons can be used. A small lead shield suspended in front of the lens can reduce the lens dose to under 5% to 10%.[325] For unilateral retrobulbar lesions, a two-field technique with an anterior and an oblique wedged-field using 4-MV to 6-MV photons usually produce a satisfactory result. Alternatively, an anterior electron beam can be used if the lesion is superficial and there is a desire to spare the posterior orbital structures (Figure 77-11). Again, shielding for the lens can be placed to spare the lens. Lens dose of 2 Gy to 3 Gy (single fraction) or >12 Gy fractionated (fraction size 1.5 Gy to 2 Gy) may lead to cataract formation.[326] Alternately IMRT can be used.[327] Damage to the bony orbit, retina, optic nerve, and soft tissues should not be seen with doses of <40 Gy.[326] However, some dryness of the eye because of lacrimal gland effects can be observed since the tolerance dose of the lacrimal gland is 40 Gy in 20 fractions.[328]

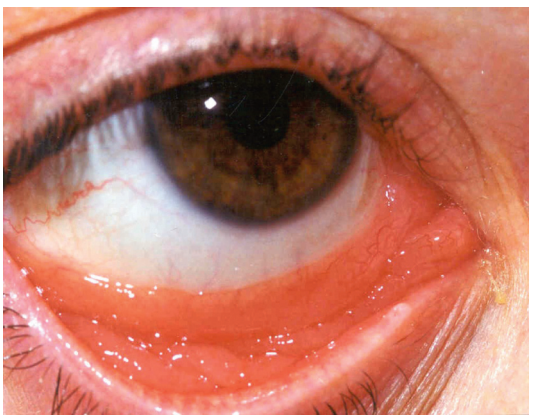


Figure 77-10 Extranodal marginal zone lymphoma of MALT type, involving the conjunctiva. The characteristic salmon-pink infiltration is seen most easily by pulling the lower eyelid downward.

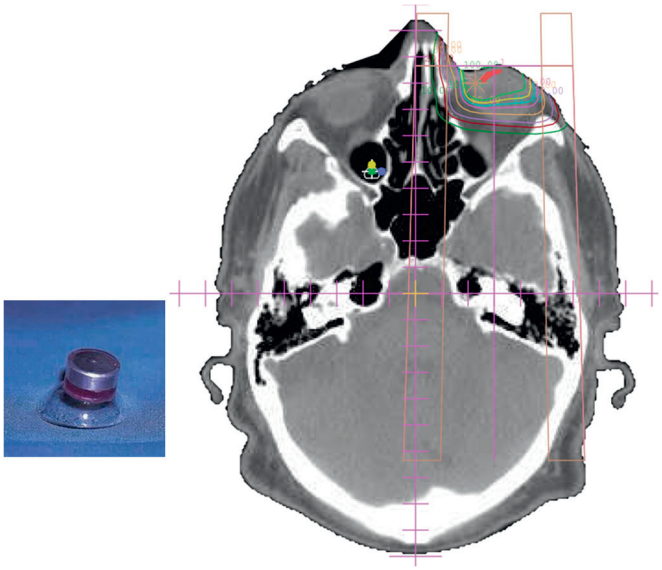


Figure 77-11 Orbital MALT lymphoma, electron therapy treating the anterior surface of the orbit (6-MeV electrons). Inset, internal lens shield to reduce dose to lens and reduce risk of cataract development.



Figure 77-12 A modified mantle field with encompassing superior mediastinal lymph nodes. Proton plan showing transverse, sagittal, and coronal views as well as dose volume histogram showing low radiation dose to organs at risk.

Thyroid Lymphoma

The RT target volume includes the thyroid bed and any involved nodes. Previously, adjacent nodal groups were targeted, often resulting in treatment of thyroid lymphoma with a modified mantle field. With improved imaging and standard use of PET-CT for staging, treatment of adjacent uninvolved nodes is no longer necessary. For an euthyroid patient, thyroid doses of 35 Gy to 40 Gy for Hodgkin's lymphoma results in a 47% risk of overt or subclinical hypothyroidism at 27 years after treatment.[329] Other abnormalities such as nodular thyroid disease, goiter, and thyroid cancer are also lifetime risks.[330,331]

Waldeyer's Ring and Salivary Gland

Where possible, an IMRT technique should be used for stages I to II Waldeyer's ring lymphomas with specific objectives to spare the parotid glands and the oral cavity. Acute morbidity of irradiation to doses of 30 Gy to 36 Gy includes xerostomia, loss of taste, and mucositis, which are usually mild to moderate in degree. Depending on the age of the patient, a degree of permanent xerostomia can be seen, as manifested in decreased saliva flow rates upon stimulation.[332] The severity of xerostomia is dependent on the total dose and the volume of salivary gland irradiated.[333] Emami et al estimated that the TD 5/5 for salivary gland function is 32 Gy and the TD 50/5 is 46 Gy.[334] Therefore, careful planning with IMRT should minimize this complication. Similarly for the treatment of unilateral salivary gland lymphomas, IMRT can be used to maximally spare the contralateral parotid gland. Maximum radiation doses of 35 Gy to 40 Gy given in 1.8-Gy to 2-Gy fractions are within the tolerance of all the other critical head and neck tissues such as the spinal cord, neurovascular structures, larynx, trachea, esophagus, oral cavity, lips, and soft tissues. However, proper attention in defining (contouring) these organs at risk to receive lesser doses is part of good IMRT treatment planning practice (Figure 77-7).

Radiation to Thoracic Structures

Because of the irregular field arrangement and contour variation, care is required to ensure dose uniformity with the use of attenuators. Customized shielding blocks are mandatory for the protection of lung and cardiac tissues. The TD5/5 for 20 fractions of whole lung radiation was 26.5 Gy (TD50 30.5 Gy) from pediatric series of patients irradiated for Wilm's tumor.[335] Partial lung irradiation with fractionated doses has been studied by Mah et al using radiographic changes as the endpoint.[336] A steep dose-response relationship was found, where the TD5 was 24.7 Gy, increasing to 33.9 Gy for TD50, and to 43.5 Gy for TD95%, normalized to 15 fractions. Many chemotherapy drugs potentiate the effects of RT on lung tissue (e.g., bleomycin, cyclophosphamide, and doxorubicin).[337] Symptomatic pneumonitis occurs in 5% to 10% of patients treated for lymphoma.[335] Use of optimal dose-fractionation parameters, careful treatment planning with evaluation of dose-volume histogram and mean doses to the lungs,[338-341] and allowing a 3-week and 4-week interval between chemotherapy and RT should minimize the incidence of symptomatic radiation pneumonitis. IMRT offers improved sparing of organs at risk in selected patients and is particularly important for retreatment of relapsed disease.[322] IMRT in combination with deep-inspiration breath-hold (DIBH) reduces radiation exposure of the coronary arteries, heart, and lungs in patients with mediastinal lymphoma.[342] A Phase II study showed that DIBH reduced the mean estimated lung dose by 2.0 Gy (median: 8.5 Gy versus 7.2 Gy) ($p < 0.01$) and the mean heart dose by 1.4 Gy.[343] Proton therapy is another treatment modality that allows for improved sparing of thoracic structures for patients with mediastinal lymphomas[344] (Figure 77-12).

Information on the cardiac tolerance to irradiation has been largely based on patients treated for Hodgkin's lymphoma. The TD 5/5 for 50% to 60% inclusion of the heart is 40 Gy in 16 fractions.[345] The commonest syndrome is delayed pericarditis with pancarditis occurring after much higher doses.[345,346] Late effects include coronary artery disease, cardiomyopathy, and myocardial infarction.[347-349] The dose per fraction should be kept under 2 Gy to minimize the risk of pericarditis.[350] The potential cardiotoxic effects of doxorubicin can also be additive to the long-term damaging effects of radiation on the heart.

Gastric Lymphoma and Issues Relating to Abdominal Irradiation

In planning radiation directed to intraabdominal structures, the radiation tolerance of the liver (TD 5/5: 25 Gy, whole

organ), bowel (small bowel, 20 cm × 20 cm fields, TD: 5/5 45 Gy), spinal cord (TD 5/5: 50 Gy), and kidneys (TD 5/5: 20 Gy) must be respected.[351-353] CT planning is extremely helpful and the principle and techniques similar to that used for gastric carcinoma can be adapted for use, with conformal fields or IMRT.[354] The intention here is to deliver a tumor dose of 30 Gy to 35 Gy to the entire stomach and limit the total dose to both kidneys to <20 Gy, while keeping a significant volume of liver to low doses. With fractionated doses of 30 Gy to 35 Gy, major serious complications to the bowel are uncommon.

Pelvic Radiation and Effects on the Reproductive System

In pelvic RT, the treatment planning must address effects of direct as well as scatter radiation to the genital organs. For example, direct doses of 20 Gy to 24 Gy to the ovaries will invariably produce ovarian ablation with loss of hormonal function resulting in menopause and sterility.[355] Therefore, treatment planning for pelvic lymph node RT should spare one ovary if possible, with ultrasound or CT guidance to locate the ovary. When bilateral pelvic irradiation is inevitable, the use of surgical oophoropexy with transposition of one ovary to the lateral abdomen and marking it with surgical clips to ensure exclusion from the radiation fields should be considered. However, this procedure alone can produce infertility because of interference with the vascular supply of the transposed ovary. Options of ovarian tissue cryopreservations should be discussed.

In males, direct radiation to the testes generally occurs in the CMT of primary testes lymphoma, or for testicular relapse of lymphoma where chemotherapy does not have full effect for this sanctuary site. Treatment planning is clinical and simulation of the field is not required. A direct anterior field with 4-MV to 6-MV photons with a visual check to encompass all scrotal contents is usually adequate. Because the germinal epithelium of the testes is extremely radiosensitive, where doses as low as 15 cGy can produce transient oligospermia,[356] and doses of 4 Gy to 6 Gy can result in permanent azoospermia, infertility is always a consequence of scrotal irradiation. Sperm banking should be considered before commencing therapy, preferably before chemotherapy. However, Leydig cell function with testosterone production can be preserved after doses of 30 Gy 35 Gy,[357] although dysfunction as manifested in a rise in luteinizing hormone (LH) and follicle-stimulating hormone (FSH) levels can be seen even for lower doses of 5 Gy to 6 Gy.[357] Based on a review of the literature, Izard concluded that approximately 50% of males receiving 14 Gy in fractionated doses will have an abnormal LH, whereas 33 Gy is required to see an abnormal testosterone level in 50%.[358]

Indirect (i.e., scatter) radiation to the testes is also a special consideration in the planning of fields close to the scrotum, particular if the field size is large. The scatter dose is mainly a function of distance from the field edge, where gonadal doses of <5% are usually achieved with a distance from the field edge of 10 cm or more, for a field size of 25 cm^2.[357] The scatter dose can be reduced further by shielding with a leaded box directly applied to the scrotum.[359]

Changing Practice in the RT Management of Malignant Lymphomas

The efficacy of RT in achieving local disease control has been accepted for many years. With excellent local control rates, attention has been focused on the optimization of chemotherapy. Rituximab improved the outcome of systemic therapy. Over the last decade, there has been significant change in clinical practice in applying RT for lymphomas. We witnessed continued reluctance to use RT for stages I and II indolent lymphomas, and a decreased utilization of RT in stages I and II aggressive lymphomas, favoring chemotherapy alone. In contrast, there is often desire to enhance local control and palliation in advanced stage disease, with RT given in conjunction with high dose programs incorporating stem-cell transplantation. There is always a desire to better define areas of "high risk" and FDG-PET has been used frequently to define active disease, and direct RT volume disposition. In indolent lymphomas, we now know that low-dose radiation results in excellent short-term palliation, with response rates for the irradiated disease often exceeding what can be achieved with systemic chemotherapy. In the midst of these changes in the pattern of practice, the question of optimal RT target volume in the majority of lymphomas has not been prospectively tested in randomized trials. Some of the challenges and controversies in the RT management of the NHL are:

1. The management of FLs:
   Despite the known efficacy of RT for localized FL utilization of RT remained low according to population-based data. The use of CMT and the role of addition of rituximab to RT in patients with localized disease require additional investigations.
2. Role of RT in DLBCL:
   Final results of the UNFOLDER Phase III trial may clarify the role of adjuvant RT in selected cases of DLBCL after R-CHOP chemotherapy. Whether RT offers additional benefit when a chemotherapy regimen more intensive than R-CHOP is used (e.g., the GELA protocol with ACVBP, followed by high-dose methotrexate with leucovorin, etoposide, ifosfomide, and cytarabine), is still not known.
3. Optimal RT dose and volume:
   Although randomized data exist suggesting 30 Gy may be adequate for patients with aggressive NHL after chemotherapy, the data did not take into account the response to modern chemotherapy. Limited data are available on optimal RT dose in the setting of partial response to chemotherapy and whether there is a role for radiation dose-deescalation after a metabolic complete response to R-CHOP chemotherapy. This question is currently being addressed in a Phase II study. Consensus-based guidelines are now available for volume definition for NHL, but additional data are needed to document the efficacy of these more limited fields for NHL.
4. Optimal RT in the setting of high-dose chemotherapy and stem cell support
   This relates to the indications, selection of patients for therapy, the use of FDG-PET to identify high-risk areas for RT, dose-fractionation parameters, and the timing with chemotherapy and ASCT.

Conclusion

NHL represents a heterogeneous group of diseases that may affect any part of the body. They are characterized by a tendency to present or progress to generalized disease. Therefore optimal systemic therapy is paramount. However lymphomas are also characterized by a high degree of radioresponsiveness and therefore RT is an important modality in controlling these malignancies. Recent progress in biology and histopathology, as well as cytogenetic techniques, has allowed us to study homogeneous patient populations and give opportunity for reassessing the role of RT in their management. Late effects of treatment manifesting as normal tissue toxicity and especially second cancers are continuing concerns following curative therapy. Attention to late morbidity while we devise treatments to improve the cure rate remains an important goal.

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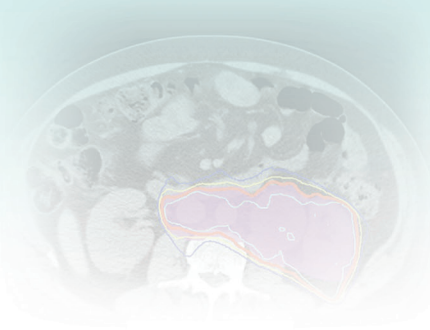
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CHAPTER

78 Multiple Myeloma and Other Plasma Cell Neoplasms



Anuj Mahindra and Andrea K. Ng

INCIDENCE AND EPIDEMIOLOGY

More than 24,000 new cases of multiple myeloma (MM) are diagnosed annually in the United States. MM accounts for 1.4% of all new cancers and 1.9% of cancer-related deaths. The rate in blacks is twice that in whites. Agricultural workers, woodworkers, and paper workers have a higher risk than other occupational groups.

ETIOLOGY AND BIOLOGIC CHARACTERISTICS

The etiology remains unknown. This hematologic malignant disease with mature plasma cell morphologic characteristics evolves from a cell late in B-cell development.

STAGING EVALUATION AND PROGNOSTIC FACTORS

The diagnosis of myeloma requires the presence of end-organ damage: anemia, elevated creatinine or calcium levels, and lytic bone lesions. Prognostic factors of most importance for MM are an increased β_2-microglobulin level and a decreased serum albumin level.

PRIMARY THERAPY AND RESULTS

Treatment of patients with symptomatic disease is indicated, excluding those with monoclonal gammopathic findings of undetermined significance or smoldering MM. The past decade has witnessed a dramatic improvement in the therapeutic options in MM. Several novel biologically targeted agents are in clinical use and have resulted in improved outcomes, including the proteasome inhibitors and immunomodulatory drugs. High-dose therapy with stem-cell transplantation remains a standard of care. A survival advantage of approximately 1 year has been shown for patients receiving high-dose therapy in two prospective randomized studies.

For solitary plasmacytoma of bone and extramedullary plasmacytoma, radiotherapy is the treatment of choice, with effective local control rates but high rates of progression to MM. Magnetic resonance imaging (MRI) may help to predict which patients are at higher risk of subsequent progression to MM.

TREATMENT OF PRIMARY REFRACTORY AND RELAPSING MYELOMA

Several promising drug therapy combinations are undergoing evaluation for refractory and relapsing myeloma. Localized radiotherapy is useful in palliation of painful or life-threatening disease.

Monoclonal gammopathies, also referred to as *paraproteinemias* or *dysproteinemias*, are a group of diseases characterized by the proliferation of a clone of plasma cells. The plasma cells produce an electrophoretically and immunologically homogeneous protein usually referred to as *monoclonal protein, M protein, M component*, or *paraprotein*. The progressive proliferation of plasma cells results in marrow replacement with a resulting normochromic or slightly macrocytic anemia. Direct infiltration of the overlying bony cortex by the malignant cells causes lytic bone disease, osteoporosis, and compression fractures of the spine. In addition, the production of a monoclonal light chain in the urine can result in a severe toxic response in renal tubules, with renal failure. Differentiation of monoclonal gammopathy of undetermined significance (MGUS) from MM and solitary plasmacytoma (SPB) is important to the selection of appropriate therapy and is discussed later in this chapter.

EPIDEMIOLOGY AND ETIOLOGY

An estimated 24,050 new cases of MM will occur in the United States in 2014, representing 1.4% of all new cases of cancer. MM accounts for 10% to 15% of all hematologic malignant diseases diagnosed in the United States, 20% of all deaths resulting from hematologic malignant diseases, and 1.4% of all cancer deaths. MM is an uncommon malignant disease in Pacific Rim countries.

The male-to-female ratio for the disease is 1.3:1. MM is a disease of older adults. The median age at diagnosis is 66 years; only 10% and 2% of patients are younger than 50 years and 40 years, respectively. The risk of developing MM is approximately 3.7-fold higher for persons with a first-degree relative with MM.

The average age of patients presenting with MM is approximately 63 years. In Olmsted County, Minnesota, the overall incidence of MM is 4.3 cases per 100,000 population per year.

Radiation has been linked to the pathogenesis of MM, but radiation exposure is found in only approximately 1% of patients. In the Hiroshima and Nagasaki tumor registries, there was no sign of an excess risk of MM.[1]

Data regarding the role of antigenic stimulation are conflicting. Epidemiologic studies in the United States have demonstrated associations between MM and agricultural workers.[2] An increasing trend for the incidence of lymphohematopoietic cancers has been associated with lifetime exposure to the chemical alachlor, a commonly used pesticide. The risk for MM gave a rate ratio of 5.66 in the highest exposure category.[3] Other occupational groups associated with the development of MM include miners, workers exposed to wood dust, and sheet metal workers.[4]

The etiology of MM remains unknown. Cytogenetic studies in MM demonstrate no consistent chromosome break point that identifies the majority of patients. Cytogenetic abnormalities, however, are less frequent in patients with MGUS, and an increase in frequency is seen as this condition evolves into MM untreated and MM relapsed. MM probably originates from a germinal center B cell of the lymph node. Receptors allow these cells to migrate from the lymph node to the bone marrow (BM).

Myeloma plasma cells express several adhesion molecules, including neural cell adhesion molecule (NCAM). Adhesion molecules are involved in homing of plasma cells to BM.

Although MM is a neoplasm of end-stage plasma cells, most investigators believe that myeloma stem cells exist as a self-renewing population derived from an earlier compartment. The identity of the cells responsible for the initiation and maintenance of MM remains unclear. Circulating B cells clonally related to MM plasma cells have been reported in some patients with myeloma. Data suggest that myeloma stem cells are CD138– B cells, whereas the terminally differentiated plasma cell is consistently CD138+, though this concept needs further validation. These CD138– B cells can replicate and differentiate into the malignant CD138+ plasma cells.[5] Overexpression of BCL-2 and BCL-6 proteins has been seen in clinical myeloma and myeloma cell lines.[6] Cytokines, including tumor necrosis factor-alpha (TNF-α), interleukin-1 (IL-1), and IL-6, play an essential role in the biology of the malignancy as well as in mediating the bony manifestations of the disease. Both IL-6 and BCL-2 have been shown to prevent apoptosis, and IL-6 has been implicated as an essential growth factor in MM.[7]

PATHOLOGY AND MOLECULAR GENETICS

The morphology of the plasma cell in MM is relevant prognostically. Immature and plasmablastic plasma cells are associated with a poor prognosis. When 3% of the plasma cells in the BM are indistinguishable from lymphoblasts, this has been defined as *plasmablastic myeloma* and is associated with a higher prevalence of renal insufficiency and bone disease. Other prognostic features seen on evaluation of the BM biopsy specimen include marked dysplasia, number of mitoses per high-power field, and packing of the BM by tumor.

MM is distinct in that the BM is involved in virtually all patients (Figure 78-1), yet the peripheral blood shows large numbers of circulating cells in only a few patients. Adhesion molecules mediate both homotypical and heterotypical adhesion of tumor cells to either extracellular matrix (ECM) proteins or BM stromal cells. They play a critical role in disease progression. After class switching in the lymph node, adhesion molecules (e.g., CD44, VLA-4, VLA-5, LFA-1, CD56, syndecan-1, and MPC-1) mediate homing of MM cells to the BM stromal cells. Syndecan-1 is a multifunctional regulator of tumor cell growth and survival as well as of bone cell differentiation, and elevated serum syndecan-1 correlates with increased tumor cell mass, decreased metalloproteinase-9 activity, and poor prognosis.[8] Syndecan-1 is shed from the surface of most MM cells, induces apoptosis and can inhibit the growth of MM cells; it also mediates decreased osteoclast and increased osteoblast differentiation.[8] Novel agents, including thalidomide, and derivatives (IMiDs), including lenalidomide, as well as the proteasome inhibitor bortezomib can target both the tumor cell and its BM microenvironment, thereby overcoming cell adhesion-mediated (CAM) conventional drug resistance.[9,10] *TP53* mutations are associated with more advanced myelomas and are related to the terminal phases of the disease.[11] Mutations of *RAS* are more prevalent in MM than in other lymphoid malignant diseases. In a study using genomic DNA in 128 patients, *RAS* mutations were far more common in patients with aggressive plasma cell leukemias (30%) than in MM patients (9%). The *RAS* mutations appear to represent a late molecular lesion in the process of myeloma evolution. When levels of *RAS* were studied in 160 patients with newly diagnosed MM, the median survival rate for patients with mutations of N-*RAS* was no different from that of patients with no *RAS* mutations. However, patients with K-*RAS* mutations had significantly higher tumor burdens at diagnosis and a median survival time of 2 years versus 3.7 years for those who did not have K-*RAS* mutations. The *RAS* mutations appear to have an independent impact on the median survival rate of patients with MM.[12]

IgH rearrangements can be found in 75% of patients. Dysregulation of cyclin D_1 can be detected in 30% of MM tumors. Cell lines that overexpress cyclin D_1 have a translocation detectable into a gamma switch region that suggests an error in VDJ recombination. V_H analysis of the clonal cells in MGUS showed much lower mutation frequencies than in MM. The clonogenic cell in MM likely originates from a preswitched but somatically mutated B cell. Genetic studies have demonstrated that the progression of MM from plateau phase to relapse does not involve a new B-cell clone, and progression beyond the plateau phase is not the result of clonal succession.[13] Advances using molecular probes for fluorescence in situ hybridization (FISH) have demonstrated aneuploid chromosomes where conventional cytogenetics are normal. Chromosome 13 abnormalities on metaphase cytogenetics have been associated with an unfavorable prognosis in patients with myeloma. The translocation t(11;14) results in up-regulation of cyclin D_1 and is the most common translocation detected in patients with MM. Sixteen percent of patients carry the t(11;14) and have better survival and response to therapy rates.[14] Immunoglobulin heavy-chain translocations are seen in 60% of patients, and these translocations are more likely to be nonhyperdiploid. Patients with light-chain myeloma never display a functional immunoglobulin heavy-chain recombination. Most patients with light-chain myeloma have one immunoglobulin heavy-chain allele with a germline configuration. The second allele is usually involved in an illegitimate recombination. Light-chain myeloma may be the result of the absence of legitimate immunoglobulin heavy-chain rearrangement at the DNA level.[15]

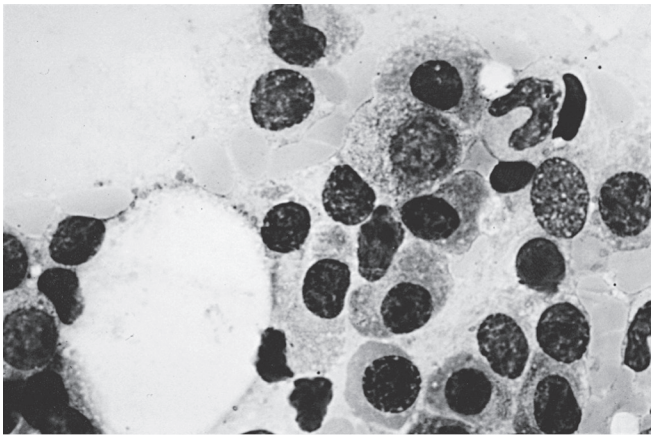


Figure 78-1 Bone marrow diagnostic for multiple myeloma. (Wright stain; original magnification ×1000.)

CLINICAL MANIFESTATIONS AND PATIENT EVALUATION

Multiple Myeloma and Monoclonal Gammopathy of Undetermined Significance

The key to early detection of MM is recognizing the associated clinical syndromes and presentations and permitting appropriate diagnostic tests to be performed. The clinician must order electrophoresis of serum and urine for all patients who present with normochromic normocytic or slightly macrocytic anemia. Electrophoresis of serum and urine can often obviate needless diagnostic investigations for gastrointestinal tract blood loss or other invasive techniques. In a patient who has



Figure 78-2 Advanced compression fractures of multiple myeloma. Note the lack of features specific for malignancy.

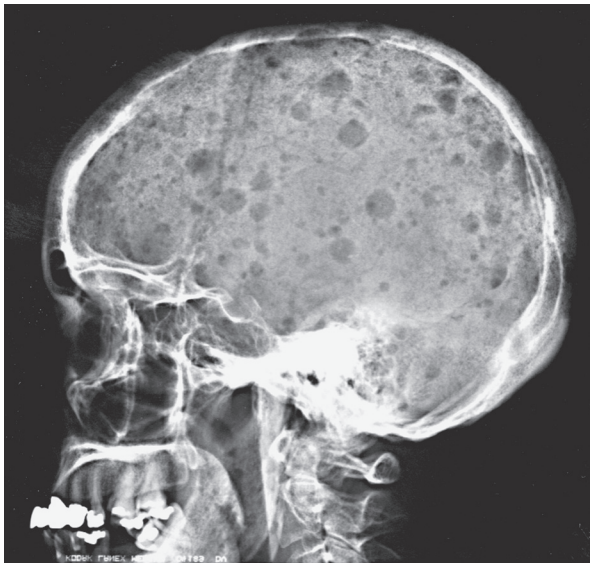


Figure 78-3 Calvarial radiograph from a patient with multiple myeloma.

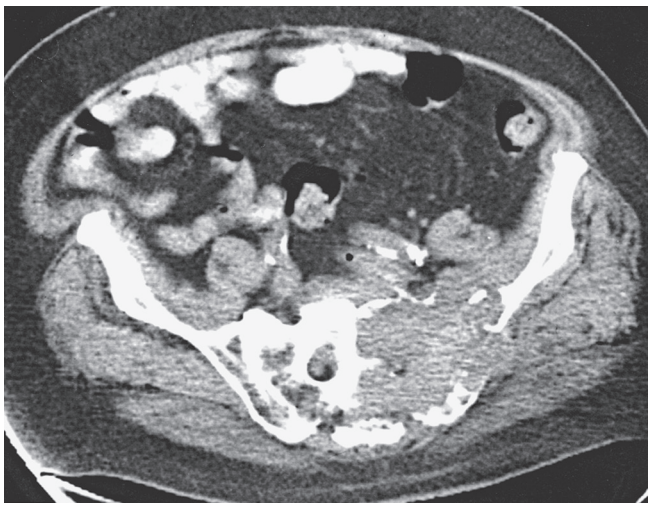


Figure 78-4 Diagnostic computed tomographic scan of pelvic plasmacytoma. Plain radiographs revealed only rarefaction and were not diagnostic.

any degree of unexplained renal insufficiency (i.e., a nonhypertensive, nondiabetic patient), urine immunoelectrophoresis often leads to recognition of myeloma cast nephropathy.

Bone involvement is frequent in patients with myeloma and bone pain is a common problem. Radiographs of the spine in patients with MM frequently show osteoporosis and compression fractures. It is virtually impossible to distinguish the compression fractures associated with MM from those seen in patients with senile osteoporosis (Figure 78-2). Spine radiographs poorly demonstrate the small lytic lesions frequently responsible for collapse of these vertebrae. All patients with back or rib pain, even with no malignant features on radiographs, should have electrophoresis of serum and urine. If a monoclonal protein is found, radiographs of the entire skeleton often demonstrate lytic lesions in the calvaria, pelvis, and long bones of the humerus and femur (Figure 78-3).

Assessment of bone disease initially requires a radiographic bone survey. Because the lesions of MM are primarily lytic, with little evidence of bony repair, radionuclide bone scans tend to be an inferior approach. In difficult cases in which osteoporosis and monoclonal gammopathy are found with no other changes, computed tomography (CT) scan or MRI of the spine and pelvis can be valuable in detecting clear-cut evidence of neoplasia (Figure 78-4). Positron emission tomography (PET) may be useful in MM because the lytic lesions are PET avid. When 66 patients were studied with PET and compared with CT and MRI, negative PET findings reliably predicted stable MGUS.[16] All patients with active myeloma had focal or diffusely positive scans, four of whom had negative full radiographic bone surveys. Extramedullary uptake was detected by PET in 23% of relapsing patients. PET also tracks response, showing a decline in lesion metabolic activity with successful intervention. It is more sensitive than other imaging techniques, and it can find additional lesions in a third of patients, which affected therapeutic decision making for a quarter of these patients.[17]

Failure to perform electrophoresis studies in patients presenting with back pain or osteoporosis can delay a diagnosis of MM. The need for screening electrophoresis cannot be overemphasized. The most common reason for a delayed diagnosis of MM is the simple finding that MM was not included in the differential diagnosis.

A second clinical problem is distinguishing MGUS from overt MM. In MGUS, the patient is expected to be asymptomatic, without evidence of anemia, hypercalcemia, bone involvement on skeletal survey, or renal insufficiency. In the absence of symptoms and with a low monoclonal protein value, regular monitoring of the level of the monoclonal protein should suffice. Patients with monoclonal gammopathies, however, should be monitored indefinitely because the risk for transformation to a malignant plasma-proliferative process is approximately 1% per year. The risk for transformation is predicted by the initial size of the M protein peak. Patients

with low monoclonal protein levels (≤0.5 g/dL) had a 6% risk for developing MM at 10 years compared with an 11% risk at 10 years for those with a 1.5-g/dL peak and a 24% risk at 10 years for those with a 2.5-g/dL peak.[18]

The frequency of monitoring patients with MGUS depends on risk factors identified at initial evaluation. Although there are no findings at diagnosis of MGUS that reliably distinguish patients who will remain stable from those who will progress to MM, the size and type of the M protein at diagnosis are predictive factors for progression of MGUS to myeloma or related malignant disease. MGUS is associated with a low risk of progression when the M protein level is less than 1.5 g/dL. Patients with IgM or IgA monoclonal protein had a significantly increased risk of progression to disease, as compared with patients having an IgG monoclonal protein. Presence of an abnormal (monoclonal) kappa/lambda free light-chain ratio in the serum is also associated with a significantly higher risk of disease progression.

Staging of Multiple Myeloma

Classification of patients with MM by stage is important. Comparison of outcomes in single-arm studies of MM depends on patient selection and case mix. Therefore, ensuring that patients have comparable severity of disease is important when comparing the outcomes of various studies. In addition, stage may be useful in selecting patients with unfavorable outcomes for more intensive therapies. Conversely, patients who are at a low stage and whose prognosis is good may be candidates for less intensive therapies and may achieve outcomes similar to those of aggressively treated patients.

The most widely accepted classification is the International Myeloma Working Group staging system, where stage III myeloma is a β_2-microglobulin level higher than 5.5 μg/mL. Stage I includes patients with a β_2-microglobulin level that is less than 3.5 μg/mL and a serum albumin level that is less than 3.5 g/dL, and stage II includes all patients who do not fit stage I or stage III (Table 78-1).

The older staging system in clinical use is that of Durie and Salmon (Table 78-2). One problem with the Durie-Salmon staging system is that the criteria for stage I MM in this scheme are also consistent with smoldering MM and indolent MM, which do not require any form of therapy. In most clinical therapy studies, no more than 10% of patients have stage I disease, and many studies exclude patients with stage I from participation. The second difficulty is the subjective nature of interpretation of advanced lytic lesions to distinguish stage II from stage III. No specific well-defined criteria exist to ensure that all institutions use the same definition of advanced MM.

Response is generally assessed by the reduction in monoclonal protein; a reduction of 25% to 50% is considered a minor response and 50% to 99% an objective response. Complete eradication of the monoclonal protein in the serum and in the urine with less than 5% plasma cells in the BM is considered a complete response. Patients who either did not have a BM test performed or whose monoclonal protein was no longer visible but detectable by immunofixation are considered to have a near-complete response. In recipients of autologous transplants, a complete response predicts improved outcome after transplantation.[19]

TABLE 78-1 International Myeloma Working Group Staging System

Stage	Criteria
I	β_2-microglobulin <3.5 μg/mL and albumin ≥3.5 g/dL
II	β_2-microglobulin <3. μg/mL and albumin <3.5 g/dL or β_2-microglobulin = 3.5-5.5 μg/mL
III	β_2-microglobulin ≥5.5 μg/mL

THERAPY FOR MULTIPLE MYELOMA

The treatment of MM is reserved for patients who are symptomatic. There are ongoing studies to assess impact of treatment in patients with high risk smoldering myeloma. Generally, outside a clinical trial, observation is currently recommended for patients with smoldering myeloma.

Most patients with MM have symptomatic disease at diagnosis and require systemic therapy. Specific indications for treatment include decreasing concentration of hemoglobin, increasing concentration of calcium and creatinine, lytic bone lesions, and extramedullary plasmacytoma.

Patients undergoing therapy for MM should have clinical and laboratory assessment to ensure both safety and efficacy of treatment (Table 78-3). Before each course of treatment, a complete blood count, including differential and platelets, should be done. Serum chemistries should be measured at

TABLE 78-2 Durie-Salmon Staging System of Multiple Myeloma

Stage	Criteria
I	All of these required: hemoglobin >10 g/dL, Ca^{2+} <10.5 mg/dL, IgG <5 g/dL or IgA <3 g/dL and light-chain loss <4 g/dL No lytic bone lesions
II	Not fitting stage I or III
III	Any one of the following: hemoglobin <8.5 g/dL, Ca^{2+} >12 mg/dL, IgG >7 g/dL, IgA >5 g/dL, or light-chain loss >12 g/dL Advanced lytic lesions
IIIA	Creatinine <2 mg/dL
IIIB	Creatinine ≥2 mg/dL

TABLE 78-3 Required Testing to Evaluate Multiple Myeloma

Category	Test
Blood	Complete blood cell count Creatinine Calcium Sodium, potassium Uric acid Albumin Alkaline phosphatase Aspartate aminotransferase Serum protein electrophoresis with immunofixation Serum free light-chain assay β_2-microglobulin Lactate dehydrogenase C-reactive protein
Urine	Urine protein electrophoresis Urine immunofixation Creatinine clearance
Radiography	Skeletal survey
Miscellaneous	Electrocardiogram Bone marrow aspirate and biopsy

least every 3 months or more often if clinically indicated. Concomitantly, monoclonal protein in the serum should be measured by immunoelectrophoresis or, preferably, using more sensitive immunofixation techniques and a serum free light-chain assay must be done in patients with light-chain disease. A skeletal survey should be done annually, with BM examination reserved for diagnosis and time of subsequent change in clinical status, in monoclonal Ig, or in hemogram. A BM examination is typically done at diagnosis and subsequently at the time of change in clinical status (i.e., for assessment of response or at time of relapse).

Treatment and Emerging Novel Therapies

In patients who are candidates for hematopoietic cell transplantation (HCT), induction chemotherapy is administered for 2 to 4 months before stem-cell collection to reduce the number of tumor cells in the BM and peripheral blood, lessen symptoms, and mitigate end-organ damage.

There has been a shift in the treatment paradigm in MM toward moving away from conventional chemotherapy and incorporating the use of novel agents. Thalidomide was used as a sedative and antiemetic in the 1950s, when it was withdrawn from the market as a result of teratogenicity. Its exact mechanism of action is unknown, but its antiangiogenic properties are thought to inhibit the growth of myeloma. Thalidomide also alters the adhesion of myeloma cells to the BM stroma. Several trials using thalidomide in the management of relapsed MM have shown response rates from 30% to 45%.[20] There is no clear relationship between dose and response. Although doses of up to 800 mg have been used, 50 mg to 200 mg is the typical dose for long-term management. The side effects of thalidomide are significant and, when combined with dexamethasone, deep vein thrombosis occurs in 16% and grade III or IV toxicities in 44% of patients.

Lenalidomide was developed as a thalidomide analog, using the structural backbone of thalidomide but with the elimination of a carbonyl group and the addition of an amine, originally to more effectively inhibit TNF-α. Several other potential mechanisms for the anti-MM effect of lenalidomide have been identified. Lenalidomide was noted to have a better side effect profile, with decreased peripheral neuropathy, somnolence, and gastrointestinal toxicity compared with thalidomide, but with greater myelosuppression. The favorable side effect profile and efficacy of lenalidomide was confirmed in two large, randomized, multicenter, double-blind, placebo-controlled studies in patients with relapsed or refractory myeloma—the MM-009 North American trial and the MM-010 European/Israeli/Australian trial.[21,22] In both studies, patients were randomized to receive 25 mg of oral lenalidomide or placebo on days 1 to 21 of a 28-day cycle. All patients received dexamethasone on days 1 to 4, 9 to 12, and 17 to 20 for the first four cycles and subsequently, after the fourth cycle, only on days 1 to 4. The median time to progression was significantly longer in the lenalidomide/dexamethasone combination (MM-009: 11.1 months; MM-010: 11.3 months) compared with placebo/dexamethasone (4.7 months in both trials). Similar superiority was seen for the lenalidomide/dexamethasone combination in terms of overall response (OR) rate (MM-009: 61%; MM-010: 60.2%) compared with placebo/dexamethasone (MM-009: 19.9%; MM-010: 24%).

In a Phase III trial conducted by the Eastern Cooperative Oncology Group (ECOG E4A03), 445 previously untreated patients with MM were randomly assigned to lenalidomide plus "standard" high-dose dexamethasone (40 mg/day by mouth on days 1 to 4, 9 to 12, and 17 to 20 of each cycle) versus lenalidomide plus lower-dose dexamethasone (40 mg by mouth on days 1, 8, 15, and 22 of each 28-day cycle).[23] The trial was stopped prematurely by the data safety monitoring committee because mortality was increased in the high-dose dexamethasone arm.

Pomalidomide, a new immunomodulatory agent, has demonstrated significant anti-MM activity in patients who have disease refractory to thalidomide, lenalidomide, or bortezomib. Pomalidomide in combination with dexamethasone has demonstrated response ~35% in patients with prior treatment with lenalidomide, thalidomide, and bortezomib.[24,25]

Prophylaxis against clotting with aspirin, Coumadin, or subcutaneous heparin is needed when patients are treated with lenalidomide or pomalidomide therapy.

Bortezomib represents a novel class of anticancer compounds, the proteasome inhibitors. These drugs induce cell death by blocking degradation of apoptotic molecules that are normally catabolized via proteasome proteolysis. They inhibit nuclear factor kappa B (NFκB) activation by stopping the cleavage of its bound suppressor. Increased NFκB activity has been described in myeloma cells, and proteasome inhibitors seem to overcome chemotherapy resistance. A Phase III study of bortezomib with dexamethasone suggested that the time to progression was prolonged in the bortezomib group. Bortezomib produces a response in approximately one third of patients with relapsed MM; its primary toxic effects are thrombocytopenia and peripheral neuropathy.[26]

The bench to bedside translation of bortezomib and approval by the U.S. Food and Drug Administration (FDA) were also rapid. NFκB was identified as a target in MM because it conferred drug resistance, modulated adhesion molecule expression on MM cells and BM stromal cells, and modulated constitutive and MM binding-induced transcription and secretion of cytokines. Phase I trials showed tolerability and early evidence of anti-MM activity. The Phase II SUMMIT trial demonstrated responses in relapsed refractory MM, including complete responses, prolongation of time to progression and survival, and associated clinical benefit.[27] The Assessment of Proteosome Inhibition for Extending Remissions (APEX) trial, which compared dexamethasone versus bortezomib therapy of relapsed MM, was unblinded because of a statistically significant prolongation in time to progression in the bortezomib-treated cohort, forming the basis for its FDA approval extending to relapsed MM.[26] With follow-up, time to progression and overall survival rates are significantly improved with bortezomib and neurologic complications manageable.

Carfilzomib is a novel irreversible proteasome inhibitor of the epoxyketone class that is selective for the chymo-trypsin-like protease, with less affinity for other proteasome proteases. In the open-label, single-arm Phase II PX-171-003-A1 study, patients received carfilzomib 20 mg/m^2 intravenously twice weekly for 3 out of 4 weeks in cycle 1, then 27 mg/m^2 for up to 12 cycles with low-dose dexamethasone as premedication. Patients had a median of five prior lines of therapy and 80% were refractory to or intolerant of both bortezomib and lenalidomide. The overall response rate was 23% with median duration of response of 7.8 months and a median overall survival of 15.6 months. Common adverse events included fatigue (49%), anemia (46%), nausea (45%), and thrombocytopenia (39%). Twelve percent of patients experienced peripheral neuropathy, primarily grades 1 to 2.[28]

In the PX-171-004 study, carfilzomib with low-dose dexamethasone premedication was given to patients with MM who were bortezomib-naïve. Patients in cohort 1 received IV carfilzomib 20 mg/m^2 for all treatment cycles, whereas those in cohort 2 received 20 mg/m^2 in cycle 1 and 27 mg/m^2 in subsequent cycles. The clinical benefit (minimal response or better) was 59% and 64% in cohorts 1 and 2, respectively. Median duration of response was 13 months and not reached in the respective cohorts, and median time to progression was

8 months and not reached, respectively. The most common treatment-related adverse events were fatigue (62%) and nausea (48%). There was a relatively low incidence of peripheral neuropathy at 17% and other nonhematologic toxicity proved manageable.[29]

The combination of bortezomib, lenalidomide, and dexamethasone has been studied in the relapsed/refractory and upfront setting. In the upfront setting, 66 patients received eight 3-week cycles of bortezomib 1 mg/m^2 to 1.3 mg/m^2 (days 1, 4, 8, and 11), lenalidomide 15 mg to 25 mg (days 1 to 14), and dexamethasone 40 mg or 20 mg (days 1, 2, 4, 5, 8, 9, 11, and 12). Responding patients proceeded to maintenance or transplant. Phase II dosing was determined to be bortezomib 1.3 mg/m^2, lenalidomide 25 mg, and dexamethasone 20 mg. The rate of partial response or better was 100% in both the Phase II population and overall, with 74% and 67% achieving a very good partial response or better. Adverse cytogenetics had no effect on the rate of response or progression-free survival (PFS).[30] The combination of lenalidomide, carfilzomib, and dexamethasone has demonstrated similar impressive results.[31]

The combination of pomalidomide, carfilzomib, and dexamethasone has been shown to have encouraging results even in patients with high-risk features in a preliminary study in patients with relapsed/refractory myeloma.[32]

Monoclonal antibodies [MoAbs] are as an important modality in the treatment of myeloma. Examples include anti-CS1 MoAb elotuzumab, anti-CD 38 MoAbs (daratumumab, SAR 650984) and anti-CD 138 antibody conjugate BT062 comprised of the anti-CD138 chimerized MAb and the cytotoxic agent DM4,[33-35] which are being evaluated in clinical trials presently.

Stem-Cell Transplantation

The use of alkylating agents (melphalan, cyclophosphamide, busulfan) in a higher-than-conventional dose followed by infusion of autologous stem cells as part of management is considered the standard of care. In one prospective randomized study, the probability of event-free survival for 5 years was 28% in the transplant group and 10% in the conventional-dose group.[36] The estimated rate of survival for 5 years was 52% in the high-dose group and 12% in the conventional-dose group (p = 0.03). The U. K. Medical Research Council, in a prospective randomized study, demonstrated a higher rate of complete response, 44%, versus 8% with conventional therapy, and an improved overall survival time of 54.1 months versus 42.3 months.[37] Patients with sensitive disease and who are less heavily pretreated have the most favorable outcomes.

In 162 patients who had allogeneic BMT for MM, the European Group for Blood and Marrow Transplantation (EBMT) reported a 32% survival rate at 4 years and a 28% rate at 7 years.[38] In the 72 patients (44%) who achieved complete remission after BMT, the overall PFS rate was 34% at 6 years. Only 9 patients, however, remained in complete remission more than 4 years after allogeneic BMT. With allogeneic BMT, some of the decreased survival time can be attributed to peritransplantation mortality, approaching 40% in some series, because of graft-versus-host disease and other complications of the procedure itself.

Because of these difficulties with allogeneic BMT, autologous peripheral blood stem-cell transplantation has become the more common procedure in the treatment of untreated, refractory, or recurrent MM. Applicability to older patients (upper age limit of 75 years in many centers) without the need for a matched donor and with less risk for transplant-related mortality (<3% in larger centers) has made this procedure accessible to more patients with MM. The disadvantages of autologous BMT in this BM malignant disease include the difficulty of removing tumor cells from the transplanted peripheral blood or marrow and the lack of a potential graft-versus-myeloma effect.

In a prospective randomized study, sequential tandem autologous transplantation demonstrated superior survival rates compared with single stem-cell transplantation. Drawbacks of this study included conditioning that does not conform to current standards and the fact that the single-transplant group achieved a median survival time of only 48 months, which is shorter than survival times in many other reported studies.[39] The second transplantation is normally completed within 6 months of the first.

The benefit of high-dose chemotherapy and autologous stem-cell transplantation in the era of novel agents is the focus of ongoing studies.

The principal characteristics that determine eligibility for HCT are performance status or the presence and severity of certain comorbid conditions. Among patients with symptomatic standard-risk MM who are not candidates for autologous HCT, we recommend a regimen consisting of lenalidomide plus low-dose dexamethasone, Velcade (bortezomib), melphalan, and prednisone (VMP) or bortezomib plus low-dose dexamethasone. In a prospective Phase III randomized trial comparing VMP with melphalan and prednisone (MP) in the treatment of 682 older adults (median age 71 years) with newly diagnosed MM at a median follow-up of 16.3 months, patients treated with VMP had a significantly longer median time to progression (24 months versus 17 months), and higher rates of overall survival (87% versus 78%) when compared with those treated with MP.[40] Combined with prior data, these results led to the approval of VMP by the FDA for the initial treatment of MM.

In a Phase III trial comparing the efficacy and safety of Revlimid and dexamethasone to that of melphalan plus prednisone and thalidomide in patients with newly diagnosed MM who were 65 years and older (median age of 73 years) or not eligible for stem-cell transplantation, patients were divided into one of three treatment groups, receiving either Revlimid plus dexamethasone (Rd) until disease progression, Rd for 72 weeks, or melphalan plus prednisone and thalidomide (MPT) for 72 weeks. The results showed that more patients responded to continuous treatment with Revlimid (75%) than 72 weeks of RD (73%) or MPT (62%). The median PFS was significantly longer for those who received continuous Rd (26 months) than for those who received Rd for 72 weeks (21 months) and those who received MPT (21 months). The differences in PFS became apparent at the 72-week mark when two of the groups discontinued treatment. The 4-year overall survival was longest for those who received continuous Rd (59%), compared to those who received Rd for 72 weeks (56%) and those who received MPT (51%). The difference was significant for continuous Rd compared to MPT.[41]

Maintenance Therapy

Novel therapies are now being evaluated to prolong PFS rates. For example, the 3-year median and overall PFS times were prolonged by the use of thalidomide following transplantation. Thalidomide with or without prednisone has been evaluated as maintenance. Because lenalidomide is an oral drug with fewer side effects, it has undergone evaluation as maintenance treatment. In a Phase III study to determine the efficacy and safety of lenalidomide in combination with melphalan and prednisone (MPR) in elderly patients with newly diagnosed MM, the PFS rate was significantly improved in patients who received MPR followed by lenalidomide maintenance

compared with those who received MP followed by placebo maintenance.[42] In a Phase III intergroup study of lenalidomide versus placebo maintenance therapy following single autologous stem-cell transplant (CALGB 100104) maintenance therapy with lenalidomide, when compared to placebo, prolonged time to disease progression. The median time to progression was 46 months in the lenalidomide group and 27 months in the placebo group ($p < 0.001$).[43]

Supportive Treatment

Newer supportive modalities are useful in the management of patients with MM. Although chemotherapy can destroy the malignant clone and may prevent progression of bony disease, it does not lead to remineralization or recalcification of previously involved bone. Monthly infusions of pamidronate or zoledronic acid for 9 consecutive months reduced the proportion of patients who had any skeletal events from 41% to 24%.[44] Patients who received pamidronate had significant decreases in bone pain and an improved quality of life. Pamidronate or zoledronic acid has a significant palliative effect in patients with bone pain secondary to metastasis. Bisphosphonates act by inhibiting bone resorption. They have a major effect on osteoclasts and reduce bone-resorbing cytokine production. Zoledronic acid is 100 times more potent than the bisphosphonate most commonly administered orally, alendronate. These agents reduce the frequency of skeletal-related events, including the need for irradiation for bone pain, pathologic fracture, and spinal cord compression. The toxic effects of bisphosphonates include an increase in the serum creatinine level, proteinuria, and osteonecrosis of the jaw. Vertebroplasty is high-pressure injection of low-viscosity material into the vertebral body, designed to stabilize painful vertebral compression fractures. It can be done on an outpatient basis by an interventional radiologist. Its risks include leak of the material and encroachment on a nerve root.

Solitary Plasmacytoma

Solitary plasmacytoma, which accounts for 5% to 10% of all plasma cell dyscrasias, is characterized by the presence of a plasmacytoma in the absence of multiple osteolytic lesions or other features of MM.[45] Approximately two thirds of the cases are solitary plasmacytomas of the bone, which most commonly involve the axial skeleton, while the remaining one third are extramedullary plasmacytomas, most frequently presenting in the upper aerodigestive tract. Progression to MM is more likely to occur in plasmacytoma of the bone than in extramedullary plasmacytoma.[46] The 5-year and 10-year rates of progression to MM in patients with solitary plasmacytoma of the bone are 30% to 50% and 70% to 90%, respectively, whereas around 10% to 35% of patients with extramedullary plasmacytoma eventually progress to MM.[47,48]

Definitive radiation therapy is considered standard therapy for patients with solitary plasmacytoma. Retrospective series using doses ranging from 35 Gy to 60 Gy showed a more than 80% local control rate. In the largest series to date reported by the European Multicenter Rare Cancer Network, which included 258 patients with solitary plasmacytoma (206 with solitary plasmacytoma of the bone and 52 with extramedullary plasmacytoma), the median dose of radiation therapy was 40 Gy (range, 20 Gy to 66 Gy).[49] At a median follow-up time of 56 months, 14% of patients developed a local recurrence (median, 20 months). The 10-year probability of progression to MM was 72% for solitary plasmacytoma of the bone and 36% for extramedullary plasmacytoma.

Several studies have evaluated optimal radiation doses for solitary plasmacytoma,[47,49-55] although most have failed to show a significant dose-response relationship. In the study by the European Multicenter Rare Cancer Network,[49] after adjusting the radiation dose to a biologically equivalent dose (BED) of 2 Gy per fraction, no dose-response relationship was observed for doses of more than 30 Gy. Of the 244 patients treated with radiation therapy, 2 (6%) of 32 patients treated with 30 Gy or less developed local failure compared with 27 (13%) of 212 patients treated with more than 30 Gy. When limiting the analysis to tumors of 4 cm or larger, there continues to be a lack of a significant dose-response relationship beyond 30 Gy. Other smaller series also failed to show significant differences in local control rates with doses of less than 30 Gy versus higher doses.[47,51,54] A meaningful evaluation of optimal radiation dose may be limited by the retrospective nature and the small patient numbers in the available studies. Suh et al reported on radiation treatment outcome of 38 patients with solitary plasmacytoma and found that radiotherapy doses of >40 Gy was associated with a significantly higher local control rate (10-year local control of 100% versus 60%, $p = 0.04$).[56] One study from France on 17 patients with extramedullary plasmacytoma of the head and neck region,[52] showed that a dose of >45 Gy to the target volume is associated with an improved local control rate (5-year local control of 100% versus 50%, $p = 0.034$). In a study from Turkey that included 80 patients with solitary plasmacytoma,[50] on multivariable analysis, doses of 50 Gy or less were associated with a significantly lower PFS rate (hazard ratio [HR], 2.3; $p = 0.04$). Although data supporting the use of higher doses are limited, most centers recommend doses of 45 Gy to 50 Gy in 1.8-Gy to 2-Gy daily fractions as definitive treatment for patients with solitary plasmacytoma.

The optimal radiation treatment volume has not been specifically addressed for solitary plasmacytoma. However, it is generally acceptable to include the gross disease plus a margin of 2 cm. Patients with extramedullary plasmacytoma, especially of the head and neck region, may benefit from treatment with intensity-modulated radiation therapy (IMRT) techniques to limit doses to normal structures and to preserve the quality of life.[47] For these patients, most series also included clinically uninvolved regional nodes in the treatment volume. In the European Multicenter Rare Cancer Network study, however, which also included 52 patients with extramedullary plasmacytoma,[49] the planning radiation treatment volume was limited to the radiographically visible gross tumor volume plus a margin; no attempt was made to cover regional lymph nodes. At a median follow-up time of 54 months, no regional nodal relapses were observed.

Investigators have explored factors predicting for local recurrence and progression to MM in patients with solitary plasmacytoma. Findings on the impact of tumor size on local control rates have been conflicting. Tsang et al showed that the 8-year local control rate was 100% for tumors of less than 5 cm as compared with 38% for tumors of 5 cm or more in diameter ($p < 0.01$).[54] Dagan et al reported local control rates of 100% and 79%, respectively, for tumors of 5 cm or less versus tumors larger than 5 cm, although the difference did not reach statistical significance ($p = 0.09$).[47] Others, however, have failed to show a significant relationship between tumor size and local control rates.[53,55,57,58]

The anatomic location of the tumor can also influence local control rates. Knobel et al demonstrated a trend to higher 10-year local control rates for presentation in vertebral bodies versus other sites (89% versus 78%; $p = 0.07$).[53] The previously described Turkish study showed that surgical resection before radiation therapy is associated with an improved PFS rate. Similarly, a study from Japan on 67 patients with solitary extramedullary plasmacytoma of the head and neck found radiotherapy combined with surgery to be an independent

prognostic factor for overall survival.[58] However, in a study by Ozsahin et al, complete or partial resection prior to radiation therapy had no impact on local control rates.[49] The same study showed that surgery alone for solitary plasmacytoma is clearly inadequate: 7 of 9 patients (78%) treated with surgery without radiation therapy relapsed locally, as compared with 29 of 248 patients (12%) who received radiation therapy. Other factors that have been associated with inferior prognosis include older age at diagnosis[49,50,53] and persistence of myeloma protein for more than 1 year after radiotherapy.[59,60]

Radiation Therapy as Palliation in Multiple Myeloma

Radiation therapy represents an effective form of palliation for patients with MM with symptomatic local involvement.[61,62] The main indications for palliative radiation therapy include bone pain with or without pathologic fractures, neurologic compromise including cord compression, impending cord compression, nerve root compression, or cranial nerve deficits. Patients with impending fractures of weight-bearing bones should first be evaluated by an orthopedic surgeon for consideration of surgical stabilization. Patients with compression fractures of vertebral bodies may also benefit from vertebroplasties or kyphoplasties before radiation therapy.[62-65] For cases of cord compression with associated acute neurologic symptoms, prompt neurosurgical intervention may improve the chance of neurologic recovery, as has been demonstrated in a randomized trial for patients with metastatic cancer and cord compression. Patients with hematologic malignant diseases were not included in this trial, however. An international multiinstitutional study on 172 patients with MM and cord compression found that radiation therapy without surgery resulted in improvement in motor function in 52% of patients.[66] This study showed that a more gradual development of motor deficits (>7 days) was associated with a better functional outcome than rapid development of motor dysfunction (1 day to 7 days). In a recent update from the same group, the overall survival in patients with MM receiving radiotherapy for cord compression was significantly associated with Eastern Cooperative Oncology Group (ECOG)-performance status ($p < 0.001$), preradiotherapy ambulatory status ($p < 0.001$), other osseous lesions ($p < 0.001$), and extraosseous lesions ($p < 0.001$).[66] One small series found that radiation therapy alone can be safe and effective even in the setting of spinal instability on radiographic images.[67] Patients with cord compression in whom radiation therapy is offered as first-line therapy should be placed on steroids before initiation of radiation therapy to reduce the risk of further neurologic compromise from acute radiation-related local inflammation.

Although plasma cell tumors are considered a radiosensitive entity, durable local control with adequate doses of radiation therapy may be important, especially in light of recent advances in MM therapy, resulting in longer life expectancies. In the multicenter study on patients with MM and cord compression described previously, it was found that long-course radiation therapy with higher BED (10 fractions of 3 Gy, 15 fractions of 2.5 Gy, and 20 fractions of 2 Gy) was associated with a significantly higher chance of motor function improvement than short-course radiation therapy (1 fraction of 8 Gy, 5 fractions of 4 Gy).[68] Motor function recovery at 1 year was found to be 76% versus 40% in patients who received long-course treatment versus short-course treatment ($p = 0.003$). In the updated study specifically addressing radiation dose fractionation and local control, there was a higher local control rate with long-course radiation therapy (10×3 Gy, 15×2.5 Gy, or 20×2 Gy) compared with short-course treatment (1×8 Gy or 5×4 Gy), with 2-year local control rates of 91% versus 68%, although the difference did not reach statistical significance ($p = 0.12$).[66] In a study from Germany on 138 patients with MM irradiated to 272 sites,[54] pain reduction was significantly lower in patients who received less than 30 Gy compared with those who received 40 Gy to 49 Gy (65% versus 92%; $p < 0.001$). On multivariable analysis for pain reduction, a daily fraction of 2 Gy was superior to daily doses of 4 Gy to 15 Gy (odds ratio [OR], 11; $p = 0.027$). Alcorn et al reported on 74 patients with MM irradiated to 117 sites to a median dose of 30 Gy, or a BED of 39 Gy.[69] At a median follow-up of 32 months, 26% recurred locally. On multivariable analysis, a BED of less than 39 Gy was significantly associated with increased local recurrence rates (OR, 2.8; $p = 0.03$). At our institution, commonly used radiation dose fractionation schemes for MM palliation include 37.5 Gy in 2.5-Gy fractions or 30 Gy in 10 fractions; although in patients with limited life expectancies, 20 Gy in 5 fractions or 8 Gy in 1 fraction can be considered.

FUTURE DIRECTIONS

Advances in our ability to treat MM and other monoclonal gammopathies depend ultimately on understanding the etiology and pathogenesis of these diseases. In the past decade, there has been an improvement in the understanding of the molecular and cellular biology of the myeloma clone. The cause of these diseases remains elusive, however, as does the identity of the myeloma precursor cell itself.

Advances in the clinical staging of MM, particularly with respect to prognostic factors such as clinical laboratory parameters, are allowing more rational decisions on appropriate therapy. Although progress has been made in the therapeutic management of MM in the past 30 years, particularly with the introduction of chemotherapy and promising results from transplant studies, curative therapy for all plasmacytomas and for MM remains to be defined. Radiotherapy combined with drugs continues to be an important modality in the treatment of MM. Much research remains to be done in finding the right schedules for transplantation, the best sources of hematopoietic stem cells, and optimal preparative regimens for transplantation.

The novel agents thalidomide, lenalidomide, and bortezomib are now first-line options for patients with both newly diagnosed and relapsed MM and provide a paradigm of drug development in MM. It is hoped that ongoing research efforts will provide additional insight regarding the optimal use of novel therapies as well as the role of other emerging new compounds with activity in MM, so as to maximize clinical benefit.

Until better therapies emerge based on an understanding of the biology of MM, clinical research in the next decade will continue to focus on more effective and less toxic drug and radiotherapy regimens. The need to find new therapeutic approaches to treat this disease remains one of the daunting challenges in oncology today.

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CHAPTER

79 Mycosis Fungoides

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INCIDENCE

The age-adjusted incidence of mycosis fungoides (MF) is approximately 6.4 cases per million. Three thousand cases per year are diagnosed in the United States, representing 72% of cutaneous T-cell lymphomas (CTCLs).

BIOLOGIC CHARACTERISTICS

MF is a chronic malignant disease of the skin involving skin-homing CD4+ T cells. The classical immunophenotype is CD2+ CD3+ CD4+ CD5+ CD45RO+ CLA+ (cutaneous lymphoid antigen) CD8– CD30–. Early disease is characterized by patches and plaques affecting the skin, with or without nodal or blood involvement. Advanced disease is characterized by cutaneous tumors, erythroderma, or lost epidermotropism and visceral involvement.

STAGING EVALUATION

TNMB staging is based on the percentage of cutaneous involvement, nature of the lesions, nodal, visceral, and blood involvement. History taking and a physical examination are needed to stage the disease. Skin biopsy with immunophenotyping and polymerase chain reaction (PCR) are performed to determine the T-cell receptor gene rearrangement. A complete blood count with manual differential, serum chemistries, liver function tests, and lactate dehydrogenase (LDH) should be performed. For stages IB to IV disease, peripheral blood flow cytometry, and peripheral blood T-cell receptor gene rearrangement should be assessed. A chest radiograph should be obtained for all patients. Computed tomography (CT) scanning should be done and positron emission tomography (PET)-CT considered for stages IB to IV disease. Suspicious lymph nodes require excisional or core biopsy.

PRIMARY THERAPY

For early-stage disease, therapy is focused on sequential skin-directed therapies, to simultaneously balance the objectives of achieving an optimally durable response but minimizing toxicity. Therapeutic options include irradiation, corticosteroids, psoralen plus ultraviolet A (PUVA), narrow band ultraviolet B, mechlorethamine, carmustine, and topical bexarotene. Total skin electron beam therapy (TSEBT) monotherapy produces a 10-year relapse-free survival rate of approximately 50% for IA disease. TSEBT provides rapid and effective palliation, with complete response rates of 95% for T1, 90% for T2, 60% for T3, and 75% for T4 disease. Total dose for TSEBT varies widely, with a growing emphasis on lower doses and repeat courses of TSEBT. TSEBT is also often followed by adjuvant maintenance therapy. However, skin-directed therapies are not anticipated to be curative over long-term follow-up, with the natural history of disease expected to be chronic and relapsing. For progressive or refractory disease, systemic therapies include interferon-α, retinoids, bexarotene, extracorporeal photochemotherapy, denileukin diftitox, vorinostat, nucleoside analogs, and cytotoxic chemotherapy. Biological response modifiers are being currently evaluated.

LOCALLY ADVANCED DISEASE

TSEBT is effective therapy for achieving durable control for most cutaneous lesions. Other skin-directed therapies are also applied for patients with locally advanced disease. Traditional multiagent systemic chemotherapy does not enhance survival times but may produce palliation. Allogeneic bone marrow transplant is a promising approach for young patients with a good performance status and is considered a curative option.

PALLIATION

Most patients require long-term therapy to relieve cutaneous symptoms. All of the skin-directed therapies produce substantial palliation. Additionally, novel biologic agents such as bexarotene, denileukin diftitox, and vorinostat (or other emerging histone deacetylase inhibitors [HDACs]) have efficacy in disease refractory to standard treatments.

MF is a low-grade, non-Hodgkin's lymphoma caused by skin-homing $CD4^+$ T cells that form cutaneous patches, plaques, and tumors.[1,2] MF was initially described in 1806 when Alibert described a patient with cutaneous tumors that he attributed to yaws. Although initially termed *pian fungoides*, he later changed the name to mycosis fungoides.[3] In 1938, Sézary and Bouvrain described a leukemic variant called the Sézary Syndrome (SS),[4] and Lutzner and Jordan elucidated the ultrastructure of the Sézary cell in 1968.[5] The term *cutaneous T-cell lymphoma* was introduced by Edelson in 1975 and encompasses a variety of cutaneous lymphoproliferative disorders including MF/SS, adult T-cell leukemia/lymphoma, primary cutaneous CD30+ anaplastic lymphoma, lymphomatoid papulosis, pagetoid reticulosis, and others.[6] In clinical practice, the terms *MF* and *CTCL* are often used interchangeably; however, such usage is incorrect.[7] MF constitutes the majority of all CTCLs and the clinical history and therapy for each subtype of CTCL are different.[2]

MF is a challenging disorder from all perspectives. Despite improving molecular techniques, diagnosis early in the course of disease is often difficult because of the nonspecific nature of skin lesions and the numerous benign dermatoses that may mimic MF. Once a diagnosis of MF has been correctly established, the optimal initial treatment strategy often remains unclear, given heterogeneity of clinical presentations and limited data from controlled studies. Although radiotherapy is the most effective single agent in the treatment of MF,[8] TSEBT is not readily available at many centers. This chapter provides a summary of the clinically relevant aspects of MF and describes the role and techniques of radiotherapy in patient management.

ETIOLOGY AND EPIDEMIOLOGY

MF primarily affects adults older than the age of 40, with incidence rates peaking in the seventh decade. The incidence of CTCL has consistently increased from 1974 through 2002, reaching a current yearly incidence rate of 9.6 cases per million (with approximately 6.4 cases per million represented by MF).[9] Risk factors for development of CTCL include black race and male gender. Both characteristics are associated with higher T stage at presentation[10] and a poor prognosis.[11] Markers of high socioeconomic status, such as residence in areas with high home values, high level of educational attainment, and high physician density are associated with an increased incidence CTCL; it is unclear whether these factors are causative or simply increase the likelihood of diagnosis.[9]

Etiologic agents for the development of MF remain highly speculative.[12] Although numerous exposures including pesticides, radiation, industrial solvents, tobacco, and alcohol have been investigated, no consistent causative factors have been identified.[13] High rates of seropositivity for both cytomegalovirus[14] and human T-cell lymphotrophic virus type I[15,16] have been reported, but these studies await further corroboration before a causal relationship can be inferred.[17-19]

The observation that MF is more common in blacks and tends to present in sun-shielded areas (i.e. "bathing suit" distribution) suggests that sun exposure may protect against the development of MF. Sun exposure may mediate its protective effect by exerting a cytotoxic effect on either the malignant CD4+ T-cell of MF or the epidermal antigen-presenting dendritic cell, also known as the Langerhans cell. This cell presents antigens to the malignant CD4+ T cells of MF and may stimulate their growth. The histologic evidence for this interaction is Pautrier's microabscess, an intraepidermal collection of malignant CD4+ T cells clustered around an antigen presenting dendritic cell. This finding is considered pathognomonic for MF and suggests that MF may be an antigen-driven malignancy, though a specific antigen has yet to be identified.[20]

TABLE 79-1 Proposed Algorithm for Diagnosis of Early Mycosis Fungoides

Criteria	Score
CLINICAL	2 points for basic + two additional criteria
Basic	1 point for basic + one additional criterion
Persistent or progressive patches or thin plaques	
Additional	
1. Nonsun-exposed location	
2. Size/shape variation	
3. Poikiloderma*	
HISTOPATHOLOGIC	2 points for basic + two additional criteria
Basic	1 point for basic + one additional criterion
Superficial lymphoid infiltrate	
Additional	
1. Epidermotropism without spongiosis	
2. Lymphoid atypia†	
MOLECULAR BIOLOGIC	1 point for clonality
Basic	
Clonal T-cell receptor gene rearrangement	
IMMUNOPATHOLOGIC	1 point for one or more criteria
1. <50% CD2+, CD3+, or CD5+ T cells	
2. <10% CD7+ T cells	
3. Epidermal/dermal discordance of CD2, CD3, CD5, or CD7‡	
Four or more points satisfy criteria for a diagnosis of early MF.	

Adapted from Pimpinelli N, Olsen EA, Santucci M, et al: Defining early mycosis fungoides. J Am Acad Dermatol 53:1053–1063, 2005.

**Poikiloderma is defined as the combination of skin atrophy, telangiectasia, and mottled pigmentation.*

†Lymphoid atypia is defined as cells with enlarged, hyperchromatic nuclei, and irregular or cerebriform nuclear contours.

‡T-cell antigen deficiency confined to the epidermis.

PREVENTION AND EARLY DETECTION

No agents have been identified that will prevent the development of MF. However, early diagnosis is critical because local therapy directed against uni- or oligolesional MF is highly curative.[21-23] The most typical presentation of early disease—an erythematous patch with scale arising in a sun-shielded area—may be confused with a number of benign dermatoses including atopic dermatitis, psoriasis, and tinea corporis.[24] At this early stage, most of the lymphocytes noted on histopathology represent reactive inflammatory cells rather than the malignant clone.[25] As a result, the histopathology of early MF mimics numerous benign inflammatory conditions,[25,26] and a rapid and correct histologic diagnosis is not always possible. In this setting, molecular studies such as PCR for the T-cell receptor will identify a clonal T-cell population in 50% to 80% of patients who ultimately develop overt histologic evidence of MF.[27,28] To improve diagnostic accuracy of early MF, the International Society for Cutaneous Lymphoma proposed a points-based algorithm for early diagnosis (Table 79-1).[29,30]

BIOLOGIC CHARACTERISTICS AND MOLECULAR BIOLOGY

A malignant clone in patch-plaque MF bears the immunophenotype of activated, skin-homing CD4+ helper T cells.[20] When a naïve T-cell identifies its cognate antigen in a skin-draining lymph node, activation occurs, and the T cells begins to express cutaneous lymphocyte antigen (CLA) and CC chemokine receptor 4 (CCR4). As these activated T cells pass through the capillaries of inflamed skin, CLA and CCR4 bind to their respective ligands on the dermal capillaries, resulting in extravasation of the activated T cells into the dermal connective tissue. Once outside the circulation, activated T cells migrate to the epidermis and interact with antigen-presenting dendritic (Langerhans) cells (Figure 79-1).

Clinically, progression of MF is associated with loss of epidermotropism and increasing tumor burden. Molecular studies have shown that progression of MF is associated with *p53* mutation,[31] numerous chromosomal rearrangements,[32] and microsatellite instability.[33] In addition, the malignant cells in MF develop mechanisms to escape destruction by the host immune system. For example, although benign activated T cells are eliminated by fas/fas-ligand mediated apoptosis, the malignant T cells of MF evade fas-mediated apoptosis via fas downregulation, mutation, or alternative splicing.[34]

As a malignancy of the immune system, MF results in substantial alteration of host immunity with consequent increased risk of infection[35] and possibly second malignancy.[36] For example, in patients with Sézary syndrome, the absolute number of normal circulating T cells often drops dramatically, reaching levels typically only seen in acquired immunodeficiency syndrome.[37] In addition, malignant CD4+ T cells produce large amounts of interleukin-10 and transforming growth factor-β, resulting in further suppression of cell-mediated

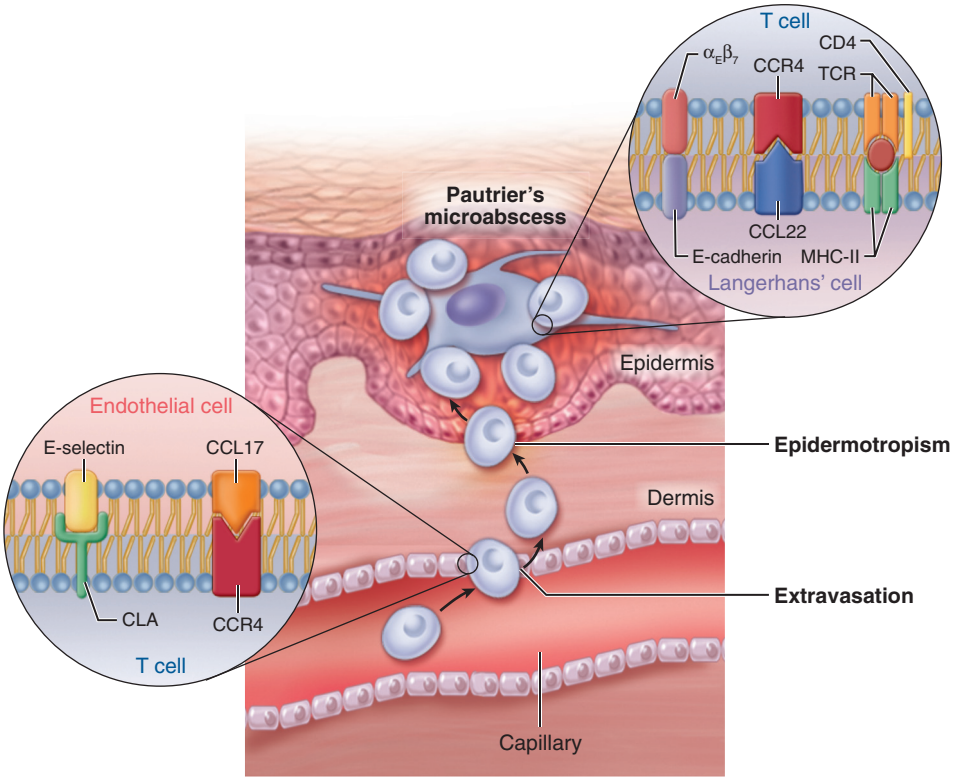


Figure 79-1 Molecular pathology of mycosis fungoides. Activated skin-homing T cells extravasate through the dermal capillaries because of interactions of cutaneous lymphocyte antigen (CLA) and chemokine receptor 4 (CCR4) with their respective ligands on the dermal capillaries, E-selectin and chemokine ligand 17 (CCL17). T cells then migrate to the epidermis and interact with antigen presenting dendritic cells.

immunity.[38,39] The malignant cells of MF also produce large amounts of soluble interleukin-2 receptor that can inactivate interleukin-2,[40] a cytokine needed to promote normal T-cell activation. Finally, the malignant cells of Sézary syndrome can elaborate large amounts of interleukin-4 and interleukin-5, producing a syndrome characterized by atopy and eosinophilia.[39]

PATHOLOGY AND PATHWAYS OF SPREAD

The diagnosis of MF remains challenging, even for the experienced clinician and dermatopathologist, as a result of both the absence of a diagnostic gold standard and the number of benign inflammatory dermatoses that may mimic MF, particularly in its early stages. Currently, diagnosis relies on integrating clinical presentation with histopathologic, immunophenotypic, and genotypic data. The current World Health Organization–European Organization for the Research and Treatment of Cancer (WHO–EORTC) pathologic classification scheme for cutaneous T-cell lymphoma is presented in Table 79-2.[41]

Histopathology

The most striking finding of early MF is profound epidermotropism, characterized by lymphocytes clustered along the basement membrane of the epidermis (Figure 79-2, *A, B*).[42] Microdissection studies have shown that virtually all of the lymphocytes in the epidermis belong to the malignant clone, whereas most dermal lymphocytes are reactive.[43,44]

Several microscopic findings help to discriminate early MF from benign inflammatory mimics. For example, an EORTC study reported that identification of epidermal lymphocytes with extremely convoluted, medium-large (7-9 μm) nuclei enabled correct diagnosis of MF with 100% sensitivity and 92% specificity (see Figure 79-2, *B*).[26] In contrast, a study from Stanford University found that intraepidermal atypical lymphocytes surrounded by a clear halo (an artifact of fixation) were the most robust indicator of MF in a multivariate model.[45] Another finding, Pautrier's microabscess, is considered pathognomonic but is seen in less than 20% of early lesions (see Figure 79-2, *D*).[45] A proposed grading system has attempted to improve diagnostic accuracy.[25,46]

As MF progresses from patch to plaque stage, the lymphoid infiltrate increases in density and begins to invade the deeper reticular dermis (see Figure 79-2, *C*). Furthermore, as a result of the increased burden of neoplastic cells, findings such as Pautrier's microabscesses (see Figure 79-2, *D*), haloed lymphocytes, and convoluted nuclei are more readily identified, resulting in improved diagnostic accuracy. Tumor formation results from vertical growth of the lymphoid infiltrate, and may be associated with complete loss of epidermotropism and sparing of the upper papillary dermis (see Figure 79-2, *E*). Erythrodermic MF often resembles patch-stage MF, although epidermotropism may be more subtle and neoplastic cells may be quite sparse.[47]

Immunophenotyping of Skin Lesions

Assessment of T-cell marker expression within the lymphoid infiltrate provides additional information that helps to establish a diagnosis of MF. The hallmark of MF is expression of CD4, the marker of mature helper T cells. A typical immunophenotype for MF is CD2+ (pan T cells), CD3+ (pan T cells),

TABLE 79-2 WHO–EORTC Classification for Cutaneous T-Cell Lymphomas

Histologic Findings	Frequency	5-year Disease-Specific Survival	Clinical Behavior
Mycosis fungoides	44%	88%	Indolent
Variants of mycosis fungoides			
Folliculotropic mycosis fungoides	4%	80%	Indolent
Pagetoid reticulosis	<1%	100%	Indolent
Granulomatous slack skin	<1%	100%	Indolent
Sézary syndrome	3%	24%	Aggressive
Adult T-cell leukemia/lymphoma	—	—	—
Primary cutaneous CD30+ Lymphoproliferative disorders			
Primary cutaneous anaplastic large cell lymphoma	8%	95%	Indolent
Lymphomatoid papulosis	12%	100%	Indolent
Subcutaneous panniculitis-like T-cell lymphoma (α/β type)	1%	82%	Indolent
Extranodal NK/T-cell lymphoma, unspecified	<1%	—	Aggressive
Primary cutaneous peripheral T-cell lymphoma, unspecified	2%	16%	Aggressive
Primary cutaneous aggressive epidermotropic CD8+ T-cell lymphoma (provisional)	<1%	18%	Aggressive
Cutaneous γ/δ T-cell lymphoma (provisional)	<1%	—	
Primary cutaneous CD4+ small/medium-sized pleomorphic T-cell lymphoma (provisional)	2%	75%	Indolent

Data from Willemze R, Jaffe ES, Burg G, et al: WHO-EORTC classification for cutaneous lymphomas. Blood 105:3768–3785, 2005.
NK, *Natural killer;* WHO–EORTC, *World Health Organization–European Organization for the Research and Treatment of Cancer.*

CD4+ (helper T cells), CD5+ (pan T cells), CD45RO+ (memory T-cell), CLA+ (cutaneous lymphoid antigen), CD8– (cytotoxic T-cell), CD30– (activated T-cell).[48] Although many benign dermatoses express a similar immunophenotype, two markers, CD7 and Leu-8, are often underexpressed in MF and may be helpful in distinguishing between MF and benign mimics. Finally, rare cases of apparently classic MF that are CD4-, but CD3+ and CD8+ have been reported.[49]

T-Cell Receptor Gene Rearrangement

Clonal T-cell receptor gene rearrangements are frequently identified in MF skin lesions and may help to differentiate between early MF patches and benign mimics. Clinical data indicate that PCR will identify a dominant clonal T-cell receptor-γ rearrangement in 63% to 90% of skin biopsies that show definite histologic evidence of MF.[50,51] Furthermore, PCR identifies a clonal T-cell population in 50% to 80% of histologically borderline biopsies obtained from patients who subsequently develop classic MF.[27,28] In contrast, T-cell clonality occurs in only 6% to 24% of benign dermatoses that contain a lymphoid infiltrate.[50,51] These observations suggest that identification of a clonal T-cell population should always be considered in light of the clinical and histologic context and may help to confirm a diagnosis of MF when already suspected on these grounds.

Transformation to Large Cell Histology

Transformation to a large cell variant occurs in up to 39% of patients initially diagnosed with MF, and the likelihood of transformation is directly correlated with higher stage.[52] Histologic diagnosis of transformation requires large cells (≥4 times the size of a small lymphocyte) comprising >25% of the lymphoid infiltrate or forming microscopic nodules.[53] Transformation is associated with expression of CD30 in 30% of cases and expression of CD20 in 45% of cases. Transformed MF is typically aggressive, with clinical behavior similar to high-grade lymphoma, and must be treated as such, particularly with the goal of allogeneic transplantation when possible.

CLINICAL MANIFESTATIONS

According to the EORTC classification of cutaneous lymphomas, the term *mycosis fungoides* should be reserved for those $CD4^+$ cutaneous lymphomas that are "characterized by the subsequent evolution of patches to more infiltrated plaques and eventually tumors."[2] Over time, MF may spread to involve lymph nodes, blood, bone marrow, and visceral organs. Symptoms may vary by degree of involvement, but weight loss, night sweats, and fever are uncommon unless infection is present.

Premycotic Phase

Early MF typically begins with mildly erythematous, slightly scaling, annular or arcuate macules that classically involve sun-shielded areas (Figure 79-3, *A*). These lesions may wax and wane for years before histologic findings show definitive evidence of MF.

Patch Phase

In this stage, patches lose their predilection for sun-shielded areas and may become eczematous, hypopigmented, or hyperpigmented. The trunk, pelvis, and proximal extremities are most commonly involved. Histologic features consistent with MF may now be discernible.

Plaque Phase

If untreated, some patches will progress to form more generalized, deeply infiltrative, scaling plaques that often have well-demarcated, palpable borders and may exhibit central clearance and arcuate morphology (see Figure 79-3, *B*). Associated findings include hyperkeratosis of the palms and soles and fissures.

Tumor Phase

More than 80% of tumors emerge in the setting of established patch-plaque MF (see Figure 79-3, *C*). The most common sites

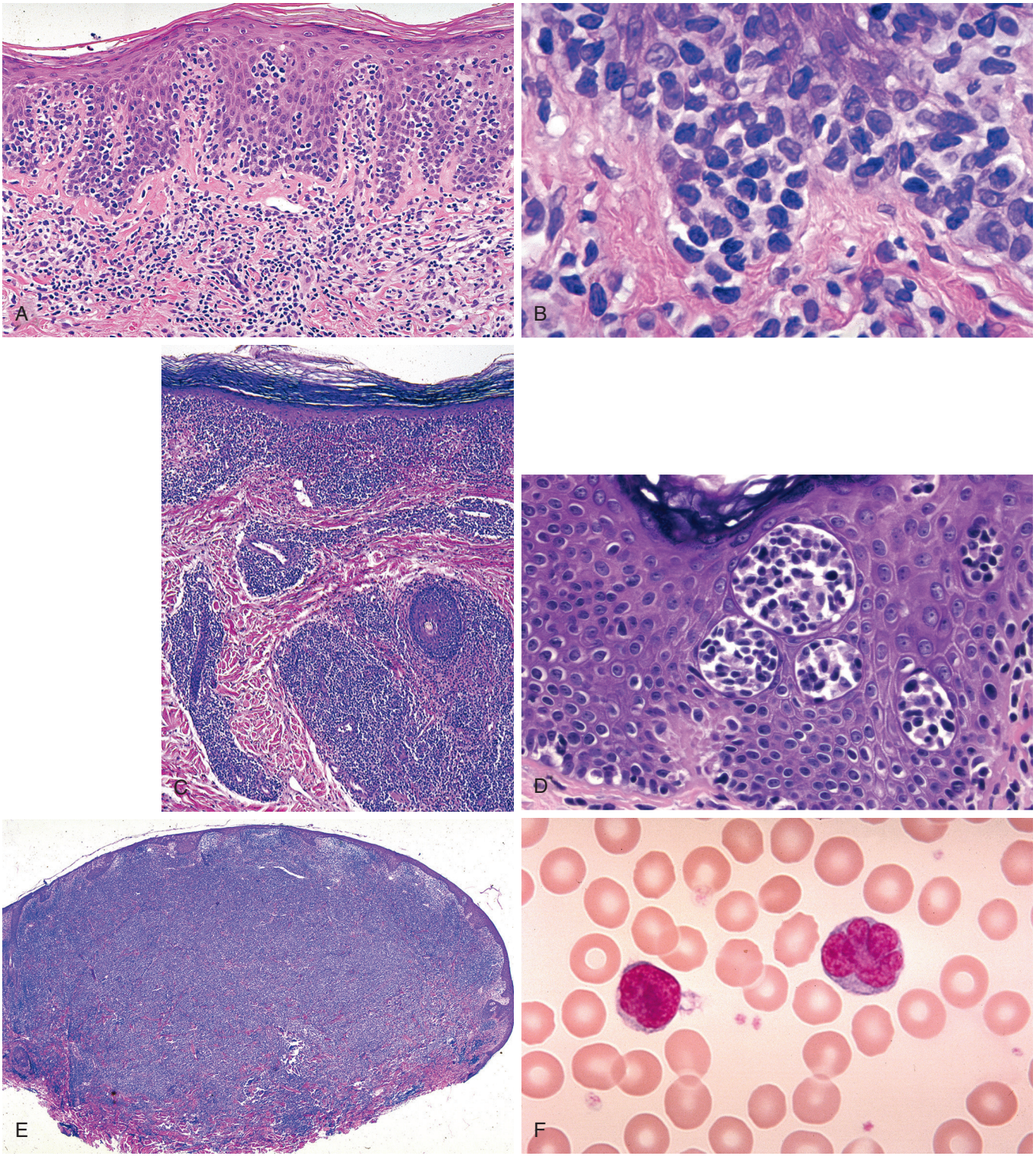


Figure 79-2 Classic histopathologic findings in mycosis fungoides (MF) and Sézary syndrome. A, Advanced patch-stage lesion of MF exhibiting abundant lymphocytes within the basal layer of the epidermis, associated with an underlying band-like lymphocytic infiltrate and papillary dermal fibrosis. **B,** Advanced patch-stage lesion of MF exhibiting enlarged, convoluted lymphocytes within the epidermis. The lymphocyte cell size approximates the width of keratinocyte nuclei. **C,** Plaque-stage MF shows, in addition, involvement of the reticular dermis. **D,** Pautrier's microabscesses are well-defined aggregates of lymphocytes within the epidermis, which are strongly indicative of MF. **E,** In tumor stage MF, the dermis is distended by the lymphocytic infiltrate. Epidermotropic capacity is often lost. **F,** Sézary cells, such as the cell at the right, are enlarged circulating lymphocytes that exhibit cerebriform nuclear convolutions.
(Photos and legend courtesy of Earl Glusac, MD). Reprinted with permission from Figure 2 in Smith BD, Wilson LD: Management of mycosis fungoides. Part 1. Diagnosis, staging, and prognosis. Oncology (Williston Park) 17:1281–1288, 2003.

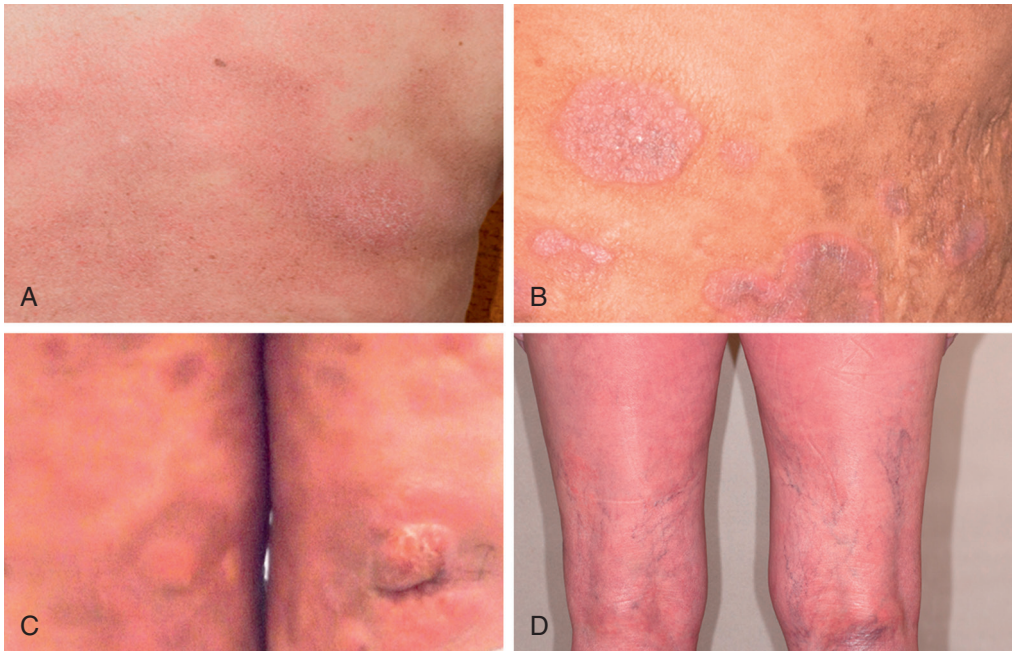


Figure 79-3 **Spectrum of cutaneous lesions observed in mycosis fungoides. A,** Patch stage. **B,** Plaque stage. **C,** Tumor stage. **D,** Erythrodermic stage.
Adapted and reprinted with permission from Figures 1-4 in Dabaja BS: Mycosis fungoides, presentation, diagnosis, and treatment strategy. In Thomas CR, Jr, editor: Radiation medicine rounds: Hematologic malignancies, New York, 2012, Demos Medical Publishing.

of tumor involvement include the face, digits, and perineum. Tumors frequently ulcerate and are prone to infection.

Tumeur d'Emblée

The term *tumeur d'emblée* refers to the rare patient who presents with tumors that arise in the absence of antecedent skin lesions; some cases may be more appropriately classified as CD30– cutaneous large T-cell lymphoma rather than MF.[54] The clinical course may be more aggressive than patients with classic MF.

Erythroderma

Erythroderma is defined as greater than 80% body surface involvement with confluent patches or plaques. It is associated with intense pruritus, hyperkeratosis of the palms and soles, skin atrophy, and lichenification (see Figure 79-3, *D*). Erythroderma may arise de novo or from progression of patch and plaque MF.

Lymph Nodes

Lymph node involvement is present in 15% of newly diagnosed patients and is associated with advanced cutaneous disease.[55] Nodes are typically non-tender, mobile, and measure from 1 cm to 4 cm, though typically a size threshold of 1.5 cm is considered clinically abnormal, and biopsy is recommended to evaluate nodes that reach this threshold.[56] Bulky adenopathy is uncommon.

Internal Organs

Visceral involvement is typically seen only in patients with advanced cutaneous disease, nodal disease, and blood involvement. The most common sites include the lungs, central nervous system, oral cavity, and oropharynx,[55,57] although MF has been observed in other sites such as the breast, thyroid, and pancreas. Visceral involvement is often subclinical and does not routinely precipitate death. Bone marrow involvement at initial staging has been reported in 6% to 28% of patients and is also associated with advanced skin and nodal disease.[58,59]

TABLE 79-3 Proposed Hematologic Criteria for Diagnosis of Sézary Syndrome

Absolute Sézary cell count ≥1000 cells/μL.
CD4/CD8 ratio ≥10 due to an increase in CD3+[1] or CD4+[1] cells by flow cytometry.
Aberrant expression of pan-T-cell markers (CD2, CD3, CD4, CD5) by flow cytometry. Deficient CD7 expression on T cells (or expanded CD4+,[1] CD7– cells ≥40%) is a tentative criterion.
Increased lymphocyte count with T-cell clone in blood identified by Southern blot or polymerase chain reaction.
A chromosomally abnormal T-cell clone.

Adapted from Vonderheid EC, Bernengo MG, Burg G, et al: Update on erythrodermic cutaneous T-cell lymphoma. Report of the International Society for Cutaneous Lymphomas. J Am Acad Dermatol 46:95–106, 2002.

Sézary Syndrome

Sézary syndrome (SS) is defined as erythroderma plus evidence of malignant circulating T cells that satisfy any of the five criteria listed in Table 79-3.[60] For the purposes of these criteria, the Sézary cell is defined as "any atypical lymphocyte with [a] moderately to highly infolded or grooved nucleus"[60] (see Figure 79-2, *F*). Clinical findings may include edema and tumorous involvement of the face leading to leonine facies, severe fissures of the palms and soles, intense pruritus, and cutaneous pain. Currently, no consensus has emerged

regarding the pathologic link between MF and SS. However, some clinical observations help to elucidate the relationship between these two disorders. SS often arises de novo without antecedent MF. MF may also evolve to an erythrodermic stage with concomitant hematologic findings that satisfy a diagnosis of SS.

VARIANTS OF MYCOSIS FUNGOIDES

The progression from subtle patches to indurated plaques, cutaneous tumors, and erythroderma represents classical, so called "Alibert-Bazin" MF. According to the EORTC classification, variants such as bullous and hyper- or hypopigmented MF manifest similar clinical behavior and should not be considered separately from classical MF.[2] Several variants sharing some clinical and pathologic features with MF have been described.

Folliculotropic Mycosis Fungoides

This entity presents with follicular papules, comedolike lesions, milialike lesions, patches, and plaques, all of which may produce alopecia.[1,41] Although it typically involves the head and neck, any skin site may be affected.[2] Pathologically, atypical lymphocytes invade follicles and may deposit acid mucopolysaccharides in the pilosebaceous units. Folliculotropic MF, often presenting with thick plaques, tends to be refractory to topical treatments such as PUVA and nitrogen mustard, and risk of relapse after treatment with TSEBT appears to be higher when compared to patients with classical MF.[61] Five-year disease-specific survival is approximately 80%[41] but only 41% by 15 years.[62]

Pagetoid Reticulosis and Woringer–Kolopp Disease

Pagetoid reticulosis, also known as Woringer–Kolopp disease, typically presents as slow-growing, hyperkeratotic or psoriasiform, localized patch or plaque involving a distal extremity. Pathologically, an abundant epidermotropic infiltrate composed of atypical large lymphocytes is noted, along with pagetoid spread of individual lymphocytes interspersed among keratinocytes. Benign-appearing small lymphocytes are found in the upper dermis.[1] The prognosis for localized pagetoid reticulosis is excellent with either surgery or radiotherapy, and disease-related deaths have not been reported.[2,41] Ketron–Goodman type is a disseminated, more aggressive cutaneous lymphoproliferative disorder that histologically resembles localized pagetoid reticulosis.

Granulomatous Slack Skin

This rare variant presents with lax skin in the axillae, neck, breasts, and inguinal regions. Histological features include epithelioid or giant cell dermal granulomas and associated destruction of elastin fibers.[2] Notably, Hodgkin lymphoma has been associated with granulomatous slack skin in roughly one third of reported cases.[63] Because of its rarity, optimal treatment has not been established.

RELATED CUTANEOUS T-CELL LYMPHOPROLIFERATIVE DISORDERS

In addition to MF and its variants, several other distinct cutaneous T-cell lymphoproliferative disorders have been described. Their clinical and pathologic features and optimal therapy is briefly reviewed here.

Primary Cutaneous Anaplastic Large Cell Lymphoma/CD30+ Large Cell CTCL

This entity typically presents as a red or flesh-colored nodule or tumor that frequently ulcerates. Histopathology shows sheets of CD30+ large lymphocytes without epidermotropism. In contrast to systemic CD30+ anaplastic large cell lymphoma, overexpression of anaplastic lymphoma kinase (ALK) is not found in primary cutaneous CD30+ large cell lymphoma. Patients with localized disease are typically treated with radiotherapy alone, and prognosis is excellent with a 5-year disease-specific survival of approximately 90% to 95%.[2,64,65] Treatment using anti-CD30 monoclonal antibody may be considered, but is typically not an upfront strategy.

Lymphomatoid Papulosis

Lymphomatoid papulosis (LyP) presents with grouped erythematous or violaceous papules or nodules at different stages of development. Lesions typically resolve spontaneously within 2 to 8 weeks, but scarring is common.[66] Three different histologic subtypes have been described, with types A and C consisting of malignant CD30+ T cells, often with an extensive inflammatory infiltrate, and type B simulating classical plaque-stage MF. For type C lesions, discrimination between LyP and CD30+ large cell lymphoma may be difficult on histologic grounds, and assessment of the clinical context may be required to ensure the proper diagnosis.[2] Although cytologically malignant, it should be emphasized that LyP is clinically benign with a 5-year survival of 100%.[2,41,64] Thus, neither aggressive chemotherapy nor radiotherapy is indicated.[67] Treatment options include PUVA or low-dose methotrexate, but neither is considered curative. In the long term, at least 15% to 20% of patients with LyP will develop a second malignancy, most commonly MF, CD30+ large cell lymphoma, or Hodgkin's disease.[67,68] In patients undergoing TSEBT for MF, a history of LyP is associated with an increased risk of relapse.[61]

Adult T-Cell Lymphoma/Leukemia

Adult T-cell Lymphoma/Leukemia (ATLL) develops in 2% to 4% of individuals infected with human T-cell lymphotrophic virus type I (HTLV-I), a retrovirus endemic in southern Japan and the Caribbean.[1,66,69,70] Skin findings are present in up to 60% of patients with ATLL and strongly resemble those of MF, including plaques, tumors, and erythroderma. The characteristic immunophenotype is CD2+ CD3+ CD4+ CD5+ CD7– CD8– and the malignant cells strongly express the high affinity interleukin-2 receptor (CD25, CD122, and CD132). Clinical features vary from an acute form presenting with B symptoms, hypercalcemia, metabolic bone disease, hepatosplenomegaly, generalized adenopathy, and leukemic infiltration to a smoldering or chronic form presenting with skin infiltration and little or no systemic involvement. Although patients often respond to conventional chemotherapy, long-term survival is rare. Other agents include denileukin diftitox[71] and interferon-α in combination with zidovudine.[72] In appropriately selected candidates, allogeneic stem-cell transplantation may be considered, though evaluation of efficacy in this scenario is ongoing.[73]

Subcutaneous Panniculitis-Like T-cell Lymphoma (α/β type)

In prior years, subcutaneous panniculitis-like T-cell lymphoma was thought to run two markedly different clinical courses—an indolent course and an aggressive course. Recently, molecular studies have indicated that the indolent form of subcutaneous panniculitis-like T-cell lymphoma is

caused by CD8+ T cells that express the α/β T-cell receptor. This entity typically presents with subcutaneous nodules or plaques involving the legs or trunk and has a 5-year disease-specific survival of approximately 82%.[41] In contrast, the more aggressive form of subcutaneous panniculitis-like T-cell lymphoma is caused by CD8– T cells that express the γ/δ T-cell receptor, and is now classified as cutaneous γ/δ T-cell lymphoma in the updated WHO–EORTC system.[41] This entity is often fatal and complicated by hemophagocytic syndrome. Treatment for the α/β type is often observation while treatment for the γ/γ type includes combination chemotherapy and possibly cyclosporine.[1,2]

PROGNOSIS AND STAGING

Early (skin involvement characterized by patches and plaques, regardless of nodal or blood involvement) versus advanced (involvement with tumor, high-grade nodal, or visceral organ) stage is the primary predictor of prognosis. Treatment strategy should be planned accordingly.[56] Skin is systematically assessed and scored using the modified Severity Weighted Assessment Tool (mSWAT), which not only quantifies the percent body surface area (BSA) involved with patch, plaque, or tumor, but further weights the total score by the type of lesion (patch = 1, plaque = 2, tumor = 4).[74,75]

Various staging systems exist and have evolved over time. Previously, the American Joint Committee on Cancer (AJCC) staging system for MF identified extent and character of skin lesions, extracutaneous disease, and leukemic transformation.[76] Shortcomings of this system included difficulty in assigning T stage for patients on the border between T1 and T2; failure to discriminate between the prognosis of patients with extensive patches as compared to extensive plaques; similarity in prognosis between patients with tumors and erythroderma; the questionable prognostic relevance of enlarged, pathologically uninvolved lymph nodes; and the rarity of the N2 descriptor because biopsies of nonpalpable lymph nodes are seldom performed.[77,78]

To address these shortcomings, the EORTC, in conjunction with the International Society for Cutaneous Lymphoma (ISCL), proposed a revised TNMB staging system (Tables 79-4 and 79-5) addressing both MF and SS and incorporating greater detail on skin and nodal involvement and also considering clonal and tumor burden in the blood.[79] Detailed definitions and descriptions of the extent and character of skin as well as nodal and visceral disease are provided to provide more systematic classification. In addition to quantification of body surface involvement, pigmentation, scale, crusting, and poikiloderma are additional important features of skin classification. On histology, folliculotropism, large-cell transformation, $CD30^+$ or $CD30^-$, and ulceration are notable. T-cell clonality requires PCR or Southern blot analysis of the T-cell receptor gene.[79]

The TNMB system has been increasingly adapted into treatment algorithms and provides a systematic approach to prospectively compare longitudinal changes in tumor burden, and hence the clinical effectiveness, of various therapies.[56,75,80] Furthermore, it provides a rational stratification of patients into "early" versus "advanced" stages, an initial categorization that drives therapeutic decision making.

T stage continues to be a strong predictor of outcome. Data from a cohort of 468 patients with newly diagnosed MF evaluated at Stanford University are presented in Table 79-6.[55] More than 60% of patients presented with patches or plaques without nodal or visceral disease. Such patients rarely developed disseminated disease, even at 20 years of follow up. In contrast, 50% to 60% of patients presenting with tumors or erythroderma will develop extracutaneous disease.

TABLE 79-4 TNMB Classification for Mycosis Fungoides/Sézary Syndrome, Based on the International Society for Cutaneous Lymphomas/European Organisation for Research and Treatment of Cancer (ISCL/EORTC) Revision

SKIN	
T1	Limited patches, papules, or plaques covering <10% of the skin surface
T2	Patches, papules, or plaques covering ≥10% of the skin surface
T3	One or more tumors (≥1 cm)
T4	Confluence of erythema covering ≥80% body surface area
NODE	
N0	No clinically abnormal peripheral lymph nodes; biopsy not required
N1	Clinically abnormal peripheral lymph nodes; histopathology Dutch grade 1 or NCI LN0-2
N1a	Clone negative
N1b	Clone positive
N2	Clinically abnormal peripheral lymph nodes; histopathology Dutch grade 2 or NCI LN3
N2a	Clone negative
N2b	Clone positive
N3	Clinically abnormal peripheral lymph nodes; histopathology Dutch grades 3-4 or NCI LN4; clone positive or negative
Nx	Clinically abnormal peripheral lymph nodes; no histologic confirmation
VISCERAL	
M0	No visceral organ involvement
M1	Visceral involvement (must have pathology confirmation and organ involved should be specified)
BLOOD	
B0	Absence of atypical circulating cells: ≤5% of peripheral blood lymphocytes are atypical (Sézary) cells‖
B0a	Clone negative
B0b	Clone positive
B1	Atypical circulating cells, low blood tumor burden: >5% of peripheral blood lymphocytes are atypical (Sézary) cells but does not meet the criteria of B2
B1a	Clone negative
B1b	Clone positive
B2	Atypical circulating cells, high blood tumor burden: ≥1000/μL Sézary cells‖ with positive clone

Adapted from Abeloff MD, Armitage JO, Niederhuber JE, et al: Abeloff's Clinical Oncology, ed 5, T107-4, 2014.

Data from Stanford showed that patients with limited patches and plaques (stage IA, T1 N0 M0) experience 10-year survival similar to a matched control population. In contrast, median survival for patients with extensive patches and plaques (T2), tumors (T3), and erythroderma (T4), was 11, 3.2, and 4.6 years, respectively.[81] Patients with either pathologically documented lymph node involvement or visceral involvement experienced a median survival of roughly one year.[55]

Another multiinstitutional study showed that survival is also related to the pattern and extent of lymph node involvement, but the prognostic strength of nodal status is debated.[82]

TABLE 79-5 Staging Classification for Mycosis Fungoides

IA	T1 N0 M0, any B
IB	T2 N0 M0, any B
IIA	T1-2 N1-2 M0, any B
IIB	T3 N0-2 M0, any B
IIIA	T4 N0-2 M0 B0
IIIB	T4 N0-2 M0 B1
IVA_1	T1-4 N0-2 M0 B2
IVA_2	T1-4 N3 M0 B0-2
IVB	T1-4 N0-3 M1 B0-2

Adapted from Abeloff MD, Armitage JO, Niederhuber JE, et al: Abeloff's Clinical Oncology, ed 5, T107-4, 2014.

TABLE 79-6 Initial Stage and Natural History of 468 Patients with Mycosis Fungoides Evaluated at Stanford University at the Time of Initial Diagnosis

	T Stage at Initial Presentation (%)	Percentage with Nodal or Visceral Involvement on Initial Diagnosis as Function of T Category	Percentage Developing Nodal or Visceral Involvement Over 20 Years as Function of T Category
T1	28	0	0
T2	36	2	10
T3	20	13	36
T4	16	25	41

Data from de Coninck EC, Kim YH, Varghese A, et al: Clinical characteristics and outcome of patients with extracutaneous mycosis fungoides. J Clin Oncol 19:779–784, 2001.

TABLE 79-7 Recommended Workup for Patients with Suspected Mycosis Fungoides

HISTORY AND PHYSICAL EXAMINATION WITH ATTENTION TO SKIN, LYMPH NODES, LIVER, AND SPLEEN

Skin Biopsy with Attention to

- Histologic findings
  - Epidermal lymphocytes with medium to large, extremely convoluted nuclei
  - Haloed epidermal lymphocytes
  - Pautrier's microabscesses
- Immunophenotype
  - Classically: CD2+ CD3+ CD4+ CD5+ CD45RO+ CD8– CD30–
  - Rarely, CD4– CD3+ CD8+
- PCR for T-cell receptor gene rearrangement

Biopsy of Enlarged Lymph Nodes with Attention to

- Histologic findings, both number of atypical lymphocytes and disruption of nodal architecture
- In dermatopathic nodes, consider PCR for T-cell clonality and immunophenotyping to rule out occult involvement

Evaluation of Blood

- CBC with manual differential, liver function tests, and serum chemistries for all patients
- In those with suspected stages IIB to IV disease
  - LDH, soluble interleukin-2 receptor
  - Flow cytometry for CD2, CD3, CD4, CD5, CD7, CD8, CD20, CD45RO
  - PCR for T-cell receptor gene rearrangement

Imaging

- Posteroanterior and lateral chest radiograph for stage IA
- CT of (neck), chest, abdomen, and pelvis for suspected stages IB to IV
- Consider PET/CT scanning for patients with suspected stages IB to IV

CBC, *Complete blood count;* CT, *computed tomography;* LDH, *lactate dehydrogenase;* PCR, *polymerase chain reaction;* PET, *positron emission tomography.*

For example, partial or complete effacement of nodal architecture by malignant lymphocytes conferred a median survival to 2.3 years. In contrast, lymph nodes with aggregates of atypical lymphocytes but preserved nodal architecture resulted in a median survival of 6 years and lymph nodes with only dermatopathic changes or few atypical lymphocytes resulted in a median survival of 9 years.

Other factors that may herald a poor prognosis include age ≥60,[83] elevated LDH,[83] elevated soluble interleukin-2 receptor levels,[40] a low percentage of $CD8^+$ tumor infiltrating lymphocytes,[84] extent of skin involvement in those with T3 disease,[85] T-cell clonality within the cutaneous infiltrate detected by PCR,[86,87] an identical T-cell clone in the skin and peripheral blood,[88] and T-cell clonality in dermatopathic lymph nodes.[89]

For those patients with transformation to a large-cell variant of MF, median survival ranges from 19 months to 36 months.[53,90] Factors predictive of poor survival after transformation include short interval between diagnosis of MF and transformation (< 2 years), and the presence of stages IIB to IV disease.[53]

PATIENT EVALUATION

All patients should have a thorough history performed by the evaluating dermatologists, radiation oncologists, and any other consultants (Table 79-7). Careful attention should be given to the duration, change in appearance, and distribution of the eruption according to the patient. Inquiry related to a history of pruritus, pain, exfoliation, fissures, bullae, and perineal discomfort should be made. Previous diagnostic considerations, procedures, and therapies should be recorded in detail to establish temporal relationships. The clinical interview, along with the examination, are the two most important aspects of the workup because they can help exclude other diagnoses and establish whether the narrative and findings are consistent with a diagnosis of MF.

Physical Examination

All patients should undergo a complete physical examination with special attention to the skin surface, lymph nodes, and abdomen for organomegaly. Specific notations should be made of the number, location, character, and distribution of cutaneous lesions and the presence of ulceration. The percentage of cutaneous involvement should also be quantified. Body surface area (BSA) along with a weighted severity score provides a systematic approach to assessing skin involvement.[75] Other non-MF cutaneous findings such as previous excision sites, pigmented lesions, or any findings consistent with other skin malignancy should be noted. Adenopathy should be carefully documented with respect to location, size (particularly ≥1.5 cm), consistency, mobility, and discomfort on palpation. Photographs of the skin for baseline documentation should be considered.

Diagnostic Testing

Pathology

A biopsy of the most indurated area of involved skin should be performed for hematoxylin and eosin evaluation. Material for immunophenotyping (including at least CD2, CD3, CD4, CD5, CD7, CD8, and a B-cell marker such as CD20 or consideration of CD30) and T-cell receptor gene rearrangement should be obtained. Excisional biopsy of adenopathy is recommended and tissue should be submitted for the same pathologic studies. Needle aspiration of nodes is not recommended.

Routine bone marrow examination is generally not required but may be considered in patients with blood or other visceral involvement. Bone marrow involvement at initial staging has been reported in 6% to 28% of patients and is associated with advanced skin and nodal disease.[58,59] However, it is unclear that marrow involvement is an independent predictor of outcome.[59,83] Furthermore, although a clonal T-cell population within the marrow is identified in 75% of patients with identical skin and peripheral blood T-cell clones, this finding does not appear to alter prognosis.[58]

Hematology and Chemistry

A complete blood count including differential and smear in addition to serum chemistries (to include renal and hepatic function) and LDH should be obtained before initiation of therapy. For patients with stages IIB to IV disease, serum levels of soluble interleukin-2 receptor and LDH reflect overall tumor burden and could be used to assess response to therapy, although this measure is not an established standard for follow-up.

A thorough examination of the peripheral blood for evidence of malignant T cells is indicated for those with stages IIB to IV MF, and may be considered for those with stages IA to IIA. Peripheral blood flow cytometry should be performed to assess expression of CD2, CD3, CD4, CD5, CD7, CD8, CD20, and CD45RO. Findings suggestive of blood involvement include an elevated CD4/CD8 ratio (normal range 0.5 to 3.5), or an expanded population of $CD4^+CD7^-$, $CD4^+CD26^-$ or $CD45RO^+$ lymphocytes.[60] If initially abnormal, findings on peripheral blood flow cytometry should be followed to assess response to therapy. If flow cytometry is unremarkable, peripheral blood PCR for T-cell receptor gene rearrangement should be considered. PCR reveals a clonal T-cell population identical to that found in the cutaneous infiltrate in 40% of patients with erythroderma and 14% of patients with patches, plaques, or tumors.[50]

Diagnostic Imaging

A minimum of chest radiography should be completed for stage IA disease. CT of the chest, abdomen, and pelvis (and neck as clinically indicated) should be considered for patients with higher stage disease, particularly patients with tumors, erythroderma, or nodal involvement.[91] The role of fluorodeoxyglucose-positron emission tomography (FDG-PET) is being refined but may be beneficial for staging patients with advanced skin disease; for example, Stanford University investigators reported that CT alone identified pathologic adenopathy by size criteria in only 5 of 13 patients, whereas the addition of PET identified hypermetabolic adenopathy in 13 of 13 patients. The standardized uptake value (SUV) of the FDG correlated with the extent of nodal involvement, with the highest SUVs noted in patients with complete nodal effacement and large cell transformation.[92] Therefore, PET-CT may be considered for patients with ≥T2 disease, palpable adenopathy, abnormal laboratory studies, or patients with large cell transformed or folliculotropic MF.[80] To confirm nodal involvement and document the presence or absence of transformation, excisional biopsy should be strongly considered for selected abnormal lymph nodes, which are radiographically identified.

PRIMARY THERAPY

Because MF is a disease of cutaneous (i.e., skin-homing) lymphocytes, therapy is quite distinct from that of nodal lymphomas. A treatment algorithm for early versus advanced MF is presented in Table 79-8.[93] Multiple treatment options are listed, which reflects the increasing variety of available therapies, heterogeneity in institutional treatment preferences, and the paucity of randomized trials directly comparing different treatment modalities.

In general, however, the treatment approach to early disease involves selecting sequential skin-directed therapies, each based on the expectation to provide the greatest duration of response with the least toxicity, including radiation therapy as an option. Once the disease trajectory proves to be increasingly relapsing or refractory, repeat radiation therapy, systemic, or combined therapies as the second line may be considered. However, allogeneic stem-cell transplant has evolved as a promising therapy for long-term durable control or even cure. Transplant is appropriate for patients who have

TABLE 79-8 Treatment Recommendations, Early and Advanced Mycosis Fungoides/Sézary Syndrome

Stage	Initial Treatment	Treatment for Relapsed or Refractory Disease
Early (IA, IB, IIA)	Topical corticosteroids PUVA UVB Topical HN2 Local radiotherapy TSEBT	Retinoids, rexinoids Interferon-α Low-dose MTX HDACi Denileukin difitox Localized, superficial radiotherapy TSEBT Evaluate for allogeneic stem cell transplant with refractory disease
Advanced (IIB)	Interferon-α TSEBT PUVA	Retinoids, rexinoids Interferon-α alone PUVA + interferon-α HDACi Denileukin difitox Novel agents Chemotherapy Evaluate for allogeneic stem-cell transplant with refractory disease
Advanced (III to IV)	Interferon-α PUVA PUVA + Interferon-α TSEBT	Rexinoids HDACi Denileukin difitox Alemtuzamab or other monoclonal antibody Novel agents Chemotherapy TSEBT Evaluate for allogeneic stem cell transplant with refractory disease

BCNU, *Bischlorethylnitrosourea;* HDACi, *histone deacetylase inhibitors,* HN2, *mechlorethamine;* MTX, *methotrexate;* PUVA, *psoralen plus ultraviolet A;* TSEBT, *total skin electron beam therapy;* UVB, *ultraviolet B.*

failed multiple primary therapies and demonstrate a progressive course with decreasing durability of response, or who have undergone large cell transformation. Notably, however, this treatment strategy is being used selectively in appropriately selected candidate (in general, younger patients with good performance status).[94-96]

The available treatments for advanced disease are similar to early disease, but systemic therapy should be considered sooner in the disease trajectory given the systemic involvement of disease. At the same time, cutaneous lesions and symptoms remain problematic, and therefore maintaining a skin-directed regimen is also important, and therefore the treatment approach requires multimodality considerations. Novel agents may be considered as second-line therapy particularly for this group with a poorer prognosis compared with patients presenting with early-stage disease, and stem-cell transplant should also be explored as a possible treatment option in this group.

For patients with disease limited to the skin, topical therapy alone produces high rates of remission and even cure. Topical therapies include corticosteroids, mechlorethamine (nitrogen mustard), carmustine (BCNU), bexarotene gel (rexinoids), PUVA, ultraviolet B (UVB), and either localized or total skin electron radiotherapy. For patients with localized unilesional MF, topical therapies alone produce long-term disease-free survival rates in excess of 85%.[21-23] For those with more than one patch or plaque but with less than 10% body surface area involvement (T1 N0 and T1 N1), topical therapies alone produce long-term disease-free survival rates ranging from 30% to 50%. For patients with more extensive patches or plaques, topical therapies may produce remission, but long-term cure is unlikely. Such patients should receive intensive topical therapy to induce a complete remission followed by less intensive adjuvant topical therapy to sustain a remission.[97,98]

Those with tumors or erythroderma experience severe cutaneous symptoms and are at high risk for extracutaneous dissemination. Of all the topical therapies, TSEBT is associated with the highest rates of complete response for this patient subgroup.[98-100] Therefore, it is recommended that TSEBT be administered to induce cutaneous remission and that adjuvant systemic or topical therapy be administered to sustain remission. Systemic therapies include interferon, retinoids, oral bexarotene, denileukin diftitox, vorinostat or other histone deacetylase inhibitors, and extracorporeal photochemotherapy (photopheresis). Cytotoxic chemotherapies considered for this group include liposomal doxorubicin, gemcitabine, and low-dose methotrexate.

In the following section, we first discuss all nonradiation topical therapies and then discuss the various systemic therapies. Finally, we discuss the clinical data for radiation and qualitatively compare this to clinical data for various topical and systemic therapies.

Skin-Directed Therapy

Topical Corticosteroids

High potency topical or intralesional glucocorticoids are an important component in the treatment of MF because of their ability to alleviate cutaneous symptoms and induce lesion regression. Typically, corticosteroids are applied to active lesions only, as widespread application can induce reversible depression of serum cortisol in 10% to 15% of patients.[101] Persistent application can lead to skin atrophy.

Mechlorethamine

Topical mechlorethamine hydrochloride (HN2), also known as nitrogen mustard, is an alkylating agent with proven activity in the treatment of MF patches and plaques. Mechlorethamine is typically applied daily and continued for at least 6 months after complete response.[77] Cutaneous intolerance, manifested by erythema and pruritus, occurs in roughly 50% of patients treated with aqueous HN2[102] but is reduced to less than 10% in patients treated with HN2 dissolved in ointment such as Aquaphor.[77] Other cutaneous side effects of HN2 may include xerosis, hyperpigmentation, and rarely, bullous reactions, urticaria, and Stevens–Johnson syndrome.[102] Bone marrow suppression is not observed because of minimal systemic absorption. The carcinogenicity of HN2 remains debated, as one series reported no increased risk of secondary skin cancers in patients treated with HN2 monotherapy,[77] whereas another series reported an eightfold increase in the risk of nonmelanoma skin cancers attributable to HN2 monotherapy.[103] HN2 may also potentiate the carcinogenicity of other topical therapies such as total skin radiation or PUVA.[104]

Carmustine

Topical carmustine (BCNU) is another alkylating agent with activity in MF. Because of systemic absorption that may produce bone marrow suppression, the drug should be applied to no more than 10% of the body surface area, duration of treatment should be limited to 4 months, and complete blood counts should be monitored. Cutaneous hypersensitivity is uncommon (7% in one series) but chronic skin telangiectasis and hyperpigmentation may occur.[105]

Topical Rexinoids

Bexarotene belongs to a new class of agents called *rexinoids* that bind to the retinoid X receptor, resulting in transcription of various genes that control cellular differentiation and proliferation.[106] Topical bexarotene gel was recently approved after Phase I and II trials demonstrated a 44% to 54% response rate in refractory cutaneous MF.[107,108] Most patients will develop an irritant dermatitis and thus require close observation and dose titration. Because of its irritant effects, bexarotene gel is not indicated for patients with more than 15% body surface area involvement. As with systemic retinoids, bexarotene in both its topical and systemic forms should be avoided in pregnant women as a result of possible teratogenicity.

PUVA and Ultraviolet B

Ultraviolet light used in the treatment of MF includes UVB (wavelength 320 nm to 290 nm), narrow-band UVB (wavelength 311 nm), or psoralen plus UVA (PUVA, wavelength 400 nm to 320 nm). Because UVB has limited penetration, its efficacy is limited to thin patches. PUVA penetrates more deeply and will effectively treat some plaque lesions. PUVA requires ingestion of a photochemotherapeutic agent, 8-methoxypsoralen, before UVA exposure. UVA activates 8-methoxypsoralen, resulting in DNA cross-linking and apoptotic cell death.[109]

Both PUVA and UVB are initially administered 2 to 3 days a week as the light dose is gradually increased. Once a complete response has been achieved, treatment frequency may be gradually reduced to once every 2 to 4 weeks. Ultraviolet treatments may be continued on a maintenance basis for several years, provided the patient remains in complete response with treatment administered once every 4 to 8 weeks.

Acute side effects of PUVA and UVB include skin erythema that may be painful, hyperpigmentation, xerosis, pruritus, and blistering. Eye goggles are used to decrease the risk of cataract formation. One side effect unique to PUVA is nausea and vomiting after ingestion of 8-methoxypsoralen (8-MOP). This

may be avoided by substituting 8-MOP for either a topical "psoralen bath" or 5-methoxypsoralen, a nonemetogenic analog that is currently available in Europe.[110] Long-term toxicity includes photoaging and increased risk of melanoma and nonmelanoma skin cancers.[111,112]

Systemic Therapy

Interferon

Interferon-α-2a (IFN-α) is an effective agent, particularly for patch and plaque disease, likely as a result of a direct antitumor effect or immunomodulation.[113] IFN-α has been used alone[113,114] or in combination with retinoids, PUVA,[115-117] and extracorporeal photopheresis.[118] A recent prospective trial showed a benefit from combining IFN-α with PUVA as compared to IFN-α plus a retinoid, but it is not clear that combination therapy is clearly superior to single-agent therapy.[119] Toxicity may include flulike symptoms, psychiatric disturbances including depression and confusion, elevated transaminases, leukopenia, thrombocytopenia, proteinuria, and myelopathy.[116,117] Despite these side effects, in a recent Phase II trial of IFN-α and PUVA, only 8% of patients withdrew as a result of toxicity.[117]

Retinoids

Oral retinoids such as isotretinoin and acitretin influence cellular differentiation and may be particularly beneficial in the treatment of folliculotropic MF. Retinoids can be safely combined with other therapies such as PUVA,[120] IFN-α, and TSEBT.[121] Side effects include photosensitivity, xerosis, myalgias, arthralgias, headaches, impaired night vision, corneal opacities, teratogenicity, elevated transaminases, hyperlipidemia, and pancreatitis.[81]

Rexinoids

Oral bexarotene has been approved by the Food and Drug Administration for use in all stages of treatment refractory MF.[122,123] Preliminary data suggest that bexarotene can be combined safely with other therapies including PUVA, extracorporeal photopheresis, IFN-α, and HN2.

Hypertriglyceridemia, the most common adverse event, occurs in 80% of treated patients and may result in reversible pancreatitis if triglyceride levels exceed 800 mg/dL.[106] Therefore, atorvastatin or fenofibrate should be initiated if triglyceride levels exceed 350 mg/dL. Gemfibrozil increases serum bexarotene concentrations, resulting in a paradoxical elevation of triglycerides, and should therefore be avoided.[106] Another side effect, central hypothyroidism, affects roughly 75% of patients but responds well to levothyroxine and resolves when treatment is discontinued.[106] Patients taking bexarotene therefore require monitoring of estimated free thyroxine, as levels of thyroid-stimulating hormone (TSH) will always be low. Other side effects include self-limited headaches, mild neutropenia, mild transaminase elevations, skin peeling, and pruritus. In the Phases II to III trial of oral bexarotene for advanced, refractory cutaneous T-cell lymphoma, only 10% of patients receiving the optimal dose withdrew as a result of an adverse event.[122]

Denileukin Diftitox

Denileukin diftitox is a recombinant fusion protein that contains portions of interleukin-2 and diphtheria toxin and has proven activity in refractory MF, stages IB to IVA.[74] It selectively targets T cells that express the high affinity interleukin-2 receptor (a complex of CD25, CD122, and CD132), resulting in endocytosis of diphtheria toxin, inhibition of protein synthesis, and cell death. In the pivotal Phase III clinical trial leading to its approval, only patients with neoplastic T cells expressing the high affinity interleukin-2 receptor received denileukin diftitox, and it is currently controversial whether or not patients without significant expression of the high affinity interleukin-2 receptor benefit from denileukin diftitox.[124] Recently published results reported 44% overall response rate, including 10% complete response and 34% partial response. This compared with 16% in the placebo group. Median time to progression exceeded 2 years in the treated group. In the randomized trial, the response rate was higher in the 18 μg/kg group versus the 9 μg/kg group.[125] Denileukin diftitox is typically administered by a 30-minute venous infusion given on 5 consecutive days and repeated every 3 weeks for up to eight cycles.

Toxicities commonly encountered in the Phase III clinical trial of denileukin diftitox included acute hypersensitivity reactions including dyspnea, back pain, hypotension, and chest pain occurred in 60% of patients. Furthermore, a vascular leak syndrome characterized by hypotension, hypoalbuminemia, and edema was encountered in 25% of patients. Other toxicities may include constitutional symptoms, thrombotic events, infections, transaminase elevations, renal impairment, and lymphopenia. In total, 21% of the patients in this trial withdrew because of adverse events.[74] Subsequent investigations have suggested that pretreatment with corticosteroids substantially reduces the risk of acute toxicity.[126]

Histone Deacetylase Inhibitors

Vorinostat is a histone deacetylase inhibitor (HDAC) approved for use in patients with MF who have progressive, persistent, or recurrent disease following treatment with at least two prior systemic therapies. HDAC inhibitors increase accumulation of acetylated histones, resulting in decreased availability of nuclear DNA to bind to transcription factors. The decrease in transcription lowers intracellular protein levels, ultimately producing cell cycle arrest and apoptosis. In preclinical studies of MF cell lines, vorinostat has been shown to induce apoptosis and downregulate stat6.[127] Phase II clinical studies have reported clinical response rates of 25% to 30% in pretreated patients, with a modest median response duration of 15 weeks to 26 weeks.[128,129] Common toxicities include diarrhea, nausea, fatigue, and anorexia. Romidepsin is another approved HDAC inhibitor for relapsed/refractory CTCL. Initial single-arm studies suggest that the duration of response in treated patients is potentially even more sustained, with several patients who achieved response lasting longer than 3 years.[130,131] Other potential novel HDAC inhibitors include belinostat and panobinostat.[132]

Other Novel Agents

Studies are planned or ongoing to evaluate the role of monoclonal antibodies, purine nucleoside phosphorylase inhibitors, proteasome inhibitors, immunomodulatory drugs, synthetic oligodeoxynucleotides, fusion toxins, protein kinase C inhibitors, Toll-like receptor agonists, and antifolate agents. However, though feasibility testing for these agents is ongoing, the efficacy and role of these agents are not yet established.

Extracorporeal Photochemotherapy

Extracorporeal photochemotherapy (EP), also known as photopheresis, is a novel immune therapy that has shown activity in the treatment of erythrodermic MF.[109,133] Peripheral blood leukocytes are harvested by leukapheresis, mixed with 8-methoxypsoralen, exposed to 2 Joules/cm^2 of ultraviolet A, and then reinfused into the patient. This results in DNA cross-linking and gradual apoptotic death of the circulating MF cells that were exposed to psoralen + UVA. For unclear reasons, monocytes are resistant to the apoptotic effects of EP, but, instead are stimulated to become immature antigen presenting

dendritic cells because of the physical process of leukapheresis. Therefore, once treated leukocytes are reinfused into bloodstream, activated dendritic cells may phagocytose remnants of the apoptotic MF cells, present their antigens on major histocompatibility class I, and stimulate expansion of antitumor CD8+ T cells.[134]

EP is typically administered on 2 consecutive days every 4 weeks, although the frequency may be increased in patients with extensive disease.[135] For patients who achieve a complete response, therapy should be maintained for roughly 6 months and then gradually tapered. In general, EP is well tolerated, although hypotension, arrhythmias, and heart failure may occur because of fluid shifts. Patients with a history of cardiac disease therefore require close monitoring.[133] EP has been safely combined with IFN-α and TSEBT.[118,136,137]

Chemotherapy

Systemic chemotherapy is typically reserved for refractory cutaneous disease, visceral disease, or large-cell transformation. Chemotherapy is not typically used in the initial management of patients with MF because a randomized Phase III trial comparing concurrent TSEBT and systemic chemotherapy to sequential topical therapy failed to show an improvement in disease-free or overall survival.[138] For advanced, relapsed/refractory disease, the durability of response may be limited.

For patients who may benefit from chemotherapy, two main strategies exist. The first relies on oral agents such as methotrexate,[139] etoposide, or chlorambucil. This strategy avoids the need for central venous lines, which are associated with a high risk of infection because of frequent bacteremia caused by open skin lesions. The second strategy relies on intravenously administered chemotherapy. One exciting new prospect is pegylated liposomal doxorubicin, an agent that tends to remain intravascular but will extravasate into the inflamed lesional skin of MF. A pilot study conducted on 34 patients with CTCL reported complete response in 15 patients, partial response in 15 patients, and six severe adverse events.[140] Another notable agent is the nucleoside analog gemcitabine, which has been shown to induce complete response rates of approximately 10% and overall response rates of 70% without an increased risk of infection.[141] Attention has also focused on purine analogs such as fludarabine, 2′-deoxycoformycin, and 2-chlorodeoxyadenosine. However, clinical trials of these agents have produced response rates ranging from only 28% to 51% and have documented substantial toxicity, including myelosuppression, infection, and pulmonary dysfunction.[142-145] Other agents with activity in MF include the lipophilic antifolate trimetrexate[146]; 5-fluorouracil; cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP)[147]; etoposide, vincristine, doxorubicin, cyclophosphamide, and prednisone (EPOCH); cisplatin; etoposide; bleomycin; vinblastine[141]; and though early results are limited, temozolamide.[148]

High-Dose Chemotherapy with Autologous or Allogeneic Bone Marrow Transplant

Increasing experience has been reported using high-dose chemotherapy with either autologous or allogeneic transplant in the treatment of advanced or refractory MF. Autologous stem-cell rescue has resulted in several complete responses; however, relapses within 1 year are the rule rather than the exception.[149-151] In contrast, myeloablative or nonmyeloablative conditioning regimens with allogeneic transplant may result in prolonged disease-free survival. One series of three patients treated with cytoreductive chemotherapy and total body irradiation (TBI) found that two of the three patients remained disease-free at 4.5 years and 15 months after transplant. The third patient recurred after allogeneic transplant but developed a second complete response on withdrawal of prophylactic cyclosporine, suggesting a graft-versus-tumor effect.[152,153] In another series, six of eight patients with heavily pretreated, refractory MF who underwent allogeneic transplant with either TBI or non-TBI preparative regimens were alive without evidence of lymphoma at a median of 56 months posttransplant, but two deaths secondary to toxicity were reported.[154] Nonmyeloablative transplants have also been reported, with one series reporting clearance of clonal T cells and durable complete remissions in three out of three patients, although one died from infectious complications.[155]

More recent series report significant improvements in overall survival and progression-free survival, particularly in patients who received matched related transplantation. Another recent experience reported 68% overall response rate and 58% complete response rate using debulking with total skin electron beam and reduced conditioning regimen. Bacterial sepsis was a major complication reported in this series.[96] Overall, cumulative evidence supports the important role of graft-versus-lymphoma effect in producing durable remissions, lasting even up to several years in some cases.[94,95,156]

Collectively, these experiences strongly support the use of allogeneic transplant for younger patients with treatment-refractory, advanced MF.

Radiotherapy

Radiation is the most effective single modality in the treatment of MF[8] and plays an important role in the treatment of localized or disseminated cutaneous disease and in the palliation of skin and nodal and visceral metastases.

Dose

In general, a dose response has been reported both for radiation of single MF lesions and for TSEBT, and given that evidence, doses >30 Gy have served as the historical standard.[99] More recently, however, lower doses for TSEBT, as low as 12 Gy, have been considered. The clinical decision for an individual patient on planned dose for a single course of therapy concomitantly considers two issues: first, the minimum dose that produces a clinical response for a single patient may be somewhat idiosyncratic; and secondly, patients are expected to require repeat skin-directed therapies including repeat courses of radiation, with chronic relapses over time.

In an earlier study of 110 lesions from 14 patients with at least of 1 year follow-up, Cotter et al reported an infield recurrence rate of 42% for those treated to a total dose ≤10 Gy, 32% for 10.01 Gy to 20 Gy, 21% for 20.01 Gy to 30 Gy, and 0% for >30 Gy.[157] In a study of 30 lesions from patients with stage IA MF treated with localized radiotherapy, Wilson et al reported local failure in 20% (4 of 20 patients) treated with ≤20 Gy, compared with 0% (0 of 10 patients) treated with >20 Gy.[22] Kim et al treated different lesions from the same patient with various total doses and fraction sizes, finding that division of the total dose into two fractions separated by 1 or 7 days did not alter local control.[158] This suggests that the malignant cells of MF have minimal ability to execute sublethal damage repair and provides justification for using low daily fraction sizes to minimize normal tissue toxicity without sacrificing local control. Collectively, these experiences initially suggested that a durable response required total doses of 20 Gy to 30 Gy. To spare normal tissue toxicity and to ensure that patients can receive TSEBT in the future, fraction sizes of 1.2 Gy to 2.0 Gy are generally recommended.

Historically, the Stanford University experience with 176 patients undergoing TSEBT from 1958 to 1975 revealed that complete response rates increased with total dose: 18% for 8 Gy to 9.9 Gy, 55% for 10 Gy to 19.9 Gy, 66% for 20 Gy to 24.9 Gy, 75% for 25 Gy to 29.9 Gy, and 94% for 30 Gy to

36 Gy.[159] Similarly, patients treated with higher doses experienced improved overall survival, regardless of T stage. The experience at Hamilton Regional Cancer Center between 1977 and 1992 further supported the importance of high-dose TSEBT. From 1977 to 1980, 25 consecutive patients received 30 Gy TSEBT. From 1980 to 1992, 121 consecutive patients received 35 Gy TSEBT.[160] Treatment with high-dose TSEBT was an independent predictor of response, with a complete response rate of 64% for the 30-Gy group and 85% for the 36-Gy group. The EORTC previously recommended that TSEBT deliver a total dose of 31 Gy to 36 Gy to the skin surface to produce a dose of 26 Gy at a depth of 4 mm in truncal skin along the central axis.[161] Such doses were classically delivered over an 8-week treatment period, though a recent alternative schedule of 30 Gy in 20 fractions delivered over 5 weeks was reported with comparable response rates.[162]

Updated data continue to note an overall response rate of 100% to TSEBT with 60% complete response rate. In patients receiving a second course of TSEBT, 100% overall response rate was also seen, with a median duration of response of 6 months.

However, in a separate retrospective analysis of patients with T2 to T4 tumors, analysis stratified by TSEBT dose still noted excellent response rates in patients treated to 10 Gy to <20 Gy of 98% compared with 20 Gy to <30 Gy of 97%.[163] Given this newer evidence, the clinical potential of lower-dose TSEBT is being revisited.[164] Currently, National Comprehensive Cancer Network (NCCN) guidelines recommend treatment doses of 12 Gy to 36 Gy,[80] and our institutional experience suggests even lower doses, on the order of 8 Gy to 10 Gy can produce durable response for some patients.[90]

Clinical Results: Limited Superficial Radiotherapy

Approximately 5% of patients with stage IA disease present with a single skin lesion, or with two or three lesions in close proximity, such that all clinically apparent disease can be encompassed by either one field or several abutting fields.[22] Radiotherapy is the treatment of choice in this situation because results from three institutions have reported long-term disease-free survival in excess of 85%.[22,23,165] Wilson et al published a series of 21 patients with minimal stage IA disease managed with local, superficial radiotherapy.[22] Ten were treated with 100 Kv to 280 Kv and 11 with 4 MeV to 12 MeV electrons with appropriate bolus. The median dose was 20 Gy, and 17 of 21 received ≥20 Gy. With a median follow up of 36 months, the rate of complete clinical remission was 97% and the long-term disease-free survival was 91% among patients receiving ≥20 Gy. Similarly, Micaily et al reported an 86% 10-year disease-free survival in 18 patients with unilesional MF treated with localized radiotherapy to a median dose of 30.6 Gy.[23] In summary, radiotherapy for unilesional stage IA disease is an excellent first-line therapy given minor acute and chronic toxicities and excellent long-term results. Because few patients with two to four lesions have been reported in the literature, optimal treatment for this subgroup remains unclear. Although some advocate limited superficial radiotherapy, others advocate a strategy such as TSEBT or PUVA to treat all skin surfaces.

Clinical Results: Total Skin Electron Beam Therapy

Limited Patches or Plaques: T1 N0 M0 (IA) and T1 N1 M0 (IIA)

Initial treatment options for patients with patches or plaques involving less than 10% body surface area include topical corticosteroids, mechlorethamine, topical carmustine, phototherapy, bexarotene gel, and TSEBT. Currently, no randomized data exist to support selection of a radiation-based strategy over another topical strategy for this patient population. Although single-institution experiences suggest that patients managed with TSEBT may experience superior complete response rates and relapse-free survival, there is little strong evidence to suggest that this will translate into improved overall survival.

For example, patients with T1 disease treated with modern TSEBT experience a complete response rate of at least 90%[99,166] (Table 79-9), compared with a complete response rate of 65% to 70% for topical mechlorethamine.[77,103] Furthermore, 10-year relapse-free survival is roughly 50% for TSEBT[167] compared with 34% for mechlorethamine.[77] However, in this group of patients whose long-term survival is similar to healthy controls, initial treatment with TSEBT has not been associated with an overall survival advantage.[166] The administration of TSEBT for patients with stage IA MF as first-line therapy remains controversial, and although some reserve TSEBT for those refractory to standard therapies, others recommend TSEBT as first-line therapy for even pauci-lesional stage IA disease. For patients with limited patches, UVB therapy results in a complete response rate of roughly 80% with a median response duration of 2 years.[168,169] PUVA is appropriate for both patches and plaques, producing complete responses rates of at least 80%. Although relapse is common, most patients will respond to additional PUVA.[170,171] Similar to mechlorethamine, topical BCNU produced a complete response rate of

TABLE 79-9 Newly Diagnosed Patch Plaque Mycosis Fungoides Managed at Hamilton, Ontario*

	Stage IA				Stage IB			
TSEBT WITHOUT ADJUVANT THERAPY	*n* = 143				*n* = 79			
Rate of complete remission	95%				89%			
Years of follow-up	2.5	5	10	15	2.5	5	10	15
Progression-free experience	62%	50%	40%	40%	44%	22%	12%	12%
Time to second progression[142]	94%	82%	66%	61%	88%	69%	49%	39%
Cause-specific survival (death from mycosis fungoides)	100%	99%	99%	96%	100%	98%	91%	91%
Overall survival (death from any cause)	99%	94%	89%	76%	99%	91%	80%	75%
TSEBT WITH 60 SESSIONS OF ADJUVANT PUVA	*n* = 11				*n* = 21			
Progression-free experience	100%	N/A	N/A	N/A	89%	N/A	N/A	N/A

PUVA, *Psoralen plus ultraviolet A;* TSEBT, *total skin electron beam therapy.*

**This table contains data from Hamilton, Ontario, updated through 2004 and representative of the results of TSEBT as first-line therapy for stages IA and IB. Results shown for 222 patients receiving TSEBT alone document high rates of complete remission. For those who fail TSEBT, limited second-line therapies[142] may produce prolonged remissions, as indicated by the time to second progression outcome measure. Results shown for 32 patients receiving TSEBT plus adjuvant PUVA indicate that PUVA significantly improves progression-free survival rates (p = 0.03), with follow-up under 5 years as of 2004.[142]*

86%, partial response rate of 12%, and 5-year relapse-free survival of 35%.[105]

Recurrent or refractory T1 disease can still respond to TSEBT,[161] class I steroids (complete response 63%, partial response 31%),[101] interferon-α monotherapy (complete response 50%, partial response 35%),[113] topical bexarotene (complete response 21%, partial response 42%),[107] and oral bexarotene (complete response 7%, partial response 47%).[123] For example, data from Hamilton showed that 70% of patients were free of disease 15 years after first-line TSEBT and second-line salvage treatments as needed.[167]

Extensive Patches or Plaques: T2 N0 M0 (IB) and T2 N1 M0 (IIA)

TSEBT in such patients can demonstrate excellent response rates and rapid palliation. For example, complete response rates for T2 disease range from 76% to 90% (Table 79-9), compared with a complete response rate of 34% for topical mechlorethamine.[77,98,161] Adjuvant therapy following TSEBT is crucial for patients with T2 disease because 10-year relapse-free survival is only 10% in those treated with TSEBT alone.[167] Retrospective data from Yale University found that patients receiving adjuvant PUVA experienced a 5-year disease-free survival of 85% versus 50% for those not receiving adjuvant PUVA.[97] A prospective pilot study at Hamilton documented a similar benefit (Table 79-9). Retrospective data from Stanford University showed that patients treated with TSEBT and adjuvant topical mechlorethamine experienced 10-year relapse-free survival of roughly 40% compared to 10% with TSEBT alone.[98]

Patients with T2 disease who are relatively asymptomatic can receive treatment similar to that recommended for T1 disease. Topical corticosteroids may also be helpful for patients with extensive patches, with data suggesting a complete response rate of 25% and partial response rate of 57%.[101]

Again, topical mechlorethamine is a reasonable choice for these patients, resulting in a complete response rate of 34%, partial response rate of 38%, and 10-year relapse-free survival rate of 20%.[77] Similarly, BCNU produced a complete response rate of 47%, partial response rate of 37%, and 5-year relapse-free survival rate of 10%.[105]

As an alternative to topical chemotherapy, topical phototherapy may be considered for extensive patch or plaque disease. UVB should be reserved for extensive patch disease only because of its superficial penetration. In contrast, PUVA may be considered for patients with patches or thin plaques and has resulted in complete response rates of 60% to 100%.[101,170,171] Phase II trials suggest promising improvements in both complete response rate and duration of remission when adding IFN-α to PUVA for the treatment of T2 disease.[116,117,119]

Cutaneous Tumors: T3 N0-1 M0 (IIB)

Radiotherapy is an important treatment modality for cutaneous tumors because of its ability to treat the full thickness of deeply infiltrative lesions. For the rare patient with asymptomatic tumors involving less than 10% of the skin, either topical skin-directed therapy, along with local radiotherapy or TSEBT are reasonable first-line treatment options, with both producing a similar 5-year overall survival of roughly 50%.[98] However, most patients with T3 disease present with extensive, symptomatic tumors. Such patients often benefit from TSEBT as a first-line, palliative treatment because of a superior complete response rate as compared with topical HN2 plus localized radiotherapy, 44% to 54% versus 8%.[98,99]

Adjuvant therapy should be strongly considered for patients after completing a course of TSEBT, even as maintenance therapy after a complete response. Retrospective data suggest that adjuvant topical mechlorethamine may improve the duration of response, resulting in 5-year relapse-free survival of 55% compared to 30% with TSEBT alone.[98] Adjuvant photopheresis is another reasonable option, with retrospective data reporting 5-year overall survival of 100% for patients receiving this modality compared with 50% in patients who did not receive adjuvant therapy.[136] Other adjuvant therapies worthy of consideration include IFN-α, bexarotene, and denileukin diftitox.[172]

Erythroderma: T4 N0-1 M0 (III)

TSEBT is an appropriate initial therapy for erythrodermic MF because of its ability to produce a rapid and sustained response, thereby ameliorating the severe cutaneous symptoms experienced by such patients. Further, data suggest that TSEBT can result in a substantial reduction in the number of malignant cells circulating in the peripheral blood, potentially altering the natural history of the disease.[173,174] Retrospective data indicate that TSEBT monotherapy produced a 100% complete response rate and 5-year progression-free survival of 69% for patients with T4 N0 M0 B0 MF.[100] However, when including those with blood or visceral involvement, the complete response rate dropped to 74% and only 36% remained progression-free at 5 years. Patients with erythroderma and blood or visceral involvement are particular candidates who may benefit from adjuvant photopheresis because retrospective data suggest that such treatment improves 2-year cause-specific survival from 69% without EP to 100% with EP.[137]

For patients without access to TSEBT, several other topical treatment options exist. For example, a series of 10 patients treated with PUVA reported a complete response rate of 70% and median progression-free survival of 5 months.[175] Although not studied in a randomized setting, prospective phase II experiences suggested that addition of IFN-α to PUVA may improve the duration of response, in advanced disease.[115-117] Another option for T4 disease is photopheresis monotherapy because 80% of patients will experience at least some cutaneous improvement.[109] Patients with a normal peripheral blood CD4/CD8 ratio appear more likely to respond.[135]

Total Skin Electron Therapy: Toxicity

TSEBT is generally well-tolerated, and toxicity is minimized by using low daily fractions sizes[176] and a shielding regimen that reduces the dose to eyes, ears, lips, hands, and feet. Common acute toxicities from TSEBT include pruritus, dry desquamation, erythema, alopecia, xerosis, bullae of the feet, edema of the hands and feet, hypohidrosis (diminished perspiration),[177] and loss of fingernails and toenails.[167,178] Rare acute side effects include gynecomastia in men, mild epistaxis, and mild parotiditis.[167] Because of the superficial penetration of electrons, patients do not experience gastrointestinal or hematologic toxicities. In general, TSEBT does not cause serious long-term complications,[179] although permanent nail dystrophy, xerosis, telangiectasias, partial scalp alopecia, and fingertip dysesthesias have been described.[160] Second cutaneous malignancies including squamous cell carcinoma, basal cell carcinoma, and malignant melanoma have been observed in patients treated with TSEBT, particularly in those exposed to multiple therapies that are themselves known to be mutagenic, such as PUVA and mechlorethamine.[104,180]

PALLIATION

In current practice, for the majority of patients, age or performance status ultimately preclude allogeneic transplant, and therefore palliative treatment options remain a mainstay of therapy. A palliative approach usually includes novel biologic agents, cytotoxic chemotherapy, and radiation. For example, oral bexarotene has shown efficacy in patients with relapsed or refractory MF, producing an overall response rate of 57%

for stage IIB, 32% for stage III, 44% stage IVA, and 40% for stage IVB.[122] Another option, denileukin diftitox, resulted in an overall response rate of 30% for patients with treatment-refractory stages IB to IVA disease.[74] Systemic chemotherapy should also be considered and may result in complete response rates of 20% to 60%.[147]

Radiotherapy, including TSEBT, plays an important role in the palliation of both cutaneous and extracutaneous disease.[181,182] For those patients with extensive skin disease recurrent after TSEBT, a second course of TSEBT may produce substantial palliation with acceptable toxicity.[183] Typically median doses for repeat TSEBT courses after an initial course of >30 Gy tend to be lower, on the order of 18 Gy to 23 Gy. However, evidence suggests that lower doses can still achieve high rates of overall and complete response.[163,184] Toxicity of repeat TSEBT is typically characterized by xerosis, telangiectasias, pigment changes, and alopecia. Criteria for retreatment include complete response to the initial course, an extended disease-free interval after the initial course, diffuse cutaneous involvement at relapse, or failure of other modalities. Localized, symptomatic skin lesions can benefit from a local radiotherapy field, with options including higher doses on the order of 20 Gy to 30 Gy, or lower doses on the order of 8 Gy in two fractions or 7 Gy in one fraction.[185] Recent evidence suggests that the lower dose approach produces complete response rates in excess of 90%, and that retreatment with higher doses of radiation is safe and effective for those patients whose tumor recurs following low dose irradiation.[186] Finally, patients with symptomatic nodal or visceral disease often benefit from a course of palliative megavoltage radiotherapy to a total dose of 20 Gy to 30 Gy delivered in 2-Gy to 3-Gy fractions.

Follow Up

Follow up after definitive treatment for MF is best carried out by a multidisciplinary team with expertise in CTCL. Because most patients managed with TSEBT now receive adjuvant treatment, they remain in close contact with their dermatologists every 1 month to 3 months for many years. Biopsy of clinically borderline or suspicious lesions is important to document relapse and to rule out transformation to a large-cell variant. In addition, close surveillance is required to detect treatment-related skin cancers and ensure that appropriate therapy is initiated promptly. Patients with an elevated CD4/CD8 ratio, LDH, or soluble interleukin-2 receptor level at initial diagnosis should have these values followed closely to determine response to therapy.

TECHNIQUES OF IRRADIATION

Historical Development

Localized radiation was first used to treat MF in 1902, shortly after the discovery of x-rays.[187] In 1939, Summerville reported treatment of extensive cutaneous MF with an "x-ray bath" of kilovoltage photons delivered with two large fields.[188] A total air exposure of 900 roentgen delivered in daily fractions of 10 roentgen produced a complete response. In 1945, Levin and Behrman proposed that the total air exposure at the skin surface should be 600 roentgen to 800 roentgen for patches or plaques and 1000 roentgen to 1600 roentgen for tumors.[189]

The development of total skin electron beam therapy began in the early 1950s. Trump et al at the Massachusetts Institute of Technology used a Van de Graaff generator to produce a vertically oriented, stationary beam of 2.5 MeV electrons incident on a motorized couch.[190] By placing the patient in the prone, supine, and lateral decubitus positions and translating the couch through the electron beam, all skin surfaces could receive a meaningful dose. This treatment approach produced complete responses in two patients with extensive MF. In 1960, Stanford University reported the first method for linear accelerator-based TSEBT.[191] With a patient standing 10 feet from the end of the accelerator, two fields were treated, one directed above the patient's head and a second directed below the patient's feet. This approach is known as the dual-field technique. In addition, patients were treated in two positions with respect to the accelerator: anteroposterior and posteroanterior. Over time, it became clear that increasing the number of treatment positions improved dose homogeneity in the lateral dimension.[192,193] Ultimately, Stanford adopted a six-treatment position technique in which patients stand in six different orientations with respect to the accelerator: anteroposterior, posteroanterior, right and left anterior oblique, and right and left posterior oblique.[194] Although commonly called the "six-field" technique, it should be remembered that two fields are actually treated for each of the six treatment positions.

The first clinical results of TSEBT were published in 1962 by a group from St. John's Hospital for Diseases of the Skin in London.[195] Using the dual-field, four treatment position technique developed at Stanford, all five patients treated for MF experienced "very good" responses at total doses ranging from 12 Gy to 18 Gy. However, four of five patients relapsed within 8 months and disease was difficult to control in the axillae and perineum because of underdosing. In 1971, Stanford University reported 107 patients with MF who received TSEBT between 1957 and 1968.[194] Using a variety of doses, they produced a 52% complete response rate. In addition, among patients with localized patches or plaques, 30% experienced long-term disease-free survival, providing the first evidence that MF could actually be cured.

Target Volumes

The target volume for TSEBT should include the epidermis and dermis.[99] The thickness of the epidermis varies from 0.05 mm to 0.50 mm and is greatest in the distal extremities. The thickness of the dermis varies from 1 mm to 4 mm and is greatest in the hands and feet. Therefore, the thickness of the skin varies from a minimum of about 2 mm on the trunk to a maximum of about 4.5 mm at the hands and soles of the feet.[99] As a result, the EORTC TSEBT consensus statement recommends that the 80% isodose line should be ≥4 mm deep to the skin surface to ensure that the epidermis and dermis fall with the high-dose region. Because of their thickness, the deep margin of cutaneous tumors is often underdosed when treated with TSEBT alone and may require supplemental boosts with appropriately selected electrons to ensure adequate dose to areas typically underdosed such as axillae and perineum.

Limited Superficial Radiotherapy

Minimal stage IA disease should be treated with a single radiation field where possible, though abutting fields may be required at a convex surface such as the scalp, an axillary fold, breast, hand, or foot. The junction of abutting fields should be shifted during the course of treatment to improve homogeneity. Field margins can be limited by lead cut-out to only 1 cm to 2 cm beyond the visible (or palpable) clinical lesion. Electrons of 4 MeV to 16 MeV energy with appropriate bolus material are usually sufficient, and the dose should be approximately 8 Gy to 30 Gy (one to two treatments per week) with the expectation of durable response. One or several fields of 6 MeV to 16 MeV electrons can also be used to encompass the limited volumes required to palliate symptomatic skin lesions, including most tumor nodules and skin ulcers. Clinical regression can be seen at 12 Gy to 14 Gy and considered adequate for a first course of treatment, and in certain cases,

as low as 8 Gy is acceptable.[22,90,99,157] Treating with the lowest dose that induces clinical remission preserves as much radiation tolerance of the skin as possible and enables future delivery of local radiotherapy or TSEBT. Furthermore, in situations of coexisting cancer diagnoses (e.g., Hodgkin's, breast, prostate or rectal cancers), radiation treatments for those diagnoses must be carefully planned to minimize the superficial skin exposure to preserve the option of TSEBT in the future.

Node, Viscera, and Blood Radiotherapy

Nodal regions (e.g., axillary and inguinal) and some visceral organs (e.g., lungs, larynx, and brain) can be encompassed using standard beam arrangements and energies. Prescriptions are typically 20 Gy to 30 Gy in 10 to 20 fractions over 2 to 4 weeks.

Several experiences using TSEBT in combination with either low dose total body irradiation[196] or total nodal irradiation[197,198] have been reported. However, such treatment may increase the risk of secondary malignancies or myelodysplastic syndrome[198] and has not demonstrated superiority over conventional systemic agents. For patients undergoing allogeneic bone marrow transplantation, incorporation of TBI in the preparative regimen may be considered.[153]

TSEBT delivers a total dose to the blood and marrow of approximately 0.4 Gy in 30 or more fractions over 6 weeks to 14 weeks. In general, hematologic values remain normal during a course of TSEBT. However, for those with Sézary syndrome, the number of circulating Sézary cells may fall by 50% to 95% and, in rare instances, may remain in a sustained remission.

Modern TSEBT

Technical advances since the initial Stanford and St. John's publications have included dose escalation to 35 Gy to 36 Gy, improvements in shielding, and integration of boost treatments to underdosed regions, culminating in the publication of a consensus statement from the EORTC regarding appropriate techniques for TSEBT (Table 79-10).[161]

The method of TSEBT used at our institution achieves these objectives with a ≥4 MeV modern linear accelerator using the dual-field, six-treatment position technique. The patient stands 3 meters from the electron source, and the gantry is angled up and down at 113 degrees and 67 degrees to produce the dual-fields. A Lucite plate is placed in front of the patient and serves to scatter the incident electrons and attenuate x-ray contamination (Figure 79-4).

TABLE 79-10 EORTC Guidelines for Total Skin Electron Beam Therapy

- Dose inhomogeneity in air at treatment distance should be <10% within vertical and lateral dimensions.
- 80% isodose line should be ≥4 mm deep to the skin surface to ensure that the epidermis and dermis fall within the high-dose region.
- 80% isodose line should receive a minimum total dose of 26 Gy.
- 20% isodose line should be <20 mm from the skin surface to minimize dose to underlying structures.
- 30 to 36 fractions should be used to minimize acute side effects.
- Total dose to bone marrow from photon contamination should be <0.7 Gy.
- Patch treatments should be used to underdosed areas, such as the perineum, scalp, and soles of feet.
- Internal and external eye shields should be used to ensure that the dose to the globe is not more than 15% of the prescribed skin surface dose.

Adapted from Jones GW, Kacinski BM, Wilson LD, et al: Total skin electron radiation in the management of mycosis fungoides. Consensus of the European Organization for Research and Treatment of Cancer (EORTC) Cutaneous Lymphoma Project Group. J Am Acad Dermatol 47:364–370, 2002.

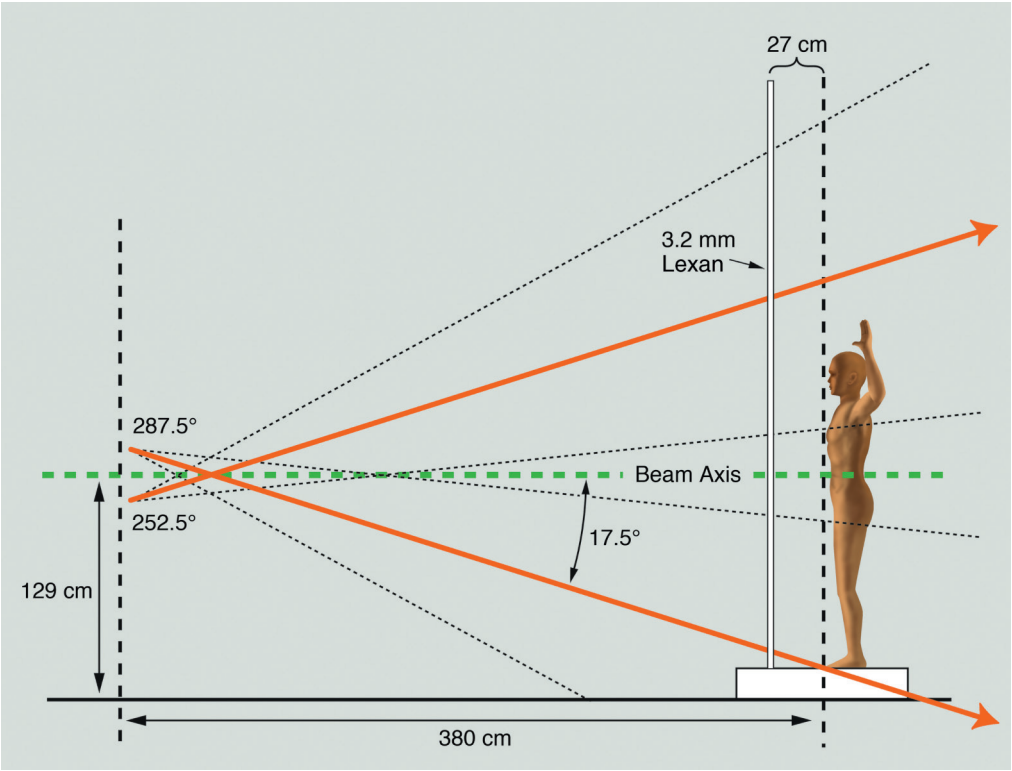


Figure 79-4 Geometry of dual-field total skin electron beam technique.



Figure 79-5 Treatment positions used in total skin electron beam therapy. Top row (*from left to right*): right anterior oblique, anteroposterior, and left anterior oblique treatment positions. Bottom row (*from left to right*): right posterior oblique, posteroanterior, and left posterior oblique treatment positions.
Adapted and reprinted with permission from Figure 6 in Dabaja BS: Mycosis fungoides, presentation, diagnosis, and treatment strategy. In Thomas CR, Jr, editor: Radiation medicine rounds: Hematologic malignancies, New York, 2012, Demos Medical Publishing.

A total of six treatment positions are designated: anteroposterior, right and left anterior oblique, posteroanterior, and right and left posterior oblique (Figure 79-5). These positions maximize skin unfolding, thereby improving dose homogeneity in the lateral dimension. Each position is treated with two fields, an upper field and a lower field to maximize dose homogeneity in the vertical dimension. For example, on cycle one, the anteroposterior, right posterior oblique, and left posterior oblique positions are treated. On cycle two, the posteroanterior, right anterior oblique, and left anterior oblique positions are treated with the same dose. Over the course of two treatment cycles, a patient will receive 2 Gy to the entire skin surface. This pattern continues, with patients receiving one to two cycles per week for classically 6 weeks to 10 weeks (Table 79-11).

This technique places the dose maximum at 1 mm, the 80% isodose line at 6 mm, and the 20% isodose line at 12 mm,[199] thus satisfying the EORTC criteria for TSEBT[167] (Table 79-10). Photon contamination because of bremsstrahlung scattering in the machine head, intervening air, scatterers or degraders, and patient, is acceptable at 1.2%. A comparison of the depth-dose curves for a single anteroposterior treatment position and for all six treatment positions is presented graphically in Figure 79-6 and by film dosimetry in Figure 79-7.[199] Using six treatment positions shifts the isodose curve toward the skin surface because of the obliquity of the incident electrons.

As a result of the shielding inherent to these treatment positions, underdosed areas must be considered for supplemental treatment. Areas of potential underdosing include the shoulders, axillae, inframammary folds, folds under any

TABLE 79-11 Sample Treatment Protocol

TREATMENT CYCLE	
Day 1	AP, RPO, LPO treatment positions
Day 2	PA, RAO, LAO treatment positions
DOSE	
Dose per cycle	2 Gy
Cycles per week	2
Total cycles	18
Total dose	36 Gy
BOOSTS	
Perineum	100 cGy/day, first 9 and last 9 treatment days
Soles of feet	100 cGy/day, first 7 and last 7 treatment days
BLOCKING	
External eye shields	First 11 cycles
Internal eye shields	Last 7 cycles
Lip shield	Cycles 1-4
Lead mitt for hands	Every other cycle
Fingernail shield	Every other cycle, alternating with mitts
Foot block	Cycles 1-3, 5, 7, 9, 11, 13, 15, 17, 18
Testicular shield	Used with perineal boost only

Data from Chen Z, Agostinelli AG, Wilson LD, et al: Matching the dosimetry characteristics of a dual-field Stanford technique to a customized single-field Stanford technique for total skin electron therapy. Int J Radiat Oncol Biol Phys 59:872–885, 2004.

AP, *Anteroposterior;* LAO, *left anterior oblique;* LPO, *left posterior oblique;* PA, *posteroanterior;* RAO, *right anterior oblique;* RPO, *right posterior oblique.*

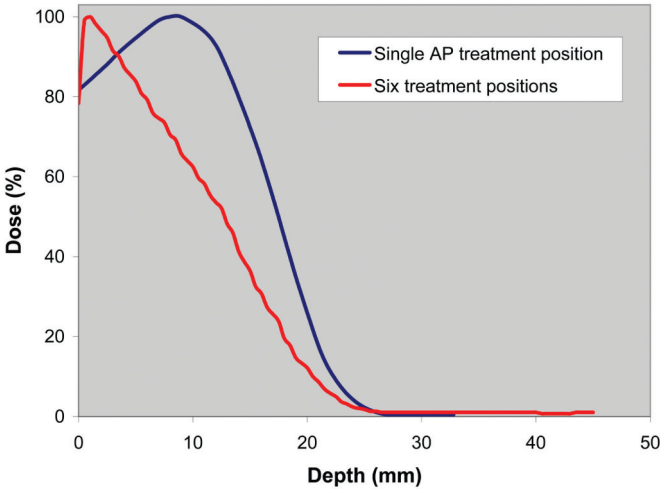


Figure 79-6 Depth dose curves for dual-field total skin electron beam therapy. *Purple line*: Depth dose curve for an anteroposterior (AP) dual-field 4 MeV electron beam incident on polystyrene, a tissue-equivalent material. Note that the surface receives roughly 80%, and that the maximum dose is deposited 8 mm from the surface. *Red line*: Depth dose curve for dual-field, six treatment position, standard TSEBT. Because of multiple beams entering the skin surface at oblique angles, the dose delivered to the skin surface rises dramatically, and drops to 80% by 8 mm.
(Graph courtesy of Zhe Chen, PhD). Adapted with permission from Figures 6 and 11 in Chen Z, Agostinelli AG, Wilson LD, et al: Matching the dosimetry characteristics of a dual-field Stanford technique to a customized single-field Stanford technique for total skin electron therapy. Int J Radiat Oncol Biol Phys 59:872–885, 2004.

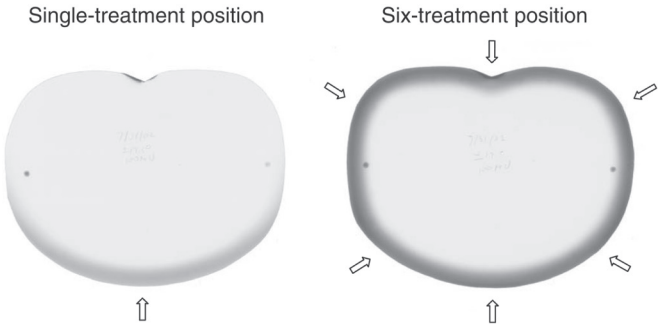


Figure 79-7 Cross-sectional dose distribution. Axial film dosimetry for single treatment position and six treatment position technique. The dark region is proportional to the electron dose delivered to the film.
Adapted with permission from Figure 5 in Chen Z, Agostinelli AG, Wilson LD, et al: Matching the dosimetry characteristics of a dual-field Stanford technique to a customized single-field Stanford technique for total skin electron therapy. Int J Radiat Oncol Biol Phys 59:872–885, 2004.

pannus, groin and medial thighs, perineum, and perianal area; though underdosed areas are dependent on body habitus. Obesity and idiosyncratic lateral and flatter regions or individual folds may determine other areas that are underdosed. The scalp may be underdosed, but is supplemented typically only if involved to decrease risk of alopecia. Therefore, supplemental patch fields should be guided by in vivo dosimetry along with clinical assessment and suspicion, to ensure that the surface dose is at least 50% of the prescribed TSEBT dose.[200,201]

The hands, and feet, as well as areas of the perineum receiving tangential beam may be overdosed as a result of a variety of factors including tissue heterogeneity (e.g., bone), high convexity, and overlap between more than three of the six primary fields.[99] Thus, these regions should be shielded for a certain proportion of the treatments to reduce the total dose to 32 Gy to 36 Gy or less. Upfront planning for cyclic blocking is warranted, particularly in the context of comorbidities such as diabetes (or other vasculopathy) that may further compromise skin integrity or worsen the morbidity associated with acute radiation skin toxicity. Detailed dosimetric measurements are typically required to determine the most appropriate shielding regimen using lead or other shielding material, for a particular treatment arrangement and patient geometry (Table 79-12). Eyes may be shielded with a combination of external eye shields and lead internal eye shields.[202] Although internal eye shields may cause conjunctival irritation and corneal abrasions, the risk is usually less than 1%[167] (Tables 79-10 and 79-11).

Because many tumors have a thickness greater than 6 mm, TSEBT alone may result in significant underdosing. As a result, for patients with bleeding, weeping, or painful tumors at presentation, an initial or concurrent boost of 10 Gy in five fractions with either 6 MeV to 16 MeV electrons or orthovoltage photons has been effective. In addition, asymptomatic plaques and tumors that persist at the end of treatment receive a similar boost to ensure adequate dose delivery at depth.

Other Radiation Management Issues

Cutaneous symptoms including xerosis, pruritus, and pain from fissures or ulceration are often severe and should be managed aggressively with topical corticosteroids, emollients, oral antihistamines, and aggressive wound care with nonocclusive dressings.[81] Acute skin toxicity from TSEBT usually responds to the above measures, although treatment breaks on the order of 1 week to 2 weeks may occasionally be required.[203]

TABLE 79-12 Dose to Anatomic Sites Using In Vivo TLD Dosimetry

	Dose/2-day TSEBT Treatment Cycle*		Total Dose with Blocking and Boosts	
	Gy	Percentage	Gy	Percentage
Central axis	2.0	100	36.0	100
Top of head	2.3	115	41.4	115
Forehead	2.4	118	42.5	118
Eye	0.1	12	2.2	6
Eyelid	—	—	24.5	68
Lips	—	—	30.0	83
Posterior neck	2.1	104	37.4	104
Shoulder	1.7	87	31.3	87
Axilla	2.2	109	39.2	109
Hand	1.6	82	15.6	43
Mid-back	2.0	100	36.0	100
Umbilicus	2.1	104	37.4	104
Flank	2.0	99	35.6	99
Lateral thigh	1.9	95	34.2	95
Perineum	0.6	31	29.0	81
Top of feet	2.3	117	28.5	79
Soles of feet	0	0	14.0	39

Data from Chen Z, Agostinelli AG, Wilson LD, et al: Matching the dosimetry characteristics of a dual-field Stanford technique to a customized single-field Stanford technique for total skin electron therapy. Int J Radiat Oncol Biol Phys 59:872–885, 2004.

TLD, *Thermal luminescent detector;* TSEBT, *total skin electron beam therapy;* —, *not reported.*

**Dose using dual-field, six-treatment position setup with scalp electron reflector and eye shields.*



Figure 79-8 Disseminated herpes simplex during the course of total skin electron beam therapy.

Large bullae that develop during TSEBT should be lanced under sterile conditions and require nonocclusive dressings until they reepithelialize.

As previously discussed, patients with advanced MF may experience a profound degree of immunosuppression. As a result, cutaneous and systemic infections are an important cause of morbidity and mortality. The most common infections include cellulitis resulting from *Staphylococcus aureus* or *β-hemolytic streptococci*, cutaneous herpes simplex or herpes zoster (both of which may disseminate cutaneously), bacteremia (most commonly with *S. aureus*), and bacterial pneumonia.[35] Signs and symptoms of such infections should be evaluated promptly and treated aggressively. Independent of MF, TSEBT also suppresses cutaneous immunity, likely as a result of destruction of normal skin-homing lymphocytes and epidermal antigen presenting dendritic cells. Thus, any new eruption that develops during the course of TSEBT should be evaluated promptly, as disseminated cutaneous bacterial, fungal, and viral infections are not uncommon[204,205] (Figure 79-8).

TREATMENT CONTROVERSIES, PROBLEMS, CHALLENGES, AND FUTURE POSSIBILITIES

A major challenge is the need for prospective randomized trials to compare radiation-based and nonradiation-based approaches to initial treatment. Adequately powered trials are problematic given the rarity of MF and difficulty in accruing patients. A recent Cochrane meta-analysis evaluated 14 trials that included 675 participants, the majority representing stages IA to IIB patients. Unfortunately, the efficacy of treatments could not be directly compared among the agents studied. Disease clearance was the primary outcome in most studies, with widely heterogeneous results, ranging from 0% to 83% response for skin-directed therapies.[206] This meta-analysis highlights ongoing challenges to prospectively evaluating treatment options for MF. In the absence of randomized data, treatment will continue to be guided by institutional expertise and patient preference.

The clinical management of patients with MF is complex and typically requires an interdisciplinary team approach that attends to the patient as a whole. Most patients require a fairly detailed understanding of the disease, its implications and risks, and all treatment options. The majority of patients are seeking a cure, which for many is unrealistic. Improvements in quality of life are possible regardless of presenting stage. The relative contributions of various factors in determining quality of life have not been systematically explored. However, clinical experience indicates that the most salient factors are controlling symptoms; achieving remission regardless of prior clinical trajectory; using treatments that are efficient and of limited duration (so as to be less disruptive to lifestyle and personal circumstances over the long term); addressing any anxiety and depression; and providing sustained and reliable support and expertise that extends into years and even decades of follow-up.

Many biologic and clinical questions pertaining to the pathophysiology and treatment of MF remain unanswered. For example, it is unclear whether the development of MF is initially driven by a specific exogenous antigen or by random mutational events occurring in activated T cells. In addition, the molecular factors that influence disease progression and response to various treatment modalities are just beginning to be elucidated. Clinically more studies with homogeneous patient populations are required to evaluate putative prognostic factors.

The future will likely bring additional novel systemic therapies for MF. For example, biologic and immunologic agents including monoclonal antibodies directed against CD4, CD52, CD25, and CD30, individualized dendritic cell-based tumor vaccines, HDACi, purine nucleoside phosphorylase inhibitors, proteasome inhibitors, immunomodulatory/immunostimulatory agents, fusion toxins, and antifolates continue to undergo investigation, with the goal of improving the

treatment of recurrent or refractory disease.[207,208] Strategies for integrating novel biologics with standard therapies such as TSEBT are needed to maximize the benefits of each. For long-term disease control and cure, allogeneic stem-cell transplant is an encouraging development, with present challenges focused on developing the optimal conditioning scheme and strategies to manage the complications.

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